NEW HOMEOPATHIC MEDICINES

Use of modern drugs according to the principle of similitude

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Volume I

Scientific Basis of the Principle of Similitude in Modern Pharmacology

Marcus Zulian Teixeira

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Scientific Basis of the Principle of Similitude in Modern Pharmacology

SUMMARY

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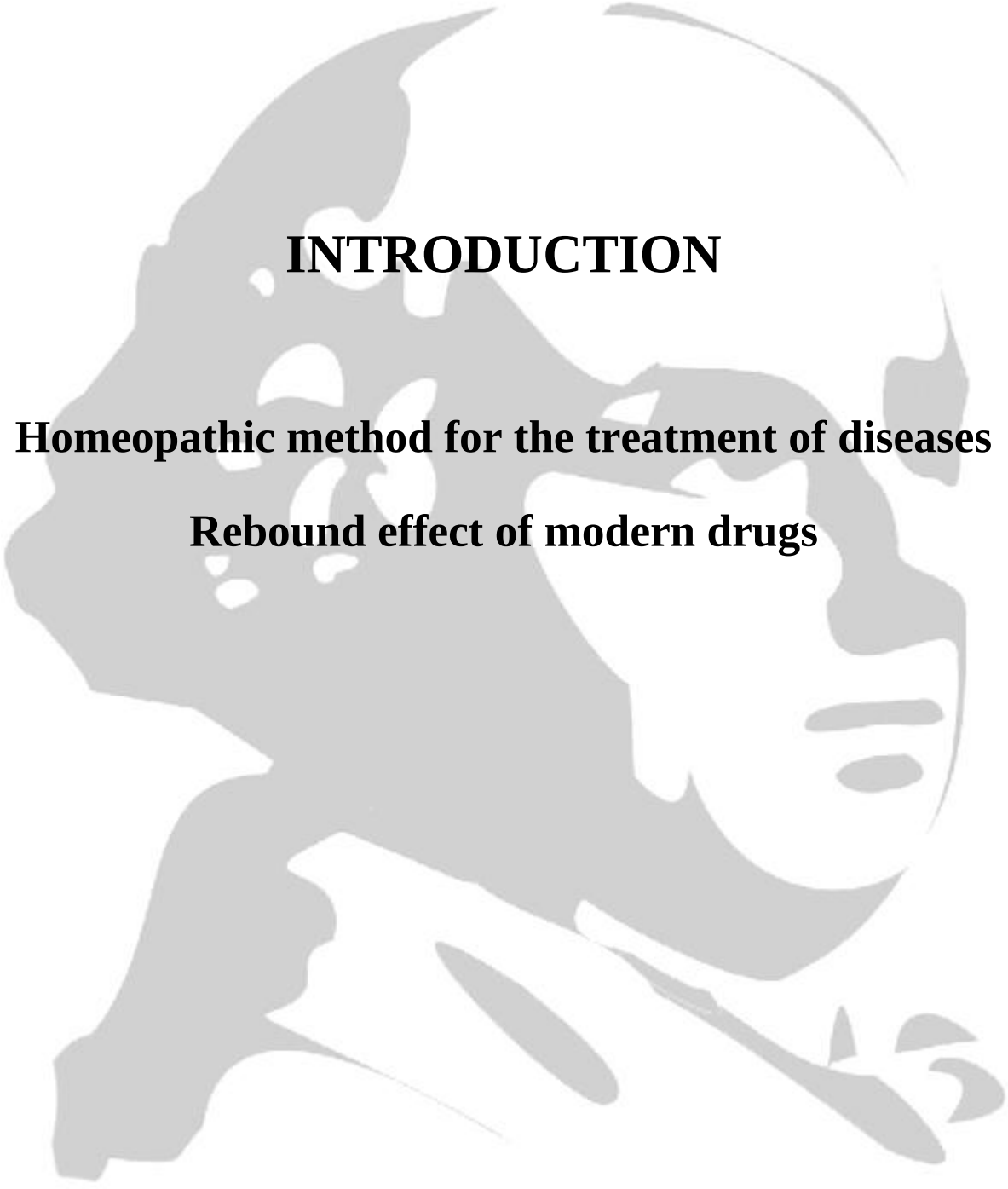

INTRODUCTION

Homeopathic method for the treatment of diseases

Rebound effect of modern drugs

Homeopathic method for the treatment of diseases[1]

In the systematization of the homeopathic method of treatment of diseases, Samuel Hahnemann makes four fundamental assumptions: *principle of cure by similitude, proving of medicinal substances on healthy individuals, use of serially diluted and agitated medicines,* and *prescription of individualized medicines.*

To apply the principle of therapeutic similitude with previously tested substances, Hahnemann indicates to select the remedy that awakened the set of symptoms most similar to the ones exhibited by the patient (characteristic symptomatic totality) in order to stimulate the reaction of the organism against the natural disease. This principle might sound odd to modern ears, since it is the polar opposite for the enantiopathic method of treatment (principle of contraries) employed by conventional medicine for the immediate palliation of the symptoms of disease.

All throughout the development of the homeopathic doctrine, Hahnemann kept a rational, scientific and experimental attitude, describing the phenomena awakened by drugs on human beings and seeking to correlate his clinical observations with the best evidence available in the contemporary medical-scientific literature.

After his initial self-experimentation of *Cinchona officinalis*, Hahnemann sought for confirmation (strong arguments) through "analogy" and "enumeration", by studying the clinical reports made by previous doctors. There he was able to find countless references that eventually led him to raise the principle of similitude to the level of a "natural law" and that also supported the use of inductive logic: *for a substance to heal definite symptoms in ill human beings it must elicit similar symptoms in healthy experimental subjects.*

In the "Introduction" to *Organon of homeopathic medicine*,[2] masterpiece of homeopathy, Hahnemann alludes to hundreds of homeopathic healings involuntarily made by doctors of the "Old School", and thus grounds his initial observations on the principle of similarity on 247 bibliographic references:

> "*Murray,* whom I selected from numerous other authorities, together with daily experience, informs us, that among the symptoms produced by the use of *tobacco,* those of *vertigo, nausea,* and *anxiety,* are the principal. Whereas *Diemerbroeck* when attacked with those very symptoms of vertigo, nausea, and anxiety, in the course of his close attendance on the victims of epidemic diseases in Holland, removed them by the use of the pipe".
>
> "The hurtful effects which some writers (among others Georgi) ascribe to the use of the *Agaricus muscarius,* by the inhabitants of Kamtschatka, and which consist of tremors, convulsions, and epilepsy, became a salutary remedy in the hands of *C. G. Whistling,* who

[1] Teixeira MZ. O princípio homeopático de cura ao longo da história da medicina [The homeopathic principle of cure along the history of medicine]. *Rev Homeopatia (São Paulo).* 2007; 70 (1-4): 55-78. Available at: ResearchGate

[2] Hahnemann S. Organon of homeopathic medicine. Third American edition. English version of the fifth German edition. New York: William Radde, 1849.

> used this mushroom with success in cases of convulsions accompanied with tremor; likewise in those of *J. C. Bernhardt*, who used it with success in a species of epilepsy".
> "[...] And whence could arise that curative power of *arsenic* which exhibits in certain species of intermittent fevers, (a virtue attested by so many thousands of examples, but in the practical application of which, sufficient precaution has not yet been observed, and which virtue was asserted centuries ago by *Nicholas Myrepsus*, and subsequently placed beyond a doubt by the testimony of *Slevogt, Molitor, Jacobi, J. C. Bernhardt, Jiingken, Fauve, Brera, Darwin, May, Jackson,* and *Fowler),* if it did not proceed from *its peculiar faculty of excit ingfever,* as almost every observer of the evils resulting from this substance has remarked, particularly *Amatus Lusitanus, Degner, Buchholz, Heun,* and *Knape.* We may confidently believe *E. Alexander,* when he tells us that *arsenic* is a sovereign remedy in some cases of angina pectoris, since *Tachenius, Guilbert, Preussius, Thilenius,* and *Pyl,* have seen it give rise to very strong *oppression of the chest; Gresselius,* to a *dyspncea approaching even to suffocation;* and *Majault,* in particular, saw it produce *sudden attacks of asthma excited by walking, attended with great depression of the vital powers*".

Hahnemann inaugurated homeopathy in 1796 with the publication of *Essay on a new principle for ascertain the healing powers of drugs* in Hufeland's Journal *(Journal der praktischen Arzneykunde)*[3,4] where he described the *direct primary actions of drugs* and the *indirect secondary action of the organism* (curative vital reaction) to them. Systematization of the pharmacological properties identified by Hahnemann in some examples results in the following descriptions:

> **Tobacco** *(Nicotiana tabacum)*. **Direct primary action:** decrease of the sensitivity of the external senses and diminution of intellectual abilities; deprives voluntary muscles from irritability and temporarily removes the influence of the power of the brain (for this reason it is used, according to the principle of contraries, in catalepsy and other disturbs with mental excitation, provoking temporary relief followed by worsening of the condition); the direct action lasts only a few hours. **Indirect secondary action:** improvement of mental weakness; tendency to epilepsy, hypochondriasis, and hysteria.
>
> **Agaric** *(Agaricus muscarius)*. **Direct primary action:** furious and drunken-like mania (combined with revengeful and audacious determination, disposition to make verses, prophecies, etc.), exaltation of strength, tremors and seizures; direct action lasts between 12 and 16 hours. **Indirect secondary action**: successfully used in epilepsy (caused by fear) combined with tremor; it heals mental affections and possession similar to those it causes.
>
> **Arsenic** *(Arsenicum album)*. **Direct primary action:** tendency to excite spasm in the blood vessels and chills, in daily paroxysms; continual use of large doses gradually causes an almost constant febrile state; decrease of the tonus of the muscular fiber and the sensitiveness of nerves (paralysis); stimulates cough; causes some chronic affections of the skin (with desquamation); direct action lasts for some days, with accumulation of the toxic effect of doses frequently repeated. **Indirect secondary action:** treatment of intermittent fever with daily recurrence,

[3] Hahnemann S. Essay on a new principle for ascertaining the curative power of drugs, and some examinations of the previous principles. *Journal der praktischen Arzneykunde.* 1796; 2: 391.
[4] Hahnemann S. Essay on a new principle for ascertaining the curative power of drugs, with a few glances at those hitherto employed. In: Dudgeon RE. The lesser writings of Samuel Hahnemann. New Delhi: B. Jain Publishers, 1995.

useful in hectic and remittent fever, in some types of paralysis, in cough, in similar diseases of the skin.

Keeping on the logical reasoning manifested in paragraphs 63-65 of *Organon of medicine*,[5] Hahnemann attempts a physiological explanation of his alleged "natural law" of healing, by classifying the phenomena observed during the human testing of medicinal substances common in his time in two main categories, namely, the *primary action of drugs*, and the *secondary action (or vital reaction) of the organism.* In this way he postulated a universal mechanism of action (pharmacodynamics) for medicines, derived from the observation of the different sensations and organic functions. Hahnemann exemplifies this mechanism with the pharmacological effects of several drugs used at that time:

> "[...] A hand bathed in hot water is at first much warmer than the other hand that has not been so treated (primary action); but when it is withdrawn from the hot water and again thoroughly dried, it becomes in a short time cold, and at length much colder than the other (secondary action). A person heated by violent exercise (primary action) is afterwards affected with chilliness and shivering (secondary action). To one who was yesterday heated by drinking much wine (primary action), today every breath of air feels too cold (counteraction of the organism, secondary action). An arm that has been kept long in very cold water is at first much paler and colder (primary action) than the other; but removed from the cold water and dried, it subsequently becomes not only warmer than the other, but even hot, red and inflamed (secondary action, reaction of the vital force). Excessive vivacity follows the use of strong coffee (primary action), but sluggishness and drowsiness remain for a long time afterwards (reaction, secondary action), if this be not always again removed for a short time by imbibing fresh supplies of coffee (palliative). After the profound stupefied sleep caused by opium (primary action), the following night will be all the more sleepless (reaction, secondary action). After the constipation produced by opium (primary action), diarrhoea ensues (secondary action); and after purgation with medicines that irritate the bowels, constipation of several days' duration ensues (secondary action). And in like manner it always happens, after the primary action of a medicine that produces in large doses a great change in the health of a healthy person, that its exact opposite, when, as has been observed, there is actually such a thing, is produced in the secondary action by our vital force". (*Organon*, § 65)

Noticing that the *secondary or indirect action of the organism* could be used as therapeutic reaction, provided it is oriented in the right direction, Hahnemann suggested to select medicines that in their *primary or direct action on the organism* elicit symptoms similar to the ones of the natural disease. In this way he widened the comprehension of the notion of therapeutic similitude: *each and every substance able to awaken definite symptoms on healthy individuals (due to the primary action of the drug) can be used to heal similar symptoms in the sick (through the secondary reaction of the organism*).

Hahnemann further employed the Aristotelian hypothetical syllogism or classic logic deductive tool known as *"modus tollens"*, a Latin term used to name the "mode that affirms through negation" and is the formal appellative of the "indirect proof" (or "null hypothesis" in modern biostatistics) to validate the homeopathic therapeutic hypothesis and

[5] Hahnemann S. Organon of medicine. 6th Edn. (Translated by William Boericke). New Delhi: B Jain Publishers, 1991.

the "natural law of similitude" by *negating the efficacy of the enantiopathic treatment of chronic diseases*, grounded on the principle of contraries (*contraria contrariis curentur*) and thus opposed to the principle of similitude *(similia similibus curentur).* In other words, according to *modus tollens*, *for the principle of similitude to be logically valid, its opposite (the principle of contraries) must be unable to heal the symptoms of disease, or actually worsen them.* Following this mode of argumentation, Hahnemann mentions countless examples of substances employed according to the *principle of contraries* that patently *worsened the symptoms of natural disease* after having been initially suppressed by enantiopathic treatment:

> "Important symptoms of persistent diseases have never yet been treated with such palliative, antagonistic remedies, without the opposite state, a relapse - indeed, a palpable aggravation of the malady - occurring a few hours afterwards. For a persistent tendency to sleepiness during the day the physician prescribed coffee, whose primary action is to enliven; and when it had exhausted its action the day - somnolence increased; - for frequent waking at night he gave in the evening, without heeding the other symptoms of the disease, opium, which by virtue of its primary action produced the same night (stupefied, dull) sleep, but the subsequent nights were still more sleepless than before; [...] - weakness of the bladder, with consequent retention of urine, was sought to be conquered by the antipathic work of cantharides to stimulate the urinary passages whereby evacuation of the urine was certainly at first effected but thereafter the bladder becomes less capable of stimulation and less able to contract, and paralysis of the bladder is imminent; - with large doses of purgative drugs and laxative salts, which excite the bowels to frequent evacuation, it was sought to remove a chronic tendency to constipation, but in the secondary action the bowels became still more confined; [...] How often, in one word, the disease is aggravated, or something even worse is effected by the secondary action of such antagonistic (antipathic) remedies, the old school with its false theories does not perceive, but experience teaches it in a terrible manner". (*Organon,* § 59)

Grounding the principle of similitude on formal deductive logic (that still remains a cornerstone of modern scientific methodology), Hahnemann tested a series of substances on allegedly healthy individuals *(homeopathic pathogenetic experimentation)* and recorded all the *new (primary or pathogenetic) symptoms* thus arising. This was the source of the *Homeopathic Materia Medica.* At the same time, in actual clinical practice, he applied such medicines to patients presenting similar symptoms, in order to awaken the secondary and curative reaction of the organism, resulting in the disappearance of the symptoms of natural disease.

In the early stage of homeopathic clinical practice, Hahnemann used *ponderable doses of medicines* chosen according to the *principle of similarity of symptoms.* However, such doses caused an intense aggravation of the similar symptoms of the natural disease due to the strong primary or direct action of the drug. In order to reduce the primary action of medicines, Hahnemann began to dilute and agitate them ("dynamization"), smoothing thus the symptoms of homeopathic aggravation. Later on, both in *pathogenetic experimentation* and *therapeutic prescriptions,* he observed that the "dynamized" (ultradiluted) medicine, besides eliciting and healing respectively the same symptoms exhibited by ill individuals, it also broadened the scope of the totality of symptoms through the appearance of further

idiosyncratic manifestations (as, e.g., mental and emotional symptoms). For this reason, he chose to use mainly this kind of doses.

It is worth to highlight that the principle of similitude (primary action of a drug followed by the secondary opposite action of the organism) is independent from the type of dose, i.e. either ponderal or infinitesimal, provided that the ill individual is sensitive to the (ponderal or infinitesimal) stimulus:

> "In those older prescriptions of the often dangerous effects of medicines ingested in excessively large doses we notice certain states that were produced, not at the commencement, but towards the termination of these sad events, and which were of an exactly opposite nature to those that first appeared. These symptoms, the very reverse of the primary action (§ 63) or proper action of the medicines on the vital force are the reaction of the vital force of the organism, its secondary action (§ 62-67), of which, however, there is seldom or hardly ever the least trace from experiments with moderate doses on healthy bodies, and from small doses none whatever. In the homoeopathic curative operation the living organism reacts from these only so much as is requisite to raise the health again to the normal healthy state". (*Organon,* § 112)

While discussing "what degree of smallness of doses is the best to achieve sure and safe effects" (*Organon,* § 278), Hahnemann emphasizes that it is mandatory for the primary or direct action of the dynamized (ultradiluted) substance to be stronger than the natural disease in order to be able to awaken the secondary or indirect action of the organism. For this reason, an effective dynamized remedy will always provoke primary effects more intense than the similar symptoms of the natural disease in order to show that it has strength enough to awaken the curative reaction of the organism; such primary effects might be or not perceived by the patient according to individual sensitiveness:

> "This pure experience shows universally that [...] *the dose of the homeopathically selected and highly potentized remedy* for the beginning of treatment of an important, especially chronic disease can never be prepared so small that it shall not be stronger than the natural disease and shall not be able to overpower it, at least in part and extinguish it from the sensation of the principle of life and thus make a beginning of a cure". (*Organon,* § 279)

For a dynamized remedy selected according to the principle of similarity to be actually effective, Hahnemann indicates that the *characteristic symptomatic totality* of the patient must be taken into account, encompassing the *most evident, singular, uncommon and peculiar symptoms of the case of disease.* According to him, only such *individualization of the medicine* allows for an ultradilution (characterized by minimal primary action and low dynamic power by comparison to ponderal doses) to be able to sensitize the receiving organism in its idiosyncratic aspects, awakening thus the corresponding healing vital reaction. Conversely, with the use of strong doses of the same substance, primary effects will be observed in all the individuals belonging to a species sensitive to it:

> "The curative power of medicines, therefore, depends on their symptoms, similar to the disease but superior to it in strength (§ 12-26), so that each individual case of disease is most surely, radically, rapidly and permanently annihilated and removed only by a medicine capable of producing (in the human system) in the most similar and complete manner the totality of its symptoms, which at the same time are stronger than the disease". (*Organon,* § 27)

In this way, the application of the homeopathic therapeutic principle involves the stimulation of a global homeostatic and curative reaction directed by the primary action of a drug that caused on human experimental subjects symptoms very similar to the characteristic and particular ones exhibited by the case of disease to be healed.

From all above, when drawing the logical path of Hahnemann's thinking in the elaboration of the theory of the principle of similitude and the application of the homeopathic treatment of disease with dynamized (ultradiluted) remedies, we emphasize the *fundamental features of the secondary action or vital reaction of the organism* according to Hahnemann's homeopathic pharmacology: (1) it appears only in susceptible individuals, i.e. those who exhibit in their constitution symptoms similar to the pathogenetic effects of the substance; (2) it is independent from the type of substance, repetition of doses and the type of symptoms (disease); (3) it appears after the primary action of the substance ceased; (4) it provokes a state diametrically opposed and more intense and/or long-lasting than the primary action of the drug; (5) its intensity is proportional to the one of the primary action (dose) of the substance. (*Organon,* § 59, 64, 69)

Rebound effect of modern drugs

Grounded on the same *modus tollens* ("null hypothesis" in modern statistics) that Hahnemann used to give logical validity to the principle of therapeutic similarity, we have been studying for some years[6,7] "the sad results of the use of the antagonistic remedies" (principle of contraries) of modern drugs according to the pharmacological-physiological notion of *rebound effect or paradoxical reaction of the organism (secondary action or vital action of the homeopathic model):*

> *"Had physicians been capable of reflecting on the sad results of the antagonistic employment of medicines, they had long since discovered the grand truth,* **that the true radical healing art must be found in the exact opposite of such an antipathic treatment of the symptoms of disease;** they would have become convinced, that as a medicinal action antagonistic to the symptoms of the disease (an antipathically employed medicine) is followed by only transient relief, and after that is passed, by invariable aggravation, the converse of that procedure, *the homeopathic employment of medicines* according to similarity of symptoms, must effect a permanent and perfect cure, if at the same time the opposite of their large doses, the most minute doses, are exhibited. But neither the obvious aggravation that ensued from their antipathic treatment, nor the fact that no physician ever effected a permanent cure of disease of considerable or of long standing unless some homoeopathic medicinal agent was accidentally a chief ingredient in his prescription, nor yet the circumstances that all the rapid and perfect cures that nature ever performed (§ 46), were always effected by the supervention upon the old disease of one of a *similar* character, ever taught them, during such a long series of centuries, this truth, the knowledge of which can alone conduce to the benefit of the sick". (*Organon,* § 61)[8]

Building a bridge between homeopathic pharmacology (principle of similitude) and modern pharmacology, one can find countless reports in pharmacological compendia and clinical and experimental trials published in the scientific media describing the *secondary reaction of the organism opposed to the primary action of the drug*, which confirm Hahnemann's theory. Such secondary action of the organism to preserve organic homeostasis is known in modern science as *rebound effect* or *paradoxical reaction.*

According to modern pharmacology, *rebound phenomena* or *symptoms* have an intensity higher than the one of the symptoms originally suppressed, and appear some time (hours to weeks) after the suspension or discontinuation of treatment, persisting for a variable period of time (hours to weeks) according to the characteristics of the involved drug and the idiosyncratic peculiarities of individuals.

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[6] Teixeira MZ. Semelhante cura semelhante: o princípio de cura homeopático fundamentado pela racionalidade médica e científica [Similar cures similar: the homeopathic cure principle based by the medical and scientific rationality]. São Paulo: Editorial Petrus, 1998. Available at: https://www.homeozulian.med.br/homeozulian_visualizarlivroautor.asp?id=3

[7] Teixeira MZ. Similitude in modern pharmacology. *Br Homeopath J.* 1999; 88(3): 112-120. Available at: https://doi.org/10.1054/homp.1999.0301

[8] Hahnemann S. Organon of medicine. 6th Edn. (Translated by William Boericke). New Delhi: B Jain Publishers, 1991.

Illustrating the assertion above, drugs used for the treatment of angina pectoris (*β*-adrenoceptor blockers, calcium channel blockers, nitrates, etc.), whose primary effect is the improvement of angina. After suspension of the drug, a rebound effect occurs, consisting of exacerbated thoracic pain, in frequency as well as intensity. Drugs utilised to control arterial hypertension (central *α*2-adrenoceptor agonists, *β*-adrenoceptor blockers, hidralazine, ACE inhibitors, MAO inhibitors, nitrates, prostaglandin A_1, sodium nitroprusside, etc.) can provoke rebound arterial hypertension as a secondary reaction. Anti-arrhythmic medications (adenosine, amiodarone, *β*-adrenoceptor blockers, calcium channel blockers, disopyramide, encainide, digitalics, flecainide, lidocaine, mexiletine, moricizine, procainamide, propafenone, quinidine, tocainide, etc.) provoke, after the interruption of treatment, exacerbation of the initial arrhythmias. Anticoagulant drugs (argatroban, bezafibrate, heparin, salicylates, warfarin, etc.) whose primary effect is prophylaxis of thrombosis, cause thrombotic complications as a secondary or rebound effect. Bronchodilators (adrenergic bronchodilators, sodium cromoglycate, ipratropium, nedocromil, long-acting bronchodilators, etc.) cause exacerbation of the bronchospasms after the suspension or discontinuation of treatment. In the psychiatric medications [anxiolytics (barbiturates, benzodiazepines, buspirone, meprobamate, etc.), sedative-hypnotics (barbiturate, bendodiazepines, morphine, promethazine, tetrahydrocannabinol, zopiclone, etc.), CNS stimulants (amphetamine, caffeine, cocaine, mazindol, methylphenidate, etc.), antidepressants (MAO inhibitors, tricyclics, SSRIs, etc.), anti-psychotics (clozapine, phenothiazines, haloperidol, pimozide, thiethylperazine, thiothixene, etc.)], a reaction of the organism trying to maintain organic homeostasis can be observed, with symptoms opposite to those expected in their primary therapeutic indication have been observed, further aggravating the initial condition. Drugs whose primary action is anti-inflammatory (ibuprofen, indomethacin, paracetamol, salicylates, etc.) induce a secondary response of the organism, increasing inflammation and the plasma concentration of mediators of inflammation. Drugs whose primary effect is analgesic (caffeine, calcium channel blockers, clonidine, ergotamine, methysergide, opioids, salicylates, etc.) may provoke, as a paradoxical reaction, hyperalgesia. Diuretics (furosemide, torasemide, triamterene, etc.) used to decrease blood volume cause rebound retention of sodium and potassium, increasing volemia. Anti-dyspeptics (antacids, H_2 receptor antagonists, misoprostol, sucralfate, proton pump inhibitors, etc.) for the treatment of gastritis and gastroduodenal ulcers, cause, after an initial decline in acidity, a rebound increase in acidity. Etc.

Analogously to homeopathic medicines, the *rebound effect of modern drugs* might be used for therapeutic purposes by stimulating favorable organic reactions. This is possible provided *they are selected on the grounds of the totality of symptoms exhibited by the patient*. For instance, oral contraceptives might be used in infinitesimal doses to promote rebound ovulation and pregnancy in women with functional sterility; ultradilutions of immunosuppressant agents might awaken paradoxical immunostimulation in immunosuppressed individuals, etc.

Just as the secondary action of homeopathic pharmacology, at the base of the principle of therapeutic similitude, also *the rebound effect of modern pharmacology exhibits the characteristics described above*, showing that both series of phenomena, described in

different times and with different words, are the same: (1) it appears in a small fraction of people (susceptible or idiosyncratic constitutions); (2) it is independent from the type of drug, duration of treatment, and severity of disease; (3) it appears after the enantiopathic effect of the drug ceased, be either by abrupt suspension or occasional discontinuation of the drug; (4) it causes a state diametrically opposed and more intense and/or long-lasting than the effect of the drug; (5) its intensity is proportional to the palliative therapeutic effect of the drug, being more evident in the drugs (or doses) more efficacious to suppress the initial symptoms of disease (second-generation drugs).

Scientific Basis of the Principle of Similitude in Modern Pharmacology

SIMILITUDE IN HOMEOPATHY

Examples of homeopathic cures verified involuntarily by doctors of the Old School

Essay on a new principle for ascertaining the curative powers of drugs

Principle of similitude

Homeopathic pathogenetic experimentation

Examples of homeopathic cures verified involuntarilyby doctors of the Old School

After glimpsing the principle of homeopathic cure, Hahnemann sought for confirmation (strong arguments) through "analogy" and "enumeration", by studying the clinical reports made by previous doctors, where he could find countless references that eventually led him to raise the principle of similitude to the level of a "natural law" as well as supported his use of inductive logic: *for a substance to heal definite symptoms in ill human beings it must elicit similar symptoms upon healthy experimental subjects.*

In the "Introduction" of the *Organon of homeopathic medicine,*[1] masterpiece of homeopathy, Hahnemann alludes to hundreds of homeopathic healings involuntarily supplied by doctors of the "Old School", and thus grounds his initial observations on the principle of similitude on 247 bibliographic references, described in detail in the original work and that will be deleted in quotes below.

"I shall here relate some examples of these homeopathic cures, which find a clear and precise interpretation in the homeopathic doctrine now discovered and acknowledged, but which we are by no means to regard as arguments in favour of the latter, because it stands firm without the aid of any such support".

"The author of the *Treatise on Epidemic Diseases,* attributed to Hippocrates, at the commencement of *lib. 5* mentions a case of *cholera morbus* that resisted every remedy, and which he cured by means of *veratrum album* alone, which, however, excites *cholera* of itself, as witnessed by *Forestus, Ledelius, Reimann,* and many others".

"The English *sweating sickness,* which first exhibited itself in the year 1485, and which, more murderous than the plague itself, carried off in the commencement, as testified by *Willis,* ninety-nine patients out of a hundred, could not be subdued until such time as they had learned to administer *sudorifics* to patients. Since that time, as *Sennertus* observes, few persons died of it".

"A case of *dysentery,* which lasted several years, threatening the patient with inevitable death, and against which every other medicine had been tried without success, was, to the great surprise of *Fischer,* cured in a speedy and permanent manner by a *purgative* administered by an empiric".

"*Murray,* whom I selected from numerous other authorities, together with daily experience, informs us, that among the symptoms produced by the use of *tobacco,* those of *vertigo, nausea,* and *anxiety* are the principal. Whereas *Diemerbroeck,* when attacked with those

[1] Hahnemann S. Organon of homeopathic medicine. Third American edition. English version of the fifth German edition. New York: William Radde, 1849.

very symptoms of vertigo, nausea, and anxiety in the course of his close attendance on the victims of epidemic diseases in Holland, removed them by the use of the pipe".

"The hurtful effects which some writers (among others *Georgi*) ascribe to the use of the *agaricus muscarius,* by the inhabitants of Kamtschatka, and which consist of *tremors, convulsions,* and *epilepsy,* became a salutary remedy in the hands of *C. G. Whistling,* who used this mushroom with success in cases of convulsions accompanied with tremor; likewise in those of *J. C. Bernhardt,* who used it with success in a species of epilepsy".

"The remark made by *Murray that* oil of *aniseed* allays pains of the stomach and flatulent colic caused by purgatives, ought not to surprise us, knowing that *J. P. Albrechtff* has observed *pains in the stomach* produced by this liquid; and *P. Forestus violent colic* likewise caused by its administration".

"If *F. Hoffman* praises the efficacy of *millefoil* in various cases of *hemorrhage;* if *G. E. Stahl, Buchwalk* and *Loseke* have found this plan useful in excessive hemorrhoidal flux; if *Quarin* and the editors of the *Bresslauer Sammlungen* speak of the cure it has effected of hemoptysis; and finally, if *Thomasius* (according to *Haller*) has used it successfully in uterine hemorrhage; these cures are evidently owing to the power possessed by the plant, of exciting of itself *hemorrhage* and *hematuria,* as observed by *G. Hoffman,* and more especially of producing *epistaxis* as confirmed by *Boecler*".

"*Scovolo* among many others, cured a case where the urinary discharge was purulent, by *arbutus uva ursi;* which never could have been performed if this plant had not the property of exciting *heat in the urinary passage with discharge of a mucous urine,* as seen by *Sauvages*".

"And though the frequent experience of *Stoerck, Marges, Planchon, Du Monceau, F. C. Junker, Schinz, Ehrmann,* and others, had not already established the fact, that *colchicum autumnale* cures a species of dropsy, still this faculty was to have been expected from it, by reason of the particular power which it possesses of *diminishing the urinary secretion,* and *of exciting at the same time a continual desire to pass water.* It likewise causes the flow of a *small quantity of urine, of a fiery red colour,* as witnessed by *Stoerck* and *de Berge*. The cure of an asthma attended with hypochondriasis effected by *Goritzft* by means of colchicum, and that of an asthma complicated with an apparent hydro thorax, performed by *Stoerck* with the same substance, were evidently grounded upon the homeopathic property which it possesses, of exciting by itself *asthma* and *dyspnoea,* as witnessed by *de Berge*".

"*Muralto* has seen what we may witness every day, viz., that *jalap,* besides creating *gripes of the stomach,* also causes *great uneasiness* and *agitation.* Every physician acquainted with the facts upon which homeopathy rests, will find it perfectly natural, that, the power so justly ascribed to this medicine by *G. W. Wedel,* of allaying the gripes, restlessness, and screaming which are so frequent in young children, and of restoring them to tranquil repose, arises from homeopathic influence".

"It is also known and has been attested by *Murray, Hillary*, and *Spielmann,* that *senna* occasions a kind of colic, and produces, according to *C. Hoffmanf* and *F. Hoffman*, *flatulency* and *agitation of the blood*, ordinary causes of *insomnolency.* It was this innate homeopathic virtue of senna, which enabled *Detharding* to cure with its aid patients afflicted with violent colic and insomnolency".

"*Stoerck,* who had so intimate a knowledge of medicines, was on the point of discovering that the bad effects of the *dictamnus,* which, as he observed himself, sometimes provokes a *mucous discharge from the vagina*, arose from the very same properties in this root by virtue of which he cured a leucorrhea of long standing".

"*Stoerck,* in like manner, should not have been astonished when curing a general chronic eruption (humid, phagedenic and psoric) with the *clematis,* having himself ascertained that this plant has the power of producing a *psoric eruption over the whole body*".

"If, according to *Murray,* the *euphrasia* cures lippitudo and a certain form of ophthalmy, how it could otherwise have produced this effect, but by the faculty it possesses of exciting a kind *of inflammation in the eyes,* as has been remarked by *Lobelius*".

"According to *J. H. Lange,* the *nutmeg* has been found efficacious in hysterical fainting fits. The sole natural cause of this phenomenon is homeopathic, and can be attributed to no other circumstance but that the nutmeg, when given in strong doses to a man in health, produces, according to *J. Schmid* and *Cullen suspension of the senses and general insensibility*".

"The old practice of applying *rose-water* externally in ophthalmic diseases looks like a tacit avowal, that there exists in the leaves of the rose some curative power for diseases of the eye. This is founded upon the homeopathic virtue which the rose possesses, of exciting by itself a species of *ophthalmia* in persons who are in health, an effect which *Echtius, Ledelius,* and *Rau,* actually saw it produce".

"If, according to *Pet. Rossi, Van Mons, J. Monti, Sybel,* and others, the *Rhus toxicodendron* and *radicans* have the faculty of producing *pimples which gradually cover the entire body*, it may be easily perceived how it could effect an homeopathic cure of various kinds of herpes, which it really has done, according to information furnished by *Dufresnoy* and *Van Mons.* What could have bestowed upon this plant (as in a case cited by *Alderson*) the power of curing a paralysis of the lower extremities, attended with weakness of the intellectual organs, if it did not of itself evidently possess the faculty of *depressing the muscular powers* by acting on the imagination of the patient to such a degree as to make him believe that he is at the point of death, as in a case witnessed by *Zadig*".

"The *dulcamara,* according to *Carrere,* has cured the most diseases emanating from colds, which could result from no other cause but that this herb, in cold and damp weather, frequently produces *similar affections to those which arise from colds,* as *Carrere* himself has observed, and likewise *Starcke. - Fritze* saw the dulcamara produce *convulsions,* and *De Haen* witnessed the *very same effects, attended with delirium;* on the other hand,

convulsions attended with delirium have yielded to small doses of the dulcamara, administered by the latter physician. - It was vain to seek amid the vast empire of hypotheses the cause that renders the dulcamara so efficacious in a species of herpes, as witnessed by *Carrere, Fouquet,* and *Poupart.* Nature, which requires the aid of homeopathy to perform a safe cure, sufficiently explains the cause, in the faculty possessed by the dulcamara of producing a certain species of herpes. *Carrere* saw the use of this plant excite herpetic eruptions which covered the entire body during a fortnight; and on another occasion where it produced the same *on the hands*; and a third time where it fixed itself on the *labia pudenda*".

"*Rucker* saw the *solanum nigrum* produce *swelling of the entire body.* This is the reason that *Gatacker* and *Cirillo* succeeded in curing with its aid (homeopathically) a species of dropsy".

"*De Haen, Sarcone,* and *Pringleff* have rendered due homage to truth and experience, by declaring freely, that they cured pleurisy with the *scilla maritima,* a root which, on account of its excessive acrid properties, ought to be forbidden in a disease of this nature, where, according to the received method, only sedative, relaxing, and refrigerant remedies are admissible. The disease in question subsided, nevertheless, under the influence of the squill, on homeopathic principles; for *T. C. Wagner* formerly saw the action of this plant alone produce *pleurisy* and *inflammation of the lungs*".

"A great many practitioners, *D. Crueger, Ray, Kellner, Kaaw Boerhaave,* and others, have observed that the *datura stramonium* excites a singular kind of delirium and *convulsions.* It is precisely this faculty that enabled physicians to cure with its aid, demonomania (fantastic madness, attended with spasms of the limbs) and other convulsions, as performed by *Sidren* and *Wedenberg*. If in the hands of *Sidren* it cured two cases of chorea, one of which had been occasioned by fright, and the other by mercurial vapour, it was because it possessed the faculty of exciting involuntary movements of the limbs, as observed by *Kaaw Boerhaave,* and *Lobstein.* Numerous observations, and among others those made by *Schenk,* have shown us that it can destroy consciousness and recollection in a very short time; therefore, it ought not to surprise us, if, according to the testimony of *Sauvages* and *Schinz,* it possesses the faculty of curing a weak memory. By the same rule, *Schmalz* succeeded in curing with the aid of this plant a case of melancholy, alternating with madness, because, according to *Acosta,* it has the power of exciting such alternate mental aberrations when administered to a person in health".

"*Percival, Stahl, Quarin,* and many other physicians have observed that *cinchona* occasions *oppression of the stomach. Morton, Friborg, Bauer,* and *Quarin* have seen this substance produce *vomiting* and *diarrhea; D. Crueger* and *Morton* a *syncope;* some an excessive *debility, Thomson, Richard, Stahl,* and *C. E. Fisher* a kind of *jaundice; Quarin* and *Fischer* a *bitterness of the mouth;* and yet others, *tension of the belly.* And it is precisely when these complicated evils occur in intermittent fevers, that *Torti* and *Cleghorn* recommend the use of cinchona alone. The advantageous effects of this bark in cases of exhaustion, indigestion, and loss of appetite resulting from acute fevers, particularly when the latter have been treated by venesection, evacuants and debilitants, are founded upon the faculty which it

possesses of *depressing excessively the vital powers, producing mental and bodily exhaustion, indigestion, and loss of appetite,* as observed by *Cleghorn, Friborg, Crueger, Romberg, Stahl, Thomson,* and others".

"How would it have been possible to stop hemorrhages with *ipecacuanha,* as effected by *Baglivi, Barbeyrac, Gianella, Dalberg, Bergius,* and others, if this medicine did not of itself possess the faculty of exciting hemorrhage homeopathically? - as *Murray, Scott,* and *Geoffroy* have witnessed. How could it be so efficacious in asthma, and particularly in spasmodic asthma, as it is described to have been, by *Akenside, Meyer, Bang, Stoll, Fouquet,* and *Ranoe,* if it did not of itself produce (without exciting any evacuation) *asthma,* and *spasmodic asthma* in particular, as *Murray, Geoffroy,* and *Scott* have seen it call forth? Can any clearer hints be required, that medicines ought to be applied to the cure of diseases according to the morbid effects which they produce?"

"It would be impossible to conceive why the *Faba Ignatia* could be so efficacious in a kind of convulsions, as we are assured it is, by *Hermann, Valentin,* and an anonymous writer, if it did not possess the power of exciting similar *convulsions,* as witnessed by *Bergius, Camelli,* and *Durius*".

"Persons, who have received a *blow* or a *contusion,* feel pains in the side, a desire to vomit, spasmodic, lancinating and burning pain in the hypochondres, all of which are accompanied with anxiety, tremors, and involuntary starts, similar to those produced by an electric shock, formication in the parts that have received the injury, etc. As the *arnica montana* produces similar symptoms, according to the observations of *Meza, Vicat, Crichton, Collins, Aaskow, Stoll,* and *J. C. Lange,* it may be easily conceived on what account this plant cures the effects of a blow, fall, or contusion, and consequently the malady itself occasioned by such a contusion, as experienced by a host of physicians, and even whole nations, for centuries past".

"Among the effects which *belladonna* excites when administered to a person in sound health, are symptoms which, taken collectively, present an image greatly resembling that species of *hydrophobia* and *rabies canina* which *Mayerne, Munch, Buchholz,* and *Neimike,* cured in a perfect manner with this plant homeopathically. *The patient in vain endeavours to sleep, the respiration is embarrassed, he is consumed by a burning thirst, attended with anxiety; the moment any liquids are presented to him, he rejects them with violence; his countenance becomes red, his eyes fixed and sparkling,* as observed by *F. C. Grimm; he experiences a feeling of suffocation while drinking,* with excessive thirst, according to *E. Camerarius and Sauter;* for the most part he is *incapable of swallowing anything,* as affirmed by *May, Lottinger, Sicelius, Buchave, D'Hermont, Manetti, Vicat,* and *Cullen;* he is *alternately actuated by terror and a desire to bite the persons who are near him,* as seen by *Sauter, Dumoulin, Buchave,* and *Mardorf; he spits everywhere around him,* (according to *Sauter; he endeavours to make his escape,* as we are informed by *Dumoulin, E. Gmelin,* and *Buc'hoz;* and a continual agility of the body is predominant, as witnessed by *Boucher E. Gmelin,* and *Sauter.* Belladonna has also effected the cure of different kinds of madness and melancholy, as in the cases reported by *Evers, Schmucker, Schmalz,* the two *Munches,* and many others, because it possesses the faculty of producing different kinds of *insanity*

like those mental diseases caused by belladonna, which are noted by *Rau, Grimm, Hasenest, Mardorf, Hoyer, Dillenius,* and others. *Henning,* after vainly endeavouring, during three months, to cure a case of amaurosis with coloured spots before the eyes, by a variety of medicines, was at length struck with the idea that this malady might perhaps be occasioned by gout, although the patient had never experienced the slightest attack; and upon this supposition he was by chance induced to prescribe belladonna, which effected a speedy cure free from any inconvenience. He would undoubtedly have made choice of this remedy at the commencement, had he known that it was not possible to perform a cure but by the aid of a remedy which produces symptoms similar to those of the disease itself; and that, according to the infallible law of nature, belladonna could not fail to cure this case homeopathically, since, by the testimony of *Sauter* and *Buchholz,* it excites, of itself, a species of *amaurosis with coloured spots before the eyes*".

"The *hyosciamus* has cured spasms which strongly resembled epilepsy; as witnessed by *Mayerne, Stoerck, Collin,* and others. It produces this effect by the very same power that it excites *convulsions similar to those of epilepsy,* as observed in the writings of *E. Camerarius, C. Seliger, Hiinerwolf, A. Hamilton, Planchon, Acosta,* and others".

"*Fothergill, Stoerck, Hellwig, and Ofterdinger* has used hyosciamus with success in certain kinds of mental derangement. But the use of it would have been attended with equal success in the hands of many other physicians, had they confined it to the cure of that species of mental alienation which hyosciamus is capable of producing in its primitive effects, viz., a kind of derangement with stupefaction, that *Van Helmont, Medel, J. G. Gmelin, La Serre, Hiinerwolf, A. Hamilton, Kiernander, J. Stedmann, Tozzetti, J. Faber,* and *Wendt* saw produced by the action of this plant".

"By taking the effects of hyosciamus collectively which the latter observers have seen it produce, they present a picture of hysteria arrived at a considerable height. We also find in *J. A. P. Gessner, Stoerck,* and in the *Act. Nat. Cur.,* that a case of hysteria, which bore great resemblance to the above mentioned, was cured by the use of this plant".

"*Schenkbechcrf* would never have succeeded in curing vertigo of twenty years' standing, if this plant did not possess, in a very high degree, the power of creating generally an analogous state, as attested by *Htinerwolf, Blom, Navier, Planchon, Sloane, Stedmann, Greding, Wepfer, Vicat,* and *Bernigau*".

"A man, who became deranged through jealousy, was for a long time tormented by *Mayer Abramson* with remedies that produced no effect on him, when, under the name of a soporific, he one day administered *hyosciamus,* which cured him speedily. Had he known that this plant excites *jealousy* and *madness* in persons who are in health, and had he been acquainted with the homeopathic law, the sole natural basis of therapeutics, he would have been able to administer hyosciamus from the very commencement with perfect confidence, and thus have avoided fatiguing the patient with remedies which (not being homeopathic) could be of no manner of service to him".

"The mixed prescriptions which were employed for a long time with the greatest success by *Hecker* in a case of *spasmodic constriction of the eyelids* would have proved ineffectual, if some happy chance had not included hyosciamus, which, according to *Wepfer*, excites a similar affection in persons who are in sound health".

"Neither did *Withering* succeed in curing a spasmodic constriction of the pharynx, with inability to swallow, until he administered hyosciamus, whose special action consists of causing a *spasmodic constriction of the throat, with the impossibility of swallowing,* an effect which *Tozzetti, Hamilton, Bernigau, Sauvages,* and *Hunerwolf* have seen it produce in a very high degree".

"How could *camphor* produce such salutary effects as the veracious *Huxhamf* says it does, in the so-called slow nervous fevers, where the temperature of the body is decreased, where the sensibility is depressed, and the vital powers greatly diminished, if the result of its immediate action upon the body did not produce a *state similar in every respect* to the latter, as observed by G. Alexander, Cullen, and *F. Hoffman*?"

"Spirituous *wines,* administered in small doses, have cured, homeopathically, *fevers* that were purely *inflammatory. C. Crivellati, H. Augenius, A. Mundella,* and two anonymous writers, have afforded us the proofs. *Asclepiades* on one occasion cured an *inflammation of the brain* by administering a *small quantity of wine.* A case of feverish delirium like an insensible drunkenness, attended with stertorous breathing, similar to that state of deep intoxication which wine produces, was cured in a single night by *wine* which *Rademacher* administered to the patient. Can any one deny the power of a medicinal irritation analogous to the disease itself *(similia similibus)* in either of these cases?"

"A strong infusion of *tea* produces *anxiety* and *palpitation of the heart* in persons who are not in the habit of drinking it; on the other hand, if taken in small doses, it is an excellent remedy against such symptoms when produced by other causes, as testified by *G. L. Rau*".

"A case resembling the agonies of death, in which the patient was convulsed to such a degree as to deprive him of his senses, alternating with attacks of spasmodic breathing, sometimes also sobbing and stertorous respiration, with icy coldness of the face and body, lividity of the feet and hands, and feebleness of the pulse, a state perfectly analogous to the whole of the symptoms which *Schweikert* and others saw produced by the use of *opium,* was at first treated unsuccessfully by *Stutz* with ammonia, but afterwards cured in a speedy and permanent manner with *opium.* In this instance, could any one fail to discover the homeopathic method brought into action without the knowledge of the person who employed it? According to *Vicat, J. C. Grimm,* and others, opium also produces *a powerful and almost irresistible tendency to sleep, accompanied by profuse perspiration and delirium.* This was the reason why *Osthoff* was afraid to administer it in cases of epidemic fever which exhibited *similar symptoms,* for the principles of the system which he pursued prohibited the use of it under such circumstances. The poor system! However, after having exhausted in vain all the known remedies, and seeing his patients at the point of death, he resolved, at all hazards, to administer a small quantity of opium, whose effects proved salutary, as they always must, according to the unerring law of homeopathy".

"*J. Lind* likewise avows that opium removes the complaints in the head, while the perspiration tediously breaks forth during the heat of the body; it relieves the head, destroys the burning febrile heat of the skin, softens it, and bathes its surface in a profuse perspiration. But *Lind* was not aware that this salutary effect of opium (contrary to the axioms of the school of medicine) is owing to the circumstance of its producing analogous morbid symptoms, when administered to a person in health. There has, nevertheless, here and there been a physician, across whose mind this truth has passed like a flash of lightning, without ever giving birth to a suspicion of the laws of homeopathy. For example, *Alston* says that *opium* is a remedy that excites heat, notwithstanding which, it certainly diminishes heat where it already exists. *De la Guerene* administered opium in a case of fever attended with violent headache, tension and hardness of the pulse, dryness and roughness of the skin, burning heat, and hence difficult and debilitating perspirations, the exhalation of which was constantly interrupted by the extreme agitation of the patient; and was successful with it, because opium possesses the faculty of creating a feverish state in healthy persons, which is perfectly analogous, as asserted by many observers, and of which he was ignorant. In a fever attended with coma, where the patient, deprived of speech, lay extended, the eyes open, the limbs stiff, the pulse small and intermittent, the respiration disturbed and stertorous (all of which are symptoms perfectly similar to those which opium excites, according to the report of *Delacroix, Rademacher, Crumpe, Pyl, Vicat, Sauvages* and many others), this was the only substance which *C. L. Hoffman* saw produce any good effects, *which were naturally a homeopathic result. Wirthenson, Sydenham,* and *Marcus* have even succeeded in curing lethargic fevers with opium. A case of lethargy of which *De Meza* effected a cure, would yield only to this substance, which, in such cases, acts homeopathically, since it produces lethargy of itself".

"*C. C. Matthai,* in an obstinate case of nervous disease, where the principal symptoms were insensibility, and numbness of the arms, legs, and belly, after having for a long time treated it with inappropriate, that is to say, non-homeopathic remedies, at length effected a cure by opium, which, according to *Stiitz, J. Young,* and others, excites similar symptoms of a very intense nature, and which as every one must perceive, only succeeded on this occasion by homeopathic means. The cure of a case of lethargy which had already existed several days, and which *Hufeland* performed by the use of opium, by what other law could this have been effected, if not by that of homeopathy, which has remained disregarded till the present time? In that peculiar species of epilepsy which never manifests itself but during sleep, *De Haen* discovered that it was not at all a sleep, but a lethargic stupor, with stertorous respiration, perfectly similar to that which opium produces in persons who are in health: it was by the means of opium alone that he transformed it into a natural and healthy sleep, while at the same time he delivered the patient of his epilepsy".

"How would it be possible that opium, which of all vegetable substances is the one whose administration, in small doses, produces the most powerful an obstinate *constipation,* as a primary effect, should notwithstanding be a remedy the most to be relied upon in cases of constipation which endanger life, if it was not in virtue of the homeopathic law, so little known - that is to say, if nature had not decreed that medicines should subdue natural diseases by a special action on their part, which consists in producing an analogous

affection? Opium, whose first effects are so powerful in constipating the bowels, was discovered by *Tralles* to be the only cure in a case of ileus, which he had till then treated ineffectually with evacuants and other unappropriate remedies. *Lentilius* and *G. W. Wedel, Wirthenson, Bell, Heister,* and *Richter,* have likewise confirmed the efficacy of opium, even when administered alone in this disease. The candid *Bohn* was likewise convinced by experience that *nothing* but *opiates* would act as purgatives in the colic called *miserere;* and the celebrated *Fr. Hoffman,* in the most dangerous cases of this nature, placed his sole reliance on opium, combined with the anodyne liquor called after his name. All the theories contained in the two hundred thousand volumes that have been written on medicine, would they be able to furnish us with a rational explanation of this and so many other similar facts, being ignorant of the therapeutic law of homeopathy? Have their doctrines conducted us to the discovery of this law of nature so clearly manifested in *every* perfect, speedy, and permanent cure - that is to say, have they taught us that when we use medicines in the treatment of diseases, it is necessary to take for a guide the resemblance of their effects upon a person in health, to the symptoms of those very diseases?"

"*Rave* and *Wedekind* have suppressed uterine hemorrhage with the aid of *sabina,* which, as every one knows, causes *uterine hemorrhage,* and consequently abortion with women who are in health. Could any one, in this case, fail to perceive the homeopathic law which ordains that we should cure *similia similibus*?"

"In that species of spasmodic asthma designated by the name of Millar, how could *musk* act almost specifically, if it did not of itself produce paroxysms of a spasmodic constriction of the chest without cough, as observed by *F. Hoffman*?"

"Could vaccination protect us from the small pox otherwise than homeopathically? Without mentioning any other traits of close resemblance which often exist between these two maladies, they have this in common - they generally appear but once during the course of a person's life; they leave behind cicatrices equally deep; they both occasion tumefaction of the axillaries glands; a fever that is analogous; an inflamed areola around each pock; and finally, ophthalmia and convulsions".

"The cow-pock would even destroy the small-pox on its first appearance, that is to say, it would cure this already existing malady, if the intensity of the small-pox did not predominate over it. To produce this effect, then, it only wants that excess of power which, according to the law of nature, ought to *correspond* with the homeopathic resemblance, in order to effect a cure. Vaccination, considered as a homeopathic remedy, cannot, therefore, prove efficacious except when employed previous to the appearance of the small-pox, which is the stronger of the two".

"In this manner it excites a disease very analogous (and consequently homeopathic) to the small-pox, after whose course the human body, which, according to custom, can only be attacked once with a disease of this nature, is henceforward protected against a similar contagion".

"It is well known that *retention of urine with ineffectual efforts to urinate,* is one of the most common and painful evils which the use of *cantharides* produces. This point has been sufficiently established by *J. Camerarius, Baccius, Van Hilden, Forest, J. Lanzoni, Van der Wiel,* and *Werlhoff.* Cantharides, administered internally, and with precaution, ought, consequently, to be a very salutary homeopathic remedy in similar cases of painful dysury. And this is in reality the case. For without enumerating all the Greek physicians who, instead of our cantharides, made use of *meloe cichorii, Fabricius ab Aquapendente, Capo di Vacca, Riedlin, Th. Bartholin, Young, Smith, Raymond, De Meza, Brisbane,* and others, performed perfect cures of very painful ischury that was not dependant upon any mechanical obstacle, with *cantharides. Huxham* has seen this remedy produce the best effects in cases of the same nature; he praises it highly, and would willingly have made use of it had not the precepts of the old school of medicine (which, deeming itself wiser than nature herself, prescribes in such eases soothing and relaxing remedies) prevented him, contrary to his own conviction, from using a remedy which, in such cases, is specific or homeopathic. In cases of recent inflammatory gonorrhea, where *Sachs von Lewenheim, Hannaeus, Bartholin, Lister, Mead,* and chiefly *Werlhoff,* administered cantharides in very small doses with perfect success, this substance manifestly removed the most severe symptoms which began to declare themselves".

"It produced this effect by virtue of the faculty it possesses (according to the testimony of almost every observer) of exciting painful ischury, urinary heat, inflammation of the urethra *(Wendt),* and even, when applied only externally, a species of inflammatory gonorrhea *(Wichman)*".

"The application of sulphur internally very often occasions, in persons of an irritable disposition, *tenesmus,* sometimes even attended with *vomiting* and *griping,* as attested by *Walther.* It is by virtue of this property which sulphur exhibits, that physicians have been able|| to cure with its aid, dysenteric -attacks, and hemorrhoidal diseases attended with tenesmus, as observed by *Werlhoff,* and according to *Rave,* hemorrhoidal colics".

"It is well known that the waters at *Toeplitz,* like all other warm sulphurous mineral waters, frequently excite the appearance of an *exanthema,* which strongly resembles the *itch,* so prevalent among persons employed in *wool-working.* It is precisely this homeopathic virtue which they possess that removes various kinds of psoric eruptions. Can there be any thing more *suffocating* than *sulphurous fumes?* Yet it is the vapour arising from the combustion of sulphur that *Bucquet* discovered to be the best means of reanimating persons in a state of asphyxia produced by another cause".

"From the writings of *Beddoes* and others, we learn that the English physicians found *nitric acid* of great utility in salivation and ulceration of the mouth, occasioned by the use of mercury. This acid could never have proved useful in such cases, if it did not of itself excite salivation and ulceration of the mouth. To produce these effects, it is only necessary to bathe the surface of the body with it, as *Scott* and *Blair* observe, and the same will occur if administered internally, according to the testimony of *Aloyn, Luke, Ferriar,* and *G. Kelly*".

"*Fritze* saw a species of *tetanus* produced by a bath impregnated with *carbonate of potash;* and *A. von Humboldt,* by the application of a solution of *salt of tartar* increased the irritability of the muscles to such a degree as to excite tetanic spasm. The curative power which caustic potash exercises in all kinds of tetanus, in which *Stutz* and others have found it so useful, could it be accounted for in a more simple or rational manner than by the faculty which this alkali possesses of producing homeopathic effects?"

"*Arsenic,* whose effects are so powerful upon the human economy that we cannot decide whether it is more hurtful in the hands of the fool-hardy than it is salutary in those of the wise, - arsenic could never have effected so many remarkable cures of cancer in the face, as witnessed by numerous physicians, among whom I will only cite *Fallopius, Bernhardt,* and *Roennow,* if this metallic oxide did not possess the homeopathic power of producing, in healthy persons, *very painful tubercles, which are cured with difficulty,* as witnessed by *Amatus Lusitanus*; very deep and *malignant ulcerations,* according to the testimony of *Heinreich* and *Knape;* and *cancerous ulcers,* as testified by *Heinze.* The ancients would not have been unanimous in the praise which they bestowed on the magnetic arsenical plaster of *Angelus Sala* against pestilential buboes and carbuncles, if arsenic did not, according to the report of Degner and *Pfann,* give rise to inflammatory tumours which *quickly turn to gangrene,* and to carbuncles or malignant pustules, as observed by *Verzascha* and *Pfann.* And whence could arise that curative power which it exhibits in certain species of intermittent fevers (a virtue attested by so many thousands of examples, but in the practical application of which, sufficient precaution has not yet been observed, and which virtue was asserted centuries ago by *Nicholas Myrepsus,* and subsequently placed beyond a doubt by the testimony of *Slevogt, Molitor, Jacobi, J. C. Bernhardt, Jiingken, Fauve, Brera, Darwin, May, Jackson,* and *Fowler*) if it did not proceed from *its peculiar faculty of excit ingfever,* as almost every observer of the evils resulting from this substance has remarked, particularly *Amatus Lusitanus, Degner, Buchholz, Heun,* and *Knape.* We may confidently believe *E. Alexander,* when he tells us that *arsenic* is a sovereign remedy in some cases of angina pectoris, since *Tachenius, Guilbert, Preussius, Thilenius,* and *Pyl,* have seen it give rise to very strong *oppression of the chest; Gresselius,* to a *dyspncea approaching even to suffocation;* and *Majault,* in particular, saw it produce *sudden attacks of asthma excited by walking, attended with great depression of the vital powers*".

"The *convulsions* which are caused by the administration of *copper,* and those observed by *Tondi, Ramsay, Fabas, Pyl,* and *Cosmier,* as proceeding from the use of aliments impregnated with copper; the reiterated *attacks of epilepsy,* which *J. Lazerme* saw result from the accidental introduction of a copper coin into the stomach, and which *Pfundel* saw produced by the ingestion of a compound of sal ammoniac and copper into the digestive canal, sufficiently explain, to those physicians who will take the trouble to reflect upon it, how *copper* has been able to cure a case of chorea, as reported by *R. Willan, Walcker, Thesussink, and Delarive,* and why preparations of copper have so frequently effected the cure of epilepsy, as attested by *Batty, Baumes, Bierling, Boerhave, Causland, Cullen, Duncan, Feuerstein, Helvetius, Lieb, Magennis, C. F. Michaelis, Reil, Russel, Stisser, Thilenius, Weissmann, Weizenbreyer, Whithers,* and others".

"If *Poterius, Wepfer, Wedel, F. Hoffman, R. A. Vogel, Thierry,* and *Albrecht,* have cured a species of phthisis, hectic fever, chronic catarrh, and mucous asthma, with *stannum,* it is because this metal possesses the faculty of producing a species of *phthisis,* as *Stahl* has observed. And how could it cure *pains of the stomach,* as *Geischlager* says it does, if it was not capable of exciting a similar malady. *Geischlager* himself, and *Stahl* before him, have proved that it does possess this power".

"The evil effects of *lead,* which produces the most *obstinate constipation,* and even the *iliac passion,* as *Thunberg, Wilson, Lazuriaga,* and others inform us, do they not also give us to understand that this metal possesses likewise the virtue of curing these two affections? Like every other medicine, it ought to subdue and cure, in a permanent manner, the natural diseases which bear a resemblance to those which it engenders, by reason of the faculty which it possesses of exciting morbid symptoms. *Angelus Sala* cured a species of ileus, and *J. Agricola,* another kind of constipation which endangered the life of the patient, by administering lead internally. The *saturnine* pills with which many physicians (*Chirac, Van Helmont, Naudeau, Pererius, Rivinus, Sydenham, Zacutus Lusitanus, Block,* and others) cured the iliac passion and obstinate constipation, did not operate merely in a mechanical manner by reason of their weight; for, if such had been the sources of their efficacy, gold, whose weight is greater than that of lead, would have been preferable in such a case; but the pills acted particularly as a saturnine internal remedy, and cured homeopathically. If *Otto-Tachenius* and *Saxtorph* formerly cured cases of obstinate hypochondriasis with the aid of *lead,* we ought to bear in mind that this metal tends of itself to excite hypochondriasis, as may be seen in the description of its ill effects given by *Lazuriaga*".

"We ought not to be surprised that *Marcus* speedily cured an inflammatory swelling of the tongue and of the pharynx with a remedy *(mercury)* which, according to the daily experience of physicians, has a specific tendency to produce *inflammation and tumefaction of the internal parts of the mouth,* phenomena to which it gives rise when merely applied to the surface of the body in the form of ointment or plaster, as experienced by *Degner, Friese, Alberti, Engel,* and many others. The *weakening of the intellectual faculties, (Swediaur) imbecility (Degner)* and *mental alienation (Larry)* which have been seen to result from the use of *mercury,* joined to the almost specific faculty which this metal is known to possess of exciting salivation, explain how *W. Perfect* was enabled, with the use of mercury, to cure in a permanent manner, a case of melancholy alternating with increased secretion of saliva. How does it happen that preparations of mercury proved so successful in the hands of *Seelig,* in the treatment of angina, accompanied with purpura; in those of *Hamilton, Hoffman, Marcus, Rush, Colden, Bailey,* and *Michaelis,* in the treatment of other kinds of malignant quinsy? It is evidently because this metal brings on of itself a species of angina of the worst description. It is certainly by homeopathic means that *Sauter* cured an ulcerous inflammation of the mouth, accompanied with aphthee and foetor of the breath, similar to that which occurs in salivation, when he prescribed a solution of corrosive sublimate as a gargle, and that *Block* removed aphthae by the use of mercurial preparations, since, among other *ulcerations of the mouth,* this substance particularly produces a species of *aphthee,* as we are informed by *Schlegelf* and *Th. Acrey*".

"*Hecker* used various medicinal compounds successfully in a case of caries succeeding small-pox. Fortunately, a portion of *mercury* was contained in each of these mixtures, to which it may be imagined that this malady will yield (homeopathically) because mercury is one of the few medicinal agents which excites of itself caries, as proved by the many excessive mercurial courses used against syphilis, or even against other diseases, among which are those related by *G. P. Michaelis.* This metal, which becomes so formidable when its use is prolonged, on account of the caries of which it then becomes the exciting cause, exercises, notwithstanding, a very salutary homeopathic influence in the caries which follows mechanical injuries of the bones, some very remarkable instances of which have been transmitted to us by *J. Schlegel, Joerdens,* and *J. M. Müller.* The cure of caries (not venereal) of another kind, which has likewise been effected by means of mercury by *J. F. G. Neu* and *J. D. Metzger,* furnishes a fresh proof of the homeopathic curative virtue with which this substance is endowed".

"In perusing the works which have been published on the subject of *medical electricity,* it is surprising to see what analogy exists between the morbid symptoms sometimes produced by this agent, and the natural diseases which it has cured in a durable manner by homeopathic influence. Innumerable are the authors who have observed that *acceleration of the pulse* is among the first effects of positive electricity: but *Sauvages, Delas,* and *Barillon,* have seen *febrile paroxysms* excited by *electricity.* The faculty it has of *producing fever,* is the cause to which we may attribute the circumstance of *Gardini, Wilkinson, Syme,* and *Wesley,* curing with it alone tertian fever, and likewise the removal of quartan fevers by *Zetzel* and *Willermoz.* It is also known that electricity occasions a contraction of the muscles which resembles a *convulsive movement. De Sans* was enabled to excite even *continued convulsions* in the arm of a young girl as often as he pleased to make the experiment. It is by virtue of this power which electricity develops, that *De Sans* and *Franklin* applied it successfully in convulsions, and that *Theden* cured with its aid a little girl ten years of age who lost her speech and partially the use of her left arm by lightning, yet kept up a constant involuntary movement of the arms and legs, accompanied by a spasmodic contraction of the fingers of the left hand. Electricity likewise produced a kind of ischias, as observed by *Jallobert* and another; it has also cured this affection by similarity of effect (homeopathically) as confirmed by *Hiortberg, Lovet, Arrigoni, Daboueix, Manduyt, Syme,* and *Wesley.* Several physicians have cured a species of ophthalmia by electricity, that is to say, by means of the power which it has of exciting of itself *inflammation of the eyes,* as observed by *P. Dickson* and *Bertholon.* Finally, it has in the hands of *Fushel* cured varices; and it owes this sanative virtue to the faculty which *Jallobert* ascribes to it of producing *varicose tumours*".

"*Albers* relates, that a warm bath at one hundred degrees of the thermometer of Fahrenheit greatly reduced the burning of an acute fever, in which the pulse beat one hundred and thirty to the minute, and that it brought back the pulsation to the number of one hundred and ten. *Loffler* found hot fomentations very useful in encephalitis occasioned by insulation or the action of the heat of stoves, and *Callisen* regards affusions of warm water on the head as the most efficacious of all remedies in cases of inflammation of the brain.

"If we except those cases where ordinary physicians have discovered (not by their own research but by *vulgar empiricism*) the specific remedy for a disease which always retained its identity, and by whose aid they could consequently cure it in a direct manner; such, for example, as mercury in the chancrous venereal disease, arnica in a malady resulting from contusions, cinchona in intermittent fevers arising from marsh miasmata, sulphur in a recent development of itch, etc.; - I say, if we except all these cases, we shall find that those which they have cured promptly and permanently by the bounty of Providence alone, are to the mass of their other irrational cures in the proportion of one to a thousand".

"Sometimes they were conducted by mere chance to a homeopathic mode of treatment; but yet they did not perceive the law of nature by which cures of this kind are and ever must be performed".

"*It is therefore highly important to the welfare of the human race, that we should examine how these cures, which are as remarkable for their rare occurrence as they are surprising in their effects, are performed.* The result is one of the deepest interests. The examples which we have cited, sufficiently prove, that these cures have never taken place but by homeopathic means, that is to say, by the faculty of exciting a morbid state similar to the disease that was to be cured. They have been performed in a prompt and permanent manner by medicines, upon which, those who prescribed them (contrary to all the existing systems of therapeutics) have fallen as it were by chance, without well knowing what they were doing or why they acted in this manner. Contrary to their inclinations, they by this fact confirmed the necessity of the sole law of nature in therapeutics, that of homeopathy; a law, which *medical* prejudices, till now, would not permit us to search after, notwithstanding the infinite number of facts and visible signs which ought to have pointed towards its discovery".

"Even in the practice of domestic medicine by persons ignorant of our profession, but who were gifted with sound judgment and discerning minds, it was discovered that the homeopathic method of cure was the safest, the most rational, and the least subject to failure".

"Frozen sourcrout is frequently applied to a limb that is recently frozen, or sometimes it is rubbed with snow".

"A cook, who has scalded his hand, exposes it to the fire at a certain distance, without heeding the increase of pain which it at first occasions, because experience has taught him that by acting thus, he can in a very short time perfectly cure the burn, and remove every feeling of pain".

"Other intelligent individuals, equally strangers to medical science - such, for example, as the lacker-workers, apply a substance to burns which excites of itself a similar feeling of *heat,* that is to say, hot *alcohol* or the *oil of turpentine,* and by these means cure themselves in a few hours, well knowing that the so-called cooling ointments would not produce the same result in an equal number of months, and that cold water would only make the evil worse."

"An experienced reaper, however little he may be accustomed to the use of *strong liquors*, will not drink cold water *(contraria contrariis)* when the heat of the sun or the fatigue of hard labour have brought him into a feverish state: he is well aware of the danger that would ensue, and therefore takes a small quantity of some heating liquor-viz. a mouthful of brandy. Experience, the source of all truth, has convinced him of the advantage and efficacy of this homeopathic mode of proceeding. The heat and lassitude which oppressed him soon diminish".

"Occasionally there have been certain physicians who guessed that medicines might cure diseases by the faculty which they possessed of exciting morbid symptoms that resembled the disease itself".

"Physicians of a later period have likewise known and proclaimed the truths of homeopathy. Thus *B. Boulduc,* for example, discovered that the purgative properties of *rhubarb* were the faculty by which this plant cured diarrhea".

"*Detharding* guessed that the infusion of *senna* would cure the colic in adults by virtue of the faculty which it possesses of exciting that malady in healthy persons".

"*Bertholon* informs us, that in diseases *electricity* diminishes and finally removes a pain which is very similar to one which it also produces".

"*Thoury* affirms that *positive electricity* accelerates arterial pulsation, also that it renders the same slower where it is already quickened by disease".

"*Stoerck* was struck with the idea, that if *stramonium* disturbs the senses and produces mental derangement in persons who are healthy, it might very easily be administered to maniacs for the purpose of restoring the senses by effecting a change of ideas".

"The Danish physician, *Stahl,* has, above all other writers, expressed his conviction on this head most unequivocally. He speaks in the following terms: - "The received method in medicine, of treating diseases by opposite remedies - that is to say, by medicines which are opposed to the effects they produce *(contraria contrariis),* - is completely false and absurd. I am convinced, on the contrary, that diseases are subdued by agents who produce a similar affection *(similia similibus):* - burns, by the heat of a fire to which the parts are exposed; the frost-bite, by snow or icy cold water; and inflammation and contusions, by spirituous applications. It is by these means I have succeeded in curing a disposition to acidity of the stomach, by using very small doses of sulphuric acid in cases where a multitude of absorbing powders had been administered to no purpose".

"Thus far the great truth has more than once been approached by physicians. But a transitory idea was all that presented itself to them; consequently, the indispensable reform which ought to have taken place in the old school of therapeutics to make room for the true curative method and a system of medicine at once simple and certain, has, till the present day, not been effected".

Essay on a new principle for ascertaining the curative powers of drugs

Inaugurating the homeopathy, Samuel Hahnemann published in 1796 his first homeopathic study in *Journal der praktischen Arzneykunde,* titled *Essay on a new principle for ascertaining the curative powers of drugs,* in which systematizes the principle of similitude and the homeopathic pathogenetic experimentation.[2,3]

After reviewing the scientific model of her time, which justified the treatment methods employed, Hahnemann states the homeopathic method of treatment of diseases, illustrating it in several drugs commonly used.

"Every powerful medicinal substance produces in the human body a kind of peculiar disease; the more powerful the medicine, the more peculiar, marked, and violent the disease".

"We should imitate nature, which sometimes cures a chronic disease by superadding another, and employ in the (especially chronic) disease we wish to cure, that medicine which is able to produce another very similar artificial disease, and the former will be cured: similia similibus".

"We only require to know, on the one hand, the diseases of the human frame accurately in their essential characteristics, and their accidental complications; and on the other hand, the pure effects of drugs, that is, the essential characteristics of the specific artificial disease they usually excite, together with the accidental symptoms caused by difference of dose, form, etc., and by choosing a remedy for a given natural disease that is capable of producing a very similar artificial disease, we shall be able to cure the most obstinate diseases".

"After these preliminary observations, I now proceed to *illustrate by examples* my maxim, *that in order to discover the true remedial powers of a medicine for chronic diseases, we must look to the specific artificial disease it can develop in the human body, and employ it in a very similar morbid condition of the organism which it is wished to remove*".

"The analogous maxim, *that in order to cure radically certain chronic diseases, we must search for medicines that can excite a similar disease (the more similar the better) in the human body* - will thereby almost become evident".

[2] Hahnemann S. Essay on a new principle for ascertaining the curative power of drugs, and some examinations of the previous principles. *Journal der praktischen Arzneykunde.* 1796; 2: 391.
[3] Hahnemann S. Essay on a new principle for ascertaining the curative power of drugs, with a few glances at those hitherto employed. In: Dudgeon RE. The lesser writings of Samuel Hahnemann. New Delhi: B. Jain Publishers, 1995.

"In my additions to Cullen's Materia Medica, I have already observed that *bark*, given in large doses to sensitive, yet healthy individuals, produces a true attack of fever, very similar to the intermittent fever, and for this reason, *probably*, it overpowers, and thus cures the latter. Now after mature experience, I add, not only *probably*, but *quite certainly*".

"I saw a healthy, sensitive person, of firm fibre, and half way through with her pregnancy, take five drops of the volatile oil of *chamomile (matricaria chamomilla)* for cramp in the calf of the leg. The dose was much too strong for her. First there was the loss of consciousness, the cramp increased; there occurred transient convulsions in the limbs, in the eyelid, etc. A kind of hysterical movement above the navel, not unlike labor pains, but more annoying, lasted for several days. This explains how chamomile has been found so serviceable in after-pains in excessive mobility of the fibre, and in hysteria, when employed in doses in which it could not perceptibly develop the same phenomena, that is, in much smaller doses than the above".

"A man who had been long troubled with constipation, but was otherwise healthy, had from time to time attacks of giddiness that lasted for weeks and months. Purgatives did no good. I gave him *arnica root (arnica montana)* for a week, for I knew that it causes vertigo, in increasing doses, with the desired result. As it has laxative properties, it kept the bowels open during its employment, by antagonistic action, as a palliative; wherefore the constipation returned after leaving off the medicine; the giddiness, however, was effectually cured. This root excited, as I and others have ascertained, besides other symptoms, nausea, uneasiness, anxiety, peevishness, headache, oppression of the stomach, empty eructation, cutting in the abdomen, and frequent scanty evacuations, with straining. These effects, not Stollen's example, induced me to employ it in an epidemic of simple (bilious) dysentery. The symptoms of it were uneasiness, anxiety, excessive peevishness, headache, nausea, perfect tastelessness of all food, rancid bitter taste on the (clean) tongue, frequent empty eructation, oppression of the stomach, constant cuttings on the abdomen, complete absence of fecal evacuations, and instead, passage of pure grey or transparent sometimes hard, white, flocculent mucus, occasionally intimately mixed with blood, or with streaks of blood, or without blood, once or twice a day, accompanied with the most painful constant straining and forcing. Though the evacuations were so rare, the strength sank rapidly, much more quickly, however (and without amelioration, but rather aggravation of the original affection), when purgatives were employed. Those affected were generally children, some even under one year old, but also some adults. The diet and regimen were proper. On comparing the morbid symptoms arnica root produces with those developed by this simple dysentery, I could confidently oppose to the totality of the symptoms arnica root produces with those developed by this simple dysentery, I could confidently oppose to the totality of the symptoms of the latter, the collective action of the former. The most remarkable good effects followed, without it being necessary to use any other remedy. Before the employment of the root, I gave a powerful emetic (without using the arnica root, the emetics took away the rancid bitter taste for but one or two days all the other symptoms symptoms remained, though they were ever so often repeated), which I had occasion to repeat in scarcely two cases, for arnica sets to right the disordered bile (also out of the body) and prevent its derangement. The only inconvenience resulting from its use in this dysentery as, that it acted as an antagonistic remedy in regard to the suppression of

faeces, and produced frequent, though scanty evacuations of excrement it was consequently a palliative the effects of this was, when I discontinued the root, continued constipation [I had to increase the dose daily, more rapidly than is necessary with any other powerful medicine. A child of four years of age got at first four grains daily, then seven, eight, and nine grains. Children of six or seven years of age could at first only bear six grains, afterwards twelve and fourteen grains were requisite. A child three quarters of a year old, which had taken nothing previously, could at first bear but two grains (mixed with warm water) in an enema latterly six grains were necessary]".

"In another less simple dysentery, accompanied by frequent diarrhea, the arnica root might be more useful and suitable, on account of this later circumstance its property of producing frequent fecal evacuations in its primary direct action would constitute it a similarly acting, consequently, permanent remedy, and in its secondary indirect action it would effectually cure the diarrhea".

"This has already been proved by experience; it has been found excellent in the worst diarrheas. It subdues them, because, *without weakening the body,* it is capable of causing frequent evacuations. In order to prove serviceable in diarrheas without fecal matter, it must be given in such small doses as not to produce perceptible purgation; or in diarrheas with acrid matters, in larger purgative doses; and thus the object will be attained".

"I saw glandular swellings occur from the misuse of an infusion of flowers of arnica; I am much mistaken if, in moderate doses, it will not remove such affections".

"We should endeavor to find out if the *millefoil (achillea millefolium)* cannot itself produce hemorrhages in *large* doses, as it is so efficacious in moderate doses in chronic hemorrhages".

"It is not to be wondered at that *valerian (valeriana officinalis)* in *moderate* doses cures chronic diseases with excess of irritability, since in large doses, as I have ascertained, it can exalt so remarkably the irritability of whole system".

"The dispute as to the whether the *brooklime (anagallis arvensis)* and the bark of the *misletoe (viscum album)* possess great curative virtues or none at all, would immediately be settled, if it were tried on the healthy whether large doses produces bad effects, and an artificial disease similar to that in which they have been hitherto empirically used".

"The specific artificial disease and the peculiar affections that the *spotted hemlock (conium maculatum)* causes are not nearly so well describe as they deserve; but whole books are filled with the empirical praise and the equally empirical abuse of this plant. It is true that it can produce ptyalism, it may therefore possess an excitement action on the lymphatic system, and be of permanent advantage in cases where it is requisite to restrain the excessive action of the absorbent vessels (If employed in inactivity of these vessels, it will first act as a palliative afterwards do little one way or other, and lastly, prove injurious, by the production of the opposite condition to that wished for). Now as it, besides this, produces pains (in *large* doses violent pains) in the glands, it may easily be conceived that

in painful induration of the glands, in cancer, and in the painful nodes that the abuse of mercury leaves, it may be the best remedy, in *moderate* doses, not only for curing almost specifically this peculiar kind of chronic pains and all other narcotic remedies which act in a different manner, but also for dispersing the glandular swellings themselves, when they either have their origin, as above described, in excessive local or general activity of the lymphatic vessels, or occur in an otherwise robust frame, so that the removal of the pains is all that is required in order to enable nature to cure the complaint herself. Painful glandular swellings from external injuries are of this description (A healthy peasant child got, from a violent fall, a painful swelling of the under lip, which increased very much in the course of four weeks in hardness, size and painfulness. The juice of the spotted hemlock applied to it, affected a cure without any relapse in fourteen days. A hitherto uncommonly healthy, robust girl had severely bruised the right breast, whilst carrying a heavy burden, with strap of the basket. A small tumor arose, which for six months increased in violence of pain, in size and hardness, at each monthly period. The external application of spotted hemlock juice cured it within five weeks. This it would have done sooner, had it not affected the skin, and produced there painful pustules, in consequence of which it had frequently to be discontinued for several days)".

"In true cancer of the breast, where an opposite state of the glandular system, a sluggishness of it, seems to predominate, it must certainly do harm on the whole (it may at first soothe the pains), and especially must it aggravate the disease when the system, as is often the case, is weakened by long-continued suffering; and it will do harm all the more rapidly, because its continued use produces, as a secondary action, weakness of the stomach and of the whole body. From the very reason that it, like other umbelliferious plants, specifically excited the glandular system, it may, as the older physicians remarked, cure an excessive secretion of milk. As it shows a tendency to paralyze the nerved of sight in large doses, it is comprehensible why it has proved for service in amaurosis. It was removed spasmodic complaints, hooping cough, and epilepsy, because it has a tendency to produce convulsions. It will still more certainly be of use in convulsions of the eyes and trembling of the limbs, because in large doses it develops exactly the same phenomena. The same with respect to giddiness".

"The fact that *fool's parsley (aethusa cynapium),* besides other affections, as vomiting, diarrhea, colicky pains, cholera, and others for the truth of which I cannot vouch (general swelling, etc.), produces so specifically imbecility, also imbecility alternately with madness, should be of use to the careful physician in this disease, otherwise so different of cure. I had a good extract of it prepared by myself, and once, when I found myself, from much mental work of various kinds coming upon me in rapid succession, distracted and incapable of reading any more, I took a grain of it. The effect was an uncommon disposition for mental labor, which lasted for several hours, until bed-time. The next day, however, I was less disposed for mental exertion".

"The *water hemlock (cicuta virosa)* causes, among other symptoms, violent burning in the throat and stomach, tetanus, tonic cramp of the bladder, lockjaw, erysipelas of the face, headache, and true epilepsy; all diseases for which we require efficient remedies, one of

which, it may be hoped, will be found in this powerfully, acting root, in the hands of the cautious but bold physician".

"Amatus the Portuguese observed that *cocculus seeds (menispermum cocculus),* in the dose of four grains, produced nausea, hiccough, and anxiety in an adult man. In animals they produced a rapid, violent, but when the dose was not fatal, a transitory stupefaction. Our successors will find in them a very powerful medicine, when the morbid phenomena these seeds produce shall be more accurately known. The Indians use the root of this tree, among others things, in malignant typhus (that accompanied by stupefaction)".

"The *fox-grape (paris quadrifolia)* has been found efficacious in cramps. The leaves cause, in large doses at all events, cramp in the stomach, according to the still imperfect experience we possess of the morbid phenomena they are capable of developing".

"*Coffee* produces, in large doses, headaches; it therefore cures, in moderate doses, headaches that do not proceed from derangement of the stomach or acidity in the primae viae. It favours the peristaltic motion of the bowels in large doses, and therefore cures in smaller doses chronic diarrheas, and in like manner the other abnormal effects it occasions might be employed against similar affections of the human body, were we not in the habit of misusing it. The effects of opium in stupefying the senses, and irritating the tone of the fibres, are removed by this berry in its character of an antagonistic palliative remedy, and that properly and effectually, for here there is no persistent state of the organism, but only transitory symptoms to be combated. Intermittent fevers, too, where there is a want of irritability and inordinate tension of the fibres, precluding the employment of otherwise specific bark, it apparently suppresses in large doses, merely as a palliative remedy; its direst action, however, in such large doses, lasts for two days".

"The *bitter-sweet (solanum dulcamara)* produces, in large doses, among other symptoms, great swelling of the affected parts and acute pains, or insensibility of them, also paralysis of the tongue and of the optic nerves. In virtue of the last powerful action, it is not to be wondered at that it has cured paralytic affections, amaurosis, and deafness, and that it will render still more specific service in paralysis of the tongue, in moderate doses. In virtue of the two first properties, it is a main remedy in chronic rheumatism, and in the nocturnal pains from the abuse of mercury. In consequence of its power of causing strangury, it has been useful in obstinate gonorrhea, and from its tendency to bring about itching and shooting in the skin, it shows its utility in many cutaneous eruptions and old ulcers, even such as arise from abuse of mercury. As it causes, in large doses, spasms of the hands, lips and eyelids, as also shaking of the limbs, we may easily understand how it has been useful also in spasmodic affections. In nymphomania it will probably be of use, as it acts so specifically on the female genital organs, and has the power of causing (in large doses) itching and pains in these parts".

"The berries of the *black nightshade (solanum nigrum)* have caused extraordinary convulsions of the limbs, and also delirious raving. It is, therefore, probable that this plant will do good in what are called possessed persons (madness, with extraordinary, emphatic, often unintelligible talking, formerly considered prophesying and the gift of unknown

tongues, accompanied by convulsions of the limbs), especially where there are at the same time pains in the region of the stomach, which these berries also produce in large doses. As this plant causes erysipelas of the face, it will be useful in that disease, as has already been ascertained from its external employment. As it causes, to a still greater degree than bitter-sweet, by being used internally, external swellings, that is, a transient obstruction in the absorbent system, its great diuretic power is only the indirect secondary result; and hence its great virtue in dropsy, *from similarity of action*, is plainly perceptible; a medicinal quality of so much the greater value, as most of the remedies we possess for this disease are merely antagonistically acting (exciting the lymphatic system in a merely transitory manner), and consequently palliative remedies, incapable of effecting a permanent cure. As, moreover, in large doses it causes not only swelling, but general inflammatory swelling, with itching, and intolerable burning pains, stiffness of the limbs pustular eruptions, desquamation of the skin, ulcers, and sphacelus, where is the wonder that its external application has cured divers pains and inflammations? Taking all the morbid symptoms together that the black nightshade produces, we cannot mistake their striking resemblance to raphania, for which it will, *most probably*, is found to be a specific remedy".

"It is probable that the *deadly nightshade (atropa belladonna)* will be useful, if not in tetanus, at least in trismus (as it produces a kind of lockjaw), and in spasmodic dysphagia (as it specifically causes a difficulty of swallowing); both these actions belong to its direct action. Whether its power over hydrophobia, if it does possess any, depends on the latter property alone, or also on its power of suppressing palliatively, for several hours, the irritability and excessive sensitiveness that are present in so great a degree in hydrophobia, I am unable to determine. Its power of soothing and dispersing hardened, painful and suppurating glands, is owing, undeniably, to its property of exciting, in its direct action, boring, gnawing pains in these glandular swellings. Yet I conceive that it acts antagonistically, that is, in a palliative and merely temporary manner, in those which proceed from excessive irritation of the absorbent system (with subsequent aggravation, as is the case with all palliatives in chronic diseases); but, by virtue of similarity, that is, permanently and radically, in those arising from torpor of the lymphatic system [Then it would be serviceable in those glandular swellings in which the *spotted hemlock (conium maculatum)* cannot be used and the latter will be useful where the former does injury]. As, however, its continued employment (by reason if its indirect secondary action) exhausts the whole body, and when given in too large, or too often repeated doses, has a tendency to produce a gangrenous fever, its good effects will sometimes be destroyed by these secondary bad consequences, and fatal result may ensue (especially in the case of cancerous patients, whose vital powers have been exhausted by the sufferings of many years), if it be not cautiously employed. It produces directly mania (as also, as above described, a kind of tonic cramp); but clonic cramps (convulsions) it only produces as a secondary action, by reason of the state of the organism that remains after the direct action of belladonna (obstruction of the animal and natural functions). Hence its power in epilepsy with furor is always most conspicuous upon the latter symptom, whilst the former is generally only changed by the antagonistic (palliative) action of belladonna, into trembling, and such-like spasmodic affections peculiar to weakened irritable systems. All the spasmodic symptoms that belladonna produces in its direct primary action are of a tonic character; true, the

muscles are in a state of paralytic relaxation; but their deficient irritability causes a kind of immobility, and a feeling of health, as if contraction were present. As the mania it excites us of a wild character, so it sooths manias of this sort, or at least deprives them of their stormy nature. As it extinguishes memory in its direct action, (It will, therefore, be useful in weakness of memory) nostalgia (home sickness) is aggravated, and, as I have seen, is even produced by it".

"Moreover, the increased discharge of urine, sweat, menses, faeces, and saliva, which have been observed, are merely consequences of the antagonistic state of the body, remaining after an excessive exaltation of the irritability, or else sensitiveness during the indirect secondary action, when the direct primary action of the drug is exhausted, during which, as I have several times observed, all these excretions are often completely suppressed by large doses for ten hours and more. Therefore, in cases where these excretions are discharged with difficulty, and excite some serious disease, belladonna removes this difficulty permanently and completely, as a similarly-acting remedy, if it be owing to tension of the fibres, and want of irritability and sensibility. I say purposely, *serious disease,* for only in such cases is it allowable to employ one of the most violent of medicines, which demands such caution in its use. Some kinds of dropsy, green sickness, etc., are of this nature. The great tendency of belladonna to paralyze the optic nerve, makes it important, as a similarly-acting remedy, in amaurosis (I have myself seen the good effects of it in this disease). In its direct action it prevents sleep, and the deep sleep which subsequently ensues is only in consequence of the opposite state produced by the cessation of this action. By virtue, therefore, of this artificial disease, belladonna will cure chronic sleeplessness (from want of irritability) more permanently than any palliative remedy".

"It is said to have been found beneficial in dysentery; probably, as in its direct action it retards the stool, in the most simple cases of diarrhea, with suppressed fecal evacuations, and rare motions, but not in dysentery with lienteric diarrhea, where is must do positive harm. Whether, however, it is appropriate for dysentery, by reason of its actions, I am unable to say".

"It produces apoplexy; and if it has, as we are told, been found serviceable in serious apoplexy, it is owing to this property. Besides this, its direct action causes an internal burning, with coldness of external parts".

"Its direct action lasts twelve, twenty four, and forty eight hours. Hence, a dose should not be repeated sooner than after two days. A more rapid repetition of ever so small a dose must resemble in its (dangerous) effects the administration of a large dose. Experience teaches this".

"The fact that *henbane (hyoscyamus niger)* in large doses diminishes remarkably the heat of the body and relaxes its tone for a short time in its direct action, and therefore is an efficacious palliative remedy when given in moderate doses inwardly and outwardly in sudden when given in moderate doses inwardly and outwardly in sudden attacks of tension of the fibres and inflammation, does not fall to be considered in this place. This is not the case, however, with the observation, that this property only enables it palliate very

imperfectly, in any dose, chronic affections with tension of the fibre; in the end, however, it rather increases than diminishes them by its indirect secondary action, which is exactly than diminishes them by its primary action. On the other hand, it will help to assist the power of the strengthening remedy in chronic relaxation of the fibres, as in its primary action it relaxes and in its secondary action it tends all the more to elevate the tone and that in a durable manner. In *large* doses it likewise possesses the power of producing hemorrhage, especially bleeding of the nose, and frequently recurring catamenial flux, as I and others have ascertained. For this reason it cures chronic hemorrhages, in small doses, in an extremely effectual and lasting manner. The most remarkable thing is the artificial disease it produces in *very large* doses, suspicious, quarrelsome, spitefully-calumnious, revengeful, destructive, fearless (the subsequent indirect secondary action is a kind of faint-heartedness and fearfulness), mania (hence, henbane was termed by the ancients altercum), and this is the kind of mania it specifically cures, only that in such cases a tenseness of fibre sometimes hinders it effects from being permanent. Difficulty of moving, and insensibility of the limbs, and the apoplectic symptoms it produces, it may also very probably be capable of curing. In large doses, it produces, in its direct primary action, convulsions, and is consequently useful in epilepsy, probably also in the loss of memory usually accompanying it, as it has the power of producing want of recollection".

"Its power of causing in its direct action sleeplessness with a much more permanent remedy than the frequently merely palliative opium, especially as it at the same time keeps the bowels open, although only by the indirect secondary action of each dose, consequently in a palliative way. It causes dry cough, dryness of the mouth and nose, in its direct action; it is, therefore, very useful in tickling cough, probably also in dry coryza. The flow of mucus from the nose, and the flow of saliva observed from its use, only belongs to its indirect secondary action. The seeds cause convulsions in the facial an ocular muscles, and by their action on the head, cause vertigo, and a dull pain in the membranes lying under the skull. The practical physician will be able to take advantage of this. Its direct action lasts scarcely twelve hours".

"The *thorn-apple (datura stramonium)* causes extraordinary waking dreams, unconsciousness of what is going on, loud delirious talking, like a person speaking in sleep, with mistakes respecting personal identity. A similar kind of mania it cures specifically. It excites very specific convulsions, and has thus often proved useful in epilepsy. Both properties render it serviceable in the case of persons possessed. Its power of extinguishing recollecting should induce us to try it in cases of weak memory. It is most useful where there is great mobility of the fibre, because its direct action in large doses is increased fibrous mobility. It causes (in its direct action?) heat and dilatation of the pupil, a kind of dread of water, swollen, red face, twitching in the ocular muscles, retarded stool, difficult breathing; in its secondary action, slow, soft pulse, perspiration, sleep".

"The direct action of large doses lasts about twenty four hours; of small doses, only three hours. Vegetable acids, and apparently citric acid in particular, suddenly put a stop to its whole action (A patient, who has always violently affected by two grains of the extract of the plant, once experienced not the slightest effects from this dose. I learned that he had partaken of the juice of a large number of red currents a considerable dose of pulverized

oyster-shells at once restored the full efficacy of the thorn apple). The other species of datura seem to act in a similar manner".

"The specific properties of *Virginia tobacco (nicotiana tabacum)* consist, among other things, in diminishing the external senses, and obscuring the intellect; it may therefore be useful in weakness of mind. Even in a very small dose, it excites the muscular action of the primae viae violently; a property which is valuable as a temporary oppositely-acting remedy (as is well known, though it does not fall to be considered here); and as a similarly acting remedy it is probably serviceable in chronic disposition to vomiting and to colics, and spasmodic constriction do the esophagus, as indeed experience partially corroborates. It diminishes the sensibility of the primae viae; hence its palliative power of lessening hunger (and thirst?). In larger doses, it deprives of their irritability the muscles of voluntary motion, and temporarily removes from them the influence of the cerebral power. This property may give it as a similarly-acting remedy, curative powers in catalepsy; but this very property makes its constant employment in large quantities (as with tobacco-smokers and snuff-takers) so injurious to the tranquil state of the muscles belonging to the animal functions, that a tendency to epilepsy, hypochondriasis, and hysteria, are in course of time developed. The remarkable fact, that the employment of tobacco is so agreeable to insane persons, arises from the instinct of those unfortunates to produce a palliative obtuseness in the sensibility of their hypochondria (To this belongs the feeling of insatiable hunger, which many insane persons suffer from, and for which they generally appear to use tobacco at least, I have seen some, who had no desire for tobacco, specially such as were affected with melancholia, who had no desire for tobacco, especially such as were affected with melancholia, who had very little hunger) and brain (the usual seats of their complaints). But as it is here an oppositely-acting remedy, it gives them but temporary relief; their desire for it increases, but the end for which it is taken is not attained, - on the whole the complaint is thereby increased, as it tenders no permanent service. Its direct action is limited is limited to a few hours, except in the case of very large doses, which extend to twenty-four hours (at the farthest)".

"The seeds of the *poison tree (strychnos nux vomica)* are very powerful; but the morbid symptoms it produces are not yet accurately known. The most I know concerning them is derived from my own observation. The primary action produce vertigo, anxiety, febrile rigour, and in their secondary action a certain immobility of all parts, at least of the limbs, and a spasmodic stretching, according to the size of the dose. Hence they are useful, not only, as is already known, in intermittent fever, but in cases of apoplexy. In their first direct action the muscular fibre has a peculiar mobility imparted to it, the sensitive system is morbidly exalted to a species of intoxication, accompanied by fearfulness and horror. Convulsions ensue. The irritability seems to exhaust it itself during this continued action on the muscular fibre, first in the animal, then in the vital functions. On passing into the indirect secondary action, there occurs a diminution of the irritability, first, in the vital functions (general perspiration), then in the animal, and lastly in the natural functions. In the latter, especially, this secondary action lasts several days. During the secondary action, there is a diminution of sensibility. Whether in the primary direct action the tonicity of the muscles is diminished, to be proportionately increased in the secondary action, cannot be

accurately determined; this much, however, is certain, that the contractility of the fibre is as much diminished in the secondary action, as it was increased in the direct action".

"If this be true, *nux vomica* produces attacks similar to hysterical and hypochondriacal paroxysms, and this explains why it is so often useful in these complaints".

"Its tendency to excite, in its primary direct action, the contractility of the muscles, and cause convulsions, and then again in its secondary action to diminish to an excessive degree the contractility of the muscles, shows such a resemblance to epilepsy, that from this very circumstance we must have inferred that it would heal this disease, had not experience already demonstrated it".

"As it excites, besides vertigo, anxiety and febrile rigour, a kind of delirium consisting in vivid, sometimes frightful visions, and tension in the stomach, so it once quickly subdued a fever in a laborious reflective mechanic in the country, which began with tension in the stomach, followed by a sudden attack of vertigo, so as to make him fall, that left behind it a kind of confusion of the understanding, with frightful, hypochondriacal ideas, anxiety, and exhaustion. In the morning he was pretty lively and not exhausted, but in the afternoon, about two o'clock, the attack commenced. He got *nux vomica*, in increasing doses, one daily, and improved. At the fourth dose, which contained seventeen grains, there occurred great anxiety, immobility and stiffness of the limbs, ending in a profuse perspiration. The fever and all the nervous symptoms disappeared, and never returned, although for many years previously he had from time to time been subject to such attacks suddenly occurring, yet unaccompanied by fever".

"Its tendency to cause cramps in the abdomen, anxiety and pain in the stomach, I availed myself of in a dysenteric fever (without purging), in persons living in the same house with dysenteric patients. In these cases it diminished the feeling of discomfort in the limbs, the feverishness, the anxiety, and the pressure in the stomach; it produced the same good results in some of the patients, but as they had simple dysentery without diarrhea, it made the evacuations still rarer, from its tendency to cause constipation. The signs of deranged biliary secretion showed themselves, and the dysenteric evacuations, though rarer, were accompanied by just as great tenesmus as before, and were of as bad a character. The symptom of loss of taste, or perverted taste, remained. Its tendency to diminish the peristaltic movements was therefore disadvantageous in the true simple dysentery. In diarrheas, even such as are of a dysenteric character, it will be more serviceable, at least as a palliative remedy. During its employment, I witnessed twitching movements under the skin, as if caused by live animals, in the limbs, and especially in the abdominal muscles".

"*St. Ignatius' bean (ignatia amara)* has been observed to produce trembling of several hours' duration, twitchings, cramps, irascibility, sardonic laughter, giddiness, cold perspiration. In similar cases it will show its efficacy, as experience has partly demonstrated. It produces febrile rigour, and (in its secondary action?) stiffness of the limbs, and thus it has cured, by similarity of action, intermittent fever, which would not yield to bark probably it was that less simple form of intermittent in which the complication consisted of excessive sensitiveness and increased irritability (especially of the primae

viae). But the other symptoms it can produce must be more accurately observed, before we can employ it in those cases for which it is exactly suited from similarity of symptoms".

"The *purple foxglove (digitalis purpurea)* causes the most excessive disgust at food; during its continued use, therefore, ravenous hunger not unfrequently ensues. It causes a kind of mental derangement, which is not easily recognizable, as it only shows itself in unmeaning words, refractory disposition, obstinacy, cunning, disobedience, inclination to run away, etc., which its continued use frequently prevents. Now as, in addition to these, it produces in its direct action violent headaches, giddiness pain in the stomach, great diminution of the vital powers, sense of dissolution and the near approach of death, a diminution of the rapidity of the heart's beats by one half, and reduction of the vital temperature, it may easily be guessed in what kind of madness it will be of service; and that it has in fact been useful in some kinds of this disease, many observations testify, only their particular symptoms have not been recorded. In the glands it creates an itching and painful sensation, which accounts for its efficacy in glandular swellings".

"It produces, as I have seen, inflammation of the Meibomian glands, and is a certain cure for such inflammations. Moreover, as it appears to depress the circulation, so does it seem to excite the absorbent vessels, and to be most serviceable where both are too torpid. The former it assists by virtue of similarity, the later by virtue of antagonism of action. But as the direct action of foxglove persists so long (there are examples of its lasting five or six days), it may, as an antagonistically acting remedy, take the place of a permanent curative agent. The last observation is in reference to its diuretic property in dropsy; it is antagonistic and palliative, but nevertheless enduring, and valuable on that account merely".

"In its secondary action it causes a small, hard, rapid pulse; it is not therefore so suitable for patients who have a similar (febrile) pulse, but rather for such as have a pulse like what *foxglove* produces in its direct action - slow, soft. The convulsions it causes in large doses, assign it in a place among the anti-epileptic remedies; probably it is only useful in epilepsy under certain conditions, to be determined by the other morbid symptoms it produces. During its use, objects not unfrequently appear of various colors, and the sight be comes obscured it will remove similar affections of the retina (Its tendency to produce diarrhea, sometimes so adverse to the cure, is counteracted, as I have ascertained, by the addition of potash)".

"As the direct action of *foxglove* lasts occasionally several days (the longer its use is continued, the longer lasts the direct action of each dose; a very remarkable fact, not to be lost sight of in practice), it is evident how erroneously those act, who, with the best intentions, prescribe it in small but frequently repeated doses (the action of the first not having expired before they have already given the sixth or eight), and thus in fact they give, although unwittingly, an enormous quantity, which not unfrequently causes death (A woman in Edinburgh got for three successive days, each day, three doses, each dose consisting of only two grains of the pulverized leaves of *foxglove*, and it was a matter of surprise that she died from such small doses, after vomiting for six days. It must be remembered, however, that it was the same as if she had taken eighteen grains at one dose).

A dose is necessary only every three or at most every two days, but the more rarely the longer it has been used (During the continuance of its direct action, cinchona bark must not be prescribed it increases the anxiety caused by foxglove, as I have found, to an almost mortal agony)".

"The *pansy violet (viola tricolor)* at first increases cutaneous eruptions, and thus shows its power to produce skin diseases, and consequently to cure the same effectually and permanently".

"*Ipecacuanha* is used with advantage in affections against wich nature herself makes some efforts, but is too powerless to affect the desired object. In these *ipecacuanha* presents to the nerves of the upper orifice of the stomach, the most sensitive part of the organ of vitality, a substance that produces a most uncongenial disgust, nausea, anxiety, thus acting in a similar manner to the morbid material that is to be removed. Against this double attack, nature exerts antagonistically her powers with still greater energy, and thus, by means of this increased exertion, the morbid matter is the more easily removed. Thus fevers are brought to the crisis, stoppages in the viscera of the abdomen and of the chest, and in the womb, put in motion, miasmata of contagious diseases expelled by the skin, cramp relieved by the cramp that *ipecacuanha* itself produces, their tension and freedom restored to vessels disposed to hemorrhage from relaxation, or from the irritation of an acrid substance deposited in them, etc. But most distinctly does it act as a similarly acting remedy to the disease sought to be cured, in cases of chronic disposition to vomit without bringing anything away. Here it should be given in very small doses, in order to excite frequent nausea, and the tendency to vomit goes off more and more permanently at each dose, than it would with any palliative remedy".

"Some benefit may be anticipated in some kinds of chronic palpitation of the heart, etc., from the administration of the *rose bay (nerium oleander)*, which has the power of causing palpitation, anxiety, and fainting. It causes swellings of the abdomen and diminution of the vital temperature, and seems to be a most powerful vegetable".

"The morbid symptoms produced by the *nerum antidysentericum* are not sufficiently known to enable us to ascertain the cause of its real remedial powers; but as it primarily increases the stools, it apparently subdues diarrheas as a similarly acting remedy".

"The *bear's berry (arbutus uva ursi)* has actually, without possessing any acridity perceptible to the senses, not unfrequently increased the difficulty of passing water, and the involuntary flow of urine, by some power peculiar to itself; thereby showing that it has a tendency to produce such affections, and hence, as experience also testifies, it is capable of curing similar disorders in a permanent manner".

"The *golden-flowered rhododendron (rhododendron chrysanthum)* shows, by the burning, formicating, and shooting pains it produces in the parts affected, that it is certainly fitted to relieve, by similarity of action, pains in the joints of various kinds, as experience also teaches. It causes difficulty of breathing and cutaneous eruptions, and thus it will prove

useful in similar disorders, as also in inflammation of the eyes, because it produces lachrymation and itching of the eyes".

"The *marsh-tea (ledum palustre)* causes, as I have ascertained, among other effects, difficult, painful respiration; this accounts for its efficacy in hooping cough, probably also in morbid asthma. Will it not be useful in pleurisy, as its power of so greatly diminishing the temperature of the blood (in its secondary action) will hasten recovery? It causes a painful shooting sensation in all parts of the throat, as I have observed, and hence its uncommon virtues in malignant and inflammatory, sore throat. Equally specific is, as I have noticed, its power of causing troublesome itching in the skin, and hence its great efficacy in chronic skin diseases".

"The anxiety and the fainting its occasions may prove of use in similar cases. As a transitory and antagonistically acting powerful diuretic and diaphoretic remedy, it may cure dropsies; more certainly however, acute, than chronic".

"On some of these properties depends its reputation in dysentery. But were they earl cases of dysentery, or some of those painful diarrheas so often taken for it? In the latter case it may, as a palliative remedy, certainly hasten the cure and even help to complete it; but in true uncomplicated dysentery, I have never seen it of any use. The long-continued weakness it occasions was against its being used for a length of time, and it ameliorated neither the tenesmus nor the character of the excretions, though these became more rare. The symptoms of deranged biliary secretion were rather worse during its used than when the patients were left without medicine. It causes a peculiar ill-humor, headache, and mental confusions; the lower extremities totter, and the pupils dilate (Do both the latter symptoms, or merely the last, belong to the secondary action only?). An infusion of ten grains once a day was a sufficient dose for a child six years old".

"The primary direct action of *opium (papaver somniferum)* consists in transitory elevation of the vital powers, and strengthening the tone of the blood-vessels and muscles, especially of those belonging to the animal and vital functions, as also in excitation of the mental organs - the memory, the imagination, and the organ of the passions; - thus, moderate doses are followed by a disposition to work, sprightliness in conversation, wit, remembrance of former times, amorousness, etc.; large doses by boldness, courage, revenge, inordinate hilarity, lasciviousness; still larger doses by furious madness, convulsions. The greater the dose, the more do the individuality, the freedom, and the voluntary power of the mind suffer in sensations, and in power of judgment and of action. Hence, inattention to external disagreeable circumstances, to pain, etc. This condition, however, does not last long. It is gradually followed by loss of ideas, the pictures of fancy fade by degrees, there supervene relaxation of the fibre, sleep. If the use of elevated doses is continued, the consequences (indirect secondary action) are, weakness, sleepiness, listlessness, grumbling, discomfort, sadness, loss of memory (insensibility, imbecility), until a new excitation by *opium*, or something similar, is produced. In the direct action, the irritability of the fibre seems to be diminished in the same proportion as its tone is increased; in the secondary action, the latter is diminished, the former increased (There occurs a marked sensitiveness, especially for things that produce disagreeable effects, for fright, grief, fear, for inclement weather, etc. If

the mobility of the fibre which occurs secondarily is called increased irritability, I have nothing to object to the term its sphere of action, however, is but small: it is either that the fibre is too relaxed, and cannot contract much, to that it is in a too contracted condition, and is relaxed easily indeed, but not sufficiently, consequently us incapable of making any powerful effort. In this condition of the fibre, the tendency to chronic inflammation is unmistakable). The direct action, still more than the secondary action, prevents the mind from taking cognizance of sensations (pain, sorrow, etc.), and hence its great pain subduing power".

"In cases where only the direct action as a cordial is necessary, it will be requisite to repeat the administration of it every three or four hours, that is, each time before the relaxing secondary action, which so much increases the irritability, ensues. In all such cases it acts merely antagonistically, as a palliative remedy. Permanent strengthening powers are not to be expected from it used in this manner, least of all in chronic weakness. This, however, is a digression".

"But if it is wished to depress permanently the tone do the fibre (I give this name to the power of the fibre to contract and relax completely), to diminish permanently the deficiency of irritability, as is the case in some cases of mania, in such circumstances we may employ *opium* with success, as a similarly acting remedy, given in elevated doses, and making use of its indirect secondary action. We must consider the treatment which consists in giving *opium* in true inflammatory diseases, *e.g.*, pleurisy, to be according to this principle".

"In such cases, a dose is necessary every twelve or twenty four hours".

"It appears that this indirect secondary action has been made use of on the principle of a similarly acting remedy; which, as far as I am aware, is not the case with any other medicine. *Opium* has, for instance, been given with the greatest success (not in true venereal diseases, for that would be a delusions), but in the disastrous effects that so often arise from the abuse of mercury in syphilis, which are sometimes much worse than the syphilis itself".

"Before illustrating this employment of *opium,* I must say something appropriate to the subject, concerning the nature of syphilis, and introduce here what I have to say concerning mercury".

"Syphilis depends upon a virus, which, besides other peculiarities that it develops in the human body, has an especial tendency to produce inflammatory and suppurating swellings of the glands (to weaken the tone?), to make the mechanical connexion of the fibres so disposed to separation, that numerous spreading ulcers arise, whose incurable character may be known by their round figure; and lastly, to increase the irritability. Now, as such a chronic disease can only cured by a remedy capable of developing a disease of similar character, no more efficacious remedy could be conceived than *mercury*".

"The most remarkable power of *mercury* consists in this, that in its direct action it irritates the glandular system (and leaves behind its glandular indurations as its secondary indirect

action) weakens the tone of the fibres and their connexion, and disposes them to separation in such a manner, that a number of spreading ulcers arise, whose incurable nature is shown by their round form; and lastly, increases uncommonly the irritability (and sensibility). Experience has confirmed it has a specific; but as there does not exist any remedy similar to the disease, so the mercurial disease (the changes and symptoms it usually produces in the body) is still very different from the nature of syphilis. The syphilitic ulcers are confined to the most superficial parts, especially the deuteropathic ones (the protopathic ulcers increase slowly in extent), they secrete a viscid fluid in place of pus, their borders are almost level with the skin (except the protopathic ones), and are almost quite painless (excepting the protopathic ulcer, that arising from the primary infection, and the suppurating inguinal gland). The mercurial ulcers burrow deeper (rapidly increase in size) are excessively painful, and secrete sometimes an acrid thin ichor; sometimes they are covered with a dirty cheesy coating, their borders also become reverted. The glandular swellings of syphilis remain but for a few days they are either rapidly resolved, or the gland suppurates. The glands attacked by *mercury* are stimulated to increased action by the direct action of this metal (and thus glandular swellings from other causes disappear rapidly under its use) or they are left in the state of cold indurations during the indirect secondary action. The syphilitic virus produces induration of the periosteum of those bones which are nearest the surface and least covered with flesh; they are the seat of excessive pains. In our days this virus, however, never produces caries, notwithstanding all my researches to discover the contrary. *Mercury* destroys the connexion of the solid parts, not of the soft parts only, but also of the bones it first corrodes the most spongy and concealed bones, and this caries is only aggravated the more rapidly by the continued use of the metal. Wounds which have arisen from external violence are changed by the use of *mercury* into old ulcers, difficult of cure; a circumstance that does not occur with syphilis. The trembling, so remarkable in the mercurial disease, does not occur in syphilis. From the use of *mercury* there ensues a slow, very debilitating fever, with thirst, and great and rapid emaciation. The emaciation and weakness from syphilis come on slowly, and remain within moderate limits. Excessive sensitiveness and sleeplessness are peculiar to the mercurial disease, but not to syphilis. The most of these symptom actions, than to the direct action of the *mercury*".

"I have been so circumstantial on this subject, because it is often very difficult [Stoll (Rat. Med. Part iii, p.442) doubts if there are certain signs of a perfectly cured syphilitic disease, *i.e.*, he himself knew not the signs whereby this disease is distinguishable from the mercurial disease] for the practitioner to distinguish the chronic mercurial disease from the symptoms of syphilis; and thus he will be apt to consider symptoms ass belonging to that disorder, whilst they are only mercurial, and go on treating them with *mercury*, whereby so many patients are destroyed; chiefly, however, because my object is to depict the mercurial disease, in order to show how *opium* can cure it, by virtue of similarity of action".

"*Opium* raises the sinking forces of patients suffering from the mercurial disease, and allays their irritability, when its direct action is kept up, that is, when it is given at least every eight hours; and this is does an antagonistically-acting remedy. This happens, however, only when it is given in large doses, proportioned to the degree of weakness and irritability, just as it is serviceable only in large and oft-repeated doses in the excessive irritability of hysterical and hypochondriacal patients and in the excessive sensibility of exhausted

individuals. The normal condition of the body seems thereby to be restored; a secret metamorphosis seems to take place in the organism, and the mercurial disease is gradually conquered. The convalescent patient can only bear smaller and smaller doses. Thus the mercurial disease seems to be vanquished by the palliative antagonistic power of the *opium*; but any one who is aware of the almost ineradicable nature of the mercurial disease, the irresistible manner in which it destroys and dissolves the animal frame when it is at its height, will be convinced that a mere palliative could never master this excessively chronic malady, were it not that the secondary effects of *opium* were very analogous to the mercurial disease, and that these tended to overcome the latter. The secondary effects of the continued use of *opium* in large doses, increased irritability, weakness of the tone, easy separation of the solids, and difficult curability of wounds, trembling, emaciation of the body, drowsy sleeplessness, are very similar to the symptoms of the mercurial disease; and only in this do they differ, that those of mercury, when they are severe, last for years, often for a lifetime whilst those of *opium* last but hours or days. *Opium* must be used for a long time, and in enormous doses, for the symptoms of its secondary action to last for weeks or longer. These brief secondary effects of *opium*, whose duration is limited to a short time, are thus the true antidote of the mercurial secondary effects in their greatest degree, which are almost unlimited in their duration; from their alone, almost, can one expect a permanent, true recovery. These secondary actions can develop their curative power during the whole treatment, in the interval betwixt the repetition of the doses of *opium*, as soon as the first direct action of each dose is passed, and when its use is discontinued".

"*Lead* produces, in its primary action on the denuded nerves (belonging to muscular action?) a violent tearing pain, and (thereby?) relaxes the muscular fibre to actual paralysis; it becomes pale and withered, as direction shows, but its external sensibility still remains, though in a diminished degree. Not only is the power of contradiction of the affected fibres diminished, but the motion that still remains is more difficult than in other similar relaxations, from almost total loss of the irritability (The convulsive vomiting and dysenteric diarrhea which sometimes follow the ingestion of large quantities of lead, must be explained on other principles, and do not fall to be considered here neither does the vomiting that ensues from large doses of *opium*). This, however, is observed only in the muscles belonging to the natural and animal functions, but in those belonging to the vital functions this effect occurs without pain and in a less degree. As the reciprocal play of the vascular system becomes slower (a hard, slow pulse), this satisfactorily explains the diminished temperature of the blood attending the action of lead".

"*Mercury* also diminishes the mutual attraction of the various parts of the muscular fibres, but increases their susceptibility for the stimulus, so as too impart to them an excessive mobility. Whether this effect be the direct or the indirect secondary action it suffices that it is very enduring; and hence, even if of the latter character, it would be very efficacious, as an oppositely acting remedy in the lead disease; if of the first character, however, it will act as a similarly-acting remedy. Rubbed in externally, as well as given internally, *mercury* has an almost specific influence over the lead disease. *Opium* increases in its direct action the contraction of the muscular fibre, and diminishes its irritability. By virtue of the former property, it acts as a palliative in the lead disease; by the latter, however, permanently, as a similarly-acting remedy".

"From the above idea of the nature of the lead disease, it will be seen that the service this metal lead has afforded, when cautiously used in diseases, depends entirely on its antagonistic, though uncommonly long-lasting, action, the consideration of which does not belong to this Essay".

"The true nature of the action of *arsenic* has not yet been accurately investigated. Thus much I have myself ascertained that it has a great tendency to excite that spasm in the blood vessels, and the shock in the nervous system, called febrile rigour. If it be given in a pretty large dose (one-sixth or one fifth of a grain) to an adult, this rigour becomes very evident. This tendency makes it a very powerful remedy as a similarly-acting medicine in intermittent fever, and this all the more, as it possesses the power, observed by me, of exciting a daily-recurring, although always weaker, paroxysm, even although its use be discontinued. In typical diseases of all kinds (periodical headache, etc.), this type-exciting property of *arsenic* in small doses (one-tenth to at most one-sixth of a grain in solution) becomes valuable, and will, I venture to guess become invaluable to our perhaps bolder more observant, and more cautious successors. As its action lasts several days, so, frequently-repeated doses, be they ever so small, accumulate in the body to an enormous, a dangerous dose. If, then, it be found necessary to give a dose daily, each successive dose should be at least a third smaller than the previous one. A better procedure is, when we have to treat short typical diseases with, say, two days' interval, always to prescribe a dose only for one fit two hours before it is expected, pass over the following fit without giving any *arsenic*, and another dose only about two hours before the third fit. It will be best to act so even in the case of quartan fever, and only commence to treat the series of the intermediate paroxysms when we have attained our object with regard to the first series of paroxysms (In the case of longer intervals, as seven, nine, eleven, and fourteen days, a dose may be prescribed before each fit). The continued use of *arsenic* in large doses gradually causes an almost constant febrile state; it will thus, as indeed experience has, to a certain degree, taught us, prove useful in hectic and remittent fever, as a similarly-acting remedy; in small doses (about one-twelfth of a grain). Such a continued employment of *arsenic*, however, will always remain a masterpiece of art, as it possesses a great disposition to diminish the vital heat and the tone of the muscular fibre (Hence the paralyses from a strong dose, or a long-continued and incautious employment of it). These latter properties will enable it to prove of service as an antagonistic remedy in pure inflammatory diseases. It diminishes the tone of the muscular fibre, by diminishing the proportion and cohesion of coagulable lymph in the blood as I have convinced myself, by drawing blood from persons suffering from the effects of *arsenic*, more especially such as had a too inspissated blood before the use of this metallic acid. But not only does it diminish the vital heat, and the tone of the muscular fibre, the sensibility of the nerves (Thus, in cases of maniacs, with tense fibre, and inspissated blood a small dose of it procures quiet sleep, in its character of an antagonistically-acting substance, where all other remedies fail. Persons poisoned by *arsenic* are more composed about their state, than might be expected. Thus it generally seems to kill more by extinguishing the vital power and sensibility, than by its corrosive and inflammatory power, which is only local and circumscribed. This being borne in mind, the rapid decomposition of the bodies of those poisoned by *arsenic*, like cases of death by mortification, will be readily comprehended). It weakens the absorbent system, a

circumstance whence, perhaps, we may one day derive some curative power (as a similarly or as an antagonistically-acting remedy?), but which must be always a powerful objection to its long continued use. I would direct attention to its peculiar power of increasing the irritability of the fibre, especially of the system of the vital functions. Hence cough, and hence the above-mentioned chronic febrile actions".

"When *arsenic* is used for a length of time, and in pretty large doses, it seldom fails, especially if diaphoretics and a heating diet be used simultaneously, to cause some chronic cutaneous disease (at least desquamation of the skin). This tendency renders it an efficacious remedy in the hands of the Indian physician, in that frightful skin disease, elephantiasis. Would it not also be serviceable in pellagra? If it be truly (as is confidently affirmed) of service in hydrophobia, it must act by virtue of its power to diminish (the influence of the nerves affirmed) of service in hydrophobia, it must act by virtue of its power to diminish (the influence of the nerves on) the attraction of the parts of the muscular fibre and its tone, as also the sensibility of the nerves, therefore antagonistically, it produces acute, continued pains in the joints, as I have seen. I shall not attempt to determine how we may avail ourselves of this property in a curative point of view".

"What influence the arsenic disease, the lead disease, and the mercurial disease may have over each other, and if the one may be destroyed by means of the other, future observations can alone decide".

"Should the accidents produced by a long-continued use of arsenic become threatening (besides the employment of sulphuretted hydrogen in drinks and baths to expirate what still remains of the substance of the metal), the free use of *opium* in the same manner as in the mercurial disease (see above) will be of service".

"I revert again to vegetable substances; and first, I shall mention a plant, which in violence and duration of action, deserves to be placed alongside the mineral poisons; I allude to the *yew (taxus baccata)*. Great circumspection must be employed in the use of its various parts, more particularly of the bark of the tree when in flower; the cutaneous eruptions, with signs of gangrenous decomposition of the fibre, which sometimes occur several weeks after the last dose, the fatal catastrophe that sometimes takes place suddenly, sometimes several weeks after the last dose, with symptoms of mortification, etc., teach us this. It produces, it appears, certain acridity in all the fluids, and inspissations of the lymph; the vessels and fibres are irritated, and yet their functions are more impeded than facilitated. The scanty evacuations, accompanied by tenesmus, the dysuria, the viscid, salt, acrid saliva, the viscid foetid sweat, the cough, the flying acute pains in the limbs after perspiration, the podagra, the inflammatory erysipelas, the pustules on the skin, the itching and redness of the skin, underneath which the glands lie, the artificial jaundice, the horripilation, the continued fever, etc., it produces, are all proofs of this. But the observations are accurate enough to enable us to determine which is the primary, which the secondary action. The direct action seems to continue for a considerable time. A lax, unexcitable state of the fibres and vessels, especially of those belonging to the absorbent system, which seem partly deprived of vital power, appears to be its secondary action. Hence the perspiration, the flow of saliva, the frequent discharge of watery urine, the hemorrhages (a dissolved state of the red parts of

the blood) and after large doses, or too long-continued employment, the dropsy, the obstinate jaundice, the petechiae, the gangrenous decomposition of the fluids. Employed cautiously in gradually-increased doses, it may, as indeed experience has partly shown, be employed with lasting advantage in a similar derangement of the fluids, and in a similar state of the solids; in a word, in similar morbid states to those it is capable of producing. In induration of the liver, jaundice, and glandular swellings, with tense fibre, in chronic catarrh, catarrh of the bladder (in dysentery, dysuria, tumors, with tense fibre?), in amenorrhea with tense fibre (On account of its long-enduring, direct action, it may sometimes be of permanent service as an antagonistically acting remedy in rachitic, in amenorrhea with relaxation, etc. But this does not belong to our subject)".

"The *monkshood (aconitum napellus)* excites formicating, also acute tearing pains in the limbs, in the chest, in the jaws; it is a prime remedy in pains of the limbs of all kinds (?); it will be serviceable in chronic tooth-ache of a rheumatic character in pleurodynia, in face-ache, and in the consequences of the implantation of human teeth. It causes chilling pressure in the stomach, occipital headache-ache, shootings in the kidneys, excessively painful ophthalmia, cutting pains in the tongue; the practitioner will be able to employ these artificial diseases in similar natural diseases. It has a peculiar tendency to produce giddiness, fainting, debility, apoplexy, and transient paralysis, general and partial paralysis, hemiplegia, paralysis of particular limbs, - of the tongue, of the anus, of the bladder, obscuration of vision and temporary blindness, and singing in the ears. It is also just as serviceable in general and partial paralysis of the parts just mentioned, as experience has in a great measure proved; - as a similarly-acting remedy, it has in several cases cured incontinence of urine, paralysis of the tongue, and amaurosis, as also paralysis of the limbs. In curable marasmus, and partial atrophies, as a remedy capable of producing similar morbid symptoms, it will certainly do more than all other known remedies. Successful cases of this kind are on record. Almost as specifically does it produce convulsions, general as well as partial, of the facial muscles, of the muscles of the lips on one side, of the muscles of the throat on one side of the ocular muscles. In all these last affections it will prove useful, as it also cured epilepsies. It causes asthma how, then, can it be wondered at, that it has several times cured different sorts of asthma? It produces itching, formication in the skin, desquamation, reddish eruption, and is hence so useful in bad cutaneous affections and ulcers. Its pretended efficacy in the most obstinate venereal sufferings, was probably only founded on its power over the symptoms of the mercury that had been previously employed in that disease and this conclusions is justified by what we know of its action. It is valuable to know that monkshood, as an exciter of pain, cutaneous affections, swellings, and irritability, - in a word, as a similarly-acting remedy, is powerful in subduing the similar mercurial disease, and is even preferable to opium, as it leaves behind it no debility. Sometimes it causes a sensation about the navel, as if a ball rose up thence, and spread a cold feeling over the upper and back part of the head; this would lead us to use it in similar cases of hysteria. In the secondary action, the primary coldness in the head seems to change into a burning sensation, In its primary action are observed general coldness, slow pulse, retention of urine, mania; in its secondary action, however, an intermitting, small, rapid pulse, general perspiration, flow of urine, diarrhea, involuntary fecal evacuation, sleepy intoxication (Like several other plants that produce a cooling effect in their primary action, it resolves glandular swellings). The mania it causes is a gay humor alternating with

despair. As a similarly-acting remedy, it will subdue manias of that sort. The usual duration of its efficacy is from seven to eight hours, excepting in cases of serious effects from very large hours, excepting in cases of serious effects from very large doses".

"The *black hellebore (helleborus niger)* causes, if used for a long time, severe headaches, (hence, probably, its power in some mental affections, also in chronic headaches) and a fever; hence its power in quartan fever, and hence also, partly, its efficacy in dropsy, the worst kinds of which are always accompanied by remitting fever , and wherein it is so useful, aided by its diuretic power (Who can tell whether this belongs to its primary, or, as I am inclined to think, its secondary action? This power is allied to its property of exciting to activity the blood-vessels of the abdomen, rectum, and uterus). Its power of causing a constrictive, suffocating sensation in the nose, would lead us to prescribe it in similar cases (as I once did in a kind of mental disease). The frequency with which it is confounded with other roots is the reason why we are only in possession of these few true data of its effects".

"The boring, cutting pain that the internal use of the *meadow anemone (anemone pratensis)* causes in weak eyes, led to its successful employment in amaurosis, cataract, and opacity of the cornea. The cutting headache caused by the internal employment of the inflammable crystalline salt obtained by distillation with water, would lead us to employ this plant in a similar case. Most likely it is on this account that it once cured a case of melancholia".

"The *clove gilliflower (geum urbanum),* besides its aromatic qualities, possesses a nausea-exciting power, which always causes a febrile state of body, and hence its service in intermittent fever, when used as an aromatic along with ipecacuanha".

"The principle that constitutes the medicinal power of the kernel of the *cherry (prunus cerasus),* of the *sour cherry (prunus padus),* of the *peach (amygdalus persica),* of the bitter variety of the *almond (amygdalus communis)* and more especially of the leaves of the *cherry-laurel (prunus laurocerasus),* possesses the peculiar property of increasing the vital power and contractility of the muscular fibre in its direct action, as notably as it depresses both in its secondary action. Moderately large doses are followed by anxiety, a peculiar cramp of the stomach, trismus, rigidity of the tongue, opisthotonos, alternately with conic cramps of various kinds and degrees, as its direct action [if it sought to deny the primary action of the principle of bitter almond, which I have represented as producing the phenomena of increased power of contraction in the muscular fibre and exaltation of the vital power, on this ground, that in some cases of monstrous doses, death occurs almost instansteously without any perceptible reaction of the vital power or pain, as great a mistake would be made, as if all pain should be denied to death by the sword, and it should be affirmed that the stroke of the sword did not produce a peculiar condition different from the death that followed it. This pain will be just as intense, although perhaps less than momentary, as the sensation of anxiety and torment will be indescribable, which may and must follow a fatal dose of cherry-laurel water, though its action lasts scarce a minute. This is proved by the case recorded by Madden, of excessive anxiety in the region of the stomach (the probable region of the chief organ of the vital power) of a person killed in a few minutes by a large dose of *cherry-laurel water*. That in this brief space of time, the whole series of phenomena that follow a not fatal dose, can not make their appearance, is

easily understood; yet it is probable that changes and impressions, similar to those of the direct action I have described from nature, do actually take place in the animal organism, in this short time (until a few instants before death, *i.e.,* the few instants that the indirect secondary action lasts). Thus, electrical phenomena may be seen, when they can be gradually passed before the eyes; but in the lightening rapidly flushing before us, we scarce can tell what we see or hear]; the irritability is gradually exhausted [A small lizard *(lacerta agilis),* that had moved about pretty rapidly for a minute in diluted cherry-laurel-water, I placed in concentrated cherry-laurel water. The motions became instantly so excessively rapid, that the eye could scarcely follow them for some seconds; then there occurred one or two slow convulsions, and then total loss of motion: it was dead)], and in the secondary action the contractility of the muscular fibre and the vital power sink in the same degree that they had previously be exalted. There follow cold, relaxation, paralysis, - which also, however, soon pass off (*Cherry-laurel water* has now and then been used as a domestic analeptic, in debility of the stomach and body, that is, as an oppositely-acting palliative, and, as might have been guessed, with bad effect. The result was paralysis and apoplexy)".

"More remarkable, and peculiarly belonging to our subject, is the curative power of its direct action (which consists in a kind of febrile paroxysm) in intermittent fever, especially, if I mistake not, in that kind of intermittent depending on a too great contractility of the muscular fibre, which is incurable by bark alone. Equally efficacious has *black cherry water* proved in the convulsions of children. As a similarly-acting remedy, *cherry-laurel water* will prove efficacious in diseases from too tense fibre, or generally where the contractility of the muscular fibre far exceeds its relaxing power; in hydrophobia, in tetanus, in the spasmodic closure of the biliary excretory ducts and similar tonic spasmodic affections, in some manias, etc. [Tonic (and clonic) spasms without an inflammatory state of the blood, and when the consciousness is little affected, appear to be the peculiar sphere of action of the principle of the bitter almonds, as it, as far as I know, does not elevate the vital temperature even in its direct action, and leaves the sensitive system unaffected], as several observations have shown. In proper inflammatory diseases it also deserves attention where it would, to some extent, operate as a similarly-acting remedy. If the diuretic property observed from the bitter almond principle lies in its indirect secondary action, we may hope much from it in dropsy, with a chronic inflammatory condition of the blood".

"The power of the bark of the *sour cluster-cherry (prunus padus)* over mitten fever lies likewise in the bitter-almond principle to contains, by means of which it comports itself as a similarly-acting remedy".

"Of the *sundew (drosera rotundifolia)* we know nothing certain, except that it excites cough, and hence it has been if use in most catarrhal coughs, as also in the influenza".

"The curative principle in the flowers and other parts of the *elder (sambacus niger),* appears to lie in its primary direct action of exalting the contractive power of the muscular fibres belonging chiefly to the natural and vital functions, and of raising the temperature of blood, whilst, in its indirect secondary action, it brings down the strength of the muscular fibre, lowers the temperature, relaxes the vital activity, and diminishes sensation itself. If this be the case, as I think it is, the good that it does in the true spasm of the finest

extremities of the arteries, in diseases from a chill, catarrhs, erysipelas, is in virtue of its similarly of action. Have not the elder species the power of producing transitory erysipelatous inflammation?"

"Various kinds of *sumach,* considered to be poisonous, *e.g., rhus radicans,* appear to possess a specific tendency to produce erysipalatous inflammation of the skin and cutaneous eruptions. May it not be useful in chronic erysipelas, and the worst kinds of skin diseases? When its action is too violent, it is checked by elder, a similarly-acting remedy?"

"*Camphor* in large doses diminishes the sensibility of the whole nervous system; the influence of the, as it were, benumbed vital spirits (if I may be allowed to use a coarse expression), on the senses and motion is suspended. There occurs congestion in the brain, an obscuration, vertigo, an inability to bring the brain, an obscuration, vertigo, an inability to bring the muscles under the dominion of the will, an incapacity for thought, for sensation, for memory. The contractile power of the muscular fibres, especially of those belonging to the natural and vital functions, seems to sink to actual paralysis; the irritability is depressed in a like degree especially that of the extreme ends of the blood-vessels (The nervous power and its condition seems to have most influence on these, - less on the larger vessels, least of all on the heart), that of the larger arteries less, and still less that of the heart. There occurs coldness of the external parts, small, hard, gradually diminishing pulse, and on account of the different state of the heart from that of the extreme ends of the blood vessels, anxiety, and cold sweat. The above condition of the fibre causes an immobility of the muscles, *e.g.,* of the jaws, of the anus, of the neck, that resembles a tonic spasm. There ensue deep slow breathing, fainting (A proof, according to Carminati, that *Camphor*, far from extinguishing the irritability, only suspends it so long as the muscles are in connexion with the benumbed state of the nerves – is, that when all sensations is extinguished by means of camphor, the heart, if cut out, continues to beat all the more strongly for hours afterwards). During the transition to the secondary action, there occur convulsions, madness, vomiting, trembling. In the indirect secondary action itself, the awaken of the sensibility and if I may be allowed the expression, the mobility of the previously benumbed nervous spirit first commence; the almost extinguished mobility of the extremities of the arteries is restored, the heart triumphs over the previous resistance. The previous slow pulsations increase in velocity and in fullness, the play of the circulating system attains, or in some cases (from larger doses of *camphor*, from plethora, etc.) surpasses, its former state, - the pulse becomes more rapid, and more full. The more motionless the blood vessels were previously, the more active of they now become; the temperature of the whole body becomes increased, with redness, and uniform, sometimes profuse, perspiration. The whole process is ended in six, eight, ten, twelve, or at most twenty-four hours. Of all the muscular fibres, the mobility of the intestinal canal returns latest. In every case where the contractile power of the muscular fibres, the mobility of the intestinal canal returns latest. In every case where the contractile power of the muscular fibres greatly preponderates over their power of relaxation, camphor, as an antagonistically-acting remedy, procures rapid but only palliative relief in some manias, in local and general inflammations, of a pure, of a rheumatic, and of an erysipelatous character, and in diseases arising from a chill".

"As in pure malignant typhus, the system of the muscular fibre, the sensitive system, and the depressed vital power, presents something analogous to the direct primary action of *camphor*, it operates as a similarly-acting remedy, that is, permanently and beneficially, The doses must, however, be sufficiently large to produce the appearance of a still greater insensibility and depression, but given seldom, only about every thirty-six or forty-eight hours".

"If *camphor* actually removes the strangury caused by *cantharides*, it does this as a similarly-acting remedy, for it also causes strangury. The bad effects of drastic purgatives it removes, chiefly as a suspender of sensation, and a relaxed of the fibre (consequently an antagonistic, palliative, but there, admirable remedy). In the bad secondary effects of squall, when they are chronic - a too easily excitable action of the contractile and relaxing power of the muscular fibre - it acts only as a palliative, and less efficaciously, unless the doses be frequently repeated. The same may be said with regard to its effects in the chronic symptoms caused by the abuse of *mercury*. As a similarly-acting remedy, it is eminently serviceable in the long-continued rigour of degenerated (comatose) intermittent fevers, as an adjunct to bark. Epilepsy and convulsions dependent in relaxed fibre deprived of its irritability, are rapidly cured by the similar action of camphor. It is an approved antidote to large doses of opium, in which it is chiefly an antagonistic palliative, but efficacious in consequence of the symptoms being but transitory. In like manner, *opium* is, as I have ascertained, an excellent antidote to large doses of *camphor*. The former raises the sunken vital power and diminished vital temperature caused by the latter antagonistically, but in this case effectually. A curious phenomenon is the action of coffee in relation to the direct action of large doses of camphor; it makes the stomach, whose irritability was suspended spasmodically mobile; there occur convulsions, vomiting, or when given in clusters, rapid evacuation; but neither does the vital power become raised, nor do the nerves become relieved from their stupefied state, they rather become more stupefied, as I think I have observed. As the most striking effect of *camphor* on the nerves consists in this, that all the passions are lulled, and a perfect indifference to external things, even of the most interesting character, occurs, as I have ascertained, it will according be of a service as a similarly-acting remedy in manias, whose chief symptom is apathy, with slow, suppressed pulse, and contracted pupil, -also, according to Auenbrugger, retracted testicles. It is by no means advisable to use it in manias of every description. Used internally, camphor removes acute general and local inflammations, and also such as is chronic, in few hours; but in the former case, the doses must be very often repeated to admit of anything efficacious being performed, *i.e.*, always a new dose before the secondary action comes on. For in its secondary action, *camphor* does but the more strengthen the tendency to renewed inflammation, makes it chronic, and predisposes the organism chiefly to catarrhal diseases, and the bad effects of a chill. Used externally for a length of time, it can do more good, and its bad effects may be easily remedied in another manner".

"The patrons of new medicines generally commit the error of carefully but injudiciously concealing the disagreeable effects of the medicines they take under their protection (Thus we often read that this or that powerful medicine has cured so many hundred cases of the worst diseases, without causing the slightest bad effects. If this last be correct, we may certainly infer the perfect inefficacy of the drug. The more serious the symptoms it causes,

the more important are it for the practitioner). Were it not for this suppression of the truth, we might, for instance, from the morbific effects the bark of the *horse-chesnut (aesculus hippocastanum)* is able to produce, form a just estimate of its medicinal powers, and determine if, for instance, it is suitable for pure intermittent fever, or some of its varieties; and if so, which. The sole phenomena we know belonging to it is, that it produces a constrictive feeling in the chest. It will accordingly be found useful in (periodical) spasmodic asthma".

"The symptoms produced on man by the *phytolacca decandra* deserve to be particularly described. It is certainly a very medicinal plant. In animals it causes cough, trembling, convulsions".

"As the bark of the *elm (ulmus campestris),* when exhibited internally, produces at the commencement [In order to draw a favorable induction from the aggravating action of a drug in a disease, this aggravation must occur at the commencement of its use, that is in its direct action in such cases only can it be considered a similarly acting efficacious remedy. The morbid aggravation occurring so often subsequently (in the indirect secondary action) proves the contrary in ill-chosen remedies] an increase of cutaneous eruptions, it is more than probable that it has a tendency to produce such affections of itself, consequently, that it will be serviceable in them, which is amply proved by experience".

"The juice of *hemp leaves (cannabis sativa)* is, it would seem, a narcotic, similar in action to opium. This is only in appearance, however, and owing to the imperfect accounts we have of its pathogenetic action. I am much mistaken if it do not possess differences indicative of peculiar medicinal powers, if we but knew it sufficiently. It produces dimness of vision; and in the madness caused by it there occur many phenomena, generally of an agreeable character".

"It appears as if *saffron (crocus sativus),* in its direct action, brought down the circulation and vital heat. Slow pulse, pale face, vertigo, exhaustion, have been observed. In this stage most probably occur the melancholy and headache that have been observed from its action, and in the second stage (the indirect secondary action), occur the senseless, extravagant gaiety, the stupefaction of the senses, the increased action in the arteries and heart, and lastly, the hemorrhage which have been observed from its use. For this reason it may be useful in restoring flows of blood that have been checked, as a similarly-acting remedy, as its power of increasing the circulation occurs first in the secondary action; consequently, the opposite must take place in its direct action. It has been found useful as a similarly-acting remedy in vertigo and headache, with slow pulse. In some cases of melancholia with slow pulse, and in amenorrhea, it appears also to be of service as a similarly-acting remedy. It has (in its direct action) produced death by apoplexy, and is said to have proved efficacious in similar affections (probably in relaxed organisms). The phenomena of its secondary action point to much increased irritability of the fibre, hence probably the cause of its readily producing hysteria".

"The *darnel (lolium temulentum)* is such a powerful plant, that he who knows its pathogenetic action must congratulate the age when, for the benefit of humanity, its

application shall be known. The chief phenomena of the direct action of the seeds acre cramps, apparently of a tonic character (a kind of immobility), with relaxation of the fibre and suspension of the vital spirits, great anxiety, exhaustion, coldness, contraction of the stomach, dyspnea, difficult deglutition, rigidity of the tongue, pressive headache and vertigo (both continue longer than is known from any other drug, in the greatest degree, for several days), noises in the ears, sleeplessness, insensibility, or weakness of the external senses, red face, staring eyes, sparks before the eyes. In the transition to the secondary action, the cramps become clonic, there occur stammering, trembling, vomiting, diuresis, and (cold) perspiration (cutaneous eruptions, ulcers on the skin?) yawning (another kind of cramp), weak sight, long sleep. In practice, cases of obstinate vertigo and headache present themselves, which we are inclined to avoid treating, from their incurability. The darnel appears to be made expressly for the worst of such case, probably also for imbecility, the opprobrium of medicine. In deafness and amaurosis something may be hoped from its use".

"*Squill (scilla maritina)* appears to possess an acrid principle that remains long on the body; the mode of operation of which, from want of accurate observation, cannot be very well separated into primary and secondary action. This acrid principle possesses a tendency to diminish for a long period the capacity of the blood for caloric, and hence to establish in the organism a disposition to chronic inflammation. Whether this power can be applied to useful purposes, instead of being, as hitherto, a stumbling-block to the use of the drug itself, I am unable, on account of the obscurity of the subject, to determine. As, however, this power must certainly have its limits, at least in the commencement, it has only an acute inflammatory action, and afterwards, especially after long-continued use, leaves behind it the slow chronic inflammatory action; so it seems to me to be rather indicated in pure inflammations with tense fibre, when its use is otherwise required, than in a cold or hectic inflammatory condition of the fluids and mobility of the fibre. The incomparable aid derived from squill in inflammation of the lungs, and the extraordinary injury inflicted by its *continued* employment in chronic purulent consumption of the lungs, as also in pituitous consumption, prove this satisfactorily; there is no question here of a palliative relief. This acrid principle puts the mucous glands in a condition to secrete a thin, instead of a viscid mucus, as is the case in every moderately inflammatory diathesis. Squill causes a great degree of strangury, shewing thereby that it must be very useful in restoring the secretion in the suppression of the urine accompanying several kinds of dropsy, as daily experience confirms. Rapid, acute dropsical swellings appear to be its chief, because it can of itself cause cough".

"That most incomparable remedy, white *hellebore (veratrum album),* produces the most poisonous effects, which should inspire the physician who aspires to perfection with caution, and the hope of curing some of the most troublesome diseases that have hitherto usually been beyond medical aid. It produces in its direct action a kind of mania, amounting from larger doses to hopelessness and despair; small doses make indifferent things appear repulsive to the imagination, although they are not so in reality. It causes in its direct action, *a)* heat of the whole body; *b)* burning in different external pats, *e.g.,* the shoulder-blades, the face, the head; *c)* Inflammation and swelling of the skin of the face, sometimes (from larger doses) of the whole body; *d)* cutaneous eruptions, desquamation of the skin; *e)* a formicating sensation in the hands and fingers, tonic cramps; *f)* constriction of the gullet, of

the larynx, sense of suffocation; *g)* rigidity of the tongue, tough mucus in the mouth; *h)* constriction of the chest; *i)* pleuritic symptoms; *h)* cramp in the calve; *l)* an anxious (gnawing?) sensation in the stomach, nausea; *m)* gripes, and cutting pains here and there in the bowels; *n)* great general anxiety; *o)* vertigo; *p)* headache (confusion of the head); *q)* violent thirst. On passing into the indirect secondary action, the tonic cramps resolve themselves into clonic cramps; there occur, *r)* trembling; *s)* stammering; *t)* convulsions of the eyes; *u)* hiccough; *v)* sneezing (from the internal use); *w)* vomiting (when at its height, black, bloody vomiting); *x)* painful, scanty evacuations, with tenesmus; *y)* local, or (from large doses) general convulsions; *z)* cold (from large doses, bloody) sweat; *aa)* watery dieresis; *bb)* ptyalism; *cc)* expectoration; *dd)* general coldness; *ee)* marked weakness; *ff)* fainting; *gg)* long profound sleep. - Some of the symptoms of its direct action, *l) m) n) p) q),* would lead us to use it in dysenteric fever, if not in dysentery. The mania it causes, together with some symptoms of its direct action, *e) f) g) h) n) q),* would lead us to employ it in hydrophobia, with hopes of a good result. A dog to which it was given had true rabies, lasting eight minutes. The ancients speak of it with approbation in hydrophobia. (In tetanus?) in spasmodic constriction of the gullet, and in spasmodic asthma, it will be found specific on account of *f)* and *h).* It will prove of permanent advantage in chronic cutaneous diseases, on account of *c)* and *d)* as experience has already shown with regard to herpes. In so-called nervous diseases, when they are dependent on tense fibre or inflammatory symptoms, *a) q)* and the symptoms in other respects resemble the veratrum disease, it will be of benefit; so also in manias of like character. - The landlord of a country inn, a man of firm fibre, robust make, red blooming countenance, and somewhat prominent eyes, had almost every morning, soon after waking, an anxious feeling in the stomachic region, which in the course of a few hours involved in the chest, producing constriction there, sometimes amounting to complete loss of breath; in the course of a few hours the affection attacked the region of the larynx, and suffocation became imminent (swallowing solids or fluids being impossible); and as the sun declined it left these parts, and became confined to the head, with timorous, despairing, hopeless suicidal thoughts, until about ten o'clock, when he fell asleep, and all the morbid symptoms disappeared. The mania resembling that peculiar to veratrum, the firm fibre of the patient, and the symptoms *f) g) h) l) n),* induced me to prescribe three grains of its every morning, which he continued for four weeks, with the gradual cessation of all his sufferings; his malady had lasted four years or more. - A woman, thirty-five years of age, after having had many epileptic attacks during her pregnancies, was affected a few days after her last delivery, with furious delirium and general convulsions of the limbs. She had been treated for ten days with emetics and purgatives, without effect. At midnight every night she was attacked by fever, with great restlessness, during which she tore all the clothes off her body, especially what she had about here neck. Cinchona bark always made the fever a few hours later, and increased the thirst and anxiety; the expressed juice of stramonium, used according to Bergius' method, soon quelled the convulsions, and produced some rational hours, in which it was ascertained that her worst symptom (except the fever) was the suffocating feeling in the throat and chest, besides pain in all her limbs. More, however, it could not do; on the contrary, its continued use seemed rather to increase the last mentioned serious symptoms; the face was swollen, the anxiety infinite, the fever greater. Emetics did no good opium caused sleeplessness, increased the restlessness; the urine was dark-brown, the bowels much constipated. Blood-letting, which was evidently not adapted to this case, was,

moreover, contra-indicated by the excessive weakness. The deliria returned, not with standing the extract of stramonium, with increased convulsions and swelling of the feet. I gave her in the forenoon half a grain of veratrum powder, and a similar dose in the afternoon at two o'clock. Deliria of another kind made their appearance, along with viscid mucus in the mouth, but no fever returned, the patient slept, and in the morning passed white cloudy urine. She was well, quiet and rational, except that the great weakness continued. The suffocating sensation in the throat was gone, the swelling of the face fell, as also that of the feet, but the following evening, without her having taken any medicine, there occurred a constrictive sensation in the chest. She therefore got another half grain of veratrum the following afternoon; this was followed by scarcely perceptible delirium, tranquil sleep, in the morning copious discharge of urine and a few small evacuations. For two more days she got half a grain of veratrum in the afternoon. All her symptoms disappeared, the fever vanished, and the weakness yielded to a good regimen".

"I shall on a subsequent occasion record a case of spasmodic colic still more rapidly cured by it. As a producer of mania and spasms it has shown itself useful in cases in persons possessed. In hysterical and hypochondriacal attacks, dependent on tense fibre, it will be useful, as it has been practically proved. Inflammation of the lungs will find in it a powerful remedy. The duration of its action is short; limited to about five, at most eight or ten hours, inclusive of the secondary action; except in the case or ten hours, inclusive of the secondary action except in the case of serious effects from large doses".

"*Sabadilla* seed causes confusion of the intellect and convulsions, which it can also cure; the peculiarities of its action, however, are not yet known. It also causes a creeping sensation through all the limbs, as I have experienced, and is said to produce pain in the stomach and nausea".

"The *agaric (agaricus muscarius)* produces, as far as I can ascertain, a furious and drunken mania (combined with revengeful, bold resolves, disposition to make verses, to prophesy, etc.), exaltation of the strength, trembling and convulsions in its primary direct action; and weariness, sleep, in its secondary action. It has therefore been employed with benefit in epilepsy (caused by fright), combined with trembling. It will remove mental affections and possession, similar to those it causes. Its direct action lasts from twelve to sixteen hours".

"The *nutmeg (myristica aromatica)* diminishes the irritability of the whole body, but especially that of the primae viae, for a considerable time (Does it not increase the contractile power of the muscular fibre, especially of the primae viae, and diminish its capability of relaxing?). In large doses it causes an absolute insensibility of the nervous system, obtuseness, immobility, loss of reason, for its direct action; headache and sleep for its secondary action. It possesses heating properties. May it not be useful in imbecility, combined with laxness and irritability of the primae viae? - against the first as a similarly, against the second as an antagonistically-acting remedy? It is said to have done good in paralysis of the gullet, probably as a similarly-acting remedy".

"*Rhubarb* is useful in diarrheas without fecal evacuations, even in the smallest doses, more in consequence of its tendency to promote the action of the bowels, than on account of its astringent power".

"The *topical pain-producing applications,* as catharides, mustard plasters, grated horse-radish, spurge-laurel bark, crushed ranunculus acris, the moxa, allay pain often permanently, by producing artificially pain of another kind".

Principle of similitude[4]

Continuing with the study of the principle of similitude, this chapter reviews the masterpiece of homeopathic doctrine, namely the *Organon of medicine*,[5] where Hahnemann expounded the results of his studies on the *law of similarity* and *experimentation on healthy subjects*.

Hahnemann begins discussing the notions of health and disease, and in this context he asserts that the healing properties of medicines are due to their ability to "alter the state of human health":

> "Now, as diseases are nothing more than alterations in the state of health of the healthy individual which express themselves by morbid signs, and the cure is also only possible by a change to the healthy condition of the state of health of the diseased individual, it is very evident that medicines could never cure disease if they did not possess the power of altering man's state of health which depends on sensations and functions; indeed, that their curative power must be owing solely to this power they possess of altering man's state of health". (*Organon,* § 19)

This possibility to alter the state of health is hidden within the intimate essence of medicines to become evident when tested in human beings. For this reason that Hahnemann emphasizes the importance of **experimenting on healthy subjects:** when a substance alters the state of health of an individual it awakens symptoms, and in this way it is demonstrated the curative *inherent power* to medicines.

> "This spirit-like power to alter man's state of health (and hence to cure diseases) which lies hidden in the inner nature of medicines can in itself never be discovered by us by a mere effort of reason; it is only by experience of the phenomena it displays when acting on the state of health of man that we can become clearly cognizant of it". (*Organon,* § 20)
>
> "Now, as it is undeniable that the curative principle in medicines is not in itself perceptible, and as in pure experiments with medicines conducted by the most accurate observers, nothing can be observed that can constitute them medicines or remedies except that power of causing distinct alterations in the state of health of the human body, and particularly in that of the healthy individual, and of exciting in him various definite morbid symptoms; so it follows that when medicines act as remedies, they can only bring their curative property into play by means of this their power of altering man's state of health by the production of peculiar symptoms; and that, therefore, we have only to rely on the morbid phenomena which the medicines produce in the healthy body as the sole possible revelation of their in-dwelling curative power, in order to learn what disease-producing power, and at the same time what disease-curing power, each individual medicine possesses". (*Organon,* § 21)

[4] Teixeira MZ. Semelhante cura semelhante: o princípio de cura homeopático fundamentado pela racionalidade médica e científica [Similar cures similar: the homeopathic cure principle based by the medical and scientific rationality]. São Paulo: Editorial Petrus, 1998. Available at: https://www.homeozulian.med.br/homeozulian_visualizarlivroautor.asp?id=3

[5] Hahnemann S. Organon of medicine. 6th Edn. (Translated by William Boericke). New Delhi: B Jain Publishers, 1991.

Grounded on this intrinsic property of medicines to alter the state of health and thus produce symptoms, Hahnemann makes a comparative analysis of the **homeopathic** and **enantiopathic** methods, this is, the therapeutic methods respectively based on *similar* and *contrary symptoms*. In a note to *Organon* paragraph 22, Hahnemann mentions a further, **allopathic method**, where the symptoms elicited by medicines are neither similar nor contrary to the symptoms of disease, but *fully heterogeneous*:

> "But as nothing is to be observed in diseases that must be removed in order to change them into health besides the totality of their signs and symptoms, and likewise medicines can show nothing curative besides their tendency to produce morbid symptoms in healthy persons and to remove them in diseased persons; it follows, on the one hand, that medicines only become remedies and capable of annihilating disease, because the medicinal substance, by exciting certain effects and symptoms, that is to say, by producing a certain artificial morbid state, removes and abrogates the symptoms already present, to wit, the natural morbid state we wish to cure. On the other hand, it follows that, for the totality of the symptoms of the disease to be cured, a medicine must be sought which (according as experience shall prove whether the morbid symptoms are most readily, certainly, and permanently removed and changed into health by similar or opposite medicinal symptoms1) have the greatest tendency to produce similar or opposite symptoms". (*Organon,* § 22)

Hahnemann describes his experience with the **enantiopathic method** to conclude that it is unable to remove and annihilate the symptoms of disease; conversely, "after apparent alleviation, the symptoms become manifestly aggravated":

> "All pure experience, however, and all accurate research convince us that persistent symptoms of disease are far from being removed and annihilated by opposite symptoms of medicines (as in the antipathic, enantiopathic or palliative method), that, on the contrary, after transient, apparent alleviation, they break forth again, only with increased intensity, and become manifestly aggravated". (*Organon,* § 23)

On the other hand, with the **homeopathic method** - i.e., by choosing a remedy that in healthy individuals exhibited a *similar totality of symptoms* to the one found in the patient - we are able to change disease into health:

> "There remains, therefore, no other mode of employing medicines in diseases that promises to be of service besides the homeopathic, by means of which we seek, for the totality of the symptoms of the case of disease, a medicine which among all medicines (whose pathogenetic effects are known from having been tested in healthy individuals) has the power and the tendency to produce an artificial morbid state most similar to that of the case of disease in question". (*Organon,* § 24)
>
> "Now, however, in all careful trials, pure experience, the sole and infallible oracle of the healing art, teaches us that actually that medicine which, in its action on the healthy human body, has demonstrated its power of producing the greatest number of symptoms similar to those observable in the case of disease under treatment, does also, in doses of suitable potency and attenuation, rapidly, radically and permanently remove the totality of the symptoms of this morbid state, that is to say (§ 6-16), the whole disease present, and change it into health; and that all medicines cure, without exception, those diseases whose symptoms most nearly resemble their own, and leave none of them uncured". (*Organon,* § 25)

After rising the principle of therapeutic similitude to the level of a *natural law* applying in both physical illnesses and moral affections, Hahnemann seeks to explain its mechanism of

operation according to the teachings of Hippocrates: two similar affections, when they belong to different species, cannot occupy one and the same body; thus the stronger one remains, while the weaker one disappears.

> "This depends on the following homeopathic law of nature which was sometimes, indeed, vaguely surmised but not hitherto fully recognized, and to which is due every real cure that has ever taken place: A weaker dynamic affection is permanently extinguished in the living organism by a stronger one, if the latter (whilst differing in kind) is very similar to the former in its manifestations". (*Organon,* § 26)

The same effect can be obtained when it is introduced in the body an artificial and transitory medicinal disease, very similar to and a little stronger than the natural disease, which it thus overcome and annihilated:

> "The curative power of medicines, therefore, depends on their symptoms, similar to the disease but superior to it in strength (§ 12-26), so that each individual case of disease is most surely, radically, rapidly and permanently annihilated and removed only by a medicine capable of producing (in the human system) in the most similar and complete manner the totality of its symptoms, which at the same time are stronger than the disease". (*Organon,* § 27)

Whereas natural morbid influences are only able to affect organisms exhibiting a given susceptibility, the artificial stimuli, i.e., medicines are able to act "all times, under all circumstances, on every living human being, and produces in him its peculiar symptoms", which can be clearly observed when remedies are prescribed in large doses (intoxication). By applying Hahnemann's notions to the modern drugs used by conventional medicine it is also possible to observe their peculiar effects when administered in large doses:

> "But it is quite otherwise with the artificial morbific agents which we term medicines. Every real medicine, namely, acts at all times, under all circumstances, on every living human being, and produces in him its peculiar symptoms (distinctly perceptible, if the dose be large enough), so that evidently every living human organism is liable to be affected, and, as it were, inoculated with the medicinal disease at all times, and absolutely (unconditionally), which, as before said, is by no means the case with the natural diseases". (*Organon,* § 32)

Emphasizing the need for the artificial disease to be **similar** to the original disorder, Hahnemann elaborates on the simultaneous occurrence of **dissimilar** diseases in one and the same organism, to conclude that in this case no alteration appears leading to cure as it happens in the instance of similar diseases:

> "The greater strength of the artificial diseases producible by medicines is, however, not the sole cause of their power to cure natural disease. In order that they may effect a cure, it is before all things requisite that they should be capable of producing in the human body an artificial disease as similar as possible to the disease to be cured, which, with somewhat increased power, transforms to a very similar morbid state the instinctive life principle, which in itself is incapable of any reflection or act of memory. It not only obscures, but extinguishes and thereby annihilates the derangement caused by the natural disease. This is so true, that no previously existing disease can be cured, even by Nature herself, by the accession of a new dissimilar disease, be it ever so strong, and just as little can it be cured by medical treatment with drugs which are incapable of producing a similar morbid condition in the healthy body". (*Organon,* § 34)

As well as other authors had also done, Hahnemann mentions several examples of *coexistence between dissimilar diseases.* This allows him to distinguish a series of patterns of interaction. In the first one, both diseases have the same strength or *the oldest is the strongest;* in the second, *the newer dissimilar is the strongest;* and the third possible situation happens when *the newer dissimilar diseases is incorporated into the older* one and both together give rise to a *complex* disease:

> "I. If the two dissimilar diseases meeting together in the human being be of equal strength, or still more if the older one be the stronger, the new disease will be repelled by the old one from the body and not allowed to affect it. A patient suffering from a severe chronic disease will not be infected by a moderate autumnal dysentery or other epidemic disease. The plague of the Levant, according to *Larry,* does not break out where scurvy is prevalent, and persons suffering from eczema are not infected by it. Rachitis, *Jenner* alleges, prevents vaccination from taking effect. Those suffering from pulmonary consumption are not liable to be attacked by epidemic fevers of a not very violent character, according to *Von Hildenbrand"*. (*Organon,* § 36)
>
> "II. Or the new dissimilar disease is the stronger. In this case the disease under which the patient originally labored, being the weaker, will be kept back and suspended by the accession of the stronger one, until the latter shall have run its course or been cured, and then the old one reappears uncured. Two children affected with a kind of epilepsy remained free from epileptic attacks after infection with ringworm (tinea) but as soon as the eruption on the head was gone the epilepsy returned just as before, as *Tulpius* observed. The itch, as *Schöpf* saw, disappeared on the occurrence of the scurvy, but after the cure of the latter it again broke out. So, also the pulmonary phthisis remained stationary when the patient was attacked by a violent typhus, but went on again after the latter had run its course. If mania occur in a consumptive patient, the phthisis with all its symptoms is removed by the former; but if that go off, the phthisis returns immediately and proves fatal. When measles and smallpox are prevalent at the same time, and both attack the same child, the measles that had already broken out is generally checked by the smallpox that came somewhat later; nor does the measles resume its course until after the cure of the smallpox; but it not infrequently happens that the inoculated smallpox is suspended for four days by the supervention of the measles, as observed by *Manget,* after the desquamation of which the smallpox completes its course. Even when the inoculation of the smallpox had taken effect for six days, and the measles then broke out, the inflammation of the inoculation remained stationary and the smallpox did not ensue until the measles had completed its regular course of seven days.6 In an epidemic of measles, that disease attacked many individuals on the fourth or fifth day after the inoculation of smallpox and prevented the development of the smallpox until it had completed its own course, whereupon the smallpox appeared and proceeded regularly to its termination. The true, smooth, erysipelatous-looking scarlatina of Sydenham, with sore throat, was checked on the fourth day by the eruption of cow-pox, which ran its regular course, and not till it was ended did the scarlatina again establish itself; but on another occasion, as both diseases seem to be of equal strength, the cow-pox was suspended on the eighth day by the supervention of the true, smooth scarlatina of Sydenham, and the red areola of the former disappeared until the scarlatina was gone, wherein the cow-pox immediately resumed its course, and went on its regular termination. The measles suspended the cow-pox; on the eighth day, when the cow-pox had nearly attained its climax, the measles broke out; the cow-pox now remained stationary, and did not resume and complete its course until the desquamation of the measles, had taken place, so that on the sixteenth day it presented the appearance it otherwise would have shown on

> the tenth day, as *Kortum* observed. Even after the measles had broken out the cow-pox inoculation took effect, but did not run its course until these measles had disappeared, as *Kortum* likewise witnessed. I myself saw the mumps (angina parotidea) immediately disappear when the cow-pox inoculation had taken effect and had nearly attained its height; it was not until the complete termination of the cow-pox and the disappearance of its red areola that this febrile tumefaction of the parotid and submaxillary glands, that is caused by a peculiar miasm, reappeared and ran its regular course of seven days. And thus it is with all dissimilar disease; the stronger suspends the weaker (when they do not complicate one another, which is seldom the case with acute disease), but they never cure one another". (*Organon,* § 38)
>
> "III. Or the new disease, after having long acted on the organism, at length joins the old one that is dissimilar to it, and forms with it a complex disease, so that each of them occupies a particular locality in the organism, namely, the organs peculiarly adapted for it, and, as it were, only the place specially belonging to it, while it leaves the rest to the other disease that is dissimilar to it. Thus a syphilitic patient may become psoric, and vice versa. As two disease dissimilar to each other, they cannot remove, cannot cure one another. At first the venereal symptoms are kept in abeyance and suspended when the psoric eruption begins to appear; in course of time, however (as the syphilis is at least as strong as the psora), the two join together, that is, each involves those parts of the organism only which are most adapted for it, and the patient is thereby rendered more diseased and more difficult to cure. When two dissimilar acute infectious diseases meet, as, for example, smallpox and measles, the one usually suspends the other, as has been before observed; yet there have also been severe epidemics of this kind, where, in rare cases, two dissimilar acute diseases occurred simultaneously in one and the same body, and for a short time combined, as it were, with each other. During an epidemic, in which smallpox and measles were prevalent at the same time, among three hundred cases (in which these diseases avoided or suspended one another, and measles attacked patients twenty days after the smallpox broke out, the smallpox, however, from seventeen to eighteen days after the appearance of the measles, so that the first disease had previously completed its regular course) there was yet one single case in which *P. Russell* met with both these dissimilar diseases in one person at the same time. *Rainey* witnessed the simultaneous occurrence of smallpox and measles in two girls. *J. Maurice,* in his whole practice, only observed two such cases. Similar cases are to be found in *Ettmuller's* works, and in the writings of a few others. *Zencker* saw cow-pox run its regular course along with measles and along with púrpura. The cow-pox went on its course undisturbed during a mercurial treatment for syphilis, as *Jenner* saw". (*Organon,* § 40)

According to Boyd,[6] the idea to use fever as a therapeutic means was probably grounded on the age-old notion asserting that *dissimilar diseases cannot inhabit simultaneously one and the same body.* In this way it was sought to replace an older chronic disease with a new and acute one:

> "The idea of using fever for therapeutic purposes was suggested by many researchers not long before Hahnemann. *Boerhaave* stated that he would be a great doctor if he could provoke fever as easily as he treated it. *Van Swieten* expressed similar ideas. *Bordeu* explicitly mentioned the treatment of fever by fever, 'the doctor must, when the strength of the patient, the degree and nature of the disease allow for, transform a chronic disease into an acute one, an older one into a recent one, a particular one into a general one […] the

[6] Boyd JL. A study of the simile in medicine. *Selecta Hom.* 1994; 2(1): 5-54.

> doctor must heal the patients by creating and triggering a crisis (in chronic diseases) either by provoking the rise of fever, or by other manifestations appearing in its place'. He also mentioned cases of cure through fever. These quotations show that the 'defensive' nature of fever was not discovered by Hahnemann, and that *Bordeu,* so to speak, had (already) reintroduced the Hippocratic simile. The reader must also notice that the idea to transform chronic conditions into acute diseases was also prefigured in these quotations. It is safe to assume that through medical literature, or by his own experience, Hahnemann was led to inquire whether drugs able to awaken some phenomena could or not be useful in the treatment of similar states […]". (*A study of the simile in medicine,* p. 37)

A scientific research demonstrated this alternation between dissimilar diseases in cases of depression, confirming the clinical observation stating that psychiatric patients hardly exhibit physical disorders, due to the fact that mental disease is deeply rooted in the organism, and for this reason it is so difficult to treat. In this way, i.e., since it is stronger than the majority of the remainder diseases, it does not allow for them to establish, or if they do, it is only temporarily. The study below evaluated the beneficial effects of inflammatory conditions (fever) on mental depression.

> "Bauer J, Hohagen F, Gimmel E, Bruns F, Lis S, Krieger S et al. Induction of cytokine synthesis and fever suppresses REM sleep and improves mood in patients with major depression. *Biol Psychiatry.* 1995; 38(9): 611-21.
>
> Abstract: Beneficial effects of inflammatory events on certain psychiatric disorders, including depression, were reported sporadically by ancient Greek physicians, but have been described also in our times by a few psychiatrists during the past decades. During febrile inflammatory events, mediators of the immune system such as interleukin-1 can be detected in the brain and may act on their respective receptors which have also been demonstrated in the brain. Since cytokines such as interleukin-1 have been shown in animal studies to exert sedative behavioral effects, to be somnogenic, and to induce slow-wave sleep (SWS), we performed a pilot study to evaluate scientifically the anecdotically reported beneficial effects of inflammatory states on depressive disorders. Mood and sleep parameters were monitored in seven drug-free, severely depressed patients before, during, and after the administration of a single dose of endotoxin. All patients responded with a short pulse of increased synthesis of the cytokines tumor necrosis factor, interleukin-1, and interleukin-6 and elevated body temperature for several hours. During the night following endotoxin administration, rapid eye movement (REM) sleep was significantly suppressed, while changes in slow wave sleep were not significant. During the next day, all patients were in a significantly improved mood; however a rebound of REM sleep was observed in the second night after endotoxin administration and mood worsened again during the next days, indicating an only transient beneficial effect of the treatment".

In therapeutic terms, the **allopathic method**[7] (*alloion = different*) is the one corresponding to the coexistence of different, i.e., dissimilar stimuli, which, according to Hahnemann, results in nefarious consequences when employed for a long time. It is worth to remind that the term "allopathic" as used by Hahnemann does not correspond to the modern and more general use of this term. Present-day allopathy employs the Hahnemannian allopathic and enantiopathic methods. A modern example of Hahnemann's allopathy, seeking to *oppose*

[7] The term *allopathy* was minted by Hahnemann to name the therapeutic method that employed medicines with a different (neither similar nor contrary), derivative, substitutive, *dissimilar* action (Ferreira, ABH. Novo Dicionário da Língua Portuguesa. 2ª ed. São Paulo: Editora Nova Fronteira, 1986).

different, i.e., dissimilar stimuli, is the use of antibiotics to control infections, where the aim is to eradicate the alleged infectious agent without acting directly on the symptoms of the manifest disease:

> "Much more frequent than the natural diseases associating with and complicating one another in the same body are the morbid complications resulting from the art of the ordinary practitioner, which the inappropriate medical treatment (the allopathic method) is apt to produce by the long-continued employment of unsuitable drugs. To the natural disease, which it is proposed to cure, there are then added, by the constant repetition of the unsuitable medical agent, the new, often very tedious, morbid conditions corresponding to the nature of this agent; these gradually coalesce with and complicate the chronic malady which is dissimilar to them (which they were unable to cure by similarity of action, that is, homeopathically), adding to the old disease a new, dissimilar, artificial malady of a chronic nature, and thus give the patient a double in place of a single disease, that is to say, render him much worse and more difficult to cure, often quite incurable. Many of the cases for which advice is asked in medical journals, as also the records of other cases in medical writings, attest the truth of this. Of a similar character are the frequent cases in which the venereal chancrous disease, complicated especially with psora or with the venereal chancrous disease, complicated especially with psora or with dyscrasia of condylomatous gonorrhoea, is not cured by long-continued or frequently repeated treatment with large doses of unsuitable mercurial preparations, but assumes its place in the organism beside the chronic mercurial affection1 that has been in the meantime gradually developed, and thus along with it often forms a hideous monster of complicated disease (under the general name of masked venereal disease), which then, when not quite incurable, can only be transformed into health with the greatest difficulty". (*Organon,* § 41)

Hahnemann also discusses the so-called **isopathic method of treatment**, namely the one that seeks to heal disease by employing the very same contagious principle that has caused it *(per idem),* represented by the Latin expression "*aequalia aequalibus*".

> "A third mode of employing medicines in diseases has been attempted to be created by means of Isopathy, as it is called - that is to say, a method of curing a given disease by the same contagious principle that produces it. But even granting this could be done, yet, after all, seeing that the virus is given to the patient highly potentized, and consequently, in an altered condition, the cure is effected only by opposing a simillimum to a simillimum. To attempt to cure by means of the very same morbific potency (per Idem) contradicts all normal human understanding and hence all experience. Those who first brought Isopathy to notice, probably thought of the benefit which mankind received from cowpox vaccination by which the vaccinated individual is protected against future cowpox infection and as it were cured in advance. But both, cowpox and smallpox are only similar, in no way the same disease. In many respects they differ, namely in the more rapid course and mildness of cowpox and especially in this, that is never contagious to man by more nearness. Universal vaccination put an end to all epidemics of that deadly fearful smallpox to such an extent that the present generation does no longer possess a clear conception of the former frightful smallpox plague. Moreover, in this way, undoubtedly, certain diseases peculiar to animals may give us remedies and thus happily enlarge our stock of homeopathic remedies. But to use a human morbific matter (a Psorin taken from the itch in man) as a remedy for the same itch or for evils arisen therefrom is! Nothing can result from this but trouble and aggravation of the disease". (*Organon,* note of § 56)

Elaborating further on the coexistence of **similar diseases** - a clinical observation that supports the **homeopathic method of treatment** - Hahnemann states that in this way it is possible to heal through a natural process. On the other hand, he affirms that it is impossible for two diseases that are similar in their manifestations and effects occurring in the same organism to behave as dissimilar diseases do, i.e., to mutually repel or interrupt one another or to coexist. In this case, the weakest is annihilated by the strongest and this happens unconditionally in any time or place:

> "Totally different, however, is the result when two similar diseases meet together in the organism, that is to say, when to the disease already present a stronger similar one is added. In such cases we see how a cure can be effected by the operations of nature, and we get a lesson as to how man ought to cure". (*Organon,* § 43)
>
> "Similar diseases can neither (as is asserted of dissimilar disease in I) repel one another, nor (as has been shown of dissimilar disease in II) suspend on another, so that the old one shall return after the new one has run its course; and just as little can two similar disease (as has been demonstrated in III respecting dissimilar affections) exist beside each other in the same organism, or together form a double complex disease". (*Organon,* § 44)
>
> "No! Two diseases, differing, it is true, in kind1 but very similar in their phenomena and effects and in the sufferings and symptoms they severally produce, invariably annihilate one another whenever they meet together in the organism; the stronger disease namely, annihilates the weaker, and that for this simple reason, because the stronger morbific power when it invades the system, by reason of its similarity of action involves precisely the same part of the organism that were previously affected by the weaker morbid irritation, which, consequently, can no longer act on these parts, but is extinguished2, or (in other words), the new similar but stronger morbific potency controls the feelings of the patient and hence the life principle on account of its peculiarity, can no longer feel the weaker similar which becomes extinguished - exists no longer - for it was never anything material, but a dynamic - spirit-like - (conceptual) affection. The life principle henceforth is affected only and this but temporarily by the new, similar but stronger morbific potency". (*Organon,* § 45)

Just as he had done in the case of dissimilar diseases, also here Hahnemann describes examples of diseases that were homeopathically cured by other diseases exhibiting similar symptoms occurring spontaneously or induced by art:

> "Many examples might be adduced of disease which, in the course of nature, have been homeopathically cured by other diseases presenting similar symptoms, were it not necessary, as our object is to speak about something determinate and indubitable, to confine our attention solely to those (few) disease which are invariably the same, arise from a fixed miasm, and hence merit a distinct name. Among these the smallpox, so dreaded on account of the great number of its serious symptoms, occupies a prominent position, and it has removed and cured a number of maladies with similar symptoms. How frequently does smallpox produce violent ophthalmia, sometimes even causing blindness! And see! By its inoculation *Dezoteux* cured a chronic ophthalmia permanently, and *Leroy* another. An amaurosis of two years' duration, consequent on suppressed scald head, was perfectly cured by it, according to *Klein*. How often does smallpox cause deafness and dyspnoea! And both these chronic diseases it removed on reaching its acme, as *J. Fr. Closs* observed. Swelling of the testicle, even of a very severe character, is a frequent symptom of small-pox, and on this account it was enabled, as *Klein* observed, to cure, by virtue of similarity, a large hard swelling of the left testicle, consequently on a bruise. And another observer saw a similar swelling of the testicle cured by it. Among the troublesome symptoms of small-pox is a dysenteric state of the bowels; and it subdued, as *Fr. Wendt* observed, a case of dysentery,

> as a similar morbific agent. Smallpox coming on after vaccination, as well on account of its greater strength as its great similarity, at once removes entirely the cow-pox homeopathically, and does not permit it to come to maturity; but, on the other hand, the cow-pox when near maturity does, on account of its great similarity, homeopathically diminish very much the supervening smallpox and make it much milder, as *Muhry* and many others testify. The inoculated cow-pox, whose lymph, besides the protective matter, contains the contagion of a general cutaneous eruption of another nature, consisting of usually small, dry (rarely large, pustular) pimples, resting on a small red areola, frequently conjoined with round red cutaneous spots and often accompanied by the most violent itching, which rash appears in not a few children several days before, more frequently, however, after the red areola of the cow-pock, and goes off in a few days, leaving behind small, red, hard spots on the skin; - the inoculated cow-pox, I say, after it has taken, cures perfectly and permanently, in a homeopathic manner, by the similarity of this accessory miasm, analogous cutaneous eruptions of children, often of very long standing and of a very troublesome character, as a number of observers assert. The cow-pox, a peculiar symptom of which is to cause tumefaction of the arm, cured, after it broke out, a swollen half-paralyzed arm. The fever accompanying cow-pox, which occurs at the time of the production of the red areola, cured homeopathically intermittent fever in two individuals, as the younger *Hardege* reports, confirming what *J. Hunter* had already observed, that two fevers (similar diseases) cannot co-exist in the same body. The measles bear a strong resemblance in the character of its fever and cough to the whooping-cough, and hence it was that *Bosquillon* noticed, in an epidemic where both these affections prevailed, that many children who then took measles remained free from whooping-cough during that epidemic. They would all have been protected from, and rendered incapable of being infected by, the whooping-cough in that and all subsequent epidemics, by the measles, if the whooping-cough were not a disease that has only a partial similarity to the measles, that is to say, if it had also a cutaneous eruption similar to what the latter possesses. As it is, however, the measles can but preserve a large number from whooping-cough homeopathically, and that only in the epidemic prevailing at the time. If, however, the measles come in contact with a disease resembling it in its chief symptom, the eruption, it can indisputably remove, and effect a homeopathic cure of the latter. Thus a chronic herpetic eruption was entirely and permanently (homeopathically) cured by the breaking out of the measles, as *Kortum* observed. An excessively burning miliary rash on the face, neck, and arms, that had lasted six years, and was aggravated by every change of weather, on the invasion of measles assumed the form of a swelling of the surface of the skin; after the measles had run its course the exanthema was cured, and returned no more". (*Organon,* § 46)

Extracting from the pure observations of instances of natural healing the grounds of the homeopathic therapeutic method, Hahnemann extends the healing power to all existing substances, provided they are employed according to the principle of similitude:

> "This therapeutic law is rendered obvious to all intelligent minds by these instances, and they are amply sufficient for this end. But, on the other hand, see what advantages man has over crude Nature in her happy-go-lucky operations. How many thousands more of homeopathic morbific agents has not man at his disposal for the relief of his suffering fellow-creatures in the medicinal substances universally distributed throughout creation! In them he has producers of disease of all possible varieties of action, for all the innumerable, for all conceivable and inconceivable natural diseases, to which they can render homeopathic aid - morbific agents (medicinal substances), whose power, when their remedial employment is completed, being overcome by the vital force, disappears

> spontaneously without requiring a second course of treatment for its extirpation, like the itch - artificial morbific agents, which the physician can attenuate, subdivide and potentize almost to an infinite extent, and the dose of which he can diminish to such a degree that they shall remain only slightly stronger than the similar natural disease they are employed to cure; so that in this incomparable method of cure, there is no necessity for any violent attack upon the organism for the eradication of even an inveterate disease of old standing; the cure by this method takes place by only a gentle, imperceptible and yet often rapid transition from the tormenting natural disease to the desired state of permanent health". (*Organon,* § 51)

In the "Introduction" of the *Organon*, when criticizing the therapeutic method employed by contemporary medicine - based on the use of sudorific, vomitive, laxative medicines, bloodletting, etc. - that sought to expel impurities and excesses out of the organism, Hahnemann also mentions countless accidental homeopathic cures, as he had also done in the *Essay on a new principle for ascertaining the curative powers of drugs*.

Going forwards in the teaching of his method, Hahnemann elaborates on the **enantiopathic (antipathic, palliative) method of treatment** chiefly described by Hippocrates and introduced in medical practice by Galen, grounded on the principle of contraries (*contraria contrariis*). Hahnemann stresses that, in the treatment of chronic diseases, such method is radically useless and damaging. This is the method at the base of present day allopathy:

> "By means of this palliative (antipathic, enantiopathic) method, introduced according to Galen's teaching *Contraria contrariis* for seventeen centuries, the physicians hitherto could hope to win confidence while they deluded with almost instantaneous amelioration. But how fundamentally unhelpful and hurtful this method of treatment is (in diseases not running a rapid course) we shall see in what follows. It is certainly the only one of the modes of treatment adopted by the allopaths that had any manifest relation to a portion of the sufferings caused by the natural disease; but what kind of relation? Of a truth the very one (the exact contrary of the right one) that ought carefully to be avoided if we would not delude and make a mockery of the patient affected with a chronic disease". (*Organon,* § 56)

Hahnemann gives examples of antipathic treatments accomplished in order to check quickly the symptoms of disease through the use of remedies able to provoke in their direct primary effect the opposite to the disease symptom to be relieved:

> "In order to carry into practice this antipathic method, the ordinary physician gives, for a single troublesome symptom from among the many other symptoms of the disease which he passes by unheeded, a medicine concerning which it is known that it produces the exact opposite of the morbid symptom sought to be subdued, from which, agreeably to the fifteen - centuries - old traditional rule of the antiquated medical school *(contraria contrariis)* he can expect the speediest (palliative) relief. He gives large doses of opium for pains of all sorts, because this drug soon benumbs the sensibility, and administers the same remedy for diarrhoeas, because it speedily puts a stop to the peristaltic motion of the intestinal canal and makes it insensible; and also for sleeplessness, because opium rapidly produces a stupefied, comatose sleep; he gives purgatives when the patient has suffered long from constipation and costiveness; he causes the burnt hand to be plunged into cold water, which, from its low degree of temperature, seems instantaneously to remove the burning pain, as if by magic; he puts the patient who complains of chilliness and deficiency of vital heat into warm baths, which warm him immediately; he makes him who is suffering from prolonged debility drink wine, whereby he is instantly enlivened and refreshed; and in like manner he

> employs other opposite (antipathic) remedial means, but he has very few besides those just mentioned, as it is only of very few substances that some peculiar (primary) action is known to the ordinary medical school". (*Organon,* § 57)

And he states that in this model of therapeutics it is approached *a single symptom in a merely one-sided manner*, i.e., *only a small part of the whole*, whence it cannot be expected the relief of the full disease. Moreover, after an initial amelioration of the symptom it is frequently observed an aggravation of the original disease. To illustrate this notion, as well as to prepare the reader from the next chapter of this work, discussing "Similitude in Modern Pharmacology", it is worth to mention that this secondary worsening of disease is what is known in conventional pharmacology as **"rebound effect of drugs"** or **"paradoxal reaction of the organism"**.

> "If, in estimating the value of this mode of employing medicines, we should even pass over the circumstance that it is an extremely faulty symptomatic treatment, wherein the practitioner devotes his attention in a merely one-sided manner to a single symptom, consequently to only a small part of the whole, whereby relief for the totality of the disease, which is what the patient desires, cannot evidently be expected, - we must, on the other hand, demand of experience if, in one single case where such antipathic employment of medicine was made use of in a chronic or persisting affection, after the transient amelioration there did not ensue an increased aggravation of the symptom which was subdued at first in a palliative manner, an aggravation, indeed, of the whole disease? And every attentive observer will agree that, after such short antipathic amelioration, aggravation follows in every case without exception, although the ordinary physician is in the habit of giving his patient another explanation of this subsequent aggravation, and ascribes it to malignancy of the original disease, now for the first time showing itself, or to the occurrence of quite a new disease". (*Organon,* § 58)

Hahnemann grounds on countless observations made in his clinical practice the *aggravation or relapse of the symptoms initially ameliorated by enantiopathic (antipathic, contrary or antagonistic) treatment.* In paragraph 59, he anticipates the **rebound phenomenon** of modern pharmacology, which he explains through the **primary effect of drugs** and **the secondary effect arising from the organism (vital reaction)**:

> "Important symptoms of persistent diseases have never yet been treated with such palliative, antagonistic remedies, without the opposite state, a relapse - indeed, a palpable aggravation of the malady - occurring a few hours afterwards. For a persistent tendency to sleepiness during the day the physician prescribed coffee, whose primary action is to enliven; and when it had exhausted its action the day - somnolence increased; - for frequent waking at night he gave in the evening, without heeding the other symptoms of the disease, opium, which by virtue of its primary action produced the same night (stupefied, dull) sleep, but the subsequent nights were still more sleepless than before; - to chronic diarrhoeas he opposed, without regarding the other morbid signs, the same opium, whose primary action is to constipate the bowels, and after a transient stoppage of the diarrhoea it subsequently became all the worse; - violent and frequently recurring pains of all kinds he could suppress with opium for but a short time; they then always returned in greater, often intolerable severity, or some much worse affection came in their stead. For nocturnal cough of long standing the ordinary physician knew no better than to administer opium, whose primary action is to suppress every irritation; the cough would then perhaps cease the first night, but during the subsequent nights it would be still more severe, and if it were again and again suppressed by this palliative in increased doses, fever and nocturnal perspiration

were added to the disease; - weakness of the bladder, with consequent retention of urine, was sought to be conquered by the antipathic work of cantharides to stimulate the urinary passages whereby evacuation of the urine was certainly at first effected but thereafter the bladder becomes less capable of stimulation and less able to contract, and paralysis of the bladder is imminent; - with large doses of purgative drugs and laxative salts, which excite the bowels to frequent evacuation, it was sought to remove a chronic tendency to constipation, but in the secondary action the bowels became still more confined; - the ordinary physician seeks to remove chronic debility by the administration of wine, which, however, stimulates only in its primary action, and hence the forces sink all the lower in the secondary its primary action, and hence the forces sink all the lower in the secondary action; - by bitter substances and heating condiments he tries to strengthen and warm the chronically weak and cold stomach, but in the secondary action of these palliatives, which are stimulating in their primary action only, the stomach becomes yet more inactive; - long standing deficiency of vital heat and chilly disposition ought surely to yield to prescriptions of warm baths, but still more weak, cold, and chilly do the patients subsequently become; - severely burnt parts feel instantaneous alleviation from the application of cold water, but the burning pain afterwards increases to an incredible degree, and the inflammation spreads and rises to a still greater height; - by means of the sternutatory remedies that provoke a secretion of mucus, coryza with stoppage of the nose of long standing is sought to be removed, but it escapes observation that the disease is aggravated all the more by these antagonistic remedies (in their secondary action), and the nose becomes still more stopped; - by electricity and galvanism, with in their primary action greatly stimulate muscular action, chronically weak and almost paralytic limbs were soon excited to more active movements, but the consequence (the secondary action) was complete deadening of all muscular irritability and complete paralysis; - by venesections it was attempted to remove chronic determination of blood to the head, but they were always followed by greater congestion; - ordinary medical practitioners know nothing better with which to treat the paralytic torpor of the corporeal and mental organs, conjoined with unconsciousness, which prevails in many kinds of typhus, than with large doses of valerian, because this is one of the most powerful medicinal agents for causing animation and increasing the motor faculty; in their ignorance, however, they knew not that this action is only a primary action, and that the organism, after that is passed, most certainly falls back, in the secondary (antagonistic) action, into still greater stupor and immobility, that is to say, into paralysis of the mental and corporeal organs (and death); they did not see, that the very diseases they supplied most plentifully with valerian, which is in such cases an oppositely acting, antipathic remedy, most infallibly terminated fatally. The old school physician rejoices that he is able to reduce for several hours the velocity of the small rapid pulse in cachectic patients with the very first dose of uncombined purple foxglove (which in its primary action makes the pulse slower); its rapidity, however, soon returns; repeated, and now increased doses effect an ever smaller diminution of its rapidity, and at length none at all - indeed - in the secondary action the pulse becomes uncountable; sleep, appetite and strength depart, and a speedy death is invariably the result, or else insanity ensues. How often, in one word, the disease is aggravated, or something even worse is effected by the secondary action of such antagonistic (antipathic) remedies, the old school with its false theories does not perceive, but experience teaches it in a terrible manner". (*Organon*, § 59)

Also Hahnemann foresees the phenomenon of **drug tolerance** frequently reported by modern pharmacology, when he observes that the enantiopathic method requires doses

increasingly larger to alleviate temporarily a symptom, eventually resulting in the production of medicinal diseases and intoxications:

> "If these ill-effects are produced, as may very naturally be expected from the antipathic employment of medicines, the ordinary physician imagines he can get over the difficulty by giving, at each renewed aggravation, a stronger dose of the remedy, whereby an equally transient suppression1 is effected; and as there then is a still greater necessity for giving ever - increasing quantities of the palliative there ensues either another more serious disease or frequently even danger to life and death itself, but never a cure of a disease of considerable or of long standing". (*Organon,* § 60)

On the other hand, being the homeopathic "the true radical healing art", he highlights the importance of observing and "reflecting on the sad results of the antagonistic employment of medicines" in order to be able to verify the principle of therapeutic similitude. Argumentation here employs *modus tollens*, an Aristotle hypothetical syllogism or deductive logic, the so-called "indirect proof" or "mode that affirms by negating" (corresponding to the present "null hypothesis" of modern statistics), to validate the hypothesis underlying the homeopathic method (*similia similibus*), by denying the efficacy of the treatment by contraries (*contraria contrariis*) in chronic diseases:

> "Had physicians been capable of reflecting on the sad results of the antagonistic employment of medicines, they had long since discovered the grand truth, *that the true radical healing art must be found in the exact opposite of such an antipathic treatment of the symptoms of disease;* they would have become convinced, that as a medicinal action antagonistic to the symptoms of the disease (an antipathically employed medicine) is followed by only transient relief, and after that is passed, by invariable aggravation, the converse of that procedure, the homeopathic employment of medicines according to similarity of symptoms, must effect a permanent and perfect cure, if at the same time the opposite of their large doses, the most minute doses, are exhibited. But neither the obvious aggravation that ensued from their antipathic treatment, nor the fact that no physician ever effected a permanent cure of disease of considerable or of long standing unless some homeopathic medicinal agent was accidentally a chief ingredient in his prescription, nor yet the circumstances that all the rapid and perfect cures that nature ever performed (§ 46), were always effected by the supervention upon the old disease of one of a similar character, ever taught them, during such a long series of centuries, this truth, the knowledge of which can alone conduce to the benefit of the sick". (*Organon,* § 61)

In this study, this very same logical path was applied to the effects of modern drugs when used according to the enantiopathic method, in order to ground the principle of therapeutic similitude on the notions of present day medical-scientific rationality.

After having demonstrated through examples the principle of healing through similarity, Hahnemann discusses its *mechanism of operation* on the ground of his underlying vitalistic philosophy. Briefly, in this study *Hahnemann's vital force is understood as an immaterial principle* that is indivisibly united with the physical body so as to permeate it completely; this principle has no intelligence or reflecting ability, but *acts in a fully instinctive, reflex and automatic manner in the sense to promote organic homeostasis*, analogously to the *vis*

medicatrix naturae of the Hippocratic tradition.[8,9,10] The vital force is manifested through the operation of all the organic physiological systems involved in the conservation of the vital conditions and the life of the individual, as e.g. the psycho-neuro-immuno-endocrino-metabolic one. In my book *Similar cures similar: the homeopathic cure principle based by the medical and scientific rationality,*[11] I have discussed this subject in detail, particularly the parallel between the modern physiology, the principle of similitude and Hahnemann's notion of the vital force.

Starting from the principle that "every medicine deranges more or less the vital force causing a certain alteration in the health of the individual", Hahnemann attributes the so-called **primary action** of drugs to their direct effect on the organism. To this effect "our vital force endeavors to oppose its own energy" in a conservative, automatic and instinctive manner called **secondary action or vital reaction**:

> "Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed primary action. [...]. To its action our vital force endeavors to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of secondary action or counteraction". (*Organon*, § 63)
>
> "During the primary action of the artificial morbific agents (medicines) on our healthy body, as seen in the following examples, our vital force seems to conduct itself merely in a passive (receptive) manners, and appears, so to say, compelled to permit the impressions of the artificial power acting from without to take place in it and thereby after its state of health; it then, however, appears to rouse itself again, as it were, and to develop (A) the exact opposite condition of health (counteraction, secondary action) to this effect (primary action) produced upon it, if there be such an opposite, and that in as great a degree as was the effect (primary action) of the artificial morbific agent on it, and proportionate to its own energy; - or (B) if there be not in nature a state exactly the opposite of the primary action, it appears to endeavor to indifferentiate itself, that is, to make its superior power available in the extinction of the change wrought in it from without (by the medicine), in the place of which it substitutes its normal state (secondary action, curative action)". (*Organon*, § 64)
>
> "Examples of (A) are familiar to all. A hand bathed in hot water is at first much warmer than the other hand that has not been so treated (primary action); but when it is withdrawn from the hot water and again thoroughly dried, it becomes in a short time cold, and at length much colder than the other (secondary action). A person heated by violent exercise (primary action) is afterwards affected with chilliness and shivering (secondary action). To one who

[8] Teixeira MZ. Concepção vitalista de Samuel Hahnemann [Vitalistic conception of Samuel Hahnemann]. São Paulo: Robe Editorial, 1996. Available at: https://www.homeozulian.med.br/homeozulian_visualizarlivroautor.asp?id=2

[9] Teixeira MZ. A concepção vitalista de Samuel Hahnemann [The vitalistic conception of Samuel Hahnemann]. *Rev Homeopatia (São Paulo).* 1996; 61(3-4): 39-44. Available at: Researchgate

[10] Teixeira MZ. A natureza imaterial do homem: estudo comparativo do vitalismo homeopático com as principais concepções médicas e filosóficas [The immaterial nature of man: comparative study of vitalism homeopathic with mainly medical and philosophical concepts]. São Paulo: Editorial Petrus, 2000. Available at: https://www.homeozulian.med.br/homeozulian_visualizarlivroautor.asp?id=4

[11] Teixeira MZ. Semelhante cura semelhante: o princípio de cura homeopático fundamentado pela racionalidade médica e científica [Similar cures similar: the homeopathic cure principle based by the medical and scientific rationality]. São Paulo: Editorial Petrus, 1998. Available at: https://www.homeozulian.med.br/homeozulian_visualizarlivroautor.asp?id=3

> was yesterday heated by drinking much wine (primary action), today every breath of air feels too cold (counteraction of the organism, secondary action). An arm that has been kept long in very cold water is at first much paler and colder (primary action) than the other; but removed from the cold water and dried, it subsequently becomes not only warmer than the other, but even hot, red and inflamed (secondary action, reaction of the vital force). Excessive vivacity follows the use of strong coffee (primary action), but sluggishness and drowsiness remain for a long time afterwards (reaction, secondary action), if this be not always again removed for a short time by imbibing fresh supplies of coffee (palliative). After the profound stupefied sleep caused by opium (primary action), the following night will be all the more sleepless (reaction, secondary action). After the constipation produced by opium (primary action), diarrhoea ensues (secondary action); and after purgation with medicines that irritate the bowels, constipation of several days' duration ensues (secondary action). And in like manner it always happens, after the primary action of a medicine that produces in large doses a great change in the health of a healthy person, that its exact opposite, when, as has been observed, there is actually such a thing, is produced in the secondary action by our vital force". (*Organon*, § 65)

In order to dispel eventual doubts that may remain on the explanation of the therapeutic application of the principle of homeopathic similitude, I would like to remind here Hahnemann's observations as described in the Preface to the 4th volume of *The chronic diseases*,[12] entitled "Inquiry into the process of homeopathic healing".

Here Hahnemann makes very clear how the vital force, through a homeopathic stimulus, succeeds to overcome the disorder that has impregnated its essence. Working as if it were an *indicator of the original illness* that captured the organic-vital unity, *the homeopathic remedy amplifies the image of the morbid enemy so that the vital principle can notice, grasp and apprehend it.* Besides its inability to oppose a stronger force to the organic disease, our instinctive vital force gets used, so to speak, to the chronic disease with which it cohabits for years (failing thus to recognize it as "disease"), but incorporates it to its very essence so that it does not mobilize efforts enough to neutralize it. On the other hand, by adding on the original *natural disease* a similar *artificial disease* a little stronger than it *(the homeopathic medicine),* the doctor provokes an *aggravation of the original disease* that thus stimulates an also stronger vital reaction (secondary action or effect) fit to combat against it:

> "Of itself this vital principle, being only an organic vital force intended to preserve an undisturbed health, opposes only a weak resistance to the invading morbific enemy; as the disease grows and increases, it opposes a greater resistance, but at best, it is only an equal resistance; with weakly patients it is not even equal, but weaker. This force is neither capable, nor destined, nor created for an overpowering resistance, which will do no harm to itself. But if we physicians are able to present and oppose to this instinctive vital force it morbific enemy, as it were magnified through the action of homeopathic medicines - even if it should be enlarged every time only by a little - if in this way the image of the morbific foe be magnified to the apprehension of the vital principle through homeopathic medicines, which in a delusive manner simulate the original disease, we gradually cause and compel this instinctive vital force to increase its energies by degrees, and to increase it energies by

[12] Hahnemann S. The chronic diseases: their peculiar nature and their homeopathic cure. New Delhi: B Jain Publishers, 1990.

> degrees, and to increase them more and more, and at last to such a degree that it becomes far more powerful than the original disease. The consequence of this is, that the vital force again becomes sovereign in its domain, can again hold and direct the reins of sanitary progress, while the apparent increase of the disease caused by homeopathic medicines, disappears of itself, as soon as we, seeing the preponderance of the restored vital force, *i. e.*, of the restored health, cease to use these remedies". (*The chronic diseases, "*Inquiry into the process of homeopathic healing")

Transferring such observations to the **experimentation on healthy individuals,** Hahnemann states that "an obvious antagonistic secondary action, however, is, as may readily be conceived, not to be noticed from the action of quite minute homeopathic doses of the deranging agents on the healthy body", because "the living organism employs against it only so much reaction (secondary action) as is necessary for the restoration of the normal condition" (*Organon*, § 66). Hahnemann emphasizes this notion in order to distinguish between the primary effects of the tested substances (compiled in the **Homeopathic Materia Medica**, which is used by homeopathic practitioners to find the remedy similar to the disturbs of a patient) and the secondary effects triggered by the organism, i.e., the neutralizing response by the vital force, that ought not to appear when the pathogenetic trial is carried out with infinitesimal doses and in healthy individuals.

By appealing to the model previously sketched, Hahnemann explains the events appearing when the **antipathic method of treatment** is used, i.e., through the notions of primary and secondary actions. When the method of contraries is used, the cessation of the primary effect of a drug - aiming at the palliation of a symptom - is followed by the secondary reaction of the organism against the stimulus, which clinically will appear as the aggravation of the initial symptom. Therefore, **the symptom of the disease, after the palliative remedy ceased to act, becomes actually worse, and so much more as stronger is the dose prescribed.** In clinical pharmacology this very phenomenon has been observed in countless drugs employed according to the enantiopathic or palliative method and was called **"rebound effect",** as it will be discussed in the second part of this work.

> "In the antipathic (palliative) mode of treatment, however precisely the reverse of this takes place. The medicinal symptom which the physician opposes to the disease symptom (for example, the insensibility and stupefaction caused by opium in its primary action to acute pain) is certainly not alien, not allopathic of the latter; there is a manifest relation of the medicinal symptom to the disease symptom, but it is the reverse of what should be; it is here intended that the annihilation of the disease symptom shall be effected by an opposite medicinal symptom, which is nevertheless impossible. No doubt the antipathically chosen medicine touches precisely the same diseased point in the organism as the homeopathic medicine chosen on account of the similar affection it produces; but the former covers the opposite symptom of the disease only as an opposite, and makes it unobservable to our life principle for a short time only, so that in the first period of the action of the antagonistic palliative the vital force perceives nothing disagreeable from either if the two (neither from the disease symptom nor from the medicinal symptom), as they seem both to have mutually removed and dynamically neutralized one another as it were (for example, the stupefying power of opium does this to the pain). In the first minutes the vital force feels quite well, and perceives neither the stupefaction of the opium nor the pain of the disease. But as the antagonistic medicinal symptom cannot (as in the homeopathic treatment) occupy the place of the morbid derangement present in the organism in the sensation of the life principle as a

similar, stronger (artificial) disease, and cannot, therefore, like a homeopathic medicine, affect the vital force with a similar artificial disease, so as to be able to step into the place of the original natural morbid derangement, the palliative medicine must, as a thing totally differing from, and the opposite of the disease derangement, leave the latter uneradicated; it renders it, as before said, by a semblance of dynamic neutralization, at first unfelt by the vital force, but, like every medicinal disease, it is soon spontaneously extinguished, and not only leaves the disease behind, just as it was, but compels the vital force (as it must, like all palliatives, be given in large doses in order to effect the apparent removal) to produce an opposite condition (§ 63-64) to this palliative medicine, the reverse of the medicinal action, consequently the analogue of the still present, undestroyed, natural morbid derangement, which is necessarily strengthened and increased by this addition (reaction against the palliative) produced by the vital force*. The disease symptom (this single part of the disease) consequently becomes worse after the term of the action of the palliative has expired; worse in proportion to the magnitude of the dose of the palliative. Accordingly (to keep to the same example) the larger the dose of opium given to allay the pain, so much the more does the pain increase beyond its original intensity as soon as the opium has exhausted its action (* Plain as this proposition is, it has been misunderstood, and in opposition to it some have asserted *that the palliative in its secondary action, would then be similar to the disease present, must be capable of curing just as well as a homeopathic medicine does by its primary action.* But they did not reflect that the secondary action is not a product of the medicine, but invariably of the antagonistically acting vital force of the organism; that therefore this secondary action resulting from the vital force on the employment of a palliative is a state similar to the symptoms of the disease which the palliative left uneradicated, and which the reaction of the vital force against the palliative consequently increased still more)". (*Organon*, § 69)

Hahnemann presents a summary of these ideas above in paragraph 70 of *Organon:*

"From what has been already adduced we cannot fail to draw the following inferences:

- That everything of a really morbid character and which ought to be cured that the physician can discover in diseases consists solely of the sufferings of the patient, and the sensible alterations in his health, in a word, solely of the totality of the symptoms, by means of which the disease demands the medicine requisite for its relief; while, on the other hand, every internal cause attributed to it, every occult quality or imaginary material morbific principle, is nothing but an idle dream;
- That this derangement of the state of health, which we term disease, can only be converted into health by another revolution effected in the state of health by means of medicines, whose sole curative power, consequently, can only consist in altering man's state of health - that is to say, in a peculiar excitation of morbid symptoms, and is learned with most distinctness and purity by testing them on the healthy body;
- That, according to all experience, a natural disease can never be cured by medicines that possess the power of producing in the healthy individual an alien morbid state (dissimilar morbid symptoms) differing from that of the disease to be cured (never, therefore, by an allopathic mode of treatment), and that even in nature no cure ever takes place in which an inherent disease is removed, annihilated and cured by the addition of another disease dissimilar to it, be the new one ever so strong;
- That, moreover, all experience proves that, by means of medicines which have a tendency to produce in the healthy individual an artificial morbid symptom, antagonistic to the single symptom of disease sought to be cured, the cure of a long-standing affection will never be effected, but merely a very transient alleviation, always follows by its aggravation; and that,

in a word, this antipathic and merely palliative treatment in long-standing diseases of a serious character is absolutely inefficacious;
- That, however, the third and only other possible mode of treatment (the homeopathic), in which there is employed for the totality of the symptoms of a natural disease a medicine capable of producing the most similar symptoms possible in the healthy individual, given in suitable dose, is the only efficacious remedial method whereby diseases, which are purely dynamic deranging irritations of the vital force, are overpowered, and being thus easily, perfectly and permanently extinguished, must necessarily cease to exist. This is brought about by means of the stronger similar deranging irritation of the homeopathic medicine in the sensation of the life principle. - and for this mode of procedure we have the example of unfettered Nature herself, when to an old disease there is added a new one similar to the first, whereby the new one is rapidly and forever annihilated and cured". (*Organon,* § 70)

Homeopathic pathogenetic experimentation[13,14,15]

In homeopathy, the healing powers of drugs are discovered by testing them on human beings; the results are compiled in the **Homeopathic Materia Medica** that, thus, contains the symptoms exhibited by sensitive trial subjects *(direct primary action);* these symptoms then are used by the homeopathic physician to select the most fitting remedy. To do so, the doctor first need to investigate the totality of the symptoms exhibited by the patient, since it represents the image of the disease, and thus allows characterizing each case on an individualized basis. This is the first step in the true art of healing. Then, the doctor must know the pathogenetic power of the medicines, namely their ability to awaken given symptoms in human in beings in order to able to choose among them, by applying the principle of similitude, the one exhibiting the most similar symptoms to the picture of the disease:

> "The second point of the business of a true physician related to acquiring a knowledge of the instruments intended for the cure of the natural diseases, investigating the pathogenetic power of the medicines, in order, when called on to cure, to be able to select from among them one, from the list of whose symptoms an artificial disease may be constructed, as similar as possible to the totality of the principal symptoms of the natural disease sought to be cured". (*Organon,* § 105)[16]
>
> "The whole pathogenetic effect of the several medicines must be known; that is to say, all the morbid symptoms and alterations in the health that each of them is specially capable of developing in the healthy individual must first have been observed as far as possible, before we can hope to be able to find among them, and to select, suitable homeopathic remedies for most of the natural disease". (*Organon,* § 106)

Hahnemann observes that to properly investigate the effects of medicines in human beings, *healthy individuals* must be preferred over the *ill* ones because in the latter the symptoms of disease become intertwined with the primary actions of the medicines and thus, no clear picture can be made. Thus, he emphasizes that testing on the *healthy* is the safest and most natural path to discover "the peculiar effects of medicines":

> "If, in order to ascertain this, medicines be given to sick persons only, even though they be administered singly and alone, then little or nothing precise is seen of their true effects, as those peculiar alterations of the health to be expected from the medicine are mixed up with the symptoms of the disease and can seldom be distinctly observed". (*Organon,* § 107)
>
> "There is, therefore, no other possible way in which the peculiar effects of medicines on the health of individuals can be accurately ascertained - there is no sure, no more natural way of accomplishing this object, than to administer the several medicines experimentally, in

[13] Teixeira MZ. Semelhante cura semelhante: o princípio de cura homeopático fundamentado pela racionalidade médica e científica [Similar cures similar: the homeopathic cure principle based by the medical and scientific rationality]. São Paulo: Editorial Petrus, 1998. Available at: https://www.homeozulian.med.br/homeozulian_visualizarlivroautor.asp?id=3

[14] Teixeira MZ. Protocolo de experimentação patogenética homeopática em humanos. Revista de Medicina (São Paulo) 2013; 92(4): 242-263. Available at: https://doi.org/10.11606/issn.1679-9836.v92i4p242-263

[15] Teixeira MZ. Protocolo de experimentação patogenética homeopática em humanos. São Paulo: Marcus Zulian Teixeira, 2013, 64 p. Available at: https://pesquisa.bvsalud.org/portal/resource/pt/hom-11710?lang=en

[16] Hahnemann S. Organon of medicine. 6th Edn. (Translated by William Boericke). New Delhi: B Jain Publishers, 1991.

> moderate doses, to healthy persons, in order to ascertain what changes, symptoms and signs of their influence each individually produces on the health of the body and of the mind; that is to say, what disease elements they are able and tend to produce1, since, as has been demonstrated (§ 24-27), all the curative power of medicines lies in this power they possess of changing the state of man's health, and is revealed by observation of the latter" (*Organon,* § 108)

Hahnemann underlines the validity of his experimental and scientific methodology for the study of the healing power of the medicines with examples clearly analogous to the ones in records of older physicians regarding the effects of drugs in healthy individuals (intoxications, suicide attempts, improper treatments, etc.). Raising the pathogenetic power to the level of a **natural, fixed and eternal law**, he extends this property to all substances in nature and to all sensitive individuals, both healthy and ill:

> "The agreement of my observations on the pure effects of medicines with these older ones - although they were recorded without reference to any therapeutic object, - and the very concordance of these accounts with others of the same kind by different authors must easily convince us that medicinal substances act in the morbid changes they produce in the healthy human body according to fixed, eternal laws of nature, and by virtue of these are enabled to produce certain, reliable disease symptoms each according to its own peculiar character". (*Organon,* § 111)

However, from all above some doubts emerge: how to standardize the "healthy experimental subjects"? The presence of any disease is an excluding criterion by default? Are there any means to distinguish between the symptoms of the disease of an ill experimental subject from pathogenetic symptoms?

In this regard it must be stressed that, although Hahnemann insisted from a theoretical point of view on **testing on healthy individuals** as the only safe and reliable method to investigate the pathogenetic symptoms elicited by drugs, in actual practice, due to the insurmountable difficulties inherent to carrying out perfectly controlled trials, he also employed the symptoms resulting from **testing on the sick**, either making profit of the reports of improper treatments accomplished in the past, or from his own observations of chronic patients he had treated. Probably, the warning in paragraph 109 regarding the risk of mixing together the symptoms of the patient and the symptoms of the tested drug with the consequent loss of precision was duly taken into account.

Therefore, it possible to take into account the **primary symptoms of drugs appearing in the treatment of ill people** (*side or adverse effects of drugs*), **provided we are able to distinguish them from the previous disease to avoid mixing the symptoms of disease and the pathogenetic symptoms of drugs**. There are countless instances of this situation in the **homeopathic materia medica**, as pointed out by Richard Hughes in the "Prefatory note to Materia Medica section" in his translation of *The chronic diseases,*[17] as well as in

[17] Hahnemann S. The chronic diseases: their peculiar nature and their homeopathic cure. New Delhi: B Jain Publishers, 1990.

the lecture "Sources of the Homeopathic Materia Medica" of his book *A manual of pharmacodynamics*.[18]

> "**I.** In 1821 Hahnemann had been compelled to leave Leipsic, and, in difficulty where to find a place in which he could practice in freedom, had been offered an asylum in the little country town of Coethen. Thither he repaired, and there he remained till his removal to Paris in 1835. He now ceased to attend acute disease, save in the family of his patron, the reigning Duke. But his fame brought him for consultation chronic suffers from all parts; and the varied, shifting, and obstinate morbid stated under which so many men and women labour were pressed closely upon his attention. The result was the theory of chronic disease which (in its latest shape) will be found in these pages, and which traces so many of its forms to a 'psoric' origin. To meet the manifold disorders thus induced it seemed to him that a new set of remedies were required. Accordingly, of the three volumes of the first edition of the present work published in 1828, the two latter contained what seem to be pathogeneses of fifteen medicines hitherto strange to his *Materia Medica Pura*, and in some cases to any Materia Medica whatever. These medicines were: *Ammonium carbonicum, Baryta carbonica, Calcarea carbonica, Graphites, Iodium, Lycopodium, Magnesia carbonica, Magnesia muriatica, Natrum carbonicum, Nitri acidum, Petroleum, Phosphorus, Sepia, Silicea, Zincum.* The pathogeneses of the foregoing (I assume them to be such from the analogy of the corresponding symptom-lists of the *Materia Medica Pura;* but they are not avowedly so) appear without a word of explanation as to how the symptoms were obtained, and without acknowledgement (as in the previous work) of fellow-observers. The absence of any co-operation on the part of others is further to be inferred from what we are told of the first announcement of the work. After six years of solitude at Coethen, Hahnemann 'summoned thither his two oldest and most esteemed disciples, Drs. Stapf and Gross, and communicated to them his theory of the origin of chronic disease, *and his discovery of a completely new series of medicaments for their cure'*. So writes Dr. Dudgeon. This was in 1827. That he should now first reveal these new remedies, and in the following year should publish copious lists of their pathogenetic effects confirms the inference to be drawn from his position and from his silence as to fellow-observers. He was himself between seventy and eighty years old, and it is hardly likely that he did anything at this time in the way of proving on his own person. We are compelled to the conclusion that he drew these symptoms mainly - if not entirely - from the sufferers from chronic disease who flocked to his retreat to avail themselves of his treatment. The prefatory notices to the several medicines still further substantiate this view, and throw some light on the doses with which the symptoms were obtained. [...] A new character is thus imprinted on the symptoms standing under the names of the several medicines, and it continues with respect to those contained in the second edition of the Chronic Diseases, published 1835-9, which is that here translated. Besides the twenty-two medicines of the first edition it contains twenty-five others, of which thirteen are new, and twelve had already appeared in the *Materia Medica Pura.* The new ones are: *Agaricus, Alumina, Ammonium muriaticum, Anacardium, Clematis, Cuprum, Euphorbium, Mezereum, Antimonium crudum, Borax, Nitrum, Platina, Sulphuris acidum.* The old ones are: *Arsenicum, Aurum, Colocynth, Digitalis, Dulcamara, Guaiacum, Hepar sulphuris, Manganum, Muriatis acidum, Phosphori acidum, Sarsaparilla, Stannum.* Those pathogeneses which had already seen the light have (generally) large additions; for all Hahnemann acknowledges contributions from fellow-observers, and for many cites symptoms from the extant literature of his day. The total number of these last is 1742. There are, it is evident, fresh features in the pathogeneses of this second edition; and there are

[18] Hughes R. A manual of pharmacodynamics. New Delhi: B. Jain Publishers, 1980.

> more than appear on the surface. Hahnemann's own additions, indeed, must be of the same character as his contributions to the first; *i. e.*, they must be collateral effects of the drugs observed on the patients to whom he gave them. [...] Of all these materials Hahnemann availed himself in the present work, which thus presents a complex whole, made up of very heterogeneous elements, and needing analysis that it may be appraised and used aright." (*The chronic diseases,* "Prefatory note to Materia Medica section")

The paragraph 112 of the *Organon* explains the theory of the *rebound effect* (*withdrawal syndrome*) described by modern clinical pharmacology, demonstrating the secondary effect of the organism (vital reaction, in homeopathic terms) seeking its own homeostasis.

Studying the reports about "medicines ingested in excessively large doses", Hahnemann observes that after the suspension of the drug, there appear "certain states that were of an exactly opposite nature to those that first appeared". He describes the nature such symptoms "exactly opposite" to the **primary action** as a "reaction of the vital force of the organism, its **secondary action**". However, he adds that "there is seldom or hardly ever the least trace from experiments with moderate doses on healthy bodies", and they lack completely when doses are indeed very small (dynamized remedies).

Later in the present work, when dealing with the reports of trials of drugs in modern pharmacology, it will be seen that very often and with drugs of very different kinds, **after the discontinuance or the suspension of treatment it is observed an intensification of the symptoms of disease that had been suppressed by the enantiopathic treatment (treatment by contraries)**. This **"rebound effect"** or **"reaction of the vital force"** (secondary effect) corroborates Hahnemann's warning regarding the fact that the treatment aiming at the mere palliation of symptoms can, as a fact, aggravate the initial picture of the disease. How many doctors do not also witness this same phenomenon in their daily clinical practice?

> "In those older prescriptions of the often dangerous effects of medicines ingested in excessively large doses we notice certain states that were produced, not at the commencement, but towards the termination of these sad events, and which were of an exactly opposite nature to those that first appeared. These symptoms, the very reverse of the primary action (§ 63) or proper action of the medicines on the vital force are the reaction of the vital force of the organism, its secondary action (§ 62-67), of which, however, there is seldom or hardly ever the least trace from experiments with moderate doses on healthy bodies, and from small doses none whatever. In the homeopathic curative operation the living organism reacts from these only so much as is requisite to raise the health again to the normal healthy state (§ 67)". (*Organon*, § 112)

Through this **rebound effect,** i.e., *the symptoms of the vital reaction or secondary action of the organism in the sense to equilibrate the internal medium*, we can infer the direct effect (*primary action*) of drugs on sensitive organisms, precisely because *they are their polar opposites:*

> "VI. As it may be almost considered an axiom, that the symptoms of the secondary action are the exact opposite of those of the direct action, it is allowable for a master of the art, when the knowledge of the symptoms of the direct action is imperfect, to supply in imagination the lacunae by induction, i. e., the opposite of the symptoms of the secondary

> action the result, however, must only be considered as an addition to, not as the basis of, his conclusions." *(Essay on a new principle)*[19]

According to Hahnemann, with the only exception of *narcotic drugs*, all medicines, when administered in "moderate doses" only provoke the appearance of the direct primary effects, while nothing is reported regarding the indirect secondary effects. However, this does not happen with the use of "excessively large doses", where the *vital reaction*, *secondary action* or *rebound effect* is evident:

> "An obvious antagonistic secondary action, however, is, as may readily be conceived, not to be noticed from the action of quite minute homeopathic doses of the deranging agents on the healthy body. A small dose of every one of them certainly produces a primary action that is perceptible to a sufficiently attentive; but the living organism employs against it only so much reaction (secondary action) as is necessary for the restoration of the normal condition". (*Organon,* § 66)
>
> "The only exceptions to this are the narcotic medicines. As they, in their primary action, take away sometimes the sensibility and sensation, sometimes the irritability, it frequently happens that in their secondary action, even from moderate experimental doses on healthy bodies, an increased sensibility (and a greater irritability) is observable". (*Organon,* § 113)
>
> "With the exception of these narcotic substances, in experiments with moderate doses of medicine on healthy bodies, we observe only their primary action, i.e., those symptoms wherewith the medicine deranges the health of the human being and develops in him a morbid state of longer or shorter duration". (*Organon,* § 114)
>
> "The more moderate, within certain limits, the doses of the medicine used for such experiments are - provided we endeavor to facilitate the observation by the selection of a person who is a lover of truth, temperate in all respects, of delicate feelings, and who can direct the most minute attention to his sensation - so much the more distinctly are the primary effects developed, and only these, which are most worth knowing, occur without any admixture of secondary effects or reactions of the vital force. When, however, excessively large doses are used there occur at the same time not only a number of secondary effects among the symptoms, but the primary effects also come on in such hurried confusion and with such impetuosity that nothing can be accurately observed; let alone the danger attending them, which no one who has any regard for his fellow-creatures, and who looks on the meanest of mankind as his brother, will deem an indifferent manner". (*Organon,* § 137)

Jumping to the subject of the **dose of drugs** either in the experiments in healthy subjects and the production of the *primary symptoms* of drugs, or in the course of homeopathic treatments according to the law of similarity, it must be remembered that Hahnemann employed all kinds of prescriptions, from ponderal doses to different dilutions and procedures of dynamization, together with the eventual use of friction on the skin or the simple olfaction of the dynamized homeopathic remedy. A large number of the symptoms of pathogenetic trials described in *Materia Medica Pura (MMP)*[20] were collected from reports of poisonings, intoxications and adverse effects of allopathic treatments, showing the precedence of the principle of similitude over the minimal doses later employed.

[19] Hahnemann S. Essay on a new principle for ascertaining the curative power of drugs, with a few glances at those hitherto employed. In: Dudgeon RE. The lesser writings of Samuel Hahnemann. New Delhi: B. Jain Publishers, 1995.
[20] Hahnemann S. Materia Medica Pura. New Delhi: B. Jain Publishers, 1994.

Continuing his explanation on how drugs affect the human organism, Hahnemann analyses how the different substances tested awaken their symptoms in the experimental subjects. According to the pattern of individual susceptibility, some symptoms appear more frequently while others are manifested only by a few idiosyncratic individuals. He thus defines **idiosyncrasy** as the ability of an individual to manifest under the influence of a given stimulus some characteristics that are uncommon in the remainder of people, i.e., the peculiar way to react to a same stimulus:

> "Some symptoms are produced by the medicines more frequently - that is to say, in many individuals, others more rarely or in few persons, some only in very few healthy bodies". (*Organon,* § 116)
>
> "To the latter category belong the so-called idiosyncrasies, by which are meant peculiar corporeal constitutions which, although otherwise healthy, possess a disposition to be brought into a more or less morbid state by certain things which seem to produce no impression and no change in many other individuals. But this inability to make an impression on every one is only apparent. For as two things are required for the production of these as well as all other morbid alterations in the health of man - to wit., the inherent power of the influencing substance, and the capability of the vital force that animates the organism to be influenced by it - the obvious derangements of health in the so-called idiosyncrasies cannot be laid to the account of these peculiar constitutions alone, but they must also be ascribed to these things that produce them, in which must lie the power of making the same impressions on all human bodies, yet in such a manner that but a small number of healthy constitutions have a tendency to allow themselves to be brought into such an obvious morbid condition by them. That these agents do actually make this impression on every healthy body is shown by this, that when employed as remedies they render effectual homeopathic service to all sick persons for morbid symptoms similar to those they seem to be only capable of producing in so-called idiosyncratic individuals". (*Organon,* § 117)

Analogously, Hahnemann attributes to each drug the ability to awaken definite particular manifestations in the human organism, which differ from the primary effects of the remainder of drugs. If on the one hand there is individual susceptibility to apprehend some characteristics of the agent, on the other the latter has its own way of affecting the human personality:

> "Every medicine exhibits peculiar actions on the human frame, which are not produced in exactly the same manner by any other medicinal substance of a different kind". (*Organon,* § 118)
>
> "As certainly as every species of plant differs in its external form, mode of life and growth, in its taste and smell from every other species and genus of plant, as certainly as every mineral and salt differs from all others, in its external as well as its internal physical and chemical properties (which alone should have sufficed to prevent any confounding of one with another), so certainly do they all differ and diverge among themselves in their pathogenetic - consequently also in their therapeutic - effects. Each of these substances produces alterations in the health of human beings in a peculiar, different, yet determinate manner, so as to preclude the possibility of confounding one with another". (*Organon,* § 119)

Due to the peculiar way in which each drug affects the organism, Hahnemann suggests to study their medicinal powers consciously and with precision, according to "pure experiments on the healthy body" in order for us to be able to apply in each specific case the right remedy to re-establish health:

> "Therefore medicines, on which depend man's life and death, disease and health, must be thoroughly and most carefully distinguished from one another, and for this purpose tested by careful, pure experiments on the healthy body for the purpose of ascertaining their powers and real effects, in order to obtain an accurate knowledge of them, and to enable us to avoid any mistake in their employment in diseases, for it is only by correct selection of them that the greatest of all earthly blessings, the health of the body and of the mind, can be rapidly and permanently restored". (*Organon,* § 120)

Going further in his **protocol of experimentation,** Hahnemann approaches the *way how to administer drugs* to the experimental subject. First he points to the need to use in this context well-known drugs in the highest degree of *purity, authenticity and activity*. To these he adds the need for the drug to be *single* and in *natural state*. As mentioned before, Hahnemann used ponderal and massive doses in his drug trials:

> "Each of these medicines must be taken in a perfectly simple, unadulterated form; the indigenous plants in the form of freshly expressed juice, mixed with a little alcohol to prevent it spoiling; exotic vegetable substances, however, in the form of powder, or tincture prepared with alcohol when they were in the fresh state and afterwards mingled with a certain proportion of water; salts and gums, however, should be dissolved in water just before being taken. If the plant can only be procured in its dry state, and if its powers are naturally weak, in that case there may be used for the experiment an infusion of it, made by cutting the herb into small pieces and pouring boiling water on it, so as to extract its medicinal parts; immediately after its preparation it must be swallowed while still warm, as all expressed vegetable juices and all aqueous infusions of herbs, without the addition of spirit, pass rapidly into fermentation and decomposition, whereby all their medicinal properties are lost". (*Organon,* § 123)

The requirement to "employ each drug fully single and perfectly pure", without any mixing with others arises from the fact that one wants to observe the effects of drugs in a pure and authentic way. Unfortunately, this warning has been negligenced by countless homeopaths, who prescribe to their patients mixtures of medicines that have been actually **experimented and evaluated separately as to their pathogenetic powers,** whereas there is no reference to the effects of such new "complex remedies" on human beings, since the **Homeopathic Materia Medica** (the only guide to the symptoms that each drug can produce in healthy human beings and consequently heal in the sick) was compiled from the reports of pathogenetic trials carried out with single, separate, individual drugs. Hahnemann condemns complex means when he tells us to prescribe single remedies if we want to observe their effects and action:

> "For these experiments every medicinal substance must be employed quite alone and perfectly pure, without the admixture of any foreign substance, and without taking anything else of a medicinal nature the same day, nor yet on the subsequent days, nor during all the time we wish to observe the effects of the medicine". (*Organon,* § 124)

Next, Hahnemann elaborates on **the ideal experimental subject** regarding dietetic habits, character and lifestyle. He emphasizes the importance of self-observation and of the ability

to express clearly sensations and feelings, besides the need to have a healthy organism, within its standards. Regarding self-observation, Hahnemann suggests to experimental subjects to perform a careful examination of the diverse modalities of manifest symptoms, i.e., the different circumstances under which aggravations and ameliorations occur, time of appearance, etc. This will supply the *characteristic particularities of each symptom*, which are needed to individualize medicines:

> "During all the time the experiment lasts the diet must be strictly regulated; it should be as much as possible destitute of spices, of a purely nutritious and simple character, green vegetables, roots and all salads and herb soups (which, even when most carefully prepared, possess some disturbing medicinal qualities) should be avoided. The drinks are to be those usually partaken of, as little stimulating as possible". (*Organon*, § 125)
>
> "The person who is proving the medicine must be pre-eminently trustworthy and conscientious and during the whole time of the experiment avoid all over-exertion of mind and body, all sorts of dissipation and disturbing passions; he should have no urgent business to distract his attention; he must devote himself to careful self-observation and not be disturbed while so engaged; his body must be in what is for him a good state of health, and he must possess a sufficient amount of intelligence to be able to express and describe his sensations in accurate terms". (*Organon*, § 126)
>
> "On experiencing any particular sensation from the medicine, it is useful, indeed necessary, in order to determine the exact character of the symptom, to assume various positions while it lasts, and to observe whether, by moving the part affected, by walking in the room or the open air, by standing, sitting or lying the symptom is increased, diminished or removed, and whether it returns on again assuming the position in which it was first observed, - whether it is altered by eating or drinking, or by any other condition, or by speaking, coughing, sneezing or any other action of the body, and at the same time to note at what time of the day or night it usually occurs in the most marked manner, whereby what is peculiar to and characteristic of each symptom will become apparent". (*Organon*, § 133)

More specifically, focusing on the character and morals of the experimental subject - who has to be a **trustworthy and conscientious person** - Hahnemann condemns the recruitment of paid and little reliable individuals, since they are liable to supply uncertain or false data:

> "Latterly it has been the habit to entrust the proving of medicines to unknown persons at a distance, who were paid for their work, and the formation so obtained was printed. But by so doing, the work which is of all others the most important, which is to form the basis of the only true healing art, and which demands the greatest moral certainty and trustworthiness seems to me, I regret to say, to become doubtful and uncertain in its results and to lose all value". (*Organon*, note of § 143)

Further, drugs must be tested in healthy individuals, both female and male, in several subjects and in repeated trials in order for us to learn all their effects, since "all the symptoms peculiar to a medicine do not appear in one person, nor all at once, nor in the same experiment". On the other hand, a homeopathically selected remedy might produce in one single ill individual all its proper manifestations and heal them, "according to an eternal and immutable law of nature, by virtue of which all its effects, are brought into operation in the case of every individual if administered to him when he is in a morbid state presenting similar symptoms":

> "The medicines must be tested on both males and females, in order also to reveal the alterations of the health they produce in the sexual sphere". (*Organon,* § 127)
> "All external influences, and more especially medicines, possess the property of producing in the health of the living organism a particular kind of alteration peculiar to themselves; but all the symptoms peculiar to a medicine do not appear in one person, nor all at once, nor in the same experiment, but some occur in one person chiefly at one time, others again during a second or third trail; in another person some other symptoms appear, but in such a manner that probably some of the phenomena are observed in the fourth, eighth or tenth person which had already appeared in the second, sixth or ninth person, and so forth; moreover, they may not recur at the same hour". (*Organon,* § 134)
> "The whole of the elements of disease a medicine is capable of producing can only be brought to anything like completeness by numerous observations on suitable persons of both sexes and of various constitutions. We can only be assured that a medicine has been thoroughly proved in regard to the morbid states it can produce - that is to say, in regard to its pure powers of altering the health of man - when subsequent experimenters can notice little of a novel character from its action, and almost always only the same symptoms as had been already observed by others". (*Organon,* § 135)
> "Although, as has been said, a medicine, on being proved on healthy subjects, cannot develop in one person all the alterations of health it is capable of causing, but can only do this when given to many different individuals, varying in their corporeal and mental constitution, yet the tendency to excite all these symptoms in every human being exists in it (§ 117), according to an eternal and immutable law of nature, by virtue of which all its effects, even those that are but rarely developed in the healthy person, are brought into operation in the case of every individual if administered to him when he is in a morbid state presenting similar symptoms; it then, even in the smallest dose, being homoeopathically selected, silently produces in the patient an artificial state closely resembling the natural disease, which rapidly and permanently (homoeopathically) frees and cures him of his original malady". (*Organon,* § 136)

Coming back to the subject of the **doses** to be prescribed in order to achieve a primary effect sufficient to sensitize a healthy individual and awaken symptoms, Hahnemann takes into account the intrinsic power of drug and the susceptibility of the experimental subject: *strong, so-called heroic substances* must be administered in weak doses; people with *robust constitutions* are less susceptible to be affected by weaker doses than individuals with *delicate constitutions, irritable and sensitive:*

> "In proving medicines to ascertain their effects on the healthy body, it must be borne in mind that the strong, heroic substances, as they are termed, are liable even in small doses to produce changes in the health even of robust persons. Those of milder power must be given for these experiments in more considerable quantities; in order to observe the action of the very weakest, however, the subjects of experiment should be persons free from disease, and who are delicate, irritable and sensitive". (*Organon,* § 121)

This experimental model lends a ground for clinical practice: the amount of medicine to be given (dose) might vary according to the individual constitution of the patient; this is a hint for the possible aggravation that may follow the prescription of strong doses (large amount, mass or volume of the drug) in fragile and sensitive individuals and, conversely, it allows us to prescribe stronger doses to patients with more vigorous constitutions. Nevertheless, this cannot be assumed as a universal rule, since the individual pattern of susceptibility prevails over the constitution.

By observing the limitation of the power of drugs in their brute state (ponderal doses) to awaken in the experimental subjects "the full amount of the powers that are hidden in them", Hahnemann instituted a new and revolutionary way to prepare the homeopathic remedies through the **process of dynamization** (*serial triturations and dilutions with violent succussions*), entering thus the realm of imponderability currently studied by modern physics: "by which simple operations the powers which in their crude state lay hidden, and, as it were, dormant, are developed and roused into activity to an incredible extent". Hahnemann recommends the use of the **30th potency**, in daily repeated doses in order to awaken the idiosyncrasy of the experimental subject to the tested drug:

> "The most recent observations have shown that medicinal substances, when taken in their crude state by the experimenter for the purpose of testing their peculiar effects, do not exhibit nearly the full amount of the powers that are hidden in them which they do when they are taken for the same object in high dilutions potentized by proper trituration and succussion, by which simple operations the powers which in their crude state lay hidden, and, as it were, dormant, are developed and roused into activity to an incredible extent. In this manner we now find it best to investigate the medicinal powers even of such substances as are deemed weak, and the plan we adopt is to give to the experimenter, on an empty stomach, daily from four to six very small globules of the thirtieth potency of such a substance, moistened with a little water or dissolved in more or less water and thoroughly mixed, and let him continue this for several days". (*Organon,* § 128)

When the response is unsatisfactory, and only weak effects appear, Hahnemann advices to increase the daily dose of globules until such effects become more clear and stronger and the alterations in the state of health become more sensitive, satisfying thus the wide variation in the responses of experimental subjects according to their *individual pattern of susceptibility:*

> "If the effects that result from such a dose are but slight, a few more globules may be taken daily, until they become more distinct and stronger and the alterations of the health more conspicuous; for all persons are not effected by a medicine in an equally great degree; on the contrary, there is a vast variety in this respect, so that sometimes an apparently weak individual may by scarcely at all affected by moderate doses of a medicine known to be of a powerful character, while he is strongly enough acted on by others of a much weaker kind. And, on the other hand, there are very robust persons who experience very considerable morbid symptoms from an apparently mild medicine, and only slighter symptoms from stronger drugs. Now, as this cannot be known beforehand, it is advisable to commence in every instance with a small dose of the drug and, where suitable and requisite, to increase the dose more and more from day to day". (*Organon,* § 129)

Still on the subject of the doses to be used in pathogenetic trials, Hahnemann distinguishes *between the use of an initial strong dose from the use of repeated weaker and increasing doses.*

In the first case, after one strong enough medicinal dose one learns "the order of succession of the symptoms" *(sequence of primary actions)* allowing the experimental subject to record with precision "the period at which each occurs, which is very useful in leading to a knowledge of the genius of the medicine". Defining some limits for the strength of such *sufficiently strong doses*, Hahnemann states that they must be as moderate as possible as to

avoid the risk of confusedly exacerbating the symptoms due to the primary effect, and awakening symptoms of the secondary effect (*reaction of the vital principle*), which might happen when we prescribe *excessively large doses.* Here also applies the piece of advice above, i.e., to begin with a small dose (amount) of the remedy to increase it only when it proves to be insufficient:

> "If, at the very commencement, the first dose administered shall have been sufficiently strong, this advantage is gained, that the experimenter learns the order of succession of the symptoms and can note down accurately the period at which each occurs, which is very useful in leading to a knowledge of the genius of the medicine, for then the order of the primary actions, as also that of the alternating actions, is observed in the most unambiguous manner. A very moderate dose, even, often suffices for the experiment, provided only the experimenter is endowed with sufficiently delicate sensitiveness, and is very attentive to his sensations. The duration of the action of a drug can only be ascertained by a comparison of several experiments". (*Organon,* § 130)
>
> "The more moderate, within certain limits, the doses of the medicine used for such experiments are - provided we endeavor to facilitate the observation by the selection of a person who is a lover of truth, temperate in all respects, of delicate feelings, and who can direct the most minute attention to his sensation - so much the more distinctly are the primary effects developed, and only these, which are most worth knowing, occur without any admixture of secondary effects or reactions of the vital force. When, however, excessively large doses are used there occur at the same time not only a number of secondary effects among the symptoms, but the primary effects developed, and only these, which are most worth knowing, occur without any admixture of secondary effects or reactions of the vital force. When, however, excessively large doses are used there occur at the same time not only a number of secondary effects among the symptoms, but the primary effects also come on in such hurried confusion and with such impetuosity that nothing can be accurately observed; let alone the danger attending them, which no one who has any regard for his fellow-creatures, and who looks on the meanest of mankind as his brother, will deem an indifferent manner". (*Organon,* § 137)

In the second case, i.e., prescription of *ever increasing doses,* the experimental subject manifests "the various morbid states this medicine is capable of producing in a general manner, but we do not ascertain their order of succession", while it is also possible for some symptoms to disappear, as well as the manifestation of opposite symptoms arising from the secondary action. However, when one wants to learn all the symptoms of an unknown remedy, including the mildest ones, without any concern with "the sequential order of the phenomena and the duration of the action of the drug", it is preferable to give them during "several successive days, increasing the dose every day":

> "If, however, in order to ascertain anything at all, the same medicine must be given to the same person to test for several successive days in ever increasing doses, we thereby learn, no doubt, the various morbid states this medicine is capable of producing in a general manner, but we do not ascertain their order of succession; and the subsequent dose often removes, curatively, some one or other of the symptoms caused by the previous dose, or develops in its stead an opposite state; such symptoms should be enclosed in brackets, to mark their ambiguity, until subsequent purer experiments show whether they are the reaction of the organism and secondary action or an alternating action of this medicine". (*Organon,* § 131)
>
> "But when the object is, without reference to the sequential order of the phenomena and the duration of the action of the drug, only to ascertain the symptoms themselves, especially

> those of a weak medicinal substance, in that case the preferable course to pursue is to give it for several successive days, increasing the dose every day. In this manner the action of an unknown medicine, even of the mildest nature, will be revealed, especially if tested on sensitive persons". (*Organon,* § 132)

Even when similar characteristics had previously appeared in the experimental subject spontaneously, "all the sufferings, accidents and changes of the health of the experimenter during the action of a medicine are solely derived from this medicine", since this refers to the *inherent power of a drug to awaken symptoms in susceptible individuals.* On the other hand, *any symptom awakened by a remedy in the experimental subject is proper to the individual him or herself,* because otherwise it would not find a predisposition in him or her allowing it to manifest:

> "All the sufferings, accidents and changes of the health of the experimenter during the action of a medicine [provided the above condition (§ 124-127) essential to a good and pure experiment are complied with] are solely derived from this medicine, and must be regarded and registered as belonging peculiarly to this medicine, as symptoms of this medicine, even though the experimenter had observed, a considerable time previously, the spontaneous occurrence of similar phenomena in himself. The reappearance of these during the trial of the medicine only shows that this individual is, by virtue of his peculiar constitution, particularly disposed to have such symptoms excited in him. In this case they are the effect of the medicine; the symptoms do not arise spontaneously while the medicine that has been taken is exercising an influence over the health of the whole system, but are produced by the medicine". (*Organon,* § 138)

When discussing the **protocol to collect and record symptoms,** Hahnemann affirms that first the experimental subject "must note down distinctly the sensations, sufferings, accidents and changes of health he experiences at the time of their occurrence" including the day they appeared and how long they lasted. The doctor who directs the pathogenetic trial must revise "the report in the presence of the experimenter, while everything is still fresh in his memory" in order to investigate the symptoms in deeper detail; thus he or she has a high responsibility in this task:

> "When the physician does not make the trial of the medicine on himself, but gives it to another person, the latter must note down distinctly the sensations, sufferings, accidents and changes of health he experiences at the time of their occurrence, mentioning the time after the ingestion of the drug when each symptom arose and, if it lasts long, the period of its duration. The physician looks over the report in the presence of the experimenter immediately after the experiment is concluded, or if the trial lasts several days he does this every day, in order, while everything is still fresh in his memory, to question him about the exact nature of every one of these circumstances, and to write down the more precise details so elicited, or to make such alterations as the experimenter may suggest". (*Organon,* § 139)

Regarding what must be recorded from the report of the experimental subject, analogously to a homeopathic interview, Hahnemann indicates that one must write down "the voluntary narration of the person who makes the experiment; nothing conjectural and as little as possible derived from answers to leading questions should be admitted":

> "If the person cannot write, the physician must be informed by him every day of what has occurred to him, and how it took place. What is noted down as authentic information on this point, however, must be chiefly the voluntary narration of the person who makes the

> experiment, nothing conjectural and as little as possible derived from answers to leading questions should be admitted; everything must be ascertained with the same caution as I have counselled above (§ 84-99) for the investigation of the phenomena and for tracing the picture of natural diseases". (*Organon,* § 140)

Once again Hahnemann **advices the doctor to experiment drugs in him or herself**; and he adds that due to obvious reasons, these are the best pathogenetic trials, besides bringing countless benefits to the doctor in terms of personal verification of the principle of similitude, development of self-knowledge and self-observation, reliability of the collected symptoms, fortification of health, etc.:

> "But the best provings of the pure effects of simple medicines in altering the human health, and of the artificial diseases and symptoms they are capable of developing in the healthy individual, are those which the healthy, unprejudiced and sensitive physician institutes on himself with all the caution and care here enjoined. He knows with the greatest certainty the things he has experienced in his own person". (*Organon,* § 141)

Finally, Hahnemann alludes to the construction of "a true materia medica - a collection of real, pure, reliable modes of action of simple medicinal substances", after methodical and careful experimentation of a large number of simple substances in healthy individuals. In this context, he criticizes all kinds of *conjectures, mere assertions or imaginary* in the **Materia Medica**:

> "If we have thus tested on the healthy individual a considerable number of simple medicines and carefully and faithfully registered all the disease elements and symptoms they are capable of developing as artificial disease-producers, then only have we a true materia medica - a collection of real, pure, reliable modes of action of simple medicinal substances, a volume of the book of nature, wherein is recorded a considerable array of the peculiar changes of the health and symptoms ascertained to belong to each of the powerful medicines, as they were revealed to the attention of the observer, in which the likeness of the (homoeopathic) disease elements of many natural diseases to be hereafter cured by them are present, which, in a word, contain artificial morbid states, that furnish for the similar natural morbid states the only true, homoeopathic, that is to say, specific, therapeutic instruments for effecting their certain and permanent cure". (*Organon,* § 143)
>
> "From such a materia medica everything that is conjectural, all that is mere assertion or imaginary should be strictly excluded; everything should be the pure language of nature carefully and honestly interrogated". (*Organon,* § 144)
>
> "Of a truth, it is only by a very considerable store of medicines accurately known in respect of these their pure modes of action in altering the health of man, that we can be placed in a position to discover a homoeopathic remedy, a suitable artificial (curative) morbific analogue for each of the infinitely numerous morbid states in nature, for every malady in the world. In the meantime, even now - thanks to the truthful character of the symptoms, and to the abundance of disease elements which every one of the powerful medicinal substances has already shown in its action on the healthy body - but few disease remain, for which a tolerably suitable homoeopathic remedy may not be met with among those now proved as to their pure action, which, without much disturbance, restores health in a gentle, sure and permanent manner - infinitely more surely and safely than can be effected by all the general and special therapeutics of the old allopathic medical art with its unknown composite remedies, which do but alter and aggravate but cannot cure chronic diseases, and rather retard than promote recovery from acute diseases and frequently endanger life". (*Organon,* § 145)

Scientific Basis of the Principle of Similitude in Modern Pharmacology

SIMILITUDE IN PHARMACOLOGY

Similitude in homeopathy

Conceptual comparisons between homeopathy and pharmacology

Scientific basis of similitude in pharmacology

Examples of similitude in modern pharmacology

Similitude in homeopathy[1]

In this chapter, we have as main goal to demonstrate the universality of the principle of homeopathic similitude through the confirmation of primary and secondary effects in modern enanthiopathic drugs, widely used by conventional medicine

Since the initial planning of this study, we believed that the veracity of homeopathic fundamentals should be confirmed in experimentations with any type of drug, natural or synthetic, of vegetable, animal or mineral origin, because the theory hahnemannian be substantiated in pure experimental observation. As we dive in the study of adverse events of modern medicines, we saw corroborated the initial hypothesis.

Initially, although commented earlier, it is important to reiterate some basic aspects of homeopathic model, in order to relate the scientific foundations of experimental Pharmacology with experimental observations of Hahnemann. We are certain that the sedimentation of these concepts shall compensate for the repeating of the same character.

Enantiopathic method of treatment

Criticizing the **enantiopathic method of treatment** *(contraria contrariis curentur)* in chronic diseases, Hahnemann says that "is the deceitful bypath in the dark forest that leads to the fatal swamp". States that after a illusory initial calm, the disease deepens even more. This is because after the primary antagonistic action of palliative medicine, occurs a secondary reaction of the organism which resembles the disease itself. Describing his experience with the enantiopathic method, he concludes that it is unable to remove and annihilate the symptoms of disease; conversely, "after apparent alleviation, the symptoms become manifestly aggravated":

> "I beseech my colleagues to abandon this method *(contraria contrariis)* in chronic diseases, and in such acute diseases as take on a chronic character; it is the deceitful bypath in the dark forest that leads to the fatal swamp. The vain empiric imagines it to be the beaten highway, and plumes himself on the wretches power of giving a few hours ease, unconcerned if, during this specious calm, the disease plants its roots still deeper". *(Essay on a new principle)*[2]
>
> "IV. Palliative remedies do so much harm in chronic diseases, and render them more obstinate, probably because after their first antagonistic action they were followed by a secondary action, which is similar to the disease itself". *(Essay on a new principle)*

[1] Teixeira MZ. Semelhante cura semelhante: o princípio de cura homeopático fundamentado pela racionalidade médica e científica [Similar cures similar: the homeopathic cure principle based by the medical and scientific rationality]. São Paulo: Editorial Petrus, 1998. Available at: https://www.homeozulian.med.br/homeozulian_visualizarlivroautor.asp?id=3

[2] Hahnemann S. Essay on a new principle for ascertaining the curative power of drugs, with a few glances at those hitherto employed. In: Dudgeon RE. The lesser writings of Samuel Hahnemann. New Delhi: B. Jain Publishers, 1995.

> "All pure experience, however, and all accurate research convince us that persistent symptoms of disease are far from being removed and annihilated by opposite symptoms of medicines (as in the antipathic, enantiopathic or palliative method), that, on the contrary, after transient, apparent alleviation, they break forth again, only with increased intensity, and become manifestly aggravated". (*Organon,* § 23)[3]

Hahnemann gives examples of antipathic treatments accomplished in order to check quickly the symptoms of disease through the use of remedies able to provoke in their direct primary effect the opposite to the disease symptom to be relieved:

> "In order to carry into practice this antipathic method, the ordinary physician gives, for a single troublesome symptom from among the many other symptoms of the disease which he passes by unheeded, a medicine concerning which it is known that it produces the exact opposite of the morbid symptom sought to be subdued, from which, agreeably to the fifteen - centuries - old traditional rule of the antiquated medical school (contraria contrariis) he can expect the speediest (palliative) relief. He gives large doses of opium for pains of all sorts, because this drug soon benumbs the sensibility, and administers the same remedy for diarrhoeas, because it speedily puts a stop to the peristaltic motion of the intestinal canal and makes it insensible; and also for sleeplessness, because opium rapidly produces a stupefied, comatose sleep; he gives purgatives when the patient has suffered long from constipation and costiveness; he causes the burnt hand to be plunged into cold water, which, from its low degree of temperature, seems instantaneously to remove the burning pain, as if by magic; he puts the patient who complains of chilliness and deficiency of vital heat into warm baths, which warm him immediately; he makes him who is suffering from prolonged debility drink wine, whereby he is instantly enlivened and refreshed; and in like manner he employs other opposite (antipathic) remedial means, but he has very few besides those just mentioned, as it is only of very few substances that some peculiar (primary) action is known to the ordinary medical school". (*Organon,* § 57)

And he states that in this model of therapeutics it is approached "a single symptom in a merely one-sided manner", i.e., "only a small part of the whole", whence it cannot be expected the relief of the full disease. Moreover, after an initial amelioration of the symptom it is frequently observed an aggravation of the original disease:

> "If, in estimating the value of this mode of employing medicines, we should even pass over the circumstance that it is an extremely faulty symptomatic treatment, wherein the practitioner devotes his attention in a merely one-sided manner to a single symptom, consequently to only a small part of the whole, whereby relief for the totality of the disease, which is what the patient desires, cannot evidently be expected, - we must, on the other hand, demand of experience if, in one single case where such antipathic employment of medicine was made use of in a chronic or persisting affection, after the transient amelioration there did not ensue an increased aggravation of the symptom which was subdued at first in a palliative manner, an aggravation, indeed, of the whole disease? And every attentive observer will agree that, after such short antipathic amelioration, aggravation follows in every case without exception, although the ordinary physician is in the habit of giving his patient another explanation of this subsequent aggravation, and ascribes it to malignancy of the original disease, now for the first time showing itself, or to the occurrence of quite a new disease". (*Organon,* § 58)

[3] Hahnemann S. Organon of medicine. 6th Edn. (Translated by William Boericke). New Delhi: B Jain Publishers, 1991.

Hahnemann grounds on countless observations made in his clinical practice the *aggravation or relapse of the symptoms initially ameliorated by enantiopathic treatment.* In paragraph 59, he anticipates the **rebound phenomenon** of modern pharmacology, which he explains through the **primary effect of drugs** and the **secondary effect or vital reaction of the organism**:

> "Important symptoms of persistent diseases have never yet been treated with such palliative, antagonistic remedies, without the opposite state, a relapse - indeed, a palpable aggravation of the malady - occurring a few hours afterwards. For a persistent tendency to sleepiness during the day the physician prescribed coffee, whose primary action is to enliven; and when it had exhausted its action the day - somnolence increased; - for frequent waking at night he gave in the evening, without heeding the other symptoms of the disease, opium, which by virtue of its primary action produced the same night (stupefied, dull) sleep, but the subsequent nights were still more sleepless than before; - to chronic diarrhoeas he opposed, without regarding the other morbid signs, the same opium, whose primary action is to constipate the bowels, and after a transient stoppage of the diarrhoea it subsequently became all the worse; - violent and frequently recurring pains of all kinds he could suppress with opium for but a short time; they then always returned in greater, often intolerable severity, or some much worse affection came in their stead. For nocturnal cough of long standing the ordinary physician knew no better than to administer opium, whose primary action is to suppress every irritation; the cough would then perhaps cease the first night, but during the subsequent nights it would be still more severe, and if it were again and again suppressed by this palliative in increased doses, fever and nocturnal perspiration were added to the disease; - weakness of the bladder, with consequent retention of urine, was sought to be conquered by the antipathic work of cantharides to stimulate the urinary passages whereby evacuation of the urine was certainly at first effected but thereafter the bladder becomes less capable of stimulation and less able to contract, and paralysis of the bladder is imminent; - with large doses of purgative drugs and laxative salts, which excite the bowels to frequent evacuation, it was sought to remove a chronic tendency to constipation, but in the secondary action the bowels became still more confined; - the ordinary physician seeks to remove chronic debility by the administration of wine, which, however, stimulates only in its primary action, and hence the forces sink all the lower in the secondary its primary action, and hence the forces sink all the lower in the secondary action; - by bitter substances and heating condiments he tries to strengthen and warm the chronically weak and cold stomach, but in the secondary action of these palliatives, which are stimulating in their primary action only, the stomach becomes yet more inactive; - long standing deficiency of vital heat and chilly disposition ought surely to yield to prescriptions of warm baths, but still more weak, cold, and chilly do the patients subsequently become; - severely burnt parts feel instantaneous alleviation from the application of cold water, but the burning pain afterwards increases to an incredible degree, and the inflammation spreads and rises to a still greater height; - by means of the sternutatory remedies that provoke a secretion of mucus, coryza with stoppage of the nose of long standing is sought to be removed, but it escapes observation that the disease is aggravated all the more by these antagonistic remedies (in their secondary action), and the nose becomes still more stopped; - by electricity and galvanism, with in their primary action greatly stimulate muscular action, chronically weak and almost paralytic limbs were soon excited to more active movements, but the consequence (the secondary action) was complete deadening of all muscular irritability and complete paralysis; - by venesections it was attempted to remove chronic determination of blood to the head, but they were always followed by greater

> congestion; - ordinary medical practitioners know nothing better with which to treat the paralytic torpor of the corporeal and mental organs, conjoined with unconsciousness, which prevails in many kinds of typhus, than with large doses of valerian, because this is one of the most powerful medicinal agents for causing animation and increasing the motor faculty; in their ignorance, however, they knew not that this action is only a primary action, and that the organism, after that is passed, most certainly falls back, in the secondary (antagonistic) action, into still greater stupor and immobility, that is to say, into paralysis of the mental and corporeal organs (and death); they did not see, that the very diseases they supplied most plentifully with valerian, which is in such cases an oppositely acting, antipathic remedy, most infallibly terminated fatally. The old school physician rejoices that he is able to reduce for several hours the velocity of the small rapid pulse in cachectic patients with the very first dose of uncombined purple foxglove (which in its primary action makes the pulse slower); its rapidity, however, soon returns; repeated, and now increased doses effect an ever smaller diminution of its rapidity, and at length none at all - indeed - in the secondary action the pulse becomes uncountable; sleep, appetite and strength depart, and a speedy death is invariably the result, or else insanity ensues. How often, in one word, the disease is aggravated, or something even worse is effected by the secondary action of such antagonistic (antipathic) remedies, the old school with its false theories does not perceive, but experience teaches it in a terrible manner". (*Organon*, § 59)

Also Hahnemann foresees the phenomenon of **drug tolerance** frequently reported by modern pharmacology, when he observes that the enantiopathic method requires doses increasingly larger to alleviate temporarily a symptom, eventually resulting in the production of medicinal diseases and intoxications:

> "If these ill-effects are produced, as may very naturally be expected from the antipathic employment of medicines, the ordinary physician imagines he can get over the difficulty by giving, at each renewed aggravation, a stronger dose of the remedy, whereby an equally transient suppression1 is effected; and as there then is a still greater necessity for giving ever - increasing quantities of the palliative there ensues either another more serious disease or frequently even danger to life and death itself, but never a cure of a disease of considerable or of long standing". (*Organon,* § 60)

Homeopathic method of treatment

In view of the numerous personal clinical observations and of other authors, Hahnemann advocates the use of **homeopathic method of treatment** *(similia similibus curentur),* which is based in the administration of a medicine capable of causing in the healthy individual the same symptoms that if want to cure in the sick person. This way, through the secondary action, the organism will react against this artificial disease similar to natural disease, eliminating both and promoting healing:

> "The curative power of medicines, therefore, depends on their symptoms, similar to the disease but superior to it in strength (§ 12-26), so that each individual case of disease is most surely, radically, rapidly and permanently annihilated and removed only by a medicine capable of producing (in the human system) in the most similar and complete manner the totality of its symptoms, which at the same time are stronger than the disease". (*Organon,* § 27)

Emphasizing that "the true radical healing art" is in "the homeopathic employment of medicines according to similarity of symptoms", Hahnemann reinforces the importance of observation and reflection of "the sad results of the antagonistic employment of medicines" so that we can support the principle of similitude. Following this logical reasoning, which employs this "mode that affirms by negating" (corresponding to the present "null hypothesis" of modern statistics), we studied the rebound effect of the use of antagonistic drugs according to modern pharmacology, in order to substantiate the universality of the principle of similitude:

> "Had physicians been capable of reflecting on the sad results of the antagonistic employment of medicines, they had long since discovered the grand truth, *that the true radical healing art must be found in the exact opposite of such an antipathic treatment of the symptoms of disease;* they would have become convinced, that as a medicinal action antagonistic to the symptoms of the disease (an antipathically employed medicine) is followed by only transient relief, and after that is passed, by invariable aggravation, the converse of that procedure, the homeopathic employment of medicines according to similarity of symptoms, must effect a permanent and perfect cure, if at the same time the opposite of their large doses, the most minute doses, are exhibited. But neither the obvious aggravation that ensued from their antipathic treatment, nor the fact that no physician ever effected a permanent cure of disease of considerable or of long standing unless some homeopathic medicinal agent was accidentally a chief ingredient in his prescription, nor yet the circumstances that all the rapid and perfect cures that nature ever performed (§ 46), were always effected by the supervention upon the old disease of one of a similar character, ever taught them, during such a long series of centuries, this truth, the knowledge of which can alone conduce to the benefit of the sick". (*Organon,* § 61)

Primary action of drugs and secondary action of the organism

Starting from the principle that "every medicine deranges more or less the vital force causing a certain alteration in the health of the individual", Hahnemann attributes the so-called **primary action of drugs** to their direct effect on the organism. To this effect "our vital force endeavors to oppose its own energy" in a conservative, automatic and instinctive manner called **secondary action** or **vital reaction**:

> "Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed primary action. [...]. To its action our vital force endeavors to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of secondary action or counteraction". (*Organon,* § 63)
>
> "During the primary action of the artificial morbific agents (medicines) on our healthy body, as seen in the following examples, our vital force seems to conduct itself merely in a passive (receptive) manners, and appears, so to say, compelled to permit the impressions of the artificial power acting from without to take place in it and thereby after its state of health; it then, however, appears to rouse itself again, as it were, and to develop (A) the exact opposite condition of health (counteraction, secondary action) to this effect (primary action) produced upon it, if there be such an opposite, and that in as great a degree as was the effect (primary action) of the artificial morbific agent on it, and proportionate to its own energy; - or (B) if there be not in nature a state exactly the opposite of the primary action, it

> appears to endeavor to indifferentiate itself, that is, to make its superior power available in the extinction of the change wrought in it from without (by the medicine), in the place of which it substitutes its normal state (secondary action, curative action)". (*Organon,* § 64)

Homeopathic pathogenetic experimentation

To get one **Materia Medica,** which can be used in accordance with the principle of similarity, Hahnemann reiterates that "nothing then remains but to test the medicines we wish to investigate on the human body itself". With the detailed description of the primary effects that the various substances cause in the human body, we will be able to choose the medicine that presents the greatest similarity to symptomatic totality we want to cure:

> "*Nothing then remains but to test the medicines we wish to investigate on the human body itself.* The necessity of this has been perceived in all ages, but a false way was generally followed, inasmuch as they were, as above stated, only employed empirically and capriciously in diseases. The reaction of the diseased organism, however, to an untested or imperfectly tested remedy, gives such intricate results, that their appreciation is impossible for the most acute physician. Either nothing happens, or there occur aggravations, changes, amelioration, recovery, death - without the possibility of the greatest practical genius being able to divine what part the diseased organism, and what the remedy (in a dose, perchance, too great, moderate, or too small) played in effecting the result. The teach nothing, and only lead to false conclusions". *(Essay on a new principle)*
>
> "The whole pathogenetic effect of the several medicines must be known; that is to say, all the morbid symptoms and alterations in the health that each of them is specially capable of developing in the healthy individual must first have been observed as far as possible, before we can hope to be able to find among them, and to select, suitable homeopathic remedies for most of the natural disease". (*Organon,* § 106)

Hahnemann observes that to properly investigate the effects of medicines in human beings, *healthy individuals* must be preferred over the *ill* ones because in the latter the symptoms of disease become intertwined with the primary actions of the medicines and thus, no clear picture can be made. Thus, he emphasizes that testing on the *healthy* is the safest and most natural path to discover "the peculiar effects of medicines":

> "If, in order to ascertain this, medicines be given to sick persons only, even though they be administered singly and alone, then little or nothing precise is seen of their true effects, as those peculiar alterations of the health to be expected from the medicine are mixed up with the symptoms of the disease and can seldom be distinctly observed". (*Organon,* § 107)
>
> "There is, therefore, no other possible way in which the peculiar effects of medicines on the health of individuals can be accurately ascertained - there is no sure, no more natural way of accomplishing this object, than to administer the several medicines experimentally, in moderate doses, to healthy persons, in order to ascertain what changes, symptoms and signs of their influence each individually produces on the health of the body and of the mind; that is to say, what disease elements they are able and tend to produce1, since, as has been demonstrated (§ 24-27), all the curative power of medicines lies in this power they possess of changing the state of man's health, and is revealed by observation of the latter" (*Organon,* § 108)

Hahnemann underlines the validity of his experimental and scientific methodology for the study of the healing power of the medicines with examples clearly analogous to the ones in records of older physicians regarding the effects of drugs in healthy individuals (intoxications, suicide attempts, improper treatments, etc.). Raising the pathogenetic power to the level of a *natural, fixed and eternal law*, he extends this property to all substances in nature and to all sensitive individuals, both healthy and ill:

> "The agreement of my observations on the pure effects of medicines with these older ones - although they were recorded without reference to any therapeutic object, - and the very concordance of these accounts with others of the same kind by different authors must easily convince us that medicinal substances act in the morbid changes they produce in the healthy human body according to fixed, eternal laws of nature, and by virtue of these are enabled to produce certain, reliable disease symptoms each according to its own peculiar character". (*Organon,* § 111)

In this regard it must be stressed that, although Hahnemann insisted from a theoretical point of view on *testing on healthy individuals* as the only safe and reliable method to investigate the pathogenetic symptoms elicited by drugs, in actual practice, due to the insurmountable difficulties inherent to carrying out perfectly controlled trials, he also employed the symptoms resulting from *testing on the sick,* either making profit of the reports of improper treatments accomplished in the past, or from his own observations of chronic patients he had treated. Probably, the warning in paragraph 109 of the *Organon* regarding the risk of mixing together the symptoms of the patient and the symptoms of the tested drug with the consequent loss of precision was duly taken into account.

Therefore, it possible to take into account the **primary symptoms of drugs appearing in the treatment of ill people** *(side or adverse effects of drugs),* **provided we are able to distinguish them from the previous disease to avoid mixing the symptoms of disease and the pathogenetic symptoms of drugs**.

Secondary action of the organism or rebound effect

In the paragraph 112 of the *Organon,* Hahnemann explains the theory of the **rebound effect** (*withdrawal syndrome*) described by modern clinical pharmacology, demonstrating the secondary effect of the organism (vital reaction, in homeopathic terms) seeking its own homeostasis.

Studying the reports about "medicines ingested in excessively large doses", Hahnemann observes that after the suspension of the drug, there appear "certain states that were of an exactly opposite nature to those that first appeared". He describes the nature such symptoms "exactly opposite" to the **primary action** as a "reaction of the vital force of the organism, its **secondary action**". However, he adds that "there is seldom or hardly ever the least trace from experiments with moderate doses on healthy bodies", and they lack completely when doses are indeed very small (dynamized remedies).

With modern drugs from various categories, *there is an intensification of symptoms initially suppressed after the abrupt discontinuation of treatment.* This **rebound effect** or reaction of the vital force (secondary action), confirms Hahnemann's warning that the initial stages of the disease may be worsened by treatment directed to the mere palliation of symptoms, effect sought by most modern antagonistic treatments:

> "In those older prescriptions of the often dangerous effects of medicines ingested in excessively large doses we notice certain states that were produced, not at the commencement, but towards the termination of these sad events, and which were of an exactly opposite nature to those that first appeared. These symptoms, the very reverse of the primary action (§ 63) or proper action of the medicines on the vital force are the reaction of the vital force of the organism, its secondary action (§ 62-67), of which, however, there is seldom or hardly ever the least trace from experiments with moderate doses on healthy bodies, and from small doses none whatever. In the homeopathic curative operation the living organism reacts from these only so much as is requisite to raise the health again to the normal healthy state (§ 67)". (*Organon,* § 112)

Through this **rebound effect,** i.e., *the symptoms of the vital reaction or secondary action of the organism in the sense to equilibrate the internal medium*, we can infer the direct effect (*primary action*) of drugs on sensitive organisms, precisely because *they are their polar opposites:*

> "VI. As it may be almost considered an axiom, that the symptoms of the secondary action are the exact opposite of those of the direct action, it is allowable for a master of the art, when the knowledge of the symptoms of the direct action is imperfect, to supply in imagination the lacunae by induction, i. e., the opposite of the symptoms of the secondary action the result, however, must only be considered as an addition to, not as the basis of, his conclusions." *(Essay on a new principle)*

Medicinal doses

With the exception of *narcotic drugs*, all medicines, when administered in "moderate doses" only provoke the appearance of the direct primary effects, while nothing is reported regarding the indirect secondary effects. However, this does not happen with the use of "excessively large doses", where the *vital reaction, secondary action* or *rebound effect* is evident:

> "An obvious antagonistic secondary action, however, is, as may readily be conceived, not to be noticed from the action of quite minute homeopathic doses of the deranging agents on the healthy body. A small dose of every one of them certainly produces a primary action that is perceptible to a sufficiently attentive; but the living organism employs against it only so much reaction (secondary action) as is necessary for the restoration of the normal condition". (*Organon,* § 66)
>
> "The only exceptions to this are the narcotic medicines. As they, in their primary action, take away sometimes the sensibility and sensation, sometimes the irritability, it frequently happens that in their secondary action, even from moderate experimental doses on healthy bodies, an increased sensibility (and a greater irritability) is observable". (*Organon,* § 113)
>
> "With the exception of these narcotic substances, in experiments with moderate doses of medicine on healthy bodies, we observe only their primary action, i.e., those symptoms

wherewith the medicine deranges the health of the human being and develops in him a morbid state of longer or shorter duration". (*Organon*, § 114)

"The more moderate, within certain limits, the doses of the medicine used for such experiments are - provided we endeavor to facilitate the observation by the selection of a person who is a lover of truth, temperate in all respects, of delicate feelings, and who can direct the most minute attention to his sensation - so much the more distinctly are the primary effects developed, and only these, which are most worth knowing, occur without any admixture of secondary effects or reactions of the vital force. When, however, excessively large doses are used there occur at the same time not only a number of secondary effects among the symptoms, but the primary effects also come on in such hurried confusion and with such impetuosity that nothing can be accurately observed; let alone the danger attending them, which no one who has any regard for his fellow-creatures, and who looks on the meanest of mankind as his brother, will deem an indifferent manner". (*Organon*, § 137)

Conceptual comparisons between homeopathy and pharmacology[4]

In this section, we relate Hahnemann's phenomenological observations to notions of modern clinical and experimental pharmacology.

Pharmacodynamics, one of the basic branches of pharmacology, studies "the biochemical and physiological effects of drugs and their mechanisms of action". Its main goal is "to identify the primary action of drugs in the human body" in order to "delineate the chemical or physical interactions between drug and cell, beyond the biochemical and physiological regulation". Acting on the so-called "physiological receptors" through their primary effects, drugs can stimulate *(agonist)* or inhibit *(antagonist)* a given biochemical or physiological function so as to respectively counterbalance their possible deficiency or excess. There are still some drugs that act directly on their target-cells without the involvement of receptors, as it is the case of chelating agents, antacid and osmolar drugs, volatile general anesthesics, chemotherapic drugs, etc.:

> "Pharmacodynamics can be defined as the study of the biochemical and physiological effects of drugs and their mechanisms of action. The latter aspect of the subject is perhaps the most fundamental challenge to the investigator in pharmacology, and information derided from such study is of basic utility to the clinician. The objectives of the analysis of drug action are to identify the primary action (as distinguished from describing resultant effects), to delineate the chemical or physical interactions between drug and cell, and to characterize the full sequence and scope of actions and effects. Such a complete analysis provides the basis for both the rational therapeutic use of a drug and the design of new and superior therapeutic agents. Basic research in pharmacodynamics also provides fundamental insight into biochemical and physiological regulation. [...] The effects of most drugs result from their interactions with macromolecular components of the organism. Such interaction alters the function of the pertinent component and thereby initiates the biochemical and physiological changes that are characteristic of the response to the drug. [...] The terms *receptive substance* and, more simply, *receptor* were coined to denote the component of the organism with wich the chemical agent was presumed to interact. [...] Many drugs act on such physiological receptors. Those that mimic the effects of the endogenous regulatory compound are termed *agonists.* Other compounds may bind to the receptor but have no intrinsic regulatory activity; the result of such binding may be interference with the effect of an agonist. Compounds that are themselves devoid of intrinsic regulatory activity but cause effects by inhibition of the action of an agonist (*e.g.*, by competition for agonist binding sites) are termed *antagonists*". (*The pharmacological basis of therapeutics*, p. 33)[5]

Unfortunately, modern clinical pharmacology does not take into account the **automatic mechanisms of homeostatic control of the organism**, i.e., the ones involved in the self-

[4] Teixeira MZ. Semelhante cura semelhante: o princípio de cura homeopático fundamentado pela racionalidade médica e científica [Similar cures similar: the homeopathic cure principle based by the medical and scientific rationality]. São Paulo: Editorial Petrus, 1998. Available at: https://www.homeozulian.med.br/homeozulian_visualizarlivroautor.asp?id=3

[5] Goodmann LS, Ral TW, Nies AS, Taylor P. The pharmacological basis of therapeutics. Eighth edition. New York: Pergamon Press, 1990.

regulation of the internal medium through the mobilization of different biochemical and physiological systems. For this reason, when one pharmacological means is used to awaken a definite primary (or direct) effect of stimulation or inhibition on a given biochemical or physiological function, it is not taken into account the reaction that the organism will direct against the disturb of the internal homeostasis (secondary or indirect effect) aiming at neutralizing the artificial dysfunction triggered by the drug. In this way, it is observed a reactive effect by the organism opposite to the expected one, which very often further complicates the original picture of the disease.

According to the pharmacodynamic mechanism of physiological receptors - in turn also "subject to many regulatory and homeostatic controls" - these phenomena of compensation can occur as a "state of *desensitization,* also referred to as *refractoriness* or *down regulation*", so that the effect following continual exposure to a drug decreases. This explains the phenomenon of organic **tolerance to drugs** or acquired hypo-reactivity. On the other hand, "hyperreactivity or super sensitivity to receptor agonists is also frequently observed to follow reduction in the chronic level of receptor stimulation". In such cases it is observed the **rebound effect** of the organism against the initial primary or direct stimulus:

> "**Regulation of Receptors.** It is important to recognize that receptors not only initiate regulation of physiological and biochemical function but also are themselves subject to many regulatory and homeostatic controls. For example, continued stimulation of cells with agonists generally results in a state of *desensitization* (also referred to as *refractoriness* or *down regulation*), such that the effect that follows continued or subsequent exposure to the same concentration of drug is diminished. This phenomenon can become very important in therapeutic situations; an example is the repeated use of *β*-adrenergic bronchodilators for the treatment of asthma. Multiple mechanisms exist that account for desensitization of different types. In some cases, only the signal from the stimulated receptor becomes attenuated, a process known as homologous desensitization. This may involve covalent modification (*e.g.*, phosphorylation) of the receptor, the destruction of the receptor, or its relocalization within the cell. Synthesis of receptors is also subject to feedback regulation. In other situations, receptors for different hormones that act on a single signaling pathway may become less effective. Such heterologous desensitization may result either from modification of each receptor by a common feedback mechanism or from effects exerted at some common point in the effector pathway distal to the receptor itself. Predictably, hyperreactivity or super sensitivity to receptor agonists is also frequently observed to follow reduction in the chronic level of receptor stimulation. Situations of this type can result from the long-term administration of antagonists such as propranolol. In at least some cases super sensitivity may result from the synthesis of additional receptors". (*The pharmacological basis of therapeutics*, p. 40-41)

By relating the **rebound effect** to the discontinuance of the primary stimulus of a drug (*withdrawal syndrome*) modern pharmacology recorded the occurrence of this phenomenon after the discontinuance of a large number of drugs:

> "**Tolerance and Physical Dependence.** In addition to the primary reinforcing effects, other factors come into play during long-term drug use that profoundly affect the pattern of use and the likelihood that the drug use will be continued. Among these factors are the capacities of some substances to produce tolerance and/or physical dependence. These phenomena, as previously defined, are often assumed to be inextricably linked to each other and to the problem of compulsive drug use. Neither of these assumptions is valid. Tolerance

and physical dependence develop not only with opioids, ethanol, and hypnotics but also after long-term administration of a wide variety of drugs that are not self-administered by animals or used compulsively by man. Such drugs include anticholinergics, dopaminergic antagonists, and imipramine. Rebound withdrawal effects may also be seen after abrupt discontinuation of β-adrenergic antagonists, Ca^{2+}-channel blockers, or α_2-adrenergic agonists. Nor does physical dependence invariably occur in every situation where tolerance develops. Tolerance is a general phenomenon observed with a host of substances, and many independent mechanisms are involved". (*The pharmacological basis of therapeutics,* p. 524)

Scientific basis of similitude in pharmacology[6]

According to the homeopathic model, therapeutics is grounded on the administration of a drug stimulus ("artificial disease") similar to the natural disease to heal, promoting in this way a reaction of the organism seeking the equilibrium of the internal medium (homeostasis). This is the basis of the **principle of therapeutic similitude**.

In theory, any drug ought to be able to elicit in "healthy" individuals the same symptoms it can heal in the "sick"; such symptoms are rated the **primary action** or **effect of the drug**. The homeopathic process of healing is accomplished through the **secondary action** or **effect of the organism** (homeostatic or paradoxical reaction), which reestablishes health by neutralizing the primary effect of a drug (artificial disease) exhibiting symptoms similar to the ones of the natural disease.

In this study, **we sought to demonstrate that the secondary action (vital reaction) of the organism can be detected with the use of a large number of modern drugs after the discontinuance or suspension of palliative treatment** (*withdrawal syndrome*), which thus confirms Hahnemann's observations. According to the founder of homeopathy, when criticizing the antipathic method of treatment, it can be observed that **after the suspension of drugs enantiopathically used to annihilate symptoms according to the principle of contraries, these very same symptoms, which were initially suppressed, come back with a higher intensity than at the beginning, confirming thus the phenomenon of secondary reaction of the organism leading to the maintenance of the internal medium.**

According to modern pharmacology, this secondary effect (homeopathic vital reaction) is defined as **rebound effect** or **paradoxical reaction of the organism**, which always manifests with a **higher intensity than the symptoms initially suppressed**, refuting thus the hypothesis arguing for the natural evolution of disease after the discontinuance of treatment.

On the other hand, some conventional drugs work according to the principle of similitude, this is, they promote the **cure of symptoms through the secondary reaction of the organism (rebound effect)**.

In order to give scientific foundations to the universal application of the principle of therapeutic similitude and the homeostatic response to pharmacological stimuli expressed through the **paradoxical reaction** or **rebound effect** of the organism, we approached the study of modern drugs as to the effects they cause on the human body.

[6] Teixeira MZ. Semelhante cura semelhante: o princípio de cura homeopático fundamentado pela racionalidade médica e científica [Similar cures similar: the homeopathic cure principle based by the medical and scientific rationality]. São Paulo: Editorial Petrus, 1998. Available at: https://www.homeozulian.med.br/homeozulian_visualizarlivroautor.asp?id=3

Our main goal is to show the universal occurrence of the **secondary action of the organism (rebound effect) manifested through of the worsening of the initial symptoms of disease after discontinuance of enantiopathic (palliative) treatment**.

The **rebound effect** is also observed in treatments poorly carried out due to the use of inadequate doses of drugs. As long as the drug is taken in doses fit to act contrarily to the symptoms of disease its antagonistic effect will be present. However, when the patient does not take the drug in the dose and frequency needed to maintain its ideal concentration in the blood – an event extremely frequent in any therapeutic scheme - or in the case of the usual discontinuance of treatment, the organism can react and give raise to secondary symptoms contrary to the ones initially sought to be annihilated through the use of the palliative treatment.

This study also showed some **instances of treatments with enantiopathic drugs according to the principle of therapeutic similarity.**

In order to establish the primary and secondary effects of modern drugs, the search of relevant data requires consulting the most reliable databases reporting on evidence found in clinical experimental pharmacology bypassing the conflicts of interest of the pharmaceutical industry. This source was supplied by *The United States Pharmacopeia Dispensing Information (USP DI, 1996)*[7] and *American Hospital Formulary Service (AHFS, 1990)*[8]:

> "The source of information described as most often used by physicians in an industry survey is the *Physicians' Desk Reference* (PDR). The brand-name manufacturers whose products appear support this book. No comparative data on efficacy, safety, or cost are included. The information is identical to that contained in drug package inserts, wich are largely based on the results of phase-3 testing; its primary value is thus in learning what indications for use of a drug have been approved by the FDA. There are, however, several inexpensive, unbiased sources of information on the clinical uses of drugs that are preferable to the industry-supported PDR. All recognize that the physician's legitimate use of a drug in a particular patient is not limited by FDA-approved labeling in the package insert. *The United States Pharmacopeia Dispensing Information* (USPDI), first published in 1980, comes in two volumes. One, *Drug Information for the Health Care Provider*, consists of drug monographs that contain practical, clinically significant information aimed at minimizing the risks and enhancing the benefits of drugs. Monographs are developed by USP staff and are reviewed by advisory panels and other reviewers. [...] The *American Hospital Formulary Service* (AHFS), published by the American Society of Hospital Pharmacists, is a collection of monographs that are kept current by periodic supplements. The monographs are written on a single drug; there are also general discussions of drugs that are included in a defined class. [...] Industry promotion, in the form of direct-mail brochures, journal advertising, displays, professional courtesies, or the detail person or pharmaceutical representative, is intended to be persuasive rather than educational. The pharmaceutical industry cannot, should not, and indeed does not purport to be responsible

[7] The United States Pharmacopeial Convention. The United States Pharmacopeia Dispensing Information. 16th ed. Easton: Mack Printing Co., 1996.
[8] American Hospital Formulary Service Drug Information. Bethesda: American Society of Hospital Pharmacists, 1990.

> for the education of physicians in the use of drugs. [...] *The United States Pharmacopeia* (USP) and *The National Formulary* (NF) were recognized as 'official compendia' by the Federal Food and Drug Act of 1906. The approved therapeutic agents used in medical practice in the United States are described and defined with respect to source, chemistry, physical properties, tests for identity and purity, assay, and storage. The two official compendia are now published in a single volume". (*The pharmacological basis of therapeutics*, p. 33)[9]

Together with the study of the symptoms elicited by drugs on human beings as described in *USP DI* and *AHFS*, we also looked for published scientific studies on the **rebound effect** or **paradoxical reaction of the organism** in indexed scientific journals. Searching with these criteria in database *Medline*[10] for a 15-year interval (1982-1997), we were able to find a number of clinical assays and experimental studies that demonstrated the occurrence of the secondary reaction of the organism *(rebound effect)* in response to enantiopathic treatments. As a rule, such secondary effect or exacerbation of the symptoms initially sought to be relieved appeared after discontinuance of drugs in variable times and with also variable durations, however usually with intensity higher than the one of the basal symptoms. The same effect was also observed in some studies on "healthy individuals".

In some of the scientific studies carried out according to a same experimental protocol, we observed contradictory results regarding the **rebound effect** of one and the same drug, which suggests the possibility of alteration of results due to alien interests. It must be admitted that unfortunately, ethics in scientific publication in medicine is a controversial issue, since it is not exempt from conflicts of interest.[11]

[9] Goodmann LS, Ral TW, Nies AS, Taylor P. The pharmacological basis of therapeutics. Eighth edition. New York: Pergamon Press, 1990.
[10] Medline/ EBSCO CDRom. Version 5.2. Maryland: EBSCO Publishing, National Library of Medicine, 1997.
[11] Institute of Medicine (US) Committee on Conflict of Interest in Medical Research, Education, and Practice (Lo B, Field MJ, editors). Conflict of Interest in Medical Research, Education, and Practice. Washington (DC): National Academies Press (US); 2009. Available at: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=nap12598

Examples of similitude in modern pharmacology[12,13]

In this last and conclusive part of the study, we surveyed the adverse events of modern drugs described in *USP DI* and *AHFS* as well as in clinical and experimental assays indexed in *Medline*. The **primary outcome** was the description of **symptoms opposing the primary effects of drugs** after they are discontinued. Such secondary effects correspond to the paradoxical reaction of the organism to the primary enantiopathic therapeutic stimulus known as **rebound effect**. The same phenomenon was observed in the case of irregular treatments (decrease of the therapeutic dosis).

As **secondary outcome** some scientific studies were found exemplifying the **use of modern drugs according to the principle of therapeutic similitude**.

From the descriptions of the effects of drugs we initially highlighted the **primary effect (therapeutic indications)** followed by **rebound effect** grouped according to the different systems of action. The sources of information are quoted according to the code below:
 # The United States Pharmacopeia Dispensing Information (USP DI, 1988, 1994, 1996);[14,15,16]
 # American Hospital Formulary Service (AHFS, 1990);[17]
Medline (1982 - 1997).[18]

[12] Teixeira MZ. Semelhante cura semelhante: o princípio de cura homeopático fundamentado pela racionalidade médica e científica [Similar cures similar: the homeopathic cure principle based by the medical and scientific rationality]. São Paulo: Editorial Petrus, 1998. Available at: https://www.homeozulian.med.br/homeozulian_visualizarlivroautor.asp?id=3
[13] Teixeira MZ. Similitude in modern pharmacology. *Br Homeopath J.* 1999; 88(3): 112-120. Disponível em: https://doi.org/10.1054/homp.1999.0301
[14] The United States Pharmacopeial Convention. The United States Pharmacopeia Dispensing Information. 8ª ed. Easton: Mack Printing Co., 1988.
[15] The United States Pharmacopeial Convention. The United States Pharmacopeia Dispensing Information. 14ª ed. Easton: Mack Printing Co., 1994.
[16] The United States Pharmacopeial Convention. The United States Pharmacopeia Dispensing Information. 16ª ed. Easton: Mack Printing Co., 1996.
[17] American Hospital Formulary Service Drug Information. Bethesda: American Society of Hospital Pharmacists, 1990.
[18] Medline/ EBSCO CDRom. Version 5.2. Maryland: EBSCO Publishing, National Library of Medicine, 1997.

CARDIOVASCULAR DRUGS

Antiarrhythmic drugs

Adenosine
Therapeutic indications: Treatment (conversion) of paroxysmal supraventricular tachycardia, including the association with Wolff-Parkinson-White syndrome.
Rebound effect:
Frequent new arrhythmias: atrial contractions and ventricular premature; bradycardia and sinus tachycardia; heart block of first, second and third degree. *(USP DI, 1996, p. 28)*

Amiodarone
Therapeutic indications: Ventricular arrhythmias and supraventricular.
Rebound effect:
Fast or irregular heartbeat [exacerbation or new arrhythmias occurred in 2-5% of patients, including paroxysmal ventricular tachycardia, ventricular fibrillation, increased resistance to cardioversion, and atypical ventricular tachycardia *(torsade de pointes)*, which may be associated to an effective extension of the range QT]. *(USP DI, 1996, p. 83; AHFS, 1990, p. 779)*

Beta-blockers *(Atenolol, Esmolol, Labetalol, Pindolol, Propranolol; Timolol, etc.)*
Therapeutic indications: Ventricular arrhythmias.
Rebound effect:
Fast or irregular heartbeat. Ventricular tachycardia with abrupt discontinuation. *(USP DI, 1996, p. 579)*
Intensification of arrhythmia, AV block, AV dissociation, full heart block or cardiac arrest. *(AHFS, 1990, p. 861, 871, 934)*
Author(s): Kantelip JP; Trolese JF; Cromarias PG; Duchene-Marullaz P / Title: Effect on heart rate over 24 hours of pindolol administered for 14 days. / Source: *Eur J Clin Pharmacol.* 1984. 27(5). P 535-8. / Abstract: The effect on heart rate of pindolol 5, 15 and 30 mg/day, a beta-adrenoreceptor blocker possessing intrinsic sympathomimetic activity, administered to 8 healthy volunteers for 14 days was studied. Heart rate was continuously recorded over 24 h during placebo treatment before each sequence, every 2 days during treatment, and then on the 15th, 17th and 18th days. Pindolol in the three doses used had no significant effect on mean heart rate over 24 h. It tended to lower mean diurnal heart rate non-significantly between noon and 6 p.m. Pindolol raised nocturnal heart rate between midnight and 6 a.m. to a comparable extent at all the doses used. Sympathetic tone is at its lowest during that period, which makes it possible to detect the intrinsic sympathomimetic activity of pindolol. After cessation of treatment, a rebound effect was observed, cardioacceleration being most marked after 30 mg/day.
Author(s): Brodde OE; Wang XL; O'Hara N; Daul A; Schiess W / Title: Effect of propranolol, alprenolol, pindolol, and bopindolol on beta2-adrenoceptor density in human lymphocytes. / Source: *J Cardiovasc Pharmacol*. 1986. 8 Suppl 6P S70-3. / Abstract: Abrupt withdrawal of beta-adrenoceptor antagonists may lead to "rebound effects." To investigate the position of the new nonselective beta-adrenoceptor antagonist bopindolol [with moderate intrinsic sympathomimetic activity (ISA)], this drug was compared with propranolol (no ISA), alprenolol (weak ISA), and pindolol (marked ISA). The effects on lymphocyte beta 2-adrenoceptor density--assessed by (+/-)-

[125I]iodocyanopindolol (ICYP) binding--were investigated in healthy volunteers aged 23-35 years. None of the test drugs changed the affinity of ICYP for beta 2 adrenoceptors. Propranolol treatment (4 X 40 mg/day) increased the density of beta 2-adrenoceptors by 25% after 2 days; during treatment beta 2-adrenoceptor density remained elevated. After withdrawal of propranolol, beta 2-adrenoceptor density declined slowly, being still significantly increased after 3 days, although propranolol was not detectable in plasma after 24 h, though heart rate was significantly increased. Alprenolol treatment (4 X 100 mg/day) did not significantly affect beta 2-adrenoceptor density. Pindolol treatment (2 X 5 mg/day) caused a 50% decrease of beta 2-adrenoceptor density after 2 days, which remained reduced during treatment. After withdrawal, beta 2-adrenoceptor density was still significantly diminished after 4 days. During and after treatment heart rate was not affected. Bopindolol treatment (2 mg/day) caused a 40% decrease of beta 2-adrenoceptor density after 2 days, which remained reduced during treatment. After withdrawal, beta 2-adrenoceptor density was still significantly diminished after 4 days. During and after treatment heart rate was not affected. It is concluded that the ISA may play an important role in modulating beta 2-adrenoceptor density and hence tissue responsiveness to beta-adrenoceptor stimulation.

Author(s): Lee SS; Braillon A; Girod C; Geoffroy P; Lebrec D / Title: Haemodynamic rebound phenomena after abrupt cessation of propranolol therapy in portal hypertensive rats. / Source: *J Hepatol*. 1986. 3(1). P 38-41. / Abstract: The haemodynamic effect of sudden termination of propranolol therapy was studied in sham-operated and portal hypertensive rats. All animals were injected with propranolol (20 mg/kg/day) or saline i.p. for 10 days, then had an isoproterenol infusion test performed 48 h or 72 h after cessation of injections. The dose of isoproterenol required to increase the heart rate by 50 beats/min (CD50), was significantly lower in both sham-operated and portal hypertensive rats at 48 h after propranolol withdrawal. Maximum chronotropic response (Rmax), was significantly higher only in portal hypertensive rats at 48 h after propranolol withdrawal. These results show the existence of a transient beta-adrenergic hypersensitivity state following propranolol withdrawal in normal and portal hypertensive rats.

Author(s): Moore LR; Corbo M; Chien YW / Institution: Controlled Drug Delivery Research Center, Rutgers, State University of New Jersey, College of Pharmacy, Piscataway. / Title: Development of the rabbit model for studying the effects of propranolol on cardiac contractility: relationship of intravenous pharmacodynamics and pharmacokinetics. / Source: *Methods Find Exp Clin Pharmacol*. 1988 Mar. 10(3). P 157-63. / Abstract: The New Zealand white rabbit (3-4 kg) was chosen as an experimental model to determine the effects of propranolol, by intravenous bolus administration, on cardiac contractility. The cardiovascular effects were measured by systolic time interval recordings for up to 8 h. The study was performed on two groups of animals with 5 rabbits receiving active drug and another 5 rabbits receiving saline placebo. All animals were anesthetized by parenteral administration of urethane/acepromazine. The results indicated that at 15 min after intravenous administration, propranolol caused a maximum decrease in heart rate (p less than 0.01), as well as a maximum increase in QS2 (p less than 0.01), LVET (p less than 0.01), PEP (p less than 0.01) and PEP/LVET (p less than 0.05). Approximately 90 min after drug administration, a significant (p less than 0.01) “rebound phenomenon” was observed in the active group which continued throughout the 8-h observation period. This preliminary study suggests that the rabbit is a useful animal model to study the effects of propranolol on cardiac contractility.

Author(s): Greenspan AM; Spielman SR; Horowitz LN; Laddu A; Senior S / Institution: Likoff Cardiovascular Institute of Hahnemann University, Philadelphia, Pennsylvania 19102. / Title: The electrophysiologic properties of esmolol, a short acting beta-blocker. / Source: *Int J Clin Pharmacol Ther Toxicol*. 1988 Apr. 26(4). P 209-16. / Abstract: Although beta-blockers have established efficacy in treating ventricular ectopy and PSVT, their applicability for acute antiarrhythmic interventions in patients with organic heart disease or COPD, is frequently limited by negative inotropic or bronchospastic side effects. The development of an ultrashort acting beta-blocker with rapid reversibility of its side effects would widen their applicability. Therefore, we tested the

electrophysiologic properties of such a new short acting beta-blocker, esmolol, in 14 patients (10 with organic heart disease) with a mean EF of 47.6 +/- 17%, undergoing standard clinical electrophysiologic studies for various indications. Like most other beta-blockers, esmolol's major direct effects were on sinus node function and AV nodal conduction characteristics; significantly prolonging sinus cycle length, cycle length to Wenckebach and AH interval in sinus rhythm and at a paced cycle length of 600 ms. In contrast to most other beta-blockers, following termination of its infusion, esmolol shortened parameters of sinus node function and AV nodal refractoriness, with respect to the control values, suggesting a possible rebound phenomena. These effects occurred within 5 min of terminating the intravenous drug infusion. Esmolol had no significant effect on systolic blood pressure, electrocardiographic intervals and had rare adverse reactions. We conclude that esmolol is an ultra-short acting beta-blocker, with typical direct electrophysiologic effects on sinus node and AV nodal function, and a possible rebound phenomenon following its discontinuation that may make it particularly suited to acute antiarrhythmic interventions in patients susceptible to adverse beta-blocker side effects.
Author(s): Ebii K; Fukunaga R; Taniguchi T; Fujiwara M; Nakayama S; Saitoh Y; Kimura Y / Institution: Department of Neurobiology, Kyoto Pharmaceutical University, Japan. / Title: Effects of chronic administration of carteolol on beta-adrenoceptors in spontaneously hypertensive rat heart. / Source: *Jpn J Pharmacol*. 1991 Aug. 56(4). P 505-12. / Abstract: We studied the effects of chronic administration of beta-adrenoceptor antagonists with and without intrinsic sympathomimetic activity (ISA): carteolol (with ISA) and propranolol (without ISA), respectively, on the heart of spontaneously hypertensive rat (SHR) and Wistar Kyoto rat (WKY). Six-week-old SHRs and WKYs were orally given carteolol or propranolol for ten weeks. The heart rate was reduced in propranolol-treated SHR, but not in carteolol-treated ones. In WKY, carteolol-treatment increased the heart rate. The number and affinities of beta-adrenoceptors were analyzed using [3H]dihydroalprenolol as a ligand. Propranolol at 30 mg/kg increased the number of cardiac beta-adrenoceptors in both SHR and WKY. In contrast, 10 mg/kg carteolol significantly decreased the number of cardiac beta-adrenoceptors in SHR, but not in WKY. These data indicate that carteolol, a beta-adrenoceptor antagonist with ISA, does not cause up-regulation of the number of cardiac beta-adrenoceptors in the rat and suggest that this fact is related to a possible lack of "rebound phenomena" after sudden discontinuation of chronic carteolol-therapy in humans.

Calcium channel blockers *(Verapamil)*
Therapeutic indications: Arrhythmias (supraventricular tachycardia).
Rebound effect:
Rapid or irregular heartbeat (tachycardia), palpitations. *(USP DI, 1996, p. 695)*
Ventricular arrhythmia or defects in the conduct. *(AHFS, 1990, p. 876)*

Disopyramide
Therapeutic indications: Ventricular arrhythmias, supraventricular tachycardia.
Rebound effect:
Tachycardia (with excessive doses). *(USP DI, 1996, p. 1260)*
Disturbances in the conduct as increase of premature ventricular complex, ventricular tachycardia and fibrillation. *(AHFS, 1990, p. 810)*

Encainide
Therapeutic indications: Ventricular arrhythmias.
Rebound effect:

Exacerbation or new ventricular arrhythmias (exacerbation of ventricular arrhythmias in 10% of patients; dose-dependent ventricular tachyarrhythmias and potentially fatal; incidence increases in patients with sustained ventricular tachycardia). *(USP DI, 1996, p. 1328)*
In the *National Heart, Lung and Blood Institute's Cardiac Arrhythmias Supression Trial (CAST),* treatment with Encainide and Flecainide has shown to be associated with excessive mortality or increase of non-fatal cardiac arrest, when compared with placebo in asymptomatic patients with recent acute myocardial infarction (AMI). *(USP DI, 1996, p. 2071)*
The largest percentage of arrhythmogenic effects occurs in patients with sustained ventricular tachycardia; new taquicardias occurred in 2% of patients. *(AHFS, 1990, p. 823)*

Digitalis *(Digoxin, Digitoxin)*
Therapeutic indications: Atrial arrhythmia (atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia).
Rebound effect:
Atrial arrhythmia (in adults, the most frequent arrhythmias are the extrasystoles, commonly occurring paroxysmal atrial tachycardia; in children, atrial arrhythmia are the most common, with atrial ectopic rhythms and paroxysmal atrial tachycardia; ventricular arrhythmias are rare). *(USP DI, 1996, p. 1222; AHFS, 1990, p. 764, 765)*

Flecainide
Therapeutic indications: Ventricular arrhythmia (tachycardia ventricular, premature ventricular contractions).
Rebound effect:
Exacerbation or new ventricular arrhythmia (ventricular tachyarrhythmia, dose-dependent and potentially fatal). *(USP DI, 1996, p. 1468)*
Exacerbation or new ventricular tachyarrhythmia; increased frequency of premature ventricular complexes. *(AHFS, 1990, p. 836)*

Lidocaine *(antiarrhythmic, vasodilator, local anesthetic)*
Therapeutic indications: Ventricular arrhythmias.
Rebound effect:
Cardiac arrhythmias. *(USP DI, 1996, p. 1902; AHFS, 1990, p. 1855)*
Author(s): Jernbeck J; Samuelson EU / Institution: Department of Plastic and Reconstructive Surgery, Karolinska Hospital, Stockholm, Sweden. / Title: Effects of lidocaine and calcitonin gene-related peptide (CGRP) on isolated human radial arteries. / Source: *J Reconstr Microsurg*. 1993 Sep. 9(5). P 361-5. / Abstract: Vasoconstriction during and after microsurgery may cause hypoperfusion and result in flap necrosis. This study investigated the vascular effects of two known vasodilators: lidocaine and the naturally-occurring substance, calcitonin gene-related peptide (CGRP). Experiments were performed in vitro on 47 human radial arterial rings from 18 patients undergoing reconstruction after head and neck tumor surgery with free radial forearm flaps. Lidocaine produced a biphasic dose-response curve, with contraction at low concentrations (1.5 x 10(-5) to 1.5 x 10(-3) M) and relaxation at higher concentrations (4.5 x 10(-3) to 1.5 x 10(-2) M). It caused significantly stronger contractions in arteries with mechanically removed endothelium, compared with arteries with intact endothelium. Prolonged rebound contraction occurred when the lidocaine concentration was decreased. Lidocaine also potentiated noradrenaline-induced

contraction. CGRP produced only dose-dependent relaxation of constricted radial arteries at low concentrations (3 x 10(-10) to 10(-7) M). The contractile effects of lidocaine should be considered when a vasodilative substance is required.

Mexiletine
Therapeutic indications: Ventricular arrhythmias (premature ventricular contractions, ventricular tachycardia, etc.).
Rebound effect:
Fast or irregular heartbeat (premature ventricular contractions); exacerbation of ventricular arrhythmias, including *"torsade de pointes". (USP DI, 1996, p. 2070)*

Moricizine
Therapeutic indications: Ventricular arrhythmia.
Rebound effect:
Ventricular tachyarrhythmia. *(USP DI, 1996, p. 2108)*

Procainamide
Therapeutic indications: Arrhythmias.
Rebound effect:
Rapid or irregular heartbeat (ventricular tachycardia). *(USP DI, 1996, p. 2472; AHFS, 1990, p. 856)*

Propafenone
Therapeutic indications: Arrhythmias (supraventricular and ventricular).
Rebound effect:
Exacerbations or new ventricular arrhythmias in approximately 5% of patients; exacerbations or new congestive hearth failure in 1% of patients; blocks of first, second and third degree by 2.5, 0.6, and 0.2% respectively. Frequent ventricular tachycardia. *(USP DI, 1996, p. 2495)*

Quinidine
Therapeutic indications: Arrhythmias (paroxysmal ventricular tachycardia, premature ventricular contractions, etc.).
Rebound effect:
Idioventricular rhythms (including fibrillation and ventricular tachycardia), paradoxical tachycardia, ectopic ventricular beats. *(USP DI, 1996, p. 2529)*
Paroxysmal fibrillation and ventricular tachycardia; premature ventricular contractions. *(AHFS, 1990, p. 867)*

Tocainide
Therapeutic indications: Ventricular arrhythmias (premature ventricular contractions, ventricular tachycardia).
Rebound effect:
Irregular heartbeat (premature ventricular contractions). *(USP DI, 1996, p. 2891)*
Increment in ventricular arrhythmias, premature ventricular contractions and ventricular fibrillation. *(AHFS, 1990, p. 874)*

Antianginal drugs

Amlodipine
Therapeutic indications: Classic angina pectoris (chronic stable angina or angina associated effort).
Rebound effect:
Chest pain (angina pectoris). *(USP DI, 1996, p. 87)*

Beta-blockers *(Atenolol; Propranolol; Timolol, etc.)*
Therapeutic indications: Classic angina pectoris.
Rebound effect:
Chest pain (exacerbation of angina with abrupt discontinuation of a beta-blocker). *(USP DI, 1996, p. 579)*
The sudden cessation of treatment for angina pectoris with Propranolol increases the frequency, duration and severity of the episodes of angina, often within 24 hours. These episodes are unstable and don't respond to nitroglycerin. *(AHFS, 1990, p. 861, 871)*
Author(s): Frishman WH; Klein N; Strom J; Cohen MN; Shamoon H; Willens H; Klein P; Roth S; Iorio L; LeJemtel T; Pollack S; Sonnenblick EH / Title: Comparative effects of abrupt withdrawal of propranolol and verapamil in angina pectoris. / Source: *Am J Cardiol.* 1982 Nov. 50(5). P 1191-5. / Abstract: The potential hazards of abrupt withdrawal of propranolol have been described in patients with angina pectoris; however, the effects of abrupt withdrawal from long-term therapy with verapamil have not previously been investigated. The comparative effects of withdrawal from long-term treatment with propranolol and verapamil were assessed in a placebo-controlled double-blind randomized crossover study of 20 patients received placebo for 2 weeks, then increasing doses of propranolol (60 to 320 mg/day) or verapamil (240 to 480 mg/day) for 3 weeks. Patients were then abruptly withdrawn from drug onto placebo for 1 week, followed by crossover to the other drug treatment and a second withdrawal period. All 20 patients were withdrawn from verapamil without evidence of a rebound increase in frequency of anginal attacks, blood pressure, heart rate, or rate-pressure product and without a rebound deterioration in exercise tolerance. In contrast, with propranolol withdrawal, 2 patients (with the highest baseline angina attack rate) had a severe exacerbation of their anginal syndrome and could not undergo formal exercise testing; the other 18 patients were withdrawn from propranolol without incident. Plasma catecholamines were increased during exercise compared with rest during all treatments; however, the levels of catecholamines during exercise were significantly higher with propranolol than with verapamil and placebo (p less than 0.05). Levels of exercise catecholamines returned to placebo baseline values after withdrawal of propranolol.
Author(s): Walker PR; Marshall AJ; Farr S; Bauminger B; Walters G; Barritt DW / Title: Abrupt withdrawal of atenolol in patients with severe angina. Comparison with the effects of treatment. / Source: *Br Heart J.* 1985 Mar. 53(3). P 276-82. / Abstract: The effects of abrupt withdrawal of atenolol, a long acting cardioselective beta-blocker, were studied in 20 patients with severe stable angina pectoris admitted to hospital for coronary arteriography. During the 144 hour postwithdrawal period no serious coronary events occurred. Mean and maximal daily heart rates rose steadily for at least 120 hours. No important arrhythmias were noted on ambulatory electrocardiographic monitoring. Treadmill exercise testing at 120 hours showed little reduction in the times to angina, ST depression, and maximal exercise when compared with those recorded at 24 hours. This deterioration was small when contrasted with the improvements in these indices

produced by atenolol treatment in a similar group of patients not admitted to hospital. No change in catecholamine concentrations or acceleration of the heart rate response to exercise occurred after atenolol withdrawal, suggesting that rebound adrenergic stimulation or hypersensitivity was absent or insignificant. Catastrophic coronary events after beta blockade withdrawal (the beta blockade withdrawal syndrome) have occurred almost exclusively in patients taking propranolol, many of whom had unstable angina at the time of withdrawal. This study showed that in patients with stable angina, even when severe, the abrupt withdrawal of atenolol can be expected to result in only minor clinical consequences. The risk to any patient of so called rebound events after withdrawal of beta blockade seems to be related to both the clinical setting and the agent being used.

Author(s): Frishman WH / Institution: Department of Medicine, New York Medical College / Title: Beta-adrenergic blocker withdrawal. / Source: *Am J Cardiol.* 1987 May 15;59(13):26F-32F. / Abstract: Abrupt withdrawal of long-term beta-blocker therapy in patients with angina may be associated with unstable angina and myocardial infarction. It appears that an "overshoot" in heart rate from pretreatment values occurs, which increases myocardial oxygen demand. This increase in heart rate may be secondary to increased beta receptor numbers or increased receptor sensitivity. Another possible mechanism for the increased risk of myocardial infarction after beta-blocker withdrawal is increased platelet aggregability. Withdrawal reactions may be less severe with beta-blockers that have partial agonist activity. In patients undergoing coronary artery bypass surgery, beta-blocker withdrawal reactions have also been observed. Maintenance of beta-blocker therapy on the morning of surgery appears to reduce this risk. Gradual withdrawal regimens in outpatients with angina may be associated with lower risk for a beta-blocker withdrawal reaction. The gradual withdrawal of beta-blockers in hypertensive patients requires further study.

Author(s): Psaty BM; Koepsell TD; Wagner EH; LoGerfo JP; Inui TS / Institution: Department of Medicine, University of Washington, Seattle. / Title: The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers. / Source: *JAMA.* 1990 Mar 23-30;263(12):1653-7. / Abstract: We conducted a population-based, case-control study of risk factors for first events of coronary heart disease in patients with high blood pressure. All subjects had hypertension treated with medication. The 248 cases presented with new coronary heart disease from 1982 through 1984, and the 737 controls were a probability sample of health maintenance organization patients free of coronary heart disease. The health maintenance organization's computerized pharmacy database identified recent stoppers--patients who did not fill their prescriptions regularly enough to be at least 80% compliant. After adjustment for potential confounding factors, subjects who had recently stopped using beta-blockers had a transient fourfold increase in the relative risk of coronary heart disease (relative risk, 4.5; 95% confidence interval, 1.1 to 18.5). The association was specific to beta-blockers but not diuretics. A withdrawal syndrome immediately following the cessation of beta-blocker use may be an acute precipitant of angina and myocardial infarction in hypertensive patients who have no prior history of coronary heart disease.

Author(s): Egstrup K / Institution: Department of Cardiology, Odense University Hospital, Denmark. / Title: Silent ischemia and beta-blockade. / Source: *Circulation.* 1991 Dec. 84(6 Suppl). P VI84-92. / Abstract: Ambulatory electrocardiographic monitoring now makes it possible to document silent ischemic type ST segment changes that are seen in patients who suffer from stable angina and that often occur during periods of modest physical activity and mental arousal. These observations suggest that ischemic episodes occur as a consequence of a relatively complicated interplay of changes in oxygen supply and demand. Furthermore, silent ischemia displays a circadian variation with the greatest frequency in the morning, a pattern similar to that noted for the onset of acute myocardial infarction and the occurrence of sudden death. Ischemic episodes, whether symptomatic or silent, carry a serious prognosis in subsets of patients with coronary artery disease; therefore, prophylactic treatment may be desirable. Ideally this should be based on an understanding of the pathophysiological processes involved and should also be directed at the other coronary artery risk factors of the patients. The effects of beta-blockers, which reduce the duration

and frequency of silent ischemic episodes, is well described. The effect is most pronounced in the morning, when the frequency of ischemia is highest, and the mechanism of action seems mainly mediated through a reduction in myocardial oxygen demand. beta-Blockers have shown effectiveness in both effort-induced angina and mixed angina, and increased anti-ischemic potency may be achieved by combination therapy with a calcium antagonist. Abrupt withdrawal of beta-blockers is associated with a rebound increase in ischemic activity, which is mainly silent. Further studies are needed to determine whether improved control of silent ischemia reduces the risk of adverse cardiac outcomes.

Calcium channel blockers *(Diltiazem; Nifedipine; Verapamil)*
Therapeutic indications: Classic angina pectoris (chronic stable angina or angina associated effort).
Rebound effect:
Chest pain (30 minutes after administration, related to reflex tachycardia). *(USP DI, 1996, p. 695)*
An increase in frequency, intensity and duration of angina occurs during the start of treatment with Nifedipine. *(AHFS, 1990, p. 851)*
Author(s): Lette J; Gagnon RM; Lemire JG; Morissette M / Title: Rebound of vasospastic angina after cessation of long-term treatment with nifedipine. / Source: *Can Med Assoc J.* 1984 May 1. 130(9). P 1169-71, 1174. / Abstract: The beneficial effect of calcium antagonists in the treatment of vasospastic angina is now well recognized. Although withdrawal symptoms have been reported following abrupt cessation of therapy with some cardiovascular drugs, there is no detailed report on similar complications of the cessation of therapy with calcium antagonists. In a 4-month period eight patients with well documented and well controlled vasospastic angina experienced a marked increase in the frequency and duration of anginal episodes at rest following the involuntary cessation of treatment with nifedipine, 10 to 20 mg four times a day. The increase began within 2 to 5 days after the cessation of treatment. Substitute therapy with isosorbide dinitrate, 30 mg, and verapamil, 80 to 120 mg, each four times a day, was effective in all cases. Although the mechanism responsible for this rebound phenomenon is not known, awareness of its existence is essential considering the widespread use of calcium antagonists.
Author(s): Martsevich SY; Koutishenko N; Metelitsa VI / Institution: Department of Preventive Pharmacology, Research Centre for Preventive Medicine of Russia, Moscow. / Title: Withdrawal phenomenon after abrupt cessation of nifedipine in stable angina pectoris. / Source: *Int J Cardiol*. 1993 Dec 31. 42(3). P 298-301. / Abstract: We investigated the effect of abrupt cessation of nifedipine after regular administration (20 mg, four times daily) for 5 weeks in seven patients with stable angina pectoris. A rebound decrease in exercise tolerance and increase of exercise-induced myocardial ischaemia were registered on the first day of nifedipine withdrawal.
Author(s): Martsevich SY; Koutishenko N; Metelitsa VI / Institution: Department of Preventive Pharmacology, Research Centre for Preventive Medicine of Russia, Moscow. / Title: Withdrawal effects of antianginal therapy: comparison of isosorbide dinitrate and nifedipine. / Source: Int J Cardiol. 1998 Apr 1;64(2):137-44. / Abstract: We compared the effects of abrupt cessation of nifedipine and isosorbide dinitrate therapy in patients with stable angina pectoris. Eighteen males were studied. Each patient received isosorbide dinitrate and nifedipine continuously for 5 weeks by randomised cross-over technique. Exercise treadmill tests were performed before each treatment period, at the beginning of treatment, 4 weeks after initiation of treatment and on the first and eighth days of drug withdrawal. At the end of treatment the antianginal effect of both agents attenuated (versus acute administration). Abrupt cessation of isosorbide dinitrate caused only a tendency towards decrease in exercise tolerance versus pre-treatment level. Alternatively, abrupt cessation of nifedipine resulted in substantial deterioration in exercise tolerance, which was statistically

significant 21 and 24 h after the last dose administration. The number of anginal attacks increased >25% in two patients after cessation of isosorbide dinitrate and in eight patients after cessation of nifedipine. In no patient rest angina episodes appeared after stopping of isosorbide dinitrate, however, after stopping of nifedipine rest angina episodes appeared in three patients. We conclude that withdrawal phenomenon of nifedipine is much more pronounced than that of isosorbide dinitrate and may emerge on the first day of drug cessation. Such a phenomenon may be evident even in patients in whom nifedipine effect have attenuated due to the development of tolerance.

Nitrates - Nitroglycerine

Therapeutic indications: Classic angina pectoris.

Rebound effect:

Patients who use the Nitroglycerin for long time report attacks of angina more frequent than usual. *(AHFS, 1990, p. 959)*

Author(s): Rehnqvist N / Title: Tolerance development during transdermal administration of nitroglycerin in angina pectoris. / Source: *Acta Pharmacol Toxicol (Copenh).* 1986. 59 Suppl 6P 113-5. / Abstract: Nitroglycerin delivered by transdermal patch technology has been used in angina pectoris patients as well as in heart failure. In angina pectoris patients the plasma concentrations are low over the 24 hours. Effects can be found especially during the first 12 hours after application of the drug even during steady state conditions. The effect of the drug wanes after 24 hours and some studies suggest reduced effect when the patches have been applied for seven to 14 days. The attenuated effects have been claimed to be due to tolerance. Tolerance is, however, never absolute and in other studies this phenomenon is not shown. Furthermore, rebound phenomena may develop when nitroglycerin therapy is withdrawn. The optimal doses and schemes for nitroglycerin administration thus remain to be clarified.

Author(s): Rehnqvist N; Olsson G; Engvall J; Rosenqvist U; Nyberg G; Aberg A; Ulvenstam G; Uusitalo A; Keyrilainen O; Reinikainen P; et al / Institution: Danderyd Hospital, Sweden. / Title: Abrupt withdrawal of isosorbide-5-mononitrate in Durules (Imdur) after long term treatment in patients with stable angina pectoris. / Source: *Eur Heart J.* 1988 Dec. 9(12). P 1339-47. / Abstract: In a single-blind study of 6 weeks' duration, 32 patients with stable angina pectoris, who had been receiving controlled-release, Durules, isosorbide-5-mononitrate (Imdur) 60 to 180 mg daily for at least 1 year, were assessed after abrupt withdrawal of the nitrate. After 2 weeks of placebo treatment nitrate therapy was re-instituted, and the patients followed for another 2 weeks. The possibility of development of tolerance and rebound phenomena was also investigated. Three patients experienced severe anginal symptoms necessitating hospitalization when controlled-release isosorbide-5-mononitrate was withdrawn abruptly. Patients complained of more severe anginal symptoms during the placebo period, experienced more frequent anginal attacks and used more glyceryl trinitrate tablets than during active treatment. ST segment changes during exercise were more pronounced with placebo. After controlled-release isosorbide-5-mononitrate was re-introduced, these variables indicated significant improvement. On the other hand, no deterioration occurred in exercise performance during the placebo phase. Responsiveness to glyceryl trinitrate was maintained, as shown by comparisons of exercise tests performed after the long term treatment and during the placebo phase. Controlled-release isosorbide-5-mononitrate retains a beneficial effect in patients with angina pectoris during prolonged use, although some attenuation of the effect is seen. Abrupt withdrawal of the drug is not recommended because of the possibility of severe exacerbation of anginal symptoms, although no clearcut rebound phenomena were seen.

Author(s): Thadani U / Institution: Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City 73190. / Title: Role of nitrates in angina pectoris. / Source: *Am J Cardiol.* 1992 Sep 24. 70(8). P 43B-53B. / Abstract: Nitrates are used extensively for the treatment of angina pectoris. However, continuous therapy with either oral nitrates or nitroglycerin patches

leads to rapid development of tolerance, with loss or diminution of antianginal and anti-ischemic effects. The only practical way to avoid the development of tolerance is to use intermittent daily therapy with nitrates. Nitroglycerin patches applied for 10-12 hours during the day increase exercise duration for 8-12 hours, but a rebound increase in anginal attacks during the nitrate-free interval may occur. Oral isosorbide-5-mononitrate, 20 mg twice a day, with the first dose administered in the morning and the second dose 7 hours later, increases exercise duration for at least 12 hours without the development of tolerance to either the morning or afternoon dose. This dosing regimen has been shown not to produce a rebound phenomenon during the periods of low nitrate levels at night and early hours of the morning. Isosorbide dinitrate (30 mg) prescribed at 7 AM and 1 PM does not produce tolerance to the 7 AM dose, but effects of the afternoon dose have not been evaluated. Recent data suggest that isosorbide dinitrate given 3 or 4 times daily produces tolerance and this dosing schedule is inadequate for antianginal prophylaxis. It should be recognized that intermittent oral or patch therapy with nitrates during the day leaves the patient unprotected at night and early hours of the morning. If this is of concern, additional therapy with another class of antianginal agent, preferably a long-acting beta-blocker or a long-acting calcium antagonist should be instituted.

Author(s): Thadani U; de Vane PJ / Institution: Cardiovascular Section, University of Oklahoma Health Sciences Center, Oklahoma City 73104. / Title: Efficacy of isosorbide mononitrate in angina pectoris. / Source: *Am J Cardiol.* 1992 Nov 27. 70(17). P 67G-71G. / Abstract: The rapid development of tolerance has limited the applicability of oral and transdermal nitrates in the long-term management of patients with chronic stable angina pectoris. Recent well-controlled trials have demonstrated that asymmetrical, or eccentric, dosing of oral isosorbide mononitrate, in which 20-mg doses are taken at 8 A.M. and 3 P.M., provides at least 12 hours of antianginal coverage. There is no evidence for the development of tolerance with this schedule, which allows for a 17-hour nitrate withdrawal period. Likewise, the asymmetrical 20-mg twice daily regimen has not been associated with the zero-hour effect that has been reported with higher oral doses of isosorbide mononitrate and with intermittent nitroglycerin patch therapy. This approach also avoids the development of a clinical rebound phenomenon, as measured by increased episodes of angina and nitroglycerin consumption, compared with the pretreatment period, during the nitrate-free interval at night and the early hours of the morning.

Author(s): Frishman WH / Institution: Department of Medicine, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York. / Title: Tolerance, rebound, and time-zero effect of nitrate therapy. / Source: *Am J Cardiol.* 1992 Nov 27. 70(17). P 43G-47G; discussion 47G-48G. / Abstract: Both nitroglycerin and long-acting nitrates have proved effective in treating acute anginal pain. In recent years, however, development of tolerance with the continuous use of these agents has been documented. A pilot study demonstrated attenuation of the therapeutic effect of high-dose, continuous transdermal nitroglycerin therapy, despite adequate plasma nitroglycerin levels. In a subsequent, larger Transdermal Nitroglycerin Cooperative Study, evidence of tolerance was detected within 24 hours of initiation of continuous nitroglycerin patch therapy at several different dose levels. Sustained pharmacologic activity has been achieved with the intermittent use of transdermal nitroglycerin, usually for 12 hours followed by a 12-hour drug-free period. When the patch is discontinued, however, some patients experience exacerbation, or rebound, of anginal symptoms and a worsening of exercise tolerance at the end of the drug-free period. Additional clinical research is therefore needed to determine the optimal intermittent dosing strategy.

Author(s): Ferratini M / Institution: Department of Cardiology, Niguarda Hospital, Milan, Italy. / Title: Risk of rebound phenomenon during nitrate withdrawal. / Source: *Int J Cardiol.* 1994 Jun 15. 45(2). P 89-96. / Abstract: Organic nitrates are first-line drugs in the therapy and prevention of angina. These compounds, are acutely effective yet some formulations demonstrate a rapid decline in effect with chronic use. In this review the mechanisms of development of nitrate tolerance and the different strategies to prevent it are considered. If frequent dosing, high dosages and long acting

preparations giving constant 24 h plasma GTN levels are more likely to cause tolerance, nitrate-low periods seem to be effective in restoring the drug's efficacy. Intermittent therapy with GTN patches, an effective way to prevent tolerance, raises the problem of the rebound phenomenon during the removal period. Considerable variations in its occurrence have been reported and in this review the factors that may influence the incidence of the rebound are discussed. The dangers of rebound can be lessened by concomitant anti-anginal drugs or avoiding any abrupt decline in blood nitrate concentrations. The use of beta-blockers or calcium channel blockers during intermittent therapy with GTN patches and oral preparations of isosorbide dinitrate or isosorbide 5-mononitrate seem to be effective for this purpose.

Author(s): Held P; Olsson G / Institution: Astra Hassle AB, Molndal, Sweden. / Title: The rationale for nitrates in angina pectoris. / Source: *Can J Cardiol*. 1995 Apr. 11 Suppl BP 11B-13B. / Abstract: Organic nitrates are among the oldest drugs used in the management of patients with ischemic heart disease. The most frequently used nitrates are nitroglycerin, isosorbide dinitrate and isosorbide-5-mononitrate. Their duration of action can be influenced by choice of substance, frequency of administration, formulation (eg, extended release) and route of administration. As well as providing effective treatment of acute angina, nitrates produce a long term prophylactic effect. Stable plasma nitroglycerin levels lasting longer than 10 to 12 h are not desirable due to the rapid development of tolerance. Simple, well-designed dosing schedules can avoid tolerance and rebound phenomena and can improve patient compliance.

Author(s): Martsevich SY; Koutishenko N; Metelitsa VI / Institution: Department of Preventive Pharmacology, Research Centre for Preventive Medicine of Russia, Moscow. / Title: Abrupt cessation of short-term continuous treatment with isosorbide dinitrate may cause a rebound increase in silent myocardial ischaemia in patients with stable angina pectoris. / Source: *Heart*. 1996 May. 75(5). P 447-50. / Abstract: To examine by Holter electrocardiographic monitoring the effect of abruptly stopping nitrate treatment in patients with stable angina pectoris. 12 men with confirmed ischaemic heart disease and stable exertional class 3 angina (Canadian). All had episodes of horizontal or down sloping ST segment depression during 24 hour electrocardiographic monitoring. All were nitrate responders. Each patient was given isosorbide dinitrate (10-30 mg four times a day) and placebo (four times a day) for three days in a randomised crossover trial. There was a washout period of 3-5 days between the two treatment periods. Holter monitoring was performed on the third day of isosorbide dinitrate and placebo administration and on the first day of their withdrawal. When treatment with isosorbide dinitrate was stopped there was a significant increase in the total number and duration of painless episodes of myocardial ischaemia. During placebo and isosorbide dinitrate administration 8 patients had episodes of painless myocardial ischaemia whereas after isosorbide dinitrate cessation they were recorded in all 12 patients. Episodes of silent myocardial ischaemia at rest appeared in 4 patients after isosorbide dinitrate withdrawal. Abrupt cessation of short-term continuous nitrate treatment in patients with severe angina may cause a rebound increase in myocardial ischaemia which is predominantly silent.

Antihypertensive drugs

Author(s): Willette RN; Punnen S; Krieger AJ; Sapru HN / Title: Hypertensive response following stimulation of opiate receptors in the caudal ventrolateral medulla. / Source: *Neuropharmacology*. 1984 Apr. 23(4). P 401-6. / Abstract: In urethane-anesthetized rats, vasodepressor neuron pools were located bilaterally in and adjacent to the A1 area of the ventrolateral medulla by injecting the neuroexcitatory amino acid, L-glutamate. Ventrolateral vasodepressor areas included the caudalateral part of the nucleus reticularis gigantocellularis, the rostrolateral part of the nucleus reticularis ventralis, and the dorsal nucleus reticularis lateralis. In

the ventrolateral vasodepressor areas L-glutamate elicited a transient fall in blood pressure (BP) and heart rate (HR). The opiate agonist (D-ala2-met5)-enkephalinamide (DAME) was used to stimulate opiate receptors in vasodepressor sites, identified with L-glutamate. In these sites, bilateral injections (0.1 microliter/site) of DAME caused a dose-related (2.5-500.0 ng) increase in blood pressure and heart rate, as well as exaggeration of the response to occlusion of the carotid. The effects of DAME on blood pressure were completely abolished by alpha-adrenergic blockade (phentolamine, 2 mg/kg, i.v.) and all effects of DAME were reversed by the administration of naloxone HCl (1 mg/kg, i.v.). Naloxone reversal was accompanied by an unexpected "rebound" hypertension. Saline had no significant effects when injected, or administered intravenously, in the absence or presence of DAME. It was concluded that stimulation of opiate receptors in the ventrolateral vasodepressor areas activated sympathetic outflow. An enkephalinergic system in this area of the brain stem may serve to modulate blood pressure, heart rate and cardiovascular reflexes.
Author(s): Grossman E; Messerli FH / Institution: Department of Internal Medicine, Ochsner Clinic, New Orleans, La. / Title: High blood pressure. A side effect of drugs, poisons, and food. / Source: *Arch Intern Med*. 1995 Mar 13. 155(5). P 450-60. / Abstract: A variety of therapeutic agents or chemical substances can induce either a transient or a sustained increase in blood pressure. These agents increase arterial pressure by either causing sodium retention and extracellular volume expansion or directly or indirectly activating the sympathetic nervous system. Some agents act directly on arteriolar smooth muscle. For certain agents, the mechanism of pressure elevation is mixed or unknown. Paradoxically, some agents that are used to lower arterial pressure may acutely increase arterial pressure. Also, a rebound increase in pressure may be encountered after discontinuation of certain antihypertensive agents. In general, these chemically induced increases in arterial pressure are small and transient; however, severe hypertension involving encephalopathy, stroke, and irreversible renal failure has been reported. Careful evaluation of a patient's drug regimen may identify chemically induced hypertension and prevent the need for evaluation and therapy. This study reviews the therapeutic agents or chemical substances that elevate blood pressure and their mechanisms of action.

Central alpha2-adrenergics *(Clonidine, Guanabenz, Guanfacine, Methyldopa, Rilmenidine)*
Therapeutic indications: Hypertension.
Rebound effect:
Hypertension (rebound hypertension typically occurs after abrupt discontinuation of Clonidine, shortcoming in 5-20% of patients). *(USP DI, 1988, p. 713, 1224, 1519; USP DI, 1996, p. 885, 1567)*
Sympathetic hyperactivity, with rebound hypertension, occurs in the period of two to seven days after the abrupt suspension of Guanfacina, with greater risk in the use of doses greater than 4 mg per day. *(USP DI, 1996, p. 1576)*
Abrupt discontinuation of oral Clonidine results in fast (8-24 hours after) increased of systolic and diastolic arterial pressures, not being well established its mechanism. With the use of transdermal Clonidine occurred severe rebound hypertension 36-72 hours after the suspension of the treatment. Whith suspension in pre-operative, rebound hypertension occurs during or after surgery. After discontinuation of Guanabenz, 33% of patients expressed a fast and great addition in systolic and diastolic pressures, staying for several days. *(AHFS, 1990, p. 912, 913, 921, 940)*
Author(s): Gan EK; Abdul Sattar MZ / Title: Effect of acute and subacute treatment of clonidine on blood pH, PCO_2 and PO2 in mice. / Source: *Clin Exp Pharmacol Physiol*. 1982 Nov-Dec. 9(6). P 675-7. / Abstract: 1. Measurements were made on blood pH, PCO2 and PO2 in mice after a single

injection and following five weeks continuous clonidine hydrochloride treatment. 2. A single injection of clonidine hydrochloride exerts no effect on blood pH, PCO2 and PO2 but five weeks of continuous clonidine hydrochloride treatment lowers the blood pH and PCO2 and raises blood PO2, suggesting acidosis has taken place. 3. The acidosis may be attributed to rebound hypertension as a result of withdrawal of clonidine treatment.

Author(s): Taira CA; Celuch SM; Enero MA / Title: Effects of acute and short-term treatment with antihypertensive drugs in sinoaortic denervated rats. / Source: *Gen Pharmacol*. 1983. 14(6). P 657-61. / Abstract: Sinoaortic denervation (SAD) produced a marked increase of the systolic blood pressure (SBP). Clonidine (50 micrograms kg-1, i.p.) reduced SBP in SAD but not in sham rats. L-alpha-methyldopa (alpha-MD) (50 mg kg-1, i.p.) also induced a more effective hypotensive action in SAD than sham rats. The withdrawal of alpha-MD in SAD rats after the first treatment was not abrupt and the hypotension persisted for several days, but after the second treatment the withdrawal induced a rapid rebound hypertension. Our results suggest that SAD increases the response to the hypotensive agents. An alteration in the availability of alpha-MD to accumulate or synthesize the active metabolites was also observed after second treatment.

Author(s): Jain AK; Hiremath A; Michael R; Ryan JR; McMahon FG / Title: Clonidine and guanfacine in hypertension. / Source: *Clin Pharmacol Ther*. 1985 Mar. 37(3). P 271-6. / Abstract: Guanfacine, 1 to 3 mg/day, and clonidine, 0.1 to 0.3 mg twice a day, were compared in a 24-week double-blind, randomized, parallel study of 42 patients with hypertension that was inadequately treated by chlorthalidone, 25 mg/day. Mean reduction of blood pressure was 18/9 mm Hg after guanfacine and 14/8 mm Hg after clonidine. To determine the incidence of rebound hypertension, subjects were hospitalized for 7 days during chlorthalidone therapy for collection of baseline data and once again immediately after abrupt withdrawal of the alpha-agonist after 24 weeks of dosing. Although blood pressure and heart rate rose significantly in both groups, the changes after clonidine withdrawal were greater and occurred earlier (day 2) than those after guanfacine withdrawal (day 4). Forty percent of the subjects receiving guanfacine and 64% of subjects receiving clonidine had diastolic blood pressure elevations greater than or equal to 10 mm Hg from baseline. There were increases in urinary norepinephrine levels in both groups after drug withdrawal, but these correlated poorly with blood pressure rise. Side effects after guanfacine were much the same as those after clonidine. Guanfacine taken once a day provides an effective and safe alternative to clonidine in the management of essential hypertension.

Author(s): Reid JL / Title: Central alpha 2 receptors and the regulation of blood pressure in humans. / Source: *J Cardiovasc Pharmacol*. 1985. 7 Suppl 8P S45-50. / Abstract: Alpha 2 receptors in the brain stem and in the periphery inhibit sympathetic activity and thus lower blood pressure. Alpha 2 receptor agonists such as clonidine or guanabenz reduce central and peripheral sympathetic overflow and via peripheral presynaptic receptors may reduce peripheral neurotransmitter release. Alpha 2 agonists lower blood pressure in many patients either alone or in combination with diuretics. Central nervous side effects are less common when lower doses are used. More recent analogues of clonidine with greater alpha 2 receptor selectivity have been found to have a longer duration of action and may be less likely to lead to a withdrawal reaction, with rebound of hypertension and symptoms, when treatment is interrupted.

Author(s): Campbell BC; Reid JL / Title: Regimen for the control of blood pressure and symptoms during clonidine withdrawal. / Source: *Int J Clin Pharmacol Res*. 1985. 5(4). P 215-22. / Abstract: Abrupt withdrawal of the centrally-acting antihypertensive agent, clonidine, is associated with a high incidence of rebound hypertension and tachycardia, with symptoms of sympathetic overactivity and increased catecholamine excretion. Gradual clonidine withdrawal has been recommended, but does not always avoid the reaction. A regimen is described comprising high doses of the alpha 1-adrenoceptor antagonist, prazosin, the cardioselective beta-blocker, atenolol, and chlordiazepoxide, specifically designed to counter both central and peripheral effects of sudden withdrawal of a central alpha 2-adrenoceptor agonist. This combination was completely successful

in preventing the haemodynamic and symptomatic features of clonidine withdrawal in eight hypertensive patients.
Author(s): Klein C; Morton N; Kelley S; Metz S / Title: Transdermal clonidine therapy in elderly mild hypertensives: effects on blood pressure, plasma norepinephrine and fasting plasma glucose. / Source: *J Hypertens Suppl*. 1985 Dec. 3(4). P S81-4. / Abstract: Twenty patients aged 60-74 years entered a study on the effect of transdermal clonidine (Catapres-TTS) as monotherapy for mild hypertension [diastolic blood pressure (DBP) 90-104 mmHg]. Seventeen patients (85%) had a positive therapeutic response (DBP reduced to less than 90 mmHg or by greater than or equal to 5 mmHg). Patient acceptance was high and side effects mild; however, one-quarter of the patients experienced localized skin reactions. A slight increase in fasting plasma glucose level (mean delta = 20 mg/dl) was consistently observed. Transdermal clonidine led to a sustained decline in plasma catecholamine levels although this effect did not seem to be closely related to the observed decreases in blood pressure. Three out of four evaluable patients had a blood pressure 'overshoot' upon discontinuation of therapy to levels above pretreatment values. Transdermal clonidine appears to be effective and generally well tolerated in the treatment of mild hypertension in the elderly; however, more studies designed to investigate effects on glucose tolerance and the possible existence of a rebound syndrome is needed.
Author(s): Leckman JF; Ort S; Caruso KA; Anderson GM; Riddle MA; Cohen DJ / Title: Rebound phenomena in Tourette's syndrome after abrupt withdrawal of clonidine. Behavioral, cardiovascular, and neurochemical effects. / Source: *Arch Gen Psychiatry*. 1986 Dec. 43(12). P 1168-76. / Abstract: Following an open trial of clonidine hydrochloride (3 to 8 micrograms/kg/day for 12 weeks), we studied the behavioral, cardiovascular, and neurochemical effects of abrupt clonidine withdrawal in seven patients with Tourette's syndrome aged 9 to 13 years. Five patients showed marked worsening of tics. After reinitiation of clonidine therapy, the time required for patients to return to prewithdrawal levels of tic symptoms ranged from two weeks to four months. Increases in motor restlessness, blood pressure, and pulse rate were also observed over the 72-hour period following abrupt withdrawal of clonidine. Plasma levels of free 3-methoxy-4-hydroxyphenylglycol, homovanillic acid, and urinary excretion of norepinephrine and epinephrine increased during the withdrawal period. Clonidine's effectiveness in Tourette's syndrome may be dependent on changes in dopaminergic as well as adrenergic mechanisms.
Author(s): Franklin SS; Tonkon MJ; Kirschenbaum MA; Dobak JD / Institution: UCLA Center for the Health Sciences, School of Medicine 90024. / Title: Randomized, double-blind comparison of transdermal clonidine with oral propranolol. / Source: *J Cardiovasc Pharmacol*. 1987. 10 Suppl 12P S244-7. / Abstract: The antihypertensive effect of transdermal clonidine (TC) vs. oral propranolol (OP) was evaluated in 32 patients with mild essential hypertension (mean BP 150/95 mm Hg). The protocol consisted of a 4-week pretreatment washout period, a 2- to 6-week titration, a 4-week maintenance phase, and a 1-week postwashout phase. BP control (diastolic BP less than 90 mm Hg) was achieved in 15 out of 17 transdermal patients, and in 12 out of 14 propranolol subjects. Comparable decreases in systolic/diastolic BP were noted (-19/15 mm Hg for TC vs. -24/13 mm Hg for OP). No rebound symptoms were reported after sudden cessation of the transdermal system during the post-treatment washout. Side effects were recorded in 3 out of 17 TC patients, and in 3 out of 15 OP patients with 1 OP dropout. A mild transient erythematous rash developed in 2 TC and 2 OP (placebo patch) patients. We conclude that the safety and efficacy of TC is comparable to OP for monotherapy in mild hypertensives.
Author(s): Jarrott B; Lewis SJ; Doyle AE; Louis WJ / Institution: Department of Medicine, University of Melbourne, Austin Hospital, Heidelberg, Victoria, Australia. / Title: Effects of continuous infusions (10 days) and cessation of infusions of clonidine and rilmenidine (S 3341) on cardiovascular and behavioral parameters of spontaneously hypertensive rats. / Source: *Am J Cardiol*. 1988 Feb 24. 61(7). P 39D-44D. / Abstract: Clonidine is a centrally acting antihypertensive drug that acts in vivo at both alpha 1- and alpha 2-adrenoceptor sites, whereas rilmenidine (S 3341)

is more selective for alpha 2 adrenoceptors. The present study compared the effects of continuous 10-day infusions of clonidine (5 micrograms/kg/hour) with those of rilmenidine (100 micrograms/kg/hour) on various cardiovascular and behavioral parameters in the spontaneously hypertensive rat. The changes in these parameters after cessation of the infusions were also compared. At these rates of infusion, clonidine and rilmenidine produced quantitatively similar reductions in mean arterial pressure (MAP), lability of MAP and cardiovascular responsiveness during normal behaviors such as eating and grooming. Neither drug infusion affected heart rate. The cessation of the clonidine infusion resulted in a "withdrawal" syndrome characterized by prominent rapid eye movement-sleep rebound, and cardiovascular and behavioral disturbances including an increased lability of MAP, exaggerated cardiovascular responses during normal behaviors, tachycardia, and an "opiate abstinence-like" syndrome including head and body shakes. Cessation of rilmenidine infusion resulted in somewhat similar cardiovascular and behavioral disturbances, but unlike clonidine there was a return to normal rapid eye movement sleep without rebound.

Beta-blockers *(Atenolol, Labetalol, Pindolol, Propranolol, Timolol, etc.)*
Therapeutic indications: Hypertension.
Rebound effect:
Hypertension (excessive doses of beta-blockers may cause tachycardia and hypertension, 1-2 hours after ingestion, due to intrinsic sympathomimetic activity or partial agonist activity, which is the ability to produce a low stimulation of beta-adrenergic receptors; however, the significance of this property is not clarified). *(USP DI, 1996, p. 579)*
Severe hypertension was observed in some schizophrenics patients who received large doses of Propranolol (used as an anxiolytic). It is not advisable to suspend abruptly treatment for hypertension with Timolol. Rebound hypertension was observed after suspension of Labetalol. *(AHFS, 1990, p. 861, 871, 934)*

Hydralazine *(vasodilator)*
Therapeutic indications: Hypertension.
Rebound effect:
Hypertension paradoxical (rebound) has been reported. *(AHFS, 1990, p. 929)*

Inhibitors of angiotensin converting enzyme (ACE) *(Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Perindopril, Quinapril, etc.)*
Therapeutic indications: Hypertension.
Rebound effect:
Author(s): Lee RM; Wang H; Smeda JS / Institution: Department of Anaesthesia, McMaster University, Hamilton, Ontario. / Title: Effects of perindopril on hypertension and stroke prevention in experimental animals. / Source: *Can J Cardiol*. 1994 Nov. 10 Suppl DP 33D-36D. / Abstract: Among the antihypertensive agents available for the treatment of hypertension, only angiotensin-converting enzyme (ACE) inhibitors have been shown to modify cardiovascular changes in structure and function. To study the effect of perindopril treatment on hypertension and stroke prevention in two genetic models of hypertensive rats. Adult (15 weeks old) spontaneously hypertensive rats (SHR) were treated with perindopril to determine the dose- and duration-dependent effects of treatment on systolic blood pressure, and the effect of withdrawal of this treatment on blood pressure and survival. In stroke-prone SHR, treatment was initiated in young animals (six weeks), and dose- and duration-dependent effects of perindopril treatment on stroke prevention were assessed. In adult SHR, perindopril caused a dose-dependent lowering of blood pressure. Blood pressure was controlled for a 24 h period with a single daily dose. The magnitude

of rebound hypertension after withdrawal of treatment was negatively correlated with duration of treatment. After 12 weeks of treatment, the blood pressure of treated SHR remained normotensive without further treatment, and the life span of treated SHR was also extended. Treatment of young, stroke-prone SHR with perindopril prevented stroke in these animals during the treatment period. After withdrawal of treatment, survival of the rats was increased in animals given a longer treatment period (24 weeks versus eight or 12 weeks). Treatment with the ACE inhibitor perindopril is effective in the prevention of hypertension and stroke in experimental animals.

Author(s): Chen DG; Jin XQ; Wang HJ; Chen SC / Institution: Hypertension Division, First Affiliated Hospital, Fujian Medical College, Fuzhou, People's Republic of China. / Title: Mechanisms responsible for sustained hypotension after captopril treatment. / Source: *J Hypertens*. 1995 Oct. 13(10). P 1113-21. / Abstract: To investigate new aspects of the relationship between sustained reduction of blood pressure and alteration of cardiovascular structure and function after cessation of early captopril treatment. Spontaneously hypertensive rats (SHR) were given captopril 20 mg/kg per day (n = 13) or 100 mg/kg per day (n = 12) from the intra-uterine period to age 16 weeks and then the treatment was stopped. Age-matched untreated SHR (n = 16) and Wistar-Kyoto (WKY) rats (n = 17) served as controls. The experiments were carried out at 40 weeks. Withdrawal of captopril treatment resulted in a rapid rebound of SBP to a level close to that of untreated SHR in the low-dose group, whereas a persistently lower SBP was maintained in the high-dose group. Both doses of captopril treatment completely prevented wall hypertrophy either of arteriolar resistance vessels or of muscular vessels. Captopril decreased left ventricular mass: body weight ratio dose-dependently. High-dose captopril improved the resting and stress systolic and diastolic function. Thoracic angiotensin converting enzyme levels were dose-dependently reduced by captopril treatment. The curves of perfusion pressure response to incremental doses of phenylephrine shifted to the right in both captopril treatment groups compared with those of the control SHR. Addition of L-NAME and L-arginine to the perfusate augmented or attenuated the vasoconstrictor activity in all of the rats, whereas high-dose captopril totally restored the abnormal hypersensitivity to L-NAME and caused less attenuation in response to L-arginine in the control SHR. The persistent lower blood pressure caused by early captopril treatment was ascribed mainly to its sustained normalization of structure and function of resistance vessels, which may be partly mediated by the improvement of endothelial cell function. The persistent reduction of angiotensin converting enzyme activity in blood vessel wall attenuated left ventricular hypertrophy, and the improvement of cardiac systolic and diastolic function may also contribute to the sustained hypotensive effect.

Author(s): Lan L; Di Nicolantonio R; Bramich C; Morgan TO / Institution: Department of Physiology, University of Melbourne, Parkville, Victoria, Australia. / Title: Brief treatment of SHR with an ACE inhibitor fails to cause long-term normotension but markedly increases mortality. / Source: *Clin Exp Pharmacol Physiol*. 1995 Dec. 22 Suppl 1P S345-6. / Abstract: 1. We examined the effect of three doses (0.03, 0.3 and 3 mg/kg per day) of the angiotensin converting enzyme (ACE) inhibitor, perindopril, on the long-term blood pressure of spontaneously hypertensive rats (SHR) of the Okamoto strain after treatment during the developmental stage of hypertension development. 2. While the 0.03 mg/kg per day dose, given between the ages of 4-10 weeks of age, failed to lower blood pressure, the two higher doses resulted in normotension over this treatment period as did the highest dose given between the ages of 4-20 weeks of age. 3. Only the 0.3 mg/kg per day dose resulted in a moderate (17%) long-term fall in blood pressure upon cessation of treatment when compared to untreated SHR controls. The highest dose, given over the 4-20 week period resulted in a significant rebound hypertension above the blood pressure level of untreated, control SHR. 4. The 3 mg/kg per day dose, whether given over the 4-10 or 4-20 week treatment period, resulted in 100% mortality in these groups by 52 weeks of age. There were no deaths in the groups receiving the two lower doses. 5. We conclude that treatment of SHR with perindopril during the developmental phase of hypertension development results in only a modest fall in long-term blood pressure upon cessation of treatment and that the relationship between the dose of this

ACE inhibitor and long-term blood pressure is not linear. The 100% mortality in the two groups receiving the highest dose of perindopril may be due to either a toxic action of this drug or vascular rupture due to insufficient hypertrophy for the rapid rise in blood pressure upon cessation of treatment.

MAO inhibitors *(Isocarboxazid, Phenelzine,Tranylcypromine)*
Therapeutic indications: Besides the main effect of antidepressant, presenting a hypotensive effect, probably by inhibition of central vasomotor centres.
Rebound effect:
Hypertension crisis. *(USP DI, 1996, p. 262; AHFS, 1990, p. 1151)*

Nitrates - Nitroglycerine
Therapeutic indications: Hypertension.
Rebound effect:
Patients using Nitroglycerin chronically, report rebound effects on hemodynamic parameters after discontinuation of drug. *(AHFS, 1990, p. 959)*
Author(s): Olivari MT; Carlyle PF; Levine TB; Cohn JN / Title: Hemodynamic and hormonal response to transdermal nitroglycerin in normal subjects and in patients with congestive heart failure. / Source: *J Am Coll Cardiol*. 1983 Nov. 2(5). P 872-8. / Abstract: The hemodynamic and hormonal responses to nitroglycerin administered transdermally in a gel-like matrix were evaluated in nine patients with severe congestive heart failure and in nine normal subjects. In normal subjects, peripheral vasodilation was accompanied by reflex sympathetic stimulation as reflected by an increase in heart rate and plasma norepinephrine. In patients with heart failure, nitroglycerin produced sustained hemodynamic effects that began 30 minutes after the application and fully persisted for at least 6 hours. A significant decrease in right and left ventricular filling pressures was associated with an increase in stroke index and a significant decrease in forearm and pulmonary vascular resistances. There was no change in heart rate and systemic arterial pressure or in plasma norepinephrine or plasma renin activity. After 24 hours, pressures had partially returned to control levels, but mean pulmonary artery pressure was still significantly lower than in the control period. After removal of the nitroglycerin, each patient exhibited a decrease in cardiac index and an increase, above the control values, in pulmonary and systemic arterial pressures and pulmonary, systemic and forearm vascular resistances. This transient rebound appeared to be unrelated to stimulation of the sympathetic or renin-angiotensin systems. Thus, transdermal absorption of this new form of nitroglycerin appears to provide a nitrate vascular effect that is sustained for 24 hours, but an endogenous vasoconstrictor effect may influence the hemodynamic response over the first 24 hours.
Author(s): Bauer JA; Fung HL / Institution: Department of Pharmaceutics, State University of New York at Buffalo 14260. / Title: Pharmacodynamic models of nitroglycerin-induced hemodynamic tolerance in experimental heart failure. / Source: *Pharm Res*. 1994 Jun. 11(6). P 816-23. / Abstract: Pharmacodynamic tolerance during continuous nitroglycerin (NTG) infusion is a significant limitation of nitrate therapy. The mechanism of this phenomenon is not well-understood but may involve physiologic compensation which involves vasoconstriction. We have obtained pharmacodynamic data on NTG-induced hemodynamic tolerance in a rat model of congestive heart failure (CHF), which we have shown to mimic human behavior toward NTG in vivo. In this report, we developed two mechanism-based pharmacokinetic/pharmacodynamic models to describe the time-dependent effects of NTG infusion on left ventricular end-diastolic pressures (LVEDP) in CHF rats and compared their abilities to describe the observed hemodynamic data. Both mathematical models introduced a counter-regulatory vasoconstrictive effect as a result of NTG-induced vasodilation and assumed the magnitude of this effect to be driven by the extent of the

initial hemodynamic effect produced by NTG. The decay of this counter-regulatory effect was described by a first-order process in both models. A model that assumed vasoconstriction to develop via two sequential first-order processes was statistically superior in describing the data, when compared to one that assumed a single first-order process and a lag phase. Both models provided similar estimates of the half-life for the disappearance of the vasoconstriction (t1/2 of vasoconstriction: 128min vs. 182min, respectively), and both predicted rebound elevation of LVEDP after abrupt NTG withdrawal. These results are consistent with a counter-regulatory mechanism of NTG-induced hemodynamic tolerance and suggest that such an approach may be useful for modeling other tolerance phenomena as well.
Author(s): Cloarec-Blanchard L; Funck-Brentano C; Carayon A; Jaillon P / Institution: Clinical Pharmacology Unit, Saint-Antoine University Hospital, Paris, France. / Title: Rapid development of nitrate tolerance in healthy volunteers: assessment using spectral analysis of short-term blood pressure and heart rate variability. / Source: *J Cardiovasc Pharmacol*. 1994 Aug. 24(2). P 266-73. / Abstract: Nitrate tolerance is characterized by a loss of nitroglycerin (NTG) vasodilating and hypotensive effects during continuous administration, but is difficult to detect clinically. We hypothesized that the decrease in arterial blood pressure (BP) and the reflex sympathetic activation and tachycardia due to baroreflex deactivation associated with rapid intravenous (i.v.) infusion of NTG would be decreased during continuous NTG patch therapy as a result of tolerance to transdermal NTG. Sympathetic activation was measured as the change in amplitude of low-frequency (66-129 mHz) oscillations in BP and heart rate (HR) recorded by a noninvasive method. Eleven healthy male volunteers received rapid i.v. infusion of 0.45 mg NTG in 1 min on 3 consecutive days: before NTG patch, after 22.5 h of patch therapy, and 22.5 h after patch removal. The maximum decrease in systolic BP (SBP) and maximum reflex tachycardia as well as the sympathetic activation produced by i.v. NTG were compared during each of the three study periods. The maximum decrease in SBP was 38 +/- 8 mm Hg before NTG patch and 27 +/- 15 mm Hg during NTG patch ($p < 0.05$), with return to baseline values (37 +/- 13 mm Hg) after patch removal. There was no significant change in amplitude of reflex tachycardia among study periods. However, low-frequency oscillations in SBP increased by 40 +/- 31% in the absence of NTG patch and by only 9 +/- 35% after 22.5 h of patch therapy ($p < 0.05$). Patch removal resulted in a significant rebound increase in these oscillations (70 +/- 51%; $p < 0.05$ vs. baseline).

Sodium nitroprusside *(reducing the heart load, vasodilator)*
Therapeutic indications: Hypertension.
Rebound effect:
Severe rebound hypertension occurs with the discontinuation of infusion used to produce hypotension during surgery. *(USP DI, 1996, p. 2192; AHFS, 1990, p. 954)*
Author(s): Karam J; Pouard P; Fiemeyer A; Mauriat P; Dubuit C / Title: [Sodium nitroprusside in hypothermic surgery under extracorporeal circulation] / Source: *Cah Anesthesiol*. 1984 Oct. 32(6). P 473-80. / Abstract: Sodium nitroprusside (SNP) is a vasodilator widely used in heart surgery. Its effects before and after bypass at normal temperature have been reported. This prospective study compares 15 patients who received SNP with 5 controls. SNP's efficacy on the systemic arterial resistance index is demonstrated during cooling and rewarming. Vasoconstriction at the end of persistent hypothermia does not respond to SNP. Neither signs of toxicity, neither biological (metabolic acidosis) nor clinical (respiratory or cardiac problems) were observed. SNP lowers pulmonary artery resistance index during normothermia and pulsed cardiac output, but a rebound appears 45 minutes after SNP withdrawal. SNP is usefull for anaesthesia in heart surgery with hypothermia.
Author(s): Fahmy NR; Gavras HP / Title: Impact of captopril on hemodynamic and hormonal effects of nitroprusside. / Source: *J Cardiovasc Pharmacol*. 1985 Sep-Oct. 7(5). P 869-74. /

Abstract: The impact of oral captopril, 2 mg/kg, on the dose and on the hemodynamic and hormonal effects of nitroprusside was studied in seven patients (Group II). A comparable group (Group I, n = 7) received nitroprusside alone. In both groups, nitroprusside produced comparable decreases in mean arterial pressure, systemic vascular resistance, and right atrial pressure; cardiac output increased because of a significant change in heart rate. Although plasma renin activity increased significantly (compared with control values) in both groups, it was greater (p = 0.01) through the operative period in patients pretreated with captopril. Plasma aldosterone concentration increased in Group I (p = 0.01) but decreased in Group II (p = 0.01). Plasma catecholamine concentrations increased (p = 0.01) with nitroprusside alone but were unchanged in captopril-treated patients. Plasma converting enzyme activity was markedly inhibited (p = 0.001) by captopril. Following cessation of nitroprusside infusion in Group I, rebound hypertension occurred in conjunction with a significant (p = 0.01) increase in systemic vascular resistance; it was associated with elevated plasma renin activity, catecholamines, and aldosterone concentrations. In contrast, captopril-treated patients showed no rebound hemodynamic changes. Nitroprusside dose was less (p = 0.01) with captopril pretreatment (2.1 +/- 0.3 vs. 4.8 +/- 0.9 microgram/kg. min). Thus, captopril is a useful adjunct to nitroprusside-induced hypotension.

Author(s): Bernard JM; Pinaud M; Francois T; Babin M; Macquin-Mavier I; Letenneur J / Institution: Departement d'Anesthesie-Reanimation Chirurgicale, Hotel-Dieu, Nantes, France. / Title: Deliberate hypotension with nicardipine or nitroprusside during total hip arthroplasty. / Source: *Anesth Analg*. 1991 Sep. 73(3). P 341-5. / Abstract: To induce deliberate hypotension during anesthesia, nicardipine was administered to patients undergoing total hip arthroplasty and was randomly compared with nitroprusside. Hemodynamic measurements were performed before and 10, 20, 30, and 60 min after starting to administer either nicardipine (n = 12) or nitroprusside (n = 12) (B, T1, T2, T3, and T4, respectively); at the end of drug infusion (T5); and 10, 20, and 60 min later (T6, T7, and T8, respectively). Plasma renin activity and catecholamine levels were measured at B, T1, T5, T6, and T7. In addition, plasma nicardipine concentration was measured in five patients at T1, T2, T5, T7, and T8. As with nitroprusside, nicardipine administration (1-3 micrograms.kg-1.min-1, after a titration dose of 4.7 +/- 1.5 mg) resulted in hypotension (up to -34% +/- 3%), a decrease in systemic vascular resistances (up to -49% +/- 4%), and increases in heart rate (up to +17% +/- 6%), cardiac index (up to +37% +/- 8%), plasma norepinephrine (up to +63% +/- 17%) and epinephrine (up to +232% +/- 68%) levels, and plasma renin activity (up to +336% +/- 207%). Ten and 20 minutes after discontinuation of the hypotensive drug, nicardipine led to persistent vasodilation and hypotension, which differed significantly from the hypertensive rebound observed after nitroprusside discontinuation, despite a similar increase in plasma renin activity and catecholamine levels. Our results indicate that after the infusion was terminated, the nicardipine-induced vasodilation was opposed to the vasoconstrictive effects of angiotensin II and catecholamines, thus avoiding hypertensive rebound.

Author(s): Abdulatif M / Institution: Department of Anaesthesia, King Fahad University Hospital, Al-Khobar, Saudi Arabia. / Title: Sodium nitroprusside induced hypotension: haemodynamic response and dose requirements during propofol or halothane anaesthesia. / Source: *Anaesth Intensive Care*. 1994 Apr. 22(2). P 155-60. / Abstract: This study was designed to investigate the influence of anaesthesia induced and maintained with propofol on the haemodynamic effects and the dose requirements of SNP during the course of induced hypotension. Twenty-four adult ASA physical status I patients undergoing middle ear surgery were randomly assigned to receive anaesthesia with either morphine, thiopentone, d-tubocurarine, halothane 0.6% end-tidal and N2O 70% in oxygen (group I n = 12), or morphine, propofol, d-tubocurarine, propofol infusion 108 micrograms.kg-1.min-1 and N2O in oxygen (group 2 n = 12). Mean arterial blood pressure (MAP) was reduced to 60-65 mmHg in all patients using a continuous infusion of sodium nitroprusside (SNP) 0.01%. Propofol produced a significant (17%) reduction in the MAP before institution of SNP infusion. This was related to a 24% reduction in the systemic vascular resistance

index (SVRI). In the halothane group SVRI was significantly reduced during SNP infusion. Halothane anaesthesia was associated with significant reflex tachycardia in response to SNP induced hypotension. Eight patients in the halothane group (66%) required propranolol 0.5-3 mg to control tachycardia. Propofol anaesthesia attenuated significantly the reflex tachycardia in response to SNP induced hypotension. Two patients in the propofol group (16%) required 0.5 mg propranolol to control reflex tachycardia. The mean SNP dose requirements were 7.25 +/- 1.6 and 2.1 +/- 1.4 micrograms. kg-1.min-1 in the halothane and propofol groups, respectively (P < 0.0001). None of the patients in the two groups developed rebound hypertension following SNP withdrawal.
Author(s): Larsen R; Kleinschmidt S / Institution: Klinik fur Anaesthesiologie und Intensivmedizin der Universitatskliniken des Saarlandes, Homburg/Saar. / Title: [Controlled hypotension] / Source: *Anaesthesist*. 1995 Apr. 44(4). P 291-308. / Abstract: Induced hypotension is defined as a reduction in mean arterial blood pressure to 50-60 mm Hg in normotensive subjects. The aim of induced hypotension is to decrease intraoperative blood loss, decrease the need for blood transfusions and improve operating conditions. Most studies indicate that induced hypotension can decrease intraoperative blood loss by 50% in many surgical procedures; however, some studies report that blood loss is not significantly reduced. Current methods of induced hypotension are based on the use of rapid and short-acting vasodilators as primary agents (nitroprusside, nitroglycerine, urapidil), supplemented by volatile anesthetics (isoflurane) and/or beta-blockers (esmolol) to improve effect, reduce dosage and prevent side effects (reflex tachycardia, tachyphylaxis, rebound hypertension). Proper positioning of the patient and controlled ventilation aid in reducing blood loss. Major risks of induced hypotension are a reduction in blood flow (i.e. ischaemia) of vital organs (brain, myocardium) and elevation of intracranial pressure in neurosurgical patients. Thus, major contraindications of induced hypotension are severe coronary artery disease, hypertension combined with arteriosclerosis of cerebral vessels and increased intracranial pressure in patients with cerebral disease. Complications are rare in otherwise healthy patients, but may be higher in elderly patients and those with underlying organ dysfunction. Therefore, careful assessment and selection of patients, together with consideration of the potential complications, appropriate choice of drugs and invasive beat-by-beat monitoring, are essential for the safe practice of induced hypotension.

Pargyline *(MAO inhibitor)*
Therapeutic indications: Hypertension.
Rebound effect:
As symptoms of possible rebound hypertensive crisis observed severe chest pain, dilated pupils, fever, severe headache, increased photosensitivity eyepiece, nausea and vomiting, sore or stiff neck. *(USP DI, 1988, p. 1716)*

Prostaglandin A1 *(vasodilator)*
Therapeutic indications: Preeclampsia (hypertension of pregnancy).
Rebound effect:
Author(s): Toppozada MK; Shaala SA; Moussa HA / Title: Therapeutic use of PGA1 infusions in severe pre-eclampsia - a major clinical potential. / Source: *Clin Exp Hypertens B*. 1983. 2(2). P 217-32. / Abstract: Pilot studies showed that, i.v. infusions of the renal prostaglandin A1 (PGA1) induced a triad of beneficial clinical responses in severe pre-eclampsia; the blood pressure became normotensive, renal function was markedly improved and labour was successfully induced. The present study was an attempt to develop a therapeutic schedule of PGA1 administration in severe toxemia. Twenty one cases of severe pre-eclampsia (in 3 equal groups) received i.v. infusions of PGA1 in a dose range of 0.1-0.5 microgram/kgm/min for 12 - 24 hours and the B.P., uterine activity and FHR were continuously monitored during and for 12 hours following the infusion period. The

0.1 microgram/Kgm/min dose for 12 hours was inadequate while 0.5 microgram/Kgm/min for 12 hours induced a good hypotensive response and the cases delivered within 48 hours but a post-infusion rebound in hypertension was observed. The dose of 0.5 microgram/Kgm/min for 24 hours appeared to be optimal in clinical terms since a satisfactory effect on B.P. was recorded and all the subjects delivered normal babies during the infusion period with minimal or no post-infusion rebound rise in B.P. This approach holds a major potential in the treatment of severe pre-eclampsia.
Author(s): Toppozada MK; Ismail AA; Hegab HM; Kamel MA / Title: Treatment of preeclampsia with prostaglandin A1. / Source: *Am J Obstet Gynecol*. 1988 Jul;159(1):160-5. / Abstract: The vasodepressor prostaglandin A1 appeared to offer a major clinical potential solution in cases of severe pregnancy-induced hypertension. Thirty pregnant women with severe pregnancy-induced hypertension and a low Bishop score were studied in three equal groups. Group 1 received prostaglandin A1 infusions alone (0.5 microgram/kg/min for a maximum of 24 hours). Group 2 had received initial priming by prostaglandin E2 vaginal gel 6 hours before the onset of the prostaglandin A1 infusion, and group 3 was treated by conventional therapy and oxytocin induction. In the first two groups blood pressure was reduced to normotensive values, and labor was induced satisfactorily in 15 of the 20 cases, but four patients in group 1 were delivered within 24 hours after infusion. Group 2 offered the most favorable results because 80% were delivered during the infusion; thus the postinfusion rebound rise in blood pressure was avoided. Group 3 presented the least acceptable results, with the highest failure rate and an increased number of operative deliveries.

Drugs for pulmonary arterial hypertension

Nitric oxide (NO)
Therapeutic indications: Pulmonary hypertension.
Rebound effect:
Author(s): Lindberg L; Sjoberg T; Ingemansson R; Steenb S / Institution: Department of Cardiothoracic Surgery, University Hospital of Lund, Lund, Sweden. / Title: Inhalation of nitric oxide after lung transplantation. / Source: *Ann Thorac Surg*. 1996 Mar. 61(3). P 956-62. / Abstract: Pulmonary hypertension is a postoperative complication that may adversely affect the outcome of lung transplantation. The effect of nitric oxide (NO) inhalation on pulmonary hemodynamic indices after lung transplantation was studied and compared with findings in control pigs. Varying concentrations of NO were inhaled by 5 pigs after left lung transplantation and right pneumonectomy and by 5 controls after right pneumonectomy at an inspired oxygen fraction of 0.21 and 0.5. Hemodynamic data were recorded continuously, and fast circulatory courses were analyzed. Inhalation of NO reduced pulmonary vascular resistance and mean pulmonary arterial pressure in all pigs, but the decrease was pronounced and dose dependent only at an inspired oxygen fraction of 0.21 in the pigs that had transplantation. These were the only pigs that became hypoxic. With the termination of NO, there was a dose-independent rebound pulmonary vasoconstriction in the controls, especially at an inspired oxygen fraction of 0.21, but not in the pigs that had transplantation. This response was transient and could be blunted with a higher inspired oxygen fraction. Inhalation of NO reduced pulmonary vascular resistance in the transplanted lung and may be useful in the treatment of pulmonary hypertension after lung transplantation. The rebound pulmonary vasoconstriction with the termination of NO inhalation stresses the need to be aware of this effect and to wean NO carefully in clinical situations. This study showed oxygen dependency, which has to be taken into consideration in dose-response studies involving NO inhalation.

Author(s): Lavoie A; Hall JB; Olson DM; Wylam ME / Institution: Department of Medicine and Pediatrics, University of Chicago, Illinois 60637, USA. / Title: Life-threatening effects of discontinuing inhaled nitric oxide in severe respiratory failure. / Source: *Am J Respir Crit Care Med*. 1996 Jun. 153(6 Pt 1). P 1985-7. / Abstract: We present the effects of abrupt discontinuation of inhaled nitric oxide (NO) in four patients with severe hypoxemic respiratory failure. These patients ranged from 9 mo to 65 yr of age. In each patient, after the initiation of inhaled NO, a marginal, but immediate, beneficial effect on gas exchange and, when measured, a reduction in pulmonary artery pressures was noted. However, during attempts to discontinue inhaled NO, not only did these patients develop worsening oxygenation and recrudescence of pulmonary hypertension but, unexpectedly, these parameters were worse than the baseline values, leading to life-threatening hemodynamic instability. These effects reversed immediately after reinstitution of inhaled NO. The mechanism of this severe ¿rebound¿ in pulmonary hypertension after abrupt withdrawal of NO is unclear, but its existence emphasizes the need to avoid a substantial risk to these patients. Moreover, we believe that both unintentional and intentional termination of inhaled NO therapy may lead to life-threatening deterioration in gas exchange and circulatory hemodynamics that exceeds the initial therapeutic benefit.

Drugs for systemic hypotension

Dextran
Therapeutic indications: Hypovolemic shock treatment.
Rebound effect:
Due to the occurrence of important secondary reaction soon after administration of drugs, patients should be observed closely during the first five minutes, to detect severe hypotension of rebound. *(AHFS, 1990, p. 1420)*

Dopamine *(cardiac stimulant, vasopressor)*
Therapeutic indications: Acute hypotension.
Rebound effect:
Hypotension (in severe cases must administer drugs with vasoconstritoras properties similar to norepinephrine). *(USP DI, 1994, p. 1234; AHFS, 1990, p. 620)*

Metaraminol *(vasopressor)*
Therapeutic indications: Acute hypotension.
Rebound effect:
Hypotension (with prolonged use or after suspension occurs hypotension recurrent). *(USP DI, 1994, p. 1850)*
With prolonged use arterial vasodilation and hypotension occurs. *(AHFS, 1990, p. 641)*

Cardiotonic agents

Nitrates - Nitroglycerin
Therapeutic indications: Treatment of congestive heart failure.
Rebound effect:

In patients with stable angina pectoris, after suspension of chronic use, acute myocardial infarction occurred. *(USP DI, 1996, p. 959)*

Author(s): Olivari MT; Carlyle PF; Levine TB; Cohn JN / Title: Hemodynamic and hormonal response to transdermal nitroglycerin in normal subjects and in patients with congestive heart failure. / Source: *J Am Coll Cardiol*. 1983 Nov. 2(5). P 872-8. / Abstract: The hemodynamic and hormonal responses to nitroglycerin administered transdermally in a gel-like matrix were evaluated in nine patients with severe congestive heart failure and in nine normal subjects. In normal subjects, peripheral vasodilation was accompanied by reflex sympathetic stimulation as reflected by an increase in heart rate and plasma norepinephrine. In patients with heart failure, nitroglycerin produced sustained hemodynamic effects that began 30 minutes after the application and fully persisted for at least 6 hours. A significant decrease in right and left ventricular filling pressures was associated with an increase in stroke index and a significant decrease in forearm and pulmonary vascular resistances. There was no change in heart rate and systemic arterial pressure or in plasma norepinephrine or plasma renin activity. After 24 hours, pressures had partially returned to control levels, but mean pulmonary artery pressure was still significantly lower than in the control period. After removal of the nitroglycerin, each patient exhibited a decrease in cardiac index and an increase, above the control values, in pulmonary and systemic arterial pressures and pulmonary, systemic and forearm vascular resistances. This transient rebound appeared to be unrelated to stimulation of the sympathetic or renin-angiotensin systems. Thus, transdermal absorption of this new form of nitroglycerin appears to provide a nitrate vascular effect that is sustained for 24 hours, but an endogenous vasoconstrictor effect may influence the hemodynamic response over the first 24 hours.

Author(s): Packer M; Medina N; Yushak M; Lee WH / Title: Hemodynamic factors limiting the response to transdermal nitroglycerin in severe chronic congestive heart failure. / Source: *Am J Cardiol*. 1986 Feb 1. 57(4). P 260-7. / Abstract: To clarify the continuing controversy concerning the use of transdermal nitroglycerin (TDN), the shortterm hemodynamic responses to sublingual, oral and transcutaneous nitrates were evaluated and compared in 22 patients with severe chronic congestive heart failure. Sixteen patients showed favorable hemodynamic effects with TDN, but the doses needed to achieve this response varied greatly: 10 mg/24 hours in 6 patients, 20 mg/24 hours in 5 patients, 40 mg/24 hours in 3 patients and 60 mg/24 hours in 2 patients. Of the 6 remaining patients, 3 did not respond to high-dose TDN even though they showed marked effects after sublingual and oral nitrate administration; 3 others did not respond to any nitrate formulation by any route. TDN produced immediate increases in cardiac index and decreases in right and left ventricular filling pressure, mean arterial pressure and systemic vascular resistance (p less than 0.01). These effects, however, became rapidly attenuated within 3 to 6 hours; after 18 to 24 hours, only modest decreases in right and left ventricular filling pressures were observed. After removal of TDN treatment, rebound decreases in cardiac index and rebound increases in mean arterial pressure and systemic vascular resistance occurred, but right and left ventricular filling pressures returned to pretreatment values without rebound changes. Isosorbide dinitrate, 40 mg orally, produced hemodynamic effects that were greater in magnitude than effects seen after administration of TDN (p less than 0.05 to 0.01), but 4 patients in whom tolerance to TDN developed showed reversible cross tolerance to oral isosorbide dinitrate.

Author(s): Vogt A; Kreuzer H / Title: [Hemodynamic effect and duration of action of Deponit 10 in patients with congestive heart insufficiency] / Source: *Z Kardiol*. 1986. 75 Suppl 3P 86-9. / Abstract: The haemodynamic effect of transdermal nitroglycerin treatment with Deponit 10 was investigated in 10 patients with chronic cardiac failure due to coronary artery disease (8 patients) or congestive cardiomyopathy (2 patients). The patients had elevated mean pulmonary artery (PA) and pulmonary capillary wedge pressures (PC) at rest (32.1 +/- 5.9 and 24.1 +/- 6.6 mm Hg). Heart rate (87 +/- 10), arterial blood pressure (133 +/- 20/77 +/- 8 mm Hg) and cardiac index (3.73 +/- 0.85 l/min/m2) were in the normal range. During treatment with Deponit 10 mean PA and PC pressures

decreased significantly (p less than 0.01) to 25.5 +/- 6.3 and 18.1 +/- 6.4 mm Hg, respectively. The effect was seen within 1 hour after application of the transdermal therapeutic system and reached its nadir after 2 hours. PA and PC pressures remained significantly below control for 12-16 hours. Heart rate, arterial blood pressure and cardiac index were not changed. After removal of the patch 4 patients showed a rebound haemodynamic deterioration. Their mean PA pressure rose by more than 4 mm Hg above the respective control values. These patients had the highest control PA pressures of the group studied (37.5 +/- 2.4 mm Hg). Thus, transdermal nitroglycerin treatment with Deponit 10 reduces cardiac preload in patients with congestive heart failure for 12-16 hours, whereas cardiac afterload remains unaffected. After removal of the patch a rebound phenomenon can occur especially in patients with severe cardiac failure.
Author(s): Bauer JA; Fung HL / Institution: Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo 14260. / Title: Effect of apparent elimination half-life on nitroglycerin-induced hemodynamic rebound in experimental heart failure. / Source: *Pharm Res*. 1993 Sep. 10(9). P 1341-5. / Abstract: Hemodynamic rebound after abrupt withdrawal may be an important consideration associated with nitroglycerin (NTG) monotherapy. This phenomenon may arise from unopposed neurohormonal vasoconstriction because of rapid elimination of NTG. The role of NTG pharmacokinetics in the development of hemodynamic rebound was examined using a rat model of congestive heart failure. NTG was infused for 90 min, then the dose was either abruptly stopped (n = 8) or gradually reduced by 20% every 20 min (n = 7). Abrupt withdrawal caused rebound elevations of left ventricular end-diastolic pressure (LVEDP) to about 25% above baseline values, at 30-60 min after drug termination ($P < 0.01$), but this was completely avoided by graded NTG withdrawal. A positive correlation was observed ($P < 0.05$) between the percentage reduction in LVEDP during infusion and the maximum percentage rebound in rats after abrupt withdrawal but not after graded withdrawal. These results suggest that NTG-induced hemodynamic rebound is related to its short biological half-life and that this phenomenon is consistent with a mechanism of neurohormonal compensation.
Author(s): Bauer JA; Fung HL / Institution: Department of Pharmaceutics, State University of New York at Buffalo 14260. / Title: Pharmacodynamic models of nitroglycerin-induced hemodynamic tolerance in experimental heart failure. / Source: *Pharm Res*. 1994 Jun. 11(6). P 816-23. / Abstract: Pharmacodynamic tolerance during continuous nitroglycerin (NTG) infusion is a significant limitation of nitrate therapy. The mechanism of this phenomenon is not well-understood but may involve physiologic compensation which involves vasoconstriction. We have obtained pharmacodynamic data on NTG-induced hemodynamic tolerance in a rat model of congestive heart failure (CHF), which we have shown to mimic human behavior toward NTG in vivo. In this report, we developed two mechanism-based pharmacokinetic/pharmacodynamic models to describe the time-dependent effects of NTG infusion on left ventricular end-diastolic pressures (LVEDP) in CHF rats and compared their abilities to describe the observed hemodynamic data. Both mathematical models introduced a counter-regulatory vasoconstrictive effect as a result of NTG-induced vasodilation and assumed the magnitude of this effect to be driven by the extent of the initial hemodynamic effect produced by NTG. The decay of this counter-regulatory effect was described by a first-order process in both models. A model that assumed vasoconstriction to develop via two sequential first-order processes was statistically superior in describing the data, when compared to one that assumed a single first-order process and a lag phase. Both models provided similar estimates of the half-life for the disappearance of the vasoconstriction (t1/2 of vasoconstriction: 128min vs. 182min, respectively), and both predicted rebound elevation of LVEDP after abrupt NTG withdrawal. These results are consistent with a counter-regulatory mechanism of NTG-induced hemodynamic tolerance and suggest that such an approach may be useful for modeling other tolerance phenomena as well.

Sulmazol

Therapeutic indications: Treatment of congestive heart failure.
Rebound effect:
Author(s): Berkenboom GM; Sobolski JC; Depelchin PE; Contu E; Dieudonné PM; Degré SG / Title: Clinical and hemodynamic observations on orally administered sulmazol (ARL115BS) in refractory heart failure. / Source: *Cardiology*. 1984. 71(6). P 323-30. / Abstract: The acute effects of an oral preparation of sulmazol, a recently synthesized cardiotonic agent, were assessed by means of a Swan-Ganz catheter in 10 patients who had advanced heart failure that persisted despite treatment with digitalis, diuretics and nitrates. All patients demonstrated a hemodynamic improvement. Pulmonary wedge pressure decreased significantly 1 h after administration from 26 +/- 2 to 16 +/- 3 mm Hg (mean +/- SEM; 32%; p less than 0.01) and this decrease remained significant at least 6 h after intake. The cardiac index increased from 1.8 +/- 0.1 to 2.4 +/- 0.1 1/min/m2 (33%; p less than 0.01) and remained significant up to 6 h later. Total systemic and pulmonary resistances were also significantly decreased (peak changes 28% and 46%, respectively) up to 6 h later. Heart rate and mean blood pressure were unaffected. Once the duration of action was assessed for each patient, a short-term oral therapy was initiated for 48 h. Hemodynamic measurements performed 24 h and 36 h following the commencement of this chronic therapy showed the sustained hemodynamic improvement. 7 patients were continued on sulmazol therapy for 3 weeks to 6 months. Side effects were nausea and vomiting (which were likely to be dose-related), worsening arrhythmias and a possible rebound phenomenon after withdrawal. Although orally administered sulmazol shows promise as a potentially useful agent in the treatment of advanced heart failure, the safety of this drug remains to be established.

Coronary artery reperfusion
Therapeutic indications: Increasing perfusion and cardiac function.
Rebound effect:
Author(s): Buda AJ; Zotz RJ; Pace DP; Krause LC; Turla M / Title: Immediate rebound followed by deterioration of regional left ventricular function with coronary reperfusion. / Source: *J Am Coll Cardiol*. 1986 Aug. 8(2). P 333-41. / Abstract: The immediate and early effects of coronary artery reperfusion initiated 1 and 3 hours after coronary artery occlusion were evaluated by two-dimensional echocardiographic measurements of overall and regional left ventricular function. A total of 29 anesthetized open chest dogs underwent one of the following: 1 hour occlusion followed by reperfusion (Group I, n = 9), 3 hour occlusion followed by reperfusion (Group II, n = 12) or 5 hour occlusion without reperfusion (Group III, n = 8). Serial two-dimensional echocardiography was performed at baseline; at 1, 3 and 5 hours of coronary occlusion; within 5 minutes of reperfusion; and at 2 hours of reperfusion. After occlusion, all groups manifested significant (p less than 0.01) increases in left ventricular diastolic and systolic area and decreases in left ventricular area ejection fraction. With coronary reperfusion, there was no improvement in these global variables in Groups I and II. However, immediately after reperfusion, there was improvement in the regional extent of dysfunction (Group I, 138 +/- 35 to 66 +/- 62 degrees, p less than 0.05; Group II, 156 +/- 51 to 85 +/- 77 degrees, p less than 0.05) as well as improvement in the regional degree of dyskinesia (p less than 0.05). These regional improvements were transient and resolved by 2 hours of coronary reperfusion. This immediate rebound of function was not associated with the duration of coronary occlusion, hemodynamic variables or ultimate infarct size. Thus, in the anesthetized open chest dog model, coronary artery reperfusion at 1 or 3 hours produces an immediate but transient improvement in regional systolic myocardial function.

Hypolipidemic drugs

***Nicotinic acid** (Niacin)*
Therapeutic indications: Treatment of hyperlipidemia.
Rebound effect:
After the discontinuation of therapy, occurs a significant increase of the blood lipid concentration. *(USP DI, 1996, p. 2168)*
Author(s): Subissi A; Criscuoli M; Biagi M; Murmann W / Title: Acute effects on plasma lipids in the rat of a new long-acting nicotinic acid derivative: LG 13979. / Source: *J Pharm Pharmacol*. 1983 Sep. 35(9). P 571-5. / Abstract: The effects on plasma lipids and nicotinic acid concentrations of a single dose of 2-(3-pyridinecarbonylamino)-2-deoxy-1,3,4,6 dihydrogen-D-glucose tetra-3-pyridinecarboxylate (LG 13979) compared with the effects of nicotinic acid and of its known derivatives niceritrol and sorbinicate, at the same doses, were studied in the fasted rat. Results show that LG 13979 has more prolonged activity on plasma free fatty acids and triglycerides, with longer lasting and more intense activity on plasma cholesterol than these three reference standards. Free fatty acid rebound occurs after administration of nicotinic acid and niceritrol, but not after LG 13979. This pharmacodynamic profile may be explained on the basis of the kinetics of nicotinic acid plasma concentrations, which are low, constant and lasting after LG 13979 administration.
Author(s): Karpe F; Frayn KN / Title: The nicotinic acid receptor - a new mechanism for an old drug. / Source: Lancet. 2004 Jun 5;363(9424):1892-4. / Abstract: Non-esterified fatty acids in plasma originate from adipose tissue. Delivery of fatty acids to the liver provides the substrate for VLDL triglycerides. Insulin-sensitive organs, overburdened by high concentrations of non-esterified fatty acids, may develop resistance to insulin action. In addition, insulin secretion from pancreatic beta-cells may be impaired by long-standing elevation of concentrations of non-esterified fatty acid in plasma. Normally, such concentrations fluctuate over the day depending on the transient suppression of lipolysis from adipose tissue by insulin released after meals. Diurnal concentrations of non-esterified fatty acid are often elevated in obesity, in particular in male-pattern upper-body fat accumulation. Nicotinic acid is the only drug that primarily lowers concentrations of non-esterified fatty acids and thereby lowers VLDL triglycerides. Nicotinic acid, or its analogues, seems to alleviate insulin resistance in the short-term whereas, paradoxically, the long-term effect is often the opposite. Suppression of lipolysis by nicotinic acid gives rise to a prominent rebound and the degree to which this occurs might explain this paradox. The exact cellular mechanism by which nicotinic acid exerts its antilipolytic effects has not been known until the recent discovery of a distinct G-protein coupled receptor. Nicotinic acid is a high affinity ligand, but the endogenous ligand is still unknown. Recently, Tina Rubic and colleagues (Biochem Pharmacol 2004; 67: 411-19) proposed a mechanism in which nicotinic acid stimulates cholesterol mobilisation from macrophages, thereby providing a potential link between regression of atherosclerosis and use of nicotinic acid. Research on signalling through the nicotinic acid receptor might give rise to novel and more effective methods to interfere with fatty-acid metabolism, with insulin resistance, hyperlipidaemia, and atherosclerosis as target diseases.
Author(s): Kamanna VS; Kashyap ML / Title: Nicotinic acid (niacin) receptor agonists: will they be useful therapeutic agents?. / Source: *Am J Cardiol.* 2007 Dec 3;100(11 A):S53-61. / Abstract: Nicotinic acid (niacin) favorably affects very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and lipoprotein (a) (LP[a]) and increases high-density lipoprotein (HDL). Emerging data indicates vascular anti-inflammatory properties to additionally account for niacin's proven effects in cardiovascular disease. Recent evidence indicates that niacin acts on GPR109A and GPR109B (HM74A and HM74, respectively), receptors expressed in adipocytes and immune cells. In adipocytes, GPR109A activation reduces triglyceride (TG) lipolysis, resulting in decreased free fatty acid (FFA) mobilization to the liver. In humans, this mechanism has yet to be confirmed because the plasma FFA decrease is transient and is followed by a rebound increase in FFA levels. New evidence indicates niacin directly inhibits diacylglycerol acyltransferase 2 (DGAT2) isolated

from human hepatocytes, resulting in accelerated hepatic apolipoprotein (apo)B degradation and decreased apoB secretion, thus explaining reductions in VLDL and LDL. This raises important questions as to whether stimulation of GPR109A in adipocytes or inhibition of DGAT2 in liver by niacin best explains the reduction in VLDL and LDL in dyslipidemic patients. Kinetic and in vitro studies indicate that niacin retards the hepatic catabolism of apoA-I but not liver scavenger receptor B1-mediated cholesterol esters, suggesting that niacin inhibits hepatic holoparticle HDL removal. Indeed, recent preliminary evidence suggests that niacin decreases surface expression of hepatic beta-chain of adenosine triphosphate synthase, which has been implicated in apoA-I/HDL holoparticle catabolism. GPR109A-mediated production of prostaglandin D2 in macrophages and Langerhan cells causes skin capillary vasodilation and explains, in part, niacin's effect on flushing. Development of niacin receptor agonists would, theoretically, result in adipocyte TG accumulation (and clinical adiposity) and increased flushing. This raises questions about niacin receptor agonists as therapeutic agents. Several niacin receptor agonists have been developed and patented, but their clinical effects have not been described. Future research is needed to determine whether niacin receptor agonists will demonstrate all the beneficial properties of nicotinic acid on atherosclerosis and without significant adverse effects.

Clofibrate
Therapeutic indications: Treatment of hyperlipidemia.
Rebound effect:
Substantial increase in concentration of triglycerides (LDL). *(AHFS, 1990, p. 889)*
Author(s): Cayen MN; Kallai-Sanfacon MA; Dubuc J; Greselin E; Dvornik D / Title: Effect of AY-25,712 on fatty acid metabolism in rats. / Source: *Atherosclerosis*. 1982 Dec. 45(3). P 281-90. / Abstract: The effect of AY-25,712 [2-methyl-2-phenyl-3(2H)-furanone-5-carboxylic acid] on various aspects of free fatty acid (FFA) and triglyceride metabolism was studied in male rats. Serum triglycerides were lowered by a single oral dose of AY-25,712 or nicotinic acid, but not of clofibrate. Unlike with clofibrate, when AY-25,712 or nicotinic acid was given in the diet, serum triglycerides were not affected. In vitro, both AY-25,712 and nicotinic acid suppressed the theophylline-induced FFA release by epididymal fat pads, but had no effect on lipolysis induced by norepinephrine. Both AY-25,712 and nicotinic acid enhanced the activity of adipose tissue lipoprotein lipase. The initial decrease in plasma FFA and triglycerides, and in liver triglycerides after a single oral dose of nicotinic acid was followed by a rebound to levels which, at later time intervals, wee significantly higher than in controls. AY-25,712 was more potent than nicotinic acid in lowering plasma FFA and triglycerides as well as liver triglycerides, but produced no such rebound effect. The data show that, except for the absence of this rebound effect, the mode of action of AY-25,712 in rats resembles that of nicotinic acid and differs from that of clofibrate.

Colestipol
Therapeutic indications: Treatment of hyperlipidemia.
Rebound effect:
Substantial increase in concentration of triglycerides (LDL). *(AHFS, 1990, p. 891)*

Colestiramine
Therapeutic indications: Treatment of hyperlipidemia.
Rebound effect:
Substantial increase in concentration of triglycerides (LDL). *(AHFS, 1990, p. 885)*

Gemfibrozil

Therapeutic indications: Treatment of hyperlipidemia.
Rebound effect:
Substantial increase in concentration of triglycerides (LDL). *(AHFS, 1990, p. 898)*

HMG-CoA reductase inhibitors *(Fluvastatin, Lovastatin, Pantethine, Pravastatin, etc.)*
Therapeutic indications: Treatment of hyperlipidemia.
Rebound effect:
Substantial increase in concentration of triglycerides (LDL). *(AHFS, 1990, p. 903)*
Author(s): Arsenio L; Caronna S; Lateana M; Magnati G; Strata A; Zammarchi G / Title: [Hyperlipidemia, diabetes and atherosclerosis: efficacy of treatment with pantethine] / Source: *Acta Biomed Ateneo Parmense*. 1984. 55(1). P 25-42. / Abstract: The hypolipidemizing effects of Pantethine were investigated by the Authors in 37 hypercholesterolemic and/or hypertriglyceridemic patients. Of these, 21 were also diabetic, in a satisfying glucidic compensation, in order to verify the action of this drug also in this metabolic condition. The study was carried out for three months and during this period the patients were given Pantethine at the dose of 600 mg/die orally. At the 30th, the 60th, the 90th day of treatment the following parameters were controlled: cholesterolemia, HDL cholesterol, apolipoproteins A and B, triglyceridemia, systolic and diastolic arterial pressure, uricemia, body weight. Thirty days after suspending the treatment, the parameters were controlled again to detect a possible "rebound" effect. The results were analyzed on the whole case-record, subdividing the patients in dislipidemic and diabetic-dislipidemic, and on the basis of the Fredrickson's classification. Pantethine induced in all groups a quick and progressive decrease of cholesterolemia, triglyceridemia, LDL cholesterol and Apolipoproteins B with increased HDL cholesterol and Apolipoproteins A. After suspending the treatment, there is a clear inversion of the state of these parameters. The Authors conclude that the present work shows that Pantethine, a natural and atoxic substance, an important component of Coenzyme A, is efficacious in determining a clear tendency towards normalization of the lipidic values.

Lifibrol
Therapeutic indications: Treatment of hyperlipidemia.
Rebound effect:
Author(s): Bell FP; St John LC / Institution: Upjohn Laboratories, Kalamazoo, Michigan 49001. / Title: Action of the new hypolipidemic agent lifibrol (K12.148) on lipid homeostasis in normal rats: plasma lipids, hepatic sterologenesis, and the fate of injected [14C]acetate. / Source: *Lipids*. 1993 Dec. 28(12). P 1079-85. / Abstract: Lifibrol, a new hypocholesterolemic agent with activity in humans, was examined in normal rats for its short-term and long-term effects on lipid homeostasis. Cholesterol (Chol) synthesis inhibition by lifibrol was demonstrated in vitro in liver minces from normal rats by following [1-14C]acetate ([14C]Ac) and DL-[2-14C]mevalonate ([14C]-MVA) incorporation into [14C]Chol. When administered at 50 mg/kg/d, lifibrol reduced plasma total Chol and triglycerides (TG) ($P < 0.001$) within 24 h. The Chol reduction was largely a result of reduction of low density and very low density lipoprotein cholesterol (LDL + VLDL-chol) and a smaller decrease in high density lipoprotein cholesterol (HDL-chol). After 10 d, however, a rebound effect emerged, and after 41 d, plasma Chol, LDL + VLDL-chol, and HDL-chol were restored. In contrast, plasma TG remained at reduced levels ($P < 0.01$). The rebound is attributed to counter-regulation of hepatic sterologenesis that was assessed both ex vivo and in vivo. The ex vivo incorporation of [14C]MVA and [14C]octanoate into [14C]Chol and total digitonin-precipitable [14C]sterols ([14C]DPS) in liver minces was increased 2-and 6-fold, respectively, in rats treated 6 d at 50 mg/kg. Similarly, in vivo incorporation of intraperitoneally injected [14C]Ac into hepatic [14C]DPS (2 h post-injection) was increased 2- to 5-fold at 50 mg/kg, and evidence for increased

sterologenesis in nonhepatic tissue was also obtained. The increased hepatic sterologenesis, evident within 48 h, persisted out to 41 d of treatment by which time increases ($P < 0.002$) in hepatic Chol and carcass total sterols were observed.

NEUROLOGICAL DRUGS, ANALGESIC AND ANESTHETIC

Intracranial hypertension drugs

Author(s): Frank JI / Institution: Department of Neurosurgery, Cleveland Clinic Foundation, OH 44195, USA. / Title: Large hemispheric infarction, deterioration, and intracranial pressure. / Source: *Neurology*. 1995 Jul. 45(7). P 1286-90. / Abstract: Neurologic deterioration from large hemispheric infarction with edema (LHIE) often leads to the use of therapies directed at decreasing intracranial pressure (ICP). Many of these ICP therapies can potentially accentuate tissue shifts from unilateral mass lesions and lead to rebound ICP elevations. We sought to determine whether ICP elevation is a common cause of deterioration from LHIE by measuring the initial ICP and cerebral perfusion pressure (CPP) in 19 patients deteriorating to stupor from LHIE within 3 hours of deterioration, after ruling out metabolic aberrations, medication side effects, infection, and seizures and prior to commencement of any ICP-lowering therapies. We evaluated 19 patients aged 23 to 77 years--14 with complete middle cerebral artery and five with complete internal carotid artery territory infarctions. Stupor began 59 +/- 37 hours after the stroke onset. ICP monitoring (12 ipsilateral Camino, five contralateral ventriculostomy, and two ipsilateral epidural) demonstrated elevation of ICP (> 15 mm Hg) in only five patients (26.3%), with group mean initial ICP = 13.4 +/- 10 mm Hg. Similarly, the initial CPP was diminished (< 55 mm Hg) in only two patients (10.5%), with group mean initial CPP = 74.9 +/- 14 mm Hg. Globally elevated ICP is not a common cause of initial neurologic deterioration from LHIE mass effect.

Glycerol

Therapeutic indications: Treatment of cerebral edema and intracranial hypertension.

Rebound effect:

Headache, nausea or vomiting; mental confusion. *(USP DI, 1996, p. 1546)*

Author(s): Node Y; Nakazawa S / Institution: Department of Neurosurgery, Nippon Medical School, Tokyo, Japan. / Title: Clinical study of mannitol and glycerol on raised intracranial pressure and on their rebound phenomenon. / Source: *Adv Neurol*. 1990. 52P 359-63. / Abstract: We have studied the effects of mannitol and glycerol on raised ICP as monitored by epidural pressure recordings in 65 patients. Four methods of infusion were assessed. In group A, 0.5 g/kg mannitol was infused within 15, 30, or 60 min. In group B, 1.0 g/kg mannitol was infused within 30, 60, or 90 min. In group C, 0.5 g/kg glycerol in 5% fructose was infused within 30, 60, or 90 min. In group D, 1.0 g/kg glycerol was infused within 60, 120, or 180 min. Results: (a) In group A, there was no difference in the reduction of ICP among the three infusion rates. In group B, the degree of ICP reduction increased with shorter times of infusion. In the groups receiving glycerol, the reduction of ICP was inversely related with the rate of infusion. (b) In every group, it appeared that the slower the infusion rate of the same dosage became, the longer the reduction of ICP lasted. (c) A rebound phenomenon occurred in 12% of the mannitol groups and 34% of the glycerol groups. The dose and the rate of mannitol infusion did not influence the occurrence of the rebound phenomenon. In the glycerol groups, the infusion method did influence the occurrence of rebound phenomenon. Our present study demonstrated that there were differences between mannitol and glycerol infusion in their effectiveness and in the occurrence of rebound phenomenon.

Author(s): Garcia-Sola R; Pulido P; Capilla P / Institution: Department of Neurosurgery, Hospital de la Princesa, Madrid, Spain. / Title: The immediate and long-term effects of mannitol and glycerol. A comparative experimental study. / Source: *Acta Neurochir (Wien)*. 1991. 109(3-4). P 114-21. / Abstract: A prolonged experimental situation of focal vasogenic oedema, producing

mild intracranial hypertension, was developed. The aim was to study the immediate and long-term effects of repeated infusions of mannitol and glycerol on intracranial pressure (ICP) and cerebral blood flow (CBF). Eighteen goats were operated on twice to implant: an epidural latex balloon in each cerebral hemisphere to measure ICP; an electromagnetic flowmeter around both internal maxillary arteries (the only cerebral blood input), after tying the extracranial branches, to measure the CBF; and two femoral catheters to measure blood pressure (BP) and for intravenous infusion (IV). Three groups of 6 goats each were formed: A) control; the BP and bilateral ICPs and CBFs were recorded under basal conditions and every 4 hours for 3 days after a cold injury (CI) was provoked; B) 20% mannitol solution 1 g/kg body weight injected every 12 hr starting at 24 hr post-CI; and C) 10.1% glycerol solution 0.5 g/kg body weight, administered as mannitol. Glycerol, as compared to mannitol, presents the following major differences among its immediate post infusion effects: a lesser decrease in ICP, but no rebound phenomenon; lesser elevation of BP; CBF increases more gradually and constantly. Long-term effects with mannitol consisted of a rebound phenomenon observed in ICP during the last 12 hr. In all 3 groups, it was observed that CBF increases in relation to the ICP level.

Author(s): Matsubara H; Kitahara M; Takeda T; Yazawa Y / Title: Rebound phenomenon in glycerol test. / Source: *Acta Otolaryngol Suppl (Stockh)*. 1984. 419P 115-22. / Abstract: The glycerol effect for endolymphatic hydrops is well known for an improvement in pure tone threshold three hours after glycerol administration. However, long-term effects of glycerol, i.e., longer than three hours after administration, are unknown. In this study, audiometric tests were administered during 10 hours following glycerol administration in order to determine the long-term effects of glycerol in cases of Meniere's disease, sudden deafness, and normal subjects. The following results were obtained; 1) The long-term effects of glycerol in the pure tone threshold were observed only in cases of Meniere's disease and were classified into the following four types: "descending type", "descending and ascending type", "ascending type" and "unchanged type". 2) The long-term effects, including rebound phenomenon, on hearing ability did not appear in cases of sudden deafness and normal subjects. 3) About 50% of patients with Meniere's disease showed rebound phenomenon on hearing ability and it was considered to be specific for Meniere's disease.

Author(s): Takeda T; Takeda S; Saito H; Hamada M; Sawada S / Title: The rebound phenomenon of glycerol-induced changes in the endolymphatic space. / Source: *Acta Otolaryngol.*1999;119(3):341-4. / Abstract: Volumetric changes of the scala media were histologically investigated in normal guinea pigs to see whether glycerol-induced volumetric change of the scala media followed a biphasic course similar to the auditory threshold in the glycerol test. Glycerol was administered orally in a 12 ml/kg dose. The volume of the scala media was assessed by examining the cross-sectional area of the scala media in the mid-modiolar sections of the cochlea. Histological study revealed that the time-course of the change in the volume of the scala media after glycerol intake showed biphasic changes. Specifically, the early phase of the glycerol effect is a decrease in endolymph volume. The volume of the scala media significantly decreased by 11.4+/-2.9% 2 h after glycerol intake. Thereafter, the volume began to increase, and reached its peak 6-12 h after intake. In addition, the volume of the scala media significantly increased by 17.6+/-1.1% after 6 h. The present study indicated that the secondary increase in the volume of the scala media following glycerol intake played an important role in the rebound phenomenon in the glycerol test, although the mechanism underlying the hearing loss with the endolymphatic hydrops remains to be elucidated.

Indomethacin *(cyclooxygenase inhibitor)*
Therapeutic indications: Prophylaxis of hypertension and intracranial hemorrhage.
Rebound effect:
Intracranial hemorrhage. *(USP DI, 1996, p. 1673; AHFS, 1990, p. 1024)*

Author(s): Biestro AA; Alberti RA; Soca AE; Cancela M; Puppo CB; Borovich B / Institution: Intensive Care Unit, Hospital de Clinicas, Faculty of Medicine, Montevideo, Uruguay. / Title: Use of indomethacin in brain-injured patients with cerebral perfusion pressure impairment: preliminary report. / Source: *J Neurosurg*. 1995 Oct. 83(4). P 627-30. / Abstract: The effect of indomethacin, a cyclooxygenase inhibitor, was studied in the treatment of 10 patients with head injury and one patient with spontaneous subarachnoid hemorrhage, each of whom presented with high intracranial pressure (ICP) (34.4 +/- 13.1 mm Hg) and cerebral perfusion pressure (CPP) impairment (67.0 +/- 15.4 mm Hg), which did not improve with standard therapy using mannitol, hyperventilation, and barbiturates. The patient had Glasgow Coma Scale scores of 8 or less. Recordings were made of the patients' ICP and mean arterial blood pressure from the nurse's end-hour recording at the bedside, as well as of their CPP, rectal temperature, and standard therapy regimens. The authors assessed the effects of an indomethacin bolus (50 mg in 20 minutes) on ICP and CPP; an indomethacin infusion (21.5 +/- 11 mg/hour over 30 +/- 9 hours) on ICP, CPP, rectal temperature, and standard therapy regimens (matching the values before and during infusion in a similar time interval); and discontinuation of indomethacin treatment on ICP, CPP, and rectal temperature. The indomethacin bolus was very effective in lowering ICP ($p < 0.0005$) and improving CPP ($p < 0.006$). The indomethacin infusion decreased ICP ($p < 0.02$), but did not improve CPP and rectal temperature. The effects of standard therapy regimens before and during indomethacin infusion showed no significant changes, except in three patients in whom mannitol reestablished its action on ICP and CPP. Sudden discontinuation of indomethacin treatment was followed by significant ICP rebound. The authors suggest that indomethacin may be considered one of the frontline agents for raised ICP and CPP impairment.

Mannitol *(osmotic diuretic)*

Therapeutic indications: Treatment of cerebral edema and intracranial hypertension.

Rebound effect:

Urinary retention, pulmonary congestion and edema of lower limbs. *(USP DI, 1996, p. 1957; AHFS, 1990, p. 1477)*

Rebound intracranial hypertension (cerebral oedema) occurs approximately 12 hours after the osmotic diuresis. *(AHFS, 1990, p. 1476)*

Author(s): Muizelaar JP; Wei EP; Kontos HA; Becker DP / Title: Mannitol causes compensatory cerebral vasoconstriction and vasodilation in response to blood viscosity changes. / Source: *J Neurosurg*. 1983 Nov. 59(5). P 822-8. / Abstract: There is no proof that osmotic agents such as mannitol lower intracranial pressure (ICP) by decreasing brain water content. An alternative mechanism might be a reduction in cerebral blood volume through vasoconstriction. Mannitol, by decreasing blood viscosity, would tend to enhance cerebral blood flow (CBF), but the cerebral vessels would constrict to keep CBF relatively constant, analogous to pressure autoregulation. The cranial window technique was used in this study to measure the pial arteriolar diameter in cats, together with blood viscosity and ICP changes after an intravenous bolus of 1 gm/kg of mannitol. Blood viscosity decreased immediately; the greatest decrease (23%) occurred at 10 minutes, and at 75 minutes there was a "rebound" increase of 10%. Vessel diameters decreased concomitantly, the largest decrease being 12% at 10 minutes, which is exactly the same as the 12% decrease in diameter associated with pronounced hyperventilation ($PaCO_2$ 30 to 19 mm Hg) in the same vessels; at 75 minutes vessel diameter increased by 12%. With hyperventilation, ICP was decreased by 26%; 10 minutes after mannitol was given, ICP decreased by 28%, and at 75 minutes it showed a rebound increase of 40%. The correlation between blood viscosity and vessel diameter and between vessel diameter and ICP was very high. An alternative explanation is offered for the effect of mannitol on ICP, the time course of ICP changes, "rebound effect," and the absence of influence on CBF, all with one mechanism.

Author(s): Domaingue CM; Nye DH / Title: Hypotensive effect of mannitol administered rapidly. / Source: *Anaesth Intensive Care*. 1985 May. 13(2). P 134-6. / Abstract: Mannitol is an osmotic diuretic commonly used to reduce intracranial pressure. While various side-effects, including hyperosmolar states, precipitate reduction in intracranial pressure, rebound phenomenon and hypervolaemia have been described, hypotension due to rapid administration has not been widely recognised.
Author(s): Kotwica Z; Persson L / Institution: Department of Neurosurgery, Medical Academy, Lodz, Poland. / Title: Effect of mannitol on intracranial pressure in focal cerebral ischemia - An experimental study in a rat. / Source: *Mater Med Pol*. 1991 Oct-Dec. 23(4). P 280-4. / Abstract: The authors studied the effects of mannitol on intracranial pressure (ICP) in experimental focal ischemia in a rat. Stroke was produced by occlusion of middle cerebral artery (MCA). The study revealed that mannitol decreases ICP in ischemic stroke much less then in healthy animals and also a significant rebound effect was seen, especially in the 5th and 7th day after MCA occlusion. The authors suggest a very limited use of mannitol in clinical treatment of elevated ICP after cerebral ischemic stroke.
Author(s): Davis M; Lucatorto M / Institution: Neuroscience Intensive Care Unit at Shadyside Hospital, Pittsburgh, Pennsylvania 15232. / Title: Mannitol revisited. / Source: *J Neurosci Nurs*. 1994 Jun. 26(3). P 170-4. / Abstract: Investigation into the use of osmotic therapy for ICP reduction began in 1919. Mannitol is the osmotic agent currently in use. Mannitol's effectiveness in reducing ICP has been shown. Osmotic therapy using mannitol reduces ICP by mechanisms that remain unclear. Mannitol is thought to decrease brain volume by decreasing overall water content, to reduce blood volume by vasoconstriction and to reduce CSF volume by decreasing water content. Mannitol may also improve cerebral perfusion by decreasing viscosity or altering red blood cell rheology. Lastly, mannitol may exert a protective effect against biochemical injury. The most common complications of therapy are fluid and electrolyte imbalances, cardiopulmonary edema and rebound cerebral edema. Nursing care of the patient receiving mannitol requires vigilant monitoring of electrolytes and overall fluid balance, and observation for the development of cardiopulmonary complications in addition to neurologic assessment.

***Urea** (osmotic diuretic)*
Therapeutic indications: Treatment of cerebral edema and intracranial hypertension.
Rebound effect:
Rebound intracranial hypertension occurs in approximately 12 hours after the onset of treatment. *(AHFS, 1990, p. 1479)*

Hyperbaric oxygen therapy
Indicação terapêutica: Treatment of cerebral edema and intracranial hypertension.
Rebound effect:
Author(s): Brown JA; Preul MC; Taha A / Institution: Department of Neurological Surgery, Medical College of Ohio, Toledo. / Title: Hyperbaric oxygen in the treatment of elevated intracranial pressure after head injury. / Source: *Pediatr Neurosci*. 1988. 14(6). P 286-90. / Abstract: This study is the first to evaluate the effect of hyperbaric oxygen (HBO) on elevated intracranial pressure (ICP) after severe head injury during documented controlled ventilation, hypocapnea, and minute-by-minute ICP data collection. We studied the effect of HBO at 2 atmospheres absolute (ATA) with 100% O2, on ICP in 2 patients, aged 5 and 21 years. Each patient had diffuse cerebral swelling after blunt trauma and after a gun shot wound, respectively. Both required controlled hyperventilation, osmotic diuretics and ICP monitoring. ICP, mean arterial blood pressure, pulse and atmospheric pressure were recorded at 1-min intervals during 1-hour treatments and for 15 min before and after HBO therapy. Controlled hyperventilation was continued

during HBO therapy and PCO; was measured at intervals. Each patient underwent 4 treatments. Data was divided into 5 phases, all at 100% O2; (1) prior to therapy; (2) during pressurization from 1 to 2 ATA; (3) at 2 ATA; (4) during depressurization from 2 to 1 ATA, and (5) after HBO therapy. During pressurization the mean ICP dropped from 13 to 8 Torr, rising to 14 Torr during HBO therapy at 2 ATA, and to 16 Torr during depressurization to 1 atmosphere, then returning to 12 Torr after HBO therapy. We conclude from this preliminary work that HBO may lower ICP in head-injured patients with diffuse cerebral swelling during the first 15 min, or pressurization phase, of therapy. However, rebound elevations in ICP may occur during or after treatment. No lasting effects of treatment were seen after concluding therapy. The effect of HBO on elevated ICP has not yet been clarified, but deserves further careful study in those patients with severe enough injury to require ICP monitoring.

Anticonvulsant drugs

Author(s): Marciani MG; Gotman J; Andermann F; Olivier A / Title: Patterns of seizure activation after withdrawal of antiepileptic medication. / Source: *Neurology*. 1985 Nov. 35(11). P 1537-43. / Abstract: Effects of withdrawal of anticonvulsant drugs on the temporal profile of occurrence and the type of seizures were investigated in 40 intractable epileptic patients who were candidates for surgical treatment. EEG and behavior were monitored while drugs were reduced to allow localization of the epileptogenic region. The rapid withdrawal of drugs caused a rebound effect, triggering either generalized seizures during a brief period or a longer-lasting increase in partial seizures. These increases in seizure frequency appeared related to change in dosage rather than to dosage itself, since they remained largely confined to the early period following reduction of an anticonvulsant.

Valproic acid
Therapeutic indications: Seizures.
Rebound effect:
Increase in the frequency of seizures. *(USP DI, 1988, p. 2168; AHFS, 1990, p. 1147)*

Dione anticonvulsants *(Parametadione, Trimethadione)*
Therapeutic indications: Seizures.
Rebound effect:
Exacerbation or new tonic-clonic seizures. *(USP DI, 1996, p. 247; AHFS, 1990, p. 1137)*

Hydantoin anticonvulsants *(Etotoina, Phenytoin, Mephenytoin)*
Therapeutic indications: Seizures, paroxysmal choreoathetosis, conduct disorders (excitement, anxiety, irritability and insomnia).
Rebound effect:
Increase in the frequency of seizures. Anxiety and agitation; uncontrolled jerky movements or torsion of the hands, arms and legs; uncontrolled movements of the lips, tongue or cheeks (choreoathetoid movements transient non-hydantoin poisoning; usually the effect lasts between 24 and 48 hours after stopping phenytoin and may stop spontaneously). Changes in behavior or mental state; excitement, nervousness and irritability non-standard. *(USP DI, 1996, p. 249)*
Author(s): Ries CR; Scoates PJ; Puil E / Institution: Department of Anaesthesia, University of British Columbia, Vancouver. / Title: Opisthotonos following propofol: a nonepileptic perspective

and treatment strategy / Source: *Can J Anaesth*. 1994 May. 41(5 Pt 1). P 414-9. / Abstract: In this report of opisthotonos during recovery from propofol anaesthesia, we relate clinical observations with scientific considerations, and propose a strategy for treatment of this rare side effect. Following a brief operative procedure, a healthy 29-yr-old woman developed recurrent opisthotonos while recovering from anaesthesia with alfentanil, propofol, and nitrous oxide. In contrast to accumulating reports, the patient remained conscious during each episode of back extension and retrocollis. The preservation of consciousness and similarities to strychnine-induced opisthotonos suggest to us that the mechanism may have a brainstem and spinal origin. Recent investigations show that propofol potentiates the inhibitory transmitters glycine and gamma-aminobutyric acid (GABA) which would enhance spinal inhibition during anaesthesia. Postanaesthetic opisthotonos, however, may be due to a propofol-induced tolerance to inhibitory transmitters. This rebound phenomenon would lead to an acute, enduring refractoriness in inhibitory pathways of the brainstem and spinal cord, resulting in increased activity of extensor motoneurons. We recommend a therapeutic strategy that restores inhibition by glycine and GABA at multiple sites; the preferred therapeutic agents would be diazepam and physostigmine. The episodes are usually short-lived, but two of the reviewed 17 patients developed recurrent retrocollis for four and 23 days following antiepileptic drug therapy. Since high doses of phenytoin and carbamazepine can result in opisthotonos, we recommend that anticonvulsants be reserved for postanaesthetic patients with electroencephalographic evidence of seizure activity.

Barbiturates
Therapeutic indications: Seizures.
Rebound effect:
Seizures (occurs 16 hours after interruption of treatment and last up to 5 days, decreasing gradually during the period of 15 days). *(USP DI, 1996, p. 511; AHFS, 1990, p. 1125)*

Benzodiazepines
Therapeutic indications: Seizures.
Rebound effect:
Convulsions. *(USP DI, 1996, p. 542; AHFS, 1990, p. 1129)*

Carbamazepine
Therapeutic indications: Seizures.
Rebound effect:
Increase in the frequency of seizures, tremors or uncontrolled movements of the body. *(USP DI, 1996, p. 730)*
Exacerbation of seizures, as a result of the activation of discharges epileptiformes by Carbamazepine. *(AHFS, 1990, p. 1143)*
Author(s): Ries CR; Scoates PJ; Puil E / Institution: Department of Anaesthesia, University of British Columbia, Vancouver. / Title: Opisthotonos following propofol: a nonepileptic perspective and treatment strategy / Source: *Can J Anaesth*. 1994 May. 41(5 Pt 1). P 414-9. / Abstract: In this report of opisthotonos during recovery from propofol anaesthesia, we relate clinical observations with scientific considerations, and propose a strategy for treatment of this rare side effect. Following a brief operative procedure, a healthy 29-yr-old woman developed recurrent opisthotonos while recovering from anaesthesia with alfentanil, propofol, and nitrous oxide. In contrast to accumulating reports, the patient remained conscious during each episode of back extension and retrocollis. The preservation of consciousness and similarities to strychnine-induced opisthotonos suggest to us that the mechanism may have a brainstem and spinal origin. Recent investigations

show that propofol potentiates the inhibitory transmitters glycine and gamma-aminobutyric acid (GABA) which would enhance spinal inhibition during anaesthesia. Postanaesthetic opisthotonos, however, may be due to a propofol-induced tolerance to inhibitory transmitters. This rebound phenomenon would lead to an acute, enduring refractoriness in inhibitory pathways of the brainstem and spinal cord, resulting in increased activity of extensor motoneurons. We recommend a therapeutic strategy that restores inhibition by glycine and GABA at multiple sites; the preferred therapeutic agents would be diazepam and physostigmine. The episodes are usually short-lived, but two of the reviewed 17 patients developed recurrent retrocollis for four and 23 days following antiepileptic drug therapy. Since high doses of phenytoin and carbamazepine can result in opisthotonos, we recommend that anticonvulsants be reserved for postanaesthetic patients with electroencephalographic evidence of seizure activity.

Mexiletine
Therapeutic indications: Seizures.
Rebound effect:
Seizures. *(USP DI, 1996, p. 2070)*

Paraldeido
Therapeutic indications: Seizures.
Rebound effect:
Seizures. *(USP DI, 1996, p. 2284; AHFS, 1990, p. 1293)*

Primidone
Therapeutic indications: Seizures.
Rebound effect:
Precipitation of *status epilepticus* with abrupt discontinuation of drug. *(USP DI, 1996, p. 2463)*

Antidyskinetic drugs

Antidyskinetics *(Amantadine, Benzatropine, Biperiden, Clozapine, Haloperidol, Metoclopramide, Procyclidine, Profenamina, Trihexifenidil, Zuclopenthixol)*
Therapeutic indications: Parkinson's disease, extrapyramidal reactions induced by drugs.
Rebound effect:
Worsening of extrapyramidal symptoms with abrupt withdrawal of anti-dyskinesia drugs (anxiety; difficulty speaking or swallowing; loss of balance; face mask or myopathic fácies; muscle spasms in the face, neck and back; restlessness or desire to stay in motion; shuffling walk; stiffness of arms and legs; tremors or shaking of hands and fingers; twisting movements of body). *(USP DI, 1996, p. 295; AHFS, 1990, p. 580)*
Author(s): Haggstrom JE / Title: Effects of sulpiride on persistent neuroleptic-induced dyskinesia in monkeys. / Source: *Acta Psychiatr Scand Suppl*. 1984. 311P 103-8. / Abstract: Five Cebus apella monkeys with persistent neuroleptic-induced dyskinesia were given a single dose of sulpiride (20 mg/kg i.m.). The dyskinesia was reduced in all five although four developed attacks of acute dystonia which had to be reversed by anticholinergic medication in three animals. In one monkey the administration of classic neuroleptics had earlier been shown to induce a typical sequence of events. First there was a similar reduction of dyskinesia as seen in the other monkeys,

1-2 days later there was noticed a rebound deterioration lasting for several days. Metoclopramide 0.5 mg/kg, caused such a rebound effect (for 2 days), whereas sulpiride did not.
Author(s): Lublin H; Gerlach J; Hagert U; Meidahl B; Molbjerg C; Pedersen V; Rendtorff C; Tolvanen E / Institution: Sct. Hans Hospital, Department P, Roskilde, Denmark. / Title: Zuclopenthixol, a combined dopamine D1/D2 antagonist, versus haloperidol, a dopamine D2 antagonist, in tardive dyskinesia. / Source: *Eur Neuropsychopharmacol*. 1991 Dec. 1(4). P 541-8. / Abstract: Animal data suggest that a D1 antagonistic component in neuroleptic drugs counteracts development of dopamine supersensitivity and of tolerance to cataleptic effect. This has led to the hypothesis that neuroleptics with D1 antagonistic activity should cause a better suppression of tardive dyskinesia (TD) and less rebound aggravation after withdrawal than pure D2 antagonists. In this study the effect of zuclopenthixol (mixed D1/D2 antagonist) and haloperidol (D2 antagonist) was evaluated in chronic psychotic patients with TD. Fifteen patients completed a randomized crossover study with blind evaluation of TD and parkinsonism. The test medications, haloperidol and zuclopenthixol, caused a significant suppression of TD and a significant increase of parkinsonism. No significant differences between haloperidol and zuclopenthixol were observed. No TD aggravation was seen. The lack of differences between the mixed D1/D2 antagonist and a D2 antagonist suggest that tolerance and DA supersensitivity play no or a minor role for development of TD.
Author(s): Tamminga CA; Thaker GK; Moran M; Kakigi T; Gao XM / Institution: Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland Medical School, Baltimore 21228. / Title: Clozapine in tardive dyskinesia: observations from human and animal model studies. / Source: *J Clin Psychiatry*. 1994 Sep. 55 Suppl BP 102-6. / Abstract: Clozapine has long been considered a useful treatment in patients who have schizophrenia with the neuroleptic-induced delayed-onset side effect tardive dyskinesia. We present data in support of the clinical impression using both an animal model of the disorder and dyskinetic patients themselves. Clozapine produces a lower rate of oral dyskinesia in laboratory rats after 6 months of chronic treatment than does haloperidol (8.6 +/- 1.3 vs. 13.6 +/- 1.4 vacuous chewing movements every 5 minutes, respectively), suggesting a lower propensity to cause tardive dyskinesia. In the human, when clozapine was compared with haloperidol in the treatment of patients with tardive dyskinesia, clozapine produced significantly greater benefit for motor symptoms after 12 months of treatment than did haloperidol ($p < .001$). Moreover, the dyskinesia rebound, which occurred equally in both drug groups at the beginning of the study, was sustained in the haloperidol group but lost in the clozapine-treated patients. These data suggest that dyskinetic patients lose their symptoms of tardive dyskinesia, along with dopaminergic hypersensitivity, with long-term clozapine treatment.

Bromocriptine
Therapeutic indications: Parkinson's disease.
Rebound effect:
Uncontrolled Movements of the body: in the face, tongue, arms, hands, head and upper body (usually associated with the use of high doses, occur in 20-25% of patients when they are treated with low doses and may persist for more than a week after the interruption of treatment). *(USP DI, 1996, p. 617; AHFS, 1990, p. 2151)*

Carbidopa, Levodopa
Therapeutic indications: Parkinson's disease (paralysis agitans; shaking palsy).
Rebound effect:
Unusual and uncontrolled bodily movements, including face, tongue, arms, hands, head and upper torso (choreiform and other involuntary movements come in 50-80% of patients, related to excess doses). *(USP DI, 1996, 737)*

Involuntary choreiform movements, dystonic and dyskinetic occur in 50% of patients, in the presence of prolonged therapy. *(AHFS, 1990, p. 2183)*

Author(s): Boyce S; Rupniak NM; Steventon MJ; Iversen SD / Institution: Merck Sharp & Dohme Research Laboratories, Harlow, England. / Title: Differential effects of D1 and D2 agonists in MPTP-treated primates: functional implications for Parkinson's disease. / Source: *Neurology*. 1990 Jun. 40(6). P 927-33. / Abstract: Administration of the indirect agonist L-dopa, the nonselective direct agonist apomorphine, or the selective D2 agonist (+)-PHNO, reversed parkinsonism and induced locomotor activation in MPTP-treated squirrel monkeys. In contrast, administration of the selective partial D1 agonist SKF38393 did not induce locomotor activity, but rather decreased activity. Choreiform movements were observed only following treatment with L-dopa. Coadministration of the D1 antagonist SCH23390 prevented L-dopa-induced chorea at the time of peak effect. However, a rebound exaggeration of chorea was observed following SCH 23390 at the time when chorea induced by L-dopa alone would normally be subsiding. Unlike chorea, dystonia could be induced by treatment with either L-dopa or (+)-PHNO. Administration of apomorphine failed to significantly induce dystonia, although a small increase was observed with the highest dose. Treatment with SKF38393 actually decreased dystonia. Our findings clearly indicate that D2 receptor stimulation appears essential for antiparkinsonian activity, and also implicate D2 receptors in the genesis of dystonia, but not chorea. D1 receptor stimulation appears to be involved in the genesis of chorea and possibly also dystonia.

Author(s): Benson R; Crowell B; Hill B; Doonquah K; Charlton C / Institution: Meharry Medical College, Department of Physiology, Nashville, TN 37208. / Title: The effects of L-dopa on the activity of methionine adenosyltransferase: relevance to L-dopa therapy and tolerance. / Source: *Neurochem Res*. 1993 Mar. 18(3). P 325-30. / Abstract: L-dopa, the major treatment for Parkinson's disease (PD), depletes S-adenosyl-L-methionine (SAM). Since SAM causes PD-like symptoms in rodents, the decreased efficacy of chronic L-dopa administered to PD patients may result from a rebound increase in SAM via methionine adenosyl transferase (MAT), which produces SAM from methionine and ATP. This was tested by administering intraperitoneally saline, or L-dopa to mice and assaying for brain MAT activity. As compared to controls, L-dopa (100 mg/kg) treatments of 1 and 2 times per day for 4 days did not significantly increase MAT activity. However, treatments of 3 times per day for 4 and 8 days did significantly increase the activity of MAT by 21.38% and 28.37%, respectively. These results show that short interval, chronic L-dopa treatments significantly increase MAT activity, which increases the production of SAM. SAM may physiologically antagonize the effects of L-dopa and biochemically decrease the concentrations of L-dopa and dopamine. Thus, an increase in MAT may be related to the decreased efficacy of chronic L-dopa therapy in PD.

Author(s): Allen RP; Earley CJ / Institution: Department of Neurology, Johns Hopkins School of Medicine, Bayview Medical Center, Baltimore, Maryland, USA. / Title: Augmentation of the restless legs syndrome with carbidopa/levodopa. / Source: *Sleep*. 1996 Apr. 19(3). P 205-13. / Abstract: Dopaminergic agents and carbidopa/levodopa have become the preferred treatment for both the restless legs (RL) syndrome and for periodic limb movements in sleep (PLMS). For once-nightly treatments with carbidopa/ levodopa, a problem with morning end-of-dose rebound increases in leg movements has been reported to occur in the about one-fourth of the patients. In our clinical studies a previously unreported but far more significant problem of markedly augmented RL symptoms occurred in the afternoon and the evening prior to taking the next nightly dose. A systematic prospective evaluation of this augmentation in 46 consecutive patients treated with carbidopa/ levodopa for RL syndrome or PLMS disorder found this augmentation to be the major adverse effect of treatment. Augmentation occurred for 31% of PLMS patients and 82% of all RL patients. It was greater for subjects with more severe RL symptoms and for patients on higher doses (> or = 50/200 mg carbidopa/levodopa) but was unrelated to gender, age or baseline severity of PLMS. This augmentation was severe enough to require medication change for 50% of the RL

patients and 13% of PLMS patients. Augmentation resolved with cessation of the medication and could be minimized by keeping the dose low.

Selegiline *(MAO B inhibitor)*
Therapeutic indications: Parkinson's disease.
Rebound effect:
Dyskinesias (increase in unusual movements of the body). *(USP DI, 1996, p. 2619)*

Antimyasthenic drugs

Cholinesterase inhibitors or cholinergic agonists *(Ambenonio, Neostigmine, Pyridostigmine)*
Therapeutic indications: Myasthenia gravis.
Rebound effect:
Increased muscle weakness or paralysis, especially in the arms, neck, shoulders and language; tingling or twitches (nicotinic effect) *(USP DI, 1996, p. 435; AHFS, 1990, p. 570)*. Cholinesterase inhibitors have the potential to produce stimulation followed by depression or paralysis of all autonomic lymphs and skeletal muscle, called nicotinic effects.[19]

Plasmapheresis *(removal of the antibodies causing autoimmune diseases)*
Rebound effect:
Author(s): Nasca TJ; Muder RR; Thomas DB; Schrecker JC; Ruben FL / Institution: Department of Medicine, Mercy Hospital, Pittsburgh, PA 15219. / Title: Antibody response to pneumococcal polysaccharide vaccine in myasthenia gravis: effect of therapeutic plasmapheresis. / Source: *J Clin Apheresis*. 1990. 5(3). P 133-9. / Abstract: The removal of specific antibody in experimental animals has been reported to result in a subsequent increase in antibody to levels equal to (rebound) or exceeding those existing prior to removal (overshoot). Anecdotal reports suggest that rebound antibody synthesis after plasmapheresis may occur in humans with autoimmune disorders. We measured the antibody response to 12 pneumococcal polysaccharide antigens in patients with myasthenia gravis (MG) receiving a variety of therapies in order to determine whether the T-cell-independent IgG response to these antigens was augmented by plasmapheresis. MG patients receiving no immunotherapy or receiving prednisone had pre- and post-immunization titers similar to those of control patients. MG patients receiving prednisone and chronic plasmapheresis had higher pre-immunization titers than did other patient groups and had significantly higher post-immunization titers against multiple pneumococcal serogroups. Aggregate post-immunization geometric mean titers were more than three-fold higher in the plasmapheresis group as compared with other MG treatment groups. Enhancement of antibody response by plasmapheresis was abolished by the concomitant administration of azathioprine. Antibody rebound and overshoot after antibody removal may have important implications for the therapy of immune disorders by plasmapheresis.

Muscle relaxant drugs

[19] Goodmann LS, Ral TW, Nies AS, Taylor P. The pharmacological basis of therapeutics. Eighth edition. New York: Pergamon Press, 1990.

Author(s): Boyett MR; Kirby MS; Orchard CH; Roberts A / Institution: Department of Physiology, University of Leeds. / Title: The negative inotropic effect of acetylcholine on ferret ventricular myocardium. / Source: *J Physiol (Lond)*. 1988 Oct. 404P 613-35. / Abstract: 1. The effects of acetylcholine (ACh) on developed tension and intracellular Ca2+ concentration (as measured with aequorin) were studied in ferret papillary muscles, and on twitch shortening, the action potential and membrane currents in ferret ventricular myocytes. 2. Addition of ACh to ferret papillary muscles resulted in decreases in developed tension and the intracellular Ca2+ transient, both of which then partially recovered in the continued presence of ACh ('fade' of the response). On wash-off of ACh both developed tension and the intracellular Ca2+ transient increased above control ('rebound') before returning to control values. 3. Addition of ACh to ferret ventricular myocytes resulted in a membrane hyperpolarization of 2 +/- 0.5 mV (mean +/- S.E.M.; n = 9), a decrease in action potential duration to 23 +/- 6% of control and a decrease in twitch shortening to 31 +/- 5% of control. In the continued presence of ACh these responses to ACh faded. Thirty seconds after the maximal effect of ACh, action potential duration had partially recovered to 34 +/- 6% of control and twitch shortening to 46 +/- 7% of control. 4. The effects of ACh on twitch shortening could be mimicked under voltage clamp by varying voltage clamp pulse duration to simulate the ACh-induced changes in action potential duration. 5. When ACh was applied during a train of voltage clamp pulses of constant duration, 81% of the cells showed less than a 20% decrease in Ca2+ current and twitch shortening. However in 19% of the cells twitch shortening and the apparent Ca2+ current decreased by more than 30%. 6. In the 81% of cells, the normal decrease in twitch shortening was wholly the result of the shortening of the action potential. This in turn was the result of an increase in an outward background current which increased the rate of repolarization during the action potential. The ACh-induced background current reversed at -89 +/- 2 mV and showed inward-going rectification; these properties suggest that it was carried by K+. 7. In the 19% of cells, the normal decrease in twitch shortening was only partly the result of the shortening of the action potential (due to both the increase in outward background current as well as the apparent decrease in Ca2+ current). In these cells the decrease in twitch shortening may also have been partly the direct result of the apparent decrease of Ca2+ current.

Author(s): Kawahara K; Nakazono Y; Kumagai S; Yamauchi Y; Miyamoto Y / Institution: Department of Information Engineering, Yamagata University, Yonezawa, Japan. / Title: Parallel suppression of extensor muscle tone and respiration by stimulation of pontine dorsal tegmentum in decerebrate cat. / Source: *Brain Res*. 1988 Nov 8. 473(1). P 81-90. / Abstract: This paper describes the pontine brainstem area responsible for the suppression of postural muscle tone as well as of respiration in acute precollicular-postmammillary decerebrate (mesencephalic) cats. Stimulation of the dorsal part of the pontine tegmentum (DTF) along the midline (P4-P7, H-5 to H-6) decreased the bilateral tone of the hindlimb extensor muscles and the diaphragmatic activity. Tonic discharges of the extensor muscles were suppressed by DTF stimulation and the suppression of muscle activity continued for more than 5 min after termination of the stimulation. In contrast, the suppression of the diaphragmatic activity, which resulted in apnea in some of the animals tested, resumed in spite of the continuation of the stimulation. However, the rebound augmentation of the diaphragmatic activity appeared immediately after the termination of the stimulation. The existence of such a rebound phenomenon suggested that the suppressive effects on the diaphragmatic activity persisted during the entire period of the stimulation. The recovery of respiratory movements during the stimulation led us to suggest that the strong respiratory drives emerge to overcome the exerted DTF-elicited suppressive effects on respiration. In the paralyzed and vagotomized animal, the DTF-elicited suppressive effects on phrenic neural discharges were minimal when the end-tidal pCO2 was set at a higher level than during spontaneous breathing.

Author(s): Kasama M; Tsutsumi T; Mashima S / Institution: Division of Cardiology, Showa University Fujigaoka Hospital, Yokohama, Japan. / Title: Transient prolongation of ventricular

action potential duration after metabolic inhibition. / Source: *Jpn Heart J*. 1995 Nov. 36(6). P 775-87. / Abstract: Transient prolongation of the action potential duration was observed in canine ventricular muscle during the reoxygenation period following metabolic inhibition. We investigated the effects of verapamil, lanthanum (La3+), and hexamethyleneamiloride (HMA) on the recovery time course of the action potential and its rebound prolongation. The time course of the intracellular resistivity was estimated from the conduction velocity and electrograms. The action potentials of canine left ventricular trabeculae were recorded by the conventional microelectrode technique. After a control tracing was obtained, the preparation was perfused with a hypoxic, acidic solution for 20 min and then reoxygenated with regular Tyrode's solution. After reoxygenation, action potential prolongation exceeding the control value by 21.0 +/- 7.3% was observed depending on the degree of metabolic inhibition. Verapamil depressed the rebound prolongation when it was added before the start of metabolic inhibition, but not when added after reoxygenation was started. La3+ and HMA depressed the rebound phenomenon. Intracellular resistivity was increased during metabolic inhibition, but showed no significant changes during the period of action potential prolongation. It was concluded that the rebound action potential prolongation was related to the accumulation of intracellular Ca2+ during metabolic inhibition. Other ions, such as Na+ and H+ may also contribute to the phenomenon by modulating outward currents.

Depolarizing neuromuscular blockers *(Atracurium, Pancuronium, Tubocuranina, etc.)*
Therapeutic indications: Relaxation of muscular skeletal for surgery.
Rebound effect:
Pain and stiffness post-operative caused by muscle fasciculações appearing after injection (arise from 12-24 hours after administration and persist for several hours until a few days). *(USP DI, 1996, p. 2150; AHFS, 1990, p. 669)*

Cyclobenzaprine
Therapeutic indications: Spasms of skeletal muscles.
Rebound effect:
Unexplained muscle stiffness. *(USP DI, 1996, p. 1119; AHFS, 1990, p. 695)*

Skeletal muscle relaxants *(Baclofen, Carisoprodol, Clorfenasina, Clorzoxazona, Cyclobenzaprine, Dantrolene, Metaxalone, Methocarbamol, Orphenadrine)*
Therapeutic indications: Treatment of skeletal muscle spasticity.
Rebound effect:
With the abrupt suspension of Baclofen occurs unexplained muscle stiffness (increase of spasticity) or unusual excitement. *(USP DI, 1996, p. 509)*
Acute exacerbation of spasticity occurs frequently with abrupt discontinuation of medication. *(AHFS, 1990, p. 690)*

Smooth muscle relaxants
Rebound effect:
Author(s): McKirdy HC; Marshall RW / Title: Effect of drugs and electrical field stimulation on circular muscle strips from human lower oesophagus. / Source: *Q J Exp Physiol*. 1985 Oct. 70(4). P 591-601. / Abstract: Sphincteric muscle from human lower oesophagus may be identifiable in vitro by its ability to develop a very high level of tone (sustained resting tension). Circular muscle strips from human lower oesophagus generally behave in a similar manner to strips from the opossum oesophagus with respect to development of tone, responses to electrical field stimulation and responses to a variety of drugs. Pharmacological analysis of responses to field stimulation in strips

from the region of the oesophago-gastric junction suggests that the typical biphasic response (relaxation followed by an after-contraction) is mediated by nerves which are neither adrenergic nor cholinergic. Of the substances examined only vasoactive intestinal peptide (VIP) cannot be excluded as a possible candidate for the role of inhibitory transmitter. The mechanism producing the after-contraction is not clear but it would seem unlikely that this is simply a rebound contraction. The after-contraction can be blocked independently of the relaxation by a variety of agents and is potentiated by metoclopramide.

Author(s): Gaba SJ; Bourgouin-Karaouni D; Dujols P; Michel FB; Prefaut C / Title: Effects of adenosine triphosphate on pulmonary circulation in chronic obstructive pulmonary disease. ATP: a pulmonary vasoregulator? / Source: *Am Rev Respir Dis*. 1986 Dec. 134(6). P 1140-4. / Abstract: Extracellular adenosine triphosphate (ATP) has potent systemic vasodilator and endothelial-dependent relaxant effects on precontracted vessels. Pulmonary uptake and metabolism of ATP have been described, but experimental effects on pulmonary vessels remain controversial in animals. The effects of an intravenously administered infusion of ATP on pulmonary hemodynamic and gasometric data were assessed in 18 patients with stable chronic obstructive pulmonary disease (COPD). Low doses of ATP (successive rates, 1 and 2 mumol/kg body weight, each for 20 min) were infused in pulmonary hypertensive (H; n = 6) and nonhypertensive (N; n = 6) patients. They were compared with a control group (C; n = 6) that received only solvent, using ANOVA. During ATP infusion, a significant pulmonary vasodilation was demonstrated as simultaneous decreases reached, respectively, -14.2% (Group H; p less than 0.005) and -13.8% (Group N; p less than 0.001) for mean pulmonary artery pressure (Ppa), and -31.7% (H; p less than 0.05) and -20.7% (N; p less than 0.01) for pulmonary vascular resistances (PVR), associated with some worsening of hypoxemia: -6.9% (H; p less than 0.01) and -11.8% (n; p less than 0.005). After ATP withdrawal, significant rebound of these data (above baseline values) reached +10.9% (H; p less than 0.05) and +4.4% (N; p less than 0.05) for Ppa and +24.9% (H; p less than 0.05) and +10.2% (N; p = NS) for PVR. At the low infusion rate used, ATP appeared to be a well-tolerated, short-acting, selective pulmonary vasolidating compound in patients with COPD, but therapeutic use remains premature.

Author(s): Lefebvre RA; Burnstock G / Institution: Heymans Institute of Pharmacology, University of Ghent Medical School, Belgium. / Title: Effect of adenosine triphosphate and related purines in the rat gastric fundus. / Source: *Arch Int Pharmacodyn Ther*. 1990 Jan-Feb. 303P 199-215. / Abstract: The effect of adenosine triphosphate (ATP) and its analogues was studied in longitudinal muscle strips of the rat gastric fundus in order to characterize the purinoceptors involved. At resting tension, 10(-4) M ATP usually induced a small initial relaxation followed by a contraction; when tone was raised by administration of carbachol (10(-7) M), ATP (10(-4) M) induced a larger relaxation followed by a smaller rebound contraction. Both the contraction at resting tension and the rebound contraction were antagonized by indomethacin. With raised tone, both ATP and 2-methylthioATP induced concentration-dependent relaxations, followed by small rebound contractions, but the slope of the concentration-response curve was very shallow. alpha, beta-MethyleneATP and adenosine induced only concentration-dependent relaxations and the maximal effect was much more pronounced than that of ATP and 2-methyl-thioATP. The rank order of potency of the purines producing relaxation was 2-methylthioATP greater than alpha, beta-methyleneATP greater than ATP greater than adenosine. The relaxant effect of ATP (10(-4) M) at raised tone was clearly antagonized by both reactive blue 2 (10(-4) M) and desensitization to alpha, beta-methyleneATP. It is concluded that the contractile effect of ATP in the rat gastric fundus is due to stimulation of prostaglandin biosynthesis, but identification of the purinoceptor subtype mediating relaxation is problematic and it may differ from the P2x- and P2y-receptors, which are clearly distinguishable in a number of other tissues.

Author(s): Postorino A; Serio R; Mulè F / Institution: Dipartimento di Biologia celluare e dello Sviluppo, Universita di Palermo. / Title: On the purinergic system in rat duodenum: existence of P1 and P2 receptors on the smooth muscle. / Source: *Arch Int Physiol Biochim*. 1990 Mar. 98(1). P 53-

8. / Abstract: In rat duodenum, in vitro, in the presence of atropine and guanethidine, ATP administration caused a tetrodotoxin-insensitive relaxation followed by a rebound contraction. A similar response was obtained also after electrical field stimulation (EFS) of non-adrenergic, non-cholinergic (NANC) nerves. alpha, beta-methylene-TP and theophylline antagonized the response to ATP, but they failed to affect the noradrenaline- and EFS-induced relaxation. These results suggest that P1 and P2 receptors are present in rat duodenum, but their activation is not responsible for the inhibitor effects due to the NANC nerves.

Author(s): Maggi CA; Giuliani S / Institution: Pharmacology Department, A. Menarini Pharmaceuticals, Florence, Italy. / Title: Multiple inhibitory mechanisms mediate non-adrenergic non-cholinergic relaxation in the circular muscle of the guinea-pig colon. / Source: *Naunyn Schmiedebergs Arch Pharmacol*. 1993 Jun. 347(6). P 630-4. / Abstract: The mechanisms responsible for nerve-mediated, non-adrenergic, non-cholinergic (NANC) relaxation in mucosa-free circular muscle strips from the proximal colon of the guinea-pig were investigated. Electrical field stimulation (EFS, 1-20 Hz, trains of 5 s duration, 100 V, 0.25 ms pulse width) in the presence of atropine (1 mumol/l) and guanethidine (3 mumol/l) evoked a triphasic motor response consisting of: (a) a primary relaxation, (b) a rebound contraction and (c) a secondary relaxation. These three responses were abolished by tetrodotoxin (1 mumol/l). B oth apamin (0.01-0.3 mumol/l), a known blocker of low conductance, calcium-activated potassium channels in smooth muscles, and L-nitro-arginine (L-NOARG) (1-100 mumol/l), a known blocker of nitric oxide (NO) synthase, increased the tone of the strips. Maximum effects on tone were observed with 0.1 mumol/l apamin (21 +/- 3% of KCl-induced contraction) and 30 mumol/l L-NOARG (26 +/- 4% of KCl response). The combined administration of 0.1 mumol/l apamin and 30 mumol/l L-NOARG produced an increase in tone (47 +/- 5% of KCl response) that was larger than that produced by either compound alone. Neither apamin (0.1 mumol/l) nor L-NOARG (30 mumol/l) affected the isoprenaline-induced relaxation. Apamin (0.1 mumol/l) depressed, but did not abolish, the primary relaxation to EFS at all frequencies without affecting the secondary relaxation.

Author(s): Bartho L; Lefebvre RA / Institution: Department of Pharmacology, University Medical School Pecs, Hungary. / Title: Nitric oxide-mediated contraction in enteric smooth muscle. / Source: *Arch Int Pharmacodyn Ther*. 1995 Jan-Feb. 329(1). P 53-66. / Abstract: Nitric oxide (NO) seems to be involved as neurotransmitter in nonadrenergic noncholinergic (NANC) smooth muscle relaxation throughout the gastrointestinal tract. Contractile responses to NO in the gastrointestinal smooth muscle have also been reported. In the guinea-pig ileal longitudinal muscle-myenteric plexus preparation at basal tone, NO induces a moderate relaxation followed by an aftercontraction; the latter is blocked by tetrodotoxin. The aftercontraction is also reduced by atropine, the remaining part being inhibited by a substance P antagonist. This indicates the activation of cholinergic and, possibly, tachykininergic neurons; it is not clear whether this represents a rebound phenomenon to the relaxation or a direct action of NO, initially masked by the relaxation. Nitrergic “off”-contractions, in response to electrical stimulation of the inhibitory NANC nerves, were reported in the opossum esophageal body and in the cat distal colon. Primary contractions to NO have been reported in the rat ileum and in the longitudinal muscle of the opossum esophagus. In the rat preparation, the contraction to NO is observed at lower concentrations than the relaxant effect. While the contraction in the opossum seems to be related to guanylate cyclase activation, this is not the case in the rat ileum, as methylene blue did not influence the contractions and 8-bromo-cGMP only had a relaxant effect. No clear-cut rise in cGMP was observed during the NO-induced contraction. The NO-induced contraction was also not influenced by ryanodine but it was concentration-dependently reduced by nifedipine, suggesting that it is related to extracellular calcium influx through L-type calcium channels. Primary contractions due to NO were also observed in the rat whole ileum and in the rat caecal longitudinal muscle, while aftercontractions, due to NO, were also obtained in the rat descending, transverse and sigmoid colon, as well as in the cat ileal longitudinal muscle.

Analgesic drugs

Author(s): Rapoport A; Stang P; Gutterman DL; Cady R; Markley H; Weeks R; Saiers J; Fox AW / Institution: New England Center for Headache, Stamford, USA. / Title: Analgesic rebound headache in clinical practice: data from a physician survey. / Source: *Headache.* 1996 Jan; 36(1): 14-9. / Abstract: Frequent, excessive use of over-the-counter or prescription analgesics may lead to analgesic rebound headache. Little is known about the magnitude of the health problem posed by analgesic rebound headache, its epidemiology, the characteristics of analgesic rebound headache sufferers, or about physicians' approaches to treatment. Four hundred seventy-three practitioners, who had previously expressed an interest in the treatment of headache, were mailed a questionnaire designed to capture information about the frequency and management of analgesic rebound headache and about the characteristics of analgesic rebound headache sufferers. Completed questionnaires were returned by 174 practitioners (37%) from 40 states, the District of Columbia, and Puerto Rico. More than 40% of respondents indicated that analgesic rebound headache was present in at least 20% of their patients. On average, the physicians reported that 73% of patients with analgesic rebound headache were women. Analgesic rebound headache was most likely to occur in patients aged 31 to 40 years. No one analgesic was consistently identified as causative, although acetaminophen, butalbital + aspirin + caffeine, and aspirin were commonly used by patients. Eighty percent of respondents indicated that depression was commonly observed in analgesic rebound headache sufferers; 77% indicated that physical conditions (especially gastrointestinal symptoms) were commonly observed. A variety of therapeutic strategies, including pharmacotherapy, were used in the management of analgesic rebound headache. Analgesic rebound headache was recognized as a distinct entity and a substantive component in more than 40% of the practices of 174 surveyed practitioners. General practitioners, who see a wide variety of patient types with a spectrum of complaints, need to be able to diagnose analgesic rebound headache by taking a good history.

Opioid analgesics *(Alfentanil, Buprenorphine, Butorphanol, Codeine, Fentanyl, Hydrocodone, Hydromorphine, Levorphanol, Pethidine, Methadone, Morphine, Nalbuphine, Opium, Oxycodone, Oxymorphine, Pentazocine, Dextropropoxyphene, Sufentanil)*

Therapeutic indications: Treatment of pain, anesthesia adjunct.

Rebound effect:

Generalized aches. With the excessive dose, together with the reduction of pain, are observed severe drowsiness, unconsciousness, cold skin, low blood pressure, pinpoint pupils, slow heartbate and breathing slow or impeded; to suspend or antidote medication with Naloxone, occurring a quick paradoxical reaction (24-72 hours) and prolonged (5-14 days) consisting of increased pain, insomnia, severe nervousness or restlessness, fever, hypertension, unusually large pupils, tachycardia and hyperpnea. *(USP DI, 1996, p. 2216; AHFS, 1990, p. 1069)*

After discontinuation of Fentanila, used as an analgesic, occurring generalized pain. *(USP DI, 1996, p. 1452)*

Author(s): Copeland RL Jr; Pradhan SN / Institution: Department of Pharmacology, Howard University College of Medicine, Washington, DC 20059. / Title: Effect of morphine on self-stimulation in rats and its modification by chloramphenicol. / Source: *Pharmacol Biochem Behav.* 1988 Dec. 31(4). P 933-5. / Abstract: The effect of morphine was studied on self-stimulation (SS)

behavior in rats implanted with bipolar electrodes in the posterior hypothalamus. A single dose (10 mg/kg) of morphine decreased SS responding within 10-20 min, reaching a minimum level between 20-40 min after which the responding gradually returned to normal. The SS responding then increased above the control level at 120-180 min postdrug, then slowly returned to normal, thus showing a rebound effect. The combination treatment with morphine (10 mg/kg) and chloramphenicol (50 mg/kg) on SS behavior produced an accentuation of the initial decrease in responding, which was prolonged before gradually returning to the control levels without showing any rebound effect. The data suggest that alterations in protein synthesis may underlie the suppressed excitatory effect of a high dose of morphine on SS behavior.

Author(s): Ekblom M; Hammarlund-Udenaes M; Paalzow L / Institution: Department of Biopharmaceutics and Pharmacokinetics, Uppsala University, Sweden. / Title: Modeling of tolerance development and rebound effect during different intravenous administrations of morphine to rats. / Source: *J Pharmacol Exp Ther*. 1993 Jul. 266(1). P 244-52. / Abstract: The development of tolerance and the rebound effect to the antinociceptive effect of morphine were investigated and correlated with morphine pharmacokinetics. Five i.v. regimens, including a bolus dose (35 mumol/kg), 2 constant rate infusions (2.5 and 4.2 mumol/hr) over 4 days, 1 saline bolus dose and 1 glucose infusion were followed for 8 days. Clearance (CL) was estimated as 148 +/- 58 ml/min*kg after the bolus dose and 108 +/- 32 ml/min*kg during infusion (N.S.). Tolerance developed during the first day of morphine infusion and no antinociceptive effect could be measured from the third day. After cessation of the infusions, rebound hyperalgesia, significant for the higher infusion rate ($P < .05$), was observed. No hyperalgesia was detected after the bolus dose. A pharmacodynamic model with separate effect and tolerance compartments was used to describe the antinociceptive effect over time. The rates of equilibration of drug between the blood and effect compartment and the blood and tolerance compartment, expressed in half-lives, were estimated as 25 +/- 8 min and 26 +/- 6 hr, respectively. It is apparent from these results that an i.v. bolus dose of morphine causes less tolerance than constant rate infusions of morphine. With the presented model it is possible to quantify the rate and extent of tolerance development of morphine.

Author(s): Espejo EF; Stinus L; Cador M; Mir D / Institution: Departamento de Enfermeria, Universidad de Sevilla, Spain. / Title: Effects of morphine and naloxone on behaviour in the hot plate test: an ethopharmacological study in the rat. / Source: *Psychopharmacology (Berl)*. 1994 Jan. 113(3-4). P 500-10. / Abstract: The objectives of this study were: i) to analyse the effects of morphine and naloxone on the rat's behaviour in the hot plate test using an ethological approach, and ii) to compare the effectiveness of repeated versus single test paradigms. Animals received either morphine (0, 3, 6 or 9 mg/kg SC) or naloxone (0, 0.01, 0.1 or 1 mg/kg SC). For repeated hot plate measures, rats were tested before and 60, 120, 180 and 240 min following morphine treatment, as well as 30, 60, 90 and 120 min after naloxone injection. For the single test schedule, rats were tested only once 60 min after morphine or 30 min after naloxone administration, or at 60, 120, 180, 240 and 300 min after 9 mg/kg morphine treatment. Behaviour was videotaped and analysed by an ethogram and ethological techniques. A cluster analysis revealed that the most frequently displayed patterns could be categorised into exploratory sniffing reactions (walk-sniff, immobile-sniff) and noxious-evoked elements, including primary (paw-licking, stamping), escape (jumping, leaning posture) and independent (hindleg-withdrawal) patterns. During repeated tests, morphine treatment induced: i) a maximum hypoalgesic effect 60 min post-injection (noxious-evoked patterns were significantly reduced), and ii) an unexpected "thermal hyperreactivity rebound effect" after 120 min (paw-licking and hindleg-withdrawal were enhanced), although changes in hindpaw-licking are more indicative of a hyperalgesic rebound effect. Most changes were quite similar during the single test schedule at 60 and 120 min after morphine injection. With regard to naloxone treatment, jumping latency was significantly decreased during the repeated test schedule, but not on single exposure to the plate. Other elements were facilitated, however, in the single test (stamping, leaning posture, hindleg-withdrawal). The results indicated that both repeated and single tests paradigms are

of value for testing the effects of morphine and naloxone on rats. However, under our conditions the single test paradigm gave a better picture of the overall effects of the drug. Learning as well as habituation and sensitization may mask certain effects during repeated tests. In conclusion, an ethological analysis of the rat's behaviour in the hot plate test following administration of morphine and naloxone has been validated in this study.

Calcium channel blockers *(Diltiazem, Felodipine, Flunarizine, Nifedipine, Verapamil, etc.)*
Therapeutic indications: Prophylaxis of headache of vascular origin (migraine).
Rebound effect:
Headache. *(USP DI, 1996, p. 695)*
Author(s): Bono G; Manzoni GC; Martucci N; Baldrati A; Farina S; Cassabgi F; De Carolis P; Nappi G / Title: Flunarizine in common migraine: Italian cooperative trial. II. Long-term follow-up. / Source: *Cephalalgia*. 1985 May. 5 Suppl 2P 155-8. / Abstract: The effects of flunarizine administration (10 mg/day, at bed time) were studied in 120 common migraine patients who were followed for 24 months with quarterly controls. Besides headache index (HI) and analgesic use, other variables were monitored, such as arousal (Tolouse Pieron test), mood (Hamilton rating scale for depression), sleep/wake (hrs) and body weight. The study was open-type and after the 6th month control some responder (R) cases (HI reduction greater than or equal to 60%) presenting HI scores less than or equal to 4 could continue the survey off-treatment. The percentage of R cases was 54.5% at the 3rd month, a figure that further increased up to 72% by the 9th month; relapses on treatment were not observed and rebound-headache occurred in 1/4 of R cases let off-treatment. Lower (p less than 0.05) baseline HI values characterized non-responders. Side-effects not requiring withdrawal were drowsiness (42% within the 1st month) and weight gain (mean 7.9 +/- 6.9 kg) in 54% of the cases, while a retarded type depression was the most frequent cause of drop-out from trial (7.5%). The results, while confirming the high prophylactic activity of flunarizine in common migraine, stress the importance of clinical long-term survey of side-effects using antimigraine drugs and suggest the need for further investigations about flunarizine effects on CNS.

Caffeine
Therapeutic indications: Treatment of vascular headaches (migraine); adjunct analgesia.
Rebound effect:
Headache; increased sensitivity to pain or tact. *(USP DI, 1996, p. 683; AHFS, 1990, p. 1235)*

Clonidine
Therapeutic indications: Prophylaxis of headache of vascular origin (migraine).
Rebound effect:
Headache. *(USP DI, 1996, p. 885; AHFS, 1990, p. 912)*

Dihydroergotamine *(Ergot derivatives)*
Therapeutic indications: Treatment of headache of vascular origin (migraine).
Rebound effect:
Headache, nausea and vomiting occur with usual doses (severe rebound headache comes up with the discontinuation of chronic use of Ergot derivatives, being very severe in the first 24-48 hours and staying for up to 72 hours after last dose). *(USP DI, 1996, p. 2968; AHFS, 1990, p. 658)*

Author(s): Silberstein SD; Schulman EA; Hopkins MM / Institution: Temple University School of Medicine, Philadelphia, PA. / Title: Repetitive intravenous DHE in the treatment of refractory headache. / Source: *Headache*. 1990 May. 30(6). P 334-9. / Abstract: We analyzed retrospectively the data for 300 patients with refractory headache who were treated with dihydroergotamine (DHE) at the Comprehensive Headache Center at Germantown Hospital. The patients had either chronic daily headache (with drug rebound -216, without rebound -42), short-duration headache (18), or cluster headache (24). Treatment consisted of withdrawal of overused medications (usually analgesics and ergots), repetitive IV administration of DHE, and use of metoclopramide and prophylactic medications, together with educational and psychological support. Overall, 91% (range, 86% to 100%) of the patients became headache-free, usually within 2 to 3 days. The average duration of hospitalization was 7.4 days. Side effects, reported in 157 (52%) of the patients, consisted primarily of nausea (32%), tightness and burning (8%), leg cramps (7%), vomiting (6%), and increased blood pressure (5%). The side effects generally resolved spontaneously or with adjustment of the DHE dose and/or adjunct medication, and necessitated withdrawal of therapy in only 2 patients (1 with drug-related claudication; 1 with somatic complaints of uncertain origin). We conclude that a regimen of repetitive intravenous DHE and metoclopramide can provide rapid relief of chronic intractable headache, and can ameliorate the effects of analgesic and ergot withdrawal in patients with chronic daily headache and rebound associated with overuse of these drugs.

Ergotamine *(Ergot alkaloids)*
Therapeutic indications: Treatment of headache of vascular origin (migraine).
Rebound effect:
According to the *National Headache Foundation,*[20] the constant use of drugs with Ergotamine tartrate increases the frequency of crises of migraine, due to the rebound effect.
Headache, visual disturbances, nausea and vomiting. *(USP DI, 1988, p. 1013).*
With the discontinuation of treatment may arise rebound headache, slightly different from the original headache. *(AHFS, 1990, p. 662)*
Author(s): Young WB / Institution: Department of Neurology, Germantown Hospital and Medical Center, Philadelphia, PA. / Title: Appropriate use of ergotamine tartrate and dihydroergotamine in the treatment of migraine: current perspectives. / Source: *Headache*. 1997; 37 Suppl 1: S42-5. / Abstract: Considerable uncertainty exists regarding the appropriate use and dose limitations for ergotamine tartrate (ET) and dihydroergotamine (DHE) for the treatment of migraine despite more than 50 years of clinical experience. The Quality Standards Subcommittee (QSS) of the American Academy of Neurology (AAN) appointed an advisory committee from experts in the Headache and Facial Pain Section. As their initial project, the committee elected to review the clinical literature on the appropriate use of these compounds in the treatment of migraine. Subsequently, clinical practice guidelines were formulated and recently published in Neurology. The Headache and Facial Plan Section and the QSS of the AAN were able to reach consensus on the basis of a thorough literature review and formulated practice parameters that describe and define the limits of ergot use, provide information on the oral and parenteral dosing of ET and DHE, and provide physicians with guidance to avoid ET overuse by patients. Because this project was completed prior to the availability of the intranasal (IN) formulation of DHE, intranasal DHE is not included in the practice parameter. Ergotamine tartrate and DHE were found to be safe and effective for the treatment of migraine as long as recommended dosages are not exceeded and high-risk patients such as those with uncontrolled hypertension, coronary or peripheral artery disease,

[20] National Headache Foundation, 428 W. St. James Pl., 2 andar, Chicago, Illinois 60614-2750. Available at: https://headaches.org/2007/10/25/ergotamine-rebound-headaches/

thyrotoxicosis, or sepsis do not receive these compounds. In addition, the committee recommended restricting the use of ET in some instances because the overuse of ET has been associated with physical and psychological dependence resulting in predictable recurrent and/or rebound headaches, and subsequent severe withdrawal symptoms, including nausea, upon discontinuance of ET. None of these symptoms have been reported for DHE. These guidelines should help physicians provide optimal antimigraine therapy with these drugs.

Ketorolac

Therapeutic indications: Treatment of pain.

Rebound effect:

Author(s): Shrestha M; Morgan DL; Moreden JM; Singh R; Nelson M; Hayes JE / Institution: Division of Emergency Medicine, University of Texas Southwestern Medical Center, Dallas, USA. / Title: Randomized double-blind comparison of the analgesic efficacy of intramuscular ketorolac and oral indomethacin in the treatment of acute gouty arthritis. / Source: *Ann Emerg Med*. 1995 Dec. 26(6). P 682-6. / Abstract: To compare the analgesic effect of IM ketorolac tromethamine with that of oral indomethacin in the treatment of acute gouty arthritis. Prospective, randomized, double-blind, controlled, parallel group clinical trial. Two urban emergency departments. Twenty consecutive patients who presented to the ED with acute gout. Each patient was randomly assigned to receive in the ED (1) 60 mg of IM ketorolac and oral placebo or (2) 50 mg of oral indomethacin and IM placebo. The patients rated the intensity of their pain on a Wong-Baker pain scale (which runs from 0 to 5) before treatment and 30, 60, 90, and 120 minutes after treatment. All the patients were discharged with instructions to take oral indomethacin and to complete pain score cards at home at 6, 12, and 24 hours. The 10 patients in each group were similar with regard to age, sex, race, and initial mean pain score. After 2 hours, the mean pain scores (+/- SD) for the ketorolac group had decreased from 4.5 +/- .71 to 1.4 +/- 1.43 ($P < .05$), and the mean score for the indomethacin group had decreased from 4.4 +/- .70 to 1.5 +/- 1.18 ($P < .05$). The difference between the two groups was not significant. At 6 hours, there was some pain rebound in the ketorolac group. IM ketorolac and oral indomethacin are similar in the relief of the pain of acute gouty arthritis in the ED.

Methysergide

Therapeutic indications: Prophylaxis of headache of vascular origin (migraine).

Rebound effect:

Headache, nausea and vomiting. *(USP DI, 1996, p. 2044)*

Author(s): Pfaffenrath V; Reiter M / Title: [Drug therapy of migraine] / Source: *Wien Med Wochenschr*. 1988 Dec 31. 138(23-24). P 591-9. / Abstract: Out of the knowledge of various headache syndromes the physician has to develop a clear diagnostical and therapeutical concept. This is especially true for migraine. Relevant pathophysiological hypotheses are presented e.g. the neurogenic-vascular model of migraine. Metoclopramide and domperidone in combination with mono-analgesics, ergotamine and nonsteroidal-antiinflammatory drugs are favoured in the treatment of the acute migraine attack. 2 to 4 mg ergotamine for the attack, respectively 16 to 20 mg per month should not be exceeded. Mixed compounds, containing ergots, analgesics, codeine, caffeine, tranquilizers and barbiturates should be avoided as these drugs may induce rebound-headache. A prophylaxis of migraine is indicated if a migraineur suffers from at least 2 attacks per month or if a migraine attack lasts longer than 4 days. In the first place, beta-blockers and flunarizine, in some cases verapamil or naproxen, should be used; the effect of dihydroergotamine is questionable. Because of its severe side effects, methysergide should only be given if all other prophylactic drugs fail. Naproxen is standard medication in the short time prophylaxis of menstrual migraine.

Salicylates *(Aspirin)*
Therapeutic indications: Treatment of headache.
Rebound effect:
Severe or continuous headache. *(USP DI, 1996, p. 2589)*

Association of analgesics *(Isometheptene, Dichloralphenazone and Acetaminophen)*
Therapeutic indications: Treatment of headache.
Rebound effect:
More frequent headaches, severe and with greater difficulty of treatment than the initials. *(USP DI, 1996, p. 1793)*

Local anesthetic drugs

Topical anesthetic *(Benzocaine, Butilcaina, Cincocaina, Lidocaine, Pramocaina, Tetracaine)*
Therapeutic indications: Relieve pain, itching and inflammation of skin diseases.
Rebound effect:
Pruritus, inflammation or abnormal sensitivity to pain, non-existent before treatment. With excessive dose of local anesthetics occured stimulation of CNS (anxiety, excitement, nervousness or restlessness not usual) followed by depression of CNS (sleepiness). *(USP DI, 1996, p. 148)*
Increased itching, pain, swelling and neurites. *(AHFS, 1990, p. 1856)*

Via ophthalmic anesthetic *(Proparacaine, Tetracaine)*
Therapeutic indications: Relieves pain, itching and ocular inflammation.
Rebound effect:
Pruritus, inflammation or abnormal sensitivity to pain (occurs shortly thereafter or several hours after applying). *(USP DI, 1996, p. 131)*

General anesthetic drugs

Alfentanil
Therapeutic indications: General or local anaesthesia.
Rebound effect:
Author(s): Ries CR; Scoates PJ; Puil E / Institution: Department of Anaesthesia, University of British Columbia, Vancouver. / Title: Opisthotonos following propofol: a nonepileptic perspective and treatment strategy. / Source: *Can J Anaesth*. 1994 May. 41(5 Pt 1). P 414-9. / Abstract: In this report of opisthotonos during recovery from propofol anaesthesia, we relate clinical observations with scientific considerations, and propose a strategy for treatment of this rare side effect. Following a brief operative procedure, a healthy 29-yr-old woman developed recurrent opisthotonos while recovering from anaesthesia with alfentanil, propofol, and nitrous oxide. In contrast to accumulating reports, the patient remained conscious during each episode of back extension and retrocollis. The preservation of consciousness and similarities to strychnine-induced opisthotonos suggest to us that the mechanism may have a brainstem and spinal origin. Recent investigations

show that propofol potentiates the inhibitory transmitters glycine and gamma-aminobutyric acid (GABA) which would enhance spinal inhibition during anaesthesia. Postanaesthetic opisthotonos, however, may be due to a propofol-induced tolerance to inhibitory transmitters. This rebound phenomenon would lead to an acute, enduring refractoriness in inhibitory pathways of the brainstem and spinal cord, resulting in increased activity of extensor motoneurons. We recommend a therapeutic strategy that restores inhibition by glycine and GABA at multiple sites; the preferred therapeutic agents would be diazepam and physostigmine. The episodes are usually short-lived, but two of the reviewed 17 patients developed recurrent retrocollis for four and 23 days following antiepileptic drug therapy. Since high doses of phenytoin and carbamazepine can result in opisthotonos, we recommend that anticonvulsants be reserved for postanaesthetic patients with electroencephalographic evidence of seizure activity.

Author(s): Feng J; Kendig JJ / Institution: Department of Anesthesia, Stanford University School of Medicine, CA 94305-5117, USA. / Title: Selective effects of alfentanil on nociceptive-related neurotransmission in neonatal rat spinal cord. / Source: *Br J Anaesth*. 1995 Jun. 74(6). P 691-6. / Abstract: We have examined the effects of alfentanil on nociceptive-related neurotransmission in isolated neonatal rat spinal cord, with particular attention to acute tolerance. Electrical stimulation of a lumbar dorsal root was used to evoke the monosynaptic reflex (MSR), a slow ventral root potential (sVRP), and the dorsal root potential (DRP). Alfentanil (0.5 nmol litre-1 to 1 mumol litre-1) depressed sVRP area by a maximum of 85%; EC50 was approximately 2 nmol litre-1. The effects of alfentanil were selective for very slow, metabotropically mediated sVRP components compared with faster NMDA receptor-mediated components. The MSR was unaffected. Alfentanil depressed DRP area by a maximum of 50% at 1 mumol litre-1. Naloxone antagonized all alfentanil effects. Morphine depressed sVRP area with an approximate EC50 of 90 nmol litre-1, giving an alfentanil: morphine potency ratio of 45:1. The effects of alfentanil on sVRP showed no biphasic time dependence up to 60 min. Naloxone administered after alfentanil produced a significant rebound in sVRP area to a level of 143 (SD 21.3)% above control. Thus, in this study there was no evidence for acute tolerance, as measured by a decrease in effectiveness over time, but there was evidence as measured by rebound following naloxone.

Author(s): Mandema JW; Wada DR / Institution: Department of Anesthesia, Stanford University School of Medicine, California, USA. / Title: Pharmacodynamic model for acute tolerance development to the electroencephalographic effects of alfentanil in the rat. / Source: *J Pharmacol Exp Ther*. 1995 Dec. 275(3). P 1185-94. / Abstract: This investigation was carried out to characterize the rate and extent of acute tolerance development to the pharmacodynamics of alfentanil in the rat with the electroencephalogram (EEG) as a measure of alfentanil's effects on the central nervous system. Alfentanil was administered by use of three different drug infusion strategies in order to develop a pharmacokinetic-pharmacodynamic model for acute tolerance: I) intravenous infusion of 0.5 mg/kg in 10 min, achieving peak alfentanil concentrations of 750 ng/ml; II) computer-controlled infusion to rapidly achieve and maintain a constant drug level of 750 ng/ml, followed by washout; III) computer-controlled infusion to step through multiple constant drug levels (up to 1500 ng/ml), followed by washout. Frequent arterial plasma samples were taken and assayed for alfentanil. EEG signals were continuously recorded until effects returned to base-line values. The amplitudes in the 0.5- to 3.5-Hz (delta) frequency band were calculated by aperiodic analysis and used as an EEG effect measure. The pharmacokinetic data were characterized by a three-compartment model with nonlinear clearance. Nonlinear kinetics was apparent from the multiple steady-state protocol III. Clearance values ranged from (S.E.) 49.7 (2.8) ml/min/kg at low alfentanil concentrations to a minimum value of 29.3 (0.8) ml/min/kg at high concentrations. The pharmacodynamic data showed profound acute tolerance development reflected as proteresis in the concentration-effect pairs after protocol I and a rapidly declining effect in the presence of stable alfentanil concentrations after protocols II and III. The effect stabilized within 15 min after a change in target concentration. A physiological tolerance model was developed to characterize the rate and

extent of tolerance development to the effects of alfentanil. The models are generally applicable and consider the physiological homeostatic mechanisms responsible for the tolerance development to be an integral part of the pharmacodynamic system. Tolerance was modeled as a negative feedback control of the drug-induced effect with a first-order transfer function. The model required only two tolerance parameters to quantify the rate and extent of tolerance development and allowed for a rebound effect. Maximum tolerance diminished alfentanil's effect by 46% and was achieved with a half-life of 7.0 min.

Halothane

Therapeutic indications: General anesthesia.

Rebound effect:

Author(s): Lester GD; Bolton JR; Cullen LK; Thurgate SM / Institution: Department of Applied Veterinary Medicine, School of Veterinary / Studies, Murdoch University, Western Australia. / Title: Effects of general anesthesia on myoelectric activity of the intestine in horses. / Source: *Am J Vet Res*. 1992 Sep. 53(9). P 1553-7. / Abstract: Myoelectric activity was monitored from the terminal ileum, cecum, and colonic pelvic flexure by use of AgpAgCl bipolar electrodes in 4 adult horses before, during, and after general anesthesia. Horses were anesthetized by way of 3 commonly used regimens, including xylazine (1.1 mg/kg of body weight) and ketamine hydrochloride (2.2 mg/kg); thiopental sodium (7.7 mg/kg), followed by halothane vaporized in oxygen; and thiopental sodium (2.5 g) in guaifenesin (100 mg/ml) solution given to effect, followed by halothane in oxygen. All 3 anesthetic regimens decreased intestinal spike-burst activity in the areas monitored. The slowest return to preanesthetic myoelectric activity was observed after xylazine and ketamine administration. After both of the barbiturate/halothane anesthetic regimens, there was a rebound increase in spike-burst frequency, without alteration in the proportion of propagative myoelectric events. All 3 anesthetic regimens appeared to reset the timing of the small and large intestinal migrating myoelectric complexes. By 9 hours after recovery from anesthesia, the effects of anesthesia, irrespective of regimen, had disappeared. Although anesthesia significantly (P less than 0.05) altered intestinal myoelectric activity, no particular anesthetic regimen had a prolonged effect. Results of our study indicate that the particular chosen regimen of general anesthesia is unimportant in development of motility disturbances in horses after anesthesia.

PSYCHIATRIC DRUGS

Anxiolytic drugs

Barbiturates *(Amobarbital, Aprobarbital, Secutabarbital, Pentobarbital, Phenobarbital, Secobarbital, Talbutal)*
Therapeutic indications: Anxiety, nervousness and tension (induction anesthetic).
Rebound effect:
Anxiety, nervousness and restlessness. *(USP DI, 1996, p. 511)*
Autor(es): Karler R; Calder LD; Turkanis SA / Título: Prolonged CNS hyperexcitability in mice after a single exposure to delta-9-tetrahydrocannabinol. / Fonte: *Neuropharmacology*. 1986 Apr. 25(4). P 441-6. / Resumo: A single exposure to delta-9-tetrahydrocannabinol (THC) resulted in a "rebound" hyperexcitability in the CNS in mice, which was assessed in terms of the susceptibility of the CNS to electrically-induced convulsions. The magnitude of the hyperexcitability was dose-related (25-150 mg/kg, i.p.), as measured 24 hr after treatment. The time-course study of the effect indicated a peak-effect at 24 hr after administration of the drug, with duration of the effect for as long as 196 hr. The time course of the rebound hyperexcitability to THC was compared to that for phenobarbital, which peaked at 48 hr after administration of the drug and returned to the control value by 96 hr. Tolerance developed rapidly to the motor-toxic effect of THC, but after 23 days of daily treatment there was no evidence of tolerance to the rebound hyperexcitability. The functional significance of the hyperexcitable state was assessed in two tests; electrical kindling to minimal convulsions was enhanced, even when the kindling procedure was initiated 120 hr after exposure to the drug; and the anticonvulsant activity of phenytoin was blocked when mice were treated with the anticonvulsant 96 hr after a single exposure to THC. The results suggest that the rebound response from a single exposure to THC represents a functionally significant prolonged increase in excitability of the CNS.
Author(s): Sullivan M; Toshima M; Lynn P; Roy-Byrne P / Institution: Department of Psychiatry and Behavioral Science, University of Washington, Seattle / Title: Phenobarbital versus clonazepam for sedative-hypnotic taper in chronic pain patients. A pilot study / Source: *Ann Clin Psychiatry.* 1993 Jun;5(2):123-8. / Abstract: A randomized, double-blind controlled trial is reported comparing phenobarbital and clonazepam for the purpose of sedative-hypnotic taper in inpatients with chronic, nonmalignant pain. After receiving the Minnesota Multiphasic Personality Inventory (MMPI) and a standardized psychiatric diagnostic interview, patients' baseline sedative-hypnotic use was assessed over 48 hours. Baseline use was converted into phenobarbital or clonazepam equivalents and administered in four doses daily using a blinded liquid pain cocktail. Baseline dose was maintained for two days and then tapered by 10% per day. Over the first week of taper, differences in mean and maximum Beck Anxiety and Benzodiazepine Withdrawal scores were not significant. However, when scales 1, 3, or 8 of the MMPI were taken as covariates, differences on the Withdrawal Scale only increased to a trend level for mean scores and to a significant level for maximum scores. These findings support the superiority of benzodiazepines over barbiturates for sedative-hypnotic taper for symptoms of withdrawal but not of recurrent or rebound anxiety.

Benzodiazepines *(Alprazolam, Chlordiazepoxide, Clorazepate, Diazepam, Halazepam, Lorazepam, Oxazepam, Prazepam, etc.)*
Therapeutic indications: Anxiety (Agorafobia, panic Syndrome, etc.).
Rebound effect:

Excitement, nervousness and irritability non-standard occur as paradoxical reaction (arise after 2-3 days, with benzodiazepines half-life intermediate or short, and after 10-20 days with benzodiazepines long half-life, after the abrupt interruption of therapeutic doses). *(USP DI, 1996, p. 542, 814)*
Nervousness, agitation and irritability occur at the beginning of treatment and with abrupt discontinuation of drug. *(AHFS, 1990, p. 1129)*
Author(s): Chouinard G; Labonte A; Fontaine R; Annable L / Title: New concepts in benzodiazepine therapy: rebound anxiety and new indications for the more potent benzodiazepines. / Source: *Prog Neuropsychopharmacol Biol Psychiatry*. 1983. 7(4-6). P 669-73. / Abstract: Abrupt withdrawal of benzodiazepine treatment in generalized anxiety patients was found to induce a rebound anxiety state in addition to minor physical symptoms. Controlled clinical trials suggest that the newer high potency benzodiazepines (alprazolam, clonazepam and bromazepam) have novel psychiatric indications and greater anxiolytic effect than the classical benzodiazepines. Alprazolam, a triazolobenzodiazepine, was superior to placebo in the treatment of panic disorder, for which medium or low potency benzodiazepines are generally inefficacious. Clonazepam, an anticonvulsant which increases 5HT synthesis, was more efficacious than lithium in reducing manic symptoms. Bromazepam, a new potent benzodiazepine, was superior to diazepam in the treatment of generalized anxiety disorder.
Author(s): Swinson RP; Pecknold JC; Kirby ME / Institution: Department of Psychiatry, Toronto General Hospital, Ont., Canada. / Title: Benzodiazepine dependence. / Source: *J Affect Disord*. 1987 Sep-Oct. 13(2). P 109-18. / Abstract: Benzodiazepines (BDPs) are widely used drugs that are effective in controlling the symptoms of anxiety. Tolerance develops rapidly to some of the effects but not to anxiolytic effect in most patients. Dependence occurs at usual therapeutic doses and in a small proportion of patients is accompanied by an enormous increase in the dose taken. The majority of subjects using very high doses are dependent on other substances concurrently. On discontinuing BDPs patients may suffer from relapse of the original condition, rebound in the severity of the symptoms of the original condition or the onset of new symptoms in an abstinence syndrome. If BDPs are discontinued abruptly there may be severe consequences such as seizures. With tapering of the dose, even if this is rapid and from high dose, high potency BDP, the subject will probably experience considerable discomfort but rarely life-threatening effects. Whilst there is concern that BDPs are used too freely, the conditions treated are accompanied by significant morbidity and mortality. The prevalence of pure BDP dependence is low and it is still a matter of debate as to how often BDPs should be prescribed, for which conditions and for what length of time.
Author(s): Lader M / Institution: Department of Psychiatry, Institute of Psychiatry, London, UK. / Title: Long-term treatment of anxiety: benefits and drawbacks. / Source: *Psychopharmacol Ser*. 1988. 5P 169-79. / Abstract: Anxiety disorders are common conditions, often chronic, occurring in the general population with a prevalence of about 3%. Long-term use of tranquilizers varies from 0.5% of the total adult population in Sweden and 1.3% in Denmark to 3.1% in Great Britain and 5% in France. This use is tending to become more and more long-term. Long-term efficacy of benzodiazepine medication has not been established. Adverse effects include psychomotor and cognitive impairment, especially in the elderly; some, but not all, effects show tolerance. Some impairment can be demonstrated even after years of use. Rebound and withdrawal reactions after long-term use are common. Practical guidelines to minimize long-term use are suggested.
Author(s): Pecknold JC; Swinson RP; Kuch K; Lewis CP / Institution: McGill University, Montreal, Quebec, Canada. / Title: Alprazolam in panic disorder and agoraphobia: results from a multicenter trial. III. Discontinuation effects. / Source: *Arch Gen Psychiatry*. 1988 May. 45(5). P 429-36. / Abstract: Preliminary reports of discontinuation of alprazolam therapy in patients with panic disorder have revealed worsening of symptoms despite gradual withdrawal of medication. In

this study, 126 patients with panic disorder and phobic avoidance received either alprazolam or placebo in doses of 2 to 10 mg daily for eight weeks. The medication was tapered over a period of four weeks, and patients were observed for another two weeks after all medication was discontinued. Sixty of the 63 alprazolam-treated patients and 49 of the 63 placebo-treated patients entered the taper and discontinuation study. After improvement in the active treatment period, the alprazolam-treated group had significant relapse between the first and last week of taper. However, during the second postdiscontinuation week, outcome scores were not significantly different from those of the placebo-treated group who did not deteriorate during taper. Twenty-seven percent of the alprazolam-treated group reported a rebound of panic attacks during taper and 13% reported a rebound of anxiety on the Hamilton Anxiety Scale. No serious or life-threatening withdrawal symptoms were reported, but distinct, transient, mild to moderate withdrawal syndrome occurred in 35% of the alprazolam-treated group and in none of the placebo-treated group. The coexistence of symptom rebound and a withdrawal syndrome occurred in 10% of the alprazolam-treated group, but both subsided by the end of the second week without alprazolam. We recommend that patients with panic disorder be treated for a longer period, at least six months, and that medication be tapered over a more prolonged period, at least eight weeks, especially where high doses are employed.
Author(s): Tesar GE / Institution: Clinical Psychopharmacology Unit, Massachusetts General Hospital, Boston 02114. / Title: High-potency benzodiazepines for short-term management of panic disorder: the U.S. experience. / Source: *J Clin Psychiatry*. 1990 May. 51 SupplP 4-10; discussion 50-3. / Abstract: Interest in benzodiazepines for treatment of panic attacks followed a report of the success of alprazolam, used for generalized anxiety, in blocking such attacks. Twelve controlled trials and several open studies have substantiated the antipanic and antiphobic activity of alprazolam and concluded it is comparable to but more rapid than antidepressants in its effects and better tolerated. In a controlled trial of clonazepam, alprazolam, and placebo, the two active agents had similar positive effects. Diazepam and lorazepam have been effective in other studies. Clonazepam, with its relatively long half-life, permits less frequent dosing than possible with benzodiazepines with shorter half-lives and more continuous control of anxiety, although around 20% of patients experience unacceptable sedative effects or no reduction in anxiety. In general, benzodiazepines are safe and well tolerated. The most common adverse effects are intoxication, dependence, rebound, withdrawal, hostility, and affective disturbances. Discontinuation of alprazolam is particularly difficult and is sometimes associated with serious rebound and withdrawal symptoms. The morbidity and mortality associated with panic disorder suggest that the benefits of benzodiazepine treatment outweigh its risks.
Author(s): Kales A / Institution: Department of Psychiatry, Pennsylvania State University College of Medicine, Hershey. / Title: Benzodiazepine hypnotics and insomnia. / Source: *Hosp Pract (Off Ed)*. 1990 Sep. 25 Suppl 3P 7-21; discussion 22-3. / Abstract: In summary, it is proposed that the more frequent or severe side effects associated with the newer triazolo-benzodiazepines are related to an interaction of several factors, including rapid elimination, high receptor-binding affinity, and unique chemical properties. Among benzodiazepine hypnotics, triazolam has a unique side effect profile for CNS adverse reactions in regard to type, frequency, and severity. All of the three factors mentioned contribute to this side effect profile: rapid elimination (the shortest half-life among benzodiazepine anxiolytics and hypnotics); high receptor-binding affinity (the highest among benzodiazepine anxiolytics and hypnotics); and unique chemical properties as a triazolo-benzodiazepine. Given these three factors, the drug's side effects can be understood as follows: Hyperexcitability states (daytime anxiety during drug administration and rebound insomnia following withdrawal) are related primarily to its rapid elimination and secondarily to the other two factors, whereas cognitive impairments (amnesia, confusion, and psychiatric symptoms) are related to the high binding affinity and unique chemical properties as well as to its rapid elimination. In contrast, benzodiazepines that are slowly eliminated and have only relatively moderate receptor-binding affinity (flurazepam) are unlikely to produce daytime anxiety and rebound insomnia and

CNS adverse reactions such as cognitive impairment. The most common side effect, daytime sedation, is easily recognized and can be managed by dose reduction and/or intermittent use. This safety profile combined with the drug's high degree of efficacy both initially and with continued use provides a high benefit-risk ratio in using the drug in the adjunctive pharmacologic treatment of insomnia. Similarly, temazepam, which has relatively weak receptor-binding affinity produces very few CNS adverse reactions. Furthermore, temazepam (15 mg) is more efficacious than triazolam (0.25 mg). However, temazepam is not as effective as flurazepam, because it is slowly absorbed and therefore has limited efficacy for sleep induction. On the other hand, triazolam's safety profile of frequent and severe adverse reactions combined with the lack of efficacy for the current dose of 0.25 mg limits the drug's usefulness. In fact, the 0.25-mg dose has such a poor benefit-to-risk ratio that there is a real question as to whether the drug should remain on the market.

Author(s): Teboul E; Chouinard G / Institution: Department of Psychiatry, McGill University, Montreal, Quebec. / Title: A guide to benzodiazepine selection. Part II: Clinical aspects. / Source: *Can J Psychiatry*. 1991 Feb. 36(1). P 62-73. / Abstract: To suit the specific needs of various clinical situations, selection of an appropriate benzodiazepine derivative should be based on consideration of their different pharmacokinetic and pharmacodynamic properties. Benzodiazepine derivatives that are rapidly eliminated produce the most pronounced rebound and withdrawal syndromes. Benzodiazepines that are slowly absorbed and slowly eliminated are most appropriate for the anxious patient, since these derivatives produce a gradual and sustained anxiolytic effect. Rapidly absorbed and slowly eliminated benzodiazepines are usually more appropriate for patients with sleep disturbances, since the rapid absorption induces sleep and the slower elimination rate may induce less tolerance to the sedative effect. Rational selection of a benzodiazepine for the elderly and for the suspected drug abuser is more problematic. The relevant pharmacokinetic and clinical considerations for these users are discussed. Certain derivatives may possess pharmacodynamic properties not shared by the entire benzodiazepine class; empirical studies have suggested the existence of anti-panic properties for alprazolam and clonazepam, antidepressant properties for alprazolam, and anti-manic properties for clonazepam and possibly lorazepam.

Author(s): Noyes R Jr; Garvey MJ; Cook B; Suelzer M / Institution: Department of Psychiatry, University of Iowa College of Medicine, Iowa City. / Title: Controlled discontinuation of benzodiazepine treatment for patients with panic disorder / Source: *Am J Psychiatry*. 1991 Apr. 148(4). P 517-23. / Abstract: The purpose of this study was to compare the effects of discontinuing treatment with intermediate- and long-acting benzodiazepines. Fifty patients with panic disorder who had taken part in a double-blind treatment study and had responded to alprazolam, diazepam, or placebo for 8 months were asked to stop taking these medications gradually. After a relatively rapid dose reduction, the majority of patients relapsed. Rebound anxiety and withdrawal symptoms were identified in a substantial minority of patients. Those who were taking alprazolam showed earlier and more intense rebound anxiety and withdrawal symptoms than did the patients who received diazepam. Both the level of pretreatment anxiety and the drug the patient was taking predicted the level of anxiety when drug treatment was discontinued. The findings indicate that withdrawal phenomena commonly occur after patients stop taking benzodiazepines and that they are more frequent after discontinuation of treatment with shorter-acting drugs.

Author(s): Ansseau M; Von Frenckell R / Institution: Unite de Psychiatrie, C.H.U. du Sart Tilman, Liege, Belgique. / Title: [Value of prazepam drops in the brief treatment of anxiety disorders]. / Source: *Encephale*. 1991 Jul-Aug. 17(4). P 291-4. / Abstract: In order to assess the clinical usefulness of benzodiazepine brief therapy with planned tapering, prazepam as drops was administered to 40 psychiatric outpatients suffering from generalized anxiety disorder. After a one-week placebo period, the patients received prazepam 40 mg daily (i.e., 10 drops in the morning, 10 drops at noon and 20 drops in the evening) during 3 weeks, with the possibility to adjust the doses after one week. The doses were then tapered at 4 mg/d (i.e., 1 drop in the morning, 1 drop at noon and 2 drops in the evening) until complete suppression of the treatment. The assessments,

performed before the placebo period, at inclusion, after 1 and 3 weeks of active treatment, and after 1 and 2 weeks of tapering, included the Hamilton anxiety scale, the Lader tranquillizer withdrawal rating scale, and the collection of side effects; moreover, the patients completed daily a visual analogue scale. Results showed a very marked anxiolytic effect of prazepam with an already very significant decrease in the scores on the various scales after 1 week of treatment when the daily dose was significantly reduced. Three quarters of the patients were able to take part in the tapering of prazepam doses without exhibiting any reappearance of anxious symptomatology, rebound anxiety, or withdrawal symptoms. The tolerance of the treatment was rated as good or very good in 91.9% of the patients. This study demonstrates the possibility of a brief anxiolytic treatment followed by tapering in a majority of patients with generalized anxiety disorders. For this strategy, the availability of a drop form represents an obvious advantage.

Author(s): Schweizer E; Patterson W; Rickels K; Rosenthal M / Institution: Department of Psychiatry, University of Pennsylvania, Philadelphia 19104-2649. / Title: Double-blind, placebo-controlled study of a once-a-day, sustained-release preparation of alprazolam for the treatment of panic disorder. / Source: *Am J Psychiatry*. 1993 Aug. 150(8). P 1210-5. / Abstract: The goals of this study were to assess the antipanic efficacy of a new, sustained-release formulation of alprazolam and to assess the safety and tolerability of once-a-day administration of 1-10 mg of sustained-release alprazolam. One hundred ninety-four patients with diagnosis of agoraphobia with panic attacks or panic disorder with limited phobic avoidance underwent a 1-week placebo washout before being randomly assigned to groups receiving 8 weeks of double-blind treatment with either sustained-release alprazolam or placebo. There was a significant treatment effect favoring sustained-release alprazolam (highest mean dose = 4.7 mg/day) across almost all measures of anxiety, panic, and phobic avoidance, despite a significantly higher dropout rate in patients receiving placebo. Eighty-five percent of the patients treated with sustained-release alprazolam, compared with 61% of the patients given placebo, reported complete blockade of panic attacks by the end of 6 weeks of treatment. Sedation was the most commonly reported adverse effect. Discontinuation of sustained-release alprazolam was associated with moderate but transient levels of distress in 48% of the patients; discontinuation of placebo led to distress in only 10% of the patients. Nonetheless, there was no difference in the proportion of patients who were able to remain off the study drug for at least 2 weeks. These results suggest that sustained-release alprazolam is highly effective in the acute treatment of panic disorder at doses comparable to those in the originally marketed compressed tablet of alprazolam. The medication was well tolerated but showed rebound effects during a rapid drug taper after 6 weeks of treatment.

Author(s): Vgontzas AN; Kales A; Bixler EO / Institution: Sleep Research and Treatment Center, Pennsylvania State University College of Medicine, Hershey 17033, USA. / Title: Benzodiazepine side effects: role of pharmacokinetics and pharmacodynamics. / Source: *Pharmacology*. 1995 Oct. 51(4). P 205-23. / Abstract: Benzodiazepines have a wide variety of indications. However, CNS and psychiatric adverse reactions, tolerance, and withdrawal effects of benzodiazepines are becoming increasingly recognized and must be better understood for proper drug use. Certain benzodiazepines are associated with memory impairment and other cognitive defects and hyperexcitability phenomena during treatment (early-morning insomnia, daytime anxiety) and following withdrawal (rebound insomnia and anxiety, seizures). Elimination half-life, receptor-binding affinity, effects on the locus coeruleus-norepinephrine (LC-NE) and hypothalamic-pituitary-adrenal (HPA) axes, and the interaction of these factors appear to be major determinants of frequency and severity of these untoward effects. Rapid drug elimination and high receptor-binding affinity were initially suggested as primary underlying factors which determine frequency, severity, and type of the side effects of benzodiazepines during administration and withdrawal. Newer data and information on triazolobenzodiazepines indicate that these psychiatric adverse reactions also relate to whether the benzodiazepine has strong direct effects on the LC-NE and HPA systems. Initial suppression of the LC-NE and HPA systems is followed, on an interdose basis, by a

significant rebound and activation. This repetitive pattern of suppression followed by rebound results in a neurophysiologic and behavioral sensitization (kindling) of the limbic system and consequently contributes to central nervous system (CNS) and psychiatric adverse reactions. The tendency of certain of these side effects to worsen over time supports empirically this neurophysiologic and biochemical model.

Author(s): Mandos LA; Rickels K; Cutler N; Roeschen J; Keppel Hesselink JM; Schweizer E / Institution: Philadelphia College of Pharmacy and Science, PA, USA. / Title: Placebo-controlled comparison of the clinical effects of rapid discontinuation of ipsapirone and lorazepam after 8 weeks of treatment for generalized anxiety disorder. / Source: *Int Clin Psychopharmacol*. 1995 Nov. 10(4). P 251-6. / Abstract: One hundred and sixty patients (mean age 39.8 years; 67% female) diagnosed with generalized anxiety disorder (GAD) who had completed a prospective, 8 week, double-blind comparison of lorazepam (mean daily dose 4.2 mg) and ipsapirone (mean daily dose 19.5 mg) were rapidly tapered by a substitution of half-strength medication for 3 days, then substitution of matched placebo for an additional 11 days. Patients treated with ipsapirone showed neither rebound anxiety on discontinuation, nor any other significant increase in withdrawal symptomatology compared to patients who had been prospectively treated with placebo. In contrast, patients treated with lorazepam showed significant emergent anxiety and/or withdrawal-related symptomatology by almost all clinical measures employed. Overall, 25% of patients treated with lorazepam showed rebound anxiety, and 40% of them utilized reserve medication because they found drug discontinuation to be intolerable. The clinical implications for discontinuation of benzodiazepines after short-term therapy are discussed.

Author(s): Busto EU; Sellers EM / Institution: Pharmacy Department & Psychopharmacological Research, Addiction Research Foundation, Toronto, Ontario, Canada. / Title: Anxiolytics and sedative/hypnotics dependence. / Source: *Br J Addict.* 1991 Dec;86(12):1647-52. / Abstract: Anxiolytics and sedative/hypnotics are commonly used drugs. Benzodiazepines have largely replaced barbiturate and non-barbiturate anxiolytics and sedative/hypnotics as they are as effective and safer. Experiments in laboratory animals have shown that chronic administration of benzodiazepines tested to date can induce physical dependence. The severity of the withdrawal syndrome is clearly related to the dose, duration of administration and elimination rate of the drugs. It is now also clear that high doses of barbiturates and benzodiazepines can induce physical dependence in humans. In addition, a withdrawal syndrome after discontinuation of chronic benzodiazepine therapeutic treatment, with and without tolerance, has been well characterized. Symptoms may resemble those of anxiety or 'rebound' phenomena but some are typical of withdrawal. A relationship between benzodiazepine discontinuation and self-administration has been well documented. Negative reinforcement associated with a reduction of withdrawal symptoms may play a role supporting persistent benzodiazepine use.

Buspirone *(selective anxiolytic action)*
Therapeutic indications: Anxiety.
Rebound effect:
Anxiety, nervousness and excitement non-standard. *(USP DI, 1996, p. 676; AHFS, 1990, p. 1274)*

Author(s): Ansseau M; Papart P; Gerard MA; von Frenckell R; Franck G / Institution: Psychiatric Unit, Centre Hospitalier Universitaire de Liege, Belgium. / Title: Controlled comparison of buspirone and oxazepam in generalized anxiety. / Source: *Neuropsychobiology*. 1990-91. 24(2). P 74-8. / Abstract: The anxiolytic activity, the tolerance, and the withdrawal symptoms of buspirone and oxazepam were compared in two groups of 14 and 12 outpatients, respectively, suffering from generalized anxiety in a double-blind study with random allocation of patients. The 6-week active period was preceded and followed by 1 and 2 weeks on placebo, respectively. Clinical assessments

were performed before and after the predrug placebo period and every 2 weeks thereafter and included Hamilton anxiety and depression scales and AMDP anxiety subscale. The initial daily dose was 15 mg buspirone or 45 mg oxazepam in 3 intakes and the mean final daily doses were 22.2 and 55.8 mg, respectively. Results showed a slower anxiolytic activity of buspirone compared to oxazepam with less improvement after 2 weeks of treatment. The rebound anxiety following abrupt discontinuation of the drug and the level of side effects did not significantly differ between the two compounds.
Author(s): Strand M; Hetta J; Rosen A; Sörensen S; Malmström R; Fabian C; Marits K; Vetterskog K; Liljestrand AG; Hegen C / Institution: Primary Care Center, Enköping, Sweden. / Title: A double-blind, controlled trial in primary care patients with generalized anxiety: a comparison between buspirone and oxazepam. / Source: *J Clin Psychiatry*. 1990 Sep;51 Suppl:40-5. / Abstract: Two hundred thirty patients with generalized anxiety and Hamilton Rating Scale for Anxiety (HAM-A) scores greater than or equal to 18 were subdivided at random, according to a double-blind design, into one group treated with 5-10 mg of oral buspirone t.i.d. or one group treated with 10-20 mg of oral oxazepam t.i.d. for 6 weeks. No anxiolytic treatment was allowed 3 months prior to trial entry. Analysis of demographic variables revealed no significant imbalance between the two treatment groups. Twenty patients were excluded from efficacy analysis because of treatment withdrawal before the first efficacy evaluation on Day 7. Another 4 patients were excluded because they were taking concomitant psychotropic medication. The remaining 206 patients displayed a decrease in HAM-A scores (mean +/- SD) from 23.9 +/- 4.1 to 10.6 +/- 7.7 in the buspirone group and from 23.9 +/- 4.2 to 11.5 +/- 8.0 in the oxazepam group. The two treatment groups were also found to be virtually identical in an "intent to treat" analysis of all 230 patients as well as in other ratings (Hamilton Rating Scale for Depression, Raskin Depression Scale, Covi Anxiety Scale, Physicians Questionnaire, global ratings, and Hopkins Symptom Checklist [HSCL]-56). However, oxazepam was never superior to buspirone in any of the efficacy analyses. Of the 230 patients, 127 spontaneously reported adverse events, including drowsiness, dizziness, headache, nausea, and nervousness. Adverse events were relatively similar in the two groups. In conclusion, buspirone and oxazepam appear to be equally effective in the treatment of generalized anxiety encountered by general practitioners. This outcome, in addition to a previously documented absence of any dependency liability, makes buspirone a clinically important anxiolytic drug.

Meprobamate
Therapeutic indications: Anxiety.
Rebound effect:
Unusual excitement (paradoxical reaction), restlessness, nervousness, nightmares and trouble sleeping. *(USP DI, 1996, p. 1991; AHFS, 1990, p. 1288)*

Hypnotic or sedative drugs

Barbiturates *(Amobarbital, Aprobarbital, Secutabarbital, Pentobarbital, Phenobarbital, Secobarbital, Talbutal)*
Therapeutic indications: Slight sedation and insomnia.
Rebound effect:
Unusual excitement (paradoxical reaction). Trouble sleeping, increase of dreams or nightmares. *(USP DI, 1996, p. 511; AHFS, 1990, p. 1127)*

Benzodiazepines *(Brotizolam, Chlordiazepoxide, Clorazepate, Diazepam, Flurazepam, Lorazepam, Lormetazepam, Oxazepam, Quazepam, Temazepam, Triazolam, etc.)*
Therapeutic indications: Conscious sedation and insomnia.
Rebound effect:
Sleep disorders (after the deprivation of unique nocturnal doses of most benzodiazepines noted rebound insomnia; after suspension of half-life long benzodiazepines rebound insomnia can arise after 10-20 days, due to delay in metabolized). *(USP DI, 1996, p. 542; AHFS, 1990, p. 1129)*
Author(s): McElnay JC; Jones ME; Alexander B / Title: Temazepam (Restoril, Sandoz Pharmaceuticals). / Source: *Drug Intell Clin Pharm*. 1982 Sep. 16(9). P 650-6. / Abstract: Temazepam is a benzodiazepine derivative indicated for the treatment of insomnia. Pharmacokinetic studies of the hard capsule formulation indicate that the mean time to peak is 2.99 hours and the mean elimination half-life is 14.7 hours. Sleep laboratory studies have demonstrated improvements in all sleep parameters except sleep onset latency. Clinically, patients report improvements in all sleep parameters including sleep onset latency. The efficacy of temazepam compares favorably with barbiturates, glutethimide, nitrazepam, lorazepam, oxazepam, and flurazepam. It has not been compared with diazepam in the clinical setting. Side effects include drowsiness, dizziness, and lethargy. The incidence of hangover effects from 15- and 30-mg doses is relatively low. Temazepam has no proven advantages over other benzodiazepine hypnotics. The major issues that need further clarification include temazepam's sleep induction properties and the relative incidence of hangover and rebound insomnia when compared with longer-acting benzodiazepines.
Author(s): Kales A; Kales JD / Title: Sleep laboratory studies of hypnotic drugs: efficacy and withdrawal effects. / Source: *J Clin Psychopharmacol*. 1983 Apr. 3(2). P 140-50. / Abstract: Flurazepam, temazepam, and triazolam are compared in terms of initial and short term efficacy, effectiveness during intermediate and long term use, withdrawal effects, and general side effects. The usefulness of temazepam is considerably restricted since the drug is slowly absorbed; peak blood concentrations are not reached until 2 to 3 hours after ingestion. Consequently, while the majority of insomniac patients complain primarily of difficulty falling asleep, temazepam is not effective for this sleep complaint. Further, the drug has an intermediate elimination half-life and induces a significant degree of morning sleepiness (hang-over). Rebound insomnia of a moderate degree occurs with some frequency following withdrawal of temazepam. Triazolam is effective initially and with short term use both for inducing and maintaining sleep. However, much of this effectiveness is lost with continued nightly use over an intermediate period (2 weeks). The drug has a rapid elimination rate; during drug administration, sleep may worsen in the final hours of the night (early morning insomnia), and following drug withdrawal, rebound insomnia is frequent, immediate, and severe. Side effects are frequent and include some morning sleepiness (before tolerance develops) and significant memory impairment and even episodes of amnesia. Triazolam may have a narrow margin of safety in that serious behavioral symptoms have been reported even with a 1-mg dose. Flurazepam is effective both for initiating and maintaining sleep with initial and short term drug administration. Further, its efficacy is maintained not only with intermediate term use but with long term drug use (4 weeks). Flurazepam is a long elimination half-life drug, and there is significant daytime sedation during short term use; with continued use this effect diminishes. Rebound insomnia has not been noted following withdrawal of flurazepam; there is a carry-over effectiveness into the first and second nights of withdrawal, and any withdrawal sleep disturbance would be expected to be infrequent, delayed in appearance, and mild in degree.
Author(s): Vela-Bueno A; Oliveros JC; Dobladez-Blanco B; Arrigain-Ijurra S; Soldatos CR; Kales A / Title: Brotizolam: a sleep laboratory evaluation. / Source: *Eur J Clin Pharmacol*. 1983. 25(1). P 53-6. / Abstract: Brotizolam 0.25 mg was evaluated in a sleep laboratory study of 10

normal subjects. The study covered 10 consecutive nights and included 4 placebo-baseline nights, 3 nights on the drug and 3 placebo-withdrawal nights, which permitted assessment of initial drug effects, side effects and withdrawal phenomena, such as rebound insomnia. There was a significant increase in total sleep time with drug administration; the improvement in sleep occurred primarily in the first third of the night following the onset of sleep. During the day after nightly drug administration, the presence of rebound anxiety was suggested by an increase in reports of anxiety/tension as compared to baseline. Following drug withdrawal there was a significant increase in total wake time above baseline level, to 40% above baseline on the first and third nights of withdrawal.

Author(s): Mitler MM; Seidel WF; van den Hoed J; Greenblatt DJ; Dement WC / Title: Comparative hypnotic effects of flurazepam, triazolam, and placebo: a long-term simultaneous nighttime and daytime study. / Source: *J Clin Psychopharmacol*. 1984 Feb. 4(1). P 2-13. / Abstract: We studied sleep and daytime function in insomniac patients who took either flurazepam, 30 mg, triazolam, 0.5 mg, or placebo 30 minutes before bedtime. Subjects were 21 patients with either a primary or a secondary diagnosis of chronic psychophysiological insomnia or insomnia associated with personality disorder. Seven subjects were randomly assigned to each condition. The study used a three group by 9 week, double-blind design with three nocturnal sleep recordings each week. During week 1, subjects took no capsules; week 2, subjects took placebo; weeks 3 to 7, flurazepam, triazolam, or placebo; weeks 8 and 9, placebo. Daytime tests for alertness and performance were administered during weeks 1, 3, 5, 7, and 8. Flurazepam showed hypnotic efficacy for weeks 3 to 5. Triazolam showed hypnotic activity for weeks 3 to 7. Although not significant overall, discontinuation of flurazepam produced rebound insomnia in six of seven subjects sometime during the two withdrawal weeks. The relationship between plasma concentration of desalkylflurazepam, the principal active metabolite of flurazepam, and sleep disturbance suggested that the onset of the rebound insomnia depended on the rate of drug washout. Discontinuation of triazolam produced significant rebound insomnia on the first and second nights of drug withdrawal. Placebo subjects showed improved sleep throughout weeks 2 to 9 of the study. Daytime testing revealed significantly decreased daytime alertness and decreased performance for flurazepam subjects during weeks 3 to 7, although these effects reverted toward baseline despite continued drug administration.

Author(s): Adam K; Oswald I / Title: Effects of lormetazepam and of flurazepam on sleep. / Source: *Br J Clin Pharmacol*. 1984 May. 17(5). P 531-8. / Abstract: Nine poor sleepers of mean age 61 years took part in a double-blind, balanced order study in which, during three periods of 3 weeks, each took lormetazepam 1 mg, lormetazepam 2.5 mg, and flurazepam 30 mg. Using electrophysiological measures, sleep was found to increase by 0.75 h with each treatment condition, mainly through more of stage 2 sleep. The treatments reduced the delay to sleep and led to fewer and shorter awakenings, with little difference among the three treatments. Slow-wave sleep was reduced by flurazepam and by lormetazepam 2.5 mg. After flurazepam intake ceased, there was evidence of persisting drug effects for as long as 7 nights. In contrast, when lormetazepam 2.5 mg ceased, there was significant rebound reduction of sleep duration below baseline for up to 3 withdrawal nights, and there was a similar though non-significant trend after lormetazepam 1 mg had ceased. Wakefulness in the final 2 h of nocturnal recording during the third week of drug intake was significantly reduced below baseline by flurazepam, but was little affected by lormetazepam. The differences among the treatment conditions could be attributed to the long-persistence of flurazepam vs the more rapid elimination of lormetazepam.

Author(s): Melo de Paula AJ / Title: Comparative study of lormetazepam and flurazepam in the treatment of insomnia. / Source: *Clin Ther*. 1984. 6(4). P 500-8. / Abstract: Lormetazepam (1 and 2 mg) was tested against flurazepam (30 mg) and placebo in 60 patients (15 per treatment group) with initial, intermediate, or late insomnia. Patients were randomly assigned to treatment groups, and a double-blind protocol was followed. The four-week study included one week of use of the placebo, followed by two weeks of treatment with the active drug (in three groups) or continued use of the

placebo (one group), and one week of use of the placebo (all four groups). Results showed that the active drugs were efficient in controlling insomnia. In some subjective parameters, only 2 mg of lormetazepam was significantly better than placebo. Tolerability of the drugs was considered good, with no interruption of treatment required because of adverse reactions. There was a rebound effect in one patient receiving 1 mg of lormetazepam and in three patients receiving flurazepam.

Author(s): Clark BG; Jue SG; Dawson GW; Ward A / Title: Loprazolam. A preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in insomnia. / Source: *Drugs*. 1986 Jun. 31(6). P 500-16. / Abstract: Loprazolam is a 1,4-benzodiazepine with hypnotic properties, advocated for use in acute or chronic insomnia. As loprazolam has a half-life of 7 to 8 hours in healthy adults it may have advantages over longer-acting hypnotics, particularly when residual sedative effects on the day after ingestion are undesirable, although at doses greater than 1 mg residual sedation may occur. In addition, it may reduce daytime anxiety, following a hypnotic dose the night before, more effectively than the short-acting drug, triazolam. In short term comparative studies loprazolam was clearly superior to placebo, and was at least as effective as triazolam, flurazepam, nitrazepam, flunitrazepam or temazepam in hastening sleep onset, reducing nocturnal awakenings and increasing total sleep duration and quality. In the small number of patients with chronic insomnia who have received extended treatment with loprazolam, no evidence of tolerance has occurred, although rebound insomnia was evident 3 days after drug withdrawal in several studies. Thus, with its 'intermediate' elimination half-life, loprazolam would appear to have some potential advantages over both long- and short-acting hypnotics in selected patients, although further studies are needed to fully elucidate its place in therapy.

Author(s): Kales A; Bixler EO; Vela-Bueno A; Soldatos CR; Niklaus DE; Manfredi RL / Title: Comparison of short and long half-life benzodiazepine hypnotics: triazolam and quazepam. / Source: *Clin Pharmacol Ther*. 1986 Oct. 40(4). P 378-86. / Abstract: Two benzodiazepine hypnotics, triazolam, 0.25 mg, with a short elimination t1/2, and quazepam, 15 mg, with a long t1/2, were evaluated in 22-night sleep laboratory studies. Quazepam improved sleep significantly during both short- and intermediate-term use. Daytime sleepiness, which decreased with continued use, was the side effect most often associated with quazepam dosing. In contrast, triazolam dosing did not significantly improve any of the major sleep efficiency parameters, and there was a rapid development of tolerance for the drug's slight initial effectiveness. In addition, there were a number of behavioral side effects including amnesia, confusion, and disinhibition. Withdrawal of triazolam was associated with sleep and mood disturbances (rebound insomnia and rebound anxiety), whereas quazepam exerted carryover effectiveness. Thus the data in this study show that the 0.25 mg dose of triazolam, which is being prescribed increasingly, has a profile of side effects that is similar to that of the 0.5 mg dose.

Author(s): Rickels K; Morris RJ; Mauriello R; Rosenfeld H; Chung HR; Newman HM; Case WG / Title: Brotizolam, a triazolothienodiazepine, in insomnia. / Source: *Clin Pharmacol Ther*. 1986 Sep. 40(3). P 293-9. / Abstract: Sixty-three outpatients with chronic insomnia were treated for 3 weeks under double-blind conditions with either brotizolam (n = 29) at a dose of 0.25 mg or 0.5 mg or placebo (n = 34). A 3-day placebo period preceded and followed the double-blind treatment phase. Brotizolam consistently produced significantly more sleep improvement than placebo but also more adverse effects. In those patients switched abruptly from brotizolam to placebo, rebound insomnia was observed, being most marked at the first post-brotizolam placebo night.

Author(s): Kales A; Bixler EO; Soldatos CR; Jacoby JA; Kales JD / Title: Lorazepam: effects on sleep and withdrawal phenomena. / Source: *Pharmacology*. 1986. 32(3). P 121-30. / Abstract: Lorazepam, an anxiolytic drug, was evaluated in a 2-mg dose using a 16-night protocol including 7 nights of drug trial. Initially and with continued use the drug was moderately effective in inducing and maintaining sleep. Side effects included episodes of memory impairment and confusion in 2 subjects and group mean increases in daytime anxiety and tension with continued drug use. Following drug withdrawal, there was a marked and significant worsening of sleep above baseline

levels (rebound insomnia) on the third night as well as significant increases in tension and anxiety the next day. The peak degree of withdrawal sleep disturbance was several times the peak degree of sleep improvement with drug administration.
Author(s): Kales A; Bixler EO; Vela-Bueno A; Soldatos CR; Manfredi RL / Institution: Department of Psychiatry, Pennsylvania State University College of Medicine, Hershey. / Title: Alprazolam: effects on sleep and withdrawal phenomena. / Source: *J Clin Pharmacol*. 1987 Jul. 27(7). P 508-15. / Abstract: Alprazolam was evaluated in chronic insomniacs in a 1-mg bedtime dose. The 16-night sleep laboratory protocol included four placebo-baseline nights followed by seven nights of drug administration and five placebo-withdrawal nights. On the first three drug nights (nights 5 to 7), the drug was highly effective in inducing and maintaining sleep with this short-term use. By the end of the one week of administration (nights 9 to 11), however, the drug had lost about 40% of its efficacy. During drug use, one subject reported some difficulty in controlling expression of inappropriate emotions when interacting with others, which suggested the presence of disinhibition. On the third night following drug termination, there was a significant increase in sleep difficulty above baseline levels (rebound insomnia). This worsening was of comparable magnitude to the peak improvement of sleep with drug administration. Thus, the clinical utility of alprazolam when administered to insomniac patients appears to be limited because of a relatively rapid development of tolerance and possible disinhibitory reactions during drug use and the occurrence of rebound insomnia following withdrawal.
Author(s): Greenblatt DJ; Harmatz JS; Zinny MA; Shader RI / Title: Effect of gradual withdrawal on the rebound sleep disorder after discontinuation of triazolam. / Source: *N Engl J Med*. 1987 Sep 17. 317(12). P 722-8. / Abstract: Sixty volunteers with insomnia participated in a randomized, double-blind, controlled clinical trial. After an initial six nights of placebo, 30 subjects (the abrupt-withdrawal group) received 0.5 mg of triazolam nightly for 7 to 10 nights, after which they received placebo. The other 30 subjects (the tapered-dosage group) received the same initial placebo treatment, then triazolam at 0.5 mg for seven nights, at 0.25 mg for two nights, and at 0.125 mg for two nights, and then placebo. As compared with the initial placebo period, the triazolam period significantly reduced the interval before the onset of sleep (sleep latency), and it prolonged sleep duration, reduced the number of awakenings, and improved the self-rated soundness of sleep in all cohorts. In the abrupt-withdrawal group, plasma levels of triazolam were undetectable the morning after the first night of placebo substitution, and subjects reported prolongation of sleep latency (57 minutes longer than base line), reduction in sleep duration (1.4 hours less than base line), and increased awakenings (1.2 per night above base line). The symptoms of rebound sleep disorder lasted one or possibly two nights, and there was a reversion toward base line on subsequent placebo nights. In the tapered-dosage group, however, plasma triazolam levels fell gradually to zero, and rebound symptoms were decreased or eliminated. Thus, rebound sleep disorder following abrupt discontinuation of triazolam can be attenuated by a regimen of tapering.
Author(s): Ankier SI; Goa KL / Institution: Charterhouse Clinical Research Unit Ltd, London. / Title: Quazepam. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in insomnia. / Source: *Drugs*. 1988 Jan. 35(1). P 42-62. / Abstract: Quazepam is a trifluoroethyl benzodiazepine hypnotic with a half-life of 27 to 41 hours, which has been shown to induce and maintain sleep in the short to long term (up to 4 weeks) treatment of patients with chronic or transient insomnia. Although its hypnotic efficacy has been well characterised against placebo, there are few clinical studies in comparison with established hypnotics, particularly over long term administration. However, preliminary evidence suggests that quazepam 15 to 30 mg is as effective as flurazepam and triazolam in usual therapeutic doses, and causes minimal rebound insomnia following its withdrawal, unlike rapidly eliminated benzodiazepines such as triazolam. The lack of rebound phenomena is likely to be attributable to the ‘carryover’ effects occurring after discontinuation of quazepam, which has pharmacologically active metabolites with half-lives of elimination similar to or longer than that of the parent drug.

Probably because of the long half-lives of quazepam's metabolites, daytime sedation, fatigue and lethargy are the most frequently reported side effects. These side effects are most intense with the 30 mg dose and least with the 7.5mg dose, which has not been studied extensively. Hence, quazepam is an effective hypnotic which may be particularly suitable for short or medium term use in patients in whom withdrawal effects or rebound insomnia may be especially bothersome. Further definition of certain characteristics of its profile--such as its long term use and potential for development of tolerance or dependence, effects on psychomotor skills, efficacy of the 7.5mg dose, and suitability in elderly patients and patients with chronic organic diseases--will assist in more clearly defining its ultimate place in therapy.

Author(s): Langley MS; Clissold SP / Institution: ADIS Drug Information Services, Manchester. / Title: Brotizolam. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy as an hypnotic. / Source: *Drugs*. 1988 Feb. 35(2). P 104-22. / Abstract: Brotizolam is a new thienotriazolodiazepine derivative with a pharmacological profile similar to that of benzodiazepines. It is indicated for use as an hypnotic in the management of insomnia, although it also has anticonvulsant, antianxiety and muscle relaxant properties in animals. In clinical trials brotizolam 0.125 to 0.5mg improved sleep in insomniacs similarly to nitrazepam 2.5 and 5mg, flunitrazepam 2mg and triazolam 0.25mg, whilst brotizolam 0.5mg was shown to be superior to flurazepam 30mg in some studies. Brotizolam is an effective hypnotic for hospital patients awaiting surgery, in which it also reduces anxiety. Brotizolam has an elimination half-life of about 5 hours, which is 'intermediate' compared with the shorter-acting hypnotic, triazolam, and longer-acting benzodiazepines. Consequently, it is able to induce sleep without producing early morning rebound insomnia, and can also maintain sleep throughout the night. Brotizolam at dosages below 0.5mg at night usually produced minimal morning drowsiness; no residual impairment of psychomotor performance occurs following dosages within the recommended range of 0.125 to 0.25 mg/kg. No serious side effects have been reported to date and the most frequently observed adverse experiences are drowsiness, headache and dizziness. Mild rebound insomnia may occur in some patients when treatment is stopped. Thus, brotizolam is a useful hypnotic which can be used in patients who have difficulty in falling asleep and also in patients who are troubled by night-time awakenings. Used in the recommended dosage it may be particularly useful for patients in whom daytime impairment of performance is unacceptable.

Author(s): Kales A; Manfredi RL; Vgontzas AN; Bixler EO; Vela-Bueno A; Fee EC / Institution: Sleep Research and Treatment Center, Pennsylvania State University College of Medicine, Hershey 17033. / Title: Rebound insomnia after only brief and intermittent use of rapidly eliminated benzodiazepines. / Source: *Clin Pharmacol Ther*. 1991 Apr. 49(4). P 468-76. / Abstract: In three parallel groups, brief and intermittent administration and withdrawal of triazolam, 0.5 mg, temazepam, 30 mg, and placebo were assessed in a 12-night sleep laboratory study of 18 subjects with insomnia. With this intermittent schedule both drugs improved sleep, with about one-third reduction in total wake time; this reduction was significant for temazepam but not for triazolam. Even though the periods of drug administration were quite brief, withdrawal of triazolam consistently produced rebound insomnia, with increases in total wake time above baseline of 61% and 51%, respectively, for the first night of each withdrawal period. With temazepam this effect was more variable, with total wake time increased only with the second withdrawal period (39%). Thus these findings indicate that even under conditions of brief, intermittent use and withdrawal, triazolam and, to a lesser degree, temazepam produce rebound insomnia after abrupt withdrawal, thereby predisposing to drug-taking behavior and increasing the potential for drug dependence.

Author(s): Roth T; Roehrs TA / Institution: Sleep Disorders and Research Center, Henry Ford Hospital, Detroit, MI 48202. / Title: A review of the safety profiles of benzodiazepine hypnotics. / Source: *J Clin Psychiatry*. 1991 Sep. 52 SupplP 38-41. / Abstract: Although over 20 years of clinical experience with benzodiazepine hypnotics have demonstrated their relative safety, flurazepam, temazepam, triazolam, and quazepam do not have identical safety profiles. Dose-

related central nervous system (CNS) depression such as daytime sedation and psychomotor impairment may be expected because they are an extension of the therapeutic action of these agents. Therefore, drug dose is an important factor in determining the expected frequency and severity of these side effects. Also, it is important for a clinician not to assume that these unwanted CNS effects relate only to the length of a drug's half-life. Half-life does appear to be an important determinant of the presence or absence of rebound insomnia.
Author(s): Benoit O / Institution: URA CNRS 1159, Hopital de La Salpetriere, Paris, France. / Title: [Benefits and risks of hypnotics]. / Source: *Neurophysiol Clin*. 1991 Oct. 21(4). P 245-65. / Abstract: Rationalisation of the war of hypnotics has recently been under discussion in France: a review of the benefits and risks of these substances may therefore be useful. Chronic insomnia is a result of multiple factors, among which individual characteristics of the personality play an important role. Hypnotic treatment is symptomatic; its beneficial influence on sleep progressively vanishes in few weeks, while some negative residual effects on daytime functioning (mood, alertness, performance, memory impairment) may persist. The main problems posed by hypnotic treatment with benzodiazepines are related to tolerance effects during the treatment period and to rebound insomnia and withdrawal phenomena after discontinuation. Practical issues for the treatment of insomnia, based on international consensus, are presented.
Author(s): Merlotti L; Roehrs T; Zorick F; Roth T / Institution: Henry Ford Hospital, Sleep Disorders and Research Center, Detroit, Michigan 48202. / Title: Rebound insomnia: duration of use and individual differences. / Source: *J Clin Psychopharmacol*. 1991 Dec. 11(6). P 368-73. / Abstract: This study assessed consistency, duration of use, and individual difference in rebound insomnia. Eleven healthy men, 20-30 years old, with normal sleep by both subjective and polysomnographic criteria, received each of four treatments in a double-blind Latin Square design (triazolam 0.50 mg for 1, 6, and 12 nights and placebo for 12 nights), followed by two placebo discontinuation nights. Triazolam increased sleep compared with placebo without differences in effects between the first and last nights of treatment. On discontinuation following active drug, sleep efficiency was reduced compared with placebo, but duration of administration did not alter the likelihood or intensity of rebound insomnia. Those subjects (5) showing poorer sleep on discontinuation from the 12-night treatment also had poorer sleep in the 1- and 6-night treatment. Subjects with rebound insomnia had poorer baseline sleep and a greater drug effect than did subjects without.

***Ethinamate** (Ethchlorvynol)*
Therapeutic indications: Insomnia.
Rebound effect:
Unusual excitement (paradoxical reaction). Anxiety, nervousness and irritability. Trouble sleeping. *(USP DI, 1996, p. 1412; AHFS, 1990, p. 1282)*

Glutethimide
Therapeutic indications: Insomnia.
Rebound effect:
Unusual excitement (paradoxical reaction). Trouble sleeping, dreams and nightmares. *(USP DI, 1996, p. 1544; AHFS, 1990, p. 1284)*

Hydrate of chloral
Therapeutic indications: Sedation, insomnia.
Rebound effect:

Unusual excitement (paradoxical reaction), nervousness, restlessness and sleepwalking. *(USP DI, 1996, p. 800; AHFS, 1990, p. 1278)*

Metiprilom
Therapeutic indications: Insomnia.
Rebound effect:
Unusual excitement (paradoxical reaction), restlessness, nervousness, increase of dreams, nightmares and trouble sleeping. *(USP DI, 1996, p. 1890; AHFS, 1990, p. 1291, 1292)*

Midazolam *(BZD short action, supporting the general anesthesia)*
Therapeutic indications: Conscious sedation.
Rebound effect:
Excitement, anxiety, nervousness, irritability or restlessness non-standard (paradoxical reaction); insomnia and sleep disorders. *(USP DI, 1996, p. 2074; AHFS, 1990, p. 1266)*
Author(s): Kales A; Soldatos CR; Bixler EO; Goff PJ; Vela-Bueno A / Title: Midazolam: dose-response studies of effectiveness and rebound insomnia. / Source: *Pharmacology*. 1983. 26(3). P 138-49. / Abstract: Midazolam, an investigational hypnotic, was evaluated for effectiveness, side effects, and withdrawal phenomena in doses of 10, 20, and 30 mg in three separate sleep laboratory studies, each including 4 placebo-baseline nights, 7 drug nights, and 3 placebo-withdrawal nights. Only a slight to moderate degree of effectiveness was shown across the three doses; this effectiveness was much more pronounced during the first third of the night. There was no dose-response effect for effectiveness with either initial or continued drug administration. In general, there was less effectiveness on the last 3 drug nights, indicating a potential for the development of tolerance over a relatively short period of time. Following withdrawal there was a marked dose-related worsening of sleep above baseline levels (rebound insomnia).
Author(s): Hegelbach-Feller DA; Tschopp JM; Christeller S; Fabre J / Institution: University of Geneva, Department of Medicine, Medical Policlinic, Switzerland. / Title: Comparison of the short-acting benzodiazepines midazolam and triazolam with placebo. / Source: *Arzneimittelforschung*. 1988 Mar. 38(3). P 387-92. / Abstract: The hypnotic effect of midazolam (Dormicum, 15 mg) and triazolam (0.5 mg) were compared with each other and with a placebo. Their effects on the quality of dreams and of morning awaking were also evaluated. 30 out-patients were included in a double-blind cross-over study for a period of 11 consecutive nights in which the order of the drugs was randomized according to the Latin squares method. The active substances and the placebo were each administered in 3-night blocks separated from each other by an intercalary placebo night. On waking each morning the patients answered a questionnaire concerning the previous night. Some of the responses were recorded on a visual analogue scale. Midazolam and triazolam significantly decreased the latency of onset of sleep and the number of nocturnal and premature morning awakenings. The patients' overall impression of their night was better under the active drugs than under placebo. However, there were no differences between placebo and the benzodiazepines as far as side effects or the quality of dreams and of morning awakening were concerned. The two drugs had an identical effect on sleep latency, but under midazolam the patients woke more frequently during the night and slightly earlier in the morning, suggesting that the duration of action is shorter. The intercalary placebo nights were better after 3 nights of placebo than after 3 nights of benzodiazepine. This rebound effect was more marked after triazolam than after midazolam. In conclusion the two benzodiazepines were both effective and well tolerated but midazolam is slightly shorter acting and has slightly less rebound effect than triazolam.
Author(s): Luger TJ; Morawetz RF; Mitterschiffthaler G / Institution: Univ. Klinik fur Anaesthesie und Allgemeine Intensivmedizin, Innsbruck, Austria. / Title: Additional subcutaneous administration of flumazenil does not shorten recovery time after midazolam. / Source: *Br J*

Anaesth. 1990 Jan. 64(1). P 53-8. / Abstract: We assessed the efficacy of subcutaneous administration of flumazenil (Anexate, Roche), a specific benzodiazepine antagonist, in preventing resedation after initial reversal of midazolam sedation in 30 patients (ASA I-II) undergoing gynaecological surgery. In the post-operative period, the patients received flumazenil i.v. and placebo s.c. (group A), flumazenil i.v. and flumazenil s.c. (group B), or placebo i.v. and placebo s.c. (control group) in a randomized, double-blind procedure. Flumazenil (group A: 0.47 (SD 0.12) mg i.v., group B: 0.48 (0.06) mg i.v.) was significantly more effective than placebo in antagonizing the sedative effects of midazolam, but was accompanied by rebound sedation after 90 min. Additional s.c. administration of flumazenil 0.1 mg (group B) did not eliminate resedation. Undesirable side effects include nausea and vomiting. Local tolerance of the subcutaneous administration of flumazenil was good.

Morphine

Therapeutic indications: Sedation, anesthesia adjunct.

Rebound effect:

Author(s): van der Laan JW; de Groot G / Institution: National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands. / Title: Changes in locomotor-activity patterns as a measure of spontaneous morphine withdrawal: no effect of clonidine. / Source: *Drug Alcohol Depend*. 1988 Oct. 22(1-2). P 133-40. / Abstract: The anti-withdrawal action of clonidine was studied in a model of spontaneous morphine withdrawal in rats. After withdrawal the behaviour of the animals was registered continuously for several days. In the initial phase of induction of dependence the locomotor activity was enhanced during daytime. Partial tolerance to this increase developed in the course of 3 weeks. In morphine withdrawn animals the activity decreased strongly at night, and this effect was maximal on the second night after removal of morphine. After four nights the nightly activity was restored. Treatment with clonidine (100 micrograms/kg s.c. twice daily) changed neither the observed decrease in nightly locomotor activity nor other withdrawal symptoms such as a decrease in food intake and loss of body weight. In non-dependent animals clonidine induced a biphasic effect in locomotor activity, i.e. a decrease in the first few hours of the night and an increase in the second part of the night. The latter can be interpreted as a rebound phenomenon occurring after only three injections. It was concluded that clonidine was not effective as an anti-withdrawal compound in a model for spontaneous morphine abstinence. The low incidence of symptoms relating to a hyperactive sympathetic system during spontaneous withdrawal may be an explanation for the absence of an effect of clonidine.

Author(s): Magnus-Ellenbroek B; Havemann-Reinecke U / Institution: Psychiatric Hospital, University of Gottingen, Federal Republic of Germany. / Title: Morphine-induced hyperactivity in rats - a rebound effect? / Source: *Naunyn Schmiedebergs Arch Pharmacol*. 1993 Jun. 347(6). P 635-42. / Abstract: The behavioural nature of the delayed hyperactivity induced by systemic administration of morphine was studied in rats. Different components of motility induced by morphine with or without naloxone or haloperidol at different times were analyzed by observation and quantified by an Opto-Varimex-3 Activity Meter. By this automatic recording system motility was discriminated into horizontal and two different vertical components and the total distance run by each of the rats was quantified by a computer program. Simultaneously the running pattern was recorded by a XY-plotter. By means of these recordings, three subsequent phases of behaviour could be recorded after morphine (15 mg/kg i.p.): 1. a depressed phase (akinesia) lasting 1.5-2 h, followed, 2. by an intermediate phase for 1-1.5 h, still dominated by akinesia but interrupted by sudden bursts of hyperactivity. Finally, 3. a hyperactivity phase lasted for 1.5-2 h, characterized by an equal enhancement of locomotor activity and stereotypy. After 30 mg/kg of morphine the hyperactivity was predominantly characterized by locomotor activity and stereotypy and rearing were less prominent than after the smaller dose. Naloxone (2 mg/kg i.p.) given at the beginning of the hyperactivity phase significantly antagonized rearing but not other motility parameters.

However, coadministration of naloxone (2 mg/kg i.p.) simultaneously with morphine (15 mg/kg) clearly antagonized akinesia and completely prevented the development of the delayed hyperactivity. Haloperidol (0.2 mg/kg i.p.) at the beginning of the hyperactivity phase clearly antagonized all of the motility parameters seen during this phase.

Promethazine *(antihistamine, adjunct to general anesthesia)*
Therapeutic indications: Sedation.
Rebound effect:
Excitement, nervousness, anxiety and irritability euphoria, continuous and unusual (paradoxical reaction); sleep disturbances and nightmares. *(USP DI, 1988, p. 1845; AHFS, 1990, p. 1294, 1295)*

Trazodone *(antidepressant)*
Therapeutic indications: Depression, hypnotic.
Rebound effect:
Author(s): Montgomery I; Oswald I; Morgan K; Adam K / Title: Trazodone enhances sleep in subjective quality but not in objective duration. / Source: *Br J Clin Pharmacol*. 1983 Aug. 16(2). P 139-44. / Abstract: Nine volunteer poor sleepers, of mean age 61 years, took trazodone 150 mg nightly for 3 weeks, preceded by 2 weeks and followed by 1 week of matching blanks, in order to examine the effects of electrophysiologically-recorded and subjectively-rated sleep. The second of the initial weeks of matching blanks served as a baseline week. In the subjective ratings, sleep improved in quality on trazodone, significantly so in the first and second weeks of intake, though with significant rebound insomnia on the second withdrawal night. Trazodone halved the frequency of arousals interrupting sleep, and it reduced the time spent in stage 1 (drowsiness). It increased the duration of slow-wave sleep (stages 3 + 4), with a negative rebound following withdrawal. It reduced the time spent in REM sleep, with a rebound above baseline levels after withdrawal. Trazodone did not change total sleep duration, nor the time required to fall asleep. The effects of trazodone were sustained or became enhanced during the period of intake. They persisted for over 24 h after the last dose, and rebound effects were maximal on the second withdrawal night.
Author(s): Otani K; Tanaka O; Kaneko S; Ishida M; Yasui N; Fukushima Y / Institution: Department of Neuropsychiatry, Hirosaki University Hospital, Japan. / Title: Mechanisms of the development of trazodone withdrawal symptoms. / Source: *Int Clin Psychopharmacol*. 1994 Summer. 9(2). P 131-3. / Abstract: Three cases developed withdrawal symptoms of trazodone despite gradual discontinuation of therapeutic doses of the drug. This report suggests that effects of trazodone and its metabolite m-chlorophenylpiperazine on the serotonergic system, which may result in noradrenergic rebound after discontinuation, and short half-lives of these compounds are involved in the development of these symptoms. From a clinical point of view, we suggest that trazodone should be tapered off at a very slow rate.

Zopiclone
Therapeutic indications: Sedation, insomnia.
Rebound effect:
Author(s): Lader M; Frcka G / Title: Subjective effects during administration and on discontinuation of zopiclone and temazepam in normal subjects. / Source: *Pharmacopsychiatry*. 1987 Mar. 20(2). P 67-71. / Abstract: The purpose of the study was to ascertain whether the new hypnotic, zopiclone, was likely to produce rebound problems after short-term use, in comparison with placebo and a standard hypnotic, temazepam, and whether tapering the dosage lessened any such effects. Ten normal volunteer subjects were administered 5 treatment sequences, each lasting 4 weeks, using a balanced design, with at least 2 weeks between sequences. The treatment sequences

were: (table: see text) Each drug was given at night before retiring to bed. Daily ratings comprised a Sleep Questionnaire, Mood Rating Scales, the Spielberger State Anxiety Inventory and Bodily Symptom Scales. Both drugs improved quality of sleep but their discontinuation was followed by some worsening which was postponed but not avoided by halving the dosage for a week. Speed of, and feeling on, awakening showed discontinuation effects with temazepam but not with zopiclone. Zopiclone was associated with feelings of being troubled, tense, antagonistic and bored whereas temazepam produced drowsiness, clumsiness, dreaminess and sadness. Some increase in these ratings was noted after stopping temazepam and these were less after having the dosage. Zopiclone was associated with minimal such effects. For bodily symptoms, zopiclone produced some headache, a metallic taste, and some blurring of vision; temazepam induced nausea, memory impairment and pins and needles. Withdrawal effects on bodily symptom ratings were inconsistent and not affected by tapering off the dose. In conclusion, the administration of zopiclone tends to be associated with some dysphoric effects, temazepam with sedation. Rebound effects are minimal with zopiclone and reducing the dosage gradually does not seem necessary.

Author(s): Pecknold J; Wilson R; le Morvan P / Institution: Department of Psychiatry, McGill University, Montreal, Canada. / Title: Long term efficacy and withdrawal of zopiclone: a sleep laboratory study. / Source: *Int Clin Psychopharmacol*. 1990 Apr. 5 Suppl 2P 57-67. / Abstract: The purpose of this study was to evaluate the short, intermediate, and long-term (8 weeks) effectiveness, as well as the withdrawal effects of zopiclone 7.5 mg. Eleven chronic insomniacs participated in the study where both EEG sleep recordings and a subjective rating scale were used to evaluate drug effects. Zopiclone significantly decreased total wake time and nocturnal awakenings, and increased total sleep time and sleep efficiency. These effects were apparent from first treatment night and tolerance to the hypnotic effect did not develop over the 8 weeks of treatment. The subjective sleep questionnaire data showed significantly decreased sleep latency time but otherwise were consistent with the sleep laboratory findings. Zopiclone decreased the percentage of Stage 1 sleep but did not significantly alter the percentage of Stage 2 sleep, slow wave sleep or REM sleep. The withdrawal of zopiclone was associated with a return of sleep variables towards pre-treatment baseline values. Although 2 patients dropped out, 1 with a marked rebound insomnia and daytime anxiety during the first week of withdrawal, the other because of side-effects and poor hypnotic efficiency, no evidence of rebound insomnia was seen on the sleep EEG or subjective questionnaire data in the study population.

Author(s): Wadworth AN; McTavish D / Institution: Adis International Limited, Auckland, New Zealand. / Title: Zopiclone. A review of its pharmacological properties and therapeutic efficacy as an hypnotic. / Source: *Drugs Aging*. 1993 Sep-Oct. 3(5). P 441-59. / Abstract: Zopiclone is a cyclopyrrolone which is chemically unrelated to the benzodiazepines and is thought to act on the GABAA receptor complex at a site distinct from, but closely related to, the benzodiazepine binding site. The hypnotic efficacy of zopiclone administered as single oral doses has been demonstrated in patients undergoing next-day surgery and in patients with insomnia, and these studies have established an optimal dose of 7.5mg for elderly patients. Using this dose, clinical studies have shown that zopiclone improved sleep in elderly patients to a similar extent as triazolam 0.125 to 0.5mg, flurazepam 15mg, and nitrazepam 5mg. Studies that also included younger patients have shown that zopiclone 7.5mg is at least as effective as triazolam 0.25 or 0.5mg, and on most sleep parameters is comparable to temazepam 20mg, nitrazepam 5mg, flunitrazepam 2mg, and flurazepam 20mg. Zopiclone causes minimal impairment to psychomotor performance and mental alertness the morning after night-time administration. The drug is generally well tolerated by patients of all ages; the most frequently reported adverse effects being bitter taste and dry mouth. Treatment withdrawal due to adverse effects is seldom required and reports of rebound insomnia after zopiclone withdrawal are rare. While symptoms of physical dependence have not been observed in clinical studies, there have been isolated reports of physical dependence in patients with a history of substance abuse. Although the latter finding should be kept in mind, it appears that

zopiclone has a low dependence liability. Thus, with its short duration of action and good tolerability profile, zopiclone is a well established alternative to the benzodiazepine hypnotics and may be particularly beneficial in those patients unable or unwilling to tolerate the residual effects associated with many other hypnotic agents.
Author(s): Soldatos CR; Dikeos DG; Whitehead A / Institution: Department of Psychiatry, University of Athens, Greece. / Title: Tolerance and rebound insomnia with rapidly eliminated hypnotics: a meta-analysis of sleep laboratory studies. / Source: *Int Clin Psychopharmacol.* 1999 Sep;14(5):287-303. / Abstract: Differences in development of tolerance and occurrence of rebound insomnia have been well established between rapidly and slowly eliminated benzodiazepine hypnotics. Based on meta-analytic methodology, this study assesses whether there are such differences among the rapidly eliminated benzodiazepine and benzodiazepine-like hypnotics (brotizolam, midazolam, triazolam, zolpidem and zopiclone). All sleep laboratory studies of these drugs (n = 137) published from 1966 to 1997 were obtained, mainly through a MEDLINE search. Rigorous selection criteria resulted in the inclusion of 75 studies employing 1276 individuals (804 insomniacs and 472 healthy volunteers). Using a mixed effects regression model, reliable estimation of the effects on insomniacs of the recommended dose of each drug could be obtained. All five rapidly eliminated hypnotics showed statistically significant initial efficacy. Tolerance with intermediate and long-term use was clearly developed with triazolam and was only marginal with midazolam and zolpidem; it could not be estimated for brotizolam or zopiclone because of insufficient data. Rebound insomnia on the first withdrawal night was intense with triazolam and mild with zolpidem; data were unavailable for brotizolam and inadequate for midazolam and zopiclone. In conclusion, there are differences among the rapidly eliminated hypnotics with respect to tolerance and rebound insomnia suggesting that, in addition to short elimination half-life, other pharmacological properties are implicated in the mechanisms underlying these side-effects.

Tetrahidrocanabinol (THC) - Dronabinol

Rebound effect:

Chronic use of Dronabinol (indicated to nausea, vomiting and anorexia nervosa) cause decreased motivation, cognition, perception and judgment; abrupt suspension of drugs cause irritability, insomnia and restlessness, which remain for a few weeks. *(USP DI, 1996, p. 1310)*

Author(s): Karler R; Calder LD; Turkanis AS / Title: Prolonged CNS hyperexcitability in mice after a single exposure to delta-9-tetrahydrocannabinol. / Source: *Neuropharmacology*. 1986 Apr. 25(4). P 441-6. / Abstract: A single exposure to delta-9-tetrahydrocannabinol (THC) resulted in a "rebound" hyperexcitability in the CNS in mice, which was assessed in terms of the susceptibility of the CNS to electrically-induced convulsions. The magnitude of the hyperexcitability was dose-related (25-150 mg/kg, i.p.), as measured 24 hr after treatment. The time-course study of the effect indicated a peak-effect at 24 hr after administration of the drug, with a duration of the effect for as long as 196 hr. The time course of the rebound hyperexcitability to THC was compared to that for phenobarbital, which peaked at 48 hr after administration of the drug and returned to the control value by 96 hr. Tolerance developed rapidly to the motor-toxic effect of THC, but after 23 days of daily treatment there was no evidence of tolerance to the rebound hyperexcitability. The functional significance of the hyperexcitable state was assessed in two tests; electrical kindling to minimal convulsions was enhanced, even when the kindling procedure was initiated 120 hr after exposure to the drug; and the anticonvulsant activity of phenytoin was blocked when mice were treated with the anticonvulsant 96 hr after a single exposure to THC. The results suggest that the rebound response from a single exposure to THC represents a functionally significant prolonged increase in excitability of the CNS.

CNS stimulating drugs

Amphetamines *(Amphetamine, Dexamphetamine, Fenfluramine, Methamphetamine)*
Therapeutic indications: Attention deficit syndrome, narcolepsy, suppression of appetite.
Rebound effect:
After stimulant effects (increased motor activity and alertness, drowsiness and decrease the feeling of fatigue) occurs tiredness or weakness; unusual drowsiness, tremor and depression. *(USP DI, 1996, p. 93; AHFS, 1990, p. 1219, 1227)*
Author(s): Porrino LJ; Rapoport JL; Behar D; Ismond DR; Bunney WE Jr / Title: A naturalistic assessment of the motor activity of hyperactive boys. Stimulant drug effects. / Source: *Arch Gen Psychiatry*. 1983 Jun. 40(6). P 688-93. / Abstract: Twenty-four-hour motor activity was assessed in a naturalistic setting in 12 hyperactive boys for four weeks (672 consecutive hours). Dextroamphetamine, 15 mg/day, or placebo was administered on alternate weeks, using a double-blind ABAB design. When the boys received dextroamphetamine, motor activity was significantly decreased for about eight hours after drug administration. This decrease was followed by a period of slight but significant increases in activity ("rebound"). Dextroamphetamine decreased activity most strikingly during structured classroom activity; during physical education, however, there was a significant drug-induced increase in motor activity.
Author(s): Hernandez L; Parada M; Hoebel BG / Title: Amphetamine-induced hyperphagia and obesity caused by intraventricular or lateral hypothalamic injections in rats. / Source: *J Pharmacol Exp Ther*. 1983 Nov. 227(2). P 524-30. / Abstract: Overeating and obesity relative to controls was produced by multiple bilateral injections of 0.5 mg of amphetamine in the lateral ventricles of female rats eating a palatable, high fat diet. This behavioral and physiological rebound following the expected period of anorexia was accompanied by long-term depletion of dopamine in the striatum and of norepinephrine in the hypothalamus. This suggested the next experiment in which 50 micrograms of amphetamine were injected repeatedly in the lateral hypothalamus; again a brief period of anorexia was followed by hyperphagia and chronic obesity. This suggests that amphetamine acts in the lateral hypothalamus not only to suppress feeding, but in high doses it may also have local neurotoxic effects that cause an upward shift in body weight maintained by overeating.
Author(s): Wolgin DL; Salisbury JJ / Title: Amphetamine tolerance and body weight set point: a dose-response analysis. / Source: *Behav Neurosci*. 1985 Feb. 99(1). P 175-85. / Abstract: The theory that amphetamine anorexia and tolerance reflect the lowering of a set point for body weight regulation was evaluated. In the first experiment, rats given either 2 or 4 mg/kg d-amphetamine and access to milk ultimately achieved comparable levels of tolerance and maintained their weight at 94%-96% of control levels. Thus, the level of maintained body weight was not dose-dependent. In the second experiment, increasing the doses resulted in renewed anorexia and weight loss, and the appearance of behavioral stereotypies. Whereas mean intake then recovered, body weight remained at 79%-82% of control levels. However, milk intake for individual rats was extremely variable. Such variability is inconsistent with the notion that body weight was actively regulated by caloric intake. Drug withdrawal had little further effect on intake, and it led to weight "rebound" in only one group. When subsequently retested with the original doses, both groups were again anorexic and showed more intense stereotypy. This finding suggests that drug withdrawal caused a general increase in sensitivity to amphetamine, rather than a set-point-related change in feeding. Taken together, the data do not support the set point theory of amphetamine tolerance.
Author(s): Winslow JT; Insel TR / Institution: National Institute of Mental Health, Poolesville, Maryland. / Title: Serotonergic modulation of rat pup ultrasonic vocal development: studies with 3,4-methylenedioxymethamphetamine. / Source: *J Pharmacol Exp Ther*. 1990 Jul. 254(1). P 212-

20. / Abstract: 3,4-Methylenedioxymethamphetamine (MDMA) has previously been shown to destroy serotonin terminals in the rat brain. Despite profound and prolonged loss of serotonin innervation, long-term behavioral effects of MDMA have not previously been reported. In this study, we monitored the short- and long-term effects of MDMA administration on the ultrasonic isolation call of the rat pup. At 30 to 60 min after a single dose of MDMA (0.5-10.0 mg/kg), isolation calls decreased as much as 90%, with a rebound increase in calling noted 10 to 25 h following administration of the highest dose. Repeated administration of 10 mg/kg MDMA (once or twice daily on postnatal days 1-4) resulted in a lasting, dose-dependent decrease in ultrasonic vocalization monitored on days 6, 9, 12 and 15. Concurrent measures of locomotor behavior, geotaxis and weight gain were not altered subsequent to repeated MDMA treatment. Both serotonin content and serotonin terminals (assessed by [3H]paroxetine binding) in cortex were reduced by repeated MDMA treatment, whereas concentrations of catecholamines and their metabolites were unaltered. Repeated prenatal MDMA exposure did not affect postnatal rates of calling or the biochemical markers of serotonin in cortex. Pups lesioned with MDMA postnatally showed not only long-term behavioral and biochemical changes but also altered responsiveness to the serotonin 1B agonist 1-[3-(trifluromethyl)phenyl]piperazine. Taken together, these studies indicate that serotonergic lesions in a sensitive phase of development can have long-term selective effects on the rat pup ultrasonic isolation call, a behavior critical for mother-infant affiliation.
Author(s): Touret M; Sallanon-Moulin M; Jouvet M / Institution: Department of Experimental Medicine, Claude Bernard University, Lyon, France. / Title: Awakening properties of modafinil without paradoxical sleep rebound: comparative study with amphetamine in the rat. / Source: *Neurosci Lett*. 1995 Apr 7. 189(1). P 43-6. / Abstract: We have studied the effect of modafinil and amphetamine, two waking drugs, on the sleep-wake cycle of Sprague-Dawley rat. Both modafinil (64 or 128 mg/kg) and amphetamine (2.5 or 5 mg/kg) cause a dose dependent increase in wakefulness. However, amphetamine wakefulness is followed by a paradoxical sleep rebound on the injection day, whereas modafinil does not produce this effect. In modafinil-treated rats, the sleep pattern on the post-injection day is similar to that of controls, while that of amphetamine-treated rats is modified.

Caffeine
Therapeutic indications: Fatigue, drowsiness.
Rebound effect:
CNS depression. *(AHFS, 1990, p. 1235)*
Author(s): Golda V / Institution: Institute of Experimental Neurosurgery, Hradec Kralove. / Title: Motor depression induced by rapid repeated transposition of rat: effect of diazepam, tranylcypromine and caffeine treatment. / Source: *Sb Ved Pr Lek Fak Karlovy Univerzity Hradci Kralove*. 1994. 37(1). P 37-42. / Abstract: Experiments were carried out in the adult males and females rats of Wistar strain (n = 80) and in the adult males and females of the genetically hypertensive rats of Koletsky type (n = 80). Total time of locomotor-exploratory activity was traced ten minutes in the great box; eight animals per group were used. In the second experimental arrangement the locomotor-exploratory activity was traced three minutes in great box, one minute in rearing box and six minutes again in the great box; eight animals per group were used. In separate groups of animals in second experimental arrangement locomotor-exploratory activity was traced under tranylcypromine (5 mg/kg), diazepam (0.5 mg/kg) and caffeine (10 mg/kg) of b.w. Motor depression induced by rapid repeated transposition of the rats from one box to the other one shows the highest level during the first, second and third minute after the last transposition (see the fifth, sixth and seventh minute in the Tables). During the fourth, fifth and sixth minute after the last transposition "rebound effect" can be found, i.e., elevation of locomotor-exploratory activity relative to the activity registered during former three minute interval. Considering the statistically

significant changes in the locomotor-exploratory activity in the first, second and third minute after the last transposition, tranylcypromine in the normotensive rats of both sexes and in the genetically hypertensive rats of both sexes in all three minutes alleviates the motor depression.

Cocaine

Rebound effect:

Author(s): Frank RA; Manderscheid PZ; Panicker S; Williams HP; Kokoris D / Institution: Department of Psychology, University of Cincinnati, OH 45221-0376. / Title: Cocaine euphoria, dysphoria, and tolerance assessed using drug-induced changes in brain-stimulation reward. / Source: *Pharmacol Biochem Behav*. 1992 Aug. 42(4). P 771-9. / Abstract: The time course of cocaine-induced changes in self-stimulation thresholds were used to evaluate cocaine euphoria and dysphoria as a function of the chronicity of drug treatment, dosage level, and the spacing of injections. It was assumed that cocaine-induced decreases in thresholds were indicative of cocaine euphoria, while increases in thresholds reflected rebound dysphoric responses to cocaine administration. Three experiments were performed using self-stimulating rats implanted with ventral tegmental area electrodes. Cocaine's threshold-lowering effects were evident 15 min postinjection (IP) with thresholds returning to baseline by approximately 3.0 h after treatment. Little evidence for cocaine-induced increases in thresholds was observed during periods of chronic cocaine treatment. However, thresholds were slightly elevated upon withdrawal from chronic cocaine treatment in Experiments 2 and 3. No evidence of tolerance or sensitization to cocaine-induced shifts in thresholds was noted with single daily injections, while multiple daily injections produced tolerance to cocaine's threshold-lowering effects. It is concluded that cocaine's ability to enhance brain-stimulation reward is highly reliable and robust, while decreases in brain-stimulation reward associated with chronic cocaine treatment are less reliable and difficult to demonstrate. The possible influence of drug dosage on the induction of cocaine dysphoria and the ability of various self-stimulation procedures to measure dysphoric effects are discussed.

Author(s): Watson R; Bakos L; Compton P; Gawin F / Institution: New Haven Sleep Disorders Center, Connecticut 06511. / Title: Cocaine use and withdrawal: the effect on sleep and mood. / Source: *Am J Drug Alcohol Abuse*. 1992. 18(1). P 21-8. / Abstract: Three recreational cocaine users (age, 26.7 years), after one adaptation night, spent 5 days and nights in the laboratory where their EEG, EOG, and submental EMG were recorded during all of their sleep. On the second afternoon and evening of the study, subjects used an estimated 1 to 2 g cocaine intranasally. They all slept between 2:00 A.M. and 9:00 A.M. that night. Blood samples were drawn each evening and morning. Absolute plasma cocaine levels and patterns of elimination were consistent with subjects report of dose and time of administration. Mood ratings were made repeatedly throughout the study. There was suppression of REM sleep during the use of cocaine followed by a rebound which is specific to REM sleep and is not seen in other stages of sleep. REM variables subsided to normal levels on the third recovery night following cocaine use.

Mazindol

Therapeutic indications: Promotes the loss of appetite, secondary to stimulation of CNS.

Rebound effect:

With the suspension of drugs occur extreme fatigue and depression. *(AHFS, 1990, p. 1226)*

Methylphenidate

Therapeutic indications: Attention deficit syndrome, narcolepsy.

Rebound effect:

Unusual tiredness or weakness; severe depression. *(USP DI, 1996, p. 2041)*

Severe depression, fatigue and drowsiness; these symptoms may persist for a long time. *(AHFS, 1990, p. 1228)*

Author(s): Pizzi WJ; Rode EC; Barnhart JE / Institution: Department of Psychology, Northeastern Illinois University, Chicago 60625. / Title: Differential effects of methylphenidate on the growth of neonatal and adolescent rats. / Source: *Neurotoxicol Teratol*. 1987 Mar-Apr. 9(2). P 107-11. / Abstract: Methylphenidate (MPH), the drug of choice in the treatment of Attention Deficit Disorders with Hyperactivity (ADD/H), has raised concern regarding its suspected potential for reducing body stature in growing patients. In a previous study we demonstrated that neonatal rats treated with MPH (35 mg/kg, SC, twice daily) showed an acute growth impairment followed by a rapid growth-rebound phenomenon. This report confirms our earlier findings in neonatal rats and extends the investigation of the growth suppressing effects of MPH to the periadolescent period of development in rats. Specifically, neonatal groups of male and female rats treated with higher and lower doses of MPH than in the original study confirmed the growth impairment and growth rebound phenomena reported earlier. Unlike neonatal rats, rats treated during the periadolescent period of development failed to show any growth impairment. These data suggest that the growth suppressing effects of MPH are the result of an acute toxicity which is readily reversible on discontinuation of the drug. Further, it is concluded that there is a low probability of long term effects on human body stature when the minimal therapeutic dose is used in clinical practice.

Author(s): Klein RG; Landa B; Mattes JA; Klein DF / Institution: Long Island Jewish Medical Center, Hillside Division, Glen Oaks, NY. / Title: Methylphenidate and growth in hyperactive children. A controlled withdrawal study. / Source: *Arch Gen Psychiatry*. 1988 Dec; 45(12): 1127-30. / Abstract: The effect of stimulants on growth has been controversial. Among hyperactive children receiving long-term methylphenidate hydrochloride treatment, we examined the effects of methylphenidate withdrawal on the growth of hyperactive children randomly assigned to be taken off, or remain on, the medication regimen over two consecutive summers. After one summer, no group difference in height was found, but weight was higher in the group that had been taken off methylphenidate therapy. In contrast, two summers of being off methylphenidate treatment had a significant positive effect on height but not on weight. The results document a linkage between exposure to methylphenidate and reduction in growth velocity. However, they do not address whether the medication has long-term effects on height.

Author(s): Klein RG; Mannuzza S / Institution: New York State Psychiatric Institute, NY 10032. / Title: Hyperactive boys almost grown up. III. Methylphenidate effects on ultimate height. / Source: *Arch Gen Psychiatry*. 1988 Dec. 45(12). P 1131-4. / Abstract: The height of young adults who were treated with methylphenidate hydrochloride in childhood because of hyperactivity (average daily dose, 45 mg; duration of treatment, six months to five years) was studied. There was no significant difference in height between the treated patients (n = 61) and controls (n = 99); both groups were at the national US norm in stature. The findings indicated that methylphenidate therapy does not compromise final height, even when it has an adverse impact on children's growth rate during the active treatment phase. A compensatory growth rate, or growth rebound, appears to occur following discontinuation of stimulant therapy.

effects on human body stature when the minimal therapeutic dose is used in clinical practice.

Pemoline

Therapeutic indications: Attention deficit syndrome.

Rebound effect:

Severe depression, fatigue and weakness; unusual drowsiness. *(USP DI, 1996, p. 2295)*

Antidepressant drugs

MAO inhibitors antidepressants *(Isocarboxazid, Phenelzine, Tranylcypromine)*
Therapeutic indications: Depression, panic disorder, anxiety.
Rebound effect:
Drowsiness, tiredness and unusual severe weakness. *(USP DI, 1996, p. 262)*
Anxiety and depression. *(AHFS, 1990, p. 1151)*

Tricyclic antidepressants *(Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin, Imipramine, Nortriptyline, Protriptyline, Trimipramine)*
Therapeutic indications: Depression.
Rebound effect:
Anxiety, drowsiness, tiredness and unusual severe weakness. *(USP DI, 1996, p. 268)*
Exacerbation of hypomania, depression, panic or anxiety. *(AHFS, 1990, p. 1157)*
Author(s): Obal F Jr; Benedek G; Lelkes Z; Obal F / Title: Effects of acute and chronic treatment with amitryptyline on the sleep-wake activity of rats. / Source: *Neuropharmacology*. 1985 Mar. 24(3). P 223-9. / Abstract: Amitriptyline (1, 5 or 15 mg/kg intraperitoneally, twice a day) was administered to rats and the sleep-wake activity was recorded for either 24 hr (1 mg/kg) or 12 hr (5 or 15 mg/kg) on the day before treatment with amitriptyline, on days 1 and 5 of the treatment and on day 6, when the drug was withdrawn. In the first 3 hr amitriptyline increased non-REM sleep (NREMS), and decreased REM sleep (REMS) and wakefulness; the effects were dose-dependent. The changes in non-REM sleep and wakefulness (W) were followed by a compensatory reaction 6-12 hr after the treatment. The effects of chronic injection of amitriptyline on non-REM sleep revealed a definite decrease only in the case of the 15 mg/kg dose. Rebound of REM sleep appeared after withdrawal of the 5 and 15 mg/kg doses. Amitriptyline at 1 mg/kg had no effect on the sleep-wake activity during the dark period. The results show that the increase in non-REM sleep is as characteristic of amitriptyline as the reduction of REM sleep, and that these effects are resistant to chronic treatment when the dose is small.
Author(s): Corral M; Sivertz K; Jones BD / Institution: Department of Psychiatry, UBC Health Sciences Centre Hospital, Vancouver. / Title: Transient mood elevation associated with antidepressant drug decrease. / Source: *Can J Psychiatry*. 1987 Dec. 32(9). P 764-7. / Abstract: The development of hypomania, mania and transient mood elevation within 2-3 days of antidepressant discontinuation, and lasting days to several weeks has been reported in unipolar depressed patients. Imipramine and desipramine are the antidepressants most frequently associated with the above phenomena. A reported case of transient mood elevation following abrupt reduction but not discontinuation of desipramine therapy in a woman with unipolar depression is described. The phenomenon was observed and documented on two separate occasions. Mood elevation occurred despite decreased plasma levels of the drug. Relapse followed despite maintenance of dose and similar drug plasma levels. Factors which could account for the transitory improvement of mood are examined. It is suggested that the patient's improvement in mood may have occurred due to a rebound paradoxical therapeutic effect. The features of the presented case history which appear to support this hypothesis are discussed. Also the clinical implications of this phenomenon are reviewed.
Author(s): Steiger A / Institution: Department of Psychiatry, University of Mainz, Federal Republic of Germany. / Title: Effects of clomipramine on sleep EEG and nocturnal penile tumescence: a long-term study in a healthy man. / Source: *J Clin Psychopharmacol*. 1988 Oct. 8(5). P 349-54. / Abstract: The effects of the tricyclic antidepressant clomipramine on sleep EEG and nocturnal penile tumescence (NPT) were investigated during a long-term study in a normal male control subject. During 21 consecutive days the subject received first placebo for 3 days, then stepwise increasing dosages of clomipramine for 10 days, and finally placebo after withdrawal for 8

days. Under clomipramine, rapid eye movement (REM) sleep was suppressed markedly; an REM rebound occurred after withdrawal. Awake and stages 1 and 2 increased while slow wave sleep was diminished under clomipramine. Those non-REM parameters returned to baseline values after drug cessation. NPT was reduced simultaneously with REM sleep under clomipramine 30 to 75 mg. Under this dosage range, full erections occurred during the later hours of sleep in association with the delayed REM periods. Clomipramine 100 mg prompted a further decrease of NPT, which exceeded the REM suppression. Most of the changes and NPT parameters depended significantly on the dosage and the plasma concentration of clomipramine. After withdrawal, NPT needed 6 days to normalize. Although NPT was disturbed distinctly, no erectile dysfunction, but a decrease of sexual interest and, once, a lack of ejaculation, were reported.

Author(s): Gillin JC; Sutton L; Ruiz C; Darko D; Golshan S; Risch SC; Janowsky D / Institution: Department of Psychiatry, San Diego Veterans Administration Medical Center, CA. / Title: The effects of scopolamine on sleep and mood in depressed patients with a history of alcoholism and a normal comparison group. / Source: *Biol Psychiatry*. 1991 Jul 15. 30(2). P 157-69. / Abstract: In order to determine the effect of an anticholinergic agent on mood and sleep, scopolamine (0.4 mg IM) was administered before bedtime for three consecutive nights to 10 depressed patients (8 with a history of alcohol abuse) and 10 normal comparison subjects. The patients had a small, statistically significant antidepressant response on the second morning of treatment. Scopolamine inhibited rapid eye movement (REM) sleep and prolonged REM latency equally in depressed patients and the normal comparison group. Partial tolerance to the REM inhibiting effect of scopolamine developed between the first and third night of treatment. A REM rebound occurred during recovery nights. These results are consistent with concepts relating central cholinergic mechanisms to the control of REM sleep. Compared with controls, patients showed a greater increase in Stage 2 and Stage 2% and a lesser and increase in Delta (Stage 3 and 4) sleep % and Stage 4% on the first night of treatment. Further, well-controlled studies are needed to determine whether anticholinergic drugs possess clinically significant antidepressant effects.

Author(s): Maudhuit C; Jolas T; Lainey E; Hamon M; Adrien J / Institution: INSERM U288, CHU Pitie-Salpetriere, Paris, France. / Title: Effects of acute and chronic treatment with amoxapine and cericlamine on the sleep-wakefulness cycle in the rat. / Source: *Neuropharmacology*. 1994 Aug. 33(8). P 1017-25. / Abstract: Antidepressant drugs, such as the tricyclics and the serotonin reuptake inhibitors, are well known to decrease paradoxical sleep and occasionally increase slow wave sleep in human and in animals. In order to examine whether amoxapine (a mixed NA reuptake blocker and 5-HT2/5-HT3 antagonist) and cericlamine (a selective 5-HT reuptake inhibitor) exert the same effect in rats, and to investigate the possible relationships between sleep, the action of antidepressants and the serotoninergic system, the effects of these two different drugs were examined under acute and chronic conditions. Acutely, amoxapine (1, 5 and 10 mg/kg; i.p.) and cericlamine (1, 8, 16 and 32 mg/kg; i.p.) decreased paradoxical sleep and increased deep slow wave sleep especially when they were given at a low dose. When administered for 14 days, amoxapine induced a sustained decrease of paradoxical sleep during the whole treatment, while some tolerance was observed with regard to the inhibitory effect of cericlamine on this state of sleep. In addition, a rebound of paradoxical sleep occurred on the first day of cericlamine withdrawal. Thus, amoxapine and cericlamine exerted the same effects on the states of vigilance in the rat as do other antidepressants. The effects of cericlamine on sleep probably reflect its blocking action on 5-HT uptake, whereas the more complex effects of amoxapine might involve its 5-HT2/5-HT3 antagonist properties.

Author(s): Kupfer DJ; Pollock BG; Perel JM; Miewald JM; Grochocinski VJ; Ehlers CL / Institution: Dept. of Psychiatry, WPIC, Pittsburgh, PA 15213-2593, USA. / Title: Effect of pulse loading with clomipramine on EEG sleep. / Source: *Psychiatry Res*. 1994 Nov. 54(2). P 161-75. / Abstract: Two different initial dosing regimens with clomipramine (CMI) were used to compare early response indicators and dose strategies. Thirty-two inpatients with major depressive disorder

were randomized in a double-blind protocol. The pulse-loading group received 150 and 200 mg of CMI on 2 consecutive evenings and then received a placebo for 8 days. The traditional dosing group began at 50 mg of CMI followed by gradual increases every second day until 200 mg was reached. After 10 days, both groups were placed on an adjustable dosing schedule of CMI, initially set at 200 mg, for an additional 2 weeks. Significant drug effects were noted on several sleep parameters demonstrating suppression of rapid eye movement (REM) sleep. In the pulse-loading group, drug responders were found to have a significantly faster and more robust rebound in REM sleep than nonresponders. Both measures of REM activity and REM sleep time showed a significant difference between the groups. In addition, a significant correlation was found between falling levels of the desmethylclomipramine metabolite of CMI and REM sleep activity during the rebound phase. The clinical and theoretical implications of these findings are discussed.

Fluoxetine

Therapeutic indications: Depression, treatment of obesity (decreased appetite).

Rebound effect:

The increased appetite was reported by more than 1% of patients. *(AHFS, 1990, p. 1169)*

Author(s): McGuirk J; Muscat R; Willner P / Institution: Psychology Department, City of London Polytechnic, UK. / Title: Effects of chronically administered fluoxetine and fenfluramine on food intake, body weight and the behavioural satiety sequence. / Source: *Psychopharmacology* (Berl). 1992. 106(3). P 401-7. / Abstract: Rats were administered fenfluramine (FF: 3 mg/kg) or fluoxetine (FX: 6 mg/kg) daily for 3 weeks. On acute administration, FF suppressed consumption of 35% sucrose (in a 40 min test) and overnight chow intake. Repeated administration saw the rapid development of extensive tolerance to these effects. FF had no effects on body weight, and no withdrawal effects were apparent. FX reduced chow intake and body weight throughout the treatment period, but there was evidence of some tolerance to the suppression of chow intake and sucrose drinking. Following FX withdrawal, normal body weight was restored in 4 days; food intake was normal during this period. A delayed rebound hyperphagia commenced on day 5 of withdrawal, and persisted for at least 6 days. The behavioural satiety sequence (drinking--activity--grooming--resting) was disrupted by acute FF; on chronic treatment, FF advanced the onset of postprandial resting, but also increased drinking time. FX advanced the behavioural satiety sequence on acute administration, but not after chronic treatment. We consider the implications of these results for the use of resting behaviour as an indicator of postprandial satiety.

Author(s): Bryois C; Rubin C; Zbinden JD; Baumann P / Institution: Clinique psychiatrique universitaire, Département Universitaire de Psychiatrie Adulte (DUPA), Prilly-Lausanne. / Title: [Withdrawal syndrome caused by selective serotonin reuptake inhibitors: apropos of a case]. / Source: *Praxis* (Bern 1994). 1998 Mar 4; 87(10): 345-8. / Abstract: During the past 4 years, several case reports have been published on the withdrawal syndrome which may be observed after acute interruption of a treatment with selective serotonin reuptake inhibiting antidepressants (SSRI). Paroxetine is the most frequently cited antidepressant in the literature, whereas fluoxetine is the less frequently cited of this type of drugs. The withdrawal symptoms appear a few days after stopping treatment or after a decrease of the dose. The typical symptoms are of the gastro-intestinal type, such as loss of appetite, nausea, vomiting, diarrhea and abdominal cramps. Other symptoms are sensation of instability, vertigo, dizziness, headache, malaise, muscular pains, asthenia, as well as a syndrome of pseudo-influenza. Brief electric shocks throughout the body, which last one or two seconds, have also been reported. A case is reported in detail by the authors, who observed some of these symptoms in a patient after stopping his treatment with paroxetine. This withdrawal syndrome may be due to a rebound phenomenon of the serotonergic systems after interruption of the treatment with SSRIs. It is, therefore, recommended that treatment with SSRIs is progressively stopped over a period of several weeks.

Moclobemide
Therapeutic indications: Depression.
Rebound effect:
Author(s): Minot R; Luthringer R; Macher JP / Institution: Departmental Psychiatric Hospital, Rouffach, France. / Title: Effect of moclobemide on the psychophysiology of sleep/wake cycles: a neuroelectrophysiological study of depressed patients administered with moclobemide. / Source: *Int Clin Psychopharmacol*. 1993 Jan. 7(3-4). P 181-9. / Abstract: The effects of moclobemide, 450 mg/day, on sleep were investigated in 12 patients with major depression. The study was carried out over six weeks, divided into three periods: (1) treatment for one week with placebo and measurement to obtain baseline values; (2) treatment with moclobemide for four weeks; and (3) one week withdrawal period. Polygraphic sleep recording, all-night sleep-EEG spectral analysis, and diurnal EEG vigilance mapping were used to determine the effects of this antidepressant. An activating effect was observed, most marked during the early phase of treatment. The most noticeable effects were on REM sleep, affecting polysomnographic and spectral sleep EEG parameters. A REM sleep habituation phenomenon was observed, and a slight REM sleep rebound effect occurred early during withdrawal. The observed neuroelectrophysiological changes appear to be specific for moclobemide and differ from those brought about by other antidepressants.

Antipsychotic drugs

Clozapine
Therapeutic indications: Treatment of psychotic disorders.
Rebound effect:
Unusual anxiety, nervousness and irritability. *(USP DI, 1996, p. 894)*
Author(s): Buchanan RW / Institution: Maryland Psychiatric Research Center, Baltimore 21228, USA. / Title: Clozapine: efficacy and safety. / Source: *Schizophr Bull*. 1995. 21(4). P 579-91. / Abstract: Clozapine (Clozaril) represents the first major advance in the pharmacological treatment of schizophrenia since the introduction of antipsychotics into clinical practice in the 1950s. Studies consistently support its efficacy for reducing positive symptoms in acutely psychotic patients and in treatment-resistant patients, for preventing positive symptom exacerbations as a maintenance treatment, and for reducing symptoms of hostility and violence. There is evidence to suggest that clozapine may improve social and occupational functioning and quality of life and may reduce affective symptoms, hospitalizations, secondary negative symptoms, and tardive dyskinesia. Its most significant side effects include agranulocytosis, seizures, weight gain, hypotension and tachycardia, sedation, and perhaps rebound psychosis (with abrupt discontinuation of medication).

Phenothiazines *(Acetofenazina, Chlorpromazine, Fluphenazine, Pericyazine, Pipotiazina, Promazine, Thioridazine, Trifluoperazine, etc.)*
Therapeutic indications: Treatment of psychotic disorders (schizophrenia).
Rebound effect:
Exacerbation of psychotic symptoms and catatonic after discontinuation of treatment. *(USP DI, 1996, p. 2362; AHFS, 1990, p. 1185)*
Author(s): Ramkumar V; el-Fakahany EE / Title: Changes in the affinity of [3H]nimodipine binding sites in the brain upon chlorpromazine treatment and subsequent withdrawal. / Source: *Res Commun Chem Pathol Pharmacol*. 1985 Jun. 48(3). P 463-6. / Abstract: Male mice were chronically treated with chlorpromazine mixed in powdered diet, and the properties of brain

calcium channels were assessed using [3H]nimodipine binding. It was found that this treatment resulted in a significant increase in the affinity of calcium channels, without a significant change in their density. These effects of chlorpromazine were time dependent. When mice were administered chlorpromazine for 2 months, then the drug was withdrawn, there was a rebound decrease in the channel affinity.
Author(s): van Sweden B / Title: Rebound insomnia in neuroleptic drug withdrawal neurophysiologic characteristics. / Source: *Pharmacopsychiatry*. 1987 May. 20(3). P 116-9. / Abstract: Rebound insomnia is one of the medical effects of reduction in dosage or discontinuation of neuroleptic drugs. The electrophysiologic features of sleep dysfunction are reported and discussed in 3 patients manifesting withdrawal-related DIMS. Electrographic anachronism and cyclic alternating pattern are signs of N-Rem sleep dysfunction. Clinical and neurophysiologic data suggest that rebound insomnia in neuroleptic withdrawal is due to an enhancement of physiologic mechanisms and rebound supersensitivity of cholinergic transmission in the ARAS.
Author(s): Costall B; Naylor RJ; Tyers MB / Institution: Postgraduate Studies in Pharmacology, School of Pharmacy, University of Bradford, West Yorkshire, U.K. / Title: The psychopharmacology of 5-HT3 receptors. / Source: *Pharmacol Ther*. 1990. 47(2). P 181-202. / Abstract: The review presents evidence that 5-HT3 receptors within the brain may contribute to the control of behavior. 5-HT3 receptor antagonists GR38032F, zacopride, ICS 205-930 and other agents are very potent in reducing mesolimbic dopamine hyperactivity caused by the injection of amphetamine or infusion of dopamine into the rat nucleus accumbens and amygdala, and the ventral striatum of the marmoset. Such actions are distinguished from those of neuroleptic agents by a failure to reduce normal levels of activity or to induce a rebound hyperactivity after discontinuation of treatment. Indeed, the 5-HT3 receptor antagonists can prevent the neuroleptic-induced rebound hyperactivity. Further evidence that 5-HT3 receptors moderate limbic dopamine function is shown by their ability to reduce both the behavioral hyperactivity and changes in limbic dopamine metabolism caused by DiMe-C7 injection into the ventral tegmental area. The 5-HT3 receptor antagonists also have an anxiolytic profile in the social interaction test in the rat, the light/dark exploration test in the mouse, the marmoset human threat test and behavioral observations in the cynomolgus monkey. They differ from the benzodiazepines by an absence of effect in the rat water lick conflict test and a withdrawal syndrome. Importantly, the 5-HT3 receptor antagonists are highly effective to prevent the behavioral syndrome following withdrawal from treatment with diazepam, nicotine, cocaine and alcohol. Intracerebral injection techniques in the mouse indicate that the dorsal raphe nucleus and amygdala may be important sites of 5-HT3 receptor antagonist action to inhibit aversive behavior. Studies with GR38032F indicate an additional effect in reducing alcohol consumption in the marmoset. The identification and distribution of 5-HT3 receptors in the brain using a number of 5-HT3 receptor ligands, [3H]65630, [3H]zacopride and [3H]ICS 205-930 correlates between studies, and the 5-HT3 recognition sites in cortical, limbic and other areas meet the criteria for 5-HT3 receptors to mediate the above behavioral effects. Thus the use of 5-HT3 receptor antagonists reveals an important role for 5-hydroxytryptamine in the control of disturbed behavior in the absence of effect on normal behavior. The profile of action of the 5-HT3 receptor antagonists has generated a major clinical interest in their potential use for schizophrenia, anxiety and in the control of drug abuse.

Haloperidol
Therapeutic indications: Treatment of psychotic disorders (schizophrenia).
Rebound effect:
Exacerbation of psychotic symptoms (including hallucinations and catatonia) after discontinuation of treatment. *(USP DI, 1996, 1593; AHFS, 1990, p. 1205)*

Author(s): Minabe Y; Tsutsumi M; Kurachi M / Institution: Department of Neuropsychiatry, Faculty of Medicine, Toyama Medical and Pharmaceutical University, Japan. / Title: Effects of chronic haloperidol treatment on amygdaloid seizure generation in cats. / Source: *Psychopharmacology (Berl)*. 1988. 94(2). P 259-62. / Abstract: We evaluated the effect of chronic haloperidol treatment (0.5-2 mg/kg/day, 21 day) on amygdala-generating seizures using a kindling procedure induced by low frequency electrical stimulations. The number of stimulating pulses required for triggering of epileptic afterdischarge (pulse-number threshold; PNT) is the indicator of the seizure generating threshold. A PNT decrease occurred, followed by a PNT increase toward the pre-treatment level during high-dose, chronic haloperidol treatment. A PNT increase occurred, followed by a PNT decrease toward the pre-treatment level during the withdrawal period after the high-dose treatment. A decrease of the triggered seizure duration occurred during the high-dose treatment. These results indicate that a transient decrease of seizure generating threshold occurs during chronic haloperidol treatment, and withdrawal of the drug is followed by what appears to be a rebound phenomenon. We suggest that this effect might be related to the antipsychotic potency and associated neurochemical changes known to be caused by chronic haloperidol treatment.

Author(s): Caul WF; Jones JR; Schmidt TA; Murphy SM; Barrett RJ / Institution: Department of Psychology, Vanderbilt University, Nashville, TN. / Title: Rebound cue state following a single dose of haloperidol. / Source: *Life Sci*. 1991. 49(17). P PL119-24. / Abstract: It has been reported that chronic administration of haloperidol produces an amphetamine-like rebound cue state. The experiments reported here were designed to assess whether a similar rebound phenomenon would result from a single dose of haloperidol. Rats were trained to discriminate .5 mg/kg amphetamine from distilled water. Five groups were formed to allow testing of haloperidol's effect at 12, 18, 24, 30, and 36 hr postinjection. Each animal was given 0, .5, 1.0, and 1.5 mg/kg haloperidol at its appropriate injection time in a counterbalanced fashion with one week between each test. A shift in the dose-response function of amphetamine that occurred during these weeks, however, precluded appropriate analysis of haloperidol's effects. Given this result, a second experiment was conducted using a between-subjects design. Half of the animals were injected with 1 mg/kg haloperidol 23 hr prior to testing, whereas the others were injected with distilled water. When tested, the haloperidol group responded 33% of the time on the amphetamine-correct lever, whereas the control group responded at 20%. The observation of posthaloperidol rebound in the between-subjects study and the failure to find significant temporal patterns of rebound phenomena using a within-subjects design have both theoretical and methodological importance.

Author(s): Caul WF; Barrett RJ; Huffman EM; Stadler JR / Institution: Department of Psychology, Vanderbilt University, Nashville, TN. / Title: Rebound responding following a single dose of drug using an amphetamine-vehicle-haloperidol drug discrimination. / Source: *Psychopharmacology (Berl).* 1996 Dec; 128(3): 274-9. / Abstract: The purpose of this research was to characterize drug-induced rebound cue states using a three-choice, agonist-vehicle-antagonist drug-discrimination procedure. Rats were trained to discriminate among 0.50 mg/kg amphetamine (AM), distilled water (DW), and 0.03 mg/kg haloperidol (HA) in a three-lever drug discrimination task. Time-dependent changes in cue state were assessed following single doses of AM (5 and 10 mg/kg), HA (1 mg/kg), and cocaine (30 and 40 mg/kg). Consistent with expectations derived from the results of a study that used a two-lever AM-HA discrimination task, single doses of AM produced rebound responding on the HA-appropriate lever that was dose-dependent and peaked at 24 h following administration. In addition, cocaine substituted for AM at 0.5-2 h post-injection and then produced HA-like rebound responding that peaked at 24-36 h post-administration. Contrary to expectations, however, rebound AM-like responding did not occur following HA administration. Perhaps two- and three-choice discrimination tasks differ in their ability to characterize qualitative aspects of the post-haloperidol cue state. Knowledge of the time course of drug-induced adaptive processes, measured as withdrawal in the present research, is necessary for a complete description of a drug's effects and is important in understanding the effects of repeated drug administration.

Pimozide
Therapeutic indications: Treatment of psychotic disorders (schizophrenia).
Rebound effect:
Insomnia, nervousness, agitation, excitement, aggressiveness, irritability, anxiety, confusion, hallucinations, nightmares, phobias and psychotic symptoms worsening. *(AHFS, 1990, p. 1213)*

Thiethylperazine
Therapeutic indications: Treatment of psychotic disorders (schizophrenia).
Rebound effect:
Paradoxical reaction (nightmares, excitement, nervousness, restlessness, irritability, etc.). *(USP DI,1996, p. 2852)*

Thiothixene
Therapeutic indications: Treatment of psychotic disorders (schizophrenia).
Rebound effect:
Paradoxical exacerbation of psychotic symptoms has been reported. Suppression syndrome and severe delusions has been reported in patients after the abrupt termination of prolonged treatment. *(USP DI, 1996, p. 2859; AHFS, 1990, p. 1216)*

ANTIALLERGIC AND IMMUNOLOGIC DRUGS

Thermoregulator drugs

Author(s): Marques PR; Spencer RL; Burks TF; McDougal JN / Title: Behavioral thermoregulation, core temperature, and motor activity: simultaneous quantitative assessment in rats after dopamine and prostaglandin E1. / Source: *Behav Neurosci*. 1984 Oct. 98(5). P 858-67. / Abstract: These studies were designed to determine the dose-response autonomic and behavioral thermoregulatory effects and the motor effects of dopamine (DA) and prostaglandin E1 (PGE1) injected into the lateral cerebral ventricles of rats. These studies were made possible with a computer-controlled thermocline that permits freely moving rats to select preferred ambient temperatures ranging between 7 and 39 degrees C. All rats were studied with the thermocline gradient both on and off to control for nonspecific effects. PGE1 (0, 0.1, 0.2, 0.5, 1.0 micrograms) produced a dose-related increase in core temperature and produced a dose-related selection of warmer ambient temperatures. Dopamine (0, 50, 100, 200, 400 micrograms) produced a dose-related hypothermia and cold-seeking behavior. Without the gradient, DA-injected rats did not become as hypothermic as in the gradient-on condition. When the gradient was available, rats showed a significant rebound increase in core temperature 50-80 min after DA which did not occur when the gradient was off. Overall, DA induced increases in motor activity, but, during the first 10 min after injection while the gradient was on, the rats made stable selections of cool ambient temperatures and showed reduced activity. Conversely, the behavioral effect of PGE1 did not facilitate the autonomically mediated heat gain. These results emphasize the necessity of creating behavioral options for animals in order to fully evaluate drug effects on thermoregulation.

Author(s): Bauer J; Hohagen F; Gimmel E; Bruns F; Lis S; Krieger S; Ambach W; Guthmann A; Grunze H; Fritsch-Montero R; et al / Institution: Department of Psychiatry, Freiburg University Medical School, Germany. / Title: Induction of cytokine synthesis and fever suppresses REM sleep and improves mood in patients with major depression. / Source: *Biol Psychiatry*. 1995 Nov 1. 38(9). P 611-21. / Abstract: Beneficial effects of inflammatory events on certain psychiatric disorders, including depression, were reported sporadically by ancient Greek physicians, but have been described also in our times by a few psychiatrists during the past decades. During febrile inflammatory events, mediators of the immune system such as interleukin-1 can be detected in the brain and may act on their respective receptors which have also been demonstrated in the brain. Since cytokines such as interleukin-1 have been shown in animal studies to exert sedative behavioral effects, to be somnogenic, and to induce slow-wave sleep (SWS), we performed a pilot study to evaluate scientifically the anecdotically reported beneficial effects of inflammatory states on depressive disorders. Mood and sleep parameters were monitored in seven drug-free, severely depressed patients before, during, and after the administration of a single dose of endotoxin. All patients responded with a short pulse of increased synthesis of the cytokines tumor necrosis factor, interleukin-1, and interleukin-6 and elevated body temperature for several hours. During the night following endotoxin administration, rapid eye movement (REM) sleep was significantly suppressed, while changes in slow wave sleep were not significant. During the next day, all patients were in a significantly improved mood; however a rebound of REM sleep was observed in the second night after endotoxin administration and mood worsened again during the next days, indicating an only transient beneficial effect of the treatment.

Steroidal anti-inflammatory drugs

***Corticosteroids** (Dexamethasone, Hydrocortisone, Prednisolone, etc.)*
Therapeutic indications: Treatment of inflammatory processes.
Rebound effect:
Author(s): Yamaki K; Nakagawa H; Tsurufuji S / Institution: Department of Biochemistry, Faculty of Pharmaceutical Sciences, Tohoku University, Sendai, Japan. / Title: Inhibitory effects of anti-inflammatory drugs on type II collagen induced arthritis in rats. / Source: *Ann Rheum Dis*. 1987 Jul. 46(7). P 543-8. / Abstract: The effects of steroidal and non-steroidal anti-inflammatory drugs on the established lesion of type II collagen induced arthritis in rats were evaluated by measuring the hind paw oedema and anti-type II collagen antibody titre. Dexamethasone, a steroidal anti-inflammatory drug, reduced the anti-type II collagen antibody titre and markedly suppressed the established lesion of type II collagen induced arthritis in rats. A rebound of the arthritis, i.e., a rapid recovery of the hind paw swelling took place after withdrawal of the treatment with steroidal anti-inflammatory drugs, including dexamethasone, prednisolone, and hydrocortisone. On the other hand, indomethacin, benoxaprofen, piroxicam, and tiflamizole, which are cyclo-oxygenase inhibitors in prostaglandin synthesis, had no effect on anti-type II collagen antibody titre, but suppressed the established lesion of the arthritis without causing an apparent rebound of the arthritis after withdrawal of the drug treatment. These results suggest that the level of anti-type II collagen antibodies has no relation to the intensity of hind paw swelling in the established lesion of the arthritis, though the antibodies contribute to the incidence of the arthritis. It also indicates that non-steroidal anti-inflammatory drugs having inhibitory action on cyclo-oxygenase are useful antiarthritic drugs without causing the rebound phenomenon, an untoward side effect after withdrawal of steroidal anti-inflammatory drugs.
Author(s): Maddux JM; Keeton KS / Title: Effects of dexamethasone, levamisole, and dexamethasone-levamisole combination on neutrophil function in female goats. / Source: *Am J Vet Res*. 1987 Jul. 48(7). P 1114-9. / Abstract: Effects of dexamethasone, levamisole, or combined dexamethasone-levamisole administration on polymorphonuclear neutrophil (PMN) function in healthy, adult female goats were studied. Goats were assigned to treated (n = 6) and control (n = 6) groups. In experiment 1, treated goats were given levamisole (6 mg/kg of body weight, IM). In experiment 2, treated goats were given 0.1 mg of dexamethasone/kg, IV, for 3 consecutive days, 1 mg of dexamethasone/kg, IV, for 6 consecutive days, and 6 mg of levamisole/kg, IM, with a 4th injection of 1 mg of dexamethasone/kg. All injections were administered 12 hours before blood collection. The PMN were evaluated for random migration and chemotaxis under agarose, ingestion of Staphylococcus aureus, cytochrome C reduction, iodination, and antibody-dependent cell-mediated cytotoxicity. Levamisole alone did not alter the function of caprine PMN. Both doses of dexamethasone caused increased random migration and decreased cytochrome C reduction and iodination. Dexamethasone resulted in no changes in chemotaxis, S aureus ingestion, and antibody-dependent cell-mediated cytotoxicity. Random migration and cytochrome C reduction returned toward base line in cells from dexamethasone and levamisole-treated goats. Although iodination activity in cells from dexamethasone-treated goats remained significantly (P less than 0.05) lower than those of controls after levamisole administration, a rebound toward base-line activity occurred.

***Corticosteroid - nasal** (Beclomethasone, Dexamethasone)*
Therapeutic indications: Nasal inflammations and allergies (rhinitis).
Rebound effect:
Nasal congestion, continuous increase of sneezing, itching, dryness, or another irritation inside the nose. *(USP DI, 1996, p. 942; AHFS, 1990, p. 1546)*

Corticosteroid - ophthalmic *(Betamethasone, Dexamethasone, Fluorometolona, Hydrocortisone, Medrisona, Prednisolone)*
Therapeutic indications: Allergic and inflammatory ophthalmic diseases (uveitis).
Rebound effect:
Signs of irritation as pain, blurred vision, itching, pain or watery eyes. A few days after discontinuation of treatment and occasionally during the therapy, may occur anterior uveitis in patients without pre-existing eye inflammation or infection. *(USP DI, 1996, p. 948; AHFS, 1990, p. 1546)*

Corticosteroid - otological *(Betamethasone, Dexamethasone, Hydrocortisone, Prednisolone)*
Therapeutic indications: Allergic external otitis, eczematid, seborreica.
Rebound effect:
Signs of local irritation such as pain, itching or stinging in the outer ear. *(USP DI, 1996, p. 806; AHFS, 1990, p. 1546)*

Corticosteroid - rectal *(Hydrocortisone)*
Therapeutic indications: Anorectal disorders (cracks, hemorrhoids, pain, itching, etc.).
Rebound effect:
Signs of local irritation as pain, rash, itching, bleeding and ampoules in the rectum, inexistent before therapy. *(USP DI, 1988, p. 1260)*

Corticosteroid - topical *(Betamethasone, Clobetasol, Desoximetasone, Dexamethasone, Diflorasona, Flumethasone, Fluocinolone, Hydrocortisone, etc.)*
Therapeutic indications: Treatment of skin inflammations as inflammatory dermatoses, dermatitis, eczema, burns, insect bites, etc.
Rebound effect:
Signs of irritation and inflammation as pain, itching, flaking and ampoules, inexistent before therapy. *(USP DI, 1996, p. 955)*
In prolonged treatment (≥ two months), "pustular rebound" can occur particularly on the face, genital and perineal region, after the discontinuation of therapy. *(AHFS, 1990, p. 2036)*

Non-steroidal anti-inflammatory drugs (NSAIDs)

Ibuprofen
Therapeutic indications: Treatment of inflammation.
Rebound effect:
In patients receiving ibuprofen can occur the emergence of aseptic meningitis with fever and coma, without any prior evidence of chronic disease. *(AHFS, 1990, p. 1022)*
Author(s): Endres S; Whitaker RE; Ghorbani R; Meydani SN; Dinarello CA / Institution: New England Medical Center Hospitals and Tufts University School of Medicine, Boston, MA, USA. / Title: Oral aspirin and ibuprofen increase cytokine-induced synthesis of IL-1 beta and of tumour necrosis factor-alpha ex vivo. / Source: *Immunology*. 1996 Feb. 87(2). P 264-70. / Abstract: We investigated the effect of oral aspirin and ibuprofen on the ex vivo synthesis of interleukin-1 alpha

(IL-1 alpha), IL-1 beta, IL-2, IL-6, tumour necrosis factor-alpha (TNF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) by stimulated peripheral blood mononuclear cells (PBMC) from healthy volunteers. Seven volunteers took 325 mg of aspirin daily for 14 days. Three weeks after ending aspirin medication, ex vivo IL-1 beta and TNF synthesis induced by exogenous IL-1 alpha was elevated threefold compared to the pre-aspirin value ($P = 0.01$ and $P = 0.005$, respectively). Using lipopolysaccharide (LPS) as a stimulus, no influence of oral aspirin was observed. The increase in cytokine synthesis did not parallel decreased synthesis of prostaglandin E2 (PGE2). Seven weeks after discontinuation of aspirin, cytokine and PGE-2 production returned to pre-aspirin levels. Another seven volunteers took 200 mg of ibuprofen daily for 12 days. Again, there was no effect on LPS- or Staphylococcus epidermidis-induced cytokine synthesis. However, IL-1 alpha-induced synthesis of IL-1 beta was elevated to a mean individual increase of 538% ($P < 0.001$) and synthesis of TNF was elevated to 270% ($P < 0.001$) at the end of ibuprofen medication and 2 weeks after discontinuation of ibuprofen. There were parallel increases in PGE2 and both returned to their pre-ibuprofen levels 5 weeks after stopping. Although inhibitors of cyclo-oxygenase blunt PGE2-mediated symptoms such as fever and pain, we conclude that short term use of either aspirin or ibuprofen results in a 'rebound' increase in cytokine-induced cytokine synthesis that is not observed in LPS-induced cytokines.

Indomethacin

Therapeutic indications: Treatment of inflammatory diseases (arthritis, spondylitis, tendinitis, pericarditis, etc.), analgesic, antipyretic.

Rebound effect:

Author(s): Seppala E; Laitinen O; Vapaatalo H / Title: Comparative study on the effects of acetylsalicylic acid, indomethacin and paracetamol on metabolites of arachidonic acid in plasma, serum and urine in man. / Source: *Int J Clin Pharmacol Res*. 1983. 3(4). P 265-9. / Abstract: The effects of acetylsalicylic acid, indomethacin and paracetamol on the plasma and serum levels and the urinary excretion of arachidonic acid metabolites in man were demonstrated. The inhibition of prostaglandin synthesis was reflected better in the urinary excretions than in the plasma levels of arachidonic acid metabolites. A clear-cut reduction by acetylsalicylic acid and indomethacin in serum T X B2 can be reached within 24 h. Paracetamol had no uniform influence on the prostaglandins studied. The values returned to the initial level in seven days after indomethacin and in two weeks after acetylsalicylic acid treatment. In some cases a rebound overshoot in prostaglandin concentrations was observed after the discontinuation of the treatment.

Author(s): Harrell JC; Stein SH / Institution: Medical College of Georgia, School of Dentistry, Department of Periodontics, Augusta, USA. / Title: Prostaglandin E2 regulates gingival mononuclear cell immunoglobulin production. / Source: *J Periodontol*. 1995 Mar. 66(3). P 222-7. / Abstract: Histological studies have revealed elevated levels of T and B lymphocytes in inflamed gingival tissue. Functional analysis of these B cells has determined that they are spontaneously secreting large amounts of immunoglobulin. Several components of bacterial plaque which accumulate during the onset of periodontal disease induce polyclonal B cell activation, and are most likely responsible for the "hyperactive" state of these gingival B lymphocytes. In addition to this exaggerated humoral response, increased levels of inflammatory mediators, such as prostaglandin (PG) E2, have been implicated in the pathogenesis of disease. Therefore, the purpose of this study was to determine if PGE2 could regulate immunoglobulin production within inflamed gingival tissue. Specimens were harvested during routine surgery of patients with chronic adult periodontitis. Utilizing an ELISA, elevated levels of IgG were detected in the supernatant of cultured gingival mononuclear cells. Inclusion of indomethacin, which inhibits arachidonic acid metabolites such as PGE2, caused a decrease in IgG levels. PGE2 exerted a biphasic effect upon IgG production, with high doses diminishing and low doses increasing IgG levels. From a clinical perspective, these

results suggest that elevated levels of PGE2 associated with inflammation will attenuate an IgG response and, as PGE2 production wanes, the local humoral response will rebound. Interestingly, the combination of low dose PGE2 and IL-4 induced a synergistic rise in IgG production. These findings support the theory that local PGE2 levels can regulate immunoglobulin production and potentiate cytokine induced class switching within gingival tissue.

Paracetamol
Therapeutic indications: Treatment of fever.
Rebound effect:
Unexplained fever. *(USP DI, 1996, p. 3; AHFS, 1990, p. 1104)*
Author(s): Seppala E; Laitinen O; Vapaatalo H / Title: Comparative study on the effects of acetylsalicylic acid, indomethacin and paracetamol on metabolites of arachidonic acid in plasma, serum and urine in man. / Source: *Int J Clin Pharmacol Res*. 1983. 3(4). P 265-9. / Abstract: The effects of acetylsalicylic acid, indomethacin and paracetamol on the plasma and serum levels and the urinary excretion of arachidonic acid metabolites in man were demonstrated. The inhibition of prostaglandin synthesis was reflected better in the urinary excretions than in the plasma levels of arachidonic acid metabolites. A clear-cut reduction by acetylsalicylic acid and indomethacin in serum T X B2 can be reached within 24 h. Paracetamol had no uniform influence on the prostaglandins studied. The values returned to the initial level in seven days after indomethacin and in two weeks after acetylsalicylic acid treatment. In some cases a rebound overshoot in prostaglandin concentrations was observed after the discontinuation of the treatment.

Salicylates *(Aspirin, Salicimida, Salsalate, etc.)*
Therapeutic indications: Treatment of inflammation (fever).
Rebound effect:
Unexplained fever, which can be very high. *(USP DI, 1996, p. 2589)*
Hyperthermia, sometimes with rectal temperature reaching 40.5 to 42.2ºC. *(AHFS, 1990, p. 992)*
Author(s): Seppala E; Laitinen O; Vapaatalo H / Title: Comparative study on the effects of acetylsalicylic acid, indomethacin and paracetamol on metabolites of arachidonic acid in plasma, serum and urine in man. / Source: *Int J Clin Pharmacol Res*. 1983. 3(4). P 265-9. / Abstract: The effects of acetylsalicylic acid, indomethacin and paracetamol on the plasma and serum levels and the urinary excretion of arachidonic acid metabolites in man were demonstrated. The inhibition of prostaglandin synthesis was reflected better in the urinary excretions than in the plasma levels of arachidonic acid metabolites. A clear-cut reduction by acetylsalicylic acid and indomethacin in serum T X B2 can be reached within 24 h. Paracetamol had no uniform influence on the prostaglandins studied. The values returned to the initial level in seven days after indomethacin and in two weeks after acetylsalicylic acid treatment. In some cases a rebound overshoot in prostaglandin concentrations was observed after the discontinuation of the treatment.
Author(s): Endres S; Whitaker RE; Ghorbani R; Meydani SN; Dinarello CA / Institution: New England Medical Center Hospitals and Tufts University School of Medicine, Boston, MA, USA. / Title: Oral aspirin and ibuprofen increase cytokine-induced synthesis of IL-1 beta and of tumour necrosis factor-alpha ex vivo. / Source: *Immunology*. 1996 Feb. 87(2). P 264-70. / Abstract: We investigated the effect of oral aspirin and ibuprofen on the ex vivo synthesis of interleukin-1 alpha (IL-1 alpha), IL-1 beta, IL-2, IL-6, tumour necrosis factor-alpha (TNF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) by stimulated peripheral blood mononuclear cells (PBMC) from healthy volunteers. Seven volunteers took 325 mg of aspirin daily for 14 days. Three weeks after ending aspirin medication, ex vivo IL-1 beta and TNF synthesis induced by exogenous IL-1 alpha was elevated threefold compared to the pre-aspirin value (P = 0.01 and P = 0.005,

respectively). Using lipopolysaccharide (LPS) as a stimulus, no influence of oral aspirin was observed. The increase in cytokine synthesis did not parallel decreased synthesis of prostaglandin E2 (PGE2). Seven weeks after discontinuation of aspirin, cytokine and PGE-2 production returned to pre-aspirin levels. Another seven volunteers took 200 mg of ibuprofen daily for 12 days. Again, there was no effect on LPS- or Staphylococcus epidermidis-induced cytokine synthesis. However, IL-1 alpha-induced synthesis of IL-1 beta was elevated to a mean individual increase of 538% ($P < 0.001$) and synthesis of TNF was elevated to 270% ($P < 0.001$) at the end of ibuprofen medication and 2 weeks after discontinuation of ibuprofen. There were parallel increases in PGE2 and both returned to their pre-ibuprofen levels 5 weeks after stopping. Although inhibitors of cyclo-oxygenase blunt PGE2-mediated symptoms such as fever and pain, we conclude that short term use of either aspirin or ibuprofen results in a 'rebound' increase in cytokine-induced cytokine synthesis that is not observed in LPS-induced cytokines.

Immunosuppressive drugs (immunomodulator treatments)

Author(s): Martin RA; Barsoum NJ; Sturgess JM; de la Iglesia FA / Title: Leukocyte and bone marrow effects of a thiomorpholine quinazosin antihypertensive agent. / Source: *Toxicol Appl Pharmacol*. 1985 Oct. 81(1). P 166-73. / Abstract: PD-88823, a thiomorpholine analog of prazosin, induced a consistent dose-related suppression of granulopoiesis with subsequent neutropenia and leukopenia in rats and dogs. Rats treated at 600 mg kg-1 day-1 had neutrophil counts reduced by 44% in males and 30% in females after 13 weeks. A 4-week observation period after drug treatment resulted in a rebound in neutrophil counts to 123 and 215% of control values in males and females, respectively. White blood cell count reductions were less evident in dogs, probably because of the lower doses. In both species, the extent of bone marrow suppression was related to duration of treatment. No other hematologic changes were manifest in either species. The mechanism for bone marrow depression and subsequent granulocytopenia was not established. The lack of reported bone marrow effects by quinazosin analogs suggests that the thiomorpholine group of PD-88823 is involved in toxicity. This correlation may be important to safety considerations for future drug design.

Author(s): Soh LT; Ang PT; Sng I; Chua EJ; Ong YW / Institution: Department of Medical Oncology, Singapore General Hospital. / Title: Fulminant hepatic failure in non-Hodgkin lymphoma patients treated with chemotherapy. / Source: *Eur J Cancer*. 1992. 28A(8-9). P 1338-9. / Abstract: Chemotherapy is the mainstay of therapy for patients with non-Hodgkin lymphoma. Among side-effects associated with the use of chemotherapy, immunosuppression is one which can be potentially fatal. In hepatitis B carriers, immunosuppression permits widespread infection of the hepatocytes and its subsequent withdrawal causes an "immunological rebound" leading to massive necrosis of hepatocytes. 4 patients who died of fulminant hepatitis following chemotherapy are reported. These were patients with positive hepatitis B serology. Caution is advised when treating non-Hodgkin lymphoma in patients from hepatitis B endemic regions.

Author(s): Greenwood BM; David PH; Otoo-Forbes LN; Allen SJ; Alonso PL; Armstrong Schellenberg JR; Byass P; Hurwitz M; Menon A; Snow RW / Institution: Medical Research Council Laboratories, Fajara, Banjul, The Gambia. / Title: Mortality and morbidity from malaria after stopping malaria chemoprophylaxis. / Source: *Trans R Soc Trop Med Hyg*. 1995 Nov-Dec. 89(6). P 629-33. / Abstract: Gambian children who had received malaria chemoprophylaxis for a variable period of time during their first 5 years of life were followed to determine whether they experienced a rebound in mortality or in morbidity from malaria during the period after chemoprophylaxis was stopped. The risk of dying between the ages of 5 years, when chemoprophylaxis was stopped, and 10 years was no higher among children who had received

chemoprophylaxis with Maloprim (pyrimethamine plus dapsone) for some period during their first 5 years of life than among children who had received placebo (21 vs. 24 deaths) and the beneficial effect of chemoprophylaxis on mortality observed during the first 5 years of life was sustained. The incidence of clinical attacks of malaria during the year after medication was stopped was significantly higher among children who had previously received Maloprim for several years than among children who had previously received placebo. However, at the end of this year, there was no significant difference in spleen rate, parasite rate or packed cell volume between the 2 groups of children. Thus, stopping chemoprophylaxis after a period of several years increased the risk of clinical malaria but did not result in a rebound in mortality in Gambian children. However, the number of deaths recorded was small, so a modest effect on mortality cannot be excluded.

Muromonab-CD3 *(monoclonal antibody)*

Therapeutic indications: Connects to T cells by blocking the generation and the function of these in response to demand antigênica.

Rebound effect:

Produces fever and chills after an hour of the first dose, staying for several hours. *(USP DI, 1988, p. 1593)*

Author(s): Billingham ME; Hicks C; Carney S / Institution: Connective Tissue Disease Research, Eli Lilly & Co., Windlesham, Surrey, UK. / Title: Monoclonal antibodies and arthritis. / Source: *Agents Actions*. 1990 Jan. 29(1-2). P 77-87. / Abstract: Monoclonal antibodies to certain cell surface constituents on lymphocytes, monocytes and macrophages have been administered to Lewis rats with developing, established or adoptively transferred arthritis, to determine any immunomodulatory properties. Anti-CD4 antibodies against helper T-lymphocytes produced a dose related inhibition of developing arthritis; high dose levels completely suppressed all symptoms of arthritis and these rats were resistant to further attempts to induce arthritis. Anti-Ia (MHCII) antibodies also inhibited arthritis in a dose related manner; anti-pan T antibodies delayed the onset of arthritis, but antibodies against CD8 and IL-2 receptor positive cells were without effect. Development of type II collagen-induced arthritis was also inhibited by anti-CD4 treatment. Established arthritis could be temporarily inhibited by anti-CD4 antibodies, but rebound of arthritis invariably occurred after stopping treatment, as is the case with cyclosporin A. Similar results with anti-CD4 antibodies were obtained during treatment of arthritis adoptively transferred by arthritogenic T-lymphocytes. From these experiments it is clear that CD4 positive T-lymphocytes have a major role in the induction of adjuvant arthritis and that interaction between CD4 and Ia bearing cells is important. The rebound of arthritis that occurred after withdrawal of anti-CD4 treatment during established disease infers that cells in addition to helper T-lymphocytes are involved in the chronicity of arthritis, but these remain to be elucidated. These findings are discussed in relation to results with monoclonal antibodies in other models of arthritis and human rheumatoid arthritis; the prospects for human therapy are also discussed.

Plasmapheresis

Therapeutic indications: Removal of proteins, lipids, hormones, toxins, antibodies, antigens and immune complexes of blood circulation; used in the treatment of autoimmune diseases.

Rebound effect:

Author(s): Verdickt W; Dequeker J; Ceuppens JL; Stevens E; Gautama K; Vermylen C / Title: Effect of lymphoplasmapheresis on clinical indices and T cell subsets in rheumatoid arthritis. A double-blind controlled study. / Source: *Arthritis Rheum*. 1983 Dec. 26(12). P 1419-26. / Abstract: The effects of lymphoplasmapheresis on immunologic indices, including T cell subsets, and on clinical parameters of rheumatoid arthritis were evaluated in a controlled double-blind trial. Twenty

patients were randomized to receive either 6 lymphoplasmapheresis sessions or a seemingly identical control procedure over a 3-week period. Lymphoplasmapheresis produced significant reduction in serum levels of total lymphocytes, erythrocyte sedimentation rate, C-reactive protein, and IgG. These serologic measures returned to baseline 5 weeks after lymphoplasmapheresis. No change in the imbalance of T cell subsets (increased helper/suppressor ratio) was observed. No changes in the serologic measures, except IgA, were observed in the control group. An improvement in some of the clinical parameters was observed in both the lymphoplasmapheresis and control groups. A rebound above baseline values for several parameters was observed in both the lymphoplasmapheresis and the sham apheresis groups.

Author(s): Nasca TJ; Muder RR; Thomas DB; Schrecker JC; Ruben FL / Institution: Department of Medicine, Mercy Hospital, Pittsburgh, PA 15219. / Title: Antibody response to pneumococcal polysaccharide vaccine in myasthenia gravis: effect of therapeutic plasmapheresis. / Source: *J Clin Apheresis*. 1990. 5(3). P 133-9. / Abstract: The removal of specific antibody in experimental animals has been reported to result in a subsequent increase in antibody to levels equal to (rebound) or exceeding those existing prior to removal (overshoot). Anecdotal reports suggest that rebound antibody synthesis after plasmapheresis may occur in humans with autoimmune disorders. We measured the antibody response to 12 pneumococcal polysaccharide antigens in patients with myasthenia gravis (MG) receiving a variety of therapies in order to determine whether the T-cell-independent IgG response to these antigens was augmented by plasmapheresis. MG patients receiving no immunotherapy or receiving prednisone had pre- and post-immunization titers similar to those of control patients. MG patients receiving prednisone and chronic plasmapheresis had higher pre-immunization titers than did other patient groups and had significantly higher post-immunization titers against multiple pneumococcal serogroups. Aggregate post-immunization geometric mean titers were more than three-fold higher in the plasmapheresis group as compared with other MG treatment groups. Enhancement of antibody response by plasmapheresis was abolished by the concomitant administration of azathioprine. Antibody rebound and overshoot after antibody removal may have important implications for the therapy of immune disorders by plasmapheresis.

Author(s): Ljaljevic M; Dimcic Z; Stefanovic Lj; Tomic V; Tomasevic Lj; Raskovic S / Institution: Clinic of Allergy and Immunology, University Clinical Center, Beograd. / Title: [Plasmapheresis in clinical practice]. / Source: *Glas Srp Akad Nauka [Med]*. 1994. (44). P 127-31. / Abstract: Plasmapheresis is an immunomodulatory procedure with immunosuppressive effect. Plasmapheresis involves taking blood, separating off the plasma and returning the red cell-enriched fraction to the patient. In plasmapheresis improvement is due to the removal of mediators of tissue damage. Therapeutic plasmapheresis has been used in many diseases in which immunological mechanisms are proved. It has been noted that there may be a “rebound” in the level of antibodies and immune complexes after plasmapheresis, perhaps due to elimination of feedback suppressor mechanisms. For that reason, plasmapheresis is only effective when used as part of an immunosuppressive regimen which also includes steroids and/or cytotoxic agents.

Author(s): Dau PC / Institution: Department of Medicine, Evanston Hospital, IL 60201, USA. / Title: Immunologic rebound. / Source: *J Clin Apheresis*. 1995. 10(4). P 210-7. / Abstract: Evidence for accelerated specific antibody (Ab) rebound or overshoot after single or multiple therapeutic plasmapheresis (TP) is fragmentary but suggested by both clinical and experimental evidence. In vitro studies showing increased peripheral blood lymphocyte turnover and total immunoglobulin production after a series of TP without immunosuppression may signify a generalized immunostimulation through removal of regulatory molecules by TP. It is known that IgG class Ab can down regulate B cells by cross linkage of their Ag and Fc receptors. Cyclophosphamide and other cytotoxic immunosuppressive agents effectively delete proliferating lymphocytes. TP could particularly foster deletion of lymphocytes actively mediating autoimmunity, since they would be more readily stimulated to proliferation by removal of Ab or other inhibitory factors than the

generally resting normal immune system. This is supported by a relatively greater reduction of autoantibody levels than total immunoglobulin after treatment with TP and cytotoxic immunosuppressives.

Antihistaminic drugs

Antihistamines *(Azatidina, Bromazina, Bromfeniramina, Carbinoxamine, Chlorphenamine, Clemastine, Dexchlorpheniramine, Dimenhidrinato, Diphenhydramine, Diphenylpyraline, Doxylamine, Fenindamina, Hydroxyzine, Mepyramine, Promethazine, Terfenadine, Tripelennamine, Triprolidine)*
Therapeutic indications: Neutralize the responses mediated by histamine in rhinitis, conjuntivites, rashes, urticaria, angioedema, sedation, dizziness, insomnia, anorexia, etc.
Rebound effect:
Rebound symptoms arise as suffocation, facial redness, shortness of breath, increase of glandular secretions, allergic reactions, formation of edemas, vertigo, hypotension, unusual excitement and nervousness, insomnia, loss of appetite, etc. *(USP DI, 1996, p. 323, 1609; AHFS, 1990, p. 2)*
Author(s): Pastel RH; Echevarria E; Cox B; Blackburn TP; Tortella FC / Institution: Department of Medical Neurosciences, Walter Reed Army Institute of Research, Washington, DC 20307. / Title: Effects of chronic treatment with two selective 5-HT2 antagonists on sleep in the rat. / Source: *Pharmacol Biochem Behav*. 1993 Apr. 44(4). P 797-804. / Abstract: The effect of chronic administration of 2(2-dimethylaminoethylthio)-3-phenylquinoline (ICI-169,369) and 2(2-dimethylamino-2-methylpropylthio)-3-phenylquinoline (ICI-170,809), two selective 5-HT2 antagonists, on sleep was studied in rats. As previously shown, the acute effect of ICI-170,809 was to increase latency to rapid eye movement sleep (REMS), decrease the number of REM periods (REMPs), suppress the cumulative amount of REMS over 12 h, and increase the duration of REMPs in the first 6 h, while having no effect on non-REM sleep (NREMS). Administration of ICI-169,369 had similar effects except no change was seen in the duration of REMPs and cumulative REMS was suppressed for 24 h. When given 2 x daily for 5 days, tolerance to the REMS suppressant effects developed in both drugs. After discontinuation of treatment, a REMS rebound occurred after ICI-170,809, but not ICI-169,369. No significant effect on NREMS was seen after administration of ICI-170,809, whereas ICI-169,369 lowered 24-h cumulative NREMS on the fifth day of administration.

Sodium cromoglycate - oral *(systemic action)*
Therapeutic indications: Systemic mastocytosis (bone pain, arthralgia and anaphylactoid symptoms).
Rebound effect:
Inflammation and joint pain, hives or angioedema, rash. *(USP DI, 1996, p. 1111; AHFS, 1990, p. 2161)*

Antiallergic drugs and nasal decongestants

Nasal corticosteroid *(Beclomethasone, Dexamethasone, Flunisolide)*
Therapeutic indications: Rhinitis, allergies or nasal inflammations.

Rebound effect:
Bloody mucus or unexplained nosebleeds; continuous nasal congestion and rhinorrhea; burning, dryness, or another irritation in the nasal mucosa; unusual increase of sneezing; atrophic rhinitis. *(USP DI, 1996, p. 945)*
Irritation and dryness of the nasal mucosa; rebound congestion; burning sensation and nasal irritation occurs in 24% of patients who used Beclomethasone intranasal (aqueous solution). Sneezing attacks occur immediately after intranasal administration of drugs in 10% of patients who used Beclomethasone (aerosol); also occurred rhinorrhea intense and nasal congestion. *(AHFS, 1990, p. 1546, 1548)*

Sodium cromoglycate - nasal
Therapeutic indications: Treatment and prophylaxis of allergic rhinitis.
Rebound effect:
Itching, stinging or irritation inside the nose; increase of sneezing; nasal drip. *(USP DI, 1996, p. 1107)*
Nasal congestion; increase of sneezing; burning, itching and nasal irritation. *(AHFS, 1990, p. 2161)*
Author(s): Busse W / Institution: Department of Medicine, University of Wisconsin School of Medicine, Madison. / Title: New directions and dimensions in the treatment of allergic rhinitis. / Source: *J Allergy Clin Immunol*. 1988 Nov. 82(5 Pt 2). P 890-900. / Abstract: Physicians who treat patients with allergic rhinitis have a number of therapeutic options, including antihistamines, decongestants, cromolyn, anticholinergics, corticosteroids, and immunotherapy. Antihistamines are widely used for the treatment of mild allergic rhinitis and are often effective, although more severe cases will require other medications. The newer antihistamines may induce less drowsiness, which is the most prominent side effect of the older antihistamines. Topical nasal decongestants give fast relief from nasal congestion, but their overuse may result in rebound congestion. Because their efficacy in allergic rhinitis is variable, oral decongestants are usually used in combination with antihistamines. Nasal cromolyn is effective for many patients with allergic rhinitis, but its effect is variable and it is useful in severe allergic rhinitis.

Ephedrine - nasal
Therapeutic indications: Nasal congestion.
Rebound effect:
Rebound nasal congestion occurs a few days after the use as nasal decongestant. *(AHFS, 1990, p. 622)*

Phenilephrine - nasal
Therapeutic indications: Nasal congestion.
Rebound effect:
Increase of nasal congestion and rhinorrhea (rebound congestion); itching, burning and irritation of the nasal mucosa. *(USP DI, 1996, p. 2389)*
Ardor and/or dryness of the nasal mucosa; rebound nasal congestion occurs frequently with an overdose of drugs. With prolonged use, increase of sneezing and rhinitis, a week after the drug is discontinued. *(AHFS, 1990, p. 1597)*

Naphazoline - nasal
Therapeutic indications: Nasal congestion (associated with chronic rhinitis).

Rebound effect:
Irritation of the nasal mucosa, with itching, dryness and ardor; sneezing. Rebound congestion characterized by chronic redness, swelling and rhinitis. *(USP DI, 1996, p. 2130; AHFS, 1990, p. 1594)*

Oxymetazoline - nasal
Therapeutic indications: Nasal congestion (associated with chronic rhinitis).
Rebound effect:
Irritation of the nasal mucosa and sneezing. Rebound congestion characterized by chronic redness, swelling and rhinitis caused by prolonged use and/or excessive doses of drugs. *(USP DI, 1996, p. 2260; AHFS, 1990, p. 1595)*
Author(s): Graf P; Juto JE / Institution: Department of Otorhinolaryngology, Karolinska Institute at Sodersjukhuset, Stockholm, Sweden. / Title: Decongestion effect and rebound swelling of the nasal mucosa during 4-week use of oxymetazoline. / Source: *ORL J Otorhinolaryngol Relat Spec*. 1994 May-Jun. 56(3). P 157-60. / Abstract: The aim of this study was to investigate whether long-term use of oxymetazoline induces a rebound swelling of the nasal mucosa and whether the decongestion effect is altered during medication. Eight healthy volunteers had oxymetazoline nasal spray (0.5 mg/ml; 0.1 ml in each nostril, three times daily) for 30 days and registrations of the mucosal surface positions were made using rhinostereometry. Compared to the registrations before the start of medication, no rebound swelling was registered after 10 days. After 30 days, however, a rebound swelling was registered in all subjects ($p < 0.001$). All of them, then, also reported nasal stuffiness. The decongested position of the nasal mucosa after one single dose of oxymetazoline was the same in the whole study. It is concluded that rhinitis medicamentosa develops after a relatively short time on oxymetazoline, even in healthy volunteers, and that the swelling probably is due to a vasodilatation rather than an edema. The study supports the recommendation that the drug should not be used over periods > 10 days.
Author(s): Graf P; Hallen H; Juto JE / Institution: Department of Otorhinolaryngology, Sodersjukhuset, Karolinska Institute, Stockholm, Sweden. / Title: Four-week use of oxymetazoline nasal spray (Nezeril) once daily at night induces rebound swelling and nasal hyperreactivity. / Source: *Acta Otolaryngol (Stockh)*. 1995 Jan. 115(1). P 71-5. / Abstract: A randomized double-blind parallel study with 20 healthy volunteers was performed to examine the effect of oxymetazoline nasal spray on the development of rhinitis medicamentosa. For 30 days, 10 subjects were given oxymetazoline nasal spray once daily at night and placebo in the morning and at noon, while the others used oxymetazoline nasal spray three times daily. Before and after the course of treatment, the mucosal surface positions were determined with rhinostereometry, followed by histamine challenge tests. In the morning and the evening just before use of the nasal spray, symptoms of nasal stuffiness were evaluated on visual analogue scales (0-100). After 30 days, rebound swelling and nasal stuffiness were found in both groups. In the group receiving oxymetazoline nasal spray once daily at night, the mean rebound swelling was 0.8 mm ($p < 0.01$) and the estimated mean symptom score for nasal stuffiness in the evening was 43 ($p < 0.05$). In the group receiving the same nasal spray three times daily, the mean rebound swelling was 1.1 mm ($p < 0.01$) and the mean evening symptom score was 43 ($p < 0.05$). The finding of an increase in histamine sensitivity in both groups was taken to indicate nasal hyperreactivity. There was no significant difference in the investigated variables between the two groups. It is concluded that the risk of developing rebound swelling and nasal hyperreactivity remains, whether oxymetazoline nasal spray is used once or three times a day for 30 days.
Author(s): Graf P; Hallen H; Juto JE / Institution: Department of Otorhinolaryngology, Sodersjukhuset, Karolinska Institute, Stockholm, Sweden. / Title: Benzalkonium chloride in a decongestant nasal spray aggravates rhinitis medicamentosa in healthy volunteers. / Source: *Clin*

Exp Allergy. 1995 May. 25(5). P 395-400. / Abstract: A randomized double-blind parallel study with 20 healthy volunteers was performed to research the effect of a preservative in a decongestant nasal spray on the development of rhinitis medicamentosa. Ten subjects received oxymetazoline nasal spray with benzalkonium chloride and the others used oxymetazoline nasal spray without the preservative three times daily for 30 days. Before starting the course of treatment and after its conclusion, recordings of the mucosal surface positions were made with rhinostereometry followed by histamine challenge tests. Symptoms of nasal stuffiness were estimated on visual analogue scales (0-100) in the morning and the evening just before using the nasal spray. After 30 days, rebound swelling and nasal stuffiness were found in both groups. In the group receiving oxymetazoline nasal spray with benzalkonium chloride the mean rebound swelling was 1.1 mm and the estimated mean evening symptom score for nasal stuffiness was 43. In the group without benzalkonium chloride the corresponding variables were significantly less marked, with a mean rebound swelling of 0.5 mm ($P < 0.05$) and a mean evening symptom score of 25 ($P < 0.05$). The increase in histamine sensitivity in both groups was interpreted as a sign of nasal hyperreactivity. A new type of nasal spray bottle was used that has been shown to prevent bacterial contamination. In conclusion, the long-term use of benzalkonium chloride in oxymetazoline nasal spray accentuates the severity of rhinitis medicamentosa in healthy volunteers.
Author(s): Graf P; Hallén H; Juto JE / Institution: Department of Otorhinolaryngology, Sodersjukhuset, Karolinska Institute, Stockholm, Sweden. / Title: The pathophysiology and treatment of rhinitis medicamentosa. / Source: *Clin Otolaryngol*. 1995 Jun. 20(3). P 224-9. / Abstract: To evaluate the treatment of rhinitis medicamentosa, 10 consecutive patients discontinued their use of topical vasoconstrictors and were treated with budesonide nasal spray, 400 micrograms, daily for 6 weeks. The thickness of the nasal mucosa, the decongestive effect of oxymetazoline and the histamine sensitivity were measured with rhinostereometry. All patients were able to stop using the vasoconstrictors and objective variables showed that they needed treatment for at least 6 weeks. The results strongly support the theory that the rebound swelling is due to interstitial oedema rather than to vasodilatation. The presence of tachyphylaxis reflected by a reduction in both the decongestive effect of oxymetazoline and a reduction of drug duration was seen.
Author(s): Graf P / Institution: Department of Otorhinolaryngology, Sodersjukhuset, Karolinska Institute, Stockholm, Sweden. / Title: Rhinitis medicamentosa: aspects of pathophysiology and treatment. / Source: *Allergy*. 1997;52(40 Suppl):28-34. / Abstract: With modern vasoconstrictors, such as oxy- and xylometazoline, the risk of developing rhinitis medicamentosa (RM) has been considered to be small or even nonexistent. However, recent studies have shown that overuse of these drugs may result in rebound congestion, nasal hyperreactivity, tolerance, and histologic changes of the nasal mucosa. Using rhinostereometry, it has also been shown that the long-term use of the preservative benzalkonium chloride (BKC) in oxymetazoline nasal spray accentuates the severity of rhinitis medicamentosa in healthy volunteers. A nasal decongestant spray composed of a combination of vasoactive substances and BKC has a long-term adverse effect on the nasal mucosa. BKC alone induces mucosal swelling after 30 days use of the nasal spray in healthy subjects, unlike placebo. According to the author, rhinitis medicamentosa can be defined as a condition of nasal hyperreactivity, mucosal swelling, and tolerance that is induced, or aggravated, by the overuse of topical vasoconstrictors with or without a preservative. An adequate treatment of these patients consists of a combination of vasoconstrictor withdrawal and a topical corticosteroid to alleviate the withdrawal process. The underlying nasal disorder must then be treated. Patients with rhinitis medicamentosa who overuse topical decongestants and are able to stop using such drugs should be careful about taking these drugs again, even for a few days. They must be informed about the rapid onset of rebound congestion upon repeated use in order to avoid the return of the vicious circle of nose-drop abuse.

Xylometazoline - nasal

Therapeutic indications: Nasal congestion.
Rebound effect:
Increase of nasal congestion and rhinorrhea (rebound effect). Itching, dryness and ardor of the nasal mucosa; sneezing. *(USP DI, 1988, p. 2199)*
Itching, dryness and ardor of the nasal mucosa; sneezing. Rebound congestion characterized by chronic redness, swelling and rhinitis, occurring often with prolonged use and/or intense drug. *(AHFS, 1990, p. 1602)*
Author(s): Graf P; Juto JE / Institution: Department of Otorhinolaryngology, Sodersjukhuset, Stockholm, Sweden. / Title: Sustained use of xylometazoline nasal spray shortens the decongestive response and induces rebound swelling. / Source: *Rhinology*. 1995 Mar. 33(1). P 14-7. / Abstract: Long-term use of topical vasoconstrictors for the nose may result in rhinitis medicamentosa, drug addiction and tachyphylaxis. Some authors also believe that the severity of rebound swelling is proportional to the period during which the drug has been used, the frequency of its administration, and the amount of drug given. It has previously been reported that four-week use of the recommended dose of oxymetazoline induces rebound swelling, a sign of rhinitis medicamentosa. To study the effect of an increased amount of vasoconstrictor on rebound swelling and the decongestive effect of the drug, nine healthy subjects were given xylometazoline nasal spray in double the recommended dose (1.0 mg/ml; 0.28 ml in each nostril thrice daily) for 30 days. After 30 days on xylometazoline, the decongestive effect was the same 1 h after drug administration as before starting the medication. Similarly, after 30 days on xylometazoline, the decongestive effect was less 5 h after drug administration than it was 6 h after drug administration at the start of medication ($p < 0.005$). After 10 days no rebound swelling was recorded, but after 30 days rebound swelling occurred in eight out of nine subjects ($p < 0.05$). When comparing the results of this trial with the corresponding results of the oxymetazoline study, no further increase in rebound swelling was found. We conclude that long-term use of xylometazoline nasal spray shortens the decongestive response in healthy volunteers. Moreover, double the recommended dose of xylometazoline did not further increase the rebound swelling seen when using the recommended dose of oxymetazoline.
Author(s): Graf P / Institution: Department of Otorhinolaryngology, Sodersjukhuset, Karolinska Institute, Stockholm, Sweden. / Title: Long-term use of oxy- and xylometazoline nasal sprays induces rebound swelling, tolerance, and nasal hyperreactivity. / Source: *Rhinology*. 1996 Mar. 34(1). P 9-13. / Abstract: It has been suggested but never confirmed, that the severity of the rebound swelling and rhinitis medicamentosa are directly proportional to the period during which the drug is used, to the frequency of its use, and to the amount of drug administered. However, no studies have been performed to evaluate the effects of various amounts of the vasoconstrictors on the development of rhinitis medicamentosa. Moreover, no in vivo studies have yet been performed to investigate whether benzalkonium chloride in nasal decongestant solutions affects the development of rhinitis medicamentosa. This study shows that rhinitis medicamentosa is a condition of nasal hyperreactivity, mucosal swelling and tolerance induced, or aggravated, by the overuse of topical vasoconstrictors with or without a preservative.

HEMATOLOGIC DRUGS

Antithrombotic drugs

Argatroban
Therapeutic indications: Antithrombotic (inhibition of thrombin).
Rebound effect:
Author(s): Gold HK; Torres FW; Garabedian HD; Werner W; Jang IK; Khan A; Hagstrom JN; Yasuda T; Leinbach RC; Newell JB; et al / Institution: Cardiac Unit, Massachusetts General Hospital, Boston, Massachusetts 02114. / Title: Evidence for a rebound coagulation phenomenon after cessation of a 4-hour infusion of a specific thrombin inhibitor in patients with unstable angina pectoris. / Source: *J Am Coll Cardiol*. 1993 Apr. 21(5). P 1039-47. / Abstract: In a Phase I clinical trial, we studied the antithrombotic and clinical effects of the synthetic competitive thrombin inhibitor, argatroban, in 43 patients with unstable angina pectoris. Thrombin has a pivotal role in platelet-mediated thrombosis associated with atheromatous plaque rupture in patients with an acute ischemic coronary syndrome. However, the efficacy of conventional heparin therapy to prevent ischemic events is limited and has been surpassed by that of specific thrombin inhibitors in experimental models of arterial thrombosis. Intravenous infusion of the drug (0.5 to 5.0 micrograms/kg per min) for 4 h was monitored by sequential measurements of coagulation times and of indexes of thrombin activity in vivo followed by a 24-h clinical observation period. Significant dose-related increases in plasma drug concentrations and activated partial thromboplastin times (aPTT), but no bleeding time prolongation or spontaneous bleeding, was observed. Myocardial ischemia did not occur during therapy but, surprisingly, 9 of the 43 patients experienced an episode of unstable angina 5.8 +/- 2.6 h (mean +/- SD) after infusion. This early recurrent angina was correlated significantly with a higher argatroban dose and with greater prolongation of aPTT but not with other demographic, clinical, laboratory and angiographic characteristics. Pretreatment plasma concentrations of thrombin-antithrombin III complex and fibrinopeptide A were elevated two to three times above normal values. During infusion, thrombin-antithrombin III complex levels remained unchanged, whereas a significant 2.3-fold decrease in fibrinopeptide A concentrations was observed. By contrast, 2 h after infusion, thrombin-antithrombin III complex concentrations increased 3.9-fold over baseline measurements together with return of fibrinopeptide A levels to values before treatment with argatroban. In patients with unstable angina, argatroban inhibits clotting (aPTT prolongation) and thrombin activity toward fibrinogen (fibrinopeptide A decrease), but in vivo thrombin (thrombin-antithrombin III complex) formation is not suppressed. However, cessation of infusion is associated with rebound thrombin (thrombin-antithrombin III complex) generation and with an early dose-related recurrence of unstable angina. Although the mechanism of this clinical and biochemical rebound phenomenon remains to be determined, its implication for the clinical use of specific thrombin inhibitors in the management of ischemic coronary syndromes may be significant

Bezafibrate
Therapeutic indications: Treatment of hyperlipidemia.
Rebound effect:
Author(s): Niort G; Bulgarelli A; Cassader M; Pagano G / Institution: Istituto di Medicina Interna, Universita di Torino, Italy. / Title: Effect of short-term treatment with bezafibrate on plasma fibrinogen, fibrinopeptide A, platelet activation and blood filterability in atherosclerotic hyperfibrinogenemic patients. / Source: *Atherosclerosis*. 1988 Jun. 71(2-3). P 113-9. / Abstract: The

effect of bezafibrate (BZF) on plasma fibrinogen levels has been studied in 62 patients with atherosclerotic vasculopathy and hyperfibrinogenemia (643 +/- 15 (SEM) mg/dl). In a preliminary study, 15-30 days of BZF therapy (400-600 mg/day) normalized fibrinogen values in 16 subjects were compared to 16 controls. The effect was rapid and dose-dependent, and discontinuation in 6 patients who could not complete the study was followed by a rebound increase. A controlled study with 400 mg/day in the other 24 patients for 15 days showed that BZF lowered fibrinogen, PF4, blood filterability and platelet aggregating thresholds to the normal range. BTG and FpA decreased significantly compared to the placebo group (12 and 12 patients randomly distributed) without any variation in potentially biassing hematologic values (WBC, PLTS, Ht, lipids and plasma glucose). BZF may be of value in chronic treatment of hyperfibrinogenemia in atherosclerotic patients with a view to improving the haemorheologic pattern and, hence, reducing activation of the coagulation pathway.

Enoxaparin
Therapeutic indications: Prophylaxis of pulmonary thromboembolism (antithrombotic).
Rebound effect:
Thrombocytopenia with pulmonary embolism. *(USP DI, 1996, p. 1330)*

Ethanol *(alcohol)*
Rebound effect:
Author(s): Baumgartner C; Zeiler K; Auff E; Dal Bianco P; Holzner F; Lesch OM; Deecke L / Institution: Neurologische Universitatsklinik, Wien. / Title: [Does alcohol consumption promote the manifestation of strokes? / Considerations on pathophysiology]. / Source: *Wien Klin Wochenschr*. 1988 Feb 19. 100(4). P 99-107. / Abstract: Arterial hypertension is the most important risk factor in all types of stroke. The significance of alcohol in the pathogenesis of stroke is less well defined. Chronic alcoholism leads to an elevation of blood pressure. Thus, the association between alcohol and stroke might be the blood pressure effect of alcohol. However, some studies have shown a significant influence of alcohol on the incidence of stroke--especially of intracerebral haemorrhage and subarachnoid haemorrhage--even after adjustment for blood pressure. Many possible pathomechanisms are discussed. Alcohol inhibits aggregation of thrombocytes, and chronic alcohol abuse may induce thrombocytopenia, which could lead to a haemorrhagic stroke. Alcohol withdrawal leads to rebound thrombocytosis. Acute alcohol ingestion induces a decrease in fibrinolytic activity and an increase in factor VIII activity, which enhances the thrombotic potential. Additionally, alcohol increases plasma osmolarity, erythrocyte aggregability, haematocrit and blood viscosity, and decreases deformability of erythrocytes. The effects of alcohol on cerebral blood flow are still under debate; there is a deterioration in autoregulation of cerebral blood flow anyway. In animal studies alcohol induced dose-dependent vasospasm of the cerebral blood vessels, which could be a possible pathomechanism in ischaemic, as well as in haemorrhagic stroke. Chronic alcoholism is the most common cause of secondary non-ischaemic cardiomyopathy, which can lead to cerebral embolism via rhythm disorders or intracardiac thrombus formation.
Author(s): Ruf JC; Berger JL; Renaud S / Institution: INSERM, Unit 63, Lyon-Bron, France. / Title: Platelet rebound effect of alcohol withdrawal and wine drinking in rats. Relation to tannins and lipid peroxidation. / Source: *Arterioscler Thromb Vasc Biol*. 1995 Jan. 15(1). P 140-4. / Abstract: We investigated in rats fed a purified diet for 2 and 4 months whether wine drinking was associated with the rebound effect on thrombin-induced platelet aggregation observed after alcohol withdrawal. With 6% ethanol drinking or its equivalent in red or white wine, platelet aggregation was reduced similarly by 70% when the animals drank the alcoholic beverages up to the venipuncture. Depriving the rats of alcoholic beverages for 18 hours was associated with an increase in the platelet response of 124% in those receiving 6% ethanol, of 46% with white wine but

a decrease of 59% in those with red wine. The protective effect of red wine on platelets could be reproduced by tannins (procyanidins) extracted from grape seeds or red wine and added to 6% ethanol, but not by glycerol or wine without alcohol. That was related to inhibition of the alcohol-induced lipid peroxidation as shown by the lowering of conjugated dienes, lipid peroxides, and the increase in vitamin E in plasma. Owing to tannins, the platelets of rats drinking red wine did not exhibit the rebound effect observed hours after alcohol drinking, eventually associated with sudden death and stroke in humans.
Author(s): Renaud SC; Ruf JC / Institution: INSERM, Unit 330, Bordeaux, France. / Title: Effects of alcohol on platelet functions. / Source: *Clin Chim Acta*. 1996 Mar 15. 246(1-2). P 77-89. / Abstract: Recent epidemiologic studies have consistently shown that moderate intake of alcoholic beverages protect against morbidity and mortality from coronary heart disease and ischemic stroke. By contrast, alcohol drinking may also predispose to cerebral hemorrhage. These observations suggest an effect of alcohol similar to that of aspirin. Several studies in humans and animals have shown that the immediate effect of alcohol, either added in vitro to platelets or 10 to 20 min after ingestion, is to decrease platelet aggregation in response to most agonists (thrombin, ADP, epinephrine, collagen). Several hours later, as, in free-living populations deprived of drinking since the previous day it is mostly secondary aggregation to ADP and epinephrine and aggregation to collagen that are still inhibited in alcohol drinkers. By contrast, in binge drinkers or in alcoholics after alcohol withdrawal, response to aggregation, especially that induced by thrombin, is markedly increased. This rebound phenomenon, easily reproduced in rats, may explain ischemic strokes or sudden death known to occur after episodes of drunkenness. The platelet rebound effect of alcohol drinking was not observed with moderate red wine consumption in man. The protection afforded by wine has been recently duplicated in rats by grape tannins added to alcohol. This protection was associated with a decrease in the level of conjugated dienes, the first step in lipid peroxidation. In other words, wine drinking does not seem to be associated with the increased peroxidation usually observed with spirit drinking. Although further studies are required, the platelet rebound effect of alcohol drinking could be associated with an excess of lipid peroxides known to increase platelet reactivity, especially to thrombin.

Epoprostenol, Taprosteno *(prostacyclin, PGI2)*
Therapeutic indications: Antiplatelet.
Rebound effect:
Author(s): Michel G; Seipp U / Institution: Department of Pharmacology, Grunenthal GmbH, Aachen, Fed. Rep. of Germany. / Title: *In vivo* studies with the stabilized epoprostenol analogue taprostene. / Effects on platelet functions and blood clotting. / Source: *Arzneimittelforschung*. 1990 Aug. 40(8). P 932-8. / Abstract: Like the native epoprostenol (prostacyclin, PGI2), the oxacyclic epoprostenol analogue taprostene affects platelet functions. In the rat taprostene inhibited in vivo induced ADP aggregation after i.v. bolus injection, i.v. infusion, s.c. and p.o. application with ED50 values of 4.6 micrograms/kg, 0.36 microgram/kg/min, 190 micrograms/kg and approximately 760 micrograms/kg, respectively. In vivo induced collagen aggregation was inhibited with an ED50 value of 17.1 micrograms/kg i.v. Referring to both bolus injection and i.v. infusion, taprostene was about 3 times less active than the native prostacyclin, but the antiaggregatory effect of taprostene was longer lasting. 5,6-Dihydroepoprostenol inhibited ADP-induced aggregation with an ED50 value of 3 micrograms/kg/min, being 10 fold less active than taprostene. Whereas epoprostenol induced a rebound effect by increasing in vivo aggregation after the end of infusion, no such effect could be seen after taprostene. In the mouse s.c. and p.o. application of taprostene inhibited aggregation with the same efficacy as in the rat. Intra-arterial infusion of taprostene into the rabbit inhibited ADP-induced aggregation ex vivo with an ED50 value of 0.49 micrograms/kg/min. An increased bleeding time was observed in rats in doses of 2.15 micrograms/kg i.v. and higher, corresponding to the antiaggregatory dose range of taprostene. Administered alone, taprostene did

not prolong the clotting time in rats. However, in heparinized rats, the heparin-induced prolongation of clotting time was further increased by taprostene with a threshold dose of 21.5 micrograms/kg (= heparin sparing effect).

Heparin
Therapeutic indications: Treatment and prophylaxis of thrombosis and thromboembolism.
Rebound effect:
With continued use, thrombotic complications may occur as a result of antiplatelet antibody development dependent on Heparin, which gives rise to a large increase of aggregation, causing organ infarction. These new thrombi are composed mainly by fibrin and platelets. This severe form of thrombocytopenia is independent of the origin of dose or route of administration of Heparin. (*USP DI*, 1996, p. 1597)
Thrombosis localized or widespread: the formation of new thrombi refers to the induction of thrombocytopenia by Heparin, consequent to the paradoxical reaction due to irreversible aggregation *(white clot syndrome). (AHFS, 1990, p. 728)*
Author(s): Averkov OV; Zateishchikov DA; Gratsianskii NA; Logutov IuA; Iavelov IS; Ianus Vm / Title: [Unstable angina: effect of aspirin and heparin on treatment outcome in hospital patients (a double-blind, placebo-controlled study)]. / Source: *Kardiologiia*. 1993. 33(5). P 4-9. / Abstract: Aspirin and heparin are regarded as drugs that improve a prognosis in patients with unstable angina, but their comparative efficiency has not been elucidated yet. A randomized double-blind placebo-controlled study of oral aspirin (165 mm once daily) versus intravenous infusion of heparin (1,000 units per hour) was carried out in 94 patients with acute unstable angina (the mean interval after the last anginal attack 5.7 +/- 4.6 hours). During hospital stay, cardiac events (Q wave myocardial infarction or cardiac death) developed in 6 out of 46 patients on aspirin and 6 out of 48 patients on heparin. A significant superiority of heparin during its infusion (1 case of myocardial infarction versus 4 on aspirin) disappeared during the following 24 hours when 2 patients on heparin developed myocardial infarction (due to rebound phenomenon?). Two patients on heparin underwent coronary artery bypass surgery. Among complications only minor bleeding occurred. The results of this study demonstrated no significant benefits of intravenous heparin infusion over oral aspirin during hospitalization in patients with unstable angina. A high incidence (13%) of poor outcomes observed with the two drugs indicates that it is necessary to search for more beneficial antithrombic interventions.

Protamine *(anti-heparin)*
Therapeutic indications: Treatment of toxicity (overdose) by Heparin.
Rebound effect:
Bleeding (rebound heparin). *(USP DI, 1996, p. 2504)*
Rebound heparin, with anti-clotting and bleeding, occurs several hours (8-9 hours) after correct neutralisation of Heparin by Protamina sulphate. *(AHFS, 1990, p. 732)*
Author(s): Kuitunen AH; Salmenpera MT; Heinonen J; Rasi VP; Myllyla G / Institution: Department of Anesthesiology, Helsinki University Central Hospital, Finland. / Title: Heparin rebound: a comparative study of protamine chloride and protamine sulfate in patients undergoing coronary artery bypass surgery. / Source: *J Cardiothorac Vasc Anesth*. 1991 Jun. 5(3). P 221-6. / Abstract: Heparin rebound has been suggested to occur when protamine sulfate, but not protamine chloride, is used to neutralize heparin. This study was undertaken to compare these two protamine salts in 32 patients undergoing coronary artery bypass surgery. Initial heparin and subsequent protamine doses were determined by constructing a heparin-activated coagulation time response curve. Heparin was neutralized either with protamine sulfate or protamine chloride. The total

protamine/heparin dose ratio was 0.71 +/- 0.05 for protamine sulfate and 0.77 +/- 0.07 (mg/100 U) for protamine chloride. The initial neutralization effect, the subsequent behavior of the plasma heparin level, and the various coagulation parameters did not differ significantly between the groups. Two hours after neutralization, a small and temporary increase of plasma heparin level was observed in both groups. The postoperative blood losses were comparable in both groups. Thus, protamine chloride was not a clinically superior antidote to heparin than protamine sulfate. The observed heparin rebound levels were low and clinically insignificant in terms of blood loss, but they were associated with slight changes in coagulation monitoring.
Author(s): Subramaniam P; Skillington P; Tatoulis J / Institution: Cardiothoracic Unit, Royal Melbourne Hospital, Parkville, Victoria, Australia. / Title: Heparin-rebound in the early postoperative phase following cardiopulmonary bypass. / Source: *Aust N Z J Surg*. 1995 May. 65(5). P 331-3. / Abstract: The incidence of the 'heparin-rebound' phenomenon after protamine neutralization of systemic heparinization required for cardiopulmonary bypass (CPB) was investigated. Heparin-effect was detected in 43% of patients studied at 2 h, 31% at 4 h, and 37% at 8 h after reversal of circuit heparin on CPB. Heparin-rebound was shown to be associated with a small but significant increase in postoperative bleeding which was not of clinical importance.

Salicylates *(Aspirin)*
Therapeutic indications: Antiplatelet.
Rebound effect:
Author(s): Mousa SA; Forsythe MS; Bozarth JM; Reilly TM / Institution: DuPont Merck Pharmaceutical Company, Cardiovascular Diseases Division, Wilmington, DE 19880-0400. / Title: Effect of single oral dose of aspirin on human platelet functions and plasma plasminogen activator inhibitor-1. / Source: *Cardiology*. 1993. 83(5-6). P 367-73. / Abstract: Previous reports documented the inhibitory efficacy of different doses of aspirin on arachidonic acid (AA)-induced platelet aggregation, however, the sensitivity of platelets toward other agonists as well as the effects of aspirin on platelet and plasma plasminogen activator inhibitor-1 (PAI-1) release and levels were not investigated. Hence, the present study was undertaken to investigate the effect and duration of action of a single oral dose (650 mg) of aspirin on human platelet functions (n = 34, normal healthy male and female volunteers) including aggregation, fibrinogen binding and PAI-1 release, and on the plasma level of PAI-1. Aspirin demonstrated a rapid onset of action (at 2 h after ingestion) in specifically inhibiting ex vivo AA-mediated functions including (a) fibrinogen binding to gel-purified platelets, (b) platelet aggregation, and (c) platelet PAI-1 release. A peak reduction of plasma PAI-1 level at 2 h was demonstrated as well. The effect of aspirin on the ex vivo AA-mediated effects (a-c) was shown to last for up to 4 days. However, aspirin treatment resulted in a rebound effect in platelet function (a-c) to other platelet agonists such as adenosine diphosphate or the combination of agonists including adenosine diphosphate, epinephrine, and AA. In conclusion, a single oral dose of aspirin has long-acting effects on AA-induced platelet activation and reduces plasma levels of PAI-1 as well.
Author(s): Beving H; Eksborg S; Malmgren RS; Nordlander R; Ryden L; Olsson P / Institution: Department of Experimental Surgery, Karolinska Hospital, Stockholm, Sweden. / Title: Inter-individual variations of the effect of low dose aspirin regime on platelet cyclooxygenase activity. / Source: *Thromb Res*. 1994 Apr 1. 74(1). P 39-51. / Abstract: Thirteen healthy men (age range 24-59 years) received three single doses (30, 75, and 150 mg/day) of aspirin for seven days, followed by a wash-out period of three weeks, in a randomized order. The arachidonic acid metabolite 12-L-5,8,10-heptadecatrienoic acid (12-HHT) was taken as a measure of platelet cyclooxygenase activity. There was a large inter-individual variation in 12-HHT production prior to and during aspirin treatment. After one week of treatment the mean reduction was 69, 72 and 83% for the doses 30, 75 and 150 mg/day respectively. When the degree of cyclooxygenase inhibition was expressed per microgram aspirin administered per kg bw, a positive correlation was established to the activity

before medication. It was found that doses exceeding 1500 micrograms per kg bw is required to achieve a predictable reduction in cyclooxygenase activity. Thus, by determining the pre-treatment cyclooxygenase activity in an individual it should be possible to adjust the enzyme activity to any desired level below 40% of its initial value. 150 mg aspirin/day for one week had a stimulating effect on the platelet basal production of 12-HHT when measured three weeks after the cessation of treatment. This rebound phenomenon was also observed up to six weeks after a single dose of 600 or 1200 mg of aspirin.

Warfarin

Therapeutic indications: Anticoagulant, antithrombotic (factor VII-dependent).

Rebound effect:

Author(s): Raskob GE; Durica SS; Morrissey JH; Owen WL; Comp PC / Institution: Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City 73190, USA. / Title: Effect of treatment with low-dose warfarin-aspirin on activated factor VII. / Source: *Blood*. 1995 Jun 1. 85(11). P 3034-9. / Abstract: Factor VII is an independent risk factor for ischemic heart disease. We performed a prospective study to evaluate the effect of combined low-dose warfarin-aspirin on activated factor VII (factor VIIa) and to determine if abruptly stopping this treatment is associated with a rebound in the level of factor VIIa. Thirty-three patients with clinically stable coronary artery disease were treated with combined 3 mg warfarin and 80 mg aspirin daily for 8 weeks. The factor VIIa level was measured before treatment, weekly during treatment, and 2 weeks after stopping treatment. The mean percent of pretreatment levels of factor VIIa for weeks 1 through 8 of treatment were 60%, 60%, 72%, 70%, 71%, 70%, 74%, and 87%, respectively ($P < .05$ compared with pretreatment for weeks 1 through 7 inclusive); 2 weeks after stopping treatment, the level was 122% (95% confidence interval [CI]; 111% to 133%; $P < .001$ compared with pretreatment). The mean percent level of factor VIIa on-treatment was 74% ($P < .001$). Factor VIIa is reduced by 26% on average during treatment. This finding provides further rationale for the antithrombotic effect of low-dose warfarin. The results suggest a rebound in the factor VIIa level may occur after treatment is stopped. The potential rebound and its clinical importance should be evaluated by further studies.

RENAL DRUGS

Cromakalim
Rebound effect:
Author(s): Smith AB; Bertelsen DL; Kau ST; Chun AL / Institution: Department of Pharmacology, ICI Americas, Wilmington, Delaware 19897-2500. / Title: Effect of cromakalim on micturition function in rats. / Source: *Neurourol Urodyn*. 1993. 12(1). P 99-108. / Abstract: Although many studies investigating the effect of cromakalim on bladder contractility exist, thus far, there are no published studies investigating its effect on micturition function in conscious rats. We measured the effect of cromakalim i.v. on urine output, frequency, volume of each micturition, and blood pressure in saline-diuresed and non-diuresed rats. In saline-diuresed rats cromakalim produced significant decreases in urine output (0.1 mg/kg, 32%; 0.3 mg/kg, 46%; 1.0 mg/kg, 68%) and average frequency (0.1 mg/kg, 36%; 0.3 mg/kg, 51%; 1.0 mg/kg, 70%) in the first 3 hours. At 3-6 hours after administration of cromakalim there were rebound increases in both urine output (0.1 mg/kg, 290%; 0.3 mg/kg, 373%; 1.0 mg/kg, 538%), and frequency (0.1 mg/kg, 147%; 0.3 mg/kg, 181%; 1.0 mg/kg, 314%) and by 6-12 hours the effects of cromakalim on micturition function were gone. Mean arterial pressure dropped to 50% of control immediately after cromakalim administration in saline-diuresed rats and began to return to control levels after 3 hours. Cromakalim produced similar results in non-diuresed rats. The decrease in urine output 0-3 hours after cromakalim administration may have been a consequence of cromakalim's profound decrease in blood pressure that occurred during that time.

Diuretics *(Furosemide, Torasemide, Triamterene)*
Therapeutic indications: Promotes the diuresis, with sodium and potassium excretion (lower in potassium-sparing diuretics like Triamterene).
Rebound effect:
Author(s): Loew D; Barkow D; Schuster O; Knoell HE / Title: Pharmacokinetic and pharmacodynamic study of the combination of furosemide retard and triamterene. / Source: *Eur J Clin Pharmacol*. 1984. 26(2). P 191-5. / Abstract: The pharmacodynamics and pharmacokinetics of the combination of furosemide retard (30 mg)/triamterene (50 mg) were compared with furosemide (30 mg) in 18 healthy male volunteers aged 39.3 +/- 6.3 years. After the administration of furosemide the onset of its effect was very rapid, reaching a maximum between 1.5 to 3 h, and followed by rebound after 9 to 10.5 h. In contrast the combination furosemide retard/triamterene showed a protracted course with a duration of effect up to 12 h. The general effect over 12h of the two preparations was equivalent with respect to the excretion of urine, sodium, chloride and calcium, but the combination caused significantly less excretion of potassium (p less than or equal to 0.05) than furosemide. After a lag-phase of 33.9 +/- 5.4 min the maximum plasma concentration of furosemide was reached after 3.47 +/- 0.66 h, and the elimination half-life was approximately 2 h. After a lag-phase of 33.0 +/- 17.8 min the maximum plasma concentration of the main metabolite of triamterene, the OH-TA sulphuric acid ester, was reached after 1.7 +/- 0.59 h, and its elimination half-life amounted to 1.25 +/- 0.37 h. Because of the sustained release of furosemide from the retard-formulation, its principal pharmacokinetic parameters were better adapted to those of triamterene. The consequences were not only a protracted effect but also an improved electrolyte profile, especially with regard to reduced loss of potassium. In the case of renal insufficiency, however, the potassium level in serum might be increased to an undesirable extent.
Author(s): Sjostrom PA; Beermann BA; Odlind BG / Institution: Department of Internal Medicine, Orebro Medical Center Hospital, Sweden. / Title: Delayed tolerance to furosemide diuresis. Influence of angiotensin converting enzyme inhibition by lisinopril. / Source: *Scand J Urol*

Nephrol. 1988. 22(4). P 317-25. / Abstract: The role of the renin-angiotensin-aldosterone system in the development of tolerance to the diuretic effect of furosemide was investigated in 12 healthy male volunteers. Furosemide in a dose of 40 mg daily for one week had a brisk acute diuretic effect, but did not lead to dehydration, hyponatremia or fall in blood pressure. The reason for this was a reduction in sodium excretion between doses (rebound effect) and a decrease in sensitivity to furosemide from day 1 to day 7. The latter phenomenon is referred to as delayed tolerance to furosemide. Inhibition of angiotensin converting enzyme with lisinopril 20 mg daily did not change the renal furosemide excretion rate, the renal sensitivity to furosemide or the tolerance development. Thus, delayed tolerance to furosemide diuresis was not related to dehydration or activation of the renin-angiotensin-aldosterone system. Other mechanisms, probably intrarenal, will have to be looked for.
Author(s): Scheen AJ / Institution: Division of Clinical Pharmacology, University of Liege, Belgium. / Title: Dose-response curve for torasemide in healthy volunteers. / Source: *Arzneimittelforschung*. 1988 Jan. 38(1A). P 156-9. / Abstract: The safety and diuretic activity of torasemide (1-isopropyl-3- ([4-(3-methyl-phenylamino)pyridine]-3-sulfonyl)urea) were investigated in a phase I single-blind clinical study. After a pretreatment control day on placebo, a single dose of torasemide was administered orally according to an escalating dosage of 2.5, 5, 10 and 20 mg, respectively, in 4 groups of 3 healthy young male volunteers, after an overnight fast and 1 h before breakfast. The peak stimulatory effect on urinary volume was observed within 1 to 2 h and was followed by a gradual decline at the 3rd or 4th h back to or even slightly below the corresponding control values. Thus, the duration of action averaged 3-4 h and only moderate rebound effects were detected. This time-related diuretic activity perfectly fitted with the pharmacokinetics data since torasemide plasma levels peaked at the 1st h after drug administration and thereafter rapidly fell to less than 10% of the maximal plasma concentrations after the 4th h. While 2.5 mg torasemide showed only minor diuretic action, urinary volume and urinary excretion of sodium, chloride and calcium increased linearly with the logarithm of the dose during the first 4 h as well as during the whole 24 h period with 5, 10 and 20 mg torasemide. Conversely, the urinary density and osmolality fell progressively as the dose of torasemide increased. There was a trend towards a moderate decrease in urinary excretion of uric acid which seemed independent of the dose given. Finally, only minimal potassium urinary losses were observed without clear tendency towards an increase with increasing drug doses.
Author(s): Reyes AJ / Institution: Institute of Cardiovascular Theory, Sotelo, Montevideo, Uruguay. / Title: Effects of diuretics on outputs and flows of urine and urinary solutes in healthy subjects. / Source: *Drugs*. 1991. 41 Suppl 3P 35-59. / Abstract: The effects of single oral doses of common formulations of diuretics (i.e. formulations on the market or designed to be marketed) on 24-hour diuresis and natriuresis in healthy subjects are considered as a measure of the renal excretory potency of diuretics. Common formulations of distal tubular diuretics (e.g. hydrochlorothiazide 25mg, xipamide 10mg and 20mg) are more potent diuretics and natriuretics than common formulations of loop diuretics [e.g. furosemide (frusemide) 40mg, torasemide 2.5, 5 and 10mg]. Indeed, some common formulations of loop diuretics, such as torasemide 2.5, do not increase 24-hour diuresis or natriuresis in healthy subjects. 24-hour kaliuresis and magnesiuresis are elevated by common formulations of distal tubular diuretics, but they are only slightly increased or (more usually) not affected by common formulations of loop diuretics, when single doses are administered to healthy individuals. Common formulations of loop diuretics have lower diuretic and natriuretic potency and lower kaliuretic and magnesiuretic effects than common formulations of distal tubular diuretics, because the pronounced elevations in urinary excretions caused by loop diuretics during the first 6 hours after dosing are followed by rebounds, with respect to post-placebo excretions, between 6 and 24 hours after dosing. These rebounds, which affect the urinary flows of fluid, chloride, sodium, potassium and magnesium, do not occur after administration of common formulations of distal tubular diuretics, at least during the first 24 hours after administration of

single doses to healthy subjects. The time courses of urinary excretions after loop diuretics are dose dependent. Higher doses produce more rapid changes in the urinary flows of fluid, chloride, sodium, potassium and magnesium than lower doses, to the extent that single administration of torasemide 2.5 or 5mg to healthy subjects is followed by urinary fluid and solute flows whose time courses resemble those after administration of hydrochlorothiazide 25mg.

Author(s): Reyes AJ; Leary WP / Institution: Institute of Cardiovascular Theory, Montevideo, Uruguay. / Title: Renal excretory responses to single and repeated administration of diuretics in healthy subjects: clinical connotations. / Source: *Cardiovasc Drugs Ther*. 1993 Jan. 7 Suppl 1P 29-44. / Abstract: Administration of an initial oral dose of hydrochlorothiazide 25 mg to healthy subjects is followed by increased 24-hour urinary outputs of sodium, chloride, and potassium. On the fourth day of once-daily dosing with hydrochlorothiazide 25 mg, 24-hour natriuresis and chloriuresis are no longer augmented, but the elevation in 24-hour kaliuresis that follows the first dose remains unchanged. Twenty-four-hour urinary calcium output is consistently reduced during repeated once-daily administration of hydrochlorothiazide 25 mg. The first oral dose of the loop diuretic torasemide augments the average natriuresis and kaliuresis in the 6 hours immediately after dosing in healthy subjects, in a dose-dependent fashion, within the 2.5 to 10-mg range. These increased urinary outputs are followed by rebounds below postplacebo values between 6 and 24 hours after dosing. As a result of this biphasic response, torasemide 2.5 mg qualifies as a nondiuretic formulation (it does not elevate 24-hour natriuresis), whereas torasemide 5 and 10 mg qualify as diuretic formulations. After the seventh dose of torasemide 5 or 10 mg during a regimen of once-daily therapy, 24-hour urinary sodium and chloride outputs no longer differ from their postplacebo counterparts. Twenty-four-hour kaliuresis tends to increase in a dose-dependent fashion after the first dose of torasemide (torasemide 2.5 and 5 mg do not augment it significantly), but this tendency is no longer present after the seventh once-daily dose, when torasemide (2.5, 5, or 10 mg) does not elevate the mean 24-hour kaliuresis. Twenty-four-hour calciuresis tends to increase in a dose-dependent manner (torasemide 2.5 mg does not elevate it significantly) after the first dose of torasemide; this calciuretic effect does not change in intensity after 7 days of once-daily treatment. The time course of natriuresis over the 24 hours following the administration of any given formulation of a loop or of an early distal tubular diuretic to healthy subjects is alike after the first and after the nth once-daily dose; therefore, it constitutes a definite characteristic of any given oral formulation. In the case of torasemide, lower doses have more protracted effects on natriuresis, to the extent that the time course of natriuresis over the 24 hours after administration of torasemide 2.5 mg to healthy subjects resembles the time course after administration of hydrochlorothiazide 25 mg, rather than the time course after administration of the overtly diuretic formulation torasemide 10 mg.

Author(s): de Jonge JW; Knottnerus JA; van Zutphen WM; de Bruijne GA; Struijker Boudier HÁ / Institution: University of Limburg, Maastricht, Netherlands. / Title: Short term effect of withdrawal of diuretic drugs prescribed for ankle oedema. / Source: *BMJ*. 1994 Feb 19. 308(6927). P 511-3. / Abstract: To determine the effect of withdrawing diuretic drugs on oedema in patients prescribed them for only ankle oedema, excluding patients with cardiac, hepatic, or renal failure. Randomised controlled trial, 15 general practices in the Netherlands, 1202 patients aged 65 years or older and taking diuretic drugs, 63 of whom were eligible for the trial. Change in volumetrically determined ankle oedema (oedema index) over six weeks. 34 patients were randomised to stop diuretics and 29 to the control group. In eight patients diuretics had to be restarted. Among patients who had diuretics withdrawn successfully, rebound oedema caused a temporary increase in mean oedema index. The peak level (3.5% (95% confidence interval 1.5% to 5.2%) was reached in the third week, after which the oedema seemed to be returning to the baseline level. Few patients who have been prescribed diuretics for only ankle oedema clearly have no contraindications to withdrawing diuretics. If patients are unlikely to have cardiac insufficiency and careful monitoring

is provided, withdrawal of diuretics seems to be feasible, though moderate rebound oedema may occur for a short time.
Author(s): Vree TB; Van Den Biggelaar-Martea M; Verwey-Van Wissen CP / Institution: Department of Clinical Pharmacy, Academic Hospital Nijmegen Sint Radboud, Netherlands. / Title: Frusemide and its acyl glucuronide show a short and long phase in elimination kinetics and pharmacodynamic effect in man. / Source: *J Pharm Pharmacol*. 1995 Nov. 47(11). P 964-9. / Abstract: The pharmacokinetics of 80 mg frusemide given orally were investigated in normal subjects using a direct HPLC method for parent drug and its acyl glucuronide conjugate. Two half-lives could be distinguished in the plasma elimination of both frusemide and its conjugate, with values of 1.25 +/- 0.75 and 30.4 +/- 11.5 h for frusemide and 1.31 +/- 0.60 and 33.2 +/- 28.0 h for the conjugate. The renal excretion rate-time profile showed two phases; the rapid elimination phase lasted from 0-15 h and the second and slow phase, from 15-96 h. During the first 15 h, 33.3 +/- 4.8% of the dosed frusemide was excreted; in the remaining period 15-96 h, 4.6 +/- 1.5% was excreted. In the same two periods the excretion of the glucuronide was 13.4 +/- 4.7 and 1.9 +/- 1.1%, respectively. The mean renal clearance of frusemide was 90.2 +/- 16.9 mL min-1 during the first period and 91.5 +/- 29.3 mL min-1 in the remaining period, during which the stimulation of urine production was absent. The renal clearance of the acyl glucuronide was 702 +/- 221 mL min-1 in the first period, but only 109 +/- 51.0 mL min-1 in the second period. The stimulated urine production in the first 6 h after administration amounted to 2260 +/- 755 mL (measured urine production minus baseline value of 1 mL min-1 (360 mL). During the second or rebound period (6-96 h after drug administration), the quantity of urine was 990 +/- 294 mL lower than what would have been expected from the baseline production of 5400 mL. This reduced production (0.82 mL min-1) is equivalent to an 18% reduction in the average urine flow rate of 1 mL min-1.

Dialysis

Therapeutic indications: Removal of urea and toxic metabolites of blood circulation.

Rebound effect:

Author(s): Pedrini LA; Zereik S; Rasmy S / Institution: Servizio di Dialisi, Ospedale S Isidoro, Trescore Balneario, Bergamo, Italy. / Title: Causes, kinetics and clinical implications of post-hemodialysis urea rebound. / Source: *Kidney Int*. 1988 Dec. 34(6). P 817-24. / Abstract: The rapid increase in end-dialysis urea concentration (Co) immediately after the end of dialysis (HD), which greatly exceeds that expected as an effect of urea generation and defined as “net rebound,” was assessed in 21 chronic HD patients. The curve of serial values of net rebound correlated (r = 0.70) with the theoretical curve predicted by the two pool urea kinetics model (UKM). A mean equilibrium concentration (Ce) was achieved in 48 minutes, with a 7.58% increase in Co. Stabilized rebound (Re) was compared after four different HD procedures, and significant correlations were found between the magnitude of Re and the indexes of HD efficiency, dialyzer clearance (r = 0.75) and Kt/V (r = 0.68). The highest values of Re (8.6% and 8.8%) were observed after the procedures with largest urea removal, irrespective of the biocompatibility conditions (new or reused dialyzers). The single pool UKM applied with the stabilized end-HD urea concentration Ce instead of Co resulted in more physiological values of urea distribution volume (56.1% vs. 50.5% of body wt) and in lower values of Kt/V (0.64 vs. 0.73, P less than 0.001) and protein catabolic rate (1.07 vs. 1.17 g/kg/day, P less than 0.001). A reequilibration process, rather than protein hypercatabolism, seems to be responsible for most rebound, the magnitude of which correlated with the efficiency of the procedure. Only by considering Ce as the true end-HD urea concentration it is possible to minimize the errors arising from the application of a single pool analysis to a two pool system.

GASTROINTESTINAL DRUGS

Antiemetic drugs

Benzquinamide
Therapeutic indications: Prevention and treatment of nausea and vomiting.
Rebound effect:
Nausea and vomiting. *(AHFS, 1990, p. 1656)*

Buclizine
Therapeutic indications: Prevention and treatment of nausea and vomiting.
Rebound effect:
Nausea and vomiting. *(AHFS, 1990, p. 1657)*

Cyclizine
Therapeutic indications: Prevention and treatment of nausea and vomiting.
Rebound effect:
Nausea and vomiting. *(AHFS, 1990, p. 1657)*

Diphenidol
Therapeutic indications: Treatment of nausea and vomiting.
Rebound effect:
Nausea and vomiting. *(AHFS, 1990, p. 1660)*

Phenothiazines *(Chlorpromazine, Perphenazine, Prochlorperazine, Trifluprомazine)*
Therapeutic indications: Treatment of nausea and vomiting.
Rebound effect:
Nausea and vomiting. *(USP DI, 1996, p. 2362; AHFS, 1990, p. 1185)*

Trimethobenzamide
Therapeutic indications: Treatment of nausea and vomiting.
Rebound effect:
Nausea and vomiting. *(USP DI, 1996, p. 2915; AHFS, 1990, p. 1665)*

Constipating drugs

Paregoric *(tincture of Opium - Morphine)*
Therapeutic indications: Treatment of diarrhea.
Rebound effect:
Diarrhea. *(USP DI, 1996, p. 2286; AHFS, 1990, p. 1629)*

Laxative drugs

Laxatives *(Hyperosmotic, Mineral Oil, Saline, Stimulants, etc.)*
Therapeutic indications: Treatment of constipation.
Rebound effect:
Prolonged use of laxatives, especially the stimulant laxatives, caused chronic constipation and intestinal function loss. *(AHFS, 1990, p. 1633)*

Antidyspeptic drugs

Author(s): Reasbeck PG / Title: Somatostatin treatment of gastrointestinal fistulas: evidence for a rebound effect on withdrawal. / Source: *Aust N Z J Surg*. 1984 Oct. 54(5). P 465-7. / Abstract: Three patients with external fistulas from the gastrointestinal tract were treated with somatostatin, a peptide which inhibits pancreatic, gastric and intestinal secretion. Although somatostatin reduced fistula output in two patients and possibly prevented haemorrhage in one, it did not induce fistula closure in any; moreover on withdrawal of somatostatin one patient developed life threatening gastrointestinal haemorrhage and a transient fistula hypersecretion occurred in the others. This experience of somatostatin treatment was less favourable than that previously reported in other small series. Positive nitrogen balance was probably not maintained during treatment in the three patients reported here and in one patient in a previous study in whom somatostatin was ineffective; the peptide may only promote fistula closure in adequately nourished patients.

Histamine H2 receptor antagonists *(Cimetidine, Famotidine, Nizatidine, Pepticidina, Ranitidine)*
Therapeutic indications: Treatment of gastric and duodenal ulcer.
Rebound effect:
#Perforations of chronic peptic ulcers occur during treatment with Cimetidine. One month after the suspension of treatment occurred recurrence of ulcers in 41% of patients, within one week after the suspension of the drug. *(AHFS, 1990, p. 1667, 1668)*
Author(s): Kozol R; Fromm D; Ray TK / Title: Effects of a naturally occurring polyamine on acid secretion by isolated gastric mucosa. / Source: *Proc Soc Exp Biol Med*. 1984 Jan. 175(1). P 52-7. / Abstract: Determination of the effects of spermine on acid secretion by isolated rabbit gastric mucosa shows paradoxical responses at neutral luminal pH. Initial inhibition of acid secretion was followed by a return to near basal rates. However, measurement of mucosal and serosal rates of CO2 release indicated that spermine causes prolonged inhibition of acid secretion. Similar prolonged inhibition is seen with mucosa exposed to an acidic luminal pH. The inhibitory effect of spermine is reversed by the addition of K+ to the mucosal side, suggesting spermine interferes with a K+ site at the secretory membrane. Serosal addition of spermine is without effect. The apparent acid secretory rebound phenomenon observed after the addition of spermine is most likely related to formation of H+ in the luminal bathing solution rather than proton secretion by the mucosa.
Author(s): Ruckebusch Y; Malbert CH; Crichlow EC / Title: Hexamethonium: a probe to assess autonomic nervous system involvement in upper gastrointestinal functions in conscious sheep. / Source: *Vet Res Commun*. 1987. 11(3). P 293-303. / Abstract: Hexamethonium, which inhibits cholinergic transmission by preventing acetylcholine release, has been considered an ideal reference drug for the blockade of autonomic ganglia, Auerbach plexus and reflex gastrointestinal secretions. The degree of inhibition of ruminant gastrointestinal functions with this reference drug was as follows: cyclical contractions of the reticulo-rumen and abomasal motility greater than gastric acid secretion and duodenal migrating myoelectrical complexes. Although reduced at high dosages, the

initiation of migrating myoelectric complexes was enhanced at clinically used dosages. The duration of the inhibition of reticular contractions was dose-related varying from 0.5 to 5 h for 1.25 to 20 mg/kg subcutaneously. Abomasal motility and acid secretion were similarly reduced but exhibited strong and long-lasting rebound effects. Inhibition of the reticulum by the blockade of muscarinic receptors by atropine was also dose-related lasting from 0.5 to 3 h for 0.5 to 2 mg/kg, whereas inhibition of the abomasal motor and secretory functions lasted from 1 to 6 h. These results suggest a higher degree of impingement of the parasympathetic pathways on abomasal acid secretion and motility than on the cyclical activity of the reticulum and only a modulatory role of the extrinsic neural activity on the cyclical motor events of the duodenum.

Author(s): Ekblad EB; Licko V / Title: Conservative and nonconservative inhibitors of gastric acid secretion. / Source: *Am J Physiol*. 1987 Sep. 253(3 Pt 1). P G359-68. / Abstract: Inhibitors of the initial step (H2-antagonist) and of the final step (thiocyanate, SCN-; and nitrite, NO2-) were used to study the dynamics of acid secretion in isolated frog gastric mucosa. Tissues were mounted in flow-through chambers, and the acid secretion rate (SR) was recorded on a pH-stat microprocessor. Continuous presence of H2-antagonist decreases the SR to a lower steady state, and on removal the SR returns to basal SR, causing a net loss of acid, the nonconservative effect. The amount of lost acid is a unique function of exposure, thus, independent of the patterns (pulses or steps) of inhibition. In contrast, continuous presence of SCN- or NO2- (below 3 mM) results in an undershoot in SR with a return to basal SR, whereas at higher concentrations there is no return. Removal of these inhibitors causes an overshoot in SR with return to basal SR. The rebound acid is equal to acid suppressed by NO2- and low concentration of SCN-, resulting in no net loss of acid, the conservative effect, whereas at high concentrations of SCN- there is an apparent loss of acid. In maximally secreting tissue the overshoot of SR is not observed. However, the acid is not lost, merely delayed. In resting tissue NO2- also merely delays the exit of the acid produced in response to forskolin. The rebound acid is proposed to reside in a sequestered “acid” pool that is stable for at least 120 min. Results with NO2- and SCN- suggest an effect on a saturable exit enzyme, possibly the K+-H+-ATPase.

Author(s): Rigaud D; Dubrasquet M; Accary JP; Laigneau JP; Lewin MJ / Institution: INSERM U 286, Faculte Bichat, Paris. / Title: Sequential somatostatin and gastrin releases in response to secretin in rat *in vivo*. / Source: *Gastroenterol Clin Biol*. 1991. 15(10). P 717-22. / Abstract: Secretin in known to inhibit gastric acid secretion. Exogenous secretin has also been shown to have a biphasic effect on acid secretion, being stimulatory then inhibitory. To explain this effect, we studied the timing of gastrin, somatostatin, and HCl releases in the gastric lumen in response to an i.v. bolus of secretin (360 pmol) or saline in conscious rats provided with a chronic double gastric fistula and having had or not antrectomy. After secretin but not saline, an immediate and transient increase in acid and gastrin secretions was first observed. After a 4 min lag, a dramatic increase in somatostatin secretion was then observed, together with a 90 percent inhibition of acid secretion and a return of gastrin release to basal level. Twenty min after secretin administration, a rebound increase in acid and gastrin outputs occurred, whereas somatostatin output returned to basal level. The secretin-induced somatostatin release was higher in rats with antrectomy than in those without antrectomy suggesting that the observed somatostatin output mostly originated from the fundus. This present study suggests that a bolus of secretin induced a gastrin release and thus could stimulate acid secretion. These pharmacological findings could provide an explanation for the so-called paradoxical secretin-induced stimulation of gastrin secretion in particular conditions.

Author(s): Fullarton GM; Macdonald AM; McColl KE / Institution: University Department of Surgery, Western Infirmary, Glasgow, UK. / Title: Rebound hypersecretion after H_2-antagonist withdrawal - a comparative study with nizatidine, ranitidine and famotidine. / Source: *Aliment Pharmacol Ther*. 1991 Aug. 5(4). P 391-8. / Abstract: Our previous study demonstrated rebound nocturnal acid hypersecretion after a 4-week course of nizatidine. Nocturnal acid output was increased by 77% two days after discontinuing treatment compared with pretreatment values. To

confirm this effect with other H2-blockers we assessed daytime intragastric pH, fasting and meal-stimulated plasma gastrin and nocturnal acid output in 9 duodenal ulcer patients in remission before, during and two days after treatment with three different drugs. Each patient received 4-week courses of 300 mg ranitidine, 40 mg famotidine or 300 mg nizatidine, taken at 20.00 hours in randomized order with a 'washout' period of 4 weeks between each course of drug. Median nocturnal acid output (mmol/10 h) decreased during treatment with ranitidine to 3 (range 0-17), famotidine to 4 (1-12) and nizatidine 6 (0-40) compared with the respective pre-treatment values, 49 (20-126; P less than 0.01), 52 (22-105; P less than 0.01) and 32 (23-114; P less than 0.01). Two days after discontinuing treatment nocturnal acid output was increased after ranitidine at 77 (28-237; P less than 0.04) and after nizatidine at 64 (17-130; P less than 0.05) compared with pre-treatment values. There was no significant change in nocturnal acid output after famotidine at 57 (27-107) compared with the pre-treatment value. There was no change in daytime intragastric pH with any drug during or after treatment compared with the pre-treatment values. Fasting and meal-stimulated plasma gastrin concentrations were increased on the final treatment day with ranitidine and famotidine but had returned to pretreatment levels two days after treatment. The rebound acid hypersecretion may contribute to the high ulcer relapse rate after discontinuation of H2-receptor antagonists.

Author(s): Debongnie JC / Institution: Service de gastroenterologie, Clinique St-Pierre, Ottignies. / Title: [Currents aspects of H_2 receptor antagonists in the treatment of ulcers]. / Source: *Acta Gastroenterol Belg*. 1992 Sep-Dec. 55(5-6). P 415-22. / Abstract: Inhibition of H2 receptors has been the first fully evaluated treatment of peptic ulcer and remains the most widely used mode of therapy. In this review, we summarize the current data on clinical pharmacology, therapeutic indications and results of the four currently used drugs: cimetidine - ranitidine - pepticidine - nizatidine. Their similarities are stressed. Recent data are underlined. The superiority or necessity of a single evening dose is questioned, as well as the clinical importance of tolerance and rebound. The effect on gastric alcohol dehydrogenase is mentioned pending further work on the clinical importance of this discovery. In the acute treatment, the antisecretory potency is of major importance in duodenal ulcer, the duration of treatment in gastric ulcer. Maintenance treatment prevents complication as well as recurrence. H2 receptor antagonists remain a primary treatment of peptic ulcer.

Author(s): Kubo K; Uehara A; Kubota T; Nozu T; Moriya M; Watanabe Y; Shoji E; Santos SB; Harada K; Kohgo Y / Institution: Dept. of Internal Medicine (III), Asahikawa Medical College, Hokkaido, Japan. / Title: Effects of ranitidine on gastric vesicles containing H^+,K^+-adenosine triphosphatase in rats. / Source: *Scand J Gastroenterol*. 1995 Oct. 30(10). P 944-51. / Abstract: To ascertain the mechanism for rebound acid hypersecretion after treatment with an H2-receptor blocker, we investigated the effects of ranitidine on gastric H+,K(+)-adenosine triphosphatase (ATPase) in rats. Male Wistar rats received ranitidine (1-50 mg/kg body weight intraperitoneally twice a day for 5 days). The rats were starved for 15 h after the last treatment and then killed, and gastric vesicles containing H+,K(+)-ATPase were prepared. Treatment with ranitidine dose-dependently increased protein content in the gastric vesicular fraction purified from the gastric mucosa without changing total protein content. Ranitidine also increased the content of a 94,000-dalton protein, the catalytic subunit of H+,K(+)-ATPase. On the other hand, ranitidine did not affect the specific activity of the enzyme (mumol/min/mg of the gastric vesicular protein). Since gastric vesicles in the fasting state mainly consist of the tubulovesicular membrane, these results suggest that ranidine administration increases total tubulovesicular H+,K(+)-ATPase content (mumol/min/rat) by increasing the number of tubulovesicles per parietal cell. The ranitidine-induced increase in total tubulovesicular H+,K(+)-ATPase activity was still evident 1 week after treatment and returned to control level 1 month later. All these findings suggest that the increased content and total activity of tubulovesicular H+,K(+)-ATPase after ranitidine treatment may contribute to the mechanism for acid rebound after H2-blocker therapy.

***Antacids** (Calcium carbonate, Aluminum hydroxide, Magnesium hydroxide)*
Therapeutic indications: Treatment of hyperacidity, gastritis and peptic ulcer.
Rebound effect:
Author(s): Herzog P / Title: [Effect of antacids on mineral metabolism]. / Source: *Z Gastroenterol*. 1983 Mar. 21 SupplP 117-26. / Abstract: Side effects of antacid therapy are dose dependant and compound related. High dose antacid intake may lead to fluid retention in the body depending on the sodium content of the different antacid preparations. Sodium bicarbonate ingestion provokes metabolic alkalosis and alkaliuria, the "nonsystemic calcium and magnesium containing antacids" cause these changes too, but to a lower degree. Urinary pH elevation favours the precipitation of calcium and magnesium salts, predisposing to renal stone formation. In patients with renal insufficiency the calcium and magnesium absorption may lead rapidly to toxic serum concentrations. Calcium and magnesium containing acids may provoke an acid rebound, which is clinically not relevant following magnesium-hydroxide-ingestion. Phosphorus depletion is an important side effect of aluminum hydroxide intake. The phosphorus depletion syndrome combined with skeletal demineralisation and osteomalacia may occur. As well as calcium and magnesium cations the tribasic aluminum will be absorbed from the gut in small amounts. In patients with renal insufficiency aluminum deposition in the brain grey matter following Al(OH)3 ingestion will occur and seems to be a co-factor for the development of a dialysis encephalopathy syndrome. The clinical relevance of aluminum absorption from gut in patients with normal renal function is unknown until now.
Author(s): Hade JE; Spiro HM / Institution: Yale University School of Medicine, New Haven, Connecticut. / Title: Calcium and acid rebound: a reappraisal. / Source: *J Clin Gastroenterol*. 1992 Jul. 15(1). P 37-44. / Abstract: We review acid rebound, the seemingly paradoxical increase in acid secretion resulting from administration of an antacid. Primarily a laboratory observation, the demonstration of the phenomenon was a major contributing factor to the swift, and possibly unjustified, fall from grace of calcium carbonate in the therapy of peptic ulcer disease despite years of apparently successful use. Calcium, as carbonate or other salts, causes an increase in gastric acid secretion owing, at least in part, to direct ionic stimulation. Another possible mode of action involves antral alkalinization with subsequent gastrin release. Other antacids, notably magnesium hydroxide and aluminum hydroxide, may therefore also cause rebound, but the data in this area are less convincing. Despite the demonstration that acid rebound occurs, no one has thoroughly investigated its clinical import. What limited data actually exist suggest no obvious clinically significant deleterious effect from use of calcium carbonate in peptic ulcer. Because of calcium carbonate's excellent acid-neutralizing capacity, its venerable past record in treating ulcer disease, and recent observations that low-dose antacids heal peptic ulcers, it is appropriate to reevaluate acid rebound, to focus on its clinical significance, if any.
Author(s): Mones J; Carrio I; Sainz S; Berna L; Clave P; Liszkay M; Roca M; Vilardell F / Institution: Servicio de Patologia Digestiva, Hospital de la Sante Crei i Sant Pau, Universitat Autonoma Barcelona, Spain. / Title: Gastric emptying of two radiolabelled antacids with simultaneous monitoring of gastric pH. / Source: *Eur J Nucl Med*. 1995 Oct. 22(10). P 1123-8. / Abstract: The aim of this study was to assess the gastric emptying rate of two antacids using an scintigraphic technique and simultaneous monitoring of gastric pH in 16 healthy male volunteers. Ten ml of Talcid (hydrotalcite 1 g) and Maalox (Mg-Al-hydroxide), with a similar neutralization capacity, were labelled with technetium-99m using a pyrophosphate bridge. Labelled antacids were given on separate days (within 2 weeks), 1 h after a standard meal. Intragastric pH was measured for at least 4 h, using ambulatory pH-metry with a dual-crystant antimony catheter. Continuous monitoring was started 1 h prior to the meal (baseline) and lasted 3 h (post-prandial, post-antacid and final periods). The antacid capacity of labelled and unlabelled antacids was similar. The mean percentages of antacids retained in the stomach fitted a linear model. The mean half-emptying time

of Talcid was 63.9 +/- 27.9 min, while that of Maalox was 57.3 +/- 23.9 min (P = NS). The recordings of gastric pH (mean values of pH for each period) showed a similar profile for both antacids. The mean pH (Maalox vs Talcid) was 1.69 vs 2.07 in the baseline period, 1.95 vs 1.93 in the post-prandial period, 1.79 vs 1.15 in the post-antacid period (P = NS) and 0.4 vs 0.52 in the final period (P < 0.05 vs prior periods). In conclusion, the gastric emptying of Talcid and Maalox was similar and pH profiles were parallel and remained unchanged for the two antacids within the first hour of intake. A significant decrease in pH was observed 1 h after intake of the antacids, suggesting a possible rebound effect.
Author(s): Hurlimann S; Michel K; Inauen W; Halter F / Institution: Department of Medicine, Inselspital, Bern, Switzerland. / Title: Effect of Rennie Liquid versus Maalox Liquid on intragastric pH in a double-blind, randomized, placebo-controlled, triple cross-over study in healthy volunteers. / Source: *Am J Gastroenterol*. 1996 Jun. 91(6). P 1173-80. / Abstract: Despite years of successful use of calcium-containing antacids in acid-related disease, allegations of gastric rebound following their intake has brought these agents into disrepute. By assessing intragastric acidity over the 24-h period, we evaluated whether antacids induce a clinically relevant acid rebound. Twelve healthy volunteers were assigned to a double-blind, placebo-controlled, triple cross-over comparison of placebo, Maalox Liquid, and a calcium-containing antacid, Rennie Liquid. The two antacids had identical neutralizing capacity. Each drug was administered at standard doses q.i.d 1 h after the main meals (at 1000, 1400, and 1900 h) and at bedtime (2300 h). Intragastric acidity was monitored by continuous ambulatory 24-h pH-metry on 3 separate days with a wash-out period of 1 wk. Special attention was given to the acidity of pre-determined postantacid time intervals during the day and night. Both antacids led to a significant increase of the median 24-h pH and the median pH of the first postantacid hour, compared with placebo. Neither Rennie Liquid nor Maalox Liquid led to a drop of intragastric pH during the putative acid rebound time (2nd and 3rd postantacid hr and at night). A marginal increase in serum calcium and gastrin concentration with Rennie Liquid, and magnesium concentration with Maalox Liquid, were observed. No gastric acid rebound was detected with the calcium carbonate-containing antacid, Rennie Liquid, or with Maalox Liquid at standard doses. An identical increase of intragastric pH was achieved with Rennie Liquid and Maalox Liquid during the first postantacid hour and the entire 24-h period.

Misoprostol *(Cytotec)*
Therapeutic indications: Treatment of NSAID-induced gastric ulcer and duodenal ulcer.
Rebound effect:
Stomach or abdominal pain in 13-40% of patients. *(USP DI, 1996, p. 2085)*
Gastric and abdominal pain, gastrointestinal bleeding and inflammation without question established; progression of AINH-induced gastric disease. *(AHFS, 1990, p. 1688)*

Sucralfate *(protector of the gastric mucosa)*
Therapeutic indications: Treatment of gastric ulcer.
Rebound effect:
Gastric pain and discomfort. *(USP DI, 1996, p. 2701; AHFS, 1990, p. 1695)*

Anti-inflammatory drugs

Mesalazine *(5-amino salicylic acid)*
Therapeutic indications: Treatment and prophylaxis of gastrointestinal inflammatory diseases (ulcerative colitis, Crohn's disease).

Rebound effect:
Acute intolerance syndrome: severe pain, stomach or abdominal cramp, diarrhea with blood, fever, severe headache and rash. *(USP DI, 1996, p. 1998; AHFS, 1990, p. 1677)*
In patients receiving the drug via rectal occurred exacerbation of acute inflammation or it is extended by the entire colon (pancolites). *(AHFS, 1990, p. 1677)*

Olsalazine *(5-amino salicylic acid)*
Therapeutic indications: Treatment and prophylaxis of gastrointestinal inflammatory diseases (ulcerative colitis, Crohn's disease).
Rebound effect:
Exacerbation of ulcerative colitis (diarrhea with blood, fever and rash). *(USP DI, 1996, p. 2209)*

Choleretic drugs (bile secretion inhibitors)

Substance P
Rebound effect:
Author(s): Magnusson I / Title: Anticholeretic effects of substance P and somatostatin. / Source: *Acta Chir Scand Suppl*. 1984. 521P 1-57. / Abstract: The aim of the present work was to study the effect of substance P (SP) and somatostatin (SST) on hepatic bile flow. For this purpose a total of 54 anesthetized mongrel dogs were used. The gallbladder was excluded by ligation of the cystic duct and a common duct fistula was created by insertion of a catheter into the common duct. Both SP and SST were found to exert an anticholeretic effect in the dog. SST was also found to be anticholeretic in man. In the dog, SP was infused at dosages from 0.5-20 ng kg-1 min-1 and exerted a significant anticholeretic effect at a dosage of 2.5 ng or higher. At dosages of 2.5 and 20 ng kg-1 min-1, SP decreased the basal bile secretion by about 20 and 40% respectively. The decrease in bile flow was accompanied by decreased outputs of sodium, potassium, chloride, bicarbonate and amylase. With taurocholate-stabilized and taurocholate-stabilized and hormone-induced bile secretion, SP had the above mentioned effects and in addition the output of bile acids decreased. The effect of SP occurred within minutes and after withdrawal of SP there was a positive rebound effect, with a magnitude of about 30% following the 20 ng dosage. SST at dosages from 20-1000 ng kg-1 min-1 induced an anticholeretic effect with a magnitude of 10-25%. With both basal and taurocholate-stabilized bile secretion, the outputs of bile, bile acids and electrolytes decreased during the infusion period and remained diminished for 10-20 min after termination of the infusion. Unlike SP, SST had no anticholeretic effect in the presence of CCK or secretin. A simultaneous infusion of SP and SST decreased bile flow more than either agent alone. The anticholeretic effect of SST was verified in five patients. They had all been operated on for choledocholithiasis. In four patients a complete diversion of bile was obtained with a Foley catheter in the common duct and in the fifth patient from an impacted stone in the common duct. During infusion of SST, 250 ug h-1, the outputs of hepatic bile and bile acids decreased while the outputs of cholesterol and phospholipids were unchanged. The serum bile acid concentration was unaffected by SST and therefore SST is suggested to exert an inhibitory effect on bile acid synthesis. The changes in electrolyte outputs induced by SST in man corresponded to those in the dog.

PULMONARY DRUGS

Author(s): Syabbalo NC; Bundgaard A; Widdicombe JG / Title: Effects of exercise on nasal airflow resistance in healthy subjects and in patients with asthma and rhinitis. / Source: *Bull Eur Physiopathol Respir*. 1985 Nov-Dec. 21(6). P 507-13. / Abstract: We studied the effect of exercise on nasal airflow resistance (Rnaw) and the relationship between exercise-induced asthma (EIA) and Rnaw. Rnaw was obtained by measurement of flow through the nose and mouth (in series) at constant inflow pressure. In seven healthy subjects, there were statistically significant decreases in Rnaw (39.5 +/- 6.3 and 49.0 +/- 8.2%; p less than 0.05) and no change in forced expired volume immediately after exercise on a bicycle ergometer at both 75 W and 100 W, but there was no significant difference between these two resistance changes. At 75 W, Rnaw returned to pre-exercise level at 15-20 min after exercise. At 100 W, Rnaw remained below the pretest value 30 min after exercise. In eleven asthmatics, treadmill running for 1, 2 and 6 min caused significant decreases (p less than 0.05) in Rnaw up to 44.8 +/- 3.3%, reaching levels similar to those of controls after exercise. With 6 min exercise, four of nine patients developed EIA; these subjects had allergic rhinitis as well, and recovery to pretest valued tended to be quicker than in those without EIA. In healthy subjects at both ergometer workloads, there was a rebound increase in Rnaw in 40-50% of the subjects appearing 20-30 min after exercise. In the patients, there was a rebound increase in Rnaw in about 60% of the subjects 5-10 min after exercise. Both for healthy subjects and patients, the rebound increase in Rnaw was smaller at the higher workloads.

Asthma drugs

Adrenergic bronchodilators *(Albuterol, Bitolterol, Ephedrine, Epinephrine, Fenoterol, Formoterol, Isoetharine, Isoprenaline, Orciprenalina, Salbutamol, Salmeterol, Terbutaline, etc.)*

Therapeutic indications: Bronchospasm of bronchial asthma and chronic obstructive pulmonary disease.

Rebound effect:

Severe difficulty breathing, increased wheezing; cough or other bronchial irritation. *(USP DI, 1996, p. 621)*

Paradoxical bronchospasm is observed with the use of salmeterol. Fatalities have been reported with excessive use of sympathomimetic bronchodilators. The cause of death is unknown, however it is suspected that cardiac arrests occur immediately after severe attacks of acute asthma with subsequent hypoxia. *(USP DI, 1996, p. 2614)*

Difficulty breathing, bronchospasm, sometimes of severe intensity and not responsive to any bronchodilator therapy. *(AHFS, 1990, p. 613, 616, 623, 627, 630)*

Author(s): Svedmyr N / Institution: Department of Clinical Pharmacology, Sahlgren's University Hospital, Gothenburg, Sweden. / Title: Action of corticosteroids on beta-adrenergic receptors. Clinical aspects. / Source: *Am Rev Respir Dis*. 1990 Feb. 141(2 Pt 2). P S31-8. / Abstract: Inhaled beta 2-stimulants are the most effective drugs for acute asthma attacks. This is probably due to functional antagonism against a large variety of possible asthma mediators. A defect in beta-receptor function is not the cause of asthma but treatment with beta 2-stimulants induces a down-regulation of beta-receptors and beta-receptor function outside the lung. There is, however, no convincing evidence that tachyphylaxis of clinical importance to the bronchodilating effect occurs

in asthmatics receiving normal doses of beta 2-receptor stimulants. A slight rebound increase of bronchial hyperreactivity has, however, been demonstrated 12 to 23 h after stopping regular treatment. This may be due to slight tachyphylaxis not visible in normal lung function tests. Inhaled steroids should be given to all asthmatics needing regular inhaled beta 2-agonist treatment, at least to adults. Steroids not only seem to reduce bronchial inflammation and hyperreactivity, and thereby the distribution of inhaled drugs, but also attend to reverse beta 2-receptor subsensitivity.

Author(s): Svedmyr N / Institution: Department of Clinical Pharmacology, Sahlgrenska University Hospital, Goteborg, Sweden. / Title: The current place of beta 2-agonists in the management of asthma. / Source: *Lung*. 1990. 168 SupplP 105-10. / Abstract: Inhaled beta 2-stimulants are the most effective drugs for acute asthma attacks. This is probably due to the functional antagonism against a large variety of possible asthma mediators. A slight rebound increase of bronchial hyperreactivity 12 to 23 h after stopping regular treatment has been proposed. This finding is not well documented and must be further studied. There is no convincing evidence that tachyphylaxis of clinical importance to the bronchodilating effect occurs in asthmatics receiving normal doses of beta 2-receptor stimulants but cannot be totally excluded. Candidates for regular inhaled beta 2-agonist treatment always have inflammation in their airways and should be given inhaled steroids. Steroids not only seem to reduce airway inflammation and hyperreactivity but they also reverse beta 2-receptor subsensitivity in experimental studies. Patients on purely prophylactic antiasthmatic drugs should be instructed always to carry their beta 2-stimulants inhalers.

Author(s): Cochrane GM / Institution: Department of Thoracic Medicine, Guy's Hospital, London, United Kingdom. / Title: Bronchial asthma and the role of beta 2-agonists. / Source: *Lung*. 1990. 168 SupplP 66-70. / Abstract: Asthma is defined as reversible airflow obstruction; the mechanism for this airflow obstruction is considered to be caused by a combination of an inflammatory process leading to a thickened edematous airway lining and bronchial smooth muscle constriction. The identification of specific beta-receptors in the autonomic system led to the development in the early 1960s of selective beta 2-agonists with their precise effects on the bronchial smooth muscle without direct action on cardiac muscle. The early beta 2-agonists such as salbutamol have a comparatively short bronchodilator action but a rapid onset of action, making them useful as "rescue" bronchodilators. Regular beta 2-agonists alone may mask the underlying pathogenesis of asthma and may be associated with tachyphylaxis or rebound bronchial hyperreactivity. The observation that a thickened airway lining may lead to disproportionate increases in airways resistance with small changes in bronchial muscle shortening suggests beta 2-agonists should be given in conjunction with anti-inflammatory therapy. With their long duration of action but slow onset the new beta 2-agonists may have a role in prophylaxis of asthma rather than rescue bronchodilation.

Author(s): Beach JR; Young CL; Harkawat R; Gardiner PV; Avery AJ; Coward GA; Walters EH; Hendrick DJ / Institution: Chest Unit, Newcastle General Hospital, University of Newcastle upon Tyne, UK. / Title: Effect on airway responsiveness of six weeks treatment with salmeterol. / Source: *Pulm Pharmacol*. 1993 Jun. 6(2). P 155-7. / Abstract: It has been suggested that the new long-acting beta 2-agonist, salmeterol, has anti-inflammatory properties--properties which should improve airway responsiveness (AR). Conversely, several recent studies have suggested that regular beta 2-agonist treatment may worsen asthma and AR. Furthermore, a short-lived rebound increase in AR has been described following cessation of regular treatment with these agents. We have consequently assessed the effects on AR of regular treatment with either salmeterol or salbutamol at conventional doses over 6 weeks. FEV1 and AR were measured five times in 20 asthmatic subjects randomly allocated to one or other treatment regimen; twice during a 2-week run-in period; and 24 h, 72 h, and 2 weeks after the last dose of the study medication. Peak expiratory flow rate (PEFR) was also recorded throughout the study period. There were no statistically significant changes in FEV1 or AR between the run-in period and any of the post treatment measurements for either of the

treatments used. Mean PEFR was significantly higher during the treatment period than the run-in period for the salmeterol group, but not the salbutamol group, confirming that therapeutically adequate doses of salmeterol had been given. We conclude that if the regular use of salmeterol is associated with beneficial or adverse effects on AR, this is not apparent after a treatment period of 6 weeks.

Author(s): Yates DH; Sussman HS; Shaw MJ; Barnes PJ; Chung KF / Institution: Department of Thoracic Medicine, National Heart & Lung Institute, London, United Kingdom. / Title: Regular formoterol treatment in mild asthma. Effect on bronchial responsiveness during and after treatment. / Source: *Am J Respir Crit Care Med*. 1995 Oct. 152(4 Pt 1). P 1170-4. / Abstract: Regular beta 2-adrenoceptor agonist therapy may lead to a rebound increase in bronchial responsiveness on discontinuation of therapy and a reduction in bronchoprotective effects. Formoterol, a long-acting beta 2-agonist, is effective in single doses in the prevention of methacholine-induced bronchoconstriction. In a double-blind, placebo-controlled cross-over study, we examined the effect of an inhaled long-acting beta 2-adrenoceptor agonist, formoterol (24 micrograms twice a day) for 2 wk on airway function and responsiveness in 17 subjects with mild asthma (mean age, 26.3 +/- 1.4 yr) who were not taking inhaled glucocorticosteroids. FEV1 and the provocative concentration of methacholine causing a 20% fall in FEV1 (PC20) were measured at 36, 60, and 108 h and at 2 wk after the last dose of regular treatment. In addition, PC20 was measured 12 h after the first and the last dose of formoterol and placebo. PC20 values at 36, 60, and 108 h and at 2 wk after formoterol treatment cessation were not significantly different from those after placebo. Mean FEV1 was 3.44 +/- 0.18 L after placebo compared with 3.79 +/- 0.20 L after formoterol ($p < 0.001$) 12 h after the first dose, and mean PC20 was 0.53 (GSEM 1.4) mg/ml after placebo compared with 2.0 (GSEM 1.4) mg/ml after formoterol ($p < 0.001$). After 2 wk of regular treatment, mean FEV1 at 12 h after the final dose of formoterol fell to 3.51 +/- 0.23 L compared with 3.41 +/- 0.18 L after the final dose of placebo ($p = 0.03$).

Author(s): de Jong JW; van der Mark TW; Koeter GH; Postma DS / Institution: Department of Pulmonology, University Hospital Groningen, The Netherlands. / Title: Rebound airway obstruction and responsiveness after cessation of terbutaline: effects of budesonide. / Source: *Am J Respir Crit Care Med*. 1996 Jan. 153(1). P 70-5. / Abstract: Regular monotherapy with inhaled beta 2-agonists may lead to a temporary increase of airway obstruction and increase of airway responsiveness after cessation of treatment. We investigated whether anti-inflammatory therapy may affect these rebound phenomena. In a double-blind, placebo-controlled study, we assessed lung function (FEV1) and airway responsiveness (PC20 methacholine [PC20]) during and after cessation of 2 wk of regular treatment with placebo and low-dose (250 micrograms) and high-dose (1,000 micrograms) inhaled terbutaline three times daily. Patients with mild allergic asthma (means [+/- SD] age of 28.2 +/- 6.6 yr, mean FEV1% of 91.9 +/- 14.6%, and geometric mean PC20 of 0.25 mg/ml) were studied. One group ($n = 16$) was randomized to budesonide treatment, 400 micrograms three times daily; the other group ($n = 14$) to placebo. PC20 and FEV1 were measured 10, 14, 34, and 82 h after the last terbutaline or placebo inhalation. A different method of statistical analysis was used, in that measurements performed at 10, 14, and 34 h were expressed relative to 82 h values in each period as an area-under-the-curve (AUC) value. FEV1 did not significantly change during placebo and budesonide treatment. Mean PC20 and morning and evening peak expiratory flow were significantly higher during budesonide treatment ($p < 0.01$). PC20 did not significantly change after cessation of terbutaline treatment in both placebo and budesonide treatment groups. AUC-FEV1 values after cessation of treatment with both doses of terbutaline were significantly different from the 82 h values ($p < 0.05$). The decrease in FEV1 was significantly greater after the last terbutaline and placebo inhalation in the placebo group compared with the budesonide treatment group ($p = 0.02$). We conclude that cessation of regular treatment after 2 wk with both low-dose and high-dose inhaled terbutaline does not result in a significant rebound airway

responsiveness in patients with mild asthma. However, the results suggest a small rebound bronchoconstriction that does not occur when asthmatic patients are also treated with budesonide.

Xanthine derivatives bronchodilators *(Aminophylline, Diprofilina, Theophylline, Choline theophyllinate)*
Therapeutic indications: Bronchospasm of bronchial asthma and chronic obstructive pulmonary disease.
Rebound effect:
Difficulty breathing and tachypnea. *(USP DI, 1996, p. 626)*
Asthmatic episodes occur with the use of Theophylline, related to concentration of sulphites, despite being unknown prevalence of sensitivity to sulphites in the general population. *(AHFS, 1990, p. 2100)*

Sodium cromoglycate - inhaled
Therapeutic indications: Bronchospasm of bronchial asthma.
Rebound effect:
Severe difficulty breathing and increased wheezing. *(USP DI, 1996, p. 1105)*
Bronchospasm, sometimes not responsive to any bronchodilator therapy. *(AHFS, 1990, p. 2160)*

Corticosteroids - inhaled *(Beclomethasone, Dexamethasone, Flunisolide, Triamcinolone)*
Therapeutic indications: Treatment of bronchial asthma and chronic obstructive pulmonary disease.
Rebound effect:
Difficulty breathing, shortness of breath, chest tightness and wheezing; bronchitis and bronchospasm. *(USP DI, 1994, p. 908)*
Bronchial asthma. *(AHFS, 1990, p. 1546, 1549, 1730, 1731)*
Author(s): Verbeek PR; Geerts WH / Institution: Division of Emergency Medicine, Sunnybrook Health Science Centre, University of Toronto, Ontario, Canada. / Title: Nontapering versus tapering prednisone in acute exacerbations of asthma: a pilot trial. / Source: *J Emerg Med*. 1995 Sep-Oct. 13(5). P 715-9. / Abstract: Controversy exists as to whether or not the dose of prednisone should be tapered in patients discharged from the emergency department after initial treatment for an acute exacerbation of asthma. We assessed the rates of relapse and rebound in a group of 28 patients treated with a nontapering course of prednisone and compared their outcomes to an historical control group of 48 patients treated with a typical tapering course of prednisone. We found no significant difference in the rates of relapse or rebound between the nontapering dose patients and the tapering dose patients within either 21 days of discharge or within 10 days after stopping prednisone. Fifty-four percent of study patients reported adverse effects that could be attributed to prednisone. Our preliminary findings suggest that tapering of prednisone may not be needed in these patients.

Epinephrine - inhaled
Therapeutic indications: Treatment of airway obstruction.
Rebound effect:

Author(s): Skolnik N / Institution: Family Practice Residency Program, Abington Memorial Hospital, Abington, Pennsylvania. / Title: Croup. / Source: *J Fam Pract*. 1993 Aug. 37(2). P 165-70. / Abstract: Viral croup is the most common form of upper airway obstruction in children 6 months to 6 years of age. It typically presents in the late fall or early winter, is often preceded by an upper respiratory infection, and is characterized by a low-grade fever, barking cough, and inspiratory stridor. Diagnosis is made on clinical grounds with no specific confirmatory test. The differential diagnosis of croup, including epiglottitis and retropharyngeal abscess, must always be considered in evaluating children with inspiratory stridor. Three therapeutic modalities are available for the treatment of croup: humidified air, racemic epinephrine, and adrenal corticosteroids. Maintaining at least 50% relative humidity in the child's room is recommended. If there is evidence of hypoxemia, a mist tent with supplemental oxygen may be helpful. Racemic epinephrine administered by nebulizer can quickly reverse airway obstruction in children with croup. The patient needs to be monitored for rebound airway obstruction for at least 2 hours after administration. The mainstay of treatment for severe croup is dexamethasone, administered 0.6 mg/kg, intramuscularly (IM). Dexamethasone is effective at decreasing the obstructive symptoms of croup, but its onset of action is approximately 6 hours after administration. Therefore, administration of racemic epinephrine is often helpful until the steroids begin to take effect. The correct dosage of dexamethasone is important, as lower steroid dosages have proven to be ineffective in treating croup. Dexamethasone IM, or an equivalent dose of oral prednisone, may be considered in children with moderately severe croup who do not require hospitalization.

Ipatropium - inhaled *(Atrovent, Duovent)*
Therapeutic indications: Bronchospasm of bronchial asthma.
Rebound effect:
Increment of bronchospasm. *(USP DI, 1996, p. 1777)*

Nedocromil - inhaled *(NSAID)*
Therapeutic indications: Prophylaxis of bronchospasm of bronchial asthma, preventing inflammation of the airways and allergic responses.
Rebound effect:
Increment of bronchospasm. *(USP DI, 1996, p. 2135)*

OPHTHALMIC DRUGS

Author(s): Gallasch G / Title: [Rebound effects following isovolemic hemodilution in venous vascular occlusions and their prevention] / Source: *Fortschr Ophthalmol*. 1987. 84(4). P 367-8. / UI:88031027
Author(s): Safran AB; Gambazzi Y / Institution: Department of Ophthalmology, Geneva University Hospital, Switzerland. / Title: Congenital nystagmus: rebound phenomenon following removal of contact lenses. / Source: *Br J Ophthalmol*. 1992 Aug. 76(8). P 497-8. / Abstract: Symptoms resulting from congenital nystagmus can be significantly reduced by wearing corneal contact lenses. A 90 minute therapeutic trial with contact lenses was performed on a 20-year-old affected patient and produced a beneficial effect. Upon removal of the lenses however the patient showed a transient rebound phenomenon with oscillopsia lasting about 20 minutes. This phenomenon, although it might be expected in theory, has apparently not previously been observed either because it is rare or because in most patients it is not clinically apparent. The purpose of this report is not to discourage treating patients with congenital nystagmus by means of contact lenses, but rather to draw attention to the occasional occurrence of such a rebound phenomenon and to discuss its theoretical significance.

Decongestant drugs

Ophthalmic corticosteroids *(Betamethasone, Dexamethasone, Fluorometolona, Hydrocortisone, Medrisona, Prednisolone)*
Therapeutic indications: Treatment of ophthalmic allergic diseases and inflammatory.
Rebound effect:
Blurred vision distinct from experienced time after applying ophthalmic ointment; pain, itching, burning and ocular laceration. *(USP DI, 1996, p. 948)*
Itching, burning and eye irritation; a few days after discontinuation of treatment and occasionally during the therapy, acute anterior uveitis may occur in patients without pre-existing ocular inflammation. *(AHFS, 1990, p. 1546)*

Sodium cromoglycate
Therapeutic indications: Treatment of ophthalmic allergic diseases.
Rebound effect:
Irritation, absent prior to treatment; severe inflammation of conjunctiva; itching and burning sensation in the eyes; increased tearing. *(USP DI, 1996, p. 1109)*

Phenylephrine *(vasoconstrictor)*
Therapeutic indications: Congestion and eye irritation.
Rebound effect:
Itching and burning eyes; tearing and eye irritation absent before therapy. *(USP DI, 1996, p. 2391)*
Blurred vision, transient irritation and epithelial keratitis; with prolonged and/or intense use, can occur rebound hyperemia and allergic conjunctivitis. *(AHFS, 1990, p. 1597)*

Naphazoline *(vasoconstrictor)*
Therapeutic indications: Congestion, itching and eye irritation.
Rebound effect:
Increased irritation (reactive hyperemia); with excessive doses and/or prolonged use can occur an increase of conjunctival irritation. *(USP DI, 1996, p. 2132)*
Reactive hyperemia and conjunctival irritation. *(AHFS, 1990, p. 1594)*

Oxymetazoline *(vasoconstrictor)*
Therapeutic indications: Congestion, itching and eye irritation.
Rebound effect:
Increase of conjunctival irritation and redness of the eyes (reactive hyperemia) by prolonged use and/or an overdose of drugs. *(USP DI, 1996, p. 2262)*

Lubricants drugs

Hydroxypropylcellulose *(Hipromelose)*
Therapeutic indications: Lubricating eye (keratoconjunctivitis, keratitis by exposure, etc.)
Rebound effect:
Irritation of eyes, missing before treatment. *(USP DI, 1996, p. 1636, 1637)*

Antiglaucoma drugs

Anticholinergics, cholinesterase inhibitors *(Demecario, Ecothiopate, Fluostigmine)*
Therapeutic indications: Treatment of glaucoma (intraocular hypertension).
Rebound effect:
After using Demecario, Ecothiopate and Fluostigmine occurred a paradoxical increase of intraocular pressure; blurred vision and visual changes in accommodation; eye pain; irritation; headache. *(USP DI, 1996, p. 313; AHFS, 1990, p. 1570)*
Author(s): Belmonte C; Bartels SP; Liu JH; Neufeld AH / Institution: Ophthalmic Pharmacology Unit, Eye Research Institute of Retina Foundation, Boston, Massachusetts 02114. / Title: Effects of stimulation of the ocular sympathetic nerves on IOP and aqueous humor flow. / Source: *Invest Ophthalmol Vis Sci*. 1987 Oct. 28(10). P 1649-54. / Abstract: Ocular sympathetic nerves were stimulated chronically in awake rabbits using electrodes unilaterally implanted on the cervical sympathetic trunk. IOP was measured by pneumatonometry and aqueous inflow was measured by fluorophotometry. In each animal, continuous trains of 1 msec pulses were delivered by means of a portable electrical stimulator. Experiments were spaced by 1 week recovery periods. Stimulation was varied over a range of amplitudes (5-15 V) and frequencies (3-12 Hz). Continuous sympathetic stimulation produced an immediate sharp decrease in IOP followed by a gradual rise to pre-stimulation values which were attained 60-90 min after onset. A rebound increase in IOP occurred when stimulation was terminated. The magnitude of the initial IOP drop, the delay in the return to pre-stimulation IOP, and the rebound rise in IOP subsequent to termination of electrical stimulation were proportional to the stimulation frequency. Maximal effects were observed at 12 Hz, and stimulation with 8-10 Hz for 180 min caused a sustained reduction in anterior chamber aqueous humor flow. Topical 2% phentolamine 1 hr before stimulation markedly reduced IOP and abolished the acute IOP changes observed in untreated stimulated animals. Topical 1% timolol did not affect

either the initial IOP drop or the rebound; however, the IOP recovered during stimulation to values greater than pre-stimulation IOP. We conclude that in rabbits the beta-adrenergic effect of prolonged sympathetic nerve stimulation is to decrease aqueous flow. Chronic electrical stimulation in awake animals provides an experimental model for studying the role of the ocular sympathetic nerves.

Antimuscarinics *(Atropine, Belladonna, Scopolamine, Hiosciamine, etc.)*
Therapeutic indications: Reduction of intraocular pressure.
Rebound effect:
Increased intraocular pressure. *(USP DI, 1994, p. 507; AHFS, 1990, p. 590)*

Carbonic anhydrase inhibitors *(Acetazolamide, Methazolamide)*
Therapeutic indications: Treatment of glaucoma.
Rebound effect:
Author(s): Fishman GA; Glenn AM; Gilbert LD / Institution: Department of Ophthalmology and Visual Sciences, College of Medicine, University of Illinois at Chicago. / Title: Rebound of macular edema with continued use of methazolamide in patients with retinitis pigmentosa. / Source: *Arch Ophthalmol*. 1993 Dec. 111(12). P 1640-6. / Abstract: To assess the effect of methazolamide on chronic macular edema in patients with retinitis pigmentosa in a double-masked, placebo-controlled, crossover study. Three subjects who had an initial improvement in their macular edema as demonstrated on fluorescein angiography received a continued course of methazolamide to assess its effect on macular edema. Seventeen subjects were enrolled in the initial study. On angiography, nine subjects demonstrated improvement in their macular edema with the use of methazolamide for 3 weeks; three of these continued receiving the drug at a dosage of 50 mg twice daily for either an additional 6 (one subject) or 12 (two subjects) weeks. All subjects were assessed at each visit with fluorescein angiography and on best corrected visual acuity, both undilated and dilated; a subjective impression was also documented. After 6 and 12 weeks of treatment, all three subjects experienced a rebound of angiographic macular edema to some extent. The visual acuity varied only slightly (up to 7 letters) from both the baseline and most recent examinations after 6 and 12 weeks of treatment. Results from these few subjects suggest that at least a partial rebound of macular edema seen angiographically may occur with the continued use of methazolamide in patients with retinitis pigmentosa and chronic macular edema. Further study is required to determine if this rebound effect also occurs in treatment of other ocular disorders with chronic macular edema.
Author(s): Fishman GA; Gilbert LD; Anderson RJ; Marmor MF; Weleber RG; Viana MA / Institution: Department of Ophthalmology and Visual Sciences, University of Illinois, Chicago College of Medicine 60612. / Title: Effect of methazolamide on chronic macular edema in patients with retinitis pigmentosa. / Source: *Ophthalmology*. 1994 Apr. 101(4). P 687-93. / Abstract: To determine the effectiveness of methazolamide for improving visual acuity and macular edema in patients with retinitis pigmentosa. Seventeen subjects with retinitis pigmentosa and chronic macular edema participated in a prospective, placebo-controlled, double-masked, crossover design study in which either methazolamide or a placebo was taken for 3 weeks. Visual acuity, fluorescein angiograms, and subjective impressions were obtained at baseline and after 3 weeks of treatment with each substance. A subgroup of subjects were enrolled in a more extended period of methazolamide treatment for an additional 3 months. Methazolamide resulted in the improvement of angiographic macular edema in 9 of 17 subjects. As a group, visual acuity statistically improved with methazolamide. However, improvement in at least one eye, of between two and four lines more than while taking placebo, occurred in only three (undilated pupils) or four (dilated pupils) subjects. Subjective improvement during treatment with methazolamide but not placebo occurred in

only one subject. An extended period of methazolamide treatment for an additional 3 months in a subgroup of patients did not result in additional beneficial effects on visual acuity. In fact, a partial rebound in the extent of macular edema was found. Although angiographic improvement of macular edema can occur in patients with retinitis pigmentosa treated with methazolamide, notable (between 3 and 4 lines) or even moderate (between 2 and 3 lines) visual acuity improvement was seen in relatively few patients. When methazolamide was administered in a placebo-controlled fashion, subjective improvement in visual function also was not readily apparent. A more substantial subjective improvement in visual function had occurred with the use of acetazolamide in five of six subjects who also had participated in a previous treatment trial with the use of acetazolamide.

Miotics *(Acetylcholine, Carbachol, Pilocarpine)*
Therapeutic indications: Treatment of glaucoma.
Rebound effect:
Blurred vision or visual changes in accommodation; headache; eye pain; irritation; nausea and vomiting. *(USP DI, 1996, p. 307)*
Increased intraocular pressure in incidence less than with anticholinesterase. *(AHFS, 1990, p. 1570)*

DERMATOLOGICAL DRUGS

Anti-inflammatory drugs

Corticosteroids - topical *(Betamethasone, Clobetasol, Desoxymethasone, Dexamethasone, Diflorasone, Flumethasone, Fluocinolone, Hydrocortisone, etc.)*
Therapeutic indications: Treatment of skin inflammations as dermatoses, dermatitis, eczema, burns and insect bites.
Rebound effect:
Signs of irritation and inflammation as pain, itching, flaking and ampoules nonexistent before treatment. *(USP DI, 1996, p. 955)*
In prolonged use (two months or more), pustular rebound occurred particularly on the face, genital and perineal region, after the discontinuation of therapy. *(AHFS, 1990, p. 2036)*
Author(s): Krutmann J; Schopf E / Institution: Universitats-Hautklinik Freiburg. / Title: [New aspects of UV-therapy of atopic dermatitis]. / Source: *Hautarzt*. 1991 May. 42(5). P 284-8. / Abstract: Atopic dermatitis (AD) is a familial inflammatory skin disease characterized by a typical morphology and distribution and a chronically relapsing course with frequent periods of exacerbation. The management of AD is primarily directed towards symptomatic relief, and treatment decisions depend on cutaneous symptoms at any given time. During periods of acute exacerbation, therapy consists almost exclusively in topical or even systemic corticosteroid therapy. Since long-term corticosteroid therapy is known to have a variety of side-effects, it is important to develop alternative modalities for treatment of AD, such as phototherapy with ultraviolet radiation (PUVA, UV-B, UV-A-B). The major disadvantages of PUVA therapy are the relatively high number of treatments required for healing, the high frequency of rebound phenomena, and as a long-term effect, the potentially increased risk of skin cancer. In contrast, UV-B/UV-A-B therapy is not associated with any major side-effects, but its beneficial effects are clearly limited and usually require several weeks of treatment. Therefore, UV-B/UV-A-B therapy is mostly used in combination with corticosteroids for the treatment of acute AD to increase the therapeutic effectiveness. Very recent data indicate that a monotherapy with pure UV-A (340-440 nm) light, if applied in higher doses (15 x 130 J/m2; High-Dose UV-A1), is very effective in the treatment of patients with acute AD. Examination of the photoimmunological events underlying the observed therapeutic effectiveness of High-Dose-UV-A1 therapy may help us to understand the pathophysiological events relevant for AD.

Antipruritic and anesthetic drugs

Benzocaine *(local anesthetic)*
Therapeutic indications: Temporary relief of pain and itching associated with burns, cuts or scratches, insect bites and irritations of the skin.
Rebound effect:
Rash and skin irritation. *(AHFS, 1990, p. 2049)*

Crotamiton
Therapeutic indications: Symptomatic relief of itching associated with dermatoses.

Rebound effect:
Skin irritation nonexistent before treatment; skin rash. *(USP DI, 1996, p. 1112)*

Dibucaine *(local anesthetic)*
Therapeutic indications: Temporary relief from pain, itching and flare caused by hemorrhoids.
Rebound effect:
Pain, itching, flare, irritation and rectal bleeding. *(AHFS, 1990, p. 2049)*

Dyclonine *(local anesthetic)*
Therapeutic indications: Temporary relief of pain and itching associated with burns, cuts or scrapes, insect bites and skin irritations.
Rebound effect:
Local irritation and itching. *(AHFS, 1990, p. 2050)*

Doxepin
Therapeutic indications: Treatment of itching associated with eczema.
Rebound effect:
At approximately 10% of patients occurs exacerbation of itching and eczema. *(USP DI, 1996, p. 1303)*

Pramoxine *(local anesthetic)*
Therapeutic indications: Temporary relief of pain and itching associated with skin diseases; burns; itching or irritation genital and rectal; anal fissure or hemorrhoids.
Rebound effect:
Irritation, itching, pain and burning site; can occur pain, itching and rectal bleeding. *(AHFS, 1990, p. 2052)*

Urea
Therapeutic indications: Treatment of pruritus.
Rebound effect:
Local Irritation and itching. *(AHFS, 1990, p. 2062)*

Drugs for seborrheic dermatitis (dandruff)

Selenium sulfide
Therapeutic indications: Treatment of seborrheic dermatitis of the scalp.
Rebound effect:
Presence of non-standard fat on the scalp. *(USP DI, 1996, p. 2622)*
Can cause "oils rebound" on the scalp; this effect has been reported after short time applying lotion 2.5% and after long time of applying lotion 1%. *(AHFS, 1990, p. 2032)*

Ultraviolet irradiation
Rebound effect:

Author(s): Lesnik RH; Kligman LH; Kligman AM / Institution: Department of Dermatology, University of Pennsylvania, School of Medicine, Philadelphia 19104-6142. / Title: Agents that cause enlargement of sebaceous glands in hairless mice. II. Ultraviolet radiation. / Source: *Arch Dermatol Res*. 1992. 284(2). P 106-8. / Abstract: We have developed a murine model to measure the effects on sebaceous glands of ultraviolet (UV) radiation. Hairless mice were irradiated with Westinghouse FS-40 tubes filtered to attenuate the radiation below 290 nm. Emission was mainly in the UVB range (peak, 313nm). Single and multiple exposures were given with fractions or multiples of one minimal erythemal dose (MED). Biopsies, fixed for light microscopy, were stained with H & E. Under high power, sebocytes of 30 glands per specimen were counted and the means determined. A single exposure of 1 MED caused a significant increase in sebocyte count, as did thrice-weekly exposures to 0.5 MED for 3 weeks. One 3-MED exposure produced sebocyte necrosis, yet 30 exposures at 4 MED failed to ablate the glands. In both cases there was rebound enlargement which had not returned to control levels by the end of the studies (24-30 weeks). Prolonged irradiation produced maximum enlargement in a few weeks. Thus, in a manner similar to other skin components, the response of sebaceous glands to UV radiation is one of hyperplasia.

Other drugs

Calcipotriene
Therapeutic indications: Treatment of psoriasis.
Rebound effect:
Worsening of psoriasis, including development of psoriasis on the face and scalp. *(USP DI, 1996, p. 689)*

Methoxsalem
Therapeutic indications: Treatment of vitiligo and psoriasis (associated with the treatment with ultraviolet radiation).
Rebound effect:
Hypopigmentation of the skin and worsening or extension of psoriasis. *(AHFS, 1990, p. 2085)*

Minoxidil
Therapeutic indications: Treatment of androgenetic alopecia.
Rebound effect:
Increase of alopecia. *(USP DI, 1996, p. 2083)*

GYNECOLOGICAL AND OBSTETRIC DRUGS

Antispasmodic drugs

Ritodrine
Therapeutic indications: Treatment and prophylaxis of preterm labor (inhibit uterine contractions).
Rebound effect:
Author(s): Hamada S; Kawarabayashi T; Ikeda M; Sugimori H; Hamasaki Y; Kumamoto T; Tsukamoto T / Institution: Department of Obstetrics and Gynecology, Saga Medical School. / Title: [Effects of short- and long-term administration of ritodrine on spontaneous contractions of longitudinal muscle strips dissected from the pregnant rat uterus]. / Source: *Nippon Sanka Fujinka Gakkai Zasshi*. 1990 Jun. 42(6). P 605-11. / Abstract: We investigated the effects of Ritodrine (10(-10)-10(-7) g/ml) on spontaneous contractions of rat myometrium at gestational days 14, 16, 18 and 21. 1. More than 10(-8)g/ml Ritodrine obviously suppressed the spontaneous contractions more than smaller doses. The inhibitory effects of smaller doses on days 14 and 16 were different from those on days 18 and 21, the former being more effective. 2. Smaller doses of Ritodrine (10(-10)-10(-8)g/ml) caused transient excitation, which was inhibited by pretreatment with Phentolamine. 3. Rebound excitation was observed in most of the specimens. 4. Spontaneous contractions reappeared during long-term administration of Ritodrine and the patterns could be classified into three types. These results suggested that the effects of Ritodrine might vary according to the number of pregnant days and that the critical Ritodrine dose for a suppressive effect is 10(-8)g/ml, and there are a transient alpha-excitatory effect, rebound excitation and three types of suppression as a result of long-term administration.

Drugs for lactation

Dopamine agonists (Bromocriptine, Cabergoline, Quinagolide)
Therapeutic indications: Treatment of amenorrhea and galactorréia; prevention of physiological postpartum lactating in situations of dead fetus or abortion.
Rebound effect:
After the suspension of the drug, amenorrhea rebound in 4-24 weeks and galactorréia in 2-4 weeks. Can occur lactation rebound after using the bromocriptina to suppress the postnatal lactation. *(USP DI, 1996, p. 617; AHFS, 1990, p. 2152)*
Author(s): Shapiro AG; Thomas L / Title: Efficacy of bromocriptine versus breast binders as inhibitors of postpartum lactation. / Source: *South Med J*. 1984 Jun. 77(6). P 719-21. / Abstract: Fifty postpartum patients were randomly given either bromocriptine (2.5 mg by mouth b.i.d. X 30 doses) or breast binders for inhibiting lactation. The breast binder group had a high incidence of symptoms (breast pain, engorgement, secretion) for the first week postpartum; these symptoms rapidly decreased by the second week. Bromocriptine successfully suppressed the breast problems in virtually all of the patients who took the drug correctly. Because of the high rate of side effects and a significant incidence of “rebound,” the dosage of bromocriptine should probably be changed, and we recommend a revised dosage.
Author(s): [No authors listed] / Title: Single dose cabergoline versus bromocriptine in inhibition of puerperal lactation: randomised, double blind, multicentre study. European Multicentre Study

Group for Cabergoline in Lactation Inhibition / Source: *BMJ*. 1991 Jun 8. 302(6789). P 1367-71. / Abstract: To compare the efficacy and safety of a single dose of 1 mg of cabergoline with that of bromocriptine 2.5 mg twice daily for 14 days in the inhibition of puerperal lactation. Prospective, randomised, double blind, parallel group, multicentre study. University of hospital departments of obstetrics and gynaecology in different European countries. 272 puerperal women not wishing to lactate (136 randomised to each drug). Women randomised to cabergoline received two 0.5 mg tablets of cabergoline and one placebo tablet within 27 hours after delivery and then placebo twice daily for 14 days. Those randomised to bromocriptine received 2.5 mg of bromocriptine and two placebo tablets within 27 hours and then 2.5 mg of bromocriptine twice daily for 14 days. Success of treatment (complete or partial) according to milk secretion, breast engorgement, and breast pain; rebound symptomatology; serum prolactin concentrations; and number of adverse events. Complete success was achieved in 106 of 136 women randomised to cabergoline and in 94 of 136 randomised to bromocriptine and partial success in 21 and 33 women respectively. Rebound breast symptomatology occurred respectively in five and 23 women with complete success up to day 15 (p less than 0.0001). Serum prolactin concentrations dropped considerably with both drugs from day 2 to day 15; a prolactin secretion rebound effect was observed in women treated with bromocriptine. cabergoline and 36 receiving bromocriptine (p = 0.054), occurring most during the first treatment day. A single 1 mg dose of cabergoline is at least as effective as bromocriptine 2.5 mg twice daily for 14 days in preventing puerperal lactation. Because of the considerably lower rate of rebound breast activity and adverse events and the simpler administration schedule cabergoline should be the drug of choice for lactation inhibition.
Author(s): Webster J / Institution: Royal Hallamshire Hospital, Sheffield, England. / Title: A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. / Source: *Drug Saf*. 1996 Apr. 14(4). P 228-38. / Abstract: Dopamine agonists are the treatment of choice for the majority of patients with hyperprolactinaemic disorders. Although characterised by a relatively high incidence of adverse effects, most commonly gastrointestinal, cardiovascular and neurological, these are usually mild and transient, and can be minimised by starting with a low dose and gradually increasing it, or taking the drug with food or while recumbent. Bromocriptine, introduced in 1971, is the reference preparation against which newer dopamine agonists are compared. It is effective in suppressing prolactin secretion, reducing prolactinoma size and restoring gonadal function. However, up to 12% of patients cannot tolerate the drug at therapeutic dosages. Cabergoline, a long-acting dopamine agonist administered once or twice weekly, has been shown to be significantly more effective than bromocriptine in suppressing prolactin secretion in hyperprolactinaemic patients, and is better tolerated, particularly in terms of nausea and vomiting. In suppressing physiological lactation, cabergoline is at least as effective as bromocriptine, and is associated with significantly fewer rebound symptoms and adverse effects. Quinagolide is a non-ergot dopamine agonist that is administered once daily. It has similar efficacy to bromocriptine, but is probably less effective than cabergoline in hyperprolactinaemic patients; it is not licensed for suppression of lactation. It is better tolerated than twice-daily bromocriptine, but is probably inferior to cabergoline in this regard. Neither bromocriptine, cabergoline nor quinagolide has been associated with any detrimental effect on pregnancy or fetal development. However, experience with bromocriptine is far more extensive; thus, for women requiring treatment for subfertility, this drug remains the treatment of choice in most centres, with cabergoline and quinagolide as acceptable second-line drugs in bromocriptine-intolerant patients. In hyperprolactinaemic men, hyperprolactinaemic women not wishing to become pregnant, and for suppression of physiological lactation, cabergoline is recommended as first-line treatment.

Lisuride (dopamine D2 receptor agonist)
Therapeutic indications: Prolactin secretion inhibitor.

Rebound effect:
Author(s): Strahl HJ; Goretzlehner G; Strahl S; Kunkel S / Title: [Lactation inhibition with various dosages of lisuride - prolactin secretion and effectiveness]. / Source: *Zentralbl Gynakol*. 1985. 107(5). P 300-3. / Abstract: The influence of lisuride in three several dosages (600, 750, and 900 micrograms) was studied on prolactin secretion and inhibition of lactation in 30 normal postpartum patients. 10 normal nursing postpartum patients served as controls. A rebound effect of prolactin secretion was demonstrable following lisuride medication during 10 days. This effect did not occur after a therapy lasting 15 days. 600 micrograms of lisuride daily showed a good inhibition of lactation and suppression of prolactin secretion. Severe side effects could be only observed during lisuride treatment with a dosage of 900 micrograms.

Contraceptive drugs

Oral contraceptives *(Anteovin)*
Therapeutic indications: Contraceptives (prevent pregnancy).
Rebound effect:
Author(s): Janerich DT; Lawrence CE; Jacobson HI / Institution: First Department of Obstetrics and Gynaecology, Semmelweis University Medical School. / Title: Fertility patterns after discontinuation of use of oral contraceptives. / Source: *Lancet.* 1976 May 15; 1(7968): 1051-3. / Abstract: Investigation of the fertility-rate after discontinuation of use of oral contraceptives shows that the monthly rate consistently follows an oscillatory pattern. This pattern appears to be unique to women who have discontinued the use of oral contraceptives. It may result from synchronisation of a previously unrecognised natural cycle, rebound changes in the reproductive system following steroidal contraception, or an infertile period associated with early intrauterine mortality.
Author(s): Kovacs I / Institution: First Department of Obstetrics and Gynaecology, Semmelweis University Medical School. / Title: Examination of the rebound effect of biphasic oral contraceptives. / Source: *Ther Hung*. 1990. 38(3). P 110-3. / Abstract: Attempt has been made to induce ovulation with temporary Anteovin administration, that is with the rebound effect following the discontinuance of treatment in 34 women with anovulatory cycles who suffered from functional sterility. Ovulation could be induced in 9 cases and among the women whose cycles had become biphasic 3 became pregnant and 2 delivered normal healthy babies before closing the study. The results proved that rebound effect may be expected even following the use of Anteovin which is satisfactory from the aspect of a future fertility in women taking the tablet for contraception.
Author(s): Chasan-Taber L; Willett WC; Stampfer MJ; Spiegelman D; Rosner BA; Hunter DJ; Colditz GA; Manson JE / Institution: Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA. / Title: Oral contraceptives and ovulatory causes of delayed fertility. / Source: *Am J Epidemiol.* 1997 Aug 1; 146(3): 258-65. / Abstract: The return of fertility for women who discontinue oral contraceptives takes longer as compared with women who discontinue other methods of contraception. It remains unclear, however, whether subsequent fertility differs according to duration or age at first use. The authors performed a nested case-control study within a cohort of 116,686 female registered nurses residing in 14 US states. Baseline information was reported on mailed questionnaires in 1989. Cases comprised 1,917 married nurses without previous pregnancy who were unable to become pregnant for at least 1 year and were subsequently diagnosed with primary ovulatory infertility. Controls comprised 44,521 married parous nurses with no history of infertility and no pregnancies lasting less than 6 months. After allowing for 2 years of suppressed fertility following discontinuation of oral contraceptive use and excluding women with signs of menstrual or hormonal disorder, the authors found that the multivariate relative risk for ovulatory causes of delayed fertility was 1.2 (95% confidence interval

0.7-1.9) for ever users. There was no statistically significant trend of increasing risk with increasing duration of use and younger age at first use. The fact that 88 percent of cases reported an eventual pregnancy by 1993 suggests that absolute fertility was not impaired.

Mifepristone *(antiprogestagen, anti-nidatory or abortive drug)*
Author(s): Ghosh D; Sengupta J / Institution: First Department of Physiology, All India Institute of Medical Sciences, New Delhi. / Title: Anti-nidatory effect of a single, early post-ovulatory administration of mifepristone (RU 486) in the rhesus monkey. / Source: *Hum Reprod.* 1993 Apr;8(4):552-8. / Abstract: The hypothesis that post-coital administration of mifepristone (RU 486) as a single dose in the early luteal phase can be an effective anti-nidatory strategy was tested using the rhesus monkey as the experimental model. Incidence of pregnancy, vaginal bleeding patterns, profiles of menstrual cyclicity and of serum levels of progesterone and oestrogen were examined following administration of RU 486 as a single dose of 10 mg/kg and 2 mg/kg body weight on the second day after ovulation. In control monkeys (group 1; n = 5) receiving the vehicle alone (benzyl benzoate:olive oil, 1:4, v/v) there was a 60% pregnancy rate. Following s.c. administration of RU 486 at both doses, no pregnancy was recorded in a total of 33 treatment cycles in 12 monkeys. Five monkeys received RU 486 at 10 mg/kg s.c. (group 2) in three consecutive cycles. All animals had complete inhibition of implantation; in addition, the treatment cycle length was prolonged ($P < 0.001$) due to an extension of the luteal phase. The subsequent follicular phase was unaffected. Mild, premature vaginal bleeding during the luteal phase was recorded in five treatment cycles, 3-5 days after drug application. Though the serum profiles of progesterone and oestrogen in these monkeys showed marked individual variations, there was a characteristic progesterone rebound about 18-20 days after drug administration. Monkeys in group 3 were given RU 486 at 2 mg/kg, s.c. either for three consecutive cycles (group 3a; n = 4) or for two consecutive cycles (group 3b; n = 3). Premature luteal phase vaginal bleeding occurred only in four treatment cycles, within 2-6 days post-treatment.

Menopause drugs

S-Calcitonin
Therapeutic indications: Treatment of post-menopausal osteoporese.
Rebound effect:
Author(s): Maini M; Bozzi M; Brignoli E; Felicetti G / Institution: Fondazione Clinica del Lavoro-IRCCS, Centro Medico di Riabilitazione-Montescano Pavia. / Title: [Medium- and long-term effects of various treatment schedules with nasal S-calcitonin spray]. / Source: *Minerva Med*. 1995 Mar. 86(3). P 121-7. / Abstract: 188 patients with high-turnover type post-menopausal osteoporosis were treated for 18 months with 4 different treatment regimens of S-calcitonin nasal spray. For a total of 18 months group 1 was given 100 IU/day, continuously; group 2, 100 IU/day daily for 30 days every other month ("ciclically"); group 3, 200 IU/day continuously, and group 4, 200 IU/day, ciclically. To monitor the effects of treatment, MOC of L2-L4, as well as serum osteocalcin and urinary hydroxyproline: creatinine levels were measured, on initiation of therapy, then at 9, 12 and 18 months, and finally at 6 and 12 months after completion of therapy. Analysis of the results yields the following major points: (A) The peak increase in bone mass occurs at 9 months the continuous therapy groups, and at 18 months in the cyclic therapy groups. In absolute values, the peak are higher in the continuous groups than in the cyclic groups. (B) The long-term increase in bone mass (measured at one year after completion of therapy) does not differ significantly between cyclic and continuous treatment groups at the same dosage. (C) During treatment, a dose-effect relationship exists when comparing dosages of 100 IU/day and 200 IU/day.

However, this disappears by one year after completion of therapy. (D) There seems to be a "rebound effect" on osseous turnover after cessation of S-calcitonin therapy. The magnitude and rapidity of onset of this effect appear to correlate directly with the dosage of S-calcitonin administered.

Author(s): Schlemmer A; Ravn P; Hassager C; Christiansen C / Institution: Center for Clinical & Basic Research, Ballerup Byvej, Ballerup, Denmark. / Title: Morning or evening administration of nasal calcitonin? Effects on biochemical markers of bone turnover. / Source: *Bone.* 1997 Jan;20(1):63-7. / Abstract: The purpose of this study was to examine the effect of intranasal salmon calcitonin (sCT) administration (200 IE), given either in the morning (8:00) or evening (21:00), on the known circadian variation in biochemical markers of bone turnover. An open, placebo-controlled, randomized, crossover study, with three 24 h studies of blood samples drawn every third hour and urine collected in 3 h aliquots was undertaken. Subjects consisted of nine healthy postmenopausal women, aged 58 +/- 7 years. Urinary CrossLaps (a measure of bone resorption) was measured by ELISA and corrected for creatinine (Cr). Serum osteocalcin (sOC) was measured by radioimmunoassay (RIA). The first 24 h study was performed without intervention. Prior to this control study the participants were randomized to either morning (8:00) or evening (21:00) sCT (200 IE). sCT administrations were given 4-5 days prior to and during the second study. After a washing-out period of 2 weeks the participants were given 200 IE of sCT at the reverse time of the day 5 days prior to and during the third study. At all timepoints, urinary CrossLaps/Cr exhibited a significant ($p < 0.001$) circadian rhythm with its zenith in early morning and nadir in late afternoon. Both morning and evening administration of sCT significantly decreased the urinary excretion of CrossLaps/Cr approximately 3-6 h after administration with a subsequent rebound effect. sOC did not exhibit a significant circadian variation and was not affected by the calcitonin. The 24 h mean urinary CrossLaps/Cr and sOC remained unchanged. Both morning and evening sCT significantly decreased the urinary excretion of CrossLaps/Cr 3-6 h after administration, with a rebound effect approximately 12 h later. However, the present study does not indicate that neither evening nor twice-daily administration is superior to morning administration.

RHEUMATIC DRUGS

See IMMUNOLOGICAL DRUGS (Non-steroidal anti-inflammatory drugs)

ACTH
Rebound effect:
Author(s): Ritter J; Kerr LD; Valeriano-Marcet J; Spiera H / Institution: Department of Medicine, Mt. Sinai School of Medicine, New York, NY 10029. / Title: ACTH revisited: effective treatment for acute crystal induced synovitis in patients with multiple medical problems. / Source: *J Rheumatol*. 1994 Apr. 21(4). P 696-9. / Abstract: To determine the effectiveness of adrenocorticotropic hormone (ACTH) for acute gouty arthritis and pseudogout in a population of patients with multiple coexisting medical problems. We retrospectively reviewed our experience with parenteral ACTH 40 or 80 units intravenous, intramuscular, or subcutaneous tid with tapering in the treatment of 38 patients. Thirty-three patients had documented acute gout and 5 patients had documented acute pseudogout. A total of 43 episodes of acute crystal induced synovitis were treated. The indications for using ACTH included congestive heart failure, chronic renal insufficiency, gastrointestinal bleeding, or no response to NSAID. All episodes of pseudogout resolved in an average of 4.2 days. Of the episodes of acute gout, 97% resolved in an average of 5.5 days. Although mild hypokalemia, hyperglycemia, fluid retention and rebound arthritis occurred as adverse effects, none was severe and all were easily controlled. ACTH is a safe and effective treatment for acute gout and pseudogout, especially in patients with multiple medical problems.

Alpha-interferon
Therapeutic indications: Modulator of immune activity (increases the phagocytic activity of macrophages and enhances the specific cytotoxic of lymphocytes).
Rebound effect:
Author(s): Chan GC; Lee SS; Yeoh EK / Institution: Medical A Unit, Queen Elizabeth Hospital, Kowloon, Hong Kong. / Title: Mono-arthritis in a chronic hepatitis B patient after alpha-interferon treatment. / Source: *J Gastroenterol Hepatol*. 1992 Jul-Aug. 7(4). P 432-3. / Abstract: A 28 year old woman with hepatitis B (HB) related chronic active hepatitis was treated with a 12 week course of alpha-interferon (alpha-IFN). She developed acute mono-arthritis 1 week after completion of treatment. Her rheumatoid factor (RF) was positive before alpha-IFN and fell steadily during therapy. This was followed by a rebound of RF level with the associated arthritis occurring 1 week after completion of the course of alpha-IFN. In absence of any medication RF gradually fell and became negative at the end of 1 year. This observation is thought to be related to the immunomodulatory effect of alpha-IFN either directly on RF production or indirectly through the control of hepatitis.

Allopurinol
Therapeutic indications: Treatment of chronic gout by decrease of serum uric acid levels.
Rebound effect:
In 1% of patients increments the acute gouty attacks, prolonging and exacerbate the inflammation during the first 6-12 months of treatment. *(AHFS, 1990, p. 2144)*

Gold compounds *(Auranofin, Aurothioglucose, Thiomalate gold sodium)*

Therapeutic indications: Treatment of arthritis (rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, etc).
Rebound effect:
Joint pain (may occur in one or two days after injection). *(USP DI, 1996, p. 1553)*

Probenecid *(uricosuric agent)*
Therapeutic indications: Treatment of chronic gout by decrease of serum uric acid levels.
Rebound effect:
Gouty acute attacks during the first months of therapy; in 20% of patients, acute gout attacks occur in the early days of treatment. *(USP DI, 1996, p. 2464)*

Sulfinpyrazone
Therapeutic indications: Treatment of chronic gout by decrease of serum uric acid levels.
Rebound effect:
Gouty acute attacks during the first months of therapy; in 20% of patients, acute gout attacks occur in the early days of treatment. *(USP DI, 1996, p. 2717)*

USE OF REBOUND EFFECT IN CLINICAL THERAPY

Below we list some experimental work with modern drugs that illustrates the use of rebound effect in a curative way, in accordance with the principle of therapeutic similitude.

Would be the case of oral contraceptives *(anteovin),* drugs that inhibiting ovulation and that after your suspending can promoted ovulation in women with functional sterility. *Methylphenidate,* a CNS stimulant, which is conventionally used in ADHD (Attention Deficit Hyperactivity Disorder) by its calming paradoxical reaction, increasing alertness and concentration of children. The same *methylphenidate,* which initially reduced body stature in growing young and after their suspension has a rapid growth rebound. Another possible therapeutic indication by similarity would be with immunosuppressive medication, drugs that caused an initial immunodeficiency (30-40%) during his administration and after their suspension caused an immune system stimulation over 120% of baseline. Reaffirming the fact observed that some exercises assist in the treatment of asthma (swimming, e.g.) we have experimental evidence that exercise-induced asthma, although initially cause a smaller nose, promoting an increase in a few minutes after the end of the exercise, assisting in improving asthma.

Oral contraceptives *(Anteovin)*

Rebound effect - therapeutic use:

Author(s): Janerich DT; Lawrence CE; Jacobson HI / Institution: First Department of Obstetrics and Gynaecology, Semmelweis University Medical School. / Title: Fertility patterns after discontinuation of use of oral contraceptives. / Source: *Lancet.* 1976 May 15; 1(7968): 1051-3. / Abstract: Investigation of the fertility-rate after discontinuation of use of oral contraceptives shows that the monthly rate consistently follows an oscillatory pattern. This pattern appears to be unique to women who have discontinued the use of oral contraceptives. It may result from synchronisation of a previously unrecognised natural cycle, rebound changes in the reproductive system following steroidal contraception, or an infertile period associated with early intrauterine mortality.

Author(s): Kovacs I / Institution: First Department of Obstetrics and Gynaecology, Semmelweis University Medical School. / Title: Examination of the rebound effect of biphasic oral contraceptives. / Source: *Ther Hung*. 1990. 38(3). P 110-3. / Abstract: Attempt has been made to induce ovulation with temporary Anteovin administration, that is with the rebound effect following the discontinuance of treatment in 34 women with anovulatory cycles who suffered from functional sterility. Ovulation could be induced in 9 cases and among the women whose cycles had become biphasic 3 became pregnant and 2 delivered normal healthy babies before closing the study. The results proved that rebound effect may be expected even following the use of Anteovin which is satisfactory from the aspect of a future fertility in women taking the tablet for contraception.

Author(s): Chasan-Taber L; Willett WC; Stampfer MJ; Spiegelman D; Rosner BA; Hunter DJ; Colditz GA; Manson JE / Institution: Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA. / Title: Oral contraceptives and ovulatory causes of delayed fertility. / Source: *Am J Epidemiol.* 1997 Aug 1; 146(3): 258-65. / Abstract: The return of fertility for women who discontinue oral contraceptives takes longer as compared with women who discontinue other methods of contraception. It remains unclear, however, whether subsequent fertility differs according to duration or age at first use. The authors performed a nested case-control

study within a cohort of 116,686 female registered nurses residing in 14 US states. Baseline information was reported on mailed questionnaires in 1989. Cases comprised 1,917 married nurses without previous pregnancy who were unable to become pregnant for at least 1 year and were subsequently diagnosed with primary ovulatory infertility. Controls comprised 44,521 married parous nurses with no history of infertility and no pregnancies lasting less than 6 months. After allowing for 2 years of suppressed fertility following discontinuation of oral contraceptive use and excluding women with signs of menstrual or hormonal disorder, the authors found that the multivariate relative risk for ovulatory causes of delayed fertility was 1.2 (95% confidence interval 0.7-1.9) for ever users. There was no statistically significant trend of increasing risk with increasing duration of use and younger age at first use. The fact that 88 percent of cases reported an eventual pregnancy by 1993 suggests that absolute fertility was not impaired.

Methylphenidate

Rebound effect - therapeutic use:

Author(s): Pizzi WJ; Rode EC; Barnhart JE / Institution: Department of Psychology, Northeastern Illinois University, Chicago 60625. / Title: Differential effects of methylphenidate on the growth of neonatal and adolescent rats. / Source: *Neurotoxicol Teratol*. 1987 Mar-Apr. 9(2). P 107-11. / Abstract: Methylphenidate (MPH), the drug of choice in the treatment of Attention Deficit Disorders with Hyperactivity (ADD/H), has raised concern regarding its suspected potential for reducing body stature in growing patients. In a previous study we demonstrated that neonatal rats treated with MPH (35 mg/kg, SC, twice daily) showed an acute growth impairment followed by a rapid growth-rebound phenomenon. This report confirms our earlier findings in neonatal rats and extends the investigation of the growth suppressing effects of MPH to the periadolescent period of development in rats. Specifically, neonatal groups of male and female rats treated with higher and lower doses of MPH than in the original study confirmed the growth impairment and growth rebound phenomena reported earlier. Unlike neonatal rats, rats treated during the periadolescent period of development failed to show any growth impairment. These data suggest that the growth suppressing effects of MPH are the result of an acute toxicity which is readily reversible on discontinuation of the drug. Further, it is concluded that there is a low probability of long term effects on human body stature when the minimal therapeutic dose is used in clinical practice.

Author(s): Klein RG; Landa B; Mattes JA; Klein DF / Institution: Long Island Jewish Medical Center, Hillside Division, Glen Oaks, NY. / Title: Methylphenidate and growth in hyperactive children. A controlled withdrawal study. / Source: *Arch Gen Psychiatry*. 1988 Dec; 45(12): 1127-30. / Abstract: The effect of stimulants on growth has been controversial. Among hyperactive children receiving long-term methylphenidate hydrochloride treatment, we examined the effects of methylphenidate withdrawal on the growth of hyperactive children randomly assigned to be taken off, or remain on, the medication regimen over two consecutive summers. After one summer, no group difference in height was found, but weight was higher in the group that had been taken off methylphenidate therapy. In contrast, two summers of being off methylphenidate treatment had a significant positive effect on height but not on weight. The results document a linkage between exposure to methylphenidate and reduction in growth velocity. However, they do not address whether the medication has long-term effects on height.

Author(s): Klein RG; Mannuzza S / Institution: New York State Psychiatric Institute, NY 10032. / Title: Hyperactive boys almost grown up. III. Methylphenidate effects on ultimate height. / Source: *Arch Gen Psychiatry*. 1988 Dec. 45(12). P 1131-4. / Abstract: The height of young adults who were treated with methylphenidate hydrochloride in childhood because of hyperactivity (average daily dose, 45 mg; duration of treatment, six months to five years) was studied. There was no significant difference in height between the treated patients (n = 61) and controls (n = 99); both

groups were at the national US norm in stature. The findings indicated that methylphenidate therapy does not compromise final height, even when it has an adverse impact on children's growth rate during the active treatment phase. A compensatory growth rate, or growth rebound, appears to occur following discontinuation of stimulant therapy.

Immunosuppressive drugs

Rebound effect - therapeutic use:

Author(s): Martin RA; Barsoum NJ; Sturgess JM; de la Iglesia FA / Title: Leukocyte and bone marrow effects of a thiomorpholine quinazosin antihypertensive agent. / Source: *Toxicol Appl Pharmacol*. 1985 Oct. 81(1). P 166-73. / Abstract: PD-88823, a thiomorpholine analog of prazosin, induced a consistent dose-related suppression of granulopoiesis with subsequent neutropenia and leukopenia in rats and dogs. Rats treated at 600 mg kg-1 day-1 had neutrophil counts reduced by 44% in males and 30% in females after 13 weeks. A 4-week observation period after drug treatment resulted in a rebound in neutrophil counts to 123 and 215% of control values in males and females, respectively. White blood cell count reductions were less evident in dogs, probably because of the lower doses. In both species, the extent of bone marrow suppression was related to duration of treatment. No other hematologic changes were manifest in either species. The mechanism for bone marrow depression and subsequent granulocytopenia was not established. The lack of reported bone marrow effects by quinazosin analogs suggests that the thiomorpholine group of PD-88823 is involved in toxicity. This correlation may be important to safety considerations for future drug design.

Exercise-induced asthma

Rebound effect - therapeutic use:

Author(s): Syabbalo NC; Bundgaard A; Widdicombe JG / Title: Effects of exercise on nasal airflow resistance in healthy subjects and in patients with asthma and rhinitis. / Source: *Bull Eur Physiopathol Respir*. 1985 Nov-Dec. 21(6). P 507-13. / Abstract: We studied the effect of exercise on nasal airflow resistance (Rnaw) and the relationship between exercise-induced asthma (EIA) and Rnaw. Rnaw was obtained by measurement of flow through the nose and mouth (in series) at constant inflow pressure. In seven healthy subjects, there were statistically significant decreases in Rnaw (39.5 +/- 6.3 and 49.0 +/- 8.2%; p less than 0.05) and no change in forced expired volume immediately after exercise on a bicycle ergometer at both 75 W and 100 W, but there was no significant difference between these two resistance changes. At 75 W, Rnaw returned to pre-exercise level at 15-20 min after exercise. At 100 W, Rnaw remained below the pretest value 30 min after exercise. In eleven asthmatics, treadmill running for 1, 2 and 6 min caused significant decreases (p less than 0.05) in Rnaw up to 44.8 +/- 3.3%, reaching levels similar to those of controls after exercise. With 6 min exercise, four of nine patients developed EIA; these subjects had allergic rhinitis as well, and recovery to pretest valued tended to be quicker than in those without EIA. In healthy subjects at both ergometer workloads, there was a rebound increase in Rnaw in 40-50% of the subjects appearing 20-30 min after exercise. In the patients, there was a rebound increase in Rnaw in about 60% of the subjects 5-10 min after exercise. Both for healthy subjects and patients, the rebound increase in Rnaw was smaller at the higher workloads.

The proposal to use the modern drugs in accordance with the principle of similarity will be developed in the next volumes of this work *(New Homeopathic Medicines: use of modern*

medicines according the principle of similitude): Homeopathic Materia Medica of Modern Drugs (Volume II) and *Homeopathic Repertory of Modern Drugs* (Volume III).

Scientific Basis of the Principle of Similitude in Modern Pharmacology

SCIENTIFIC PUBLICATIONS

Similitude in modern pharmacology

Evidenced of the principle of similitude in modern fatal iatrogenic events

Anti-inflammatory, myocardial infarction, rebound effect and similitude

Bronchodilators, fatal asthma, rebound effect and similitude

Antidepressants, suicidality and rebound effect

Statins, vascular complications, rebound effect and similitude

Gastric acid suppressing drugs, rebound acid hypersecretion and similitude

Rebound effect of drugs: fatal risk of allopathy and pharmacological basis of homeopathy

Antiresorptive drugs (bisphosphonates), atypical fractures and rebound effect: new evidence of similitude

Immunomodulatory drugs (natalizumab), worsening of multiple sclerosis, rebound effect and similitude

Other scientific publications

Similitude in modern pharmacology[1,2]

[References: Teixeira MZ. Similitude in modern pharmacology. *Br Homeopath J.* 1999; 88(3): 112-120. Disponível em: https://doi.org/10.1054/homp.1999.0301. / Teixeira MZ. O princípio da similitude na moderna farmacologia. *Rev Homeopatia (São Paulo)*. 1999; 64(1-4): 45-58. Disponível em: ResearchGate.]

Abstract

The principle of similitude, the basis of the homeopathy, meets correspondences in clinical studies of the secondary effects of a large number of modern pharmacos through the observations of the rebound effect of these drugs. Therefore, through clinical Pharmacology, a component of the present medical-scientific rationality, we propose a model to base the scientificism of the homeophatic model. We have studied the effects of present drugs in the human body using pharmacological compendia and recent scientifical works, and confirming the mechanism of homeophatic medicines' action through the verification of the primary action of the drugs and the consequent secondary action of the organism in hundreds of classical pharmacos. Treatment through the rebound effect (curative vital reaction) may also be observed. With this work, we suggest a research of the methodology of modern medicines in order to base scientifically the therapeutic principle through similitude.

Introduction

Homeophaty is based on four pillars that support it as a therapeutic technique: similitude principle, experimentation in a healthy man, dynamized medicine (infinitesimal doses) and unique medicine.

Although the similitude principle and experimentation in a healthy man are the essential prerogative for the homeophatic therapeutic practice, great importance is given to the use of minimum doses (greatly diluted substances) when the homeophaty is scientifically called into question. We must remember that Hahnemann himself worked with ponderable doses in human experimentation and therapeutic practice according to similitude law.

Rather than limiting ourselves to prove scientifically the action of high dilutions in living organism that wouldn't confirm the homeophatic therapeutics by themselves, we should focus on research of the similitude principle in order to approximate the homeophatic model to the modern scientific rationality. This way, we tried to look for the action of the

[1] Teixeira MZ. Similitude in modern pharmacology. *Br Homeopath J.* 1999; 88(3): 112-120. Available at: https://doi.org/10.1054/homp.1999.0301

[2] Teixeira MZ. O princípio da similitude na moderna farmacologia [Similitude in modern pharmacology]. *Rev. Homeopatia.* (São Paulo) 1999; 64 (1-4): 45-58. Available at: ResearchGate

principle of similitude in clinical application of modern medicines, following the study model of the drugs proposed by Hahnemann.

Observing that after a primary action of drugs in the human economy occurred a reaction of the organism (secondary action or vital reaction) to neutralize the initial disturbance (maintaining of the internal homeostasis), Hahnemann proposed a therapeutical method which used this vital and instinctive reaction: every drug which causes a disturbance in a healthy organism (artificial disease) is capable of curing this very same disturbance in a sick organism *(similia similibus curentur)* as it awakes an organic reaction contrary to the initial symptom provoked, nullifying the similar symptom of the natural disease.

In classical pharmacology, this secondary reaction of the organism to void the drug's primary effect is named *rebound effect,* described in the use of a large number of modern drugs of different classes.

The use of this rebound effect in clinical therapeutics is suggested in some modern scientifical works, and we propose, following this initial work, the elaboration of clinical tests with several present drugs to verify undisputedly the universality of the therapeutic similitude principle.

Material

To know the effects of modern drugs in the human organism, we have used *The United States Pharmacopeia Dispensing Information (USP DI, 1996)* [1] and the *American Hospital Formulary Service (AHFS, 1990)* [2] as a reference. To complete this study, we have made a research on the main medical periodicals within the last fifteen years (1982-1997), seeking for scientifical works which proved the data priorly gathered.

Method

In the work that inaugurates the homeophaty *(Essay on a new principle to ascertaining the curative powers of drugs, 1796),* Hahnemann describes the pharmacological properties of a great number of medicines used at his time, which had a secondary curative power decurrent from a similar primary effect. In this essay, the drugs are analyzed according to the primary action of causing organic alterations and the secondary effect of the organism, to try to nullify these medicinal disturbances. This is the responsible factor for the curative vital reaction of the homeophatic treatment.

In paragraphs 56 to 67 of *Organon of medicine* [3], Hahnemann describes about the enantiopathic treatment method, mentioning a large number of drugs of his time that were used according to the primary palliative effect to the disturbed symptom, demonstrating that "after such short antipathic amelioration, aggravation follows *in every case without exception*" (*Organon,* paragraph 58). Based upon these clinical observations of the

palliative therapeutic procedure to embase the "mechanism of drug action" in paragraphs 63 to 65 of the *Organon,* through the primary action and of the secondary action or vital reaction.

Bringing the drug study to our days, we have analyzed pharmaco by pharmaco according to its primary and secondary actions in human organism, performing a thorough study of the drugs related to the indication use, mechanism of action, duration of action, side/adverse effects and general dosing information according to the *USP DI* [1] and *AHFS* [2].

After identifying the *secondary action (rebound effect)* in a series of substances described in the pharmacological compendia, we based these reports on a large number of scientifical works about the subject. This complementary research was done through the *Medline* data bank, between 1983 to 1998, using the keywords: "feedback", "self-recovery", "paradoxal reaction" and "rebound effect".

We have also seeked for data related to treatments that had used the rebound effect as a curative answer, using modern drugs.

Results

For homeophaty, the real therapeutic should be based upon the administration of a medicinal stimulus (artificial disease) similar to the natural disease that is to be fought, promoting a reaction of the organism towards the equilibrium of the internal environment (homeostasis). This is what the principle of similitude is based upon.

Theoretically, every drug should be able to produce in a healthy individual the same symptoms that should cure in a sick individual. These symptoms are considered as primary action of the medicinal substance. The process towards the cure of the symptoms occurs through the secondary action of the organism (homeostatic reaction), which after nullifying the primary drug effect with similar symptoms to a natural disease, restores the organic health.

In this work, we have tried to demonstrate that the secondary action (vital reaction) of the organism is observed in a great number of modern pharmacos. The discontinuity of the enantiophatic or palliative treatment confirms the innumerable observations of Hahnemann.

Following the reasoning of the homeophaty's founder when criticize the therapeutical method of his time *(contraria contrariis curentur)* in paragraphs 56 to 67 of *Organon,* we verify that after withdrawing the present enantiophatic drugs used to eliminate determined symptoms according to the principle of the contraries, the very same symptoms that were initially suppressed return with stronger intensity than the initial one. This proves the secondary reaction of the organism towards the maintenance of the internal environment.

In modern pharmacology this secondary action or homeophatic vital reaction is defined as a "rebound effect" or "paradoxical reaction" of the organism. It always returns with stronger intensity than the initial disturbance, proving the secondary reaction of the organism towards the maintenance of the internal environment.

To emphasize that it is in *"the homeopathic employment of medicines"* a real and solid cure method, Hahnemann highlights in paragraph 61 of *Organon* the importance *"of reflecting on the sad results of the antagonistic employment of medicines",* in order to make it possible for us to prove the principle of similitude. According to this proposal we have studied the results of the antagonistic medicines usage as stated by the modern pharmacology in order to base the universality of the principle of similitude.

The following are listed some drugs that make clear the secondary action of the organism (rebound effect), concerning a complete study of hundreds of drugs to the work *"Similar cures similar: the homeopathic cure principle based by the medical and scientific rationality"* [4].

I. Confirmation of the secondary effect of the organism (rebound effect)

1) Antiarrythmic drugs
Beta-adrenoceptors blockers
Therapeutic indications: Ventricular arrythmia.
Rebound effect: Fast or irregular heart beat. The abrupt cessation of a beta-blocker may cause ventricular tachycardia (*USP DI, 1996,* p. 579).
Other references: [5], [6], [7], [8], [9], [10].

2) Antianginal drugs
Nitrates - Nitroglycerin
Therapeutic indications: Classical angina pectoris.
Rebound effect: Patients who use Nitroglycerin for a long period present angina attacks more frequently than the usual ones after withdrawing the drug (*AHFS, 1990,* p. 959).
Other references: [11], [12], [13], [14], [15], [16], [17], [18].

3) Antihypertensive drugs
Central alfa2-adrenoceptors agonists
Therapeutic indications: Arterial hypertension.
Rebound effect: Arterial hypertension (with clonidine, the rebound hypertension usually occurs after the abrupt withdrawal of the medication, being symptomatical in 5 to 20% of the patients). Sympathetic hyperactivity with rebound hypertension may occur in a period of 2 to 7 days after the abrupt withdrawal of guanfacine, with greater risk during the use of doses higher than 4 mg/day (*USP DI, 1996,* p. 885, 1567, 1576). The abrupt withdrawal of oral clonidine results in a fast (after 8-24 hours) increase of the systolic and diastolic blood pressures, not being well determined its mechanism. With the use of transdermal clonidine a severe rebound hypertension occurred 36-72 hours after the treatment cessation. When

the treatment is interrupted before surgery, the rebound hypertension occurs during or after the surgery. With guanabenzo, in 33% of the patients occurs a fast and important increase of the systolic and diastolic pressures after withdrawing the medication, lasting for several days (*AHFS, 1990*, p. 912, 913, 921, 940).
Other references: [19], [20], [21], [22], [23], [24], [25], [26].

4) Drugs for intracranial hypertension
Mannitol (osmotic diuretic)
Therapeutic indications: Symptomatical relief of the edema; treatment of the intracranial hypertension (cerebral edema).
Rebound effect: Urinary retention, pulmonary congestion, edema of the lower limbs (*USP DI, 1996*, p. 1957; *AHFS, 1990*, p. 1477). A rebound increase on the intracranial pressure may occur approximately 12 hours after the osmotic diuresis is used to reduce the cerebral edema and intracranial pressure (*AHFS, 1990*, p. 1476).
Other references: [27], [28], [29], [30].

5) Antihypotensive drugs
Dextran
Therapeutic indications: Treatment of the hypovolemic shock.
Rebound effect: Due to the possibility of an important secondary reaction occurs just after the administration of the drug, the patients must be closely watched during the first five minutes, with an eye to detect severe hypotension rebound (*AHFS, 1990*, p. 1420).

Dopamine (cardiac stimulate, vasopressor)
Therapeutic indications: Acute hypotension.
Rebound effect: Arterial hypotension (in severe cases, drugs with properties similar to norepinephrine should be given) (*USP DI, 1996*, p. 1234; *AHFS, 1990*, p. 620).

6) Antihypercholesterolemic drugs
Chlofibrate
Therapeutic indications: Treatment of hyperlipoproteinemia.
Rebound effect: Substancial increase on the triglyceride concentration (LDL) (*AHFS, 1990*, p. 889).
Other reference: [31].

Inhibiting of HMG-CoA redutase
Therapeutic indications: Treatment of the hyperlipoproteinemia.
Rebound effect: Substancial increase in the triglyceride concentration (LDL) (*AHFS, 1990*, p. 903).
Other reference: [32].

7) Ansiolitic drugs
Benzodiazepines
Therapeutic indications: Anxiety (Agoraphobia, Panic disorder, etc.).
Rebound effect: Unusual excitation, nervosity or irritability occur as a paradoxical reaction (they usually appear within 2-3 days with benzodiazepines of intermediate or short

half-life, and within 10-20 days with benzodiazepines of long half-life, after abrupt cessation of therapeutical doses giving continuously during several months) (*USP DI, 1996*, p. 542, 814). Nervosity, excitement and irritability may occur after abrupt cessation of the medicine (*AHFS, 1990,* p.1129).
Other references: [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44].

8) CNS stimulating drugs
Amphetamines
Therapeutic indications: Lack of attention syndrome, narcolepsy, appetite suppression.
Rebound effect: After the stimulating effects (increase of the motor activity and of the sleep-awake state, sleep decrease and fadigue sensation), unusual tiredness or debility, sleepiness, shiver, mental depression may occur (*USP DI, 1996,* p. 93; *AHFS, 1990,* p. 1219, 1227).
Other references: [45], [46], [47], [48], [49].

9) Antidepressant drugs
Tricycle antidepressants
Therapeutic indications: Mental depression, mania, panic.
Rebound effect: Unusual anxiety, sleepiness, tiredness or severe debility (*USP DI, 1996*, p. 268). Exacerbation of depression, hypomania, panic or anxiety (*AHFS, 1990,* p.1157).
Other references: [50], [51], [52], [53], [54], [55].

10) Anticonvulsant drugs
Anticonvulsants of the hidantoine group
Therapeutic indications: Convulsive crisis, paroxysmal coreoathetosis, behavior disturbances (excitement, anxiety, irritability and insomnia).
Rebound effect: Increase of the frequency on convulsive crisis. Restless or agitation; uncontrollable spasmodic movements or hands, arms and legs twisting; lips, tongue or cheeks uncontrollable movements (momentary coreoathetoid movements not related to the hidantoine intoxication; the effect usually lasts within 24 to 48 hours after the withdrawal of fenitoine and may end spontaneously. Changes of the behavior or mental state; unusual excitement, nervosity or irritability (*USP DI, 1996,* p. 249).
Other references: [56], [57].

Barbiturics
Therapeutic indications: Convulsive crisis.
Rebound effect: Convulsive crisis (may occur 16 hours after the interruption of the treatment and last until 5 days, decreasing gradually within 15 days) (*USP DI, 1996*, p. 511; *AHFS, 1990,* p. 1125).

11) Antipsychotic drugs
Phenotiazines
Therapeutic indications: Treatment of psychotic disorders (schizophrenia).
Rebound effect: Exacerbation of the psychotic and catatonic symptoms after discontinuation of the treatment (*USP DI, 1996,* p. 2362; *AHFS, 1990*, p. 1185).
Other references: [58], [59], [60].

Haloperidol
Therapeutic indications: Treatment of psychotic disorders (schizophrenia).
Rebound effect: Exacerbation of the psychotic symptoms (including hallucinations and catatonia) after the discontinuation of the treatment (*USP DI, 1996,* 1593; *AHFS, 1990,* p. 1205).
Other references: [61], [62].

12) Antidyskinetic drugs
Antidyskinetics
Therapeutic indications: Parkinson's disease; extrapyramidal reactions induced by drugs.
Rebound effect: Worsen the extrapyramidal symptoms with the abrupt withdrawal of the antidyskinetics (anxiety; difficulty to speak or swallow; loss of the equilibrium control; mask face or myopathic face; muscular spasms on the face, neck and back; disquiet or need to be in movement; march and dragging the feet; stiffness of arms and legs; shiver or agitation of hands and fingers; movements of twisting the body) (*USP DI, 1996,* p. 295; *AHFS, 1990,* p. 580).
Other references: [63], [64], [65].

13) Muscular relaxant drugs
Relaxants of the skeletal musculature
Therapeutic indications: Treatment of the spasticity of the skeletal muscle.
Rebound effect: With abrupt withdrawal of baclofeno, inexplicable muscular stiffness is verified (increase of the spasticity) or unusual excitement (*USP DI, 1996,* p. 509). Acute exacerbation of the spasticity frequently occurs with the abrupt withdrawal of the medication (*AHFS, 1990,* p. 690).

Relaxants of smooth musculature
Therapeutic indications: Treatment of the spasticity of the smooth muscle.
Rebound effect: Rebound spasticity.
References: [66], [67], [68], [69], [70], [71].

14) Analgesic drugs
Opioid analgesics
Therapeutic indications: Treatment of the pain; coadjutant of the anaesthesia.
Rebound effect: Generalized pains. With an excessive dose, along with the decreasing of the pain, we notice severe sleepiness, loss of consciousness, cold skin, arterial hypotension, punctate pupils, slow heart beats and slow or difficult breathing; when we discontinue or antidote the medication with Naloxone, a fast paradoxical reaction (24 to 72 hours) and a long one (5-14 days) are observed composed by the increase of the pain, insomnia, severe nervosity or disquiet, fever, arterial hypertension, unusual big pupils, tachycardia and hyperpnea (*USP DI, 1996,* p. 2216; *AHFS, 1990,* p. 1069). After the discontinuation of the phentanile, used as an analgesic, generalized pains through the body are observed (*USP DI, 1996,* p. 1452).
Other references: [72], [73], [74], [75].

Ergotamine/ Dihydroergotamine (Ergot's derivatives)
Therapeutic indications: Treatment of the headache of vascular origin (migraine).
Rebound effect: According to the *National Headache Foundation* [76], the constant use of medicines which contain tartrate of ergotamine makes the migraine crisis become more frequently due to the rebound effect. The tolerance to the drug depends on the individual idiosyncrasy. With the discontinuation of the treatment with ergotamine, rebound headache may occur, that is slightly different of the original migraine headache (*AHFS, 1990,* p. 662). Headache, nausea and vomits may occur with usual doses (severe rebound headache appears with the discontinuation of the chronic use of Ergot's derivatives, being very severe on the first 24-48 hours and lasting up to 72 hours after the last dose) (*USP DI, 1996*, p. 2968; *AHFS, 1990,* p. 658).
Other reference: [77].

15) Anti-inflammatory drugs
Corticosteroids
Therapeutic indications: Treatment of the inflammatory processes.
Rebound effect: Rebound inflammation after withdrawing the treatment.
References: [78], [79].

Salicylates
Therapeutic indications: Treatment of the inflammation (fever).
Rebound effect: Inexplicable fever, maybe very high (*USP DI, 1996,* p. 2589). Hyperthermia, sometimes with rectal temperature reaching 40.5 to 42.2ºC (*AHFS, 1990,* p. 992). Rebound increase of the inflammation, after withdrawing the drug.
Other references: [80], [81].

16) Anticoagulant drugs
Heparin
Therapeutic indications: Treatment and prophylaxis of thrombosis and thromboembolism.
Rebound effect: With the continuous use, thrombotic complications may occur originated by the development of antiplatelet antibodies dependent on heparin, which permits a great increase of the platelet aggregation, causing infarct of the organs. These new thrombos are composed mainly by fibrin and platelets. This severe kind of thrombocitopenia doesn't depend on the origin, dose or administration way (*USP DI, 1996,* p. 1597). Located or disseminated thrombosis: the formation of new thrombos is related to the induction of thrombocitopenia by heparin, a consequence to the paradoxical reaction resulted of the irreversible platelet aggregation (white clot syndrome) induced by it (*AHFS, 1990,* p. 728).
Other reference: [82].

Protamine (anti-heparinic)
Therapeutic indications: Treatment of the toxicity (overdose) by heparin.
Rebound effect: Hemorrhages (rebound of the heparinic activity) (*USP DI, 1996,* p. 2504). Heparinic rebound with anticoagulation and hemorrhages have been reported occasionally several hours (8 to 9 hs) after the correct neutralization of the heparin by the protamine sulfate (*AHFS, 1990,* p. 732).

Other references: [83], [84].

17) Antihistaminic drugs
Antihistaminics
Therapeutic indications: Neutralize the answers mediated by the histamine in rhinitis, conjunctivitis, pruritus, urticaria, angioedema, vertigo, sedation, insomnia, anorexia, etc.
Rebound effect: Rebound symptoms appear, which are actions of the histamin, such as suffocation and facial flush, airless feeling, increase of the glandular secretions, allergic reactions, formation of edemas, vertigo, hypotension, unusual excitement and nervosity, insomnia, loss of apettite, etc. (*USP DI, 1996*, p. 323, 1609; *AHFS, 1990*, p. 2).
Other reference: [85].

18) Diuretic drugs
Diuretics
Therapeutic indications: Promote the diuresis, with the excretion of sodium and potassium [lower in potassium savers (Triamterene)].
Rebound effect: Rebound retention of sodium and potassium.
References: [86], [87], [88], [89], [90], [91], [92], [93].

19) Anti-dyspeptic drugs
Antagonists of the histaminic H2 receptor
Therapeutic indications: Treatment of the gastric and duodenal ulcers.
Rebound effect: Perforation of chronic peptic ulcers was reported during the treatment with cimetidin. One month after withdrawing the treatment recurrence of ulcers in 41% of the patients was observed, possibly occurring within one week after its withdrawal (*AHFS, 1990*, p. 1667, 1668).
Other references: [94], [95], [96], [97], [98], [99], [100].

Antacids
Therapeutic indications: Treatment of the hyperacidity, gastritis and peptic ulcer.
Rebound effect: Rebound acidity.
References: [101], [102], [103], [104].

20) Drugs for bronchial asthma
Adrenergic bronchodilators
Therapeutic indications: Bronchospasms of the bronchial asthma and of the chronic obstructive pulmonar disease.
Rebound effect: Severe difficulties to breath, increase of the sibilances; cough or other bronchial exacerbation (*USP DI, 1996*, p. 621). Paradoxical bronchospasms are observed with the use of salmeterol. Fatalities have been reported with the excessive use of sympatheticomimetic bronchodilators. The *causa mortis* is unknown; however, it is suspected that heart failures occur immediately after severe crisis of acute asthma with following hypoxia (*USP DI, 1996*, p. 2614). Difficulty to breath; bronchospasms, sometimes of severe intensity and non-responsive to any bronchodilating therapeutic (*AHFS, 1990*, p. 613, 616, 623, 627, 630).
Other references: [105], [106], [107], [108], [109], [110].

Corticosteroids – via inhalant
Therapeutic indications: Treatment of the bronchial asthma and of the chronic obstructive pulmonar disease.
Rebound effect: Difficulty to breath, airless feeling, chest oppression and sibilances; bronchitis, bronchospasms (*USP DI, 1994*, p. 908). Bronchial asthma (*AHFS, 1990*, p. 1546, 1549, 1730, 1731).
Other reference: [111].

21) Nasal decongestant drugs
Oximetazoline - via nasal
Therapeutic indications: Nasal congestion (associated to the chronic rhinitis).
Rebound effect: Exacerbation of the nasal mucosa and sneezes. Rebound congestion characterized by chronic redness, swelling and rhinitis, caused by the long lasting use and/or excessive doses of the drug (*USP DI, 1996*, p. 2260; *AHFS, 1990*, p.1595).
Other references: [112], [113], [114], [115].

22) Antiglaucomatous drugs
Colinergic antiglaucomatous (anticolinesterasics)
Therapeutic indications: Treatment of the glaucoma (intraocular hypertension).
Rebound effect: After the use of demecario, ecotiopato or fluostigmine it is possible to produce a paradoxical increase of the intraocular pressure; blotched vision or changes in the visual accomodation; ocular pain; ocular exacerbation; headache (*USP DI, 1996*, p. 313; *AHFS, 1990*, p. 1570).
Other reference: [116].

23) Lactation drugs
Dopamin agonists
Therapeutic indications: Treatment of amenorrhea and galactorrhea; prevention of the physiological lactation postpartum in situations of fetal death or abortion.
Rebound effect: After withdrawing medicine, rebound amenorrhea within 4 to 24 weeks and rebound galactorrhea within 2 to 4 weeks usually appear. Rebound lactation may occur after the use of bromocriptine to suppress the postpartum lactation (*USPDI*, p. 617; *AHFS, 1990*, p. 2152).
Other references: [117], [118], [119].

Other examples of drugs that the rebound effect is described: Nifedipine, Hidralazine, ACE inhibitors, MAO inhibitors, Sodium nitroprusside, PGA1, Nitric oxide, Glycerol, Indomethacin, Sulmazol, Colestiramine, Lifibrol, Buspirone, Midazolam, Prometazine, Trazodone, Zopiclone, Dronabinol, Caffeine, Cocaine, Methylphenidate, Fluoxetine, Moclobemide, Anticonvulsivants of the dione group, Carbamazepine, Clozapine, Pimozide, Bromocriptine, C-dopa and L-dopa, Flunarizine, Metisergide, Alfentanil, Halotane, Ibuprofen, Indomethacin, Monoclonal antibodies, Bezafibrate, Thrombin inhibitor, Epoprostenol, Warfarin, Cromakalin, Misoprostol, Mezalazine, Olsalazine, Epinefrine, Ipatropio, Xylometazoline, Mathazolamide, Calcipotrien, Minoxidil, Ritodrine, Lisuride, S-calcitonin, Alpha-interferon, etc.

II. Confirmation of the therapeutic similitude principle

To confirm the use of the conventional drugs according to the therapeutic principle of similitude, we looked for the confirmation of the symptoms cure through the secondary actions of the organism or rebound effect. Unfortunately, we have found just one study with this specific purpose, although the others suggest the applicability of these methods to other drugs.

In the mentioned experiment, the rebound effect (secondary action) was used to induce the ovulation in women who presented functional sterility, through the application of a biphasic contraceptive, a drug that shows as primary action the property of inducing functional sterility in healthy women. Therefore, a drug capable of producing a determined symptom in healthy individuals may cure this very symptom when given to sick individuals: *similia similibus curanter.*

Anteovin
Therapeutic indications: Biphasic oral contraceptive (to avoid ovulation and pregnancy).
Rebound effect: Induces ovulation (pregnancy), after withdrawing the drug. The ovulation induction was tried with the temporary administration of the anteovin (biphasic oral contraceptive), using the rebound effect that appears after the discontinuation of the treatment in 34 women with unovulating cycles who suffered of a functional sterility. The ovulation could be induced in 9 cases and among women whose cycles became biphasic 3 got pregnant, with 2 developing healthy babies before the end of the study. The results prove that the rebound effect may be also expected after the use of anteovin as a satisfying aspect for a future fertility in women who stop taking contraceptives. [120]

Similarly to this experiment with anteovin, biphasic contraceptive compound by a progestagen-oestragen combination, Kovács mentions other studies that had used the rebound effect of the contraceptives enoved, lyndiol, anovlar and infecundin to induce the ovulation in women that presented functional sterility.
Other references: [121], [122], [123], [124], [125], [126].

Discussion

Through the mentioned data, the mechanism of the homeophatic medicines action was evidenced for a great number of modern medicines, based upon Hahnemann in paragraphs 63 and 64 of *Organon* on the primary action of drugs and on the secondary action of the organism.

The homeophatic curative effect *(similia similibus curentur)* was also demonstrated in the treatment of women with functional sterility using a drug that causes functional sterility in healthy women.

In spite of the verification that the rebound effect of some drugs was related to the "up regulation" of the number of receptors or to the half-life of the pharmaco in question, these observations make evident an intermediate mechanism of the phenomenon itself. In the great majority of the analyzed experiments the physiologic explanation for the phenomenon is unknown, despite of the evident confirmation of it.

According to modern scientific methodology, the experimental observation of a phenomenum repeatedly constitutes a sufficient proof that this can be accepted - premise defended by Hahnemann in the first thirty paragraphs of *Organon.*

As it was said initially, we can find a physiologic justification for the rebound effect and homeophatic similitude principle through the complex mechanism of the organism's internal control, initially mentioned by Claude Bernard (1859) as a "constancy of the internal environment" *(fixité du milieu intérieur)* and better explained by Cannon in 1929, through the greek term homeostasis (homeos = similar, alike; stasis = state, condition). Presently, through the studies about the psycho-neuro-immuno-endocrine-metabolic regulator system (reactions to stress, for example) we found subsidies to understand the hierarchy, the organization and communication among the homeostatic systems placed in several levels. We can relate this complex maintenance mechanism of the internal balance to the *modus operandi* of Hahnemann's vital force *(vis medicatrix naturae).*

Therefore, the usage of the rebound effect as a therapeutic technique means a way to stimulate the internal mechanisms of cure, as well as through homeopathy we stimulate an intelligent homeostatic reaction in complex systems. We have to understand that the most important purpose of the homeopathic therapy is to stimulate the organism to react against the unbalance that affects it, using the homeopathic medicine to indicate the correct way that this vital reaction should occur towards the cure, avoiding the organic's automatic and instinctive responses which can become harmful to the system without a rational control.

With reference to the question about the administration of doses to awake the rebound effect, in most of published works, therapeutic doses are used for a long period, although there are studies of single dose in the cited references. We observed that the rebound effect occurs when a new "disturbance" (physiologic alteration caused by the drug) is incorporated to the metabolism and it is abruptly withdrawn. In case of gradual discontinuation of the drug, the rebound effect is minimized. In the example where the contraceptive cause the ovulation in sterile women after the withdrawal usage of therapeutic doses of enoved, lyndiol, anovlar and infecundin for many years is reported; in the case of anteovin, the pharmaco was used for shorter periods (only 3 months).

With the presupposition that the organism answers to the artificially induced unbalance through a contrary homeostatic response, with the intention of neutralizing it, we understand that this rebound effect can occur with the use of infinitesimal doses of the drugs, as the "information" is incorporated to the metabolism of the susceptible individual. As we know, in case of strong doses (intoxication), the susceptibility is surpassed, making all people tested be aware and react to the stimulus.

Regarding the validity of using ponderal and repeated doses of the findings mentioned in this work, we must remember that Hahnemann used the same during the initial phase of homeopathy, even in the treatments as in the pathogenetic experiments, since the similitude principle was observed, considering the homeophatic fundaments. The dynamization appeared with the purpose of reducing the aggravation of the massive doses and also to avoid the secondary actions (rebound effects) be mixed with primary actions of the experiment (*Organon,* paragraph 66).

Hahnemann mentions the usage of ponderal doses (*Organon,* paragraph 128) in pathogenic experiments of the substances saying that we are only loosing "the full amount of the powers", that continues to be hidden in the raw state and is awaked through the process of dynamization.

We must remember that the majority part of the symptoms aggregated to the Homeophatic Materia Medica are fruit of the report of drug intoxication and adverse events of conventional treatments, being constantly used in the homeophatic clinic without differentiation from the others (ideal pathogenetic experimentation), confirming the observations mentioned in paragraph 112 of *Organon,* in which Hahnemann compares without any doubt the effect of the modern rebound effect to the homeopathic secondary action or vital reaction.

> "In those older prescriptions of the often dangerous effects of medicines ingested in excessively large doses we notice certain states that were produced, not at the beginning, but towards the termination of these sad events, and which were of an exactly opposite nature to those that first appeared. These symptons, the very reverse of the *primary action* (§ 63) or proper action of the medicines on the vital force, are the reaction of the vital force of the organism, its *secondary action* (§ 62-67), of which, however, there is seldom or hardly ever the least trace from experiments with moderate doses on healthy bodies, and from small doses none whatever". (*Organon,* § 112)

Still in the theme of doses, Hahnemann uses repeated doses (chronic use) in the treatment of disease as in the experiments since the effects of a only dosage are weak and not alter the health state of less healthy sensitive individuals (*Organon*, paragraphs 129-132). From eighter form will produce the desired primary effects that will awake the vital reaction or the secondary action (rebound effect).

Another doubt that could arise to the reader would be about the validity of the data collected in the experimentation in sick individuals, in the contrary to the experiment in healthy individuals and diffused by Hahnemann as an ideal model. We would like to mention that for some drugs mentioned were used in healthy individuals which were observed a similar rebound effect with the usage in sick individuals.

Notwithstanding the greatness of the experimentation in healthy individuals for us to verify the awakened symptoms by the substances in an accurate and particular form, Hahnemann experimented the majority of medicines of the *Chronic Diseases* in chronic patients under treatment as it is mentioned by Richard Hughes in the "Preliminary note to Materia Medica

section" in his referred translation. The same is found in a large number of symptoms aggregated to the Homeopathic Materia Medica in the report of cure and intoxications of the past.

As Hahnemann did, we could experiment substances in sick individuals since we separate the pre-existent symptoms of the individual from the ones that might appear after the ingestion or suspension of the medicine.

Conclusion

With this work, we have proposed to evidence the truth about homeophatic experimental observations according to the modern pharmacological model.

In the original work [4], we have found references to the vital reaction or rebound effect in hundreds of classical drugs in spite of the usage of them in ponderable doses, i.e.. in lack of minimum doses (infinitesimal) proposed by Hahnemann.

Observing the effects of modern drugs in the human body, we have identified a great number of reactions that may be used according to the homeophatic therapeutic model, as in the example of the contraceptive priorly mentioned.

It would be the case to use the immuno-suppressers in infinitesimal doses as the thiomorfoline quinazozin, used initially as a hypertensive agent and after causing an initial immunosuppression of 30 to 40% provoked, in the period of four weeks after withdrawing the drug as a rebound effect an immuno-stimulation of 125% of the basic values. [127]

So, we could use hypertensive agents (dextran, dopamine, metaraminol, etc.) in minimal doses in hypertensives patients expecting a therapeutic rebound hypertension or hypertensive agents (beta-blockers, central alfa-2 agonists, nitrates, etc.) in patients presenting hypovolemic shock, expecting a curative rebound hypertension.

Mentioning one more example among uncountable possible ones, we could use mivacurina, a muscular relaxant drug that provoked as a primary malignum hypertemia effect in swines, in treatment of this same pathology in humans with the necessity of a dosage balance.

Without mentioning the word "homeophaty", we could study it in any clinical or pharmacological department of great research centres, according to the following model: *"Rebound effect - clinical confirmation and therapeutical usage".* With this proposal we have been pleading to the Medical Universities an opportunity to develop clinical assays that confirm the similitude principle in a series of modern pharmacos.

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Evidenced of the principle of similitude in modern fatal iatrogenic events[3]

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Abstract

Determining the purposes of the homeopathic model, Samuel Hahnemann attributed primordial importance to the principle of similitude, promoting it to the "natural law" category. Observing that the enanthiopathic treatment (use of medicinal substances with antagonistic or opposed pharmacological properties to the undesirable symptoms) produced enduring aggravation of the disease symptoms, after a brief and transitory initial relief, he systemizes the homeopathic treatment, giving to the patient substances that present the property of awakening similar symptoms in healthy individual. Based on clinical and experimental observations, he anticipates the physiologic conception of homeostasis ("life-preserving power"), describing the effect of the substances in the human health state: primary action of the medicine followed by secondary action or reaction of the organism. This vital reaction, known as rebound effect or paradoxical reaction by the modern pharmacology, used to awake the curative answer of the body when we apply the principle of similitude, is responsible for several iatrogenic diseases when we use the principle of the contraries as therapeutic proposal. In this study, the author evidences the role of this paradoxical reaction of the organism (rebound effect or vital reaction) in the fatal side effects of four important modern drugs, used according to the model of enantiopathic treatment of the symptoms. Warned by Hahnemann for more then two centuries, the palliative or antipathetic treatment for the symptoms of the diseases can break out serious adverse events, causing danger of life and death itself, presently evidenced in the use of acetylsalicylic acid, rofecoxib, antidepressants and bronchodilators of long duration, besides the chronicity and incurability of several modern diseases. Assuming importance in the public health, the disastrous consequences of the antipathetic treatment could be decreased if the health professionals valued the organic homeostasis, minimising the rebound effect of the organism with the slow and gradual suspension of the palliative drugs.

Introduction

Samuel Hahnemann, founding the homeopathic method of treatment of the diseases in paragraphs 22-70 of the *Organon of Medicine* [1], discourses about the particularities of the principle of similitude, raised to the "natural law" category by the several observations and experiments that document the existence of this incontestable phenomenon.

[3] Teixeira MZ. Evidence of the principle of similitude in modern fatal iatrogenic events. *Homeopathy*. 2006; 95(4): 229-236. Available at: https://doi.org/10.1016/j.homp.2006.06.004

Relating the principle of similitude to the symptomatic manifestation of the diseases, he discourses about the homeopathic and antipathetic (enantiopathic or palliative) methods of treatment (*Organon*, paragraphs 51-70), which seek for morbid symptoms administering the medicines that produce, respectively, symptoms opposite or similar observed in the patients. Relating the brief and transitory relief produced by the enantiopathic treatment, followed by evident aggravation of the disease, he justifies his choice for the use of the homeopathic method.

Criticising the contrary method of the treatment of the diseases *(contraria contrariis curentur),* mentioned by Hipocrates and divulged by Galeno until nowadays, Hahnemann cites several examples in which "after such short antipathetic amelioration, aggravation follows in every case without exception" (*Organon*, paragraphs 58-59), inciting the ordinary physician to the progressive increase of the doses, causing "another more serious disease or frequently incurability, even danger of life and death itself, *but never a cure* of a disease of considerable or of long standing" (*Organon*, paragraph 60).

It guides us to the reflection about the adverse effects of the antagonistic employment of medicines, as a way to evidence the validity of the opposite procedure, the homeopathic use of medicines according to similarity of symptoms (principle of similitude):

> "Had physicians been capable of reflecting on the sad results of the antagonistic employment of medicines, they had long since discovered the grand truth, *that the true radical healing art must be found in the exact opposite of such an antipathetic treatment of the symptoms of disease;* they would have become convinced, that as a medicinal action antagonistic to the symptoms of the disease is followed by only transient relief, and after that is passed, by invariable aggravation, the converse of that procedure, *the homoeopathic employment of medicines* according to similarity of symptoms, must effect a permanent and perfect cure […]". (*Organon*, paragraph 61)

Following this orientation, let's demonstrate through serious or fatal iatrogenic events of modern enantiophatic treatments, causer of danger of life and death itself, the validity of the principle of similitude.

Similitude and homeostasis

Observing the alterations that the medicines used to cause in the health state, during short and long period, Samuel Hahnemann describes the mechanism of action of the drugs in the organism, through an immediate "primary action" of the medicine and of a late "secondary action or vital reaction" of the organism:

> "Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed *primary action.* […] To its action our vital force endeavours to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of *secondary action* or *counter-action".* (*Organon*, paragraph 63)

He mentions several examples of the primary action of the external agents in our organism and the consequent reaction of the vital force, which acts in an instinctive way in a sense to preserve the homeostasis or the balance of the internal environment ("life-preserving power"), producing intense and opposite symptoms to the alteration initially induced:

> "[...] Excessive vivacity follows the use of strong coffee (primary action), but sluggishness and drowsiness remain for a long time afterwards (reaction, secondary action), if this be not always again removed for a short time by imbibing fresh supplies of coffee (palliative). After the profound stupefied sleep caused by opium (primary action), the following night will be all the more sleepless (reaction, secondary action). After the constipation produced by opium (primary action), diarrhoea ensues (secondary action); and after purgation with medicines that irritate the bowels, constipation of several days' duration ensues (secondary action) […]". (*Organon,* paragraph 65)

Influenced by the vitalist thought of his time, Hahnemann utilises the term "reaction of the vital force" to explain the automatic phenomenon of organic self-regularisation observed in an empiric way (secondary action or antagonistic reaction in response to a primary action), confirmed in 1929 by the physiologist W.B. Cannon through the Greek concept "homeostasis", defined as "the ability or tendency of an organism or cell to maintain internal equilibrium by adjusting its physiological processes". These physiological processes or homeostatic mechanisms are present in all of the levels of biological organization, from the simple cellular to the complex psychic and emotional functions, which can be stimulated by the homeopathic medicines as they provoke in the homeopathic experimentations symptoms regarding the systems in subject. In the search of a "global homeostatic reaction" with larger therapeutic effect, Hahnemann stipulates the use of the "totality of characteristic symptoms" to choose the ideal medicine, so that several levels of the biological organization were stimulated simultaneously.

Observing that the use of medicines according to the principle of the contraries (antipathetic, palliative, antagonistic, enantiopathic treatment) used to cause harmful effects (iatrogenic diseases) to the human economy, Hahnemann proposes a therapeutic through the similar, stimulating the body itself to react against its symptoms, administering to the patients substances that awake similar symptoms in the healthy experimenters.

It is noteworthy that, in the beginning of the homeopathy, Hahnemann applied the similitude principle with ponderal doses of the substances, using the ultra-dilution medicines in subsequent phase of his clinical practice, in view of the secondary action (homeostatic reaction) to be wakened with large or infinitesimal doses (*Organon*, paragraph 112).

Similitude and modern pharmacology

In the study about *rebound effect* or *paradoxical reaction* of the organism, denominations used by the modern pharmacology and physiology to the secondary action or vital reaction of the homeopathic model, we found the scientific validation to the phenomenon previously

described, usually observed after the interruption or discontinuation of hundreds of modern medicines, from several classes.

For example, we can look at traditional drugs used for the treatment of angina pectoris (amlodipine, beta-adrenoceptor blockers, calcium channel blockers, nitrates), whose primary effect is the improvement of angina. After suspension of the drug, a rebound effect of the organism is awaked, which exacerbates the thoracic pain, in frequency as well as intensity, and in some cases the pain is not responsive to any type of therapy. Drugs utilised to control arterial hypertension (central alpha2-adrenoceptor agonists, beta-adrenoceptor blockers, hidralazine, ACE inhibitors, MAO inhibitors, nitrates, prostaglandin A_1, sodium nitroprusside) can awake a rebound arterial hypertension as a secondary reaction of the organism to the primary stimulus. Anti-arrhythmic medications (adenosine, amiodarone, beta-adrenoceptor blockers, calcium channel blockers, disopyramide, encainide, digitalics, flecainide, lidocaine, mexiletine, moricizine, procainamide, propafenone, quinidine, tocainide) awake, after the interruption of treatment, exacerbation of initial arrhythmias. Anticoagulant drugs (argatroban, bezafibrate, heparin, salicylates, warfarin) utilised for their primary effect in the prophylaxis of blood thrombosis, cause thrombotic complications as a secondary or rebound effect. In the utilisation of psychiatric medications, anxiolytics (barbiturates, benzodiazepines, buspirone, meprobamate), sedatives-hypnotics (barbiturate, bendodiazepine, morfine, promethazine, tetrahydrocannabinol, zopiclone), CNS stimulants (amphetamine, caffeine, cocaine, mazindol, methylphenidate), antidepressants (MAO inhibitors, tricyclics, SSRIs), anti-psychotics (clozapine, phenothiazines, haloperidol, pimozide, thiethylperazine, thiothixene), a reaction of the organism trying to maintain organic homeostasis can be observed, awaking symptoms opposite to those expected in their primary therapeutic utilisation, further aggravating the initial condition. Drugs whose primary action is anti-inflammatory (ibuprofen, indomethacin, paracetamol, salicylates) induce a secondary response of the organism, increasing inflammation and the plasma concentration of mediators of inflammation. Drugs whose primary effect is analgesic (caffeine, calcium channel blockers, clonidine, ergotamine, methysergide, opioids, salicylates) present, as a paradoxical reaction, evident hyperalgesia. Diuretics (furosemide, torasemide, triamterene) utilised enantiopathically to decrease blood volume (swelling, arterial hypertension, cardiac insufficiency, etc.), cause a rebound increase in the retention of sodium and potassium, increasing blood volume. Medicines utilised primarily as anti-dyspeptics (antacids, H_2 receptor antagonists, misoprostol, sucralfate) for the treatment of gastritis and gastroduodenal ulcers, cause, after an initial decline in acidity, a rebound increase in acidity potentially causing perforations of chronic gastroduodenal ulcers; etc. [2-4]

According to the pharmacological concepts, the paradoxical or rebound symptom presents intensity sometimes superior to the primarily suppressed symptom, expressing itself in variable period (hours to weeks) after the interruption or discontinuation of the medicine and also with a variable duration (hours to weeks), according to the individual susceptibility (idiosyncrasy).

Accepted as a natural phenomenon expressed to the attentive observers, the principle of cure through similitude starts to awake interest in non-homeopathic researchers, who apply

distinct denominations to the same system described by the homeopathy for more than two centuries, plagiarizing the homeopathic model and arrogating to the right of exclusivity on a phenomenon described since the prehistory of Medicine. [5]

Material and Methods

After studying the rebound or paradoxical effect of the organism before the modern pharmacology [2-4], we have come following, in the last years, the progression of these studies through the periodical set-ups in the *Medline* (with the key words: rebound effect and paradoxical reaction) and in the search systems of the internet (with the key words: fatal or serious adverse drug reaction, rebound effect and paradoxical reaction), prioritising the sites of universities and governmental health agencies, selecting the best evidences that indicated to the serious or fatal iatrogenic events caused by the rebound effect of drugs of impact in the worldwide public health.

Similitude and aspirin

The acetylsalicylic acid (ASA) belongs to the non-steroidal anti-inflammatory drugs (NSAID) classes non-selective of the cycloxigenase enzyme (COX), which catalyse the conversion of the arachidonic acid into prostaglandins (COX-2) and thromboxane (COX-1). Largely utilised to prevent thromboembolic events, when applied according to the principle of the contraries, ASA presents as *primary action* or *enantiopathic* therapeutic effect the peculiarity of avoiding the development of thrombus, inhibiting the cycloxigenase 1 (mediator of the blood platelet activity stimulating the TXA_2 synthesis) and the blood platelet aggregation.

Experimental studies, *in vitro* and *in vivo,* have been evidenced that after the interruption or discontinuation of ASA or others drugs for thromboembolism prophylaxis, the organism can react (mobilised by the automatic instinct of conservation and maintenance of the internal homeostasis, modified by the primary action of the drug), producing a secondary action or vital reaction that stimulates the COX-1 production and the blood platelet activity (TXA_2) to values much higher than the basal ones, increasing the development of thrombus and the probability of stroke event [instable angina (IA), acute myocardial infarction (AMI), cerebral vascular accident (CVA), etc.] in susceptible individuals, as much in the use of ponderal doses [6-15], as in the use of infinitesimal doses [16,17]. Other experiments showed the effect of ponderal [18] or ultra low [19-23] doses of aspirin in prophylaxis or reduction of hemorrhagic risks (reducing the bleeding time or the anti-thrombotic effect), neutralising the side effect of previous aspirin high doses (identity principle).

In a retrospective study, a total of 1.236 patients hospitalised for acute coronary syndrome (ACS) were questioned in order to determine whether prophylactic aspirin intake had been interrupted, finding that fifty-one of these ACSs occurred within 1 month after aspirin withdrawal. This represents 4.1% of all coronary events but 13.3% of recurrences. Among

those patients who relapsed, the incidence of ST-segment elevation ACS was higher in those who stopped aspirin when compared to the 332 patients who did not stop aspirin (39% vs. 18%; P = 0.001). Mean delay between aspirin withdrawal and the acute coronary event was 10 ± 1.9 days. The results support the hypothesis that aspirin withdrawal in coronary patients may represent a real risk for the occurrence of a new coronary event. [24,25]

Emile Ferrari, co-author of the study and Professor of Cardiology of the University Hospital Pasteur, in an interview for Aetna InteliHealth (Harvard Medical School) [26], said that in spite of the "benefits of aspirin therapy in coronary patients are well known, the effects that aspirin withdrawal has on this group of patients are just now being studied". As this study showed that "aspirin therapy can not be safely stopped in any case, but especially in patients with a history of coronary disease", Ferrari emphasises that it "serves as a reminder for all medical professionals who treat coronary patients that aspirin withdrawal should not be advised, and that alternative recommendations should be considered".

In the same interview, Richard S. Irwin, President of The American College of Chest Physicians, concludes that "this study not only reinforces the importance of compliance with aspirin therapy in coronary patients, but it sends a message to all medical professionals that the decision to discontinue aspirin therapy should not be taken lightly".

Seeking for relating the discontinuation of aspirin therapy as a risk factor for ischemic stroke (IS), Maulaz et al realised a case-control study with 309 patients with IS or transient ischemic attack (TIA) undergoing long-term aspirin treatment before their index event and 309 controls who had not had an IS in the previous 6 months, comparing the frequency of aspirin therapy discontinuation during 4 weeks before an ischemic cerebral event in patients and the 4 weeks before interview in controls. Stopping aspirin therapy was associated with an odd ratio of 3.4 for IS or transient ischemic attack (95% CI, 1.08-10.63; P < 0.005), in other words, a risk 3.4 times larger of developing ischemic accidents in patients that interrupted the treatment. These results highlight the importance of aspirin therapy compliance and give an estimate of the risk associated with the discontinuation of aspirin therapy in patients at risk for IS, particularly those with coronary heart disease. [27]

Similarly, other classes of non-steroidal anti-inflammatory drugs (NSAID) non-selective of the cycloxigenase enzyme (COX) increase the risk of AMI after the interruption of the treatment. Confirming the results of experimental studies, in which NSAIDs stimulated the platelet adhesion and the thrombin activity [28,29], a large case-control analysis on the British General Practice Research Database, with 8.688 cases and 33.923 controls, studied the risk of AMI during NSAID exposure and after the cessation of NSAID therapy, finding that the risk of AMI was 1.52 (95% CI, 1.33-1.74) for subjects who stopped taking NSAIDs 1 to 29 days prior to the index date, compared with non-users. These results suggest that the risk of AMI is increased during several weeks after the cessation of NSAID therapy [30].

Studying the frequency of stroke occurring after anti-platelet drugs (APD) discontinuation, Sibon et al found that only 4.49% of strokes were related to a recent APD discontinuation, but all cases occurred between 6 and 10 days after drug discontinuation ($P < 0.0001$). [31]

In view of the known importance of the use of aspirin to prevent thromboembolic accidents, whose benefits surpass the risks [32], physicians and patients should be alerted to the danger of the abrupt suspension of the medication, in order to minimise serious iatrogenic thromboembolic accidents. [33]

Similitude and COX-2 inhibitors

In September, 2004, we were surprised by the news that the anti-inflammatory Vioxx (rofecoxib, Laboratory Merck Sharp & Dohme), from the selective inhibitors group of the cycloxigenase 2 (COX-2), which reduce the inflammation without affecting the cycloxigenase 1 (COX-1, stomach and kidneys protector), was being immediately withdrawn from the market due to an investigative study that showed the increasing of the risk of heart attacks in patients who used the medicine in high dosages and for a long-term period. The following month (October/2004), the Laboratory Pfizer warned that the anti-inflammatory Bextra (COX-2 inhibitor) could cause the same risks.

This retrospective incision study (cohort) [34], sponsored by Food and Drug Administration (FDA), was presented by epidemiologists during a conference in Bordeaux (France), in which the researchers analysed the medical history of 1.4 million of patients drug users (1999-2001). From this total, 8.199 patients (0.58%) suffered a heart attack during the use of rofecoxib. According to David Graham, coordinator of the study, FDA would have to decide if the increasing risk of a heart attack, up to three times, would compensate the use of the medicine.

Before this result, other researches demonstrated that the chronic consumption of rofecoxib in high doses (> 50 mg/day) could elevate the risk of serious cardiovascular problems, confirmed by present studies. [35-37]

As scientific explanation to the serious adverse event observed, two mechanisms were proposed: firstly, non-selective NSAIDs, COX-1 and COX-2 inhibitors (aspirin, ibuprofen, indometacin, nitrofenac, etc.) would be cardio-protectors, due to the inhibitory effect on the thromboxane A2 (TXA_2) mediated by the COX-1, which causes the blood platelet aggregation; second, selective COX-2 inhibitors (rofecoxib), would have deleterious cardiovascular effects because they don't block the TXA_2, but selectively block the salutary vascular effect and protector of the prostacyclin (PGI_2) mediated by COX-2.

According to John Vane [38], researcher of the Willian Harvey Research Institute (St. Bartholomew's Hospital Medical College, London, UK), "these results provide strong evidences that the PGI_2 modulates the cardiovascular action of the TXA_2 in vivo", concluding that the "maintenance of cardiovascular homeostasis" would be explained by

the balance between these two eicosanoids (TXA_2 vs. PGI_2). However, the balance of the cardiovascular homeostasis comprehend more complex and subtle procedures, mentioned and used by the homeopathy for more than two hundred years, but disregarded by the modern scientific rationality.

Despite the majority of research with rofecoxib does not evidence the inhibition of the blood platelet aggregation as primary action of the medicine (normal to the non-selective NSAIDs previously mentioned), experiments *in vitro* demonstrated reduction of the blood platelet aggregation induced by different agonists and inhibition of the thrombogenesis mediated by blood platelets, in larger intensity than the ASA, suggesting that the thrombogenic mechanism previously mentioned for the aspirin can also occur with rofecoxib. [39]

Confirming this hypothesis, previous observational studies observed a particularly high risk of AMI for new users of rofecoxib [40,41], with events occurring in short time after the suspension of low doses of the therapy, likely to the dynamic of the rebound effect. Using data collected in a previous population-based cohort study [42], a recent case-control study evaluated the temporal nature of the risk of a first AMI associated with the use of rofecoxib and celecoxib, observing that the risk of AMI was higher following first-time use of rofecoxib (RR 1.67, 95% CI 1.21-2.30), with events occurring within a median of 9 (6-13) days after therapy has started. Treatment duration was not associated with increasing risk, and the risk remained elevated for the first 7 days after rofecoxib was discontinued (RR 1.23, 95% CI 1.05-1.44) but appeared to return to baseline between day 8 and 30 (RR 0.82, 95% CI 0.61-1.09), characterising the rebound phenomenon [43].

Similitude and antidepressants

With the antidepressants, it's occurring the same "rebound phenomenon": studies have been demonstrating an increase of 100% in the incidence rate of suicidal thoughts and behaviours among young patients with depression, in use of "selective serotonin reuptake inhibitors" or SSRIs (Seroxat, Paxil, Zoloft, Efexor, etc.), when compared to patients treated with placebo. [44-50]

In conformity with previous recommendations of the Psychopharmacologic Drugs Advisory Committee and the Paediatric Drugs Advisory Committee, the FDA Public Health Advisory published in October/2004 an alert on "Suicidality in children and adolescents being treated with antidepressant medications" [51], explaining the society on this serious iatrogeny: "The risk of suicidality for these drugs was identified in a combined analysis of short-term (up to 4 months) placebo-controlled trials of nine antidepressant drugs, including the selective serotonin reuptake inhibitors (SSRIs) and others, in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders. A total of 24 trials involving over 4.400 patients were included. The analysis showed a greater risk of suicidality during the first few months

of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%".

Although the psychiatrists justify the suicidal attitudes mentioned to the "syndrome of activation", where the initial effect of the antidepressant (psychomotricity improvement prior to the mood improvement), would allow that the patient left from the state of inactivity and lethargy, getting strength to achieve the wish of taking his/her own life out, this hypothesis doesn't apply to the former studies, because the suicidal tendency was observed during all treatment and not only in its beginning, principally when the dose is changed.

Relating the appearing of paradoxical symptoms to the alteration of the applied dose, indispensable factor to awake the vital or homeostatic reaction, FDA reinforces the hypothesis of aggravation of the disease as a result of the rebound phenomenon of the enanthiopathic drugs: "Paediatric patients being treated with antidepressants for any indication should be closely observed for clinical worsening, as well as agitation, irritability, suicidality, and unusual changes in behaviour, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. This monitoring should include daily observation by families and caregivers and frequent contact with the physician. It is also recommended that prescriptions for antidepressants be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose". [51]

On July 1st, 2005, the FDA advised: "Several recent scientific publications suggest the possibility of an increased risk for suicidal behaviour in adults who are being treated with antidepressant medications. Even before these reports became available, the FDA began a complete review of all available data to determine whether there is an increased risk of suicidality (suicidal thinking or behaviour) in adults being treated with antidepressant medications. It is expected that this review will take a year or longer to complete. In the meantime, FDA is highlighting that adults being treated with antidepressant medications, particularly those being treated for depression, should be watched closely for worsening of depression and for increased suicidal thinking or behaviour. Close watching may be especially important early in treatment, or when the dose is changed, either increased or decreased". [52]

On May 12, 2006, GlaxoSmithKline (the maker of Paxil) and the FDA warning that its own re-analysis of clinical trials involving nearly 15.000 adults (8.958 in group Paxil vs. 5.953 in group Placebo) did indeed turn up evidence that patients, ages 18 to 64, who were given Paxil had six time more the incidence of suicidal behaviour as patients who received dummy pills (11/3455 or 0.3% in group Paxil vs. 1/1978 or 0.05 in group Placebo), with high incidence between young adults (ages 18 to 30): "The FDA stressed that all patients, especially young adults and those who are improving, should be carefully monitored when treated with Paxil". [53]

Following the thought of the principle of similitude to try to explain these facts, in its *primary action* or *enantiopathic therapeutic effect*, the SSRIs antidepressants would keep

the concentration of the serotonin neurotransmitter in the synapses for more time, promoting an improvement of the symptoms of depression, and are also being used for the anxiety, bipolar perturbation and anorexia treatments through its active principles (fluoxetin, paroxetin, sertralin, etc.). As well as other ansiolitics-sedatives [54-56] and antidepressants [57-64], the SSRIs [65-69] also would awake, after their interruption or discontinuation ("when the dose is changed"), as *secondary action* or *vital reaction*, an exacerbation of the suppressed symptoms by the primary action of the drug (depression, anxiety, mania, panic, somnolence, etc.).

Similitude and bronchodilators

Along of the last decades, several works have been realised to confirm the clinical and experimental observation that a "rebound bronchoconstriction" occurs after the partial interruption and discontinuation of the bronchodilators, with an asthma aggravation and increasing of the bronchial reatictivity. [70-86]

In November/2005, the FDA Public Health Advisory informed about the danger of the long-acting beta-2 agonists (salmeterol: Serevent; formoterol: Foradil, Oxeze), inclusively when combined with the steroid fluticasone (Advair, Symbicort), "may increase the chance of severe asthma episodes, and death when those episodes occur" [87], ordered the Laboratory GlaxoSmithKline to put a "black box" warning on the treatment's packaging, alerting doctors to the fact that the medicine could have potentially fatal side-effects.

At the request of the FDA, due to reports of serious paradoxical bronchospasm associated with the use of salmeterol and the previous epidemics of asthma-related deaths in patients taking other long-acting beta agonists, the Laboratory GlaxoSmithKline initiated in 1996 a randomised trial compared salmeterol to placebo (Salmeterol Multicenter Asthma Research Trial - SMART), that was prematurely halted in September/2002 after an interim analysis suggested an increased risk of asthma-related death in patients who use the drug as compared to a placebo.

The data on the 26.353 patients were presented at 69th Annual International Scientific Assembly of The American College of Chest Physicians (CHEST 2003, Orlando, EUA) [88], concluding that "the interim analysis was inconclusive". Although not conclusive, the SMART study suggests that risks may be higher in African-American patients and in those patients who were not being treated with inhaled corticosteroids at the start of the study.

Relating the rebound effect (secondary action) of the organism to the bronchodilator therapeutics, after the interruption or discontinuation of the doses, as probable hypothesis to the paradoxical bronchoconstriction mentioned followed by death, FDA and The Health Canada recommend: "Patients who are currently taking Serevent should not discontinue their treatment without first consulting a physician. Abruptly stopping medications may result in acutely deteriorating asthma control, which may be life-threatening". [89,90]

Evidencing the conflicts of interest that cover fatal iatrogenic events as those previously described, which demonstrate the validity of the principle of the similitude, Wolfe and Lurie, in their critical analyses of the facts to the The Lancet, conclude [91]: "It is now approaching 3 years since the SMART study was terminated. The results have still not found their way into print and the drugs' labels have still not been finalised. Instead, the company, seemingly under little pressure from the FDA, has succeeded in drawing out the process and initially misleading the agency, physicians, and patients with not-per-protocol analyses that diminished the drug's apparent risks. In the absence of the transparency associated with Advisory Committee meetings, these deceptions would never have come to public attention. In 2001, however, only 21% of new drug approvals were preceded by Advisory Committee meetings, allowing most drugs to avoid similar public scrutiny".

Discussion

Investigated by the integrative physiology through the complex system psicho-neuro-immuno-endocrine-metabolic, the homeostasis ("life-preserving power") promotes organic reactions in a sense of rescuing the balance of the internal environment altered by medicines, external stimulus and emotional factors.

The secondary action or vital reaction of the homeopathic model is based on studies about the rebound effect or paradoxical reaction of hundreds of modern medicines, utilised according to the contrary principle. The development of tolerance to a repeatedly administered drug to be the result of a same regulated adaptive process.

The intensity and the seriousness of the paradoxical reactions mentioned, awakening serious or fatal iatrogenic events, are in conformity with the pharmacological conceptualisation of rebound effect, in which the rebound phenomenon sometimes presents intensity superior to the similar phenomenon firstly suppressed.

In spite of the rebound effect manifest in a small proportion of the individuals, in view of their idiosyncratic nature, these serious or fatal paradoxical events assume epidemiological importance when we consider the enormous current consumption of the enanthiopathic drugs. In the controlled studies, in relation to the placebo, a risk of ischemic accidents 3.4 times larger after aspirin withdrawal, 1.52 times larger after NSAIDs withdrawal and 1.67 times larger after rofecoxib withdrawal; a risk of suicidal behaviours 6 times larger after SSRI antidepressants withdrawal; and a "inconclusive" but important risk of fatal paradoxical bronchospasm after long-acting beta agonists withdrawal, were found.

After the suspension of the therapy, the time of appearing of the serious paradoxical reaction didn't present great variations among the drugs: average of ten days for aspirin, two weeks for the NSAIDs and nine days for the rofecoxib. The duration of the rebound effect was mentioned only in the study with the rofecoxib, remaining for a period of 30 days in the maximum. In this same study, the duration of the treatment, before the

interruption of the drug, did not show association with the risk of awakening the serious paradoxical event.

The empiric observation that an association between the dose of the substance and the paradoxical reaction would not exist, expressed by Hahnemann in paragraph 121 of the *Organon*, was confirmed in two lines of research that investigated the effect of the antithrombotic drugs in the thromboembolism and in the haemorrhage induced by aspirin. The first experimental model evidenced the paradoxical or secondary thromboembolism to a primary decrease in the blood platelet aggregation, after the administration of ponderal [6-15] or ultra low [16,17] doses of antithrombotic agents (rebound effect). The second model showed the effect of ponderal [18] or ultra low [19-23] aspirin doses in prophylaxis or reduction of hemorrhagic risks (reducing the bleeding time or the antithrombotic effect), neutralising the side effect of previous aspirin high doses administered (identity principle or curative rebound effect).

In view of the difficulty of the classic models of homeostasis in describing tolerance development to repeated drug administrations, a Mathematical model is being proposed to study the rebound effect and the tolerance of the organism to the several classes of drugs, in which the oral detection and analysis of exogenous substances are proposed to be the primary stimulus for these mechanisms: reproducing the gradual decrease in drug effect when tolerance develops, the high sensitivity to small changes in drug dose, the rebound phenomenon and the large reactions following withdrawal in dependence. The mathematical model verifies the proposed theory and provides a basis for the implementation of mathematical models of specific physiological processes. In addition, it establishes a relation between the drug dose at any moment, and the resulting drug effect and relates the magnitude of the reactions following withdrawal to the rate of tolerance and rebound effect. [92,93]

A great number of iatrogenic diseases could be avoided if the medical class was elucidated about the "homeostatic maintenance controlled through the rebound effect or vital reaction", preventing the paradoxical aggravation of the clinical state with the slow and gradual discontinuation of the drugs used according to the principle of the contraries.
Using the inductive thought and the pure observation, Hahnemann overran to the scientific thought of his time, tracing guidelines to the treatment of the diseases that remain effective in the present, though they are disrespected by the contemporary science.

> "These incontrovertible truths, which spontaneously offer themselves to our notice in nature and experience, explain to us the beneficial action that takes place under homoeopathic treatment; whilst, on the other hand, they demonstrate the perversity of the antipathetic and palliative treatment of diseases with antagonistically acting medicines". (*Organon*, paragraph 67)

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Anti-inflammatory, myocardial infarction, rebound effect and similitude[4]

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Abstract

In this article were cited new evidences of the rebound effect of anti-inflammatory as causing myocardial infarction and stroke, described in recent meta-analysis.

Results

In the last issue of *Homeopathy*, I published a paper in which the evidence of the similitude principle in the light of fatal iatrogenic events of modern medicines was discussed in relation to the rebound effect or paradoxical reaction of the organism (secondary action or vital reaction of the homeopathic model) [1]. I mentioned some work on nonsteroidal anti-inflammatory drugs (NSAIDs) and increased the risk of acute myocardial infarction (AMI) after interruption of treatment [2,3]. These reflect the results of experimental studies in which NSAIDs stimulate rebound platelet adhesion and thrombin activity [4,5]

Very recently, McGettigan and Henry have published a systematic review of 23 observational studies (17 case-control and 6 cohort studies) of the effects NSAIDS: both selective and nonselective inhibitors of cyclooxygenase 2, on cardiovascular events in a population of 1.6 million of patients [6]. A dose-related risk was evident with rofecoxib, relative risk (RR) with 25 mg/day or less, 1.33 (95% confidence interval [CI], 1.00-1.79; 6 studies) and 2.19 (95% CI, 1.64-2.91; 7 studies) with more than 25 mg/day. Among the older, nonselective drugs, diclofenac had the highest risk with an RR of 1.40 (95% CI, 1.16-1.70; 9 studies), meloxicam RR 1.25 (95% CI, 1.00-1.55; 3 studies) and indometacin RR 1.30 (95% CI, 1.07-1.60; 6 studies). The data indicate that the risk increases early in treatment (first 30 days) and on first cardiovascular events.

In recent case-control study (33309 cases; 138949 controls) of the risks of hospitalisation with myocardial infarction and use of NSAIDs [7], the RR estimates are: rofecoxib, 1.36 (95% CI, 1.18-1.58; 12 studies); diclofenac, 1.40 (95% CI, 1.19-1.65; 10 studies); meloxicam, 1.24 (95% CI, 1.06-1.45; 4 studies); indometacin, 1.36 (95% CI, 1.15-1.61; 7 studies). In another meta-analysis, Kearney et al studied the effects of selective and nonselective NSAIDs on the risk of serious vascular events for a period of at least 4 weeks duration (145373 participants), reviewing data from 138 randomised trials and estimated a

[4] Teixeira MZ. NSAIDs, Myocardial infarction, rebound effect and similitude. *Homeopathy*. 2007; 96(1): 67-68. Available at: https://doi.org/10.1016/j.homp.2006.11.009

RR for rofecoxib of 1.42 (95% CI, 1.13-1.78) and for diclofenac of 1.63 (95% CI, 1.12-2.37) [5].

In elaborating a pathophysiological hypothesis for these cardiovascular events, I highlighted certain points: the events tend to occur after a short period of treatment (<30 days); are dose-dependent and often serious; they do not depend on a previous cardiovascular disease (first cardiovascular events). Studies of rebound effects or paradoxical reaction of the organism have found similar characteristics [8-11]: the symptoms are of larger intensity than those initially suppressed; the reaction is fast, within 30 days after the suspension of the medicine (related to the half-life of the drug); the effect is proportional to the intensity of the initial contrary action (dose-dependent); the rebound effect is idiosyncratic, unrelated to previous disease or risk factors.

The precise mechanisms by which NSAIDs including COX-2 inhibitors increase cardiovascular risk are not clear: reduced prostacyclin production in the vascular endothelium, suppression of nitric oxide synthesis, diminished neovascularization, abolition of adrenomedullin activity, and increased free-radical production have all been implicated. Platelets play a pivotal role in the development of these cardiovascular events, and all these mechanisms also affect platelet activity.

Linking the rebound effect and platelet activity and considering that antiplatelet therapy with aspirin is associated with reduced vascular mortality, Serebruany et al. [12] sought to determine the effect of use and withdrawal of NSAIDs on platelet activity. Platelet characteristics from 34 aspirin-naive volunteers who were receiving unselective NSAIDs or selective COX-2 inhibitors were compared with 138 drug-free controls. Platelets were assessed twice at baseline (at least 1 month of treatment) and after a 14-day washout. Platelet activity during treatment was similar and unremarkable between groups. However, there was a highly significant increase of platelet activity after withdrawal of non selective NSAIDs and selective COX-2 inhibitors. The authors concluded that drug cessation, rather than continuous therapy with these drugs, may be associated with rebound platelet activation, which may predispose to a higher risk of vascular events. Suspension of Ibuprofen and other antiplatelet agents can also provoke rebound increase of platelet aggregation, with increased thrombus formation and cardiovascular events (AMI) [13, 14].

If the similitude principle is a “natural law”, whose expression is modulated by individual idiosyncrasy (individualisation), the occurrence of serious iatrogenic events after withdrawal of enantiopathic drugs demonstrates the importance of the rebound effect (paradoxical reaction or homeopathic vital reaction) in promoting deep alterations in the organic balance. Homeopathy turns this effect on its head, using it to therapeutic advantage.

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Bronchodilators, fatal asthma, rebound effect and similitude[5]

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Abstract

In this article were cited new evidences of the rebound effect of bronchodilators as causing fatal bronchoconstriction, described in recent meta-analysis.

Results

After the publication of the article "Evidence of the principle of similitude in modern fatal iatrogenic events" [1], in similar way to the non-steroidal anti-inflammatory drugs (NSAIDs) [2], new important studies were published reinforcing the hypothesis that the long-acting bronchodilators (beta-agonists) may increased the risk for severe or fatal asthma exacerbations, as a consequence of the irreversible paradoxical bronchospasms (rebound effect of modern pharmacology or vital reaction of the homeopathic model).

After countless protests of the scientific class, since the *GlaxoSmithKline* presented the partial data of the "Salmeterol Multicenter Asthma Research Trial (SMART)" at the 69ª Annual International Scientific Assembly of The American College of Chest Physicians (CHEST 2003), claiming that "the interim analysis was inconclusive", the results of the general analysis of 26,355 randomized subjects were published in 2006. Following the review of the "interim analysis", exploratory analyses of each outcome event within subpopulations were conducted, finding that there was a significant increase in respiratory-related deaths (RR 2.16, 95% CI 1.06-4.41) and asthma-related deaths (RR 4.37, 95% CI 1.25-15.34), and in combined asthma-related deaths or life-threatening experiences (RR 1.71, 95% CI 1.01-2.89) in subjects receiving salmeterol vs.placebo. The imbalance occurred largely in the African-American subpopulation (compared with Caucasian subjects): respiratory-related deaths or life-threatening experiences (RR 4.10, 95% CI 1.54-10.90) and combined asthma-related deaths or life-threatening experiences (RR 4.92, 95% CI 1.68-14.45) in subjects receiving salmeterol vs. placebo. [3]

In 2006, Salpeter et al published a meta-analysis of 19 randomized, placebo-controlled trials involving 33,826 participants with asthma followed for 16,848 patient-year (mean trial duration was 6.0 months). Approximately 15% of the participants were African-American. The long-acting beta-agonists used in the studies were salmeterol, formoterol, and eformoterol. During the trials, concomitant inhaled corticosteroids were used in approximately 53% of participants in both groups. The objective of the study was to assess

[5] Teixeira MZ. Bronchodilators, fatal asthma, rebound effect and similitude. *Homeopathy*. 2007; 96(2):135-7. Available at: https://doi.org/10.1016/j.homp.2007.02.001

the effects of long-acting beta-agonists on severe asthma exacerbations requiring hospitalization, life-threatening asthma attacks, and asthma-related deaths. Were used subgroup analyses to compare results for salmeterol and formoterol and for children and adults. [4]

The OR for hospitalization was 2.6 (95% CI 1.6-4.3) for long-acting beta-agonists compared with placebo. The authors not include SMART in this analysis because the investigators did not provide information on hospitalization due to asthma, just life-threatening exacerbations. When they include the SMART data on life-threatening exacerbations, the OR was 2.1 (95% CI 1.5-3.0). The risk for hospitalization was increased with salmeterol (OR 1.7, 95% CI 1.1-2.7), formoterol (OR 3.2, 95% CI 1.7-6.0), children (OR 3.9, 95% CI 1.7-8.8) and adults (OR 2.0, 95% CI 1.0-3.9).

The OR for life-threatening asthma attacks attributed to long-acting beta-agonists was 1.8 (95% CI 1.1-2.9), with did not significantly differ between trials of salmeterol and formoterol or between children and adults. The OR for asthma-related deaths was obtained from the SMART (OR 3.5, 95% CI 1.3-9.3, P = 0.013). In general, the risks for severe exacerbations and asthma-related deaths were increased by 2- to 4-fold.

In the physiologic explanation of the phenomenon, the authors associate the regular beta-agonist use (associate or not with inhaled corticosteroids) with tolerance to the drug's effects and a worsening of disease control [5-10]. This effect results from a negative feedback mechanism of the □-adrenergic system that is an adaptive response to stimulation of receptors. Stimulating results in uncoupling and internalization of receptors, which is know as "desensitization", followed by a decrease in receptor density and receptor gene expression, which is know as "downregulation" [11]. Regular use of beta-agonists has been shown to increase bronchial hyperreactivity despite maintenance of some degree of bronchodilation. These effects, along with a reduction in response to subsequent rescue beta-agonists use, may worsen asthma control without giving any warning of increased symptoms. [10,12]

Although the term "rebound effect" it was not used in the meta-analysis (besides in the "search terms" of Methods), several studies have confirmed that "rebound hyperreactivity" occurs after interruption of bronchodilation (primary action; enantiopathic or antipathetic effect), with "rebound bronchoconstriction" (secondary action, vital or homeostatic reaction) and a worsening of asthma. [13-16]

Despite the acquaintance protecting effect of inhaled corticosteroids, the authors separately evaluated trials in which more than 75% of participants were receiving concomitant inhaled corticosteroids and found that the risk for hospitalizations was still increased 2-fold (OR 2.1, 95% CI 1.3-3.4), evidencing the importance of the rebound effect in the organic physiology.

Asthma mortality rates increased worldwide in the 1960s, when inhaled beta-agonists were introduced on the market [17-20], with an increment in the last decade since long-acting beta-agonists were introduced [21-23].

In this meta-analysis, the absolute increase in asthma-related deaths was estimated to be 0.06% to 0.07% over 6 months, indicating that long-acting beta-agonists cause as excess of approximately 1 death per 1000 patient-years of use. Being known that the salmeterol is one of the most widely prescribed medications on the world, with an estimated 3.5 million adults treated in the United States in 2004 [24,25], this indicates that the salmeterol may be responsible for approximately 4,000 to 5,000 asthma-related deaths that occur in the United States each year (3.5 million adults represent, approximately, 20% of the total of asthmatic of the United States). [26]

In view of the asthma to be underdiagnosed and undertreated or inappropriately treated, approximately 350 million people worldwide currently have the disease [27]. If we suppose the use of long-acting beta-agonists in 10% of this population, according to the modern treatment guidelines [28], we will have the number of 40,000 to 50,000 asthma-related deaths a year in world.

Describing the sad results that the enanthiopathic or antipathic method of treatment can cause in the individuals, through pathological addressing of the rebound effect or paradoxical reaction of the organism, Samuel Hahnemann emphasizes the importance of using the homoeopathic method in the treatment of the chronic diseases, being used of the Aristotelian deductive logic of the "couple-denial" or "modus tollens":

> "Had physicians been capable of reflecting on the sad results of the antagonistic employment of medicines, they had long since discovered the grand truth, *that the true radical healing art must be found in the exact opposite of such an antipathic treatment of the symptoms of disease*; they would have become convinced, that as a medicinal action antagonistic to the symptoms of the disease (an antipathically employed medicine) is followed by only transient relief, and after that is passed, by invariable aggravation, the converse of that procedure, the homoeopathic employment of medicines according to similarity of symptoms, must effect a permanent and perfect cure […]." (*Organon*, paragraph 61) [29]

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Antidepressants, suicidality and rebound effect[6]

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Abstract

Samuel Hahnemann, following the steps of Hippocrates in the meticulous observation of the human nature, noticed that application of the palliative treatment**s** (antipathic, enantiopathic, contrary or "allopathic") to the symptoms of chronic diseases, after an initial improvement, provoked symptoms similar to, and stronger than the initially suppressed symptoms. This was regarded as a consequence of the vital reaction of the organism, understood as an automatic and instinctive capacity of the sensations and functions (homeostasis) to return to the initial health condition, altered by the enantiopathic medicines. Using this homeostatic reaction of the organism as **a** treatment method, Hahnemann proposed the therapy by similarity, administering to the patients medicines capable of waking up, in healthy individuals, similar symptoms to the natural disease. Based on empiric and experimental observations, he stipulated the universal mechanism of action of any medicine on the human health (primary action of the drug, followed by the secondary and opposite action of the organism), inaugurating the homeopathic pharmacology, and alerting others about the harmful consequences that the palliative medicines could cause in susceptible individuals, with risk**s** of death, incurability and chronicity of the diseases. These iatrogenic events can be observed at the present time, after the withdrawal (discontinuation or dosage alteration) of modern enantiopathic medicines, according to the study of the rebound effect or paradoxical reaction of the organism, the evidences of which that I have been studying during the last decade. Considering the studies of the anti-inflammatory and bronchodilator drugs published recently, I will talk in this work about the recent studies that describe the emergence of suicidality (suicidal ideation, suicidal attempts or suicidal behavior) after the suspension or discontinuation of antidepressants of the second generation, according to the hypothesis of the rebound effect or paradoxical reaction of the organism (homeopathic secondary action or vital reaction).

Introduction

Similitude law and scientific rationality

During the development of the homeopathic doctrine, Samuel Hahnemann maintained a scientific and experimental stance, recording the phenomena caused by medicinal substances in the human health, and correlating his observations with evidences from medical literature. In the "Introduction" of the first edition of the *Organon* (*Organon of the*

[6] Teixeira MZ. Antidepressants, suicidality and rebound effect: evidence of similitude? *Homeopathy*. 2009; 98(2): 114-121. Available at: https://doi.org/10.1016/j.homp.2009.02.004

Rational Art of Healing, 1810), he talks about hundreds of "examples of accidental homeopathic cure", with dozens of medicinal substances, described by hundreds of doctors of all historical periods, basing his homeopathic cure principle on 247 bibliographical references of several authors.

As well as in all their studies, he uses the premises of modern scientific thought *(Aristotelian logic)* to elaborate the work that inaugurates the Homeopathy *(Essay on a new principle for ascertaining the curative power of drugs)* [1], using the methods of the "analogy" and of "enumeration" of hundreds of evidences found in medical literature, and adding others observed by himself, enunciating that through "strong arguments" he could infer a "truth or universal law": *a substance is capable of curing symptoms in a sick person, if it wakes up similar symptoms in healthy people.*

He sketches a physiological explanation for this "natural law of cure", separating the phenomena, observed in the human experimentation of several medicinal substances, in two different classes, *"primary action of the medicines"* and *"secondary action or vital reaction of the organism"* (*Organon of medicine,* paragraphs 63-65) [2], systematizing a mechanism of "universal action for the medicines", observed in the several sensations and organic functions:

> "Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed *primary action.* […] To its action our vital force endeavours to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of *secondary action* or *counter-action".* (*Organon,* paragraph 63)

Following these premises and using the *inductive Aristotelian logic,* Hahnemann enunciates the principle of the healing similarity: *every substance capable to cause certain symptoms in healthy people (direct or primary action of the drug), can be used to cure similar symptoms in a sick person, according to the similitude principle (indirect or secondary action of the organism).*

Hahnemann also uses the *deductive Aristotelian logic "modus tollens"* (latin for "mode that affirms by denying", is the formal name for "indirect proof" or "proof by contrapositive") to validate scientifically the hypothesis of the homeopathic treatment and of the "similitude natural law" [3], denying the effectiveness of the enantiopathic treatment in chronic diseases, based as it is in the principle of the contrary *(contraria contrariis curentur),* opposite to the principle of similitude *(similia similibus curentur): for the principle of similitude to be valid, its opposite (principle of the contrary) should not be capable of curing the symptoms of chronic diseases, causing instead their aggravation (modus tollens).*

Following this "indirect proof", he mentions countless examples of substances used according to the principle of the contrary, which caused aggravation of the symptoms of the disease, initially suppressed by the enantiopathic treatment (*Organon,* paragraph 59). Hahnemann also alerts for the serious damage that the antipathic treatment of the chronic

diseases can bring to the health condition, as "another, more serious disease or, frequently, incurability, even danger of life and death itself", without progresses in the healing process (*Organon*, paragraph 60).

Using this same *"modus tollens"* of the *deductive Aristotelian logic*, suitable for Hahnemann explicitly in the paragraph 61 of *Organon*, I have been describing, in the last years, the "sad results" of the use of modern enantiopathic medicines [4-10], in accordance with the current pharmacophysiological concepts of "rebound effect" or "paradoxical reaction" of the organism (secondary action or vital reaction of the pharmacophysiological homeopathic model):

> "Had physicians been capable of reflecting on the sad results of the antagonistic employment of medicines, they had long since discovered the grand truth, *that the true radical healing art must be found in the exact opposite of such an antipathetic treatment of the symptoms of disease;* they would have become convinced, that as a medicinal action antagonistic to the symptoms of the disease is followed by only transient relief, and after that is passed, by invariable aggravation, the converse of that procedure, *the homoeopathic employment of medicines* according to similarity of symptoms, must effect a permanent and perfect cure […]". (*Organon*, paragraph 61)

Vital reaction, secondary action, rebound effect or withdrawal symptom

In order to establish a relationship with the "rebound effect" or "paradoxical reaction" of the conventional pharmacophysiological model, it is important matters to emphasize fundamental aspects of the "secondary action" or "vital reaction" mentioned in the homeopathic pharmacophysiological model: 1) it appears only in susceptible individuals, in other words, in individuals that present in their constitution similar symptoms to the pathogenetic effects of the substance; 2) it does not depend on the substance, on the repetition of the doses or on the type of symptoms (disease); 3) it appears after the primary action of the substance, as an automatic manifestation of the organism; 4) it induces an organic state (symptoms) exactly opposite and superior in intensity and/or duration to the primary action of the substance; 5) its effect magnitude is proportional to the intensity of the primary action (dose) of the substance. (*Organon*, paragraphs 59, 64, 69)

In an initial literature review, Hodding et al. [11] described conceptual distinctions, evaluation criteria and scientific evidences of the "withdrawal syndrome" of some modern drugs (anticoagulants, anticonvulsivants and antipsychotic drugs, barbiturates, benzodiazepines, cimetidine, clonidine, costicosteroids, opiates, propranolol, tricyclic antidepressants, etc.). As in other recent revisions, the authors considered the terms "wythdrawal or discontinuation symptoms" as synonym of "rebound symptoms". They distinguished the rebound or withdrawal syndrome from the natural evolution of the disease: "Symptoms resulting from discontinuation of a medication may need to be distinguished from reappearance of disease symptoms or a 'catching up' of the basic disease state, may emerge in the absence of the pharmacological action of the drug". They mentioned three criteria to certify a withdrawal symptom: a trial of gradual versus abrupt drug termination; the appearance of symptoms more severe than the baseline symptoms; or the onset of symptoms in newborn infants whose mothers had been taking the drug. A

gradual tapering of the dose of these drugs is recommended when therapy must be discontinued.

Objectives

(i) To correlate the characteristics of the antidepressants rebound reaction with the homeopathic vital reaction.

(ii) To describe the scientific evidences that make it possible to relate the suicidality to the antidepressants rebound effect.

Material and Methods

With the intention of broadening the understanding of the similitude principle, according to modern pharmacology and scientific logic [4-10], a revision of the literature was accomplished, using the Medline database and the key words "antidepressant", "rebound", "withdrawal syndrome" and "suicidality", and then selecting the most consistent papers and discussing the scientific described evidences according to Hahnemann's teachings.

Results

Antidepressants and rebound effect

In the same way as other classes of enantiopathic medicines, the antidepressants present a rebound effect of the symptoms of the depression after the withdrawal of treatment (discontinuation or dose alteration, even in single missed doses with susceptible constitutions and/or short half-life drugs), with evident changes in the mediators involved in the process (receptor sensitization and neurotransmissor levels).

In a review about this subject, Wolfe [12] says that antidepressants can cause a variety of withdrawal reactions, *starting within a few days to a few weeks of ceasing to administer the drug and persisting for days to weeks.* Both tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) cause similar syndromes, most commonly characterized by gastrointestinal or somatic distress, sleep disturbances, mood fluctuations and movement disorders. Treatment involves restarting the antidepressant and tapering it more slowly. Some experimental studies confirm the rebound effect in several classes of antidepressants (Table 1).

Table 1. Examples of experimental studies that confirm the rebound effect of the antidepressants

Drug	Source Publication Type	Results or Conclusions

IMAO	Oniani et al.,[13] 1988. Research Support.	After the cessation of the action of the IMAO in cats (suppression of paradoxical sleep and significant decrease in wakefulness), a selective rebound of wakefulness is observed against the background of complete or partial absence of paradoxical sleep.
Clomipramine	Kupfer et al.,[14] 1994. Randomized Controlled Trial.	Significant drug effects were noted on several sleep parameters, demonstrating suppression of rapid eye movement (REM) sleep. In drug responders were found a significantly faster and more robust rebound in REM sleep than non-responder.
SSRIs	Smith et al,[15] 1995. Research Support	Animal model (rats) used for studying adaptive changes in the 5-HT(2A) receptor system (serotonergic system, related to SSRIs), showed that a single large dose of quipazine (serotonin receptor agonist) produced a rebound ketanserin-like effect (serotonin receptor antagonist) at 20 hours after administration.
Tricyclics	Wolfe,[12] 1997. Review	Most symptoms related to tricyclic antidepressant withdrawal are believed to be caused by rebound excess of cholinergic activity after prolonged anticholinergic effect on cholinergic receptors (analogous to the adrenergic rebound that occurs after beta-blocker withdrawal).
Fluoxetine	Borrelli et al.,[16] 1999. Randomized. Controlled Trial.	During the on-drug phase, placebo participants gained weight linearly, exceeding the fluoxetine groups. Unlike the placebo group, drug discontinuation produced dose-dependent weight rebound.
Fluvoxamine Paroxetine	Pace-Schott et al.,[17] 2001. Research Support.	Decrease in dream frequency during SSRIs treatment was observed in normal volunteers that may reflect serotonergic REM suppression, while the augmented report length and bizarreness during acute SSRIs discontinuation may reflect cholinergic rebound from serotonergic suppression.
Imipramine	D'Aquila et al.,[18] 2004. Research Support.	The results showed that animals treated with chronic imipramine, 40 days after treatment interruption, display a rebound depressive-like behavior (might depend upon parallel changes in the mesolimbic dopamine system sensitivity).
Bupropion	Lerman et al.,[19] 2004. Randomized Controlled Trial.	Patients who received bupropion are more likely to experience a decrease in depressive symptoms during active treatment but are also more likely to experience a rebound in depressive symptoms when the drug is discontinued.
Olanzapine	Huang et al.,[20] 2006. Research Support.	Examining regional changes in rat brain mRNA levels encoding 5-HT(2A) receptor following chronic olanzapine treatment showed immediate effect was a down-regulation of 5-HT(2A) receptor mRNA expression, predominantly in the hypothalamus, limbic system and striatum, while a rebound effect was observed 48 h later. Correlations between 5-HT(2A) receptor mRNA expression and total food intake, weight gain and energy efficiency were observed.

In a recent review, Lader [21] enhances the understanding of the antidepressant discontinuation syndrome (rebound phenomenon) with further data and studies: "The phenomenon has been postulated to be associated with rebound symptoms such as return of depression following abrupt discontinuation. Discontinuation symptoms are now known to be associated with most classes of antidepressants, if medication is stopped without appropriate down-tapering of dose and/or dose frequency. The phenomena associated with stopping almost all antidepressants including the SSRIs are believed to result not from true dependence but from a reduction in intra-synaptic serotonin (5-HT) levels following receptor down-regulation".

This syndrome is characterised by the "time-loched emergence of new", clearly defined and quantifiable signs and symptoms, which develop on cessation or reduction of an antidepressant that has been taken for more than a few weeks [22]. Typically, patients describe transient symptoms that begin and peak within 1 week of treatment interruption, are mild in severity and follow a finite time-course, usually lasting between 1 day and 3 weeks [23]. In spite of the data from the published literature showing that the incidence of these mild, self-limiting rebound symptoms is generally < 5% [23,24], recent data indicate that a severe and disabling withdrawal syndrome occurs in up to 5% of patients, requesting prompt modification of the management strategy in these idiosyncratic individuals [25]. The literature reveals that paroxetine is associated with a significantly greater proportion of withdrawal reactions (~ 5%) than the other SSRIs (fluoxetine, for example), with deterioration in various aspects of health and functioning [23,26-29]. The explanation for the difference most likely reflects the long half-life of the main metabolite of fluoxetine, thus acting as a natural taper [30].

Like in other classes of drugs [8-10], the rebound reactions are not specific to the particular condition (disease) in wich the drug is being used, and the antidepressant discontinuation syndrome are similar both in incidence, nature and extent throughout depressant, panic disorder, generalised anxiety disorder, social anxiety disorder, and obsessive-compulsive disorders. In a similar way, the duration of treatment does not influence withdrawal reactions. [31]

In accordance with these studies, the occurrence of the antidepressant rebound phenomenon follows premises similar to the previously mentioned for the secondary action or homeopathic vital reaction: 1) it appears in a small proportion of the people (susceptible or idiosyncratic constitutions) [23-29]; 2) it does not depend on the drug, on the duration of treatment, on the type of symptoms or on the acuteness of the disease [11,12,21,31]; 3) it appears after the primary effect of the drug, when there occurs discontinuance or an occasional alteration of the doses [12,21-23]; 4) it induces an organic state (symptoms) exactly opposite and superior in intensity and/or duration to the primary action of the drug [11,12,21]; 5) its magnitude is proportional to the intensity of the primary action of the substance, presenting the most evident reactions in the most effective drugs (dose) for suppressing the initial symptoms of the disease [26-30].

Neurobiological mechanisms of the antidepressant rebound effect

In a revision on the neurobiological mechanisms of the antidepressant withdrawal syndrome, Harvey et al. [32] proposing a preliminary molecular perspective and hypothesis on the neuronal implications of medication discontinuation, described the evidences that support an association between the antidepressant rebound effect and disturbances in brain glutamate activity, nitric oxide synthesis, and □-amino butyric acid:

> "Inappropriate discontinuation of drug treatment and noncompliance are a leading cause of long-term morbidity during treatment of depression. Increasing evidence supports an association between depressive illness and disturbances in brain glutamate activity, nitric oxide synthesis, and gamma-amino butyric acid. Animal models also confirm that suppression of glutamate N-methyl-D-aspartate (NMDA) receptor activity or inhibition of

> the nitric oxide-cyclic guanosine monophosphate pathway, as well as increasing brain levels of gamma-amino butyric acid, may be key elements in antidepressant action. Imaging studies demonstrate, for the most part, decreased hippocampal volume in patients with depression, which may worsen with recurrent depressive episodes. Preclinical models link this potentially neurodegenerative pathology to continued stress-evoked synaptic remodeling, driven primarily by the release of glucocorticoids, glutamate, and nitric oxide. These stress-induced structural changes can be reversed by antidepressant treatment. In patients with depression, antidepressant withdrawal after chronic administration is associated with a stress response as well as functional and neurochemical changes. Preclinical data also show that antidepressant withdrawal evokes a behavioral stress response that is associated with increased hippocampal NMDA receptor density, with both responses dependent on NMDA receptor activation". [32]

The symptoms that follow antidepressant discontinuation include: dizziness, nausea, gastrointestinal distress, headache, gait instability, lethargy, paresthesia, anxiety, irritability, vivid dreams, lowered mood, etc. While cholinergic overdrive may explain certain symptoms after tricyclic antidepressants withdrawal, many of these symptoms suggest increased excitability of serotonergic neurons. In the same way that chronic antidepressant treatment results in desensitization of post and presynaptic 5-HT_{1A} receptors, abrupt cessation of 5-HT reuptake inhibition will cause a temporary deficit of available intra-synaptic 5-HT in the face of these down-regulated receptors, resulting in a neurochemical and behavioral pattern caused by loss of inhibitory 5-HT_{1A} mediated synaptic control and an increase in circulating 5-HT. [32,33]

In severe and disabling withdrawal syndrome (5% of patients) [21], overtly raised synaptic 5-HT levels may be detrimental to neuronal function and integrity, enhancing brain glutamate NMDA receptor efficacy. Reiterating the premises previously mentioned, these severe rebound phenomenon will be determined by various factors, such as the pharmacological profile of the antidepressant, the time-point and duration of withdrawal, whether withdrawal or noncompliance is repeated and how often, and the impact of associated contributors such as inherent genetic and environmental factors (idiosyncratic constitution) [32].

Antidepressants and rebound suicidality

My initial hypothesis is that the enantiopathic treatment of the symptoms of the depression with antidepressants of the second generation, after the withdrawal (discontinuation or dose alteration), provokes a significant worsening of the depression symptoms initially suppressed (for example, suicidal ideation, suicidal attempts or suicidal behavior), as a consequence of the rebound effect or paradoxical reaction of the organism.

In the first most comprehensive meta-analysis that intended to investigate the relationship between antidepressant drugs and suicidality in pediatric patients participating in placebo-controlled trials, Hammad et al. [34] included all studies submitted to the Food and Drug Administration (FDA). The evaluated data was derived from 4,582 patients in 24 trials [23 trials conducted in 9 drug company {fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, bupropion, venlafaxine, nefazodone and mirtazapine) and 1 multicenter trial

(TADS) [35] that evaluated only fluoxetine}. Sixteen trials studied patients with major depressive disorder (MDD), 4 trials studied patients with obsessive-compulsive disorder (OCD), and 4 trials studied patients with non-obsessive-compulsive anxiety disorder (non-OCD anxiety). Only 20 trials were included in the risk ratio analysis of suicidality because 4 trials had no events in the drug or placebo groups. The multicenter trial (TADS) was the only individual trial to show a statistically significant risk ratio (RR 4.62; 95% CI, 1.02-20.92). The overall risk ratio for selective serotonin reuptake inhibitors (SSRIs) in depression trials was 1.66 (95% CI, 1.02-2.68) and for all drugs throughout all indications was 1.95 (95% CI, 1.28-2.98). The overall risk difference (RD) for all drugs within all indications was 0.02 (95% CI, 0.01-0.03). The FDA concluded that these medications pose a 2-fold (4% verum vs.2% placebo) increased risk for "suicidal behavior" or "suicidal ideation", a modestly increased risk of suicidality.

In a recent meta-analysis [36] to assess the efficacy and risk in reported suicidality (occurrence of suicidal ideation, suicidal attempt or suicidal behavior) of antidepressant treatment for pediatric disorders, 27 randomized controlled trials of pediatric antidepressant treatment were selected (MDD = 15; OCD = 6; non-OCD anxiety = 6), and risk differences (RD) for response and for suicidal ideation/suicide attempts estimated by random-effect methods. Pooled risk differences in rates of primary study-defined measures of responder status (treatment response and the prospectively identified scalar variable assessing change in symptoms from baseline to the end of treatment) significantly favored antidepressants for MDD (RD 11.0%; 95% CI, 7.1% to 14.9%), OCD (RD 19.8%; 95% CI, 13.0% to 26.6%), and non-OCD anxiety disorders (RD 37.1%; 95% CI, 22.5% to 51.7%). While there was increased risk difference of suicidal ideation/suicide attempt in all trials and indications for drug *versus* placebo [RD 0.7%; 95% CI, 0.1% to 1.3% (number needed to harm, 143, 95% CI, 77 to 1000)], the pooled risk differences within each indication were not statistically significant: MDD (RD 0.9%; 95% CI, -0.1% to 1.9%), OCD (RD 0.5%; 95% CI, -1.2% to 2.2%), and non-OCD anxiety disorders (RD 0.7%; 95% CI, -0.4% to 1.8%). There were no completed suicides. Age-stratified analyses showed that for children younger than 12 years with MDD, only fluoxetine showed any benefit over placebo. With the placebo as a reference point, antidepressants are efficacious for pediatric MDD, OCD, and non-OCD anxiety disorders, although the effects are strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD. The relationship among the rates of treatment of emergent suicidality, antidepressant groups (verum and placebo) and the disorders can be observed in Table 2.

Table 2. Relationship among the rates of treatment emergent suicidality, antidepressant groups (verum and placebo) and the disorders [36]

Drug (Pooled trials estimates)	**Rate of Suicidality Nº Events/Total (%)**		**Risk Difference % (95% CI)**
	Verum	**Placebo**	
Major Depressive Disorder			
Fluoxetine	17/287 (6)	11/289 (4)	2 (-3 to 6)
Paroxetine	12/377 (3)	4/285 (1)	2 (-1 to 4)
Sertraline	5/189 (3)	2/184 (1)	2 (-1 to 4)
Citalopram/Escitalopram	11/348 (3)	9/338 (3)	-0 (-3 to 2)

Venlafaxine	8/182 (4)	0/179 (0)	4 (1 to 8)
Nefazodone	0/279 (0)	0/189 (0)	0 (-1 to 1)
Mirtazapine	1/170 (1)	0/89 (0)	1 (-2 to 3)
Obsessive-Compulsive Disorder			
Fluoxetine	1/86 (1)	0/46 (0)	1 (-4 to 6)
Fluvoxamine	2/57 (4)	0/53 (0)	4 (-2 to 9)
Paroxetine	1/99 (1)	0/107 (0)	1 (-2 to 4)
Sertraline	0/120 (0)	1/123 (1)	-1 (-4 to 2)
Non-Obsessive- Compulsive Anxiety Disorders			
Fluoxetine	0/37 (0)	0/37 (0)	0 (-5 to 5)
Fluvoxamine	0/63 (0)	0/65 (0)	0 (-3 to 3)
Paroxetine	3/165 (2)	0/156 (0)	2 (-1 to 4)
Sertraline	0/11 (0)	0/11 (0)	0 (-16 to 16)
Venlafaxine	3/297 (1)	1/313 (0)	1 (-1 to 2)

In a conclusion similar to the FDA's analysis [34], the authors found an overall increased risk of suicidal ideation/suicide attempt associated with antidepressant treatment. Our pooled estimates of risk differences (RD) are smaller than those from the FDA report, because they used random-effects rather than fixed-effects models for combining studies and also because they included 7 additional studies not covered in the FDA report (when they reanalyzed the data using fixed-effects models, results were more similar to those of the FDA). The authors defend their analysis method because it does not assume that there is a common effect across all studies, including studies in which there were no events in either cell. However, in the FDA's analysis, of a total of 24 selected studies only 4 trials (17% of the total trials) were excluded for the risk ratio (RR) calculation because there were no events in any of their groups, whereas all 24 trials were used for the risk difference (RD) calculation (4% vs.2%), finding "a modestly increased risk of suicidality".

In conventional analysis [37], several factors may contribute to high rates of suicidality in randomized antidepressant clinical trials: (1) recruitment of acutely depressed subjects early in an episode, when suicidal risks are especially high; (2) adverse selection of less treatment-responsive depressed patients into trials; (3) intensive monitoring for adverse events, including suicidal thoughts; (4) typical delay of antidepressant effects; (5) evident lack of a suicide risk-reducing effect of short-term antidepressant treatment; (6) unrecognized, antidepressant-induced mixed or psychotic states, particularly in misdiagnosed bipolar disorders; and (7) rate (events per time) inflation based on identifying suicidal events in brief time samples early in acute depressive illnesses.

Important aspects discussed in the last meta-analysis[36] can be related with the probable hypothesis of the withdrawal syndrome or rebound effect, which I will discuss below: *a) age-stratified analyses showed that for adolescents with MDD, only fluoxetine showed benefit over placebo, being related the largest effectiveness of the drug to her long half-life (more than 5 days); b) among adolescent participants treated with placebo, the risk of suicidal ideation/suicide attempt was greater in MDD trials compared with non-OCD anxiety disorders trials (odds ratio 9.9; 95% CI, 1.6-406.3) and OCD trials (odds ratio 5.8; 95% CI, 0.9-237);* similar to the FDA's analysis, *c) the multicenter trial (TADS), that*

evaluated only fluoxetine in MDD, to show a greater risk difference of suicidality (RD 7%; 95% CI, 1% to 12%).

The epidemiology, clinical course and antidepressant treatment of MDD presents other relevant aspects [38] for the argument of the relationship between suicide and rebound effect (withdrawal reaction): *d) suicidal thinking and attempts are more common in depressed adolescents (35–50% will attempt suicide, and 2–8% will complete suicide over a decade); e) the risk of new-onset of suicidal behavior is greatest in the first 2 weeks of treatment and in adolescents with their first episode of depression (86% of all TADS participants); f) compared with adults, youths who take antidepressants have an increased risk of behavioral activation, hypomania or mania, and new-onset suicidal thoughts and behaviors; g) an antidepressant should not be discontinued abruptly, as antidepressant withdrawal symptoms can be severe; h) the risk of increased suicidal behavior with any antidepressant is highest if the dosage is increased or decreased.*

It is important to stress that the adverse events assessed in these meta-analysis [34,36] were only those that occurred during the double-blind acute treatment period (4-16 weeks) or within 1 day of the end of this period, underestimating the rebound effect of the antidepressant drugs with larger half-life than 24 hours (fluoxetine, for example). By definition [11,12,21], the more evident rebound effects of the organism happen after withdrawal of enantiopathic treatment, with decrease or elimination of the drug serum concentration and the consequent partial or total vacating of the receptors, allowing the manifestation of the paradoxical reaction of the organism in the sense of returning to the initial homeostasis altered by the pharmacological agent, producing symptoms with intensities superior to the symptoms initially suppressed by the palliative drugs. How does one observe the real magnitude of the rebound phenomenon if the minimum time (half-life) was not taken into account for the total metabolisation of the drug?

The aspects mentioned previously support the physiopathological hypothesis that relates the exacerbation of the depressive symptoms (suicidality) with the rebound effect (secondary action or vital reaction) of the organism, after the antidepressant's withdrawal. (Table 3)

Table 3. Relationship among the premises of the rebound effect (vital reaction) and the aspects mentioned in the studies on suicidal risk in antidepressant drugs

Rebound effect or vital reaction	Suicidality risk in antidepressant drugs
1) It appears in a small proportion of the people (susceptible or idiosyncratic constitutions).	*g) compared with adults, youth who take antidepressants have an increased risk of behavioral activation, hypomania or mania, and new-onset suicidal thoughts and behaviors.*
2) It does not depend on the drug, on the duration of treatment, on the type of symptoms or on the acuteness of the disease.	*e) the risk of increased suicidal behavior with any antidepressant is highest during the first weeks of treatment; e) the risk of new-onset suicidal behavior is greatest in adolescents with their first episode of depression.*
3) It appears after the primary effect of the drug, when there occurs discontinuance or an occasional	*h) the risk of increased suicidal behavior with any antidepressant is highest if the dosage is increased or*

alteration of the doses.	*decreased; f) an antidepressant should not be discontinued abruptly, as antidepressant withdrawal symptoms can be severe.*
4) It induces an organic state (symptoms) exactly opposite and superior in intensity and/or duration to the primary action of the drug.	*d) suicidal thinking and attempts are more common in depressed adolescents; b) among adolescent participants treated with placebo, the risk of suicidal ideation/suicide attempt was greater in MDD trials compared with non-OCD anxiety disorders trials and OCD trials; f) an antidepressant should not be discontinued abruptly, as antidepressant withdrawal symptoms can be severe.*
5) Its magnitude is proportional to the intensity of the primary action of the substance, presenting the most evident reactions in the most effective drugs (dose) for suppressing the initial symptoms of the disease.	*a) that for adolescents with MDD, only fluoxetine showed benefit over placebo, being related the largest effectiveness of the drug to her long half-life (more than 5 days); c) the multicenter trial that evaluated only fluoxetine in MDD, to show a greater risk difference of suicidality (RD 7%; 95% CI, 1% to 12%).*

Assessing the risk for other age groups, on May 2nd, 2007, the FDA proposed that makers of all antidepressant medications update the existing black box warning on their products' labeling to include warnings about increased risks of suicidality in young adults (ages 18 to 24) during initial treatment (generally the first one to two months). The drug agency reached its conclusions after a comprehensive review of 295 individual antidepressant trials that included over 77,000 adult patients with major depressive disorder (MDD) and other psychiatric disorders. The analysis found no increased risk of completed suicides in patients taking the medications, but 21 suicide attempts were reported among the 3,810 participants with 18 to 24 years of age then taking the drug, working out to a 0.55% *(for every 1,000 people treated with antidepressants, five will exhibit suicidal thinking or behavior),* twice the risk in adults of the same age who took placebo pills. [39]

If current estimates suggest that 3 million Americans in this age group received at least one prescription for an antidepressant last year, we could infer that 16,500 young adults treated with antidepressants in the USA will inhibit suicidal thinking or behavior.

Discussion

In the same way that I did with the non-steroidal anti-inflammatory drugs (NSAIDs) [9] and the long-acting bronchodilator drugs (LABA) [10], in this study I brought new evidences of the relationship between antidepressants and suicide mentioned previously [8].

The most common explanation for this phenomenon is attributed to the "syndrome of activation", where the antidepressant produces psychomotor improvement prior to mood improvement, but this hypothesis does not apply to all studies, because the suicidal tendency was observed throughout treatment, mainly when the dose is changed.

It has also been postulated that serotonin (5-HT) is a modulator, which modulates the homeostasis between dopamine, noradrenaline and amino butyric acid (GABA), which mediate the thought processes, anxiety and mood, respectively. When this homeostasis gets disturbed, depression sets in. The therapeutic mechanism of action of serotonergic drugs (SSRIs) involves an alteration in the 5-HT system, inhibition of the neuronal uptake pump of serotonin and reinstating the homeostasis. The plethora of biological substrates, receptors and pathways for 5-HT are candidates to mediation not only of the therapeutic actions of SSRIs, but also of their side effects. A hypothesis to explain these immediate side effects is that 5-HT is increased at specific 5-HT receptor subtypes in discrete regions of the body where the relevant physiologic processes are regulated. [40]

In 5% of the patients [21], these stress-induced neurochemical changes can promote events with insidious and malignant implications for the outcome of the depression, as a consequence of the increase in brain glutamate activity and nitric oxide synthesis, and decrease in amino butyric acid levels. These disturbances alter the expression of critical cellular resilience proteins and synaptic plasticity, changing the neuronal response [32].

I postulate the hypothesis that the suicidality, observed in the initial discontinuance of the treatment with SSRIs, in individuals with MDD and more susceptible to the primary actions of these medicines (verified by the evident initial enantiopathic actions in the palliation of the depressive symptoms), and after the suspension or occasional alteration in the daily dosage of the drug, are the result of the vital reaction or rebound effect of the organism, that promotes a depletion of intra-synaptic 5-HT levels after an initial plethora.

Counterarguing this hypothesis, Jeffrey et al. comment in the last meta-analysis [36]: "While there has been some speculation that an emergent suicidal ideation/suicide attempt might be induced by withdrawal effects found particularly in those drugs with shorter half-lives, we found no such association when comparing the risk of suicidal ideation/suicide attempt in fluoxetine, a drug with a longer half-life (5 days) than those of the other drugs (all substantially shorter than 24 hours) ($P = 0.58$). Furthermore, the risk of incident suicidal ideation/suicide attempt does not appear to be a consequence of lack of efficacy, insofar as the size of increased risk is as similar for anxiety as it is for depression in adolescents, even though antidepressants are more efficacious for anxiety than for depression".

The disregard of the premises of the rebound effect induced the authors to the incorrect analysis mentioned previously: the magnitude of the rebound effect *("the multicenter trial that evaluated only fluoxetine in MDD, to show a greater risk difference of suicidality")* is proportional to the effectiveness of the drug *("for adolescents with MDD, only fluoxetine showed benefit over placebo, the largest effectiveness of the drug being related to her long half-life"),* and not to the "lack of efficacy" as the authors suppose. This way, a longer period of observation after the suspension of the fluoxetine should be considered, if we want to evaluate to real magnitude of the rebound effect.

In spite of the low effectiveness of the antidepressants in the MDD *("relative to placebo, the effects of antidepressants are strongest in non-OCD anxiety disorders, intermediate in*

OCD, and more modest in MDD"), we could relate the largest suicidality risk observed in this group ("*among adolescent participants treated with placebo, the risk of suicidal ideation/suicide attempt was greater in MDD trials compared with non-OCD anxiety disorders trials and OCD trials"*) to the fact that suicidal symptoms are more common in MDD, and rarer in the other analyzed disorders (OCD and non-OCD anxiety). As in the premises mentioned previously, *"the magnitude of the rebound effect is proportional to the intensity of the primary action of the substance, presenting the most evident reactions in the drugs most effective in suppressing the initial symptoms of the disease".*

In other words, the severe and disabling antidepressant withdrawal syndrome (secondary action or rebound effect of the organism) will only be possibly observed in constitutions susceptible to the enantiopathic effect of the medicine, and when the symptoms of the disease are efficiently suppressed by the primary action of the palliative; they are not observed in disorders (OCD and non-OCD anxiety) in which a direct and strong relationship doesn't exist between the natural symptoms of the disease (suicidality) and the contrary action of the drug (anti-suicidality). Hahnemann enunciated this need to stimulate the vital reaction *("if there be in nature a state exactly the opposite of the primary action")* two hundred years ago:

> "During the primary action of the artificial morbific agents (medicines) on our healthy body, as seen in the following examples, our vital force seems to conduct itself merely in a passive (receptive) manner, and appears, so to say, compelled to permit the impressions of the artificial power acting from without to take place in it and thereby alter its state of health; it then, however, appears to rouse itself again, as it were, and to develop (A) the exact opposite condition of health (counteraction, secondary action) to this effect (primary action) produced upon it, if there be such an opposite, and that in as great a degree as was the effect (primary action) of the artificial morbific agent on it, and proportionate to its own energy; - or (B) if there be not in nature a state exactly the opposite of the primary action, it appears to endeavor to indifferentiate itself, that is, to make its superior power available in the extinction of the change wrought in it from without (by the medicine), in the place of which it substitutes its normal state (secondary action, curative action)". (*Organon*, paragraph 64)

To confirm this causality between suicidality and the antidepressant's rebound effect, described in previous studies for other depressive symptoms, new clinical trials need to be carried out, prioritizing the initial alterations of humor (primary action) and the side effects (secondary action) that can happen in a longer period after the suspension of the drugs, so that the rebound effect (secondary action) of the organism can fully manifest itself. In this process, it is important to emphasize the surveillance on the occasional discontinuance of the doses.

Comparatively to the studies of other drugs (NSAIDs and LABA) [9,10], certain analogies with the antidepressant rebound phenomenon can be described:

(i) Rebound symptoms are much more intense than the symptoms initially suppressed by the primary action of the enantiopathic drugs;

(ii) Although they reach a small percentage of the individuals (idiosyncratic constitutions), the fatal rebound events assume epidemic importance when we consider the great consumption of medicines by the population: long-acting beta-agonists (LABA) cause approximately 1 death per 1,000 patient-years of use, meaning 4,000-5,000 asthma-related deaths a year in the USA only; SSRIs cause approximately 5 suicidality cases per 1,000 young adult patient-years of use, meaning 16,500 instances of suicidal thinking or behavior a year in the USA only.

(iii) In controlled studies, compared to the placebo, the risk of ischemic fatal events was 3,4 times larger after the suspension of aspirin, 1,52 times larger after the suspension of AINHs and 1,67 times larger after the suspension of rofecoxib; the risk of fatal bronchoconstriction was 2-4 times larger after the suspension of LABA; the risk of suicidality was 6 times larger after the suspension of the short half-life SSRIs.

(iv) The time of manifestation of the paradoxical reaction after the suspension of the treatment didn't vary among the different classes of drugs: 10 days for aspirin, 14 days for AINHs, 9 days for rofecoxib and 7 days for the antidepressants.

(v) The duration of the rebound phenomenon for rofecoxib reached up to 30 days, and up to 3 weeks for the antidepressants.

(vi) The duration of the treatment didn't show a direct relationship with the manifestation of the rebound effects.

(vii) Drugs with more intense enantiopathic performance, suppressing the primary symptoms of the disease more intensely, manifested proportional paradoxical reactions.

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Statins withdrawal, vascular complications, rebound effect and similitude[7]

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Abstract

In view of its growing indications in primary and secondary prevention of cardiovascular diseases, statins are widely consumed today. Besides reducing cholesterol biosynthesis, statins provide vasculoprotective effects (pleiotropic effects), including improvement of endothelial function, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory and thrombogenic responses, stabilization of atherosclerotic plaques, and others. However, recent studies suggests that suspension of statin treatment leads to a rebound impairing of vascular function, and increasing morbidity and mortality in patients with vascular diseases. Similarly to other classes of modern palliative drugs, this paradoxical effect of the organism is the same as a secondary action or vital reaction described by Samuel Hahnemann, and used in homeopathy as a therapeutic response. In this review, I brought the evidence of the rebound effect of statins that support the curative similitude principle.

Introduction

Applying the deductive Aristotelian logic *"modus tolens"* or "indirect proof" in the scientific justification of the homeopathic treatment, Samuel Hahnemann attributes to "cure by symptom similarity" (similitude principle) the quality of "therapeutic law of nature", stating that after a short-term relief of the enantiopathic treatment (contrary, antipathic, antagonistic, palliative), aggravation of the original disease follows *in every case without exception* (*Organon of medicine*, paragraphs 55-61) [1].

> "Had physicians been capable of reflecting on the sad results of the antagonistic employment of medicines, they had long since discovered the grand truth, *that the true radical healing art must be found in the exact opposite of such an antipathic treatment of the symptoms of disease* [...]". (*Organon*, paragraph 61)

In physiological explanation of this phenomenon, he says that a *"secondary action* or *counteraction*" occurs automatically after the *"primary action"* of *every medicine* (*Organon*, paragraphs 63-69).

> "Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed *primary action.* […] To its action our vital force endeavours to

[7] Teixeira MZ. Statins withdrawal, vascular complications, rebound effect and similitude. *Homeopathy*. 2010; 99(4): 255-262. Available at: https://doi.org/10.1016/j.homp.2010.01.001

> oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of *secondary action* or *counter-action".* (*Organon,* paragraph 63)
>
> "[...] A hand bathed in hot water is at first much warmer than the other hand that has not been so treated (primary action); but when it is withdrawn from the hot water and again thoroughly dried, it becomes in a short time cold, and at length much colder than the other (secondary action). A person heated by violent exercise (primary action) is afterwards affected with chilliness and shivering (secondary action). To one who was yesterday heated by drinking much wine (primary action), today every breath of air feels too cold (counter-action of the organism, secondary action). An arm that has been kept long in very cold water is at first much paler and colder (primary action) than the other; but removed from the cold water and dried, it subsequently becomes not only warmer than the other, but even hot, red and inflamed (secondary action, reaction of the vital force). Excessive vivacity follows the use of strong coffee (primary action), but sluggishness and drowsiness remain for a long time afterwards (reaction, secondary action), if this be not always again removed for a short time by imbibing fresh supplies of coffee (palliative). After the profound stupefied sleep caused by opium (primary action), the following night will be all the more sleepless (reaction, secondary action). After the constipation produced by opium (primary action), diarrhoea ensues (secondary action); and after purgation with medicines that irritate the bowels, constipation of several days' duration ensues (secondary action). And in like manner it always happens, after the primary action of a medicine that produces in large doses a great change in the health of a healthy person, that its exact opposite, when, as has been observed, there is actually such a thing, is produced in the secondary action by our vital force". (*Organon,* paragraph 65)

Describing the sad results of the indiscriminate antipathic employment of medicines (contrary principle), Hahnemann quantifies the *magnitude* of this undesirable vital reaction of the organism in paragraphs 59-61 of the *Organon:*

> "If these ill-effects are produced, as may very naturally be expected from the antipathic employment of medicines, the ordinary physician imagines he can get over the difficulty by giving, at each renewed aggravation, a stronger dose of the remedy, whereby an equally transient suppression1 is effected; and as there then is a still greater necessity for giving ever - increasing quantities of the palliative there ensues either another more serious disease or frequently even danger to life and death itself, but never a cure of a disease of considerable or of long standing". (*Organon,* paragraph 60)

Despite the natural and universal character of this secondary action of the organism, its expression is related to some *basic conditions* (*Organon,* paragraphs 59, 64, 69): (1) it appears only in susceptible individuals, who present in their constitution similar symptoms to the pathogenetic effects of the substance; (2) it does not depend on the substance, repetition of the doses or on the type of symptoms (disease); (3) it appears after the primary action of the substance (discontinuation), as an automatic manifestation of the organism; (4) it induces an organic state (symptoms) opposite and greater in intensity and/or duration to the primary action of the substance; (5) its effect magnitude is proportional to the intensity of the primary action (dose) of the substance.

The secondary action or vital reaction of the organism is the same as the "rebound effect" or "paradoxical reaction" of modern clinical pharmacophysiology, been described after discontinuation of several classes of currently drugs ("withdrawal syndrome").

For example, drugs used for the treatment of angina pectoris (*β*-adrenoceptor blockers, calcium channel blockers, nitrates, etc.), whose primary effect is the improvement of angina. After suspension of the drug, a rebound effect occurs, consisting of exacerbated thoracic pain, in frequency as well as intensity. Drugs utilised to control arterial hypertension (central *α*2-adrenoceptor agonists, *β*-adrenoceptor blockers, hidralazine, ACE inhibitors, MAO inhibitors, nitrates, prostaglandin A_1, sodium nitroprusside, etc.) can provoke rebound arterial hypertension as a secondary reaction. Anti-arrhythmic medications (adenosine, amiodarone, *β*-adrenoceptor blockers, calcium channel blockers, disopyramide, encainide, digitalics, flecainide, lidocaine, mexiletine, moricizine, procainamide, propafenone, quinidine, tocainide, etc.) provoke, after the interruption of treatment, exacerbation of the initial arrhythmias. Anticoagulant drugs (argatroban, bezafibrate, heparin, salicylates, warfarin, etc.), whose primary effect is prophylaxis of thrombosis, cause thrombotic complications as a secondary or rebound effect. Bronchodilators (adrenergic bronchodilators, sodium cromoglycate, ipratropium, nedocromil, long-acting bronchodilators, etc.) cause exacerbation of the bronchospasms after the suspension or discontinuation of treatment. In the psychiatric medications [anxiolytics (barbiturates, benzodiazepines, buspirone, meprobamate, etc.), sedative-hypnotics (barbiturate, bendodiazepines, morphine, promethazine, tetrahydrocannabinol, zopiclone, etc.), CNS stimulants (amphetamine, caffeine, cocaine, mazindol, methylphenidate, etc.), antidepressants (MAO inhibitors, tricyclics, SSRIs, etc.), anti-psychotics (clozapine, phenothiazines, haloperidol, pimozide, thiethylperazine, thiothixene, etc.)], a reaction of the organism trying to maintain organic homeostasis can be observed, with symptoms opposite to those expected in their primary therapeutic indication have been observed, further aggravating the initial condition. Drugs whose primary action is anti-inflammatory (ibuprofen, indomethacin, paracetamol, salicylates, etc.) induce a secondary response of the organism, increasing inflammation and the plasma concentration of mediators of inflammation. Drugs whose primary effect is analgesic (caffeine, calcium channel blockers, clonidine, ergotamine, methysergide, opioids, salicylates, etc.) may provoke, as a paradoxical reaction, hyperalgesia. Diuretics (furosemide, torasemide, triamterene, etc.) used to decrease blood volume cause rebound retention of sodium and potassium, increasing blood volume. Anti-dyspeptics (antacids, H_2 receptor antagonists, misoprostol, sucralfate, etc.) for the treatment of gastritis and gastroduodenal ulcers, cause, after an initial decline in acidity, a rebound increase in acidity.

Similarly to enantiopathic drugs mentioned above and studied in the past [2-9], we will describe in this review the scientific evidence that demonstrate the undesirable vital reaction that the suspension of *statins* awakens in the human physiology, confirming Hahnemann's postulates and the homeopathic method of treatment of diseases.

Material and Methods

We reviewed the literature using the Medline database and the keywords “statin”, “rebound” and “withdrawal”, and then selecting the most relevant papers and discussing the scientific evidence.

Results

Primary action or enantiopathic therapeutic effect of statins

Statins are the most widely prescribed cholesterol-lowering drugs and are considered to be first-line therapeutics for the prevention of coronary heart disease and atherosclerosis (the major cause of death in developed countries). Statins act by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme in endogenous cholesterol biosynthesis, which catalyzes the reduction of HMG-CoA to mevalonic acid. Inhibition of this enzyme has proven to be effective for lowering plasma total cholesterol, low-density lipoprotein-cholesterol, and triglyceride levels in humans and can therefore be useful to treat atherosclerotic and dyslipidemic disorders.

However, the clinical benefits of statins appear to extend beyond their lipid-lowering effects. Besides reducing cholesterol biosynthesis, inhibition of mevalonate by statins also leads to a reduction in the synthesis of important intermediates, such as the isoprenoids (farnesyl pyrophosphate, geranylgeranyl pyrophosphate, coenzyme Q10, dolichol, isopentenyladenosine, etc.).

These intermediates are involved in the posttranslational prenylation of several proteins (e.g., Ras, Rho, Rac) that modulate a variety of cellular processes including cellular signaling, differentiation, and proliferation. Given the central role of these isoprenylated proteins in endothelial function, atherosclerotic plaque stability, platelet activity, coagulation, oxidation, and inflammatory and immunologic responses, it could be anticipated that these compounds may exert multiple beneficial primary effects in a broad spectrum of disorders including cardiovascular disease, osteoporosis, Alzheimer’s disease and related vascular dementia, viral and bacterial infection, and others.

These cholesterol-lowering-independent effects of statins are termed “pleiotropic effects”, and involving vasculoprotective actions that include improvement of endothelial function, increased nitric oxide (NO) bioavailability, antioxidant properties, inhibition of inflammatory and thrombogenic responses, immunomodulatory actions, regulation of progenitor cells, and stabilization of atherosclerotic plaques. **[**10-12]

Secondary action or rebound effect of statins

Regardless of the rebound increase in cholesterol biosynthesis, recent scientific evidence suggests that sudden discontinuation of statin treatment leads to a rebound impairing of vascular function, and increasing morbidity and mortality in patients with vascular

diseases: withdrawal of statin treatment leads to an overshoot activation of heterotrimeric G-proteins Rho and Rac, causing production of reactive oxygen species and suppression of NO bioavailability.

In humans, discontinuation of statin therapy leads to a prooxidant, proinflammatory and prothrombotic state, with impaired endothelium function. Recent epidemiological studies indicated that cessation of statin medication in acute myocardial infarction (AMI) and ischemic stroke patients confers a significantly higher likelihood of early cardiological and neurological deterioration, respectively, and poor outcome. In summary, withdrawal of statin therapy results in a rapid return to endothelial dysfunction and amplification of the oxidative and inflammatory processes, which may increase cardiac and cerebrovascular risks. **[**13-16]

Increase of cholesterol biosynthesis

To define the effect of statin on cholesterol biosynthesis in normal subjects, Stone et al. [17] investigated the effect of a single oral dose of lovastatin and a 4-week treatment period of lovastatin on mononuclear leukocyte (ML) sterol synthesis as a reflection of total body sterol synthesis. In parallel, they measured serum lipid profiles and HMG-CoA reductase activity in ML microsomes that had been washed free of lovastatin. The higher dose of lovastatin (40 mg bid) decreased ML sterol synthesis by 16 ± 3% ($P < 0.05$) and induced HMG-CoA reductase to 53.7 times ($P < 0.01$) the baseline value at 4 weeks. Stopping this dose effected, a rebound in ML sterol synthesis to 140 ± 11% of baseline ($P < 0.01$) was observed, while HMG-CoA reductase remained 12.5 times baseline ($P < 0.01$) over the next 3 days. No rebound in serum cholesterol was observed.

To determine in human subjects whether cessation of statin therapy leads to induction above-normal rates of cholesterol biosynthesis, Pappu et al. [18] measured urinary concentrations of mevalonic acid (an indicator of cholesterol biosynthesis) after the cessation of therapy with lovastatin and simvastatin (80 mg/day) in patients with heterozygous familial hypercholesterolemia. Plasma concentrations of low-density lipoprotein cholesterol (LDL-C) increased promptly on discontinuation of therapy but did not increase above pretreatment levels at any point after drug discontinuation. Similarly, the 24-hour urinary excretion of mevalonic acid was reduced during treatment with lovastatin or simvastatin and increased promptly on discontinuation of drugs.

Chu et al. [19] investigated the serial changes of soluble CD40 ligand (sCD40L) and two adipocytokines, adiponectin and resistin, after short-term statin therapy and withdrawal in 32 patients with hypercholesterolaemia who received atorvastatin 10 mg/day for 3 months. Serum lipid profiles, and levels of sCD40L, adiponectin and resistin, were assessed before and immediately after 3 months' statin therapy. Serum levels of sCD40L and adiponectin were also measured on the three consecutive days after statin withdrawal. After 3 months' statin therapy, levels of sCD40L (1.93 ± 1.13 vs. 1.30 ± 0.97 ng/mL), total cholesterol and LDL-C were all reduced significantly ($P < 0.05$). However, sCD40L level tended to increase towards baseline on the first and second days after statin withdrawal, but was not significantly elevated until the third day after withdrawal (1.89 ± 1.28 vs. 1.30 ± 0.97

ng/mL, $P < 0.05$). Total cholesterol and LDL-C levels did not increase during the 3 days of statin withdrawal. No significant changes of adiponectin and resistin levels were shown after statin therapy.

In thirty patients with established coronary artery disease (CAD), Chen et al. [20] investigated the effects after withdrawal of simvastatin on serum total cholesterol and LDL-C. After treatment with 20 mg/day for 4 weeks, abrupt discontinuation of simvastatin leads to a rebound of serum total cholesterol (21.3%) and LDL-C (18.2%) in patients within 1 week, but they were still lower than the baseline values ($P < 0.05$ for each parameter).

Worsening of endothelial function

Statins improve endothelial function by upregulating endothelial nitric oxide (NO) production that is mediated by inhibiting the isoprenylation of rho GTPase. Withdrawal of statin treatment could suppress endothelial NO production and may impair vascular function. To test this hypothesis, normocholesterolemic mice were treated with atorvastatin (10 mg/kg) for 14 days, followed by treatment withdrawal: this led to the upregulation of endothelial NO synthase expression and activity by 2.3- and 3-fold, respectively; withdrawal of statins resulted in a dramatic, 90% decrease of NO production after 2 days. Experimental studies with mouse aortas and cultured endothelial cells clarify the molecular mechanisms that regulate this phenomenon rebound: statins upregulated the expression of rho GTPase in the cytosol, but statins blocked isoprenoid-dependent rho membrane translocation and GTP-binding activity. Inhibiting the downstream targets of rho showed that rho expression is controlled by a negative feedback mechanism mediated by the actin cytoskeleton. Measuring rho mRNA half-life and nuclear run-on assays demonstrated that statins or disruption of actin stress fibers increased rho gene transcription but not rho mRNA stability. Therefore, treatment with statins leads to the accumulation of nonisoprenylated rho in the cytosol. Withdrawing statin treatment restored the availability of isoprenoids and resulted in a massive membrane translocation and activation of rho, causing downregulation of endothelial NO production. In summary, the underlying molecular mechanism is a negative feedback regulation of rho gene transcription mediated by the actin cytoskeleton. [21]

In a similar study, 129/SV mice were treated with atorvastatin (10 mg/kg) for 14 days and then withdrew treatment. Treatment with atorvastatin conferred stroke protection by 40% after filamentous occlusion of the middle cerebral artery followed by reperfusion. Withdrawal of statin treatment, however, resulted in the loss of stroke protection after 2 and 4 days. In mouse aortas and brain vasculature, statins upregulated endothelial nitric oxide synthase (eNOS) message 2.3- and 1.7-fold, respectively, as measured by reverse transcription-polymerase chain reaction. Withdrawal of statins resulted in 5- and 2.7-fold downregulation of eNOS mRNA in aorta and brain, respectively, after 2 days. Statin treatment decreased RhoA GTPase membrane expression to 48%, while withdrawal of statins resulted in 4-fold increase of RhoA in the cellular membrane. [22]

To investigate the relationship between simvastatin withdrawal, suppression of endothelial NO production, and vascular injury, Chen et al. [20] exposed human umbilical vein

endothelial cells (HUVECs) to simvastatin. After 24 hours cells were repeatedly washed to remove the drugs, and the conditioned mediums were collected at the indicated time points. The nitric oxide (NO) production and levels of eNOS mRNA after 24 hours of withdrawal of statins were examined. In HUVECs, a maximum decrease of nitrite levels (-80%) was observed at 6 hours after stopping simvastatin treatment, which was below the control levels. Twenty-four hours after stopping 10^{-5} and 10^{-6} mmol/L simvastatin treatment, eNOS mRNA expression decreased to -71% and -42% ($P < 0.05$), respectively. The authors concluded that vascular injury may be related to the suppression of endothelial NO production, which are dose-dependent, and independent of cholesterol levels.

The effect of initiation and withdrawal of statin therapy on resting and functionally activated cerebral hemodynamics was investigated in healthy young volunteers: 60 normocholesterolemic students were subjected to a placebo-controlled, double-blind crossover study with a washout phase between blocks of 4 weeks; in the verum group, 20 mg pravastatin was taken for 2 weeks followed by 40 mg for 4 weeks. As main outcome, resting and evoked hemodynamic responses due to a visual stimulation task in the posterior cerebral artery were obtained at baseline and then weekly and the day after discontinuation. The day after statin withdrawal, evoked flow velocity responses were significantly lower (11 ± 4% vs. 13 ± 5% at baseline, $P < 0.01$) indicating inappropriate blood supply of active neurons. This reduction in evoked flow velocity responses reflects reduced nitric oxide bioavailability and therefore supports molecular findings of acute statin withdrawal. [23]

Increase of inflammation and oxidative stress

In addition to its lipid-lowering properties, statin decreases the level of C-reactive protein (CRP) that is considered a risk factor for coronary artery disease (CAD). Withdrawal of statin therapy, stimulating the growth rebound in the level of CRP, could increase the incidence of cardiac events in patients with atherosclerotic heart disease. To test this hypothesis, twenty patients with hyperlipidemia received statin (atorvastatin, 10 mg/day) therapy for 3 months. The levels of lipid profiles and CRP were assessed before receiving the statin therapy, immediately after 3 months of therapy, and on the 3 consecutive days after withdrawal of statin treatment. After 3 months of statin therapy, the total cholesterol, low-density lipoprotein cholesterol (LDL-C), and CRP were significantly reduced (264.94 ± 16.23 vs 183.44 ± 16.34 mg/dl, 183.17 ± 34.56 vs 122.00 ± 17.66 mg/dl, and 2,309.00 ± 437.85 vs 1,257.95 ± 207.99 ng/ml, respectively). The level of CRP increased on the second day after withdrawal of statin therapy (2,590.14 ± 1,045.05 vs 1,257.95 ± 207.99 ng/ml); however, the total cholesterol and LDL-C did not increase during the 3-day period after withdrawal of statin therapy. [24]

Li et al. [25] investigated whether acute termination of statin treatment could result in rebound of inflammatory markers, such as CRP and interleukin-6 (IL-6), in patients with hyperlipidemia. Seventeen patients with hyperlipidemia were given 40 mg/day of pravastatin for 6 weeks. The concentrations of plasma CRP and IL-6 were evaluated before receiving the statin therapy, immediately after 6 weeks of pravastatin therapy, and at days 1, 3 and 7 after withdrawal of pravastatin therapy. The lipid profile was also evaluated at baseline, 6 weeks of therapy, and at day 7 after terminating pravastatin. Pravastatin therapy

induced significant reductions in total cholesterol. Although the lipid profile did not change during the 7-day period after withdrawal of pravastatin therapy, the concentrations of CRP and IL-6 increased significantly at day 3 and at day 7 after withdrawal of pravastatin therapy. No correlation between increase of CRP as well as IL-6 and small changes of LDL-cholesterol concentrations was found after withdrawal of pravastatin therapy at day 7.

To assess whether variations in antioxidant and anti-inflammatory parameters occur with short term administration and discontinuation of atorvastatin in normocholesterolemic CAD patients, forty CAD patients with near normal serum cholesterol levels (total cholesterol < 240 mg/dl, LDL cholesterol < 130 mg/dl) were continuously enrolled and randomized to groups A and B (20 patients taking atorvastatin) and groups C and D (20 patients not taking atorvastatin). Atorvastatin (10 mg/day) was continued in group A, withdrawn in group B and started in groups C and D for 6 weeks. Thereafter atorvastatin was withdrawn in group A and C, restarted in group B, and continued in group D for further 6 weeks. C-reactive protein and markers of oxidative stress (phenolic antioxidants FRAP and TBARS) were assessed at baseline, 6 weeks and 12 weeks in all the groups. The results showed that administration and withdrawal of atorvastatin caused changes in markers of oxidative stress which closely correlated with changes in marker of inflammation. Further, the salutary effects were of quick onset, but were rapidly reversed on withdrawal of atorvastatin. [26]

In a prospective observational cohort, Sposito et al. [27] verified the existence of a rebound inflammatory effect after statin withdrawal in the acute phase of myocardial infarction (MI): changes in CRP between the first and the fifth day after MI were evaluated in 249 consecutive patients who were using statins prior to and during MI (SS), statins prior to but not during MI (SN), no statin prior to but during MI (NS), and no statin prior to nor during MI (NN). At baseline, statin users presented a trend to lower median CRP values as compared with those without this treatment before the MI (NN 1.0 mg/dL vs NS 1.0 mg/dL vs SS 0.5 mg/dL vs SN 0.6 mg/dL, $P = 0.08$). By the fifth day, median CRP was significantly higher in the SN (18.1 mg/dL) group as compared with other groups (NN 10.5 mg/dL vs NS 2.9 mg/dL vs SS 1.1 mg/dL, $P < 0.0001$). At the fifth day, the median CRP in the NN group was lower than in the SN group ($P < 0.0001$), but higher than the NS and SS groups ($P < 0.0001$). There was no significant correlation between CRP change and the change of LDL-cholesterol, HDL-cholesterol or triglycerides. The present study has provided evidence for the existence of an important rebound inflammatory effect after statin cessation.

Stimulation of thrombogenic response

The use of statins is associated with a primary reduced thrombosis burden and diminished platelet activity (pleiotropic effects), reducing cardiovascular events. To test the platelet activity rebound after statin withdrawal, Puccetti et al. [28] evaluated platelet activity after cerivastatin discontinuation in eighteen subjects and in sixteen subjects continuing treatment with simvastatin, measuring LDL-C (chromogenic method), oxidized-LDL (ox-LDL; ELISA), platelet P-selectin (P-sel) expression (flow cytometry detection), platelet aggregation (% change of transmitted light), and intracellular citrullin production (iCit; HPLC), as an indicator of intracellular NO synthase activity, at baseline and 7, 14, 28, 60

days after statin discontinuation. P-sel expression and platelet aggregation were increased at 14 days ($P < 0.001$ and $P < 0.05$, respectively) in association with raised ox-LDL (r = 0.30, $P < 0.05$) and decreased iCit (r = 0.53, $P < 0.01$). Increased LDL-C was related to P-sel and platelet aggregation at 28 days (r = 0.30, $P < 0.05$). Subjects continuing statin treatment had no significant changes of P-sel at 28 ($P = 0.221$) and 60 days ($P = 0.238$).

Observational studies

Heeschen et al. [29] investigated the effects of statins on the cardiac event rate in 1,616 patients of the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM), study who had coronary artery disease (CAD) and chest pain in the previous 24 hours, recording death and nonfatal myocardial infarction during the 30-day follow-up. Baseline clinical characteristics did not differ among 1,249 patients without statin therapy, 379 patients with continued statin therapy, and 86 patients with discontinued statin therapy after hospitalization. While statin therapy was associated with a reduced event rate at 30-day follow-up compared with patients without statins (adjusted hazard ratio 0.49, 95% CI 0.21-0.86, $P = 0.004$), if the statin therapy was withdrawn after admission, cardiac risk increased compared with patients who continued to receive statins (2.93, 95% CI 1.64-6.27, $P = 0.005$) and tended to be higher compared with patients who never received statins (1.69, 95% CI 0.92-3.56, $P = 0.15$). This was related to an increased event rate during the first week after onset of symptoms and was independent of cholesterol levels. Just as in subsequent reassessment of the data [30], the authors concluded that discontinuation of statins after onset of symptoms completely abrogates the primary beneficial effect.

An observational study compared 13,871 patients with acute coronary syndrome (non-ST-segment elevation myocardial infarction) previously receiving statins before hospital admission (9,001 patients continued receiving statins within 24 hours of hospital admission, and 4,870 patients discontinued therapy) with 54,635 patients who did not receive statins at any time before or during hospitalization, enrolled in the National Registry of Myocardial Infarction 4. Patients who discontinued treatment had increased hospital morbidity and mortality rates relative to patients in whom therapy was continued, with higher rates of heart failure, ventricular arrhythmias, shock, and death. In multivariate analyses, these patients were at statistically significant increased risk of hospital death compared with those continuing statin therapy and at similar risk compared with those not receiving statins before or during hospitalization. [31]

Using the same database (AMI in the National Registry of Myocardial Infarction 4), Fonarow et al. [32] analysed in-hospital morbidity and mortality comparing patients who continued statin therapy received before the index AMI hospitalization (n = 17,118) or newly started statin therapy within the first 24 hours of hospitalization (n = 21,978) and patients who did not receive early statin treatment (n = 126,128) or whose statin therapy was discontinued (n = 9,411). While new or continued treatment with a statin in the first 24 hours was associated with a decreased risk of mortality compared with no statin use (4.0% and 5.3%, respectively, compared with 15.4% no statin), discontinuation of statin treatment was associated with a slightly increased risk of mortality (16.5%). Propensity analysis yielded mortality odds ratios of 0.46 for continued therapy, 0.42 for newly started therapy,

and 1.25 for discontinued therapy for matched pairs versus no statin therapy (all *P* values < 0.0001).

Aiming to assess the effect of perioperative statin withdrawal on postoperative cardiac outcome, Schouten et al. [33] studied 298 consecutive statin users who underwent major vascular surgery on days 1, 3, 7, and 30 of postoperative. End points were postoperative troponin release, myocardial infarction, and a combination of nonfatal myocardial infarction and cardiovascular death. Statin discontinuation was associated with an increased risk for postoperative troponin release (hazard ratio 4.6, 95% CI 2.2-9.6) and the combination of myocardial infarction and cardiovascular death (hazard ratio 7.5, 95% CI 2.8-20.1). In conclusion, the present study showed that statin withdrawal in the perioperative period is associated with an increased risk for perioperative adverse cardiac events.

Retrospective analyses of data from the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM), the National Registry of Myocardial Infarction 4, and the Global Registry of Acute Coronary Events (GRACE) trials revealed that the benefits of statins on acute coronary outcomes are rapidly lost and outcomes worsened if statins are discontinued during a patient's hospitalization for an acute coronary syndrome.Withdrawal of statin therapy in the first 24 hours of hospitalization for non-ST-elevation myocardial infarction increased the hospital morbidity and mortality rate versus continued therapy (11.9% vs 5.7%, $P < 0.01$). In patients with acute coronary syndromes who discontinue statins, the rapid increase in risk of an event may result not only from the lost benefits from the therapy, but also from rebound inhibition of vascular protective substances and activation of vascular deleterious substances. The authors concluded that acute removal of pleiotropic effects and rebound vascular dysfunction may be more important in an acute coronary event, where inflammation promotes rupture of atherosclerotic plaques and inflammatory and prothrombosis markers are present in high concentration, than in stable chronic vascular disease. [34]

Vascular endothelium, which can be affected by statins, is believed to play a substantial role in subarachnoid hemorrhage (SAH). In order to estimate the association between use and withdrawal of statins and the risk of SAH, Risselada et al. [35] conducted a population-based case-control study within the PHARMO database: a case was defined as a person hospitalized for SAH in the period 1998-2006, and ten randomly chosen controls were matched to each case on age, gender, and calendar date. During the study period, 1,004 incident cases of SAH were identified, and current use of statins did not significantly decrease the risk of SAH (OR 0.77, 95% CI 0.55-1.07). The odds ratio for recent withdrawal compared to nonusers was 1.62 (95% CI 0.96-2.73). Compared to current use, recent withdrawal was associated with an increased risk of SAH (OR 2.34, 95% CI 1.35-4.05). Interaction analysis showed that the effect of statin withdrawal was highest in patients who had also recently stopped antihypertensive drugs (OR 6.77, 95% CI 2.10-21.8). The authors concluded that statin withdrawal increased the risk of SAH by a factor 2, even more in patients who had also recently stopped their antihypertensive treatment.

In a retrospective analysis of the relationship between compliance and treatment effect in 1,677 patients (after a successful first percutaneous coronary intervention) enrolled in LIPS (Lescol Intervention Prevention Study: 844 in the fluvastatin group and 833 in the placebo group), Lesaffre et al. [36] showed that discontinuing fluvastatin without switching to another lipid-lowering medication increased the risk of major adverse cardiac events (MACE) compared with that of patients who stayed on fluvastatin (RR 2.27, 95% CI 1.60-3.23, $P < 0.001$) and the increase in the risk of MACE was greater than that associated with discontinuing placebo ($P = 0.032$).

Aiming to assess the impact of discontinued statin therapy on clinical outcome in patients discharged after an acute ischemic stroke, Colivicchi et al. [37] followed for twelve months 631 consecutive stroke survivors without clinical evidence of coronary heart disease. Within 12 months from discharge, 246 patients (38.9%) discontinued statin therapy; the mean time from discharge to statin discontinuation was 48.6 ± 54.9 days (median time 30 days, interquartile range 18-55 days). During follow-up, 116 patients died (1-year probability of death 0.18, 95% CI 0.15-0.21). Multivariate analysis demonstrated that after adjustment for all confounders and interactions, statin therapy discontinuation (hazard ratio 2.78, 95% CI 1.96-3.72, $P = 0.003$) was an independent predictor of all-cause 1-year mortality. The authors concluded that a large number of patients discontinue their use of statins early after acute stroke. Moreover, patients discontinuing statins have a significantly increased mortality during the first year after the acute cerebrovascular event.

In a controlled randomized study, Blanco et al. [38] investigated the influence of statin pretreatment and its withdrawal on the outcome of acute ischemic stroke patients: from 215 patients admitted within 24 hours of a hemispheric ischemic stroke, 89 patients on chronic statin treatment were randomly assigned either to statin withdrawal for the first 3 days after admission (n = 46) or to immediately receive atorvastatin 20 mg/day (n = 43). The primary outcome event was death or dependency [modified Rankin Scale (mRS) score > 2] at 3 months. Early neurologic deterioration (END) and infarct volume at days 4 to 7 were secondary outcome variables. In a secondary analysis, outcome variables were compared with the nonrandomized patients without previous statin therapy (n = 126). Patients with statin withdrawal showed a higher frequency of mRS score > 2 at the end of follow-up (60.0% vs 39.0%, $P = 0.043$), END (65.2% vs 20.9%, $P < 0.0001$), and greater infarct volume (74 vs 26 mL, $P = 0.002$) compared with the non-statin-withdrawal group. Statin withdrawal was associated with a 4.66-fold increase in the risk of death or dependency, a 8.67-fold increase in the risk of END, and an increase in mean infarct volume of 37.63 mL (SE 10.01, $P < 0.001$) after adjusting for age and baseline stroke severity. Compared with patients without previous treatment with statins, statin withdrawal was associated with a 19.01-fold increase in the risk of END and an increase in mean infarct volume of 43.51 mL (SE 21.91; $P = 0.048$). The authors concluded that statin withdrawal is associated with increased risk of death or dependency at 90 days.

Chen et al. [20] investigated the effects after withdrawal of simvastatin on brachial artery endothelial function in 30 patients with established CAD compared to 20 healthy subjects as control group. Endothelial dependent flow-mediated vasodilation (FMD) was assessed in

the brachial artery using high-resolution ultrasound at baseline, 4 weeks during simvastatin treatment, and 1 week after termination of therapy. A significant decreased of FMD (-59.3%) was observed in patients after discontinuation of simvastatin in 1 week, and furthermore, the FMD was even lower than the baseline levels (4.6% vs 5.6%, $P < 0.05$). In healthy subjects, abrupt discontinuation of therapy caused a rapid and significant decrease in FMD from 10.6% to 5.2% at day 1, but it returned to baseline levels within 1 week.

Discussion

Despite the numerous studies that demonstrate the primary vasculoprotective action of statins (pleiotropic effects), recent scientific evidence suggests that discontinuation of treatment results in a rapid (< 7 days) return to endothelial dysfunction and amplification of the oxidative and inflammatory processes (rebound effects), increasing morbidity and mortality in patients with coronary artery and cerebrovascular diseases.

Experimental studies have described the physiological and molecular mechanisms involved in "statin withdrawal syndrome", expanding the knowledge of the spectrum of action of this "vital reaction":

(i) *increase of markers of cholesterol biosynthesis:* decrease of 12.5-fold in HMG-CoA reductase [17], and increase in ML synthesis baseline(1.4-fold) [7], oxidized-LDL [28], LDL-C (18-30%) [18,20,28], urinary concentrations of mevalonic acid [18] and soluble CD40 ligand [19];

(ii) *worsening of endothelial function:* in mice, decrease in NO production (90%) [21], downregulation of endothelial nitric oxide synthase (eNOS) in aorta and brain (2.7 to 5-fold) [22], and increase of RhoA GTPase in cellular membrane (4-fold) [22], in human, decrease in NO production (decrease of 90% in eNOS mRNA expression in human umbilical vein endothelial cells) [20] and in intracellular citrullin production (iCit) [28];

(iii) *increase of inflammation and oxidative stress:* increase in the level of C-reactive protein (0.8 to 2.5-fold) [24-27], in IL-6 [25] and in markers of oxidative stress (phenolic antioxidants FRAP and TBARS) [26];

(iv) *stimulation of thrombogenic response:* increase in P-selectin expression and platelet aggregation [28].

As I suggested with antidepressants [9], plasma concentrations of cholesterol profile did not increase above pretreatment levels after statin discontinuation [18-20], probably, because the time of observation was small (< 7 days).

In a general analysis, the cited observational studies [30-35] showed that statins withdrawal resulted in an increased risk of mortality (secondary to fatal vascular events) when compared with the maintenance (2.3 to 7.5-fold) and the absence (1.25 to 1.69-fold) of

treatment. The interventional studies showed that the suspension of statins led to a significantly increased risk of mortality in relation to maintenance treatment (4.66-fold) [38], and a significantly increased risk of fatal vascular events regarding the maintenance of treatment (2.27 to 8.67-fold) [36,38], the absence of treatment (19.01-fold) [38] and the placebo [36]. Statin therapy discontinuation was also considered an independent predictor of all-cause 1-year mortality [37].

For their therapeutic primary action (lipid-lowering effect cholesterol and vasculoprotective effect), statins represent a class of drugs with greater consumption in the present. In 2002, Pfizer Laboratory survey estimated that 44 million people worldwide consume atorvastatin, surpassing 100 million users when added to other statins (simvastatin, pravastatin, lovastatin, fluvastatin) [39]. In 2007, it was estimated that 145 million people using atorvastatin, while all statins were consumed by 250 million people [40].

In view of the need for continuous and prolonged use of statins (> 1 year) to achieving the desired vasculoprotetor effects, studies have showed that approximately 50% of patients discontinued medication within 6 months of starting therapy [41-42], predisposing, according to estimates cited, 125 million of users to the ocurrence of automatic secondary action of the organism.

In his idiosyncratic aspect, this withdrawal syndrome affects a small portion of the population (< 5%), but may affect 125 to 625 thousand people considering their prevalence around 0.1 to 0.5%, index described for the long acting agonists (LABA) and the selective serotonin reuptake inhibitors antidepressants (SSRIs), respectively. [6-9]

The recent recommendation of the indiscriminate use of statins in primary and secondary prevention of vascular events, including healthy individuals [43-44], tends to make this undesirable paradoxical reaction in a problem of great impact to public health, if users are not warned about the risks of abrupt discontinuation of treatment [45].

Again, the modern scientific evidence confirming Hahnemann's postulates and the principle of similitude employed in the homeopathic treatment.

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Gastric acid suppressing drugs, rebound acid hypersecretion and similitude[8]

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Abstract

Using the homeostatic reaction of the organism as a therapeutic method, Samuel Hahnemann proposed the treatment by similitude, administering to sick individuals medicines that caused similar symptoms to the natural disease. Based on experimental observations he stipulated the universal mechanism of action of drugs on the human health (primary action of the drug, followed by the secondary and opposite action of the organism), inaugurating the homeopathic pharmacology, and alerting about the harmful consequences that the palliative medicines could cause in susceptible individuals. These iatrogenic events can be observed currently after the withdrawal of numerous modern enantiopathic drugs, according to the study of the rebound effect or paradoxical reaction of the organism. In accordance with other antagonistic drugs studied in the past, we described in this review the scientific evidence that demonstrate the rebound acid hypersecretion after withdrawal of gastric acid suppressing drugs, confirming Hahnemann's postulates and basing the homeopathic method of treatment of diseases.

Introduction

After glimpsing the principle of "like cures like", Samuel Hahnemann sought for confirmation using the scientific method of analogy and enumeration by studying the clinical reports made by previous doctors, where he could find countless references that eventually led him to raise the principle of similitude to the level of a "natural law" as well as supported his use of inductive logic: *for a substance to heal definite symptoms in ill human beings it must elicit similar symptoms upon healthy experimental subjects.*

In the study that inaugurates the homeopathy *(Essay on a new principle for ascertaining the curative powers of drugs, 1796)* [1], Hahnemann systematizes the principle of similitude, describing the pharmacological properties of a several drugs commonly used, which had a direct primary action of causing organic disturbances in large doses, and the indirect secondary action of cure same disorders in moderate doses:

> "[…] We should endeavor to find out if the *millefoil (achillea millefolium)* cannot itself produce hemorrhages in *large* doses, as it is so efficacious in moderate doses in chronic hemorrhages. […] The *bear's berry (arbutus uva ursi)* has actually, without possessing any acridity perceptible to the senses, not infrequently increased the difficulty of passing water,

[8] Teixeira MZ. Rebound acid hypersecretion after withdrawal of gastric acid suppressing drugs: new evidence of similitude. *Homeopathy*. 2011; 100(3-4). Available at: https://doi.org/10.1016/j.homp.2011.05.003

> and the involuntary flow of urine, by some power peculiar to itself; thereby showing that it has a tendency to produce such affections, and hence, as experience also testifies, it is capable of curing similar disorders in a permanent manner. […] The *agaric (agaricus muscarius)* produces, as far as I can ascertain, a furious and drunken mania, exaltation of the strength, trembling and convulsions in its primary direct action; and weariness, sleep, in its secondary action. It has therefore been employed with benefit in epilepsy (caused by fright), combined with trembling. It will remove mental affections and possession, similar to those it causes. Its direct action lasts from twelve to sixteen hours […]". [1]

In the "Introduction" of the *Organon of homeopathic medicine* [2], Hahnemann alludes to hundreds of homeopathic healings involuntarily supplied by doctors of the "Old School", and thus grounds his initial observations on the principle of similitude on 247 bibliographic references:

> "[…] If *F. Hoffman* praises the efficacy of *millefoil* in various cases of *hemorrhage;* if *G. E. Stahl, Buchwalk* and *Loseke* have found this plan useful in excessive hemorrhoidal flux; if *Quarin* and the editors of the *Bresslauer Sammlungen* speak of the cure it has effected of hemoptysis; and finally, if *Thomasius* has used it successfully in uterine hemorrhage; these cures are evidently owing to the power possessed by the plant, of exciting of itself *hemorrhage* and *hematuria,* as observed by *G. Hoffman,* and more especially of producing *epistaxis* as confirmed by *Boecler*. *Scovolo* among many others, cured a case where the urinary discharge was purulent, by *arbutus uva ursi;* which never could have been performed if this plant had not the property of exciting *heat in the urinary passage with discharge of a mucous urine,* as seen by *Sauvages.* […] The hurtful effects which some writers (among others *Georgi*) ascribe to the use of the *agaricus muscarius*, by the inhabitants of Kamtschatka, and which consist of *tremors, convulsions,* and *epilepsy,* became a salutary remedy in the hands of *C. G. Whistling,* who used this mushroom with success in cases of convulsions accompanied with tremor; likewise in those of *J. C. Bernhardt,* who used it with success in a species of epilepsy […]". [2]

In paragraphs 56 to 62 of *Organon of medicine* [3], Hahnemann describes the enantiopathic (antipathetic, palliative or antagonistic) method of treatment, mentioning a large number of drugs of his time that were used according to the primary palliative effect to the disturbed symptom, reporting that "after such short antipathic amelioration, aggravation follows *in every case without exception*".

Observing the alterations that the drugs cause in the health state, during short and long time, Hahnemann describes the *physiological mechanism of drug action* through an immediate "primary action" of the drug and of a late "secondary action or counter-action" of the organism:

> "Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed *primary action.* […] To its action our vital force endeavours to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of *secondary action* or *counter-action".* (*Organon,* paragraph 63) [3]

He mentions several examples of the primary action of the medicines in our organism and the consequent reaction of the vital force (secondary action), which acts in an instinctive

way in a sense to preserve the homeostasis or the balance of the internal environment ("life-preserving power"), producing intense and opposite symptoms to the alteration initially induced:

> "[...] Excessive vivacity follows the use of strong coffee (primary action), but sluggishness and drowsiness remain for a long time afterwards (reaction, secondary action), if this be not always again removed for a short time by imbibing fresh supplies of coffee (palliative). After the profound stupefied sleep caused by opium (primary action), the following night will be all the more sleepless (reaction, secondary action). After the constipation produced by opium (primary action), diarrhea ensues (secondary action); and after purgation with medicines that irritate the bowels, constipation of several days' duration ensues (secondary action). And in like manner it always happens, after the primary action of a medicine that produces in large doses a great change in the health of a healthy person, that its exact opposite, when, as has been observed, there is actually such a thing, is produced in the secondary action by our vital force". (*Organon,* paragraph 65) [3]

It guides us to the reflection about the adverse events of the antagonistic employment of drugs in the past and currently, Hahnemann uses the *modus tollens* of the *deductive Aristotelian logic* ("null hypothesis" of modern statistic) as a way to evidence the validity of the opposite procedure, the homeopathic use of medicines according to similarity of symptoms (similitude principle):

> "Had physicians been capable of reflecting on the sad results of the antagonistic employment of medicines, they had long since discovered the grand truth, *that the true radical healing art must be found in the exact opposite of such an antipathetic treatment of the symptoms of disease;* they would have become convinced, that as a medicinal action antagonistic to the symptoms of the disease is followed by only transient relief, and after that is passed, by invariable aggravation, the converse of that procedure, *the homeopathic employment of medicines* according to similarity of symptoms, must effect a permanent and perfect cure […]". (*Organon,* paragraph 61) [3]

Observing the iatrogenic events caused by method of treatment by contraries, Hahnemann proposes a therapeutic through the similar, stimulating the body itself to react against its symptoms (secondary action or vital reaction), administering to the patients substances that awake similar symptoms in the healthy experimenters. In the beginning of the homeopathy, he applied the similitude principle with ponderal doses of the medicinal substances [4,5], using the infinitesimal doses in subsequent phase of his clinical practice, in view of the secondary action (homeostatic reaction) to be wakened with ponderal or infinitesimal doses:

> "In those older prescriptions of the often dangerous effects of medicines ingested in excessively large doses we notice certain states that were produced, not at the commencement, but towards the termination of these sad events, and which were of an exactly opposite nature to those that first appeared. These symptoms, the very reverse of the primary action or proper action of the medicines on the vital force are the reaction of the vital force of the organism, its secondary action, of which, however, there is seldom or hardly ever the least trace from experiments with moderate doses on healthy bodies, and from small doses none whatever. In the homeopathic curative operation the living organism reacts from these only so much as is requisite to raise the health again to the normal healthy state". (*Organon,* paragraph 112) [3]

In the study of the *rebound effect (paradoxical reaction)* observed after discontinuation of numerous modern palliative drugs, designations used by the pharmacology and physiology to explain the *secondary action* or *vital reaction* of the homeopathic model, we found the scientific basis to the principle of similitude. [6-12]

According to the modern pharmacological concepts, the paradoxical or rebound symptoms present intensity sometimes superior to the primarily suppressed symptons, expressing itself in variable period (hours to weeks) after the interruption or discontinuation of the medicine and also with a variable duration (hours to weeks), according to the individual susceptibility (idiosyncrasy).

Similarly to others enantiopathic drugs studied in the past [6-12], we will describe in this review the scientific evidence that demonstrate the *rebound acid hypersecretion (secondary action* or *vital reaction of the organism)* after the withdrawal of *gastric acid suppressing drugs (proton pump inhibitors),* confirming Hahnemann's postulates and basing the homeopathic method of treatment of diseases.

Material and Methods

Aiming to expand the understanding of the similitude principle according to modern pharmacology, we reviewed the literature using the PubMed database and the keywords "proton pump inhibitor" and "rebound", selecting the most relevant papers and discussing the scientific evidence in conformity with the homeopathic premises.

Results

Physiology of gastric acid secretion [13-15]

With its secretion stimulated by acetylcholine (vagal nerves), gastrin and histamine, the main functions of gastric acid are preventing bacterial overgrowth and enteric infections, besides facilitating the digestion of proteins and the absorption of iron, calcium, and vitamin B_{12}. Opposing these benefits, high levels of acid secretion affect the mucosal defense mechanisms causing acid-peptic disorders. To prevent such damage, gastric acid secretion is regulated at four crucial pathways, showing a complex homeostatic autoregulation: (1) the *parietal cells* of the oxyntic mucosa (corpus and fundus of the stomach), which produce *hydrochloric acid;* (2) the *enterochromaffin-like (ECL) cells* of the oxyntic mucosa, which produce *histamine*, the main paracrine stimulant of acid secretion; (3) the *G cells* of the pyloric mucosa (antrum), which produce *gastrin,* the main hormonal stimulant of acid secretion; and (4) the *D cells* of oxyntic and pyloric mucosa, which produce *somatostatin,* the main paracrine inhibitor of acid secretion. Released from postganglionic neurons of the enteric nervous system, acetylcholine stimulates acid secretion by activating parietal cells; however, vagal stimulation is inferior to gastrin or histamine in stimulating acid secretion.

Parietal cells contain abundant intracellular tubulovesicles that sequester H^+K^+-adenosine triphosphatase (H^+K^+-ATPase), the proton pump, which when stimulated fuse with apical membrane activating the H^+K^+-ATPase, enabling hydrochloric acid. Proton pump inhibitors (PPIs) interrupt this process. Histamine is stored in secretory vesicles of ECL cells and is released upon stimulation by gastrin, diffusing to neighboring parietal cells and stimulates acid secretion by binding to H_2 receptors expressed in their surface. Gastrin is the principal mediator of meal-stimulated acid secretion and is critical to the growth of parietal and ECL cells mass of gastric mucosal. During the interdigestive phase, a feedback mechanism involving acid-induced somatostatin secretion serves to attenuate acid secretion: somatostatin inhibits acid secretion by acting directly on parietal cells and indirectly by inhibiting histamine secretion from ECL cells and gastrin secretion from G cells. When acid concentration (secretion) is diminished (antacids, antisecretory drugs, or atrophic gastritis), somatostatin secretion is inhibited, and thus gastrin secretion is stimulated, resulting in rebound hypergastrinemia. This hypergastrinemia is the cause of rebound acid hypersecretion after discontinuation of gastric acid suppressing drugs.

Pathophysiology of rebound acid hypersecretion [16-18]

According to Food and Drugs Administration (FDA, 2000) [19], rebound acid hypersecretion is defined as an increase in gastric acid secretion (basal and/or stimulated) above pretreatment levels following discontinuation of antisecretory therapy. Rebound was initially reported in studies following the use of histamine H_2-receptor antagonists and was thought to be due to increased serum gastrin and/or up regulation of the H_2-receptors. Elevated gastrin levels or hypergastrinemia is a secondary effect that occurs during chronic inhibition of gastric acid secretion, such as with long-term antisecretory therapy. In man, gastrin is the primary regulator of gastric acid secretion, which is mediated by histamine released by the enterochromaffin-like (ECL) cells. Increased plasma gastrin stimulates and up regulates ECL cells to produce and release more histamine to stimulate the parietal cells. In addition, an increase in parietal cell mass may occur with the chronic use of antisecretory agents, and this may be an additional mechanism for increased acid secretion that can occur after discontinuation of therapy. Another possible cause of rebound acid secretion is increased sensitivity to histamine.

Rebound acid hypersecretion after antacids

Although not an antisecretory therapy, the neutralization of gastric acidity by antacids can also cause the rebound phenomenon after discontinuation of treatment. To measure the rebound acid hypersecretion after antacids (aluminum/magnesium hydroxide and calcium carbonate) cited in previous reviews [20,21], clinical trials confirmed this hypothesis observing rebound phenomenon in healthy volunteers after one hour of standard dose of antacids [22,23]. Following similar methodology, the studies that evaluated the rebound acidity within 2-3 hours after suspension did not observe the manifestation of the phenomenon [24,25]. As we shall see, the rebound effect of any drug is manifested in a specific time-point after cessation of treatment, usually related to half-life of drugs and/or

normalization of physiological changes. With antacids, it occurs within 1 hour after single dose.

Rebound acid hypersecretion after H_2-receptor antagonists

Similarly to other competitive antagonists that act on other physiological systems (beta-blockers in the heart, for example), the H_2-receptor antagonists cause rebound hyperfunction (acid hypersecretion) after withdrawal of the drugs. Although the exact mechanism remains unclear, the main hypothesis are that the rebound phenomenon may be caused by an increased responsiveness (up regulation) of the H_2-receptor to histamine stimulation after chronic, competitive inhibition, and an impairment of the inhibitory arm of acid secretion (oxyntic mucosal inhibitory control). [26-29]

For any drug, time-point after drug withdrawal and appropriate primary or direct stimulus are of vital importance in the observation of the rebound effect, and studies that have despised these aspects have not described the occurrence of the phenomenon [30-33]. Taking these factors into account, Frislid et al. [34] demonstrated that there was a significant rebound acid hypersecretion to a meal 60-64 hours after a one month course of ranitidine, despite the continuing presence of trace amounts of ranitidine at this time-point. This phenomenon was also observed studying nocturnal acid secretion 2-3 days after 4 weeks of nizatidine, ranitidine or cimetidine [35-38]. Another study with ranitidine showed that acid hypersecretion occurred 60 hours after cessation of treatment, returning to baseline after 10 days [29]. Studying asymptomatic healthy volunteers, Smith et al. [39] demonstrated in a placebo-controlled trial that the median duration of rebound dyspeptic symptoms was 2 days, with symptom severity being maximal on the second day after completion of the ranitidine tablets. However, as noted in the earlier studies at 3-11 days [31-33], Kummer et al. [38] not observed significant alteration in maximal acid secretion 3 days after treatment. Thus, the rebound acid hypersecretion after H_2-receptor antagonists occurred within 2-3 days after 4 weeks of therapy, lasting 10 days.

Tolerance or tachyphylaxis to H_2-receptor antagonists

As for rebound acid hypersecretion, there is a well-established tolerance/tachyphylaxis phenomenon with the chronic use of H_2-receptor antagonists, manifesting a loss of efficacy in the acid secretion suppression [40-45]. As in the rebound effect, the magnitude of tolerance does not change with doses or treatment time [46,47], in the same way that similar mechanisms explain both phenomena: an enhanced responsiveness of the H_2-receptor to histamine, or an impairment of the neuro-hormonal control of acid secretion, or the hypergastrinemia are possible explanations for tolerance. As main clinical relevance, H_2-receptor antagonists tolerance can cause ulcer relapse [48-51], and complications in the healing of esophagitis [52,53].

Rebound acid hypersecretion after proton pump inhibitors

As previously mentioned, proton pump inhibitors (PPIs) block the final step in acid secretion, resulting in a profound and persisting gastric hypoacidity that diminish antral D-

cell release of somatostatin, with concomitant increase G-cell release of gastrin and hypergastrinemia [54,55]. This rebound hypergastrinemia results in a continuous stimulation of ECL cells and consequently hyperhistaminemia, which does not produce increase in gastric acid secretion since the proton pump is effectively blocked [56]. Moreover, the stimulation of ECL cell proliferation induces an increase in the ECL cell mass, which will persist longer than the effect of the PPI when the drug is discontinued. As in any rebound phenomenon, rebound acid hypersecretion is evident at a certain time-point after treatment, in view of the half-life of drugs and the regeneration period (half-life) of physiological changes. Studies that disrespected these conditions did not demonstrate the rebound acid [57]. Rebound acid hypersecretion after a sufficient period of PPI treatment will therefore occur from the second week (duration of proton-pump inhibition or PPI's half-life) until normalization of the ECL cell mass (the half-life of the ECL cell is probably about 2 months), i.e., 2-3 months after stopping treatment. This phenomenon is prolonged, lasting to at least two months after a two months treatment course, persisting significantly elevated submaximal and maximal acid hypersecretion. [58-64]

Paradoxically, although there is a tendency towards rebound also in patients *H. pilory*-positive, rebound acid hypersecretion after PPI was more prolonged and pronounced in patients not infected, despite *H. pilory*-positive developing more intense hypergastrinemia than *H. pilory*-negative during PPI therapy [61,62,65]. The difference between *H. pylori*-negative and -positive patients most likely is due to different pretreatment gastrin values moving the post-treatment gastrin values to parts of the concentration-response curve with a different slope with respect to the trophic effect on the ECL cells [66]. Moreover, in patients with *H. pylori*-induced gastritis not only in the antral but also in the oxyntic mucosa: atrophic gastritis will reduce the capacity to secrete acid (interleukin-1 is a very potent inhibitor of acid secretion) and therefore the magnitude and consequences of rebound acid hypersecretion. It should also be recalled that PPI treatment leads to increased oxyntic gastritis in *H. pylori*-positive individuals. [67-72]

In summary, the difference between *H. pylori*-negative and -positive groups with regard to rebound hypersecretion after PPI treatment may be due to persistence of this increased oxyntic gastritis, which can mask any rebound phenomena in the infect subjects by enhanced elaboration of inflammatory mediators in the acid-secreting mucosa. However, the vanishing of *H. pylori* infections (antibiotic therapy) makes individuals more prone to development clinical important rebound acid hypersecretion after PPI treatment. [73,74]

Tolerance to proton pump inhibitors

Similar to the H_2-receptor antagonists, rebound acid hypersecretion after PPI provides a theoretical basis for the possible development of tolerance to these drugs with chronic therapy, although there are few studies on the effects of long-term use. [75]

Other consequences of rebound hypergastrinemia [17,18,76]

Hypergastrinemia and neoplasia

Gastrin has trophic effects on many tissues and stimulates a number of tumor cell lines in culture, including colon cancer cells. Although there have been suggestions that hypergastrinemia is associated with an increase risk of colon cancer, two population-based case-control studies conducted in United Kingdom (1987-2002) and Denmark (1989-2005) found no evidence of such increase in patients using PPIs. [77,78]

Moreover, there is reason to believe that patients with reflux disease will be more affected during the rebound acid hypersecretion period after a course of PPI treatment than before. The increase in gastroesophageal reflux disease seen during the last decades may be due to worsening of reflux symptoms caused by low-threshold PPI use to treat reflux symptoms. For the same reason, there is a possible effect of hypergastrinemia on the progression of Barrett's esophagus to cancer, in view of the marked rise in the incidence of adenocarcinoma at the cardioesophageal junction over the past two decades, as acid-suppressive therapy for gastroesophageal reflux disease has greatly increased. [79-81]

Experimental studies with animal models showed that initial induction of hypergastrinemia causing acid hypersecretion was followed by decreased acid secretion and atrophy, with eventual development of gastric cancer [82-84]. A population-based cohort study in Denmark (1990-2003) showed increased incidence for gastric cancer among PPI users with the largest number of prescriptions or the longest follow-up compared with H_2-receptor antagonist users or non-users [85]. These observations suggested that hypergastrinemia may be a risk factor for development of gastric cancer, which one can suggest might also be relevant to the proton pump inhibitor situation.

Hypergastrinemia and carcinoid tumors

Carcinoid tumors have long been recognized as a consequence of the hypergastrinemia of the Zollinger-Ellison syndrome and atrophic gastritis. Rats exposed to long-term high doses of omeprazole developed enterochromaffin-like cell hyperplasia and gastric carcinoids [86]. It was probable that proton pump inhibitor inducing hypergastrinemia was leading to the enterochromaffin-like cell hyperplasia and carcinoid tumors, since similar results could be obtained with long-term administration of gastrin [87]. However, there are no studies that show similar results in humans.

Analogous to the foregoing, the increased incidence of gastric carcinoids in last three decades (400% in men and 900% in women) is also associated with the widespread marketing of PPIs [88-90]. According to McCarthy [76], the scientific basis for expecting long-term PPI use to cause carcinoid tumors is quite strong and merits serious attention. Hypergastrinemia may also stimulate carcinoid development or growth in other sites.

Clinical evidences of rebound acid hypersecretion after PPI withdrawal

Extending a previous study [61] in order to estimate the duration of hypersecretion and to elucidate the role of ECL cell in rebound acid hypersecretion, Fossmark et al. [64] studied patients waiting for anti-reflux surgery who discontinued the use a PPI daily > 1 year, measuring gastrin, serum chromogranin-A (CgA) and pentagastrin stimulated acid output

before and at 4, 8, 16 and 26 weeks postoperatively. Oxyntic mucosal biopsies were collected before and 26 weeks after operation for counting of histidine decarboxylase (HDC) immunoreactive cells. Pentagastrin stimulated acid secretion was higher at 4 and 8 weeks than at 26 weeks after surgery while gastrin and CgA were significantly reduced at 4 and 8 weeks. The number of HDC immunoreactive cells was reduced by 60% at 26 weeks postoperative. These results suggest that rebound acid hypersecretion lasts more than 8 weeks, but less than 26 weeks after long-term PPI, and not only the parietal cell mass, but also ECL cell mass and activity are involved in the mechanism of acid hypersecretion.

To evaluate the occurrence and the clinical relevance of rebound acid hypersecretion after discontinuation of PPIs, Hunfeld et al. [91] to perform a systematic review including eight studies (sample size 6-32). Five studies (including four randomized studies) did not find any evidence for rebound acid hypersecretion after PPI withdrawal. Of the remaining three uncontrolled trials, two studies suggested that rebound acid hypersecretion may occur in *H. pylori*-negative patients after 8 weeks of PPIs. The authors concluded that there is no strong evidence for a clinically relevant increased acid production after withdrawal of PPI therapy. Criticizing the studies included in this systematic review, which despised a sufficient duration of PPI therapy to develop significant ECL cell hyperplasia and subsequent acid rebound, Fossmark and Waldum [92] reiterated that it is impossible to evaluate rebound acid hypersecretion after one single dose of PPI, nor after 25 days use, although the studies had a randomized design: "these five studies merely show that PPI must be used more than 1-25 days to induce rebound acid hypersecretion".

In a double-blind, placebo-controlled trial properly designed, 120 healthy volunteers were randomized to 12 weeks of placebo or 8 weeks of esomeprazole 40 mg/day followed by 4 weeks with placebo. The Gastrointestinal Symptom Rating Scale (GSRS) was filled out weekly, and a score of > 2 on 1 of the questions regarding heartburn, acid regurgitation, or dyspepsia was defined as a clinically relevant acid-related symptoms. As indirect measures of gastric acid secretion and ECL cell mass, plasma levels of gastrin (P-gastrin) and serum levels of chromogranin-A (P-CgA) were measured at weeks 0, 4, 8 and 12. There were no significant differences between groups in GSRS scores during weeks 0-9. GSRS scores for acid-related symptoms were significantly higher in the PPI group at week 10 (1.4 ± 1.4 vs. 1.2 ± 0.9; $P = 0.023$), week 11 (1.4 ± 1.4 vs. 1.2 ± 0.9; $P = 0.009$), and week 12 (1.3 ± 1.2 vs. 1.0 ± 0.3; $P = 0.001$). Forty-four percent (26/59) of verum group reported ≥ 1 relevant, acid-related symptoms in weeks 9-12 compared with 15% (9/59; $P < 0.001$) in the placebo group. The proportion reporting dyspepsia, heartburn, or acid regurgitation in the PPI group was 22% (13/59) at week 10, 22% (13/59) at week 11, and 21% (12/58) at week 12. Corresponding figures in the placebo group were 7% at week 10 ($P = 0.034$), 5% at week 11 ($P = 0.013$), and 2% at week 12 ($P = 0.001$). In the PPI group, P-gastrin was significantly correlated with the GSRS score at week 8 and 12. Compared to placebo group, P-CgA was significantly higher and above the normal range in the PPI group at weeks 8 and 12, reflecting proliferative changes of the ECL cells and sustained increased acid secretory capacity. Authors conclude that PPI therapy for 8 weeks induces rebound acid hypersecretion in a significant proportion of asymptomatic subjects after withdrawal, and this phenomenon is equally relevant in patients treated long term with PPIs. [93]

In similar study, 48 healthy *H. pylori*-negative volunteers were randomized in a double-blinded manner to treatment with either pantoprazole (40 mg/day) or placebo for 28 days. Dyspeptic symptoms were registered daily using the Glasgow Dyspepsia Score (GDS) 2 weeks before, during, and 6 weeks after treatment. Plasma levels of gastrin and serum levels of CgA were measured before, during, and after treatment. No significant differences between the symptom severity scores of the two groups were shown during the treatment period. During the first week after discontinuation of treatment, the pantoprazole group had a mean symptom score of 5.7 ± 11.7 vs. 0.74 ± 2.6 in the placebo group ($P < 0.01$). In the verum group, a total of 11 out of 25 (44%) individuals developed dyspepsia compared with 2 out 23 (9%) in the placebo group. During the second week, the verum group had a mean symptom score of 1.6 ± 3.4 vs. 0.0 ± 0.0 in the placebo group ($P < 0.05$); a total of 6 out 25 (24%) participants developed dyspepsia in verum group compared with none in the placebo group ($P = 0.003$). During the remaining 4 weeks, the symptom score did not significantly differ between the groups. In the verum group, the median duration of rebound symptoms was 4 days, and the onset of symptoms was most commonly observed at days 5 and 6 after cessation of therapy. During the first week after treatment withdrawal, symptom scores correlated with basal ($P < 0.01$) and meal-stimulated ($P < 0.01$) gastrin levels at the end of treatment suggesting that these symptoms are due to acid rebound hypersecretion and seem to be related to the degree of acid inhibition. Authors concluded that a 4-week course of pantoprazole seems to induce acid rebound hypersecretion in previously asymptomatic healthy *H. pylori*-negative individuals. [94]

Indirectly assessing whether the rebound acid hypersecretion also occurs in symptomatically treated patients, studies described the recurrence of symptoms in approximately 70% of long-term PPI users after discontinuation of therapy. [95,96]

Discussion

In the same way that we did with other classes of drugs (anti-inflammatories, bronchodilators, antidepressants, statins, etc.) [8-12], in this study I brought evidences of the relationship between gastric acid suppressing drugs (proton pump inhibitors) withdrawal and rebound acid hypersecretion, with worsening of dyspeptic diseases.

Proton pump inhibitors are among the most frequently used medicines worldwide and are an important economic spending for health-care system in many countries, being prescribed for a wide variety of upper gastrointestinal symptoms on the basis that they might be acid induced and therefore may benefit from such treatment [97-101]. For instance, the total use of PPIs increased 7-fold from 1993 to 2007 in Denmark, with the use increased substantially from 20 to 33 defined daily doses per 1,000 individuals per day from 2003 to 2007. In 2006, approximately 7% of the Danish population was treated with a PPI. While the utilization of H_2-receptor antagonists declined 72% from 1995 to 2006 in Australia, the use of combined PPIs increased by 1318%. [102-105]

Although this liberal employment of PPIs has been recommended recently by many dyspepsia guidelines [106-108], it is well documented that these drugs are often inappropriately prescribed for minor symptoms and without clear indications, where the effects of acid-suppressive therapy is controversial [100,104,109-113]. As a result, a large proportion of patients now prescribed PPIs do not have acid-related symptoms and therefore have no true indications for such therapy. Studies also have shown that up to 33% of patients who initiate PPI treatment redeem repeated prescriptions without an obvious indication for maintenance therapy [100,114]. This empirical conduct may complicate PPIs discontinuation because of the development of rebound acid hypersecretion, leading to recurrence of symptoms of underlying acid-related disease (heartburn, acid regurgitation and dyspepsia) that might result in resumption of therapy. [95,96]

According to the initially cited Hahnemann's observations "on the sad results of the use of antagonistic employment of medicines", McColl and Gillen [115] say that "these drugs induce symptoms means that such liberal prescribing is likely to be creating the disease the drugs are designed to treat and causing patients with no previous need for such therapy to require intermittent or long-term treatment". They propose a series of changes in prescribing habits of PPIs, among them efforts to try to restrict PPI use to disorders likely to derive benefit, and obliged information to patients about rebound acid hypersecretion and its potential effects.

This authors' warning, signaling that *improper use of PPIs may cause similar diseases to those which are designed to treat,* endorses Hahnemann's alerts about the harmful effects of enantiophatic or palliative treatment, and indirectly corroborating the principle of "like cures like". Creating or exacerbating dyspeptic diseases, as well as leading to cancer, the indiscriminate use of PPIs may cause "another more serious disease or, frequently, incurability, even danger to life and death itself":

> "If these ill-effects are produced, as may very naturally be expected from the antipathic employment of medicines, the ordinary physician imagines he can get over the difficulty by giving, at each renewed aggravation, a stronger dose of the remedy, whereby an equally transient suppression1 is effected; and as there then is a still greater necessity for giving ever - increasing quantities of the palliative there ensues either another more serious disease or, frequently, incurability, even danger to life and death itself, but never a cure of a disease of considerable or of long standing". (*Organon,* paragraph 60) [3]

In accordance with the cited clinical studies, there is evidence that the acid rebound occurs within 1 hour after standard dose of antacids, 2 days after 4 weeks of H_2-receptor antagonists, and 1 or 2 weeks after 4 or 8 weeks of PPIs. The rebound phenomenon lasts for 10 days after 4 weeks of H_2-receptor antagonists, and 2 or 4 weeks after 4 or 8 weeks of PPIs. Around 40% of users of PPI reported rebound acid hypersecretion. The *American Hospital Formulary Service* described recurrence of peptic ulcers in 41% of patients after 1-4 weeks of discontinuing chronic therapy with cimetidine. Perforation of chronic peptic ulcers was also reported. [6,7,116]

In consequence of the complexity of the phenomenon, PPIs therapies longer expresses acid rebound later (2-3 months after withdrawal) consequently an increase in the ECL cell mass

and the corresponding longer period for its physiological normalization. In such cases, the rebound acid hypersecretion may also be more prolonged (2 months), causing major consequences.

Confirming the principle of similarity as "natural law", the continuing reports of increased iatrogenic events after withdrawal of palliative modern drugs demonstrates the importance of the rebound phenomenon in promoting deep alterations in the homeostatic balance. Using this rebound effect of curative form (homeopathic vital reaction), homeopathy stimulates the body to react against their own diseases.

Conclusion

The secondary action or vital reaction of the homeopathic model is based on studies about the rebound effect or paradoxical reaction of hundreds of modern drugs, utilised according to the contrary principle. The development of tolerance to a repeatedly administered drug to be the result of a same regulated adaptive process.

Despite the rebound effect becomes apparent in a small proportion of the individuals, in view of their idiosyncratic nature, these paradoxical events assume epidemiological importance when we consider the enormous current consumption of the enantiopathic drugs [9-12]. In the case of PPIs, the rebound effect assumes greater importance because they are used by a large portion of the population ("liberal employment") and the phenomenon being awakened in a large percentage of users (around 40%).

Analogously to traditional homeopathic medicines, the rebound effect of modern drugs can be used for therapeutic purposes, namely to stimulate homeostatic healing reactions provided they are prescribed according to the principle of similitude of symptoms as it was described in previous studies. [6,7,117,118]

Following the logical reasoning of Hahnemann in this proposal, we will incorporate 1,250 new substances to Homeopathic Materia Medica, broadening the spectrum of action of homeopathic therapy and the scientific basis of "like cures like" principle [119]. Requesting the cooperation of homeopathic professionals in the expansion, improvement and application of these proposal, we will soon be available online the project entitled *"New Homeopathic Medicines: use of modern drugs according to principle of similitude"*, divided into three modules: (1) *Scientific Basis of the Principle of Similitude in Modern Pharmacology;* (2) *Homeopathic Materia Medica of Modern Drugs;* and (3) *Homeopathic Repertory of Modern Drugs.* [120]

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Rebound effect of drugs: fatal risk of conventional treatment and pharmacological basis of homeopathic treatment[9,10,11]

[Reference: Teixeira MZ. Rebound effect of modern drugs: serious adverse event unknown by health professionals. *Rev Assoc Med Bras.* 2013; 59(6): 629-638. Available at: https://www.scielo.br/j/ramb/a/3StmPbRxwB4BzSSV8z6xtSN/?lang=en.]

Abstract

The homeopathic model applies the secondary action or vital reaction of the organism as a therapeutic method and thus prescribes treatment by similitude principle, which consists in administering to ill individuals substances that cause similar symptoms in healthy individuals. The vital, homeostatic or paradoxical reaction of the organism might be explained scientifically by means of the rebound effect of modern drugs, which might cause fatal iatrogenic events after discontinuation of antipathic (a term used in alternative medicine for palliative treatment, also known as enantiopathic) treatment. Although the rebound effect is studied by modern pharmacology, it is poorly communicated to and discussed among healthcare professionals, who are thus deprived of crucial information needed for the safe management of modern drugs. This article presents an up-to-date review on the rebound effect of modern drugs that grounds the homeopathic principle of healing and calls the attention of doctors to this type of adverse effect that is usually unnoticed. The rebound effect of modern palliative drugs, which was pointed out by Hahnemann more than two centuries ago, might cause fatal adverse events, which might be illustrated with the examples of acetylsalicylic acid, anti-inflammatory agents, bronchodilators, antidepressants, statins, proton-pump inhibitors, etc. Although the rebound effect is expressed by a small fraction of (susceptible) individuals and might be avoided by gradual tapering of antipathic drugs, it exhibits epidemiologic importance as a function of the massive use of such palliative drugs and lack of knowledge in its regard.

Introduction

The homeopathic method of treatment of diseases is based on four pillars: *principle of cure by similitude, proving of medicinal substances on healthy individuals, use of serially diluted and succussed (dynamized) medicines,* and *prescription of individualized medicines.* Although great importance was attributed to 'dynamized medicines' (ultra-high dilutions),

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which were introduced later to minimize the aggravation of symptoms, the first two pillars are the proper foundation of homeopathic epistemological model remaining to individualized medicine the essential condition for awakening the therapeutic response.

After his self-proving of *Cinchona officinalis*, Samuel Hahnemann sought to confirm the 'law of similarity' by means of the scientific methods of 'analogy' and 'enumeration' and the study of clinical reports performed by previous doctors. In those reports he was able to find countless references that eventually led him to raise the principle of similitude to the level of a 'natural law' and that supported his use of inductive logic: *for a substance to heal definite symptoms in ill individuals, it must cause similar symptoms in healthy individuals.*

Inaugurating homeopathy in 1796 with the publication of the *Essay on a new principle to ascertain the curative power of drugs* [1], Hahnemann described the *direct primary actions of drugs* and the consequent *indirect secondary action of the organism* to them, systematizing these biphasic pharmacological effects in dozens of palliative drugs used in his time. To illustrate with the example of *Agaricus muscarius:*

> *Direct primary action:* furious and drunken-like mania (combined with revengeful and audacious determination, disposition to make verses, prophecies, etc.), exaltation of strength, tremors and seizures; direct action lasts between 12 and 16 hours. *Indirect secondary action:* successfully used in epilepsy (caused by fear) combined with tremor; it heals mental affections and possession similar to those it causes.

In the introduction of the first edition of the *Organon of medicine* [2], Hahnemann described hundreds of "examples of homeopathic cures verified involuntary by doctors of the old school". Thus he was able to ground his earlier observations in regard to the principle of therapeutic similitude on 247 bibliographic references stemming from different authors. To continue with the example of *Agaricus muscarius:*

> "The hurtful effects which some writers (*Georgi*, among others) ascribe to the use of the *Agaricus muscarius*, by the inhabitants of Kamtschatka, and which consist of tremors, convulsions, and epilepsy, became a salutary remedy in the hands of *C. G. Whistling*, who used this mushroom with success in cases of convulsions accompanied with tremor; likewise in those of *J. C. Bernhardt*, who used it with success in a species of epilepsy".

In paragraphs 63 to 65 of the *Organon* [2], Hahnemann suggested a physiological explanation for this "natural law of healing", which based the principle of similitude on the *primary action of the drug* and the corresponding and opposite *secondary action* or *vital reaction of the organism:*

> "Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed *primary action.* [...]. To its action our vital force endeavors to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of *secondary action* or *counteraction*". (Organon, paragraph 63)

Hahnemann exemplified this 'universal' mechanism of action of medicines ('universal' pharmacodynamics), observed in the different changes of sensations and organic functions

(signals and symptoms), in the biphasic pharmacological effects of palliative (antipathic or enantiopathic) treatments used at that time:

> "[...] A hand bathed in hot water is at first much warmer than the other hand that has not been so treated (primary action); but when it is withdrawn from the hot water and again thoroughly dried, it becomes in a short time cold, and at length much colder than the other (secondary action). A person heated by violent exercise (primary action) is afterwards affected with chilliness and shivering (secondary action). To one who was yesterday heated by drinking much wine (primary action), today every breath of air feels too cold (counteraction of the organism, secondary action). An arm that has been kept long in very cold water is at first much paler and colder (primary action) than the other; but removed from the cold water and dried, it subsequently becomes not only warmer than the other, but even hot, red and inflamed (secondary action, reaction of the vital force). Excessive vivacity follows the use of strong coffee (primary action), but sluggishness and drowsiness remain for a long time afterwards (reaction, secondary action), if this be not always again removed for a short time by imbibing fresh supplies of coffee (palliative). After the profound stupefied sleep caused by opium (primary action), the following night will be all the more sleepless (reaction, secondary action). After the constipation produced by opium (primary action), diarrhea ensues (secondary action); and after purgation with medicines that irritate the bowels, constipation of several days' duration ensues (secondary action). And in like manner it always happens, after the primary action of a medicine that produces in large doses a great change in the health of a healthy person, that its exact opposite, when, as has been observed, there is actually such a thing, is produced in the secondary action by our vital force". (Organon, paragraph 65)

The homeopathic method of treatment employs this secondary action or vital reaction of the organism for therapeutic purposes by administering to ill individuals drugs that cause similar symptoms in healthy individuals (principle of similitude) to awake a healing reaction of the organism against the disease.

By emphasizing that such secondary action of the organism (opposed in character to the primary action of the drug) is observed "in each and every instance with no exceptions" with ponderable or infinitesimal doses in both healthy and ill individuals, Hahnemann raised the principle of similitude to the level of a 'natural law' (Organon, paragraphs 58, 61, 110-112):

> "In those older prescriptions of the often dangerous effects of medicines ingested in excessively large doses we notice certain states that were produced, not at the commencement, but towards the termination of these sad events, and which were of an exactly opposite nature to those that first appeared. These symptoms, the very reverse of the primary action (§ 63) or proper action of the medicines on the vital force are the reaction of the vital force of the organism, its secondary action (§ 62-67), of which, however, there is seldom or hardly ever the least trace from experiments with moderate doses on healthy bodies, and from small doses none whatever. In the homoeopathic curative operation the living organism reacts from these only so much as is requisite to raise the health again to the normal healthy state". (Organon, paragraph 112)

Upon alluding to the "sad results" of the indiscriminate palliative use of medicines (Organon, paragraphs 59-61), Hahnemann warns against the risk represented by this undesirable secondary action of the organism that may produce "more serious disease or

frequently even danger to life or death itself". Therefore, in addition to denying the efficacy of conventional or palliative treatment (principle of contraries), Hahnemann validates the homeopathic treatment (principle of similitude) through the Aristotelian syllogism or the *modus tollens* of classic deductive logic ('mode that affirms through negation', 'indirect proof' or 'null hypothesis' of modern biostatistics):

> "If these ill-effects are produced, as may very naturally be expected from the antipathic employment of medicines, the ordinary physician imagines he can get over the difficulty by giving, at each renewed aggravation, a stronger dose of the remedy, whereby an equally transient suppression is effected; and as there then is a still greater necessity for giving ever - increasing quantities of the palliative there ensues either another more serious disease or frequently even danger to life and death itself, but never a cure of a disease of considerable or of long standing". (Organon, paragraph 60)

In the terms of modern scientific reason and physio-pharmacological concepts, the *primary action* employed by Hahnemann corresponds to the *therapeutic, adverse* and *side effects* of conventional drugs. The *secondary action* or *vital reaction*, in turn, corresponds to the *rebound effect* or *paradoxical reaction of the organism,* which was observed after the discontinuation of several classes of drugs that act contrarily to the symptoms of diseases (conventional drugs, palliative, enantiopathic or antipathic).

Following in the footsteps of Hahnemann, beginning 1996 we have been studying the rebound effect of modern drugs with the intention to ground the homeopathic healing principle (principle of similitude or 'like cures like') on notions of experimental and clinical pharmacology [3-10]. To call the attention of the medical community to this type of adverse events that is frequently unnoticed, in the present updated review we address the main features of the rebound effect and the care needed when discontinuing conventional drugs to minimize these iatrogenic events, which might be fatal.

Material and methods

Aiming at broadening the understanding of the principle of similitude according to modern pharmacology, we reviewed the literature cited in Pub Med database using search terms 'rebound', 'withdrawal', 'acetylsalicylic acid', 'anti-inflammatory', 'bronchodilator', 'antidepressant', 'statin', and 'proton pump inhibitor'. Adding other references cited in the initial reviewed articles, the most relevant papers were selected to discuss the scientific evidence available in association with the homeopathic postulates. Therefore, evidences that support the principle of therapeutic similitude from Hahnemann's to our times were gathered from classic homeopathic sources mentioned in the introduction as well as by hundreds of scientific articles published in peer-reviewed journals.

Rebound effect in modern pharmacology

An adverse event (AE) or reaction (AR) to a drug is defined by the World Health Organization (WHO) [11] as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of

disease, or for the modification of physiological function". Despite 'rebound effect' is an adverse event that might have serious consequences, it is little divulgated and discussed by healthcare professionals, who are thus deprived of important knowledge needed for the management of modern drugs.

According to Webster's New World Medical Dictionary [12], the term 'rebound' is defined as "the reversal of response upon withdrawal of a stimulus", while 'rebound effect' means "the production of increased negative symptoms when the effect of a drug has passed or the patient no longer responds to the drug; if a drug produces a rebound effect, the condition it as used to treat may come back even stronger when the drug is discontinued or loses effectiveness". Also named by the term 'paradoxical reaction' of the organism, one of the ironies of this phenomenon is that it makes the patients experience the very same effects they had hoped to make disappear by using palliative drugs, thus deconstructing the main pillar of modern pharmacological therapy, i.e., the treatment by principle of contraries.

In general terms, rebound effect is the result of the attempts by the organism to bring itself back into balance (homeostasis) after a drug was taken in order to neutralize disease symptoms. Described in 1860 by Sorbonne professor Claude Bernard as "fixité du milieu intérieur", the term 'homeostasis' was minted in 1929 by Harvard physiologist Walter Bradford Cannon to name the tendency or ability of living beings to keep their internal environment constant through self-adjustment of their physiological processes. Such physiological processes or homeostatic mechanisms are present at all levels of the biological organization from the simplest of cells to the most complex mental and emotional functions.

Although its exact mechanism remains unclear, the main hypothesis to explain the rebound effect is that it might be caused by increased responsiveness (up-regulation) of the receptors of the involved drug. According to pharmacological evidences, rebound effects exhibit greater intensity or frequency than the corresponding original symptoms that were suppressed (which thus allows distinguishing a paradoxical reaction from the natural reappearance of a disease after drug suspension), appear at variable intervals after the discontinuation of drugs, and last also variable periods of time.

In a literature review, Hodding et al. [13] described conceptual distinctions, assessment criteria, and scientific evidences in regard to the 'withdrawal syndrome' of several modern drugs (anticoagulants, anticonvulsants, antipsychotics, barbiturates, benzodiazepines, cimetidine, clonidine, corticosteroids, opiates, propranolol, tricyclic antidepressants, etc.). As in other reviews [14-16], also those authors considered the terms 'withdrawal or discontinuation symptoms' as synonym of 'rebound symptoms'. They distinguished the rebound or withdrawal syndrome from the natural evolution of disease: "symptoms resulting from discontinuation of a medication may need to be distinguished from reappearance of disease symptoms or a 'catching up' of the basic disease state, may emerge in the absence of the pharmacological action of the drug". They also mentioned that the appearance of symptoms is more severe than the baseline ones, and the gradual tapering of the dose is recommended when therapy must be discontinued.

By definition [13-16], the more evident rebound effects occur with the withdrawal of palliative (enantiopathic or antipathic) drugs after decrease or elimination of the drug serum concentration and the consequent partial or total vacating of the receptors (absence of biological effect). This lack of biological effect of the drug allows for the expression of the paradoxical reaction of the organism in the sense of returning to the initial homeostasis altered by the pharmacological agent by producing symptoms with intensities superior to the symptoms initially suppressed by the palliative drugs. As an intrinsic aspect of the phenomenon, the minimum time (time-point) should be taken into account to observe the real magnitude of the rebound effect, which is longer than the metabolism (half-life) of the drug and/or the normalization of the physiological changes (absence of biological effect).

Studying carefully the rebound effect or paradoxical reaction of the organism after the interruption or partial discontinuation of various classes of modern drugs, we found many descriptions of increase of the intensity and/or frequency of symptoms compared to the state of the patients at the onset of treatment, which corresponds to the secondary action or vital reaction of the organism (homeopathic model) to maintain its internal balance after it was broken by the action of palliative drugs.

To illustrate this phenomenon, drugs classically used in the treatment of angina pectoris (beta-blockers, calcium channel blockers, nitrates, and others) that induce beneficial effects during their primary effect (anti-angina), might awaken paradoxical increase of the frequency and intensity of the chest pain after discontinuation or irregular use of doses, which sometimes does not respond to any therapeutic means. Drugs used for the control of arterial hypertension (alpha-2 agonists, beta-blockers, angiotensin converting enzyme inhibitors, monoamine oxidase inhibitors, nitrates, sodium nitroprusside, hydralazine, and others) might induce rebound arterial hypertension as paradoxical reaction of the organism to the primary stimulus; antiarrhythmic drugs (adenosine, amiodarone, beta-blockers, calcium channel blockers, disopyramide, flecainide, lidocaine, mexiletine, moricizine, procainamide, quinidine, digital, and others) may induce rebound exacerbation of basal ventricular arrhythmias when treatment is interrupted. Hypolipidemic drugs (clofibrate, colestipol, colestiramine, nicotinic acid, fluvastatin, lovastatin, pravastatin, and others) to treat hyperlipidemia due to their primary action promote increased rebound of lipid levels after their interruption. Antithrombotic drugs (argatroban, bezafibrate, heparin, salicylates, warfarin, clopidogrel, and others) used in the prophylaxis of thrombosis due to their primary effects may promote thrombotic complications as paradoxical reaction of the organism. The use of psychiatric drugs such as anxiolytics (barbiturates, benzodiazepines, carbamates, and others), sedative-hypnotics (barbiturates, benzodiazepines, morphine, promethazine, zopiclone, and others), stimulants of the central nervous system (amphetamines, caffeine, cocaine, mazindol, methylphenidate, and others), antidepressants (tricyclic, MAO inhibitors, selective serotonin reuptake inhibitors, and others) or antipsychotics (clozapine, phenothiazines, haloperidol, pimozide, and others) might be associated with a paradoxical reaction of the organism seeking to keep the organic homeostasis, and thus induce the appearance of symptoms contrary to the ones expected from their primary therapeutic use, consequently worsening the initial clinical state. Drugs with anti-inflammatory primary action (corticoids, ibuprofen, indometacin, paracetamol, salicylates, and others) might trigger paradoxical reactions of the organism that increase

inflammation together with the serum concentration of its mediators. Drugs with analgesic primary action (caffeine, calcium channels blockers, clonidine, ergotamine, methysergide, opiates, salicylates, and others) may exhibit significant hyperalgesia as rebound effect. Diuretics (furosemide, torasemide, triamterene, and others) enantiopathically used to diminish the volume of plasma (edema, arterial hypertension, congestive heart failure, and others) may cause rebound retention of sodium and potassium, thus increasing the basal plasma volume. Drugs primarily used as anti-dyspeptic (antacids, H_2 antagonists, misoprostol, sucralfate, protons pump inhibitors, and others) in the treatment of gastritis and gastro-duodenal ulcers might promote after the primary decrease of acidity rebound increase of hydrochloric acid production by the stomach, eventually causing perforation of chronic gastro-duodenal ulcers. Bronchodilators (adrenergic drugs, sodium chromoglycate, epinephrine, ipratropium, nedocromil, formoterol, salmeterol, and others) used in the treatment of bronchial asthma might worsen bronchoconstriction as paradoxical response of the organism to the interruption or partial discontinuation of treatment, and others. [3-10]

In addition to the need of a variable period of time or 'time-point' (hours to weeks) after the discontinuation of treatment for the phenomenon to appear, the rebound effect or paradoxical reaction of the organism also lasts a variable period of time (hours to weeks) depending on the properties of drugs and individual idiosyncrasy.

Evidenced by clinical and experimental pharmacology (5-10), some properties of the rebound effect or paradoxical reaction of the organism are exhibited by all classes of drugs: (i) it appears only in susceptible individuals (idiosyncrasy), who exhibit symptoms similar to the primary effects of the drug; (ii) it does not depend on the drug, repetition of doses, nor the type of symptoms (disease); (iii) it follows the primary action of the drug (discontinuation) as an automatic manifestation of the organism; (iv) it induces an organic state (symptoms) opposite and greater in intensity and/or duration to the ones of the primary action of the drug; (v) the magnitude of its effect is proportional to the intensity of the primary action of the drug.

Despite the idiosyncratic nature of rebound effect, which appears in a small fraction of individuals, contemporary scientific evidences point to the occurrence of 'severe and fatal iatrogenic events' as a function of the paradoxical reaction of the organism following the discontinuance of several classes of modern palliative drugs.

Rebound effect of antiplatelet drugs [5,6]

Acetylsalicylic Acid (ASA)

Acetylsalicylic acid (ASA) is a non-steroidal anti-inflammatory drug (NSAID) belonging to the class of non-selective inhibitors of enzyme cyclooxygenase (COX), which catalyzes the transformation of arachidonic acid into prostaglandins (COX-2) and thromboxane (COX-1). Largely used to prevent thromboembolic events, in its primary effect it is able to prevent the formation of clots by ASA inhibiting COX-1 [a mediator of activity of blood platelets activity that stimulates the synthesis of thromboxane (TXA_2)] and platelets aggregation.

Experimental studies [17-24] showed that after the discontinuation of drugs used in the prophylaxis of thromboembolism, the organism might react by means of a rebound effect or paradoxical reaction that stimulates the production of COX-1 as well as the activity of platelets (TXA_2) to levels much higher than the initial ones, thus increasing the production of clots and the probability of stroke events [instable angina (IA), acute myocardial infarction (AMI), cerebral vascular accident (CVA), and others] in susceptible individuals.

In a retrospective study [25], a total of 1,236 patients hospitalized for acute coronary syndrome (ACS) were questioned to establish whether prophylactic ASA intake had been interrupted. The results showed that 51 cases of ACS had occurred within one month after aspirin withdrawal, i.e., 4.1% of all coronary events and 13.3% of relapses. Among the patients with relapse, the incidence of ACS with ST-segment elevation was higher in those who had stopped ASA compared to 332 patients who had not stopped ASA (39% vs. 18%, $P = 0.001$). Mean delay between ASA withdrawal and the acute coronary event was 10 ± 1.9 days. Those results support the hypothesis that ASA withdrawal in coronary patients may represent a real risk for the occurrence of a new coronary event.

Investigating discontinuation of ASA therapy as risk factor for ischemic stroke (IS), Maulaz et al. [26] conducted a case-control study with 309 patients with IS or transient ischemic attack (TIA) undergoing long-term ASA treatment before their index event and 309 controls who had not had IS in the previous six months, and compared the frequency of discontinuation of ASA therapy during 4 weeks before an ischemic cerebral event in patients and the 4 weeks before interview in controls. Stopping ASA therapy was associated with an odds ratio of 3.4 for IS or TIA (OR 3.4, 95% CI 1.08-10.63, $P < 0.005$), in other words, a risk 3.4 times larger of developing ischemic accidents in patients who had interrupted treatment. These results emphasize the importance of compliance with ASA therapy and give an estimate of the risk associated with the discontinuation of ASA therapy in patients at risk for IS, particularly those with coronary heart disease.

A systematic review and meta-analysis [27] on the hazards of discontinuing or not adherence to ASA was performed with 50,279 patients (six studies) at risk for coronary artery disease (CAD). One study (31,750 patients) focused on adherence to aspirin therapy in the secondary prevention of CAD, two studies (2,594 patients) on aspirin discontinuation in acute CAD, two studies (13,706 patients) on adherence to aspirin therapy before or shortly after coronary artery bypass grafting, and another (2,229 patients) on aspirin discontinuation among patients undergoing drug-eluting stenting. Overall, aspirin non-adherence/withdrawal was associated with three-fold higher risk of major adverse cardiac events (OR = 3.14, 95% CI 1.75-5.61, $P = 0.0001$). This risk was higher in patients with intracoronary stents, as discontinuation of antiplatelet treatment was associated with an even higher risk of adverse events (OR = 89.78, 95% CI 29.90-269.60).

To evaluate the risk of myocardial infarction and death from coronary heart disease after discontinuation of aspirin low dose in patients with a history of cardiovascular events, a recent case-control study was designed in the United Kingdom with 39,513 individuals who received a first prescription of ASA (75-300 mg/day) for secondary prevention of

cardiovascular outcomes. Individuals were followed up for a mean of 3.2 years to identify cases of non-fatal myocardial infarction or death from coronary heart disease, found 876 non-fatal myocardial infarctions. Compared with current users, individuals who had recently stopped taking ASA had a significantly increased risk of non-fatal myocardial infarction or death from coronary heart disease combined (RR 1.43, 95% CI 1.12-1.84) and non-fatal myocardial infarction alone (RR 1.63, 95% CI 1.23-2.14). There was no significant association between recently stopping ASA low dose and risk of death from coronary heart disease (RR 1.07, 95% CI 0.67-1.69). For every 1,000 patients, over a period of one year there were about four more cases of non-fatal myocardial infarction among patients who discontinued treatment with ASA low dose (recent discontinuers) compared with patients who continued treatment. [28,29]

Studying the frequency of stroke occurring after discontinuation of antiplatelet drugs (APD), Sibon et al. [30] found that only 4.49% of strokes were related to recent APD discontinuation, but all cases occurred between 6 and 10 days after drug discontinuation ($P < 0.0001$).

Confirmed by countless evidences as a natural and universal phenomenon, all classes of antiplatelet drugs (aspirin, heparin, warfarin, clopidogrel, and others) induce rebound thromboembolism after suspension, and may cause cardiovascular accidents. [31-37]

In view of the known importance of the use of aspirin to prevent thromboembolism, whose benefits might surpass the risks, physicians and patients should be alerted to the danger of the abrupt suspension of ASA to minimize serious iatrogenic thromboembolic events consequential to the rebound effect. [38-40]

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

The precise mechanisms by which NSAIDs including COX-2 inhibitors increase cardiovascular risk are not clear: reduced prostacyclin production in the vascular endothelium, suppression of nitric oxide synthesis, diminished neovascularization, abolition of adrenomedullin activity, and increased free-radical production have all been implicated. Platelets play a pivotal role in the development of these cardiovascular events, and all these mechanisms also affect platelet activity.

Similarly to ASA, other classes of NSAIDs non-selective COX inhibitors increase the risk of AMI after interruption of treatment. Confirming the results of experimental studies in which NSAIDs stimulated platelet adhesion and thrombin activity [41,42], a large case-control analysis conducted at the British General Practice Research Database [43] with 8,688 cases and 33,923 controls studied the risk of AMI during NSAID (diclofenac) exposure and after cessation of NSAID therapy. The results showed that the risk of AMI was 1.52 higher (95% CI 1.33-1.74) in the subjects who had stopped NSAIDs one to 29 days prior to the index event compared to non-users. These results suggest that the risk of AMI is increased during several weeks after the cessation of NSAID therapy. Withdrawal of ibuprofen provokes rebound platelet aggregation with increased thrombus formation and cardiovascular events (AMI) [44]. The use of NSAIDs also appears to be independently

associated with increased cerebrovascular event risk in stable atherothrombosis patients [45].

To evaluate the cardiovascular risks of selective COX-2 inhibitors, a retrospective cohort study analyzed the medical history of 1.4 million drug users (1999-2001) [46], showing that 8,199 patients (0.58%) suffered a heart attack during the use of rofecoxib. Before that study, other researches demonstrated that the chronic consumption of rofecoxib in high doses (> 50 mg/day) could elevate the risk of serious cardiovascular problems, which was further confirmed by other studies [47-50].

Linking the rebound effect to platelet activity and considering that antiplatelet therapy with ASA is associated with reduced vascular mortality, Serebruany et al. [51] sought to determine the effect of the use and withdrawal of NSAIDs on platelet activity. Platelet characteristics from 34 aspirin-naive volunteers who were receiving unselective NSAIDs or selective COX-2 inhibitors were compared to 138 drug-free controls. Platelets were assessed twice at baseline (at least one month of treatment) and after 14-day washout. Platelet activity during treatment was similar and unremarkable in both groups. However, there was a highly significant increase of platelet activity after withdrawal of non-selective NSAIDs and selective COX-2 inhibitors. Those authors concluded that drug cessation, rather than continuous therapy with these drugs, may be associated with rebound platelet activation, which may predispose to higher risk of vascular events. *In vitro* experiments also demonstrated that the thrombogenic mechanism previously mentioned for others NSAIDs also occur with rofecoxib [52].

Confirming this hypothesis, previous observational studies found particularly high risk of AMI for new users of rofecoxib [53,54], with events occurring short time after the suspension of low doses of the therapy, likely to the dynamic of the rebound effect. Using data collected in a previous population-based cohort study [55], a case-control study evaluated the temporal nature of the risk of a first AMI associated with the use of rofecoxib and celecoxib, observing that the risk of AMI was higher following first-time use of rofecoxib (RR 1.67, 95% CI 1.21-2.30), with events occurring within a median of 9 (6-13) days after therapy was started. Treatment duration was not associated with increasing risk, and the risk remained elevated for the first 7 days after rofecoxib was discontinued (RR 1.23, 95% CI 1.05-1.44) but appeared to return to baseline between days 8 and 30 (RR 0.82, 95% CI 0.61-1.09), thus characterizing the rebound phenomenon [56].

In an important systematic review of the effects of NSAIDs (both selective and nonselective inhibitors of COX-2) on cardiovascular events, 23 observational studies were analyzed (17 case-control and six cohort studies) in a population of 1.6 million of patients [57]. A dose-related risk was evident with rofecoxib, relative risk (RR) of 1.33 (95% CI 1.00-1.79; 6 studies) with 25 mg/day or less, and 2.19 (95% CI 1.64-2.91; seven studies) with more than 25 mg/day. Among the older, nonselective drugs, diclofenac had the highest risk with RR of 1.40 (95% CI 1.16-1.70; 9 studies), meloxicam RR 1.25 (95% CI 1.00-1.55; 3 studies) and indometacin RR 1.30 (95% CI 1.07-1.60; 6 studies). These data indicate that risk increases early in treatment (first 30 days) and on first cardiovascular events.

In a case-control study (33,309 cases; 138,949 controls) of the risk of hospitalization with myocardial infarction and use of NSAIDs [58], the RR estimates were: rofecoxib, 1.36 (95% CI, 1.18-1.58; 12 studies); diclofenac, 1.40 (95% CI 1.19-1.65; 10 studies); meloxicam, 1.24 (95% CI 1.06-1.45; 4 studies); indometacin, 1.36 (95% CI 1.15-1.61; 7 studies). In another meta-analysis, Kearney et al. [59] studied the effects of selective and nonselective NSAIDs on the risk of serious vascular events for a period of at least 4-week duration (145,373 participants), reviewing data from 138 randomized trials and estimated a RR for rofecoxib of 1.42 (95% CI 1.13-1.78) and for diclofenac of 1.63 (95% CI 1.12-2.37).

Enhancing the validity and the causality of the rebound phenomenon, recent studies showed similar results [60-64]. Analogously to ASA, physicians and patients should be alerted to the danger of the abrupt suspension of NSAIDs, to minimize fatal cardiovascular events [65-70].

Rebound effect of bronchodilator drugs [5,7]

Along the last decades, several studies confirmed the clinical and experimental observation that 'rebound bronchoconstriction' occurs after partial interruption or discontinuation of bronchodilators, with 'asthma aggravation' and increasing of the 'bronchial reactivity'. [71-82]

At the request of the FDA (U.S. Food and Drug Administration), due to reports of serious paradoxical bronchospasm associated with the use of long-acting beta-2 agonist (LABA) salmeterol and the previous epidemics of asthma-related deaths in patients taking other long-acting beta agonists, laboratory GlaxoSmithKline initiated in 1996 a randomized trial comparing salmeterol to placebo (Salmeterol Multicenter Asthma Research Trial, SMART) that was prematurely halted in September 2002 after an interim analysis suggested increased risk of asthma-related death in the patients who used the drug compared to the placebo group.

Since 2005, the FDA Public Health Advisory informed about the danger of LABA (salmeterol, formoterol), inclusively when combined with steroid fluticasone, "[they] have been associated with an increased risk of serious asthma exacerbations and asthma-related death", initially ordering the laboratory GlaxoSmithKline to put a 'black box' warning on the treatment's packaging, alerting doctors to the fact that the medicine could have potentially fatal side-effects [83].

After countless protests of the scientific community [84], since GlaxoSmithKline presented the partial data of SMART at the 69ª Annual International Scientific Assembly of The American College of Chest Physicians (CHEST 2003) claiming that "the interim analysis was inconclusive", the results of the general analysis of 26,355 randomized subjects were published in 2006 [85]. Following the review of the interim analysis, exploratory analyses of each outcome event within subpopulations were conducted, finding that there was significant increase in respiratory-related deaths (RR 2.16, 95% CI 1.06-4.41) and asthma-

related deaths (RR 4.37, 95% CI 1.25-15.34), and in combined asthma-related deaths or life-threatening experiences (RR 1.71, 95% CI 1.01-2.89) in subjects receiving salmeterol versus placebo. The imbalance occurred largely in the African-American subpopulation (compared with Caucasian subjects): respiratory-related deaths or life-threatening experiences (RR 4.10, 95% CI 1.54-10.90) and combined asthma-related deaths or life-threatening experiences (RR 4.92, 95% CI 1.68-14.45) in subjects receiving salmeterol versus placebo.

In 2006, Salpeter et al. [86] published a meta-analysis of 19 placebo-controlled trials involving 33,826 participants with asthma followed for 16,848 patient-years (mean trial duration was 6 months). Approximately 15% of the participants were African-American. The LABA used in the studies were salmeterol, formoterol, and eformoterol. During the trials, concomitant inhaled corticosteroids were used in approximately 53% of the participants in both groups. The aim of the study was to assess the effects of LABA on severe asthma exacerbations requiring hospitalization, life-threatening asthma attacks, and asthma-related deaths. Subgroup analyses were used to compare the results for salmeterol and formoterol and for children and adults. The OR for hospitalization was 2.6 (95% CI 1.6-4.3) for long-acting beta-agonists compared with placebo. Those authors did not include SMART in this analysis because the investigators had not provided information on hospitalizations due to asthma, but only on life-threatening exacerbations. When they included the SMART data on life-threatening exacerbations, the OR was 2.1 (95% CI 1.5-3.0). The risk for hospitalization was increased with salmeterol (OR 1.7, 95% CI 1.1-2.7), formoterol (OR 3.2, 95% CI 1.7-6.0), children (OR 3.9, 95% CI 1.7-8.8) and adults (OR 2.0, 95% CI 1.0-3.9). The OR for life-threatening asthma attacks attributed to LABA was 1.8 (95% CI 1.1-2.9), which did not significantly differ between trials of salmeterol and formoterol or between children and adults. The OR for asthma-related deaths was obtained from SMART (OR 3.5, 95% CI 1.3-9.3, P = 0.013). As a whole, the risks of severe exacerbations and asthma-related deaths increased by 2- to 4-fold. Despite the known protecting effect of inhaled corticosteroids, those authors evaluated separately trials in which more than 75% of the participants were receiving concomitant inhaled corticosteroids, and found that the risk of hospitalization was still increased 2-fold (OR 2.1, 95% CI 1.3-3.4), thus evidencing the importance of the rebound effect on the organic physiology.

In the physiologic explanation of the rebound phenomenon, authors correlated regular beta-agonist use (associated or not with inhaled corticosteroids) with tolerance to the drug's effects and worse control of disease [87-92]. Tolerance results from a negative feedback mechanism of the beta-adrenergic system that is an adaptive response to the stimulation of receptors causing uncoupling and internalization of receptors, which is known as 'desensitization', followed by a decrease in receptor density and receptor gene expression, which is known as 'down regulation' [93]. Regular use of beta-agonists has been shown to increase bronchial hyperreactivity despite the maintenance of some degree of bronchodilation. These effects, along with a reduction in the response to subsequent rescue beta-agonists may worsen asthma control without giving any warning of increased symptoms [92,94]. As cited in previous studies [71-82], 'bronchial hyperreactivity' is the same as 'rebound hyperreactivity' or 'rebound bronchoconstriction' [95].

A recent meta-analysis that included 17 randomized controlled trial (RCTs) (7,032 participants) compared the efficacy and safety profile of adding either daily LABA or anti-leukotrienes (LTRA) in adults and children with asthma who remain symptomatic on regular inhaled corticosteroids (ICS). The results showed that serious adverse events were more common with LABA than LTRA (RR 1.35, 95% CI 1.00 to 1.82), and that the risk of withdrawal for any reason in adults was significantly lower with LABA and ICS compared to LTRA and ICS (RR 0.84, 95% CI 0.74 to 0.96). [96]

In a recent retrospective cohort study, which studied the risk of serious asthma exacerbations associated with LABA among 940,449 patients with asthma, LABA use was found to be positively associated with hospitalizations and intubations compared to short-acting beta agonists. [97]

Other studies confirm severe rebound bronchoconstriction after suspension of LABAs, requiring a risk evaluation and mitigation strategy to facilitate the safe use of the products that includes a medication guide for patients and a plan to educate health care professionals about the appropriate use of these drugs [98-101].

Rebound effect of antidepressant drugs [5,8]

As other classes of palliative or antipathic drugs, also antidepressants exhibit rebound effect of the symptoms of depression after withdrawal of treatment (discontinuation or alteration of doses, including even one single dose missed in susceptible constitutions and/or with short half-life drugs), with evident changes in the mediators involved (receptor sensitization and neurotransmitter levels).

In a review about this subject, Wolfe [12] states that antidepressants may cause a variety of withdrawal reactions, "starting within a few days to a few weeks of ceasing to administer the drug and persisting for days to weeks". Both tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) cause similar syndromes, most commonly characterized by gastrointestinal or somatic distress, sleep disorders, mood fluctuations and movement disorders. Treatment involves restarting the antidepressant and tapering it more slowly.

In a review, Lader [102] enhances the understanding of the antidepressant discontinuation syndrome (rebound phenomenon) with further data and studies: "The phenomenon has been postulated to be associated with rebound symptoms such as return of depression following abrupt discontinuation. Discontinuation symptoms are now known to be associated with most classes of antidepressants, if medication is stopped without appropriate down-tapering of dose and/or dose frequency. The phenomena associated with stopping almost all antidepressants including the SSRIs are believed to result not from true dependence but from a reduction in intra-synaptic serotonin (5-HT) levels following receptor down-regulation".

This syndrome is characterized by the 'time-locked emergence of new' (time-point), clearly defined and quantifiable signs and symptoms, which develop on cessation or reduction of an antidepressant that has been taken for more than a few weeks [103]. Typically, patients describe transient symptoms that begin and peak within one week of treatment interruption, are mild in severity and follow a finite time-course, usually lasting between one day and three weeks [104]. In spite of the data from the published literature showing that the incidence of these mild, self-limiting rebound symptoms is generally smaller than 5% [104,105], recent data indicate that severe and disabling withdrawal syndromes occur in up to 5% of patients, requesting prompt modification of the management strategy in these idiosyncratic individuals [106]. The literature reveals that paroxetine is associated with significantly greater proportion of withdrawal reactions (around 5%) than the other SSRIs (fluoxetine, for example), with deterioration in various aspects of health and functioning [104,107-110]. The explanation for this difference most likely reflects the long half-life of the main metabolite of fluoxetine, thus acting as a natural taper [111].

Like in other classes of drugs, the rebound reactions are not specific to the particular condition (disease) in which the drug is used, whereas the antidepressant discontinuation syndromes are similar both in incidence, nature and extent throughout depression, panic disorder, generalized anxiety disorder, social anxiety disorder, and obsessive-compulsive disorders. In a similar way, the duration of treatment does not influence withdrawal reactions. [112]

In a revision of the neurobiological mechanisms of the antidepressant withdrawal syndrome, Harvey et al. [113] suggested a preliminary molecular perspective and hypothesis on the neuronal implications of the discontinuation of medication, and described the evidences that support association between antidepressant rebound effect and disorders of the brain glutamate activity, nitric oxide synthesis, and gamma-amino butyric acid:

> "Inappropriate discontinuation of drug treatment and noncompliance are a leading cause of long-term morbidity during treatment of depression. Increasing evidence supports an association between depressive illness and disturbances in brain glutamate activity, nitric oxide synthesis, and gamma-amino butyric acid. Animal models also confirm that suppression of glutamate N-methyl-D-aspartate (NMDA) receptor activity or inhibition of the nitric oxide-cyclic guanosine monophosphate pathway, as well as increasing brain levels of gamma-amino butyric acid, may be key elements in antidepressant action. Imaging studies demonstrate, for the most part, decreased hippocampal volume in patients with depression, which may worsen with recurrent depressive episodes. Preclinical models link this potentially neurodegenerative pathology to continued stress-evoked synaptic remodeling, driven primarily by the release of glucocorticoid, glutamate, and nitric oxide. These stress-induced structural changes can be reversed by antidepressant treatment. In patients with depression, antidepressant withdrawal after chronic administration is associated with a stress response as well as functional and neurochemical changes. Preclinical data also show that antidepressant withdrawal evokes a behavioral stress response that is associated with increased hippocampal NMDA receptor density, with both responses dependent on NMDA receptor activation". [113]

The symptoms that follow the discontinuation of antidepressants include dizziness, nausea, gastrointestinal distress, headache, gait instability, lethargy, paresthesia, anxiety, irritability,

vivid dreams and lowered mood among others. While cholinergic overdrive may explain certain symptoms after tricyclic antidepressants withdrawal, many of these symptoms suggest increased excitability of serotonergic neurons. In the same way that chronic antidepressant treatment results in desensitization of post and presynaptic serotonin (5-HT_{1A}) receptors, abrupt cessation of 5-HT reuptake inhibition will cause temporary deficit of available intra-synaptic 5-HT (down-regulated receptors), resulting in a neurochemical and behavioral pattern caused by loss of inhibitory 5-HT_{1A} mediated synaptic control and an increase of circulating 5-HT. [113-115]

In severe and disabling withdrawal syndromes (around 5% of patients) [102], overtly raised synaptic 5-HT levels may be detrimental to neuronal function and integrity by enhancing the efficacy of the brain glutamate NMDA receptor. Reiterating the previously mentioned premises of the rebound effect, these severe rebound phenomena are determined by various factors, such as the pharmacological profile of the antidepressant, the time-point and duration of withdrawal, whether withdrawal or noncompliance is repeated and how often, and the impact of associated contributors such as inherent genetic and environmental factors (idiosyncratic constitution) [114].

In recent years, countless studies called the attention to the relationship between antidepressants and suicidality. As initial hypothesis for this relationship, withdrawal of antidepressants provokes significant worsening of the depressive symptoms initially suppressed (for example, suicidal ideation, attempts or behavior) as consequence of the rebound effect. [8,116-120]

In the first meta-analysis that intended to investigate the relationship between antidepressant drugs and suicidality in pediatric patients participating in placebo-controlled trials, Hammad et al. [121] included all studies submitted to the FDA. The evaluated data was derived from 4,582 patients in 24 trials. Sixteen trials studied patients with major depressive disorder (MDD), 4 trials studied patients with obsessive-compulsive disorder (OCD), and 4 trials studied patients with non-obsessive-compulsive anxiety disorder. Only 20 trials were included in the risk ratio analysis of suicidality because 4 trials had no events in the drug or placebo groups. The multicenter trial TADS [122] was the only individual trial to show a statistically significant risk ratio (RR 4.62, 95% CI 1.02-20.92). The overall risk ratio for SSRIs in depression trials was 1.66 (95% CI 1.02-2.68) and for all drugs throughout all indications was 1.95 (95% CI 1.28-2.98). The overall risk difference (RD) for all drugs within all indications was 0.02 (95% CI 0.01-0.03). The FDA concluded that these medications pose a 2-fold (4% verum vs. 2% placebo) increased risk for ‘suicidal behavior’ or ‘suicidal ideation’, a modestly increased risk of suicidality.

It is worth to stress that the adverse events assessed by those meta-analyses were only the ones that occurred during or immediately after the double-blind acute treatment period, and thus underestimated the rebound effect of antidepressants with longer half-life. Some studies showed that abrupt interruption of continuous SSRIs therapy for 3 to 8 days was associated with greater emergence of somatic and psychological rebound symptoms (worsening of depression and increased suicidality, for example) in patients treated with

short half-life antidepressants (paroxetine, sertraline, venlafaxine, and others) than in those treated with fluoxetine (longer half-life antidepressant). [116,117,120,123-125]

Other recent meta-analysis and prospective multicenter studies also evaluated the risk of suicidality in youths and adults and found similar results, warning doctors and patients on the care required by suspension of SSRIs. [126-132]

Rebound effect of antihypercholesterolemic drugs (statins) [9]

Statins are the most widely prescribed cholesterol-lowering drugs and are considered to be first-line therapeutics for the prevention of coronary heart disease and atherosclerosis (the major cause of death in developed countries). Statins act by inhibiting enzyme 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme in endogenous cholesterol biosynthesis, which catalyzes the reduction of HMG-CoA to mevalonic acid. Inhibition of this enzyme has proven to be effective for lowering the plasma total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and triglyceride levels in humans, and can therefore be useful to treat atherosclerotic and dyslipidemic disorders.

However, the clinical benefits of statins appear to extend beyond their lipid-lowering effects. Besides reducing cholesterol biosynthesis, inhibition of mevalonate by statins also leads to reduction in the synthesis of important intermediates such as isoprenoids (farnesyl pyrophosphate, geranylgeranyl pyrophosphate, coenzyme Q10, dolichol, isopentenyladenosine, and others). These intermediates are involved in the posttranslational prenylation of several proteins (e.g., Ras, Rho, Rac) that modulate a variety of cellular processes including cellular signaling, differentiation, and proliferation. Given the central role of these isoprenylated proteins in the endothelial function, atherosclerotic plaque stability, platelet activity, coagulation, oxidation, and inflammatory and immunologic responses, it might be anticipated that these compounds may exert multiple beneficial primary effects in a broad spectrum of disorders including cardiovascular disease, osteoporosis, Alzheimer's disease and related vascular dementia, viral and bacterial infection, and others. These cholesterol-lowering-independent effects of statins are termed 'pleiotropic effects', and involve vasculoprotective actions that include improvement of the endothelial function, increased nitric oxide (NO) bioavailability, antioxidant properties, inhibition of inflammatory and thrombogenic responses, immunomodulatory actions, regulation of progenitor cells, and stabilization of atherosclerotic plaques. [133-135]

Regardless of the rebound increase in cholesterol biosynthesis, scientific evidence suggests that sudden discontinuation of statin treatment leads to rebound impairing of the vascular function, and increased morbidity and mortality of patients with vascular diseases. Withdrawal of statin treatment leads to overshoot activation of heterotrimeric G-proteins Rho and Rac, causing production of reactive oxygen species and suppression of NO bioavailability. In humans, discontinuation of statin therapy leads to a prooxidant, proinflammatory and prothrombotic state with impaired endothelial function. Epidemiological studies indicated that cessation of statin medication in AMI and ischemic stroke patients confers a significantly higher likelihood of early cardiologic and neurological deterioration, respectively, and poor outcome. In summary, withdrawal of

statin therapy results in a rapid return to endothelial dysfunction and amplification of the oxidative and inflammatory processes, which may increase the cardiac and cerebrovascular risk. [136-139]

Experimental studies described the physiological and molecular mechanisms involved in the statin withdrawal syndrome, thus broadening the knowledge on the scope of action of the rebound effect: (i) increase of markers of cholesterol biosynthesis [140-144]; (ii) worsening of the endothelial function [141,145-147]; (iii) increase of inflammation and oxidative stress [148-151]; and (iv) stimulation of the thrombogenic response [141-144].

Clinical studies found that discontinuation of statins (rebound phenomenon) particularly after acute events (e.g. AMI or stroke) has a harmful effect on cardiovascular outcomes and all-cause mortality: patients who discontinued their statin therapy had worse outcomes than those who were never prescribed statins. Observational studies [152-157] showed that statins withdrawal resulted in increased risk of mortality (secondary to fatal vascular events) compared to maintenance (2.3- to 7.5-fold) and absence (1.25 -to 1.69-fold) of treatment. Interventional studies showed that suspension of statins led to significantly increased risk of mortality compared to maintenance treatment (4.66-fold) [160], and significantly increased risk of fatal vascular events compared to maintenance (2.27- to 8.67-fold) [158,160] and the absence of treatment (19.01-fold) [160] as well as to placebo [158]. Statin therapy discontinuation was also considered an independent predictor of all-cause one-year mortality [159].

Other recent studies on individuals without history of cardiovascular disease further broaden the scope of evidence. Such studies showed that withdrawal of statins caused rebound impairment of the vascular function, and thus predispose to coronary and cerebrovascular diseases. Consequently, practitioners ought to become more aware of such effects and counsel their patients to adhere to their statin therapy. [161-172]

Rebound effect of gastric acid suppressing drugs [10]

According to the FDA [173], rebound acid hypersecretion is defined as an increase of the gastric acid secretion (basal and/or stimulated) above pretreatment levels following discontinuation of antisecretory therapy. Rebound was initially reported in studies following the use of histamine H_2-receptor antagonists and was thought to be due to increased serum gastrin and/or up-regulation of the H_2-receptors. Elevated gastrin levels or hypergastrinemia is a secondary effect that occurs during chronic inhibition of gastric acid secretion, such as it happens with long-term antisecretory therapy. In humans, gastrin is the primary regulator of the gastric acid secretion, which is mediated by histamine released by the enterochromaffin-like (ECL) cells. Increased plasma gastrin stimulates and up-regulates ECL cells to produce and release more histamine to stimulate the parietal cells. In addition, an increase of the parietal cell mass may occur together with the chronic use of antisecretory agents, and this might be an additional mechanism explaining the increased acid secretion that might occur after discontinuation of treatment. Another possible cause of rebound acid secretion is increased sensitivity to histamine. [174]

The neutralization of the gastric acidity by antacids (aluminum/magnesium hydroxide or calcium carbonate), although it is not an antisecretory treatment might, also cause the rebound phenomenon after discontinuation of treatment. Clinical trials confirmed this hypothesis after observing the occurrence of rebound effects in healthy volunteers 1 hour after a standard dose of antacids. [175,176]

Similarly to other competitive antagonist drugs, the H_2-receptor antagonists (cimetidine, famotidine, nizatidine and ranitidine) cause rebound acid hypersecretion after drug withdrawal. Although the exact mechanism remains unclear, the main hypotheses are that the rebound phenomenon may be caused by increased responsiveness (up-regulation) of the H_2-receptor to histamine stimulation after chronic competitive inhibition, or that the inhibitory arm of acid secretion is impaired [177]. Studies with patients and healthy individuals showed that rebound acid hypersecretion after discontinuance of H_2-receptor antagonists occurred within 2 or 3 days after 4 weeks of treatment and lasted 10 days [178-183].

Proton-pump inhibitors (esomeprazole, lansoprazole, omeprazole and pantoprazole) block the final step in the secretion of acid, which results in severe and persistent gastric hypoacidity with concomitant increased release of gastrin. This rebound hypergastrinemia results in continuous stimulation of the ECL cells and consequent hyperhistaminemia that, however, does not lead to increased gastric acid secretion because the proton pump is effectively blocked. In addition, the stimulation of ECL cells proliferation induces increase of their mass, which remains longer than the effect of the proton-pump inhibitors (PPI) when the drug is discontinued. As in any instance of rebound phenomenon, rebound acid hypersecretion is evident at a certain time-point after treatment withdrawal as a function of the half-life of drugs (absence of biological effects). Rebound acid hypersecretion after a sufficient period of PPI treatment occurs from the second week (PPI's half-life) until the normalization of the ECL cell mass (about 2 months), i.e., 2 or 3 months after stopping treatment. This phenomenon is prolonged, lasts at least 2 months after a 2-month treatment course, with persistence of significantly elevated submaximal and maximal acid hypersecretion. [184-190]

Gastrin has trophic effects on many tissues and stimulates a number of tumor cell lines in culture, including colon cancer cells. Although according to some suggestions hypergastrinemia is associated with increased risk of colon cancer, 2 population-based case-control studies conducted in United Kingdom (1987-2002) and Denmark (1989-2005) found no evidence of such increase in patients using PPI [191,192]. In addition, there are reasons to believe that patients with reflux disease are more affected during the period of rebound acid hypersecretion after a course of PPI treatment than before. The increase of the gastroesophageal reflux disease observed during the last decades might be due to low-threshold PPI overuse to treat reflux symptoms. Due to the same reason, hypergastrinemia might have a possible effect on the progression of Barrett's esophagus to cancer, as a function of the marked rise in the incidence of adenocarcinoma at the cardioesophageal junction over the past 2 decades, inasmuch as acid-suppressive therapy for gastroesophageal reflux disease has greatly increased. [193-196]

A population-based cohort study conducted in Denmark (1990-2003) showed increased incidence of gastric cancer among PPI users with the largest number of prescriptions or the longest follow-up compared with H_2-receptor antagonists' users or non-users [197]. According to the authors, these data suggest that hypergastrinemia might be a risk factor for the development of gastric cancer, in consequence of excessive use of PPIs by the population.

Carcinoid tumors have long been recognized as consequence of hypergastrinemia in Zollinger-Ellison's syndrome and atrophic gastritis [198]. Analogous to the previous described suggestion, the increased incidence of gastric carcinoids in the last 3 decades (400% in males and 900% in females) is also associated with the widespread marketing of PPI [199-201]. According to McCarthy [196], the scientific basis to expect long-term PPI use to cause carcinoid tumors is quite strong and deserves serious consideration. Hypergastrinemia may also stimulate the development of carcinoid tumors or their growth in other sites.

To evaluate the occurrence and clinical relevance of rebound acid hypersecretion after discontinuation of PPI, Hunfeld et al. [202] performed a systematic review that included 8 studies (sample size 6-32). Five studies (including 4 randomized trials) did not find any evidence for rebound acid hypersecretion after PPI withdrawal. From the remaining 3 uncontrolled trials, 2 studies suggested that rebound acid hypersecretion may occur in *H. pylori*-negative patients after 8 weeks of treatment with PPI. Those authors concluded that there is no strong evidence for clinically relevant increased acid production after withdrawal of PPI therapy. Upon criticizing the studies included in this systematic review, which did not take into account the need of a duration of PPI therapy sufficient to allow for development of significant ECL cells hyperplasia and subsequent acid rebound, Fossmark and Waldum [203] reiterated that it is impossible to evaluate rebound acid hypersecretion after 1 single dose of PPI, nor after 25-day use, although the included studies had a randomized design: "these 5 studies merely show that PPI must be used more than 1 to 25 days to induce rebound acid hypersecretion".

Clinical evidences for rebound acid hypersecretion after PPI withdrawal were found in recent interventional studies [204-208]. Upon assessing indirectly whether rebound acid hypersecretion also occurs in patients without gastroesophageal reflux disease, some studies described relapse of symptoms in approximately 70% of long-term PPI users after discontinuation of therapy [204,207].

Proton-pump inhibitors are some of the most frequently used drugs worldwide and represent an important financial onus for the healthcare system of many countries, because they are prescribed for a wide variety of allegedly acid-induced upper gastrointestinal symptoms [209-213]. For instance, the total use of PPI increased 7 times between 1993 and 2007 in Denmark, and a substantially increased from 20 to 33 defined daily doses per 1,000 individuals per day from 2003 to 2007. In 2006, approximately 7% of the Danish population was treated with 1 PPI [214-216]. Whereas the use of H_2-receptor antagonists declined 72% between 1995 and 2006 in Australia, the use of combined PPI increased by 1,318% [217].

Between 1999 and 2004, the use of PPI in the United States increased steadily, whereas the use of H_2-receptor antagonists decreased also steadily. In 2007, esomeprazole, lansoprazole, and pantoprazole were the 4th, 8th, and 14th leading brand-name prescription drugs sold in the United States, with 26.4, 20.4, and 16.1 million prescriptions, respectively. Comparatively, ranitidine and famotidine ranked 47th and 120th among the generic drugs, with 13 and 3 million prescriptions dispensed, respectively. Neither cimetidine nor nizatidine ranked among the top 200 drugs sold in 2007. [218]

Although this liberal use of PPI has been recently recommended by many guidelines for dyspepsia [219,220], it is well documented that these drugs are often inappropriately prescribed for minor symptoms and without clear indications, where the effects of acid-suppressive therapy is controversial [212,214,221-225]. As a result, a large proportion of patients currently prescribed PPI do not have acid-related symptoms and thus, have no true indication for such therapy. Some studies also showed that up to 33% of patients who initiate PPI treatment redeem repeated prescriptions without any obvious indication for maintenance therapy [212,226]. This empirical behavior may complicate PPI discontinuation, due to the development of rebound acid hypersecretion, leading to the relapse of the symptoms of the underlying acid-related disease (heartburn, acid regurgitation and dyspepsia) that might result in resumption of therapy [204,205].

Other recent reviews that concluded for the existence of the rebound phenomenon after suspension of PPI warn practitioners to ponder on the risks and benefits before starting them [227-232].

Homeopathic use of conventional drugs: therapeutic application of the rebound effect [233-236]

Some instances of involuntary homeopathic cures with conventional drugs are reported in the scientific literature. Biphasic contraceptives (anteovin) were used to promote rebound ovulation and consequent pregnancy in women with functional sterility; stimulants of the central nervous system (methylphenidate) were used to calm down and improve the attention in children with attention deficit hyperactivity disorder (ADHD); stimulants of gonadotropin releasing hormone (leuprorelin) were used in the treatment of testosterone-dependent prostate tumors; immunosuppressants (thiomorpholine analogous to prazosin) induced rebound immunostimulation after primary immunosuppression, and so forth [3,4].

Retracing the steps of classical homeopathy to conclude an earlier stage of the present research [233-236], we systematized the use of modern drugs according to the principle of therapeutic similitude. Consistently, we suggest that the healing paradoxical reaction (vital reaction) of the organism might be stimulated by means of drugs (in infinitesimal doses) that caused similar symptoms on human beings.

To make this proposal feasible, a *Homeopathic Materia Medica of Modern Drugs* was needed that grouped together all the primary effects (therapeutic, adverse and side effects) of drugs as described in *The United States Pharmacopoeia Dispensing Information* (USP

DI, 2004) according to the traditional scheme of chapters of works on homeopathic materia medica.

To facilitate the selection of an individualized medicine (similar to the totality of the patient's symptoms) – which is the essential premise for successful homeopathic treatment – the second stage involved the elaboration of a *Homeopathic Repertory of Modern Drugs*, where symptoms and their corresponding medicines are arranged as in the classic homeopathic repertories.

This research project is entitled *New Homeopathic Medicines: use of modern drugs according to the principle of similitude*, and it is distributed across three volumes: *Scientific Basis of the Principle of Similitude in Modern Pharmacology; Homeopathic Materia Medica of Modern Drugs;* and *Homeopathic Repertory of Modern Drugs.* Aiming at divulgating this project among homeopaths worldwide as well as to allow for its improvement, it is available online at www.newhomeopathicmedicines.com. [237]

Discussion

The notion of secondary action or vital reaction included in the homeopathic therapeutic model is supported by studies on the rebound effect or paradoxical reaction of the organism associated with modern drugs used according to the therapeutic principle of contraries (palliative, enantiopathic or antipathic effects). Investigated by integrative physiology through the complex psycho-neuro-immune-endocrine-metabolic system, homeostasis ("life-preserving power") promotes organic reactions to restore the balance of the internal environment altered by drugs, external stimuli or psychological factors.

Seeking to extend the paradoxical (homeostatic or vital) reaction of the organism to psychological factors (namely, mental, emotional or behavioral features), some experimental studies showed that 'thought suppression' (by cognitive therapy, for example) might have paradoxical effects resulting in the subsequent increase of the suppressed ideas. Such effects might be implicated in the etiology or worsening of obsessions (obsessive-compulsive disorder, etc.), phobias (social phobia, agoraphobia, etc.), addictions (smoking, binge eating, etc.), or other psychopathological conditions [238-245]. These evidences based the therapeutic application of the principle of similitude to the mental aspects of the individuality.

The severity of the paradoxical reactions mentioned above and eventually leading to serious or fatal iatrogenic events agree with the pharmacological notion of the rebound effect, where the paradoxical reaction of the organism sometimes is greater than the similar phenomenon initially suppressed. Although the rebound effect manifests in a small proportion of individuals as a function of their idiosyncratic nature, these serious or fatal paradoxical events assume epidemiological importance when we consider the enormous current consumption of enantiopathic or palliative drugs.

In the above mentioned placebo-controlled studies, the risk of ischemic accidents was 3.4 times greater after ASA withdrawal, 1.52 times greater after NSAIDs withdrawal, 1.67 times greater after rofecoxib withdrawal, and 1.69 times greater after statins withdrawal. The risk of suicidal behaviors was 6 times greater after SSRI antidepressants withdrawal, whereas the risk of fatal paradoxical bronchospasm was 4 times greater after LABA withdrawal.

The time for appearance of the paradoxical reaction does not exhibit remarkable variation after the discontinuance of palliative drugs: it was average 10 days for ASA, 14 days for NSAIDs, 9 days for rofecoxib, 7 days for SSRI, 7 days for statins, and 7 to 14 days for PPI. The duration of the rebound effect was 30 days with rofecoxib, 21 days with SSRI, and 30 days with PPI. The duration of treatment before the interruption of drugs did not show association with the risk of inducing paradoxical events.

Similar to the fatal iatrogenic events of the above mentioned drugs, the asthma mortality rates increased worldwide in the 1960s, when inhaled beta-agonists were introduced in the market [246-248], and further rose in the last decade after LABA were introduced [249-251]. LABA cause about 1 case of rebound bronchospasm followed by death per 1,000 patients-year-use [86], which corresponded to 4,000-5,000 deaths in the USA in 2004 (40,000-50,000 worldwide) [7]. SSRI cause about 5 rebound suicidality events per 1,000 adolescents-year-use [252], which corresponded to 16,500 suicidal behaviors or ideas in the USA in 2007 [8]. ASA causes about 4 rebound acute myocardial infarctions per 1,000 patients-year-use [28,29]. Some studies reported increased incidence of gastric carcinoids in the last decades (400% in men and 900% in women) associated with the growing consumption of PPIs.

In addition to the above mentioned drugs, recent studies warn about the risks associated with the suspension of analgesics [253-255] and psychiatric drugs [256-259] also associated with their huge and growing current consumption.

Within this context, it is worth mentioning the risk of developing immune reconstitution inflammatory syndrome (IRIS), which is confounded with progressive multifocal leukoencephalopathy (PML), after the withdrawal of natalizumab (humanized monoclonal antibody) used in the treatment of multiple sclerosis, in addition to the worsening of the activity of the disease [260-265].

Widely used in the treatment of osteoporosis and the prevention of fractures, bisphosphonates (alendronate, etidronate, zoledronate, among others) increase the bone density, by hindering the dissolution of hydroxyapatite crystals and inhibiting the activity of osteoclasts (bone cells that reabsorb those crystals). Recently, several studies demonstrated rebound effect after discontinuation of bisphosphonates (and other treatments such as estrogen and denosumab) with increase of the activity of osteoclasts and paradoxical atypical subtrochanteric and diaphyseal femoral fractures. [266-277]

Conclusion

A large number of iatrogenic diseases might be avoided if doctors were advised to the maintenance of homeostasis associated with the rebound effect or vital reaction of the organism, and thus prevent the paradoxical aggravation of the clinical condition of patients by discontinuing slowly and gradually drugs used according to the principle of contraries. Although they are not considered as conventional adverse events of drugs, "drug discontinuation effects are part of the pharmacology of a drug" [16], and should be routinely incorporated into the teaching of modern pharmacology.

According to the observations by Hahnemann cited at the beginning of this article "on the sad results of the use of antagonistic employment of medicines", reputed researchers and doctors are increasingly pointing to the risks associated with the rebound effect of modern palliative treatments. Thus they confirm the validity of the application of the principle of similitude through Aristotelian deductive logic '*modus tollens'* ('mode that affirms through negation' or 'indirect proof'):

> "Had physicians been capable of reflecting on the sad results of the antagonistic employment of medicines, they had long since discovered the grand truth, *that the true radical healing art must be found in the exact opposite of such an antipathic treatment of the symptoms of disease*; they would have become convinced, that as a medicinal action antagonistic to the symptoms of the disease (an antipathically employed medicine) is followed by only transient relief, and after that is passed, by invariable aggravation, the converse of that procedure, the homoeopathic employment of medicines according to similarity of symptoms, must effect a permanent and perfect cure […]". (Organon, paragraph 61)

After observing the iatrogenic effects of discontinuation of ASA in coronary patients [25], Emile Ferrari said that "aspirin therapy cannot be safely stopped in any case, but especially in patients with a history of coronary disease", and emphasized that this evidence "serves as a reminder for all medical professionals who treat coronary patients that aspirin withdrawal should not be advised, and that alternative recommendations should be considered" [38]. In the same interview, Richard Irwin, president of The American College of Chest Physicians, concluded that "this study not only reinforces the importance of compliance with aspirin therapy in coronary patients, but it sends a message to all medical professionals that the decision to discontinue aspirin therapy should not be taken lightly". Analogously, McColl and Gillen [228] pointed to "evidence that proton-pump inhibitor therapy induces the symptoms it is used to treat", signaling that the fact that PPI "induce symptoms means that such liberal prescribing is likely to be creating the disease the drugs are designed to treat and causing patients with no previous need for such therapy to require intermittent or long-term treatment".

In addition to confirming the principle of similitude as a 'natural law', the continual contemporary reports of increased iatrogenic events after withdrawal of modern palliative drugs demonstrate the importance of the rebound phenomenon (homeopathic vital reaction) in promoting deep alterations of the organic balance. Conversely, by using the rebound effect to achieve cures, homeopathy stimulates the organism to react against disease.

Based on pure observation, Hahnemann went beyond the scientific thought of his time, and draw guidelines for the treatment of diseases that remain effective even in the present time, although they are dismissed by mainstream medicine:

> "These incontrovertible truths, which spontaneously offer themselves to our notice in nature and experience, explain to us the beneficial action that takes place under homeopathic treatment; whilst, on the other hand, they demonstrate the perversity of the antipathetic and palliative treatment of diseases with antagonistically acting medicines". (Organon, paragraph 67)

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Antiresorptive drugs (bisphosphonates), atypical fractures and rebound effect: new evidence of similitude[12]

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Abstract

Homeopathy uses the treatment by similitude ('like cures like') administering to sick individuals the medicines that caused similar symptoms in healthy individuals, employing the secondary and opposite action of the organism as therapeutic response. Such vital or homeostatic reaction of the organism is scientifically explained through the rebound effect of modern drugs, which cause worsening of symptoms after suspension of the palliative treatment effect. Despite evidence of reduction of typical fractures in patients using bisphosphonates for osteoporosis, recent studies reported 'atypical' fractures of the femur after finishing the biological effect of the drug, suggesting that the rebound effect can be the causal mechanism. Review of the literature concerning the relationship between femur atypical fractures and antiresorptive drugs (bisphosphonates), identifying the pathogenesis of this adverse event. Several studies have described multiple cases of 'unusual' low-impact subtrochanteric stress fractures or completed fractures of the femur. These fractures are often bilateral, preceded by pain in the affected thigh, may have a typical x-ray appearance, and may have delayed healing, suggesting the 'rebound of osteoclastic activity' after suspension of antiresorptive drugs effect as the more plausible mechanism to explain this phenomenon. As well as studied in other classes of drugs, the rebound effect of antiresorptive drugs supports Hahnemann's similitude principle (primary action of the drugs followed by secondary and opposite action of the organism), and clarifies this 'unresolved' issue. Unfortunately, the rebound effect is little publicized and discussed between health professionals, depriving them of the fundamental knowledge to secure management of modern drugs.

Introduction

Opposed to the 'dose-dependent' concept of current biomedical model, great importance is dedicated to the 'dynamized medicine' (*ultra-high dilutions*) in the research lines that aim to scientifically justify the homeopathic assumptions. However, the proposal to employ infinitesimal doses was introduced later in the homeopathic treatment,[1] in order to minimize the possible symptomatic aggravations. The first two homeopathic foundations, 'principle of similitude' and 'pathogenetic proving of medicinal substances', are the pillars

[12] Teixeira MZ. Antiresorptive drugs (bisphosphonates), atypical fractures and rebound effect: new evidence of similitude. *Homeopathy.* 2012; 101(4): 231-242. Available at: https://doi.org/10.1016/j.homp.2012.07.001

of homeopathic episteme, remaining to 'individualized medicine' the essential condition for awakening the homeopathic curative response.

In paragraphs 63-65 of the *Organon of medicine*,[2] Hahnemann described a physiological explanation for the principle of therapeutic similitude, basing on the 'primary or direct action of the drug' and the corresponding and opposite 'secondary or indirect action of the organism':

> "Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed *primary action.* [...]. To its action our vital force endeavors to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of *secondary action* or *counteraction*". (Organon, paragraph 63)

Hahnemann illustrates this 'universal mechanism of action of medicines' ('universal pharmacodynamic') in the pharmacological effects of enantiopathic or palliative treatments used in his time:

> "[...] Excessive vivacity follows the use of strong coffee (primary action), but sluggishness and drowsiness remain for a long time afterwards (reaction, secondary action), if this be not always again removed for a short time by imbibing fresh supplies of coffee (palliative). After the profound stupefied sleep caused by opium (primary action), the following night will be all the more sleepless (reaction, secondary action). After the constipation produced by opium (primary action), diarrhea ensues (secondary action); and after purgation with medicines that irritate the bowels, constipation of several days' duration ensues (secondary action). And in like manner it always happens, after the primary action of a medicine that produces in large doses a great change in the health of a healthy person, that its exact opposite, when, as has been observed, there is actually such a thing, is produced in the secondary action by our vital force". (Organon, paragraph 65)

The homeopathic treatment employs this secondary action or vital reaction of the organism as therapeutic response, administering to the sick individuals the drugs that caused similar symptoms in healthy individuals, with the goal of awakening a healing reaction of the organism against the disease itself. Emphasizing that such secondary action of the organism (opposed in character to the primary action of the drug) is observed "in each and every instance with no exceptions", with ponderable or infinitesimal doses, in both healthy and ill individuals, Hahnemann raises the principle of similitude to the level of 'natural law of healing' (Organon, paragraphs 58, 61, 110-112).

Describing the sad results of the indiscriminate palliative employment of medicines (Organon, paragraphs 59-61), Hahnemann alerts to the risks of this undesirable vital reaction of the organism that can produce "more serious disease or frequently even danger to life and death itself". This way, negating the efficacy of the conventional or palliative treatment (principle of contraries), Hahnemann validates the homeopathic treatment (principle of similitude) through the Aristotelian hypothetical syllogism or classical deductive logic 'modus tollens' ('mode that affirms through negation', 'indirect proof' or 'null hypothesis' of modern biostatistics).

In the terms of modern scientific rationality (physio-pharmacological concepts), the 'primary action' adduced by Hahnemann corresponds to the 'therapeutic, adverse and side effects' of conventional drugs. The 'secondary action' or 'vital reaction', in turn, corresponds to the 'rebound effect' or 'paradoxical reaction' of the organism, which has been observed after the discontinuation of action of several classes of conventional drugs that act contrarily (palliative, enantiopathic or antipathic) to the symptoms of the diseases.

Following in the footsteps of Hahnemann, since 1996 we've seen studying systematically the rebound effect of modern drugs basing the homeopathic principle ('like cures like') in the clinical pharmacology and experimental.[3-10] In this review, a new evidence of similitude is described in recent studies that demonstrate the occurrence of 'atypical fractures of femur' after finishing the biological effect (half-life) of antiresorptive drugs (bisphosphonates), in accordance with the rebound phenomenon.

Methods

Literature from the 2000 to 2012 cited in PubMed database was reviewed using 'atypical fracture', 'bisphosphonates', 'antiresorptive' and 'bone turnover' as search terms, adding other references cited in the initial reviewed articles. After identifying the studies that indicated bisphosphonates use as risk of atypical femoral fractures', clinical manifestations and pathogenic mechanisms were discussed in accordance with experimental evidence. Showing typical characteristics of the rebound effect, this phenomenon arises as the main explanation to the pathogenesis of cited atypical fractures, expanding the scientific basis of the principle of similitude and clarifying this 'unresolved' issue.

Results

Bisphosphonates and osteoporosis

Osteoporosis is associated with significant morbidity and mortality.[11,12] Approximately 50% of women older than 50 years will sustain an osteoporosis-related fracture during their lifetime, and 1 of 5 patients with an osteoporosis-related fracture will die within 12 months.[13,14] Bisphosphonates (BPs) are considered first line treatment for reduce the risk of osteoporotic fractures and they are prescribed for millions of geriatric patients. Inhibiting bone resorption by decreasing the activity of osteoclasts, alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva), and zoledronic acid (Zometa, Reclast) decrease bone turnover and increase bone mineral density (BMD), reducing fracture risk.[15-19]

BPs have specific pharmacological properties which differentiate tem from others inhibitors of bone resorption, including long-term retention in skeleton and persistence of their effect after discontinuation of treatment.[20,21] When discontinued after 5 years, the physiologic and clinical effects of alendronate continues for at least 5 years, with no

increase in fracture risk compared with patients who continued treatment for more 5 years.[22] This result is a consequence of the incorporation of alendronate on bone matrix and its long biological half-life (5 years). It is important to highlight that this 'long biological half-life' hinders the observation of the specific 'time-point' of loss of biological effect of the drug and the subsequent rebound effect.

Bone turnover (osteoclast-mediated bone resorption) is a natural part of maintaining bone health. It has been suggested that long-term residence time of BPs in bone and prolonged suppression of bone turnover may impair the ability of bone to remodel, leading to accumulation of microdamage and compromised bone strength.[23]
Despite the safety profile of the BPs, a number of potential side effects have been identified such as atypical fractures, osteonecrosis of the jaw and esophageal cancer.[24]

Atypical fractures

An atypical fracture was defined as a simple, transverse, or short oblique subtrochanteric (ST) or femoral shaft (FS) fracture in areas of thickened cortices, with a unicortical breaking.[25]

According the American Society for Bone and Mineral Research (ASBMR),[26] atypical femoral fractures are observed most commonly in the proximal one-third of the femoral shaft but may occur anywhere along the femoral diaphysis. The fracture may be complete, extending across the entire femoral shaft, often with the formation of a medial spike. Complete atypical femoral fractures generally are transverse, although they may have a short oblique configuration, and are not comminuted. The atypical ST/ FS fracture usually occurs as a result of no or minimal trauma (low-energy trauma), suggesting a systemic cause, because approximately 75% of complete ST/ FS fractures are associated with major trauma such as motor vehicle accidents,[27] in which the energy transmitted to the bone results in the propagation of multiple fracture lines, thus producing comminution.

Both complete and incomplete fractures are commonly associated with a periosteal stress reaction and thickening of the lateral cortex at the fracture site, abnormalities indicative of a stress fracture. In addition, there may be generalized bilateral thickening of both the medial and lateral cortices. Either complete or incomplete atypical fractures may be bilateral. Healing of the fractures may be delayed. There are often prodromal symptoms such as a pain in the groin or thigh.

Atypical fractures may be associated with a variety of comorbidity conditions and the use of pharmaceutical agents. The diagnosis of atypical femoral fractures should specifically exclude fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with local primary or metastatic bone tumors, and periprosthetic fractures.

While hip fracture incidence has declined since BPs began to be used in the USA, ST and FS fractures increased over the same period.[28,29] Recent data from the Study of Osteoporotic Fractures (SOF),[30] a prospective population-based US study of 9,704 white

women 65 years of age and older followed for as long as 24 years indicate that the incidence of ST fractures is very low (3 per 10,000 persons-years) compared with the overall incidence of hip fracture (103 per 10,000 persons-year). Despite these types of fractures represent a small subset (5-10%) of all hip/ femur fractures,[27-29] ST fractures exert major effects on mortality and morbidity, with outcomes similar to those seen with hip fractures: a 2-year prospective study of 87 patients with ST fractures showed mortality rate of 8% at 4 months, 14% at 12 months, and 25% at 24 months; revision surgery was required in 8%; at the final follow-up only 46% of patients regained their prefracture walking ability, and only 71% could live in conditions similar to those before the fracture.[31]

Bisphosphonates and atypical fractures

Despite the proven use of BPs to reduce typical fractures in osteoporotic patients, in recent years has been described an increasing number of case reports of atypical fractures of the subtrochanteric and diaphyseal femoral shaft that occur with minimal or no trauma during long-term use. In 2010, the US Food and Drug Administration (FDA) announced an ongoing review about this problem,[32] and the ASBMR has released a task force report to address a number of key questions related to this disorder.[26] Other systematic reviews discussed the clinical and experimental evidence on this serious adverse event secondary to the employment of BPs, seeking to understand the pathogenesis of the phenomenon.[24,33-37]

Bisphosphonates and atypical fractures - Case series and case reports

General analyses of several case series and multiple case reports[26,35] suggested that some ST (defined as within 5 cm distal to the lesser trochanter of the femur) and FS fractures (usually not the distal shaft) occur in patients who have been treated with long-term BPs. Clinical features included prodromal pain for weeks to months prior to the fracture,[38-41] lack of precipitating trauma,[38-41] bilaterality (either simultaneous or sequential),[38,39,42,43] poor fracture healing,[38,44] and normal or low bone mass but not osteoporosis in the hip region.[42,45,46] Radiographic features that appear distinctive include presence of stress reaction (focal uptake on bone) on the affected and/or unaffected side,[38-40,43,47] transverse or short oblique fractures[40] (in contrast to the more common osteoporosis-related spiral or longitudinal fracture) and cortical hypertrophy or thickness.[38]

According to the wide analysis of the task force of the ASBMR[26] the total number of reported cases of atypical ST/ FS fractures was 310 after overlapping case reports had been excluded (286 cases occurred in association with BP treatment for osteoporosis and 5 for malignancy), the subjects ranged in age from 36 to 92 years, the majority (160 of 189) occurred after oral alendronate monotherapy, and the median duration of BP therapy was 7 years. The presence of prodromal pain was present in 70% (158 of 227). Concomitant glucocorticoids therapy was assessed in 76 of 310 patients and were present in 34% (26 of 76), increasing the risk of ST fractures with the use by more than 6 months, in one series.[47] Bilateral fractures were assessed in 215 of the 310 patients and were present in 28% (60 of 215). Bilateral radiologic changes were assessed in 224 of the 310 patients and were present in 28% (63 of 224). Healing was assessed in 112 of the 310 patients and was

reported to be delayed in 26% (29 of 112). Of the 67 patients who had bone densitometry recorded, 45 (67%) had osteopenia or normal BMD.

With similar results, Giusti *et al.*[36] conducted a systematic review of 141 cases (women; mean age of 67 years) with postmenopausal osteoporosis treated with BPs (median duration of treatment of 5 years; 24% received treatment for less than 3 years) who sustained ST/ FS fractures. There were 58 FS and 41 ST fractures; 19 fractures were diagnosed at presentation as insufficiency fractures, with 12 of these progressing to a complete fracture. Overall, 53 (44.2%) of the 120 patients with available data had a contralateral fracture (32 of which were insufficiency fractures), either concurrently or subsequently to the initial fracture, 34 (64.2%) of which occurred in the same anatomical location of the first fracture. Prodromal pain was present in 64%, and in 40% of cases the fracture occurred spontaneously with no previous history of trauma. Delayed or absent healing (poor callus formation) was reported in 39% of cases with available data. Contrary to the currently held view of the association of atypical femur fractures with long-term (average of 7 years) BP treatment, this study revealed that in about half of the patients atypical fractures occurred within 5 years of BP treatment, and 25% of cases were treated less than 3 years. In addition, ST fractures appeared to be more frequent in women treated for less than 5 years. Justifying this data, the authors "emphasized that the effect of BPs on bone turnover is fully exerted within the first year of treatment, thereafter remaining at a constant level without any evidence of a cumulative effect over time".[48,49]

With chronic and growing use of BPs, dozens of new case reports of atypical femur fractures are described every year in specialty meetings,[26] further increasing these statistics. As described, clinical (prodromal pain for weeks to months prior to the fracture, lack of precipitating trauma, bilaterality, poor fracture healing, and normal or low bone mass but not osteoporosis in the hip region) and radiological (presence of stress reaction on the affected and/or unaffected side, transverse or short oblique fractures, and cortical hypertrophy or thickness) features specific of these fractures suggest an 'unusual' phenomenon with a probable systemic pathogenesis.

Bisphosphonates and atypical fractures - Epidemiologic studies

The association between BPs use and ST/ FS fractures was examined in several controlled epidemiologic studies. In a retrospective case-control study[50] of postmenopausal women, 41 cases of low-trauma ST/ FS fractures were identified and matched by age, race, and body mass index to one intertrochanteric (IT) and one femoral neck (FN) fracture occurring within the same period (2000 to 2007). BP use was observed in 37% (15 of 41) of ST/ FS fracture patients compared with 11% (9 of 82) of IT/ FN fracture patients (OR 4.44, 95% CI, 1.77-11.35). Duration of BP use was longer in ST/ FS cases compared with both hip fracture control groups ($P = 0.001$). Radiographs showed fractures with a transverse or oblique orientation, cortical thickening, and localized diffuse bone formation on the lateral cortex in 67% (10 of 15) of patients on a BPs and in 11% (3 of 26) of patients who were not taking a BPs (OR 15.33, 95% CI, 3.06-76.90, $P < 0.001$).

In a cross-sectional of 11,944 Danish people over age 60 years, Abrahamsen *et al.*[51] compared age-specific fracture rates, BP exposure, and trauma mechanisms between different types of proximal femur fractures. Alendronate exposure was the same (around 7%) in patients with atypical (ST/ FS) and typical (IT/ FN) fractures. In a register-based cohort analysis, they also showed that patients with atypical femur fractures were no more likely to be on alendronate treatment than patients with typical fractures. However, these designs of studies cannot distinguish between atypical and typical fractures through the radiographic features, that is an important limitation. This same problem occurred in another similar epidemiologic studies.[52-54]

In another case-control study to explore the association between BP use and fracture in a cohort of women aged 68 years or older from Ontario, Canada, Park-Wyllie *et al.*[55] identified 716 women who sustained a ST/ FS fracture following initiation of BP therapy and 9,723 women who sustained a typical osteoporotic fracture of the IT/ FN region. Compared with transient (< 100 days) BP use, treatment for 5 years or longer was associated with an increased risk of ST/ FS fracture (adjusted odds ratio 2.74, 95% CI, 1.25-6.02). A reduced risk of typical osteoporotic fractures occurred among women with more than 5 years of BP therapy (adjusted odds ratio 0.76, 95% CI, 0.63-0.93). This association was not present among those with short-term (100 days to 3 years) BP use (adjusted odds ratio 0.90, 95% CI, 0.48-1.68) and was increased but not statistically significant among intermediate (3 to 5 years) BP use (adjusted odds ratio 1.59, 95% CI, 0.80-3.15). Among 52,595 women with at least 5 years of BP therapy, a ST/ FS fracture occurred in 71 (0.13%) during the subsequent year and 117 (0.22%) within 2 years.

In another large national cohort study comprising a total of 197,835 subjects (679,500 patients-years), Abrahamsen *et al.*[56] examined the risk of subtrochanteric or diaphyseal femur fracture in long term uses of alendronate in 39,567 treated patients (132,500 patient-years) and 158,268 untreated controls (547,000 patient-years). Subtrochanteric/ diaphyseal fractures occurred at a rate of 13 per 10,000 patient-years in untreated women and 31 per 10,000 patients in women receiving alendronate [adjusted hazard ratio (HR) 1.88, 95% CI, 1.62-2.17]. Rates for men were 6 and 31 per 10,000 patient-years, respectively (HR 3.98, 95% CI, 2.62-6.05). The HR for hip fracture was 1.37 (95% CI, 1.30-1.46) in women and 2.47 (95% CI, 2.07-2.95) in men. Risks of subtrochanteric/ diaphyseal fractures were similar in patients who had received 9 years of treatment (highest quartile) and patients who had stopped therapy after the equivalent of 3 months of treatment (lowest quartile). As another studies, the most important limitation to the present study is the lack of access to radiographs of patients to verify fracture locations and examine signs of atypia. In conclusion, this large national health database study confirms that atypical fractures are common in BP users than can be explained by age, sex, and available information on comorbidity and comedications, but there seems to be no relationship to the cumulative amount of alendronate used (the risk was significantly lower with greater cumulative amounts of alendronate), suggesting another pathogenic mechanism than the currently accepted (increase secondary mineralization and accumulation of microdamage), as indicates the systematic review of Giusti *et al.*[3]

The association between BP use and atypical fracture was confirmed in another recent population-based study conducted in Sweden with 12,777 women 55 years of age or older.[57] Were reviewed radiographs of 1,234 of the 1,271 women who had a ST/ FS fracture and identified 59 patients with atypical fractures. The relative risk (RR) of atypical fracture associated with BP use was 47.3 (95% CI, 25.6 to 87.3); however, the increase in absolute risk was only 5 per 10,000 patient-years (95% CI, 4 to 7). A total of 78% of the case patients and 10% of the controls had received BPs, corresponding to a multivariable-adjusted odds ratio (OR) of 33.3 (95% CI, 14.3 to 77.8). The risk was independent of coexisting conditions and of concurrent use of other drugs with known effects on bone. The duration of use influenced the risk (OR 1.3 per 100 daily doses, 95% CI, 1.1 to 1.6). Of particular interest, also suggesting another pathogenic mechanism than the currently suggested, the study reported that the risk of atypical fracture decreased rapidly after discontinuation of BP therapy. The study estimated that the risk of atypical fracture decreased by 70% annually after discontinuation (OR 0.28, 95% CI, 0.21-0.38) and that the crude incidence among those who last used BP 1 to 2 years ago was 0.1 per 10,000 patient-years, only slightly above that among those who never used BP (crude incidence 0.09 per 10,000 patient-years).

In these epidemiological studies it is clear the association between the occurrence of atypical fractures of femur and the use of BPs for a variable period of time (3 months to 9 years), indicating no relationship to the cumulative amount of alendronate used. It is worth mentioning that this variable period of time (time-point) for the manifestation of the phenomenon is related to the 'long biological half-life' of the BPs (5 years of action after 1 year of treatment), peculiar aspect of the drug's pharmacodynamic that prevents the immediate observation of the 'rebound effect' after the suspension of the same. This specific pharmacological property (long-term retention in skeleton and persistence of their effect after discontinuation of treatment) also justify the manifestation of atypical fractures after a period of 5 years of treatment, observed in many clinical studies.

Antiresorptive drugs and atypical fractures - Pathogenic mechanisms

BPs have a very high affinity for bone mineral, because they bind to hydroxyapatite crystals. Accordingly, BP skeletal retention depends on availability of hydroxyapatite binding sites because BPs are preferentially incorporated into sites of active bone remodeling, as commonly occurs in conditions characterized by accelerated bone turnover. In addition to their ability to inhibit calcification, BPs inhibit hydroxyapatite breakdown, thereby effectively suppressing the osteoclastic activity and bone resorption. This fundamental property of BPs has led to their utility as clinical agents. In experimental animals,[58-60] alendronate has been shown to inhibit normal repair of microdamage arising from marked suppression of bone turnover, resulting in accumulation of microdamage. A 2- to 7-fold increase in microdamage accumulation after pharmaceutical suppression of bone remodeling was associated with a 20% reduction in bone toughness (the ability to sustain deformation without breaking), without reduction in bone strength.[59-61]

In addition to microdamage accumulation, chronic over suppression of bone turnover by alendronate may allow secondary mineralization to continue,[62] producing hyper

mineralized bone that may be more brittle. The degree of mineralization has been shown to affect the material properties of bone, with low mineralization levels (as seen in osteomalacia) causing reduced stiffness and strength, and hypermineralization likely contributing to reduced fracture toughness.[63,64] However, the clinical significance of these changes in biomechanical measurements has not yet been well defined.

With the purpose of broadening the understanding of the pathogenesis of atypical fractures after BPs therapy, few reports included bone turnover markers (BTMs). When measured, however, bone resorption markers (osteoclastic activity) are usually within the normal premenopausal range and occasionally are elevated. In only minority of cases have BTMs been suppressed.[26] To study the 'biphasic anti-osteoclastic action' of BPs, Kitano *et al.*[65] analyzed the changes in urinary cross-linked N-telopeptides of collagen (u-NTx), the most dynamic and reliable BTM,[66] and urinary calcium (u-Ca) after intravenous alendronate therapy in ten patients with multiple myeloma bone disease. In all patients, the levels of u-NTX and u-Ca decreased within a week. After the maximum decrease of the both BTMs started increasing (rebound) in half of the patients. However, this further increase in u-NTX decreased again without any additional therapy. Disease severity and pretreatment u-NTx concentration did not differ between patients with and without the rebound phenomenon. Patients who did not have rebound had decreased bone marrow monocytes and decreased serum concentrations of interleukin 18, which is produced by monocytes, possible osteoclast precursors.[67]

The mechanism of these 'biphasic anti-osteolytic effects' of alendronate ('rebound of osteoclastic activity') is explaining by the authors: "Alendronate is adsorbed onto the bone mineral surface and the osteoclasts that are present on the bone mineral surface selectively absorb alendronate. This induces the apoptosis of the activated osteoclasts, leading to a decrease in osteolytic markers. However, osteoclast precursors, which are not present on the bone mineral surface, survive and generate new osteoclasts, with the help of osteolysis-inducing factors. The new osteoclasts, which infiltrate the bone mineral surface, may contribute to a rebound of bone resorption. Apoptosis is induced in the newly infiltrated osteoclasts due to absorption of the remaining alendronate present on the bone mineral surface. In this hypothesis, rebound refers to newly generated osteoclasts.[…] An osteoclast is a terminally differentiated, multinuclear cell with a unique ability to absorb bone. Mononuclear precursor cells that differentiate into osteoclasts circulate in the monocytes population".

Analogously, few reports have included histology or histomorphometry of bone taken from or close to the ST fracture site (unlike a substantial number of case studies that included histomorphometric analysis of iliac crest bone biopsies, ineffective to elucidate pathogenesis of atypical fractures). Somford *et al.*[42] reported clinical, biochemical and radiological findings of a 76-year-old woman with rheumatoid arthritis who had been treated with alendronate for 8 years prior to admission for a ST stress fracture of her left femur, which subsequently fracture completely. Nine months after the left femur fracture, she sustained a ST fracture of her right femur. At that time, biopsies were obtained from the iliac crest and the right femur. The histomorphometric indices from the ST fracture site suggested, again, a 'rebound of osteoclastic activity': "Cancellous bone parameters of

structure and microarchitecture were normal compared with age- and sex-matched controls. The bone formation parameters in the iliac crest were highly decreased but were within the previously described range in patients with postmenopausal and glucocorticoid-induced osteoporosis treated with alendronate. In contrast, the eroded surfaces were markedly increased: these were 3-fold higher than controls, and 6.5- to13-fold higher than after alendronate treatment of glucocorticoid-induced and postmenopausal osteoporosis, respectively. The number of osteoclasts was also increased, being 4-fold higher than that previously reported after alendronate treatment. Despite the absence of control values for femoral cortex, the eroded surfaces appeared extended with numerous osteoclasts. The osteoclasts number was six times higher in the femoral cortex than in iliac cancellous bone. They had all the morphological characteristics of active osteoclasts, contained several nuclei, and were in contact with the cremated bone surfaces. Only a few of them contained more than 15 nuclei. These osteoclasts were different from the giant apoptotic osteoclasts reported after treatment with alendronate, which have a lightly stained cytoplasm, contain a high number of pyknotic nuclei, and are detached from a shallow resorption cavity. As in cancellous bone, the static bone formation parameters were low".

Somford *et al.*[42] also took the opportunity to assess the mineralization density of the bone tissue at the fracture site because some have suggested that prolonged BP treatment may lead to hypermineralized and, therefore, brittle bone matrix. Presenting similar data to histomorphometric analysis of Giusti *et al.*,[36] there was no evidence of hypermineralization and no change in hydroxyapatite crystal size, although the crystals were more mature than in control subjects, consistent with the known effects of alendronate on bone turnover and secondary mineralization. These data suggest an alternative pathogenic mechanism that involves increased resorption coupled with reduced bone formation (imbalance between bone resorption and bone formation at the affect femur rather than excessive suppression of bone turnover), consistent with the rebound effect of palliative drugs.

Boonen *et al.*[37] reinforced the theory of "imbalance between bone resorption and bone formation" as the more plausible explanation of pathogenesis of bone fractures: "During antiresorptive therapy, the magnitude of BTM suppression achieved differs depending on the marker being measured and the agent administered. BTM levels generally increase from their on-treatment level when treatment is discontinued, although the magnitude and speed of this offset differs among agents. The degree of offset that occurs following treatment discontinuation may fall into one of two categories: (1) BTM levels slowly increase toward pretreatment baseline levels but usually do not reach baseline levels at the end of follow-up (up to 5 years with bisphosphonates) or (2) BTM levels increase to above pretreatment baseline levels within 1 year after discontinuation (rebound effect). These scenarios also pertain to posttreatment changes in BMD. The magnitude and rate of BMD or BTM offset may be of clinical significance because, even in treated patients, bone density and bone remodeling may be determinants of bone strength and thus, fracture risk".[68] It should be noted that the rapidity and the magnitude of BTM change are dependent on the marker being measured, with C-telopeptide type I collagen being the most dynamic and reliable marker among other commonly used BTMs.[66,69]

The authors described the rebound effect of bone resorption after withdrawal of others antiresorptive drugs (hormone therapy and human monoclonal antibody).[37] Hormone therapy (HT) produces significant increases in BMD and reductions in BTMs. With discontinuation of HT, efficacy against hip fracture is lost after 3 to 5 years (compared with on-treatment values).[70,71] This loss of fracture protection is accompanied by a decrease in BMD and an increase in BTM levels that temporary exceed baseline (rebound effect).[72-74] Denosumab is a fully human monoclonal antibody that inhibits receptor activator of nuclear factor kB ligand (RANKL), a ligand required for osteoclast formation, function, and survival.[75] The 3-year Fracture Reduction Evaluation of Denosumab in Osteoporosis (FREEDOM) every 6 months RCT demonstrated that denosumab significantly reduced the risk of new radiographic vertebral fractures, hip fractures, and nonvertebral fractures in postmenopausal women with osteoporosis.[76] Denosumab therapy is associated with BMD increases and BTM decreases, both of which continue with treatment beyond 3 years for up to 6 years (Phase II study).[77,78] Hip and spine BMD continue to increase throughout the initial 3 years and during the extension follow-up, in contrast to the plateau in BMD usually observed with bisphosphonates after 2 to 3 years. Similarly to HT, has been observed the decline in BMD and the rise in BTMs following discontinuation of denosumab in both a Phase II multidose trial and a Phase III osteoporosis prevention study.[78,79]

The BMD decline that occurs after denosumab discontinuation is mirrored by an increase of BTM levels to above pretreatment baseline levels. In the Phase II multidose trial, discontinuation of denosumab after 24 months led to increases in serum C-telopeptide of type I collagen and bone-specific alkaline phosphatase (BSAP) levels to values substantially above the pretreatment baseline within 12 months of treatment cessation. This rebound of BTMs is accompanied by a reactivation of basic multicellular units (new osteoclasts) with a new focus of bone remodeling and a prominent BMD loss. Levels of both markers returned toward baseline in the second year of discontinuation even with no further therapy. The rebound rise of BTMs above baseline after denosumab discontinuation is similar to the pattern seen after discontinuation of estrogen therapy (HT), although with denosumab, rebound occurs earlier. A similar pattern was also observed with odanacatib (a selective cathepsin K inhibitor that reduces the function of osteoclasts and the bone resorption), in a 2-year study in which a transient rise in BTMs above baseline after treatment discontinuation was seen.[80] According to the authors, the implication of this 'rebound effect' on the clinical outcomes "is not clear".[37]

Despite the initial hypotheses of the pathogenesis of atypical fractures suggest that long-term residence time of BPs in bone and prolonged suppression of bone turnover may impair the ability of bone to remodel, leading to accumulation of microdamage and compromised bone strength, histomorphometric analysis and clinical significance of these changes in biomechanical measurements do not confirm this pathogenic mechanism. On the other hand, experimental studies confirm the 'biphasic anti-osteolytic effects' of alendronate (rebound of osteoclastic activity) as the main mechanism of action in the genesis of atypical fractures.[42,65,36]

Rebound effect in modern pharmacology

Adverse event (AE) or reaction (AR) to drugs are defined by the World Health Organization (WHO)[81] as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function". Despite the 'rebound effect' be an adverse event which may take serious consequences, it is little publicized and discussed before health professionals, depriving them of a fundamental knowledge to secure management of modern drugs.

According to Webster's New World Medical Dictionary,[82] the term 'rebound' is defined as "the reversal of response upon withdrawal of a stimulus", while 'rebound effect' means "the production of increased negative symptoms when the effect of a drug has passed or the patient no longer responds to the drug; if a drug produces a rebound effect, the condition it as used to treat may come back even stronger when the drug is discontinued or loses effectiveness". Also described by the term 'paradoxical reaction' of the organism, one of the ironies of this phenomenon is that the rebound effect causes the patient to experience the very same effects they were hoping nullify through palliative drugs use, deconstructing the main pillar of modern pharmacological therapy.

As a general physiological explanation, rebound effect is what happens when the body tries to bring itself back into balance (homeostasis) after a drug has been taken by pulling in the opposite direction of the drug. Although the exact mechanism remains unclear, the main hypothesis is that the rebound phenomenon may be caused by an increased responsiveness (up regulation) of the receptors to the drug. By definition, the more evident rebound effect of the organism happen after withdrawal of palliative (enantiopathic or antipathic) treatment, with decrease or elimination of the drug serum concentration and the consequent partial or total vacating of the receptors, allowing the manifestation of the paradoxical reaction of the organism in the sense of returning to the initial homeostasis altered by the pharmacological agent, producing symptoms with intensities superior to the symptoms initially suppressed by the palliative drugs. As intrinsic aspect to the observation of the phenomenon, the minimum time (time-point) should be taken into account to observe the real magnitude of the rebound effect, which generally corresponds to the biological half-life of the drug. The rebound effect or paradoxical reaction of the organism also lasts a variable period of time (hours to weeks), depending on the properties of drugs and of individual idiosyncrasy.[83-86]

Studying carefully the rebound effect or paradoxical reaction of the organism after the suspension or discontinuation of various classes of modern drugs, numerous descriptions of worsening of symptoms in intensity and/or frequency greater than the start of treatment are found, which correspond to the secondary action or vital reaction of the organism (homeopathic model) to maintain the internal balance changed initially by palliative action of drugs.[3-10]

Evidenced by clinical and experimental pharmacology,[5-10] the common properties of the rebound effect or paradoxical reaction of the organism are described to all classes of drugs: (i) it appears only in susceptible individuals, who present in their constitution symptoms similar to the pathogenetic effects of the drug; (ii) it does not depend on the drug, repetition

of doses or type of symptoms (disease); (iii) it appears after the primary action of the drug (discontinuation), as an automatic manifestation of the organism; (iv) it induces an organic state (symptoms) opposite and greater in intensity and/or duration than the primary action of the drug; (v) the magnitude of its effect is proportional to the intensity of the primary action of the drug.

Despite the idiosyncratic nature of such phenomenon, which appears in a minority of individuals, contemporary scientific evidences point to the occurrence of 'severe and fatal iatrogenic events' as a function of the paradoxical reaction of the organism following the discontinuance of several classes of modern palliative drugs.[5-10]

Rebound effect of antiresorptive drugs

Contrary to what was believed initially as main hypothesis for the emergence of atypical fractures of the femur after use of BPs,[45] histomorphometric analysis of biopsies obtained from affected femur revealed 'no evidence of hypermineralized bone' and 'no change in hydroxyapatite cristal size', indicating that there is an increase in the mineral maturity after alendronate treatment without any modifications in the crystallinity index. Analogously, lacking evidence that 'suppression of bone turnover', particularly of cortical bone with already low remodeling rates, may 'impair the ability of bone remove microdamage', resulting in its accumulation and consequently impairment of its strength. Authors suggest that atypical fractures are a separate entity representing an 'uncommon' adverse event of alendronate treatment.[36,42,87-89]

Although there are few studies that correlate atypical fractures of femur with the 'biphasic anti-osteolytic effect' or 'rebound of osteoclastic activity' after BPs withdrawal, the increase of BTMs (C-telopeptide type I collagen) after a maximum decrease caused by BPs action is an irrefutable proof of the rebound phenomenon. As other evidence, the histomorphometric analysis of biopsies from the ST fracture site also suggests a rebound of osteoclastic activity, showing a significant increase of the eroded surfaces (3-fold higher than controls; 6.5- to 13-fold higher than after alendronate treatment of glucocorticoid-induced and postmenopausal osteoporosis, respectively). The number of active osteoclasts (several nuclei) was also increased, being 4-fold higher than that previously reported after alendronate treatment, and 6-fold higher in the femoral cortex than in iliac cancellous bone. These data suggest that after a primary (direct) action of BPs inhibiting the osteoclastic activity occurs a secondary (indirect) and opposite reaction of the organism to maintain the constancy of internal environment (homeostase) increasing significantly the osteoclastic activity.[36,42,65]

Another data that demonstrates an 'unusual' mechanism is that the decrease in bone formation observed in these biopsies was not coupled to a decrease in bone resorption as expected by antiresorptive therapy. Worth to emphasize that bone resorption parameters (eroded surfaces and osteoclast number) were higher than those measured in osteoporotic patients treated with alendronate and were markedly increased in the femur specimen. The increase in osteoclast number in the femur was not caused by the BP action, because these cells were attached to the bone surface and were morphologically active. The possibility

that these were caused by the fracture itself is also unlikely. In this way, these data provide evidence that an imbalance between bone resorption and bone formation at the affected femur rather than excessive suppression of bone turnover may be the mechanism underlying the occurrence of ST/ FS fractures in patients treated with BPs.[36,42,90-92]

As other intrinsic aspect of the rebound phenomenon, the 'long biological half-life' of the antiresorptive drugs should be taken into account. Contrary to the currently association of atypical fractures with long-term BP treatment and/or long biological half-life of BPs,[20-22] the systematic review of 141 cases[36] revealed that in 25% of patients atypical fractures occurred within less than 3 years of BP treatment, and ST fractures appeared to be more frequent in women treated for less than 5 years. Justifying this data, the authors "emphasized that the effect of BPs on bone turnover is fully exerted within the first year of treatment, thereafter remaining at a constant level without any evidence of a cumulative effect over time" (long-term BP treatment), indicating that the 'long biological half-life' of BPs is responsible to the late manifestation of the rebound effect after drug withdrawal.[48,49] Analogously, a large case-control study[56] showed that risk of ST/ FS fractures were similar in patients who had received 9 years of treatment and patients who had stopped therapy after 3 months of treatment, indicating no relationship to the cumulative amount of alendronate used, reinforcing the rebound effect as pathogenic mechanism of these atypical fractures.

The rebound bone resorption, increasing BTMs, osteoclastic activity and propensity to fractures, is also described after withdrawal of others antiresorptive drugs (hormone therapy, human monoclonal antibody, and selective cathepsin K inhibitor).[37]

In the so-called bisphosphonate-related osteonecrosis of the jaw (BRONJ),[24,33,93,94] despite the absence of studies with BTMs and histology/ histomorphometric analysis of biopsies that indicating in this direction, probably the similar mechanism of bone injury (rebound effect) is related to the 'unclear' pathogenesis of this serious adverse event.

Discussion

Osteoporosis is a disease characterized by reduced bone mass and increased skeletal fragility affecting 10 million Americans, and more than 75 million people worldwide (20-30% of postmenopausal women). Bisphosphonates are widely prescribed to avoid typical fractures in osteoporotic patients; more than 150 million prescriptions were dispensed in the USA to outpatients between 2005 and 2009.[95,96]

Fragility or insufficiency fractures are a type of stress fracture that occurs in osteoporotic bone subjected to normal levels of stress. They typically occur in the vertebrae, hip, distal radius, and the proximal humerus following minimal or no trauma, but only rarely in the proximal femur. The subtrochanteric region of the femur is one of the strongest parts of the femur and it is unlikely to fracture in low-energy trauma unless extreme osteoporosis is present. The reports of multiple cases of low-impact femoral fractures in patients who were

taking alendronate, a previously rare event, have therefore called for the possible connection between alendronate and such fractures.[33,97,98]

These atypical ST/ FS fractures are characterized by unique radiographic features (transverse or short oblique orientation, absence of comminution, cortical thickening, stress fracture or stress reaction on the symptomatic and/or contralateral side) and unique clinical features (prodromal pain, bilaterality and delayed healing). While the incidence of atypical femur fracture is quite low, considerable morbidity ensues, especially in the fairly frequent case of bilaterality.

Analogously with the preliminary observations of the rebound effect in other classes of palliative drugs,[3-10] experimental studies indicate a secondary increase in the osteoclastic activity after a primary decrease by bisphosphonates. According to the definition of the rebound effect, the increase in the osteoclastic activity was sometimes more intense than the basal values, both on the eroded surface and in the osteoclast number. This magnitude of the phenomenon explains the fracture without trauma in one of the strongest regions of femur, as well as the orientation of fracture and the delayed healing. These points reinforce the rebound effect as a pathogenic mechanism of atypical fractures of the femur.

While hip fracture incidence has declined since BPs began to be used in the USA, ST/ FS fractures increased over the same period.[28,29] Although the incidence of ST fractures is much lower than other femoral fractures, they are not rare and account for about 3-5% of all femoral fractures in the elderly.[27-29,99] If these estimates were applied to the UK, then more than 2,000 ST fractures are expected to occur each year, and approximately 48,000 are expected annually worldwide.[100,101]

With similar estimates to the rebound effect of other drugs, epidemiologic studies showed that the number of atypical subtrochanteric fractures in association with bisphosphonates is estimated in 1-3 per 1,000 patient-years (0,1-0,3%).[55,56,99] Long-acting beta-agonists cause approximately 1 rebound bronchospasm followed by death every 1,000 patient-years, corresponding to 4,000-5,000 death-years in 2004 in the USA alone (40,000-50,000 worldwide).[7] Selective serotonin reuptake inhibitors cause approximately 5 rebound suicidality events every 1,000 patient-teenager-years, corresponding to 16,500 suicidal behavior or thoughts in 2007 only in USA.[8] Salicylates cause approximately 4 rebound acute myocardial infarction every 1,000 patient-years.[102,103] Studies described the increased incidence of gastric carcinoids in last decades (400% in men and 900% in women) in view of the growing consumption of the proton pump inhibitors.[10]

Conclusion

If doctors and other health professionals were aware of the possibility of occurrence of the rebound effect of modern palliative drugs, a large number of serious adverse events could be avoided, preventing the paradoxical aggravation of the clinical state with the slow and gradual discontinuation of the drugs.[104] Although they are not included to the conventional

adverse event of drugs, "drug discontinuation effects are part of the pharmacology of a drug",[86] and should be routinely incorporated into the teaching of modern pharmacology.

In all studies that confirmed the relationship between atypical femoral fractures and BPs use, the authors warn of the care required in the approach of these patients, avoiding serious consequences: "Physicians need to be aware that patients on bisphosphonates who experience low-impact femoral fractures may require additional evaluation and treatment along with surgical fixation. This might include bone scans to detect other stress fractures, stopping alendronate therapy, and referral to specialists knowledgeable in treating these unusual cases".[33]

It is worth mentioning that Hahnemann made this same warning more than two centuries ago (Organon, paragraphs 59-61), evidencing the precocity and validity of homeopathic assumptions before the modern scientific knowledge.

Confirming the principle of similitude as 'natural law', the continuing modern reports of increased iatrogenic events after withdrawal of palliative drugs demonstrates the importance of the rebound phenomenon (homeopathic vital reaction) in promoting deep alterations in the organic balance. Using this rebound effect of curative form, homeopathy stimulates the body to react against their own diseases.

Analogously to traditional homeopathic medicines, the rebound effect of 'allopathic' drugs can be used for therapeutic purposes, namely to stimulate homeostatic healing reactions provided they are prescribed according to the principle of similitude as it was described in previous studies (www.newhomeopathicmedicines.com).[1]

Exemplifying this proposal in the homeopathic treatment of osteoporosis, are described in the *Homeopathic Repertory of Modern Drugs* (HRMD),[105] chapter 'Generalities', rubric 'Osteopenia, osteoporosis', 20 conventional drugs that caused osteopenia/ osteoporosis as adverse event (primary action or pathogenetic manifestation), which could be employed in accordance with the principle of therapeutic similitude on osteoporotic patients, in order to wake up a curative rebound effect (secondary action or reaction vital) of the organism. (Table 1)

Table 1. Osteopenia/ osteoporosis in HRMD (Chapter Generalities)

Osteopenia, osteoporosis.

- density, bone, decreased: *Leup-syst.*, *Mom-inhloc.*
  - males who have had an orchiectomy or who have been treated with a gonadotropin-releasing hormone analog [GnRHa]): *Gos-syst.*
  - mineral density, loss of.
    - female patients: **Nafa-syst.**
  - vertebral trabelucar bone density, loss of: *Leup-syst.*
- osteopenia (bone pain, tenderness, or aching; loss of appetite; muscle weakness; unusual weight loss): *Barb-syst.*, *Carbam-syst.*, *Cortic-rec.*, *Isot-syst.*
  - osteopenic effect, weak.
    - dogs: *Dal-syst.*
- osteoporosis (pain in back, ribs, arms, or legs; decrease in height; includes vertebral

compression and long bone pathologic fractures): *Cholest-orloc.*, *Cortic-inhloc.*, *Cortic-rec.*, *CorticG-syst.*, *Dal-syst.*, *Fluda-syst.*, *Fludro-syst.*, *Flut-inhloc.*, *Hepar-syst.*, *Isot-syst.*, *Nad-syst.*, *Proge-syst.*, **Sir-syst.**, *Tacro-syst.*

- fracture, osteoporotic (pain or swelling in arms or legs without any injury): *Proge-syst.*
- risk of: *Nad-syst.*
- vertebral compression and long bone pathologic fractures, with: *CorticG-syst.*

Barb-syst.: Barbiturates (Systemic); Carbam-syst.: Carbamazepine (Systemic); Cholest-orloc.: Cholestyramine (Oral-Local); Cortic-inhloc.: Corticosteroids (Inhalation-Local); Cortic-rec.: Corticosteroids (Rectal); CorticG-syst.: Corticosteroids Glucocorticoid Effects (Systemic); Dal-syst.: Dalteparin (Systemic); Fluda-syst.: Fludarabine (Systemic); Fludro-syst.: Fludrocortisone (Systemic); Flut-inhloc.: Fluticasone (Inhalation-Local); Gos-syst.: Goserelin (Systemic); Hepar-syst.: Heparin (Systemic); Isot-syst.: Isotretinoin (Systemic); Leup-syst.: Leuprolide (Systemic); Mom-inhloc.: Mometasone (Inhalation-Local); Nad-syst.: Nadroparin (Systemic); Nafa-syst.: Nafarelin (Systemic); Proge-syst.: Progestins (Systemic); Sir-syst.: Sirolimus (Systemic); Tacro-syst.: Tacrolimus (Systemic).

As stated in the referred proposal *(New homeopathic medicines: use of modern drugs according to the principle of similitude),*[1,105] the individualization of homeopathic medicine in accordance with the symptomatic totality is a fundamental premise for the therapeutic success, and the *Homeopathic Materia Medica of Modern Drugs*[105] should be queried to achieve this goal. Completing this therapeutic approach, any 'allopathic' drug prescribed by the law of similarity should be administered in the 'dynamized' form (*ultra-high dilutions*), to avoid possible adverse events or aggravations.

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Immunomodulatory drugs (natalizumab), worsening of multiple sclerosis, rebound effect and similitude[13]

[Reference: Teixeira MZ. Immunomodulatory drugs (natalizumab), worsening of multiple sclerosis, rebound effect and similitude. *Homeopathy*. 2013; 102(3): 215-224. Available at: https://doi.org/10.1016/j.homp.2013.05.001.]

Abstract

Homeopathic treatment is based on the principle of similitude ('like cures like') administering to sick individuals substances that cause similar symptoms in healthy individuals, employing the paradoxical or biphasic action of the organism as therapeutic response. This homeostatic, vital or secondary action of the organism is scientifically explained by the rebound effect of drugs, resulting in worsening of symptoms after enantiopathic treatment withdrawal. Natalizumab reduces relapses in patients with active multiple sclerosis (MS), but recent studies report severe worsening of MS after suspension of treatment, as a consequence of the rebound effect. Extending this source of evidence, this work reviews research that demonstrates secondary worsening of multiple sclerosis (MS) after discontinuation of natalizumab, a human monoclonal antibody that suppresses the disease inflammatory activity as primary action. Several studies refer to the immune reconstitution inflammatory syndrome (IRIS) as a plausible explanation of reactivation of MS after withdrawal of natalizumab: a rebound effect or secondary action of the organism in response to the primary immunosuppression caused by the drug. Relapses of MS after discontinuation of natalizumab treatment indicate rebound of disease activity, supporting the homeopathic principle and warning healthcare professionals about this serious iatrogenic event.

Introduction

The pharmacodynamic action of homeopathic medicine or principle of similitude ('like cures like') is based on the 'primary action of the drug followed by secondary and opposite action of the organism', described many times in various classes of drugs[1,2]:

> "Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed *primary action.* […] To its action our vital force endeavors to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of *secondary action* or *counter-action".* (*Organon*, paragraph 63)

Proposing to employ such 'secondary action' in a curative way, Hahnemann suggested employ medicines that in their 'primary action' elicit symptoms similar to the ones of

[13] Teixeira MZ. Immunomodulatory drugs (natalizumab), worsening of multiple sclerosis, rebound effect and similitude. *Homeopathy*. 2013; 102(3): 215-224. Available at: https://doi.org/10.1016/j.homp.2013.05.001.

natural disease, widening thus the notion of curative similitude: 'every substance capable to provoke certain symptoms in healthy individuals (due to the primary action of the drug), can be used to cure similar symptoms in the sick (through the secondary reaction of the organism), according to the therapeutic similitude principle'. (*Organon,* paragraphs 24-28)

Hahnemann claimed that such secondary action is observed "in each and every instance with no exceptions", with substantial or infinitesimal doses, in both healthy and ill individuals, raising the principle of similitude to the level of "natural law of cure". (*Organon,* paragraphs 58, 61, 110-112)

Criticizing the method of treatment by contraries (enantiopathic, antipathic or palliative treatment), which "after such short antipathic amelioration, aggravation follows in every case without exception" (*Organon*, paragraphs 58, 59, 65), Hahnemann refers to the serious damage that this secondary action of the organism can bring to the health condition, as "another, more serious disease or, frequently, incurability, even danger of life and death itself" (*Organon,* paragraphs 60, 61).

In the terms of modern pharmacology, Hahnemann's 'primary action' corresponds to the 'therapeutic, adverse and side effects' of conventional drugs, whereas the 'secondary action' (vital or homeostatic reaction) corresponds to the 'rebound effect' or 'paradoxical reaction' of the organism, appearing after the discontinuance or alteration of dosage *(withdrawal syndrome)* of drugs acting contrarily to the symptoms of diseases.

As I have pointed out in previous studies,[3-11] the properties of the rebound effect are the same as the secondary action or vital reaction described by Hahnemann: (i) it appears only in susceptible individuals, who present in their constitution similar symptoms to the pathogenetic effects of the substance; (ii) it does not depend on the substance, repeated doses or type of symptoms (disease); (iii) it appears after the primary action of the substance, as an automatic manifestation of the organism; (iv) it induces an organic state opposite and greater in intensity and/or duration to the primary action of the substance; (v) its magnitude is proportional to the intensity of the primary action of the substance. The rebound effect of modern drugs can also be used in a therapeutic sense, stimulating curative homeostatic reactions.[12,13]

Broadening such evidence to a new drug class, this study describes scientific research demonstrating secondary worsening (paradoxical or rebound) of multiple sclerosis after discontinuation of natalizumab, a human monoclonal antibody (immunomodulatory drug or biologic response modifier) whose intended primary action is improvement in the disease progression.

Methods

I reviewed the literature (2002-2012) using the Medline database and the keywords 'multiple sclerosis', 'natalizumab', 'rebound', 'progressive multifocal

leukoencephalopathy' and 'immune reconstitution inflammatory syndrome', selecting the most consistent papers and discussing the scientific evidences according to Hahnemann's postulates.

Results

Multiple sclerosis and natalizumab

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) that affects some 2.5 million people worldwide. Although the exact disease mechanism is not completely clear, it is known that both environmental and genetic factors influence the development of MS. MS usually starts in the third or fourth decade of life and follows a relapsing clinical course, the most common form is: relapsing-remitting MS (RRMS). The majority of these patients enter a disease phase characterized by continuous, irreversible neurological decline: secondary progressive MS (SPMS). Approximately 50% of all patients require help in walking 15 years after diagnosis, the median time to reaching a high degree of disability is some 30 years. A substantial percentage of MS patients have their first attack during childhood.[14-16]

The objective of any therapy seeking to modify MS is to reduce the frequency and severity of relapse, and to prevent or delay evolution toward a progressive phase. The evidence available suggests that MS is a disease of autoimmune etiology and its treatment is currently based on immunomodulatory drugs such as glucocorticosteroid, interferon (IFN), glatiramer acetate, natalizumab, fingolimod, among others. Current hypotheses hold that a core event in the pathogenesis of MS is the activation of auto-reactive T lymphocytes in the periphery that, after proliferating and crossing the blood-brain barrier, trigger a cascade of inflammatory events in the CNS culminating in axonal demyelination and damage. The migration of leukocytes across the blood-brain barrier requires the interaction between adhesion molecules expressed on the cell surface, such as selectins and integrins, and their endothelial receptors. In particular, the combination of the high affinity between α4β1 and α4β7 integrins and the vascular cell adhesion molecule-1 (VCAM-1) allows the cells to adhere to the vascular endothelium and initiate transendothelial migration.[17]

Natalizumab (Tysabri) is a humanized monoclonal antibody that keeps leukocytes from migrating across the blood-brain barrier. In May 2012, approximately 99,600 MS patients had received natalizumab worldwide, for at least 12 months.[18] With an IgG4 structure, natalizumab is a selective adhesion molecule inhibitor that recognizes and binds specifically to the α4 subunit of α4β1 and α4β7 integrins. This drug blocks binding between the endothelial VCAM-1 and the α4β1 and α4β7 integrins expressed on the surface of activated T lymphocytes and other mononuclear leukocytes, keeping them from adhering to the endothelium, preventing cell migration and recruitment toward the parenchyma, and the subsequent inflammatory activity in the CNS. Natalizumab has a good risk-benefit ratio in MS patients, reducing the frequency of outbreaks, the progression of disability, and the

lesions quantified by neuroimaging. It has also been investigated for the treatment of Crohn's disease and rheumatoid arthritis.[15,19,20]

When doses of between 1-3 mg/kg of natalizumab are administered to healthy volunteers or to MS patients, drug concentrations are detectable in blood for 3-8 weeks. After a single dose, peak serum concentrations are reached slowly, over the course of 1-2 hours following administration, despite the fact that the drug is distributed mainly in the vascular system and hardly diffuses to the tissues. The concentration in blood slowly reduces, with a half-life of 1-2 weeks, maintaining elevated levels of α4 integrin saturation during this time. Persistence in blood is increased by increasing the dose the normal dose is 300 mg intravenously every 4 weeks. With this schedule, the saturation of α4 integrin is greater than 70% four weeks after the last dose of natalizumab. If the drug is suspended, its plasma concentrations and biological effects can persist for up to 12 weeks. If its elimination must be accelerated, measures such as plasmapheresis or plasma exchange (PLEX) are used. These decrease natalizumab plasma concentrations by 92% after three exchanges of 1.5 plasma volumes. However, the α4 integrin saturation may not decrease in parallel. Five exchanges of 1.5 plasma volumes alternate days lower natalizumab concentrations to below 1 μg/mL and α4 integrin saturation to less than 50% in 95% of patients. For this reason the biological effects can persist for several months after the suspension of natalizumab.[15,21,22]

Efficacy of natalizumab in the treatment of multiple sclerosis

Two main randomized controlled trials (AFFIRM study, 900 patient-years; and SENTINEL study, 1,200 patient-years)[23,24] evaluated the efficacy of natalizumab in the treatment of RRMS, including patients with an Expanded Disability Scale Score (EDSS: 0 to 5.0), lesions on cerebral magnetic resonance imaging (MRI) compatible with MS, and suffering at least one relapse in the preceding 12 months. The SENTINEL study also required prior treatment with IFNβ-1a for at least 12 months before randomization. In both trials the efficacy and safety of 300 mg intravenously of natalizumab every 4 weeks were compared to placebo.

The proportion of relapse-free patients during the 2 years in the AFFIRM and SENTINEL studies was 67 and 54% in the natalizumab groups, as compared to 41 and 32% in the placebo groups, respectively ($P < 0.001$). The cumulative likelihood of progression of disability at the 2-year endpoint was also significantly less in the natalizumab groups, with hazard ratios of 0.58 and 0.76 (EDSS), a decrease of 42 and 24%, respectively, in the risk of progression of disability versus placebo. The MRI findings in the natalizumab groups showed 83% fewer new or growing hyperintense lesions in T2-weighted sequences versus placebo ($P < 0.001$), and 89-92% fewer gadolinium-enhancing lesions in T1-weighted sequences ($P < 0.001$) after 2 years of treatment. These data suggest a sustained and relevant effect of treatment with natalizumab in the clinical and radiological response.[23-25]

In a retrospective analysis in patients from the AFFIRM study,[26] a significantly larger proportion of patients treated with natalizumab was found to be free of clinical activity (64% vs. 39%; $P < 0.0001$), free of radiological activity (58% vs. 14%; $P < 0.0001$), and

free of disease activity (37% vs. 7%; P < 0.0001) compared to the placebo group during the 2-year study period.

The more common adverse events reported with natalizumab were headache, dizziness, vomiting, nausea, arthralgias, urinary tract infection, nasopharyngitis, tremors, fever, fatigue, urticaria, and hypersensitivity reactions. Treatment with natalizumab is associated with an increase in plasma concentrations of lymphocytes, monocytes, eosinophils, and basophils. This effect is consistent with drug's mechanism of action, which decreases cell migration outside the bloodstream. Similarly to what is seen with other peptidic therapeutic agents, natalizumab can induce the formation of anti-natalizumab antibodies during its administration.[15]

Natalizumab and progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is a rare but serious demyelinating opportunistic infection of the central nervous system (CNS), encountered most frequently in the setting of immunodeficiency. The disease is caused by the human polyomavirus JC virus (JCV), a widespread infection in humans. In developed countries, between 70-90% of all adults have detectable antibodies against the JCV. Primary infection takes place at young ages and is typically asymptomatic, the mechanisms of transmission are not clearly understood. Subsequently, the virus remains quiescent in the kidneys, lymph organs, and possibly, in the CNS. PML typically appears when the immune system is compromised and it has been postulated that it occurs as a consequence of the reactivation of the latent JCV or due to an adaptive mutation that fosters infection of the CNS. PML is now mostly frequently associated with human immunodeficiency virus (HIV) infection. JCV in the cerebrospinal fluid (CSF) provides the laboratory confirmatory diagnosis of PML in patients whose clinical symptoms and MRI findings are consistent with the disease.[27-29] There is no treatment of proven efficacy for PML, the disease generally progresses to death, with a mean survival of 6 months.[30]

To confirm the diagnosis of PML, three criteria are required: progressive clinical disease, MRI findings typical of PML, and detectable JCV in the CSF.[31] Clinically, PML is characterized by subacute onset of neurological deficits, including cognitive, visual, and motor disorders. The MRI scan of the brain generally reveals bilateral, asymmetric sub-cortical lesions on the brainstem and cerebellum, hypointense in T2-weighted sequences and fluid-attenuated inversion recovery (FLAIR), without enhancement after the administration of contrast and without significant mass effect. In an appropriate clinical and radiological context, the diagnosis is supported by PCR detection of JCV DNA in the CSF, with an approximate sensitivity of 80% and specificity exceeding 95%.[27,28] This test may initially be negative (false negative rate of 3%), and in case of diagnostic suspicion, it is recommended that it be repeated. In PML cases, viral persistence and neurological deficits have continued for several years, indicating that once initiated, JCV infection may not entirely clear.[15,29,32] Other authors state that clinical vigilance is the most important factor in diagnosis of PML, because there is no firm evidence that JCV DNA can predict which patients ultimately develop PML .[33-39]

In February 2005, shortly before it was completed, the SENTINEL study was suspended as a result of 2 reports of PML in patients who had been receiving natalizumab in combination with IFNβ-1a; subsequently, another case of PML was reported in a patient treated with natalizumab for Crohn's disease.[40-43] Still in 2005, Yousry *et al.* conducted an evaluation to determine new cases of PML in 3,417 patients who had participated in clinical trials with natalizumab for MS, Crohn's disease or rheumatoid arthritis.[31] No new cases were identified, and the incidence of PML was estimated to be 1.0 per 1,000 treated patients (mean of 18 doses monthly). In view of this result and the demonstrated clinical efficacy, natalizumab was reintroduced for the treatment of RRMS in June 2006.

Although postmarketing experience has substantiated the impressive efficacy of natalizumab, the ability of this agent to increase the development of PML in a small percentage of patients has also been confirmed. In recent years, one to two cases per month have been reported, with 31 cases reported by the end of January, 2010.[44] Based on the 170 cases reported worldwide in 2011, the overall risk of PML in patients exposed to natalizumab was estimated to be 1.82 per 1,000 treated patients.[45-47] In accordance with recent alert of the US Food and Drug Administration (FDA),[48] the risk of getting PML is greatest (about 11 per 1,000 treated patients) if the patient has all three known risk factors: the presence of anti-JCV antibodies, which reflects prior exposure to JCV; treatment with natalizumab longer than 2 years; and prior treatment with immunosuppressive agents. By early 2012[18], 242 cases of PML had been reported (90 in the United States., 141 in Europe and 11 in the rest of the world).

The concept of PML being an opportunistic infection arising during immune suppression dates back to its earlier description as a disease and the impaired immune surveillance provoked by natalizumab therapy is at least a partial explanation for causality. Details of how JCV is transformed to an agent with the capability of invading and targeting the CNS are not entirely clear, but the direct relationship between the duration of therapy with natalizumab and incidence of PML has been established.[18,47,49,50]

Natalizumab withdrawal, immune reconstitution inflammatory syndrome (IRIS) and rebound effect

Although the bases of the causal relation between exposure to natalizumab and PML are uncertain, discontinuation of natalizumab is a priority in the treatment of PML.[27,30] Since the biological effects of natalizumab may last for months, PLEX is one method to accelerate its elimination, although its efficacy may be limited due to high affinity of natalizumab for α4 integrin, which can cause sustained immunosuppression despite having eliminated the drug from the circulation.[21]

However, natalizumab withdrawal in patients with MS and PML can be associated with an immune reconstitution inflammatory syndrome (IRIS) that causes a serious paradoxical worsening of neurologic deficits or previous condition (exacerbation of symptoms or enlarging lesions or increased gadolinium enhancement on MRI). While classically associated with enhanced inflammatory responses to infectious processes (PML-IRIS for example), IRIS has also been associated with noninfectious immune-mediated conditions

including systemic lupus erythematosus and autoimmune thyroid disorders. Potential mechanisms for this syndrome include reconstitution or recovery of the immune system after natalizumab withdrawal: a rebound effect to a higher level than prior to treatment. According to recent data, many patients in whom natalizumab was withdrawn due to PML and who underwent PLEX developed IRIS days to weeks after the procedure. In these cases, glucocorticosteroid treatment may be considered.[18,22,51-53]

Some authors describe the natalizumab-related IRIS with a similar mechanism directed against normal myelin antigens as an explanation of this rebound. Natalizumab therapy is associated with a reduction in cerebrospinal fluid CD4 and CD8 T lymphocytes, CD19 B cells and CD138 plasma cells, and a reduction in the cerebrospinal fluid CD4/CD8 ratio. Reporting a clinical MS relapse in the patients with the highest total cerebrospinal fluid CD4 and CD8 T cell count after cessation of natalizumab therapy, the same authors suggested that a more rapid return of immune surveillance and function may be associated with IRIS in patients with MS. Histologically, actively demyelinating lesions that are otherwise typical of MS are seen.[18,52,54]

A number of effects on peripheral lymphocyte populations, as a result of changes in levels of pro-inflammatory and anti-inflammatory cytokines, have been described in chronically treated patients. In some cases, these mimic changes seen during acute exacerbations, which may explain the reported postnatalizumab rebound in MS disease activity.[18,52,55,56]

Even without serologically-documented PML, some MS patients develop a paradoxical worsening of clinical symptoms after cessation of natalizumab, suggesting that IRIS can occur even if there is no viral infection or viral antigen to drive the process. This 'CNS IRIS sans PML infection' is referred as 'natalizumab withdrawal syndrome' or 'natalizumab rebound effect'.[18]

Confirming this physio-pathological mechanism, Metz et al.[53] described IRIS histopathology observed in brain biopsy tissue of four MS patients with negative JCV DNA, and who had discontinued natalizumab. Immunohistological analysis of brain tissue showed inflammatory demyelinating lesions and nondemyelinated white and grey matter, both with an extensive CD8-dominated T cell infiltrate.

Natalizumab withdrawal and rebound effect - Observational studies (Table 1)

Contrasting studies denied rebound effects,[23,24,57-59] while others showed worsening of the initial disease activity in a variable period of observation after natalizumab withdrawal ('CNS IRIS sans PML' or rebound effect). Vellinga *et al.*[60] compared the annualized number of new MRI lesions in the period before patients started with natalizumab vs. the 15-month interval after withdrawal of natalizumab. In a group of 21 patients from the AFFIRM[23] and SENTINEL[24] studies, the median annualized number of active T2 lesions increased in the postwithdrawal interval compared with the pretreatment period, suggesting "a significant rebound increase in the development of new and enlarging T2 lesions in patients with MS who discontinued natalizumab treatment". In view of that the "biological

effects of natalizumab may be observed up to 6 months after withdrawal". The authors also question the short follow-up period after drug suspension of other studies.[57,58]

The half-life of biological effects of any drug should be considered in studies aimed at assessing the occurrence of the rebound effect, because the secondary action of the organism usually occurs when after the primary action of the drug. Recall that α4 integrin saturation decreases more slowly than the natalizumab plasma concentrations, and biologic effects of the natalizumab can be observed several months after total drug depletion (PLEX).[21,22] Ignoring this factor can lead to bias in the analysis of the rebound phenomenon. [31,57-59,61]

Tubridy *et al.*,[62] reported an early phase II trial of a two natalizumab infusions for acute MS relapses and observed a rebound increased relapse rate compared to placebo in the second 12-week period following treatment. Other authors relate the rebound effect of the study of Vellinga *et al.*[60] to short-term treatment (mean of 2 doses).[63,64] However, several studies have demonstrated the rebound effect after the suspension of long-term treatment, with negative anti-natalizumab antibodies and undetectable JCV in the CSF.

In a series of 7 cases that receiving between 7-14 doses of natalizumab, an altered mental state or fatigue was detected 3 months after treatment withdrawal with multiple gadolinium-enhancing lesions on cerebral MRI (mean: 14; range: 8 to 21). Treatment with corticosteroids resulted in clinical and radiological resolution. The authors suggest that this phenomenon might be due to restitution of the lymphocytic flow in the CNS (rebound effect) and propose the name CIRIS (CNS IRIS).[15,65]

Killestein *et al.*[39] report observations in 10 patients with RRMS who after 12 months of natalizumab treatment had a favorable clinical and radiological response to the drug, then discontinued treatment for a variety of reasons. At 6-7 months after treatment withdrawal, a combination of clinical relapse and new and/or enhanced lesions on cerebral MRI had occurred in 7 of 10 patients (disease activity started to occur about 3 months after discontinuation of natalizumab). The extent of clinical and radiological disease activity was striking, and none of the patients showed clinical or radiological signs and symptoms that suggested PML. These data suggested a possible rebound of disease activity in some patients.

West *et al.*[66] reviewed medical records of 84 patients with MS who received 12 or more infusions of natalizumab of which 84% (68/84) underwent a dosage interruption. Of those with a treatment withdrawal, 28% (19/68) experienced a clinical relapse within 6 months of suspension (median 3 months), whereas none who had continuous treatment experienced a flare during months 12-18 of treatment (P = 0.0017). 7 patients (7/68, 10%) experienced unusually severe flare with a mean number of 16 gadolinium-enhancing lesions on cerebral MRI (range: 6-40), associated with limited recovery of neurological function. Their median EDSS at natalizumab discontinuation was 3.0 and increased to 6.0 during the flare (P = 0.0008). PML was ruled out by either cerebral MRI or lumbar puncture (undetectable JCV). The authors concluded that natalizumab dosage interruption is associated with clinical flares and return of radiographic inflammatory disease activity. Some of these

flares were alarmingly severe, with a high number of contrast-enhanced lesions, suggesting a rebound of disease activity in 10% of the patients.

Reviewing the data of 28 cases of PML in patients with MS treated with natalizumab over three years (2006-2009), Clifford *et al*.[51] conclude that "exacerbation of symptoms and enlargement of lesions on MRI have occurred within a few days to a few weeks after PLEX, indicative of immune reconstitution inflammatory syndrome (IRIS)". Despite the authors diagnosing PML, the data indicate probable rebound of disease activity: initial diagnosis of exacerbation of MS in several patients; development of enlarging MRI gadolinium-enhancing lesions in 43% (12/28) of patients; undetectable JCV in 57% (16/28) of patients; and 71% of patients survived with the aggressive use of corticosteroids, an unusually high rate for PML.

A clinical and radiological retrospective analysis[67] studied a total of 27 patients with very active RRMS before natalizumab (mean annualized relapse rate of 2.3, MRI activity in 21 of 27 patients). Within 6 months of discontinuing natalizumab treatment for more than 12 months, 18 patients (67%) experienced clinical relapse and 3 patients had radiological activity, without clinical relapse. According to the authors, four patients (15%) experienced a rebound of disease activity, with both severe relapse and 20 or more gadolinium enhancing lesions on MRI.

After a 4 month drug holiday, a prospective cohort study analyzed recurrent MS disease activity in 32 patients who had received at least 12 consecutive natalizumab infusions.[52] 38% patients with RRMS and SPMS experienced relapses during therapy interruption, but relapses were severe with unusually widespread with evidence of inflammatory activity on MRI in several patients with SPMS with greater inflammatory disease activity prior to starting natalizumab therapy. Imaging and CSF findings in these cases were suggestive of IRIS, not PML. Overall, relapses occurred more often in younger patients with fewer natalizumab infusions prior to therapy interruption. In patients who experienced a relapse, the mean (SD) number of gadolinium-enhancing lesions after drug holiday was significantly greater than prior to starting natalizumab therapy [9.5 (12.4) vs. 2.0 (2.6), $P < 0.001$], with an estimated increase of 4.8 gadolinium-enhancing lesions. The authors concluded that MRI and clinical disease activity returned, often aggressively (rebound effect), following discontinuation of natalizumab therapy.

Another prospective study reported clinical and radiological outcomes of 23 patients with MS treated with natalizumab for 24 months and submitted with a treatment interruption of 90-150 days, receiving monthly intravenous steroid pulse to avoid the risk of developing PML. MRI scanning was scheduled at baseline (30 days prior to starting natalizumab) and after 6, 12, and 24 months of therapy. Despite the steroid cover, seven patients (30%) had an active scan with one or more contrast-enhancing lesions after a mean time of 105 days (interval 60-143). Two patients (9%), completely stable during natalizumab treatment, showed a dramatic return of disease activity, with severe disabling relapse and numerous large contrast-enhancing lesions at MRI scan, significantly higher than the baseline (rebound effect).[68]

In a recent series of four cases, Baumgartner *et al.*[69] described patients who experienced a clear clinical and radiological rebound reactivation of disease activity several months after cessation of long-term natalizumab therapy (15-29 months). Three patients experienced a severe clinical relapse between 3 and 9 months after therapy withdrawal, and the fourth developed cerebral MRI activity showing more than 20 gadolinium-enhanced lesions. According to the authors, "it needs to be considered whether the disease reactivation described here can actually be defined as disease reactivation or rebound characterized by a higher disease activity after treatment discontinuation compared with the disease activity before treatment initiation. Most likely, the pretreatment natural high disease activity returned after the cessation of the highly potent therapy with natalizumab. However, the fact that three out of four patients developed disease activity despite immunomodulatory therapy might indicate a rebound phenomenon. Moreover, the severe clinical and radiological progression in fourth patient indicates a rebound phenomenon. A possible rebound could be based on immunological mechanism similar to those of immune reconstitution inflammatory syndrome".[52] As in the other studies cited above, these patients remained stable during the treatment phase, and the disease activity returns to normal with the reintroduction of the therapy (corticosteroid or natalizumab), suggesting 'CNS IRIS sans PML' or rebound effect.

Havla *et al.*[70] described a striking rebound of SM activity in a patient that discontinued long-term therapy with fingolimod, a new oral immunomodulatory agent that causes selective retention of lymphocytes in lymph nodes, and reduces their infiltration into the CNS.[71] Three months after discontinuation of treatment, the patient experienced a severe relapse with EDSS score progression from 2.5 to 4.5. Brain and spinal MRI showed a rebound of disease activity with a drastic increase of gadolinium-enhancing lesions (> 20). In 2011,[72] it was estimated that approximately 25,000 patients were treated with fingolimod and more than 20,000 patient-years of exposure; with more than 20,000 patients on the drug.

Anti-tumor necrosis factor (TNF) drugs (infliximab, adalimumab, etanercept), are another class of biologic response modifier that have significantly improved functional outcomes in patients with rheumatoid arthritis (RA). But onset or aggravation of demyelinating diseases, probably due to the rebound increased of pro-inflammatory cytokines after suspension of treatment has been described.[73]

Table 1. Observational studies of worsening of multiple sclerosis due to rebound effect after natalizumab withdrawal

Authors	Patients (N)	Natalizumab treatment	JCV in CSF	Results - Rebound effect
Vellinga *et al.*[60]	21	2 doses	undetectable	Increase of active T2 lesions on cerebral MRI
Perumal *et al.*[65]	7	7-14 doses	undetectable	Altered mental state or fatigue with multiple (8-21) active T2 lesions
Killestein *et al.*[39]	10	12 doses	undetectable	Clinical relapse and new and/or active T2 lesions in

				70% of patients
West *et al*.[66]	84	≥ 12 doses	undetectable	Severe clinical relapse with a high number of active T2 lesions in 10% of patients
Clifford *et al*.[51]	28	36 doses	undetectable in 57% of patients	Exacerbation of symptoms and enlargement of T2 lesions in 43% of patients
Kerbrat *et al.*[67]	27	> 12 doses	undetectable	Severe clinical relapse and multiple (> 20) active T2 lesions in 15% of patients
Miravalle *et al.*[52]	32	12 doses	undetectable	Severe clinical relapse and increase of active T2 lesions in 38% of patients
Borriello *et al.*[68]	23	24 doses	undetectable	Increase of active T2 lesions in 30% of patients, with 9% with severe disabling relapse and numerous large active T2 lesions
Baumgartner *et al.*[69]	4	15-29 doses	undetectable	Severe clinical relapse in 3/4 patients and multiple (> 20) active T2 lesions in 1/4 of patients

JCV in CSF: JC virus in cerebrospinal fluid

Discussion

The current hypotheses concerning the pathogenesis of MS is that is related to the activation of auto-reactive T lymphocytes in the periphery that, after proliferating and crossing the blood-brain barrier, trigger a cascade of inflammatory events in the CNS culminating in axonal demyelination and damage.

Several observational studies suggest that the immune reconstitution inflammatory syndrome ('CNS IRIS sans PML') is a more plausible explanation of MS reactivation after natalizumab withdrawal than progressive multifocal leukoencephalopathy (PML), CNS IRIS is defined as worsening of neurologic deficits during the restoration of cellular immunity following discontinuation of natalizumab, corroborated by inflammatory changes on neuroimaging. In its primary immunomodulatory action, natalizumab impacts the trafficking of immune cells and blocked the autoimmune action. Secondarily, the cessation of natalizumab effects can cause immunologic rebound with IRIS, typically with recovery of immune surveillance in the CNS. Natalizumab is associated with peripheral sequestration of proinflammatory cells, cytokine-producing T cells, which may be the direct action of natalizumab or a secondary action from peripheral accumulation. The peripheral proinflammatory cytokines and activated cells are increased so that when natalizumab is removed the rebound restoration of immune response is overwhelming.[22,74]

Thus IRIS is the result of the rebound effect or secondary action of the organism in response to the primary immunosuppression caused by natalizumab.

Other aspects described in previous studies support a rebound mechanism (as opposed to PML) as the pathogenetic mechanism of the worsening of MS after suspension of natalizumab. Viral persistence and neurological deficits have continued for several years in PML, indicating that once initiated, JCV infection may not entirely clear. However, although the diagnosis of PML is clearly supported by PCR detection of JCV DNA in the CSF, with 80% of sensitivity and more than 95% of specificity, but was negative or undetectable in the vast majority of the cited cases.

Natalizumab discontinuation is a priority in the treatment of PML. However, it is precisely the suspension of natalizumab that triggers of deterioration of MS activity. There is no treatment for PML and the disease generally progresses to death. However, in the reported patients, the disease activity returns to normal with the reintroduction of the therapy (natalizumab or corticosteroids), without the fatal outcome described in PML.

The cited rebound of disease activity was “unusually”, “alarmingly”, “aggressively” or “drastic”, with severe clinical relapses and high number of enhancing lesions on MRI, “with greater inflammatory disease activity prior to starting natalizumab therapy”. This also explains the fact that the most severe relapses were observed in patients with greater inflammatory disease activity prior to starting natalizumab.

Individual susceptibility or idiosyncrasy must also be taken into account in the analysis of the phenomenon, allowing that relapses occurred more often in younger patients with fewer natalizumab infusions prior to therapy interruption.

According to cited studies, the incidence of rebound disease activity after discontinuation of natalizumab was greater than 10% (9-15%), higher than the estimates for PML. Considering that in 2012 more than 99,600 patients with MS had received natalizumab worldwide, one can infer that more than 10,000 patients may have severe worsening of disease activity after suspension of the drug.

As well as having been observed with natalizumab, fingolimod and TNF antagonists drugs, recent studies have demonstrated a high frequency and intensity of rebound effect after suspension of other immunomodulatory agents in other diseases,[75-79] alerting to the possible risks of this new class of antagonistic drugs (biologic response modifiers), which presents more effective physiological action than other classes. This observation is based on an intrinsic property to the rebound phenomenon, in which the magnitude of the secondary action of the organism is directly proportional to the intensity of the primary action of the drug.

Conclusion

Despite the idiosyncratic nature of the rebound phenomenon, which manifests in a minority of individuals, contemporary scientific evidence points to the occurrence of severe and fatal iatrogenic events as a function of this paradoxical reaction of the organism following the discontinuance of several classes of modern palliative drugs. In recent years, researchers raised alerts to the increased risk of the rebound effect of drugs,[80] strengthening the scientific basis of the principle of similitude in modern pharmacology. Broadening the scope of evidence described in previous studies[5-11], new researches reinforce the occurrence of the rebound effect after discontinuation of aspirin,[81-84] anti-inflammatory drugs,[85-87] statins,[88-92] long-acting β-agonist bronchodilators,[93-99] antidepressant drugs,[100-103] and proton-pump inhibitors.[104-106]

Natalizumab is a recombinant monoclonal antibody raised against α-4 integrin. It is indicated for the treatment of patients with multiple sclerosis (MS). Although it has high therapeutic efficacy, natalizumab has been linked to progressive multifocal leukoencephalopathy (PML) as a serious adverse effect. Furthermore, drug discontinuation sometimes induces rebound disease activity or CNS IRIS. This rebound effect cause worsening of MS with increased of demyelinating lesions in more than 10% of the patients that discontinuing the treatment, with serious complications if not diagnosed and treated in a timely manner.

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Other scientific publications

Title: Fundamentação científica do princípio de cura homeopático na farmacologia moderna.
Author: Marcus Zulian Teixeira
Source: *Revista de Homeopatia (São Paulo)* 2017; 80(Supl 1/2): 27-51.
Summary: Introdução: O modelo homeopático de tratamento utiliza o 'princípio dos semelhantes' como método terapêutico, administrando medicamentos que causam determinados sintomas em indivíduos sadios para tratar sintomas semelhantes em indivíduos doentes *(similia similibus curantur),* com o intuito de despertar uma reação secundária e curativa do organismo contra os seus próprios distúrbios. Essa reação secundária (vital, homeostática ou paradoxal) do organismo está embasada no 'efeito rebote' dos fármacos modernos, evento adverso observado após a descontinuação de diversas classes de drogas que utilizam o 'princípio dos contrários' *(contraria contrariis curantur)* como método terapêutico. Objetivo: Esta revisão visa fundamentar cientificamente o princípio de cura homeopático perante a farmacologia clínica e experimental, através do estudo sistemático do efeito rebote dos fármacos modernos ou reação paradoxal do organismo. Métodos: Empregando como fonte de referência os estudos e revisões sobre o tema que vimos publicando desde 1998, atualizamos os dados acrescentando pesquisas recentes citadas na base de dados PubMed. Resultados: O efeito rebote ocorre após a descontinuação de inúmeras classes de fármacos com ação terapêutica contrária aos sintomas das doenças, exacerbando-os a níveis superiores aos anteriores do tratamento. Independente da doença, da droga, da dose e da duração do tratamento, o fenômeno rebote se manifesta numa pequena proporção de indivíduos suscetíveis. Seguindo as premissas homeopáticas, os fármacos modernos também podem ser utilizados segundo o princípio da similitude terapêutica, empregando o efeito rebote (reação paradoxal) de forma curativa. Conclusões: Evidenciado em centenas de estudos que atestam a similaridade de conceitos e manifestações, o efeito rebote dos fármacos modernos fundamenta cientificamente o princípio de cura homeopático. Embora o fenômeno rebote seja um evento adverso estudado pela farmacologia moderna, ele não é conhecido pelos profissionais da saúde, privando a classe médica de um saber indispensável ao manejo seguro dos fármacos.
Available at: ResearchGate

Title: Scientific basis of the homeopathic healing principle in modern pharmacology.
Author: Marcus Zulian Teixeira
Source: *Revista de Homeopatia (São Paulo. Online)* 2017; 80(3/4): 36-81.
Summary: Introduction: Homeopathy employs the so-called 'principle of similars' as therapeutic method, which consists in administering medicines that cause certain symptoms in healthy individuals to treat similar symptoms in sick individuals *(similia similibus curantur)* to arouse a secondary and healing reaction by the body against its own disorders. This secondary (vital, homeostatic or paradoxical) reaction of the body is based on the 'rebound effect' of modern drugs, a type of adverse event that occurs following

discontinuation of several classes of drugs prescribed according to the 'principle of contraries' *(contraria contrariis curantur).* Aim: The present review sought to scientifically substantiate the homeopathic healing principle vis-à-vis experimental and clinical pharmacology through a systematic study of the rebound effect of modern drugs or paradoxical reaction of the body. Methods: Employing as reference the studies and revisions on the subject that we have published since 1998, we updated the data adding recent studies cited in database PubMed. Results: The rebound effect occurs after discontinuation of several classes of drugs with contrary action to the symptoms of diseases, exacerbating them to levels above the ones present before treatment. Regardless of disease, drug, dose and duration of treatment, the rebound phenomenon manifests in a small proportion of susceptible individuals. Following the homeopathic premises, modern drugs might also be used according to the principle of therapeutic similitude, thus employing the rebound effect (paradoxical reaction) in a curative manner. Conclusions: Evidenced in hundreds of studies that attest to the similarity of concepts and manifestations, the rebound effect of modern drugs scientifically substantiates the principle of homeopathic cure. Although the rebound phenomenon is an adverse event studied by modern pharmacology, it is not known by healthcare professionals, thus depriving doctors of knowledge indispensable for a safe management of drugs.
Available at: http://revista.aph.org.br/index.php/aph/article/view/408

Title: Fundamentação científica do princípio de cura homeopático na farmacologia moderna.
Author: Marcus Zulian Teixeira
Source: *Revista de Homeopatia (São Paulo. Online)* 2017; 80(1/2): 40-48.
Summary: Introdução: O modelo homeopático de tratamento utiliza o 'princípio dos semelhantes' como método terapêutico, administrando medicamentos que causam determinados sintomas em indivíduos sadios para tratar sintomas semelhantes em indivíduos doentes *(similia similibus curantur),* com o intuito de despertar uma reação secundária e curativa do organismo contra os seus próprios distúrbios. Essa reação secundária (vital, homeostática ou paradoxal) do organismo está embasada no 'efeito rebote' dos fármacos modernos, evento adverso observado após a descontinuação de diversas classes de drogas que utilizam o 'princípio dos contrários' *(contraria contrariis curantur)* como método terapêutico. Objetivo: Esta revisão visa fundamentar cientificamente o princípio de cura homeopático perante a farmacologia clínica e experimental, através do estudo sistemático do efeito rebote dos fármacos modernos ou reação paradoxal do organismo. Métodos: Empregando como fonte de referência os estudos e revisões sobre o tema que vimos publicando desde 1998, atualizamos os dados acrescentando pesquisas recentes citadas na base de dados PubMed. Resultados: O efeito rebote ocorre após a descontinuação de inúmeras classes de fármacos com ação terapêutica contrária aos sintomas das doenças, exacerbando-os a níveis superiores aos anteriores do tratamento. Independente da doença, da droga, da dose e da duração do tratamento, o fenômeno rebote se manifesta numa pequena proporção de indivíduos suscetíveis. Seguindo as premissas homeopáticas, os fármacos modernos também podem ser utilizados segundo o princípio da similitude terapêutica, empregando o efeito rebote (reação paradoxal) de forma curativa. Conclusões: Evidenciado em centenas de estudos que

atestam a similaridade de conceitos e manifestações, o efeito rebote dos fármacos modernos fundamenta cientificamente o princípio de cura homeopático. Embora o fenômeno rebote seja um evento adverso estudado pela farmacologia moderna, ele não é conhecido pelos profissionais da saúde, privando a classe médica de um saber indispensável ao manejo seguro dos fármacos.
Available at: http://revista.aph.org.br/index.php/aph/article/view/391

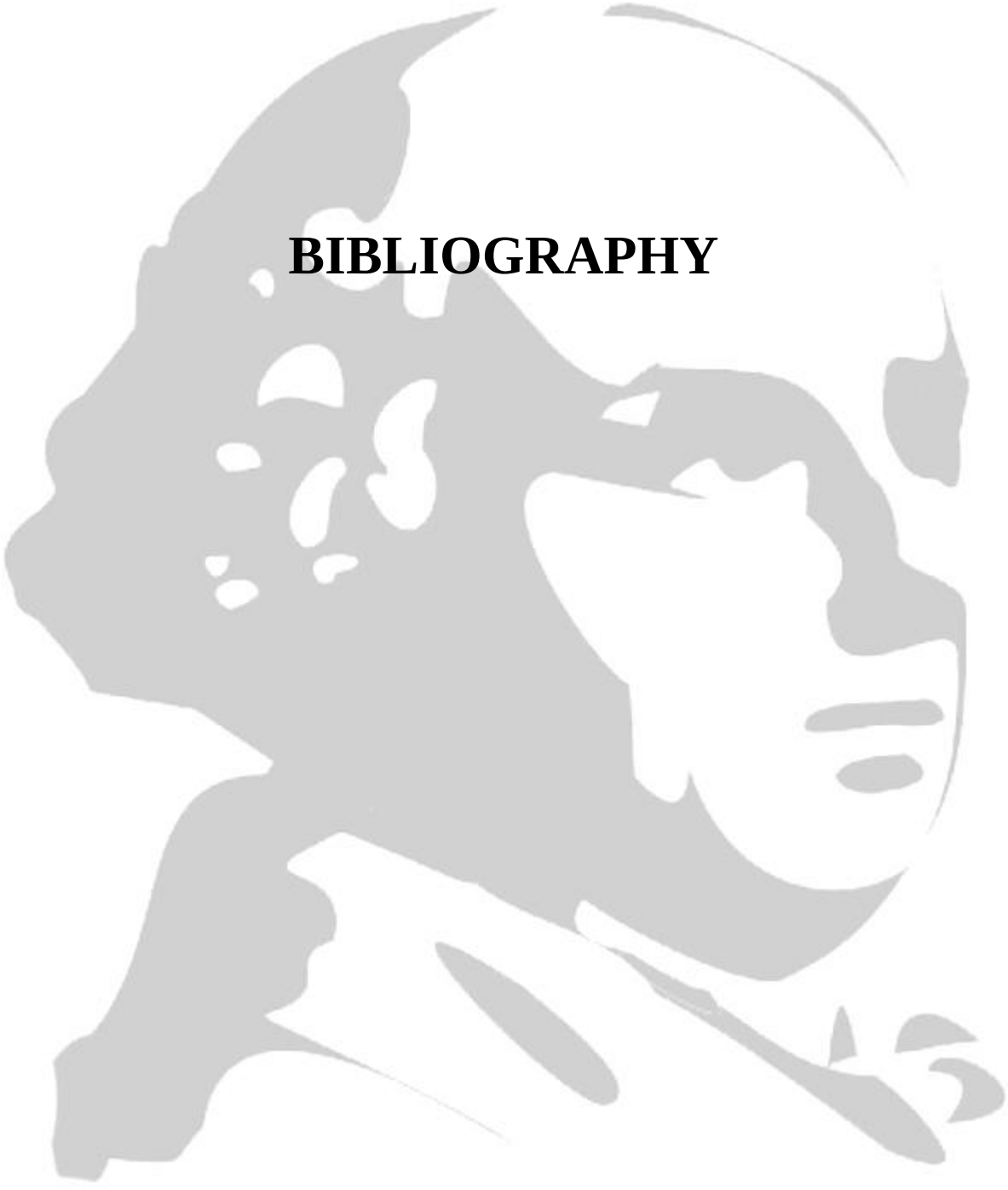
Title: Therapeutic use of the rebound effect of modern drugs: "New homeopathic medicines" [Uso terapêutico do efeito rebote dos fármacos modernos: "Novos medicamentos homeopáticos"].
Author: Marcus Zulian Teixeira
Fonte: *Revista da Associação Médica Brasileira* 2017; 63(2): 100-108.
Summary: The homeopathic treatment is based on the principle of therapeutic similitude, employing medicines that cause certain disorders to treat similar manifestations, stimulating a reaction of the organism against its own ailments. The occurrence of this secondary reaction of the organism, opposite in nature to the primary action of the medicines, is evidenced in the study of the rebound (paradoxical) effect of several classes of modern drugs. In this work, in addition to substantiate the principle of similitude before the experimental and clinical pharmacology, we suggest a proposal to employ hundreds of conventional drugs according to homeopathic method, applying the therapeutic similitude between the adverse events of medicines and the clinical manifestations of patients. Describing existing lines of research and a specific method for the therapeutic use of the rebound effect of modern drugs (http://www.newhomeopathicmedicines.com), we hope to minimize prejudices related to the homeopathy and contribute to a broadening of the healing art.
Available at: https://doi.org/10.1590/1806-9282.63.02.100

Title: Biological therapies (immunomodulatory drugs), worsening of psoriasis and rebound effect: new evidence of similitude [Terapias biológicas (drogas imunomoduladoras), agravamento da psoríase e efeito de rebote: novas evidências da similitude].
Author: Marcus Zulian Teixeira.
Fonte: *Homeopathy* 2016; 105(4): 344-355.
Summary: *Background:* Homeopathic treatment is based on the principle of similitude ('like cures like') administering to sick individuals substances that cause similar symptoms in healthy individuals, employing the paradoxical or biphasic action of the organism as therapeutic response. This homeostatic, vital or secondary action of the organism is scientifically explained by the rebound effect of drugs, resulting in worsening of symptoms after enantiopathic treatment withdrawal. Natalizumab reduces relapses in patients with active multiple sclerosis (MS), but recent studies report severe worsening of MS after suspension of treatment, as a consequence of the rebound effect. *Method:* Extending this source of evidence, this work reviews research that demonstrates secondary worsening of MS after discontinuation of natalizumab, a human monoclonal antibody that suppresses the disease inflammatory activity as primary action. *Results:* Several studies refer to the

immune reconstitution inflammatory syndrome (IRIS) as a plausible explanation of reactivation of MS after withdrawal of natalizumab: a rebound effect or secondary action of the organism in response to the primary immunosuppression caused by the drug. *Conclusion*: Relapses of MS after discontinuation of natalizumab treatment indicate rebound of disease activity, supporting the homeopathic principle and warning healthcare professionals about this serious iatrogenic event.
Available at: https://doi.org/10.1016/j.homp.2016.09.002

Title: Similitude and rebound effect of drugs: scientific evidence and therapeutic application [Similitude e efeito rebote das drogas: evidência científica e aplicação terapêutica].
Author: Marcus Zulian Teixeira.
Source: *Homoeopathic Links* 2014; 27(2): 105-107.
Summary: *Samuel Hahnemann* systematised the homeopathic model and the effects of drugs on the state of human health, describing a primary action of the drugs followed by a secondary and opposite action of the organism. In modern pharmacology, this secondary action is known as the rebound effect or paradoxical reaction of the organism, being described after the discontinuation of several classes of palliative (enantiopathic) drugs, i.e., those that act according to the principle of contrary *(contraria contrariis curentur).* Besides being able to cause severe and fatal iatrogenic events when appearing after the palliative use of modern drugs, the rebound effect might awaken a healing reaction if the very same drugs involved were employed according to the principle of similitude *(similia similibus curentur).*
Available at: https://doi.org/10.1055/s-0034-1368339

Scientific Basis of the Principle of Similitude in Modern Pharmacology



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