REVIEW ARTICLE
ARTIGO DE REVISÃO

Economic evaluation of antipsychotics for the treatment of schizophrenia: a systematic review

Avaliação econômica de antipsicóticos para o tratamento da esquizofrenia: uma revisão sistemática

André Soares Santos[1], Isabella Piassi Godói[1], Carlos Eduardo Leal Vidal[2], Cristina Mariano Ruas[3]

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Keywords:
schizophrenia, antipsychotic agents, review, cost-benefit analysis

ABSTRACT

Objective: The aim of this study is to conduct a systematic review on cost-effectiveness analysis of oral antipsychotic agents to identify the trend of cost-effectiveness of drugs available for the treatment of schizophrenia. **Methods:** A search was conducted in three databases (MEDLINE, LILACS and PsycINFO) for head-to-head economic comparisons of antipsychotic agents. A manual search in journals, dissertations and theses databases, congresses abstracts and the Cochrane Library was also conducted to ensure comprehensiveness. After evaluation by independent reviewers, complete economic evaluations of oral antipsychotic medications were included in the final analysis. **Results:** Twenty four studies were included in the final analysis. The trend observed in the pooled studies showed that risperidone, olanzapine and clozapine were the most cost-effective drugs included to treat schizophrenia. Aripiprazole and haloperidol were considered comparable to quetiapine or ziprasidone and less cost-effective than olanzapine and risperidone in the pooled analysis. After removal of comparisons that had sponsored drugs included, risperidone, olanzapine and clozapine were still considered the most cost-effective strategies to treat schizophrenia. The analysis of only cost-utility studies shows approximately the same results of the other analysis. **Conclusions:** An analysis that consider first- vs. second-generation antipsychotics polled together might be biased by the different profiles of the specific drugs, not considering the heterogeneity of the group of second-generation antipsychotics. There seems to be a difference in the cost-effectiveness profiles between specific antipsychotic drugs. Risperidone, olanzapine and clozapine seem to be the drugs most considered cost-effective to treat schizophrenia. This result was robust to changes in funding.

Palavras-Chave:
esquizofrenia, antipsicóticos, revisão, análise de custo-benefício

RESUMO

Objetivo: O objetivo deste estudo é conduzir uma revisão sistemática de custo-efetividade de antipsicóticos orais para identificar uma tendência de custo-efetividade dos medicamentos disponíveis para o tratamento da esquizofrenia. **Métodos:** Uma busca eletrônica foi realizada nas bases de dados Medline (via PubMed), Lilacs (via VS) e PsycINFO para avaliações econômicas comparando *head-to-head* medicamentos antipsicóticos para esquizofrenia. Uma busca manual complementar foi realizada para garantir abrangência. **Resultados:** Depois da avaliação por revisores independen-

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1. Department of Social Pharmacy, *Universidade Federal de Minas Gerais* (UFMG), Belo Horizonte, MG, Brazil.
2. Department of Psychiatry, *Faculdade de Medicina de Barbacena* (FAME), Barbacena, MG, Brazil; Barbacena Psychiatric Hospital Centre, *Fundação Hospitalar do Estado de Minas Gerais (FHEMIG)*, Barbacena, MG, Brazil.
3. Department of Social Pharmacy, *Universidade Federal de Minas Gerais* (UFMG), Belo Horizonte, MG, Brazil.

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Corresponding author: André Soares Santos. Av. Antônio Carlos, 6627, Pampulha, Faculdade de Farmácia da Universidade Federal de Minas Gerais, Sala 4130. Belo Horizonte, MG, Brazil. 31270-901. Telephone: (+55 31) 99180-8788. E-mail: andressantos111@gmail.com

tes, 24 avaliações econômicas completas de antipsicóticos orais para esquizofrenia foram incluídas na análise final. A tendência observada no conjunto dos estudos mostrou que a risperidona, a olanzapina e a clozapina foram mais comumente consideradas os medicamentos mais custo-efetivos para esquizofrenia. Aripiprazol e olanzapina foram considerados comparáveis a quetiapina ou ziprasidona e menos custo-efetivos, no geral, que olanzapina e risperidona. Após a remoção das comparações que incluíam medicamentos dos patrocinadores dos estudos, a mesma tendência foi observada. A análise apenas de estudos de custo-utilidade mostra o mesmo padrão. **Conclusões:** Análises que consideram medicamentos de primeira e segunda geração agrupados podem trazer vieses por conta da heterogeneidade entre medicamentos específicos. Parece haver uma diferença de custo-efetividade entre os medicamentos. Risperidona, olanzapina e clozapina são mais comumente consideradas custo-efetivas. Esse resultado foi robusto a mudanças no financiamento.

Introduction

Schizophrenia is a debilitating chronic condition characterized by disorders in thought, affect and behavior. It is costly to society because of its long course, high occurrence of comorbidities and lack of a universally effective pharmacological treatment. Its prevalence is estimated between 0.3 and 1% of the world's population (Mari & Leitão, 2000; Daltio *et al.*, 2007; Messias *et al.*, 2007; Weinberger & Harrison, 2011). The pharmacological treatment of schizophrenia is based on the prescription of antipsychotics, but their efficacy is limited, culminating in discontinuation of treatment for various causes, relapses and readmissions in health services. The efficacy of first- and second-generation antipsychotics is considered to be similar for the treatment of positive symptoms (American Psychiatric Association, 1994; Stroup *et al.*, 2006; Brunton *et al.*, 2011; Weinberger & Harrison, 2011; American Psychiatric Association, 2013; Brasil, 2013; National Institute for Health and Care Excellence, 2014). Studies that evaluate the efficacy, effectiveness and safety of antipsychotics found that the results depend on the outcome of choice, medication doses and the company that funded the study, but demonstrated that there can be differences between drugs (Breier *et al.*, 2005; Lieberman *et al.*, 2005; Mcevoy *et al.*, 2006; Stroup *et al.*, 2006; Stroup *et al.*, 2007). The adverse effects profile of the drugs can be very different, especially considering the higher risks of extrapyramidal syndrome with first-generation antipsychotics, metabolic syndrome with olanzapine and clozapine, hyperprolactinemia with risperidone and agranulocitosis with clozapine (Breier *et al.*, 2005; Lieberman *et al.*, 2005; Mcevoy *et al.*, 2006).

Health Technology Assessment is important for the efficient allocation of resources in the health sector. The pharmacoeconomic analyses provide data for decision makers about costs and outcomes of alternative therapies. The costs of the treatment of schizophrenia are high worldwide. The disease has high societal costs related to the loss of productivity (Genduso & Haley, 1997; Behan *et al.*, 2008). The most relevant healthcare cost is hospitalization and the costs of medication seen not to be very substantial (Genduso & Haley, 1997; Knapp *et al.*, 2004; Jones *et al.*, 2006). The relative importance of drug costs to the direct costs of schizophrenia will depend on the setting and can be very different for low and high income countries (Knapp *et al.*, 2004). The drugs can, however, influence the hospitalization rates and productivity, becoming very important in the economics of schizophrenia (Lieberman *et al.*, 2005; Liu-Seifert *et al.*, 2011). McEvoy reported that, in the USA, between 1991 and 2002, the hospitalization costs decreased, but the costs of outpatient treatment and medication increased (Mcevoy, 2007). Knapp *et al.* conducted a systematic review of studies of Cost-of-Illness on schizophrenia and concluded that these costs are high, variable in different locations and relevant to the health system and that the intangible costs *per se* already justify investments in research and development of new treatments (Knapp *et al.*, 2004).

Considering the lack of a universal effective treatment, associated with the different costs of the drugs and the progressive higher expenditures with the pharmacological treatment of schizophrenia by health systems, it is necessary to evaluate the cost-effectiveness profile of antipsychotic drugs to allow an adequate choice of pharmacotherapy for the patient in accordance with the financial reality of the health systems (World Health Organization, 1998; Brandão *et al.*, 2011; Brunton *et al.*, 2011; Machado *et al.*, 2011; Weinberger & Harrison, 2011). The aim of this study is to conduct a systematic review of the literature on cost-effectiveness analysis of head-to-head comparisons of antipsychotics in schizophrenic populations to identify a trend of cost-effectiveness of drugs available for the treatment of schizophrenia.

Methods

A systematic review of economic evaluations was conducted to identify studies comparing oral antipsychotic drugs for schizophrenia. This study was approved by the Research Ethics Committee of *Fundação Hospitalar do Estado de Minas Gerais* (FHEMIG) under the protocol number 031/2012.

Database search

The databases Medline (via PubMed), PsycINFO and LILACS (via BVS) were searched, in August 2015, using the terms

schizophrenia, cost-benefit analysis, cost-effectiveness, cost-utility and economic evaluation. An online manual search was conducted, for studies that may have not been included, in the journals Value in Health, Pharmacoeconomics, *Revista Brasileira de Psiquiatria*, Schizophrenia Bulletin and American Journal of Psychiatry, in the dissertations and theses databases of *Universidade Federal de Minas Gerais*, *Universidade de São Paulo* and ProQuest®, in the Cochrane Library (in Economic Evaluations) and in abstracts of the ISPOR Annual Meeting and International Congress on Schizophrenia, between 2010 and 2015.

Study selection

To be included, a study had to: be a complete pharmacoeconomic analysis; be conducted in a population diagnosed with schizophrenia, schizophreniform disorder or schizoaffective disorder as described by the International Statistical Classification of Diseases and Related Health Problems (ICD) (World Health Organization, 1997) or the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 1994; 2013); be a head-to-head comparison of the oral antipsychotic drugs haloperidol (HAL), chlorpromazine (CHL), quetiapine (QUE), risperidone (RIS), ziprasidone (ZIP), olanzapine (OLA), clozapine (CLO) or aripiprazole (ARI); report data of total effectiveness and total cost by drug and the Incremental Cost-Effectiveness Ratio (ICER), when convenient; take the perspective of the health system; be published after 2005. The studies included could be based on models or longitudinal studies. Other types of economic evaluations, new analysis of subpopulations of already included studies, evaluations of therapy switch and comparisons of more than one stage of treatment at the same time were excluded. The references found were added to EndNote® reference manager. The duplicate excluded were all checked before deletion. The analysis of titles and abstracts were conducted by two independent researchers (A.S. and I.G.) and the divergent references were evaluated by a third researcher (C.B.) to decide for its inclusion or exclusion. The eligible studies were than evaluated in their complete content by the two main researchers (A.S. and I.G.) and the inclusions were decided by consensus.

Data analytic procedures

Data collection was conducted by the first author (A.S.) and checked by the second author (I.G.) using a predetermined form containing: first-author's last name, year of publication, country, currency, discount rate, population, interventions evaluated, time horizon, recommended strategy, conflicts of interest and main outcome measure (Brandão *et al.*, 2012). The data of total cost, total health outcome and ICER were collected to expand the comparison of the results. When the ICER were not reported for all the possible comparisons in a study, it was calculated using the expression: $(C_1 - C_2)/(E_1 - E_2)$, where C_1 is the total cost of one drug, C_2 is the total cost of the other drug, E_1 is the total effectiveness of one drug and E_2 is the total effectiveness of the other drug (Folland *et al.*, 2008; Rascati, 2010; Acurcio, 2013). The results were expressed in ICERrep when the authors of the paper reported the ICER for the comparison and ICERcalc when it was calculated with the formula above.

Heres *et al.* (2006) found that, in head-to-head comparisons of antipsychotics, the results favor the sponsor in 90% of the studies (Heres *et al.*, 2006). For the sensitivity analysis, initially, the head-to-head comparisons that included drugs from the sponsor of the studies were removed from data to evaluate the cost-effectiveness profile of the other drugs. Then, an analysis of studies that adopted Quality-Adjusted Life Years (QALY) or Disability-Adjusted Life Years (DALY) as principal outcome was conducted to evaluate the cost-utility relationship between the pharmacological strategies.

The assessment of quality of the economic evaluations included in the final analysis were performed in accordance to the checklist recommended by Drummond and colleagues (Drummond *et al.*, 2005). No attempt was made to adjust for purchasing power parity or to conduct statistical inter-country comparisons. The currencies used in the original articles were retained, as the objective is to show a trend and not to demonstrate an aggregate statistical result.

Results

The search at Medline (n = 842), LILACS (n = 7) and PsycINFO (n = 430) resulted in 1,279 references. The manual search contributed with one study, totalizing 1,280 references added to the reference manager. After duplicate elimination, 1,078 articles were included for title and abstract evaluations. After this phase, 78 references were eligible for complete evaluation and 24 articles were included in the final analysis (Figure 1).

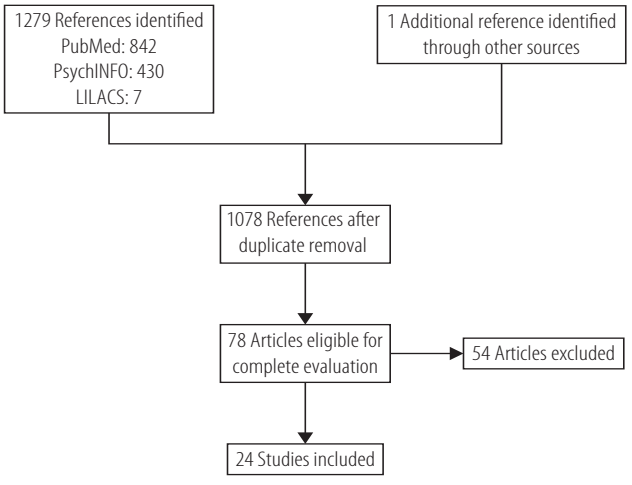

Figure 1. Study flow diagram.

Characteristics of the included studies

The 24 studies included represent data from 14 countries: eight articles from the USA (Rosenheck *et al.*, 2006; Tunis *et al.*, 2006; Bounthavong & Okamoto, 2007; Edwards *et al.*, 2008; Furiak *et al.*, 2009; Ascher-Svanum *et al.*, 2011; Ascher-Svanum *et al.*, 2012; O'day *et al.*, 2013), two from Canada (Cooper *et al.*, 2008; Mcintyre *et al.*, 2010) and Spain (Garcia-Ruiz *et al.*, 2012; Treur *et al.*, 2012) and one from Slovenia (Obradovic *et al.*, 2007), Italy (Colombo *et al.*, 2008), Greece (Geitona *et al.*, 2008), Belgium (De Ridder & De Graeve, 2009), Brazil (Lindner *et al.*, 2009), Mexico (Mould-Quevedo *et al.*, 2009), China (Yang *et al.*, 2009), Norway (Kim & Aas, 2011), Sweden (Lindström *et al.*, 2011), Germany (Zeidler *et al.*, 2013) and Vietnam (Anh *et al.*, 2015). One study evaluated the cost-effectiveness of antipsychotics in European countries (Knapp *et al.*, 2008). A utility component was found in 13 included studies, 12 of them reported effectiveness in measures of QALYs (Rosenheck *et al.*, 2006; Knapp *et al.*, 2008; De Ridder & De Graeve, 2009; Furiak *et al.*, 2009; Lindner *et al.*, 2009; Mcintyre *et al.*, 2010; Ascher-Svanum *et al.*, 2011; Lindström *et al.*, 2011; Ascher-Svanum *et al.*, 2012; Garcia-Ruiz *et al.*, 2012; Treur *et al.*, 2012; Zeidler *et al.*, 2013) and one of them in DALYs averted (Anh *et al.*, 2015). Regarding the source of data and modeling, three studies were based on Randomized Clinical Trials (RCTs) (Rosenheck *et al.*, 2006; Tunis *et al.*, 2006; Ascher-Svanum *et al.*, 2011), three studies analyzed data from observational studies (Cooper *et al.*, 2008; Knapp *et al.*, 2008; De Ridder & De Graeve, 2009), nine studies built Markov models with literature data (Lindner *et al.*, 2009; Mould-Quevedo *et al.*, 2009; Mcintyre *et al.*, 2010; Kim & Aas, 2011; Lindström *et al.*, 2011; Ascher-Svanum *et al.*, 2012; O'day *et al.*, 2013; Zeidler *et al.*, 2013; Anh *et al.*, 2015) and nine studies only reported a decision analysis model with literature data (Bounthavong & Okamoto, 2007; Obradovic *et al.*, 2007; Colombo *et al.*, 2008; Edwards *et al.*, 2008; Geitona *et al.*, 2008; Furiak *et al.*, 2009; Yang *et al.*, 2009; Garcia-Ruiz *et al.*, 2012; Treur *et al.*, 2012). Most studies adopted time horizons of one year (Tunis *et al.*, 2006; Obradovic *et al.*, 2007; Cooper *et al.*, 2008; Edwards *et al.*, 2008; Geitona *et al.*, 2008; Knapp *et al.*, 2008; Furiak *et al.*, 2009; Mould-Quevedo *et al.*, 2009; Ascher-Svanum *et al.*, 2011; Garcia-Ruiz *et al.*, 2012) and five years (Colombo *et al.*, 2008; Lindner *et al.*, 2009; Mcintyre *et al.*, 2010; Kim & Aas, 2011; Lindström *et al.*, 2011; Treur *et al.*, 2012; O'day *et al.*, 2013; Zeidler *et al.*, 2013). Chlorpromazine was not evaluated in any of the included studies. Regarding the funding, six studies were not funded by any pharmaceutical company (Rosenheck *et al.*, 2006; Bounthavong & Okamoto, 2007; Obradovic *et al.*, 2007; Lindner *et al.*, 2009; Kim & Aas, 2011; Anh *et al.*, 2015), six studies were funded by Eli Lilly companies (Tunis *et al.*, 2006; Knapp *et al.*, 2008; De Ridder & De Graeve, 2009; Furiak *et al.*, 2009; Ascher-Svanum *et al.*, 2011; Ascher-Svanum *et al.*, 2012), seven studies by Janssen-Cilag companies (Cooper *et al.*, 2008; Edwards *et al.*, 2008; Geitona *et al.*, 2008; Yang *et al.*, 2009; Garcia-Ruiz *et al.*, 2012; Treur *et al.*, 2012; Zeidler *et al.*, 2013), one study by Bristol-Myers Squibb (Colombo *et al.*, 2008), one study by Sunovion (O'day *et al.*, 2013), one study by H. Lundbeck (Lindström *et al.*, 2011) and two studies by Pfizer companies (Mould-Quevedo *et al.*, 2009; Mcintyre *et al.*, 2010) (Table 1).

Table 1. Description of the characteristics of the included studies

Study	Country/ Currency	Study Design	Time Horizon	Discount rate	Compared Drugs	Outcome	Funding
Rosenheck *et al.* (2006)	USA/USD	RCT	18 months	NA	Perphenazine Risperidone Quetiapine Ziprasidone Olanzapine	QALY	National Institute of Mental Health (USA)
Tunis *et al.* (2006)	USA/USD	RCT	1 year	NA	Risperidone Olanzapine FGA	Days with positive response	Eli Lilly
Bounthavong & Okamoto (2007)	USA/USD	Decision Analysis Model	16 weeks	NA	Haloperidol Risperidone Olanzapine	Improvement (> 20% PANSS)	None
Obradovic *et al.* (2007)	Slovenia/EUR	Decision Analysis Model	1 year	NA	Haloperidol Haloperidol LAI Risperidone Aripiprazole Amisulpride Olanzapine Ziprasidone Quetiapine Risperidone LAI	Remission	None

Study	Country/ Currency	Study Design	Time Horizon	Discount rate	Compared Drugs	Outcome	Funding
Colombo *et al.* (2008)	Italy/EUR	Decision Analysis Model	5 years	3%	Aripiprazole Olanzapine	Relapses avoided	Bristol-Myers Squibb
Cooper *et al.* (2008)	Canada/CAD	Observational study	1 year	NA	Risperidone Olanzapine	Effective treatment (365 days without hospitalization)	Janssen-Cilag
Edwards *et al.* (2008)	USA/USD	Decision Analysis Model	1 year	NA	Aripiprazole Olanzapine Paliperidone ER Quetiapine Risperidone Ziprasidone	Relapses avoided	Janssen-Cilag
Geitona *et al.* (2008)	Greece/EUR	Decision Analysis Model	1 year	NA	Paliperidone ER Risperidone Olanzapine Quetiapine Aripiprazole Ziprasidone	Stable days	Janssen-Cilag
Knapp *et al.* (2008)	Various/GBP	Observational study	1 year	NA	Olanzapine Quetiapine Amisulpride Risperidone Clozapine FGA	QALY	Eli Lilly
De Ridder & De Graeve (2009)	Belgium/EUR	Observational study	2 years	3%	Risperidone Olanzapine	QALY	Eli Lilly
Furiak *et al.* (2009)	USA/USD	Decision Analysis Model	1 year	NA	Olanzapine Ziprasidone Risperidone Quetiapine Aripiprazole	QALY	Eli Lilly
Lindner *et al.* (2009)	Brazil/USD	Markov Model	5 years	3%	Haloperidol Risperidone Olanzapine	QALY	Brazilian Ministry of Health e CNPq
Mould-Quevedo *et al.* (2009)	Mexico/MXN	Markov Model	1 year	NA	Ziprasidone Olanzapine Risperidone Clozapine Haloperidol	Months free from psychotic symptoms	Pfizer
Yang *et al.* (2009)	China/RMB	Decision Analysis Model	2 years	3%	Risperidone LAI Olanzapine Quetiapine	Clinical response	Janssen-Cilag
McIntyre *et al.* (2010)	Canada/CAD	Markov Model	5 years	5%	Ziprasidone Quetiapine Olanzapine Risperidone	QALY	Pfizer
Ascher-Svanum *et al.* (2011)	USA/USD	RCT	28 weeks	NA	Olanzapine Aripiprazole	QALY	Eli Lilly
Kim & Aas (2011)	Norway/NOK	Markov Model	5 years	4%	Olanzapine Risperidone	PANSS	None
Lindström *et al.* (2011)	Sweden/SEK	Markov Model	5 years	5%	Sertindole Aripiprazole Risperidone Olanzapine Haloperidol	Time without relapse and QALY	H. Lundbeck

Study	Country/ Currency	Study Design	Time Horizon	Discount rate	Compared Drugs	Outcome	Funding
Ascher-Svanum *et al.* (2012)	USA/USD	Markov Model	1 year	NA	Olanzapine Risperidone Aripiprazole	QALY	Eli Lilly
García-Ruiz *et al.* (2012)	Spain/EUR	Decision Analysis Model	1 year	NA	Amissulprida Aripiprazole Olanzapine Paliperidone ER Risperidone Haloperidol	QALY	Janssen-Cilag
Treur *et al.* (2012)	Spain/EUR	Decision Analysis Model	5 years	3%	Paliperidone ER Olanzapine Aripiprazole	QALY	Janssen-Cilag
O´Day *et al.* (2013)	USA/USD	Markov Model	5 years	3%	Aripiprazole Lurasidona Olanzapine Quetiapine Risperidone Ziprasidone	Hospitalization avoided	Sunovion
Zeidler *et al.* (2013)	Germany/EUR	Markov Model	5 years	3%	Paliperidone LAI Quetiapine Risperidone LAI Olanzapine Risperidone Zuclopentixol LAI Olanzapine LAI Típicos Orais Atípicos Orais	QALY and relapses avoided	Janssen-Cilag
Anh *et al.* (2015)	Vietnam/Int$	Markov Model	15 years old to end of life	3%	Típicos Risperidone Olanzapine Clozapine	DALY	None

NA = Not Applicable; ND = Not available; DALY = Disability-adjusted Life Years; QALY = Quality-adjusted Life Years; ER = Extended Release; LAI = Long-Acting Injection; FGA = First-Generation Antopsychotics; PANSS = Positive and Negative Syndrome Scale.

Head-to-head comparisons of antipsychotics

Haloperidol vs. risperidone

Haloperidol and risperidone were concomitantly evaluated by seven included articles. In none of them, haloperidol was dominant over risperidone. Risperidone was found dominant over haloperidol in five studies (Bounthavong & Okamoto, 2007; Mould-Quevedo *et al.*, 2009; Lindström *et al.*, 2011; Garcia-Ruiz *et al.*, 2012; Zeidler *et al.*, 2013). In two studies, treatment with haloperidol resulted in lower costs and lower effectiveness than treatment with risperidone with ICERrep of 39,890 USD/QALY (Lindner *et al.*, 2009) and ICERcalc of 5,379 EUR/remission (Obradovic *et al.*, 2007).

Haloperidol vs. quetiapine

Haloperidol and quetiapine were evaluated concomitantly by two included studies. In one of them, haloperidol was considered dominant over quetiapine (Obradovic *et al.*, 2007) and, in the other, haloperidol was considered less effective and less costly then quetiapine with ICERcalc of 31,627 EUR/QALY (Zeidler *et al.*, 2013).

Haloperidol vs. ziprasidone

Haloperidol and ziprasidone were concomitantly evaluated by two included studies. Haloperidol was considered dominant in one of them (Obradovic *et al.*, 2007) and dominated in the other (Mould-Quevedo *et al.*, 2009).

Haloperidol vs. olanzapine

Haloperidol and olanzapine were concomitantly evaluated by seven included studies. In two of them, olanzapine was considered dominant over haloperidol (Bounthavong & Okamoto, 2007; Mould-Quevedo *et al.*, 2009). In the other five studies, treatment with haloperidol resulted in lower costs and lower effectiveness with ICERcalc of 8,009 EUR/remission (Obradovic *et al.*, 2007), 119,704 USD/QALY (Lindner *et*

al., 2009), 41,412 SEK/QALY (Lindström *et al.*, 2011), 3,555 EUR/QALY (Zeidler *et al.*, 2013) and ICERrep of 23,621 EUR/QALY (Garcia-Ruiz *et al.*, 2012).

Haloperidol vs. clozapine

Haloperidol and clozapine were evaluated concomitantly in only one included study in which clozapine was considered dominant over haloperidol (Mould-Quevedo *et al.*, 2009).

Haloperidol vs. aripiprazole

Haloperidol and aripiprazole were simultaneously evaluated by three included studies. In all of them, treatment with haloperidol resulted in lower costs and lower effectiveness than aripiprazol with ICERcalc of 14,350 EUR/remission (Obradovic *et al.*, 2007), 315,625 SEK/QALY (Lindström *et al.*, 2011) and ICERrep of de 94,558 EUR/QALY (Garcia-Ruiz *et al.*, 2012).

Risperidone vs. quetiapine

Risperidone and quetiapine were evaluated simultaneously by nine included studies. In six of them, risperidone was considered dominant over quetiapine (Obradovic *et al.*, 2007; Edwards *et al.*, 2008; Geitona *et al.*, 2008; Furiak *et al.*, 2009; Mcintyre *et al.*, 2010; O'day *et al.*, 2013). In the other three studies, risperidone resulted in lower costs and lower effectiveness than quetiapine with ICERcalc of 8,786 USD/QALY (Rosenheck *et al.*, 2006), 85,747 £/QALY (Knapp *et al.*, 2008) e 57,540 EUR/QALY (Zeidler *et al.*, 2013).

Risperidone vs. ziprasidone

Risperidone and ziprasidone were concomitantly evaluated by eight included studies. One study found that ziprasidone was dominant over risperidone (Mould-Quevedo *et al.*, 2009). In five studies, risperidone was dominant over ziprasidone (Obradovic *et al.*, 2007; Edwards *et al.*, 2008; Geitona *et al.*, 2008; Furiak *et al.*, 2009; O'day *et al.*, 2013). In two studies, risperidone was found to be less expensive and less effective than ziprasidone with ICERcalc of 16,333 USD/QALY (Rosenheck *et al.*, 2006) and ICERrep de 218,060 C$/QALY (Mcintyre *et al.*, 2010).

Risperidone vs. olanzapine

Risperidone and olanzapine were simultaneously evaluated by 20 included studies. In five studies, olanzapine was dominant over risperidone (Rosenheck *et al.*, 2006; Tunis *et al.*, 2006; Geitona *et al.*, 2008; Furiak *et al.*, 2009; Kim & Aas, 2011). Risperidone was found dominant over olanzapine by six studies (Bounthavong & Okamoto, 2007; Cooper *et al.*, 2008; Mould-Quevedo *et al.*, 2009; Mcintyre *et al.*, 2010; Lindström *et al.*, 2011; Anh *et al.*, 2015). Risperidone was found to be more costly and more effective than olanzapine by one study with ICERrep of 5,779 EUR/QALY (De Ridder & De Graeve, 2009). Risperidone was found to be less costly and less effective than olanzapine by nine studies with ICERcalc of 466 USD/extra stable day (Edwards *et al.*, 2008), 8,911 EUR/remission (Obradovic *et al.*, 2007), 43,467 USD/QALY (Ascher-Svanum *et al.*, 2012), 50,652 EUR/QALY (Garcia-Ruiz *et al.*, 2012), 47,922 USD/hospitalization avoided (O'day *et al.*, 2013) and 38,891 EUR/QALY (Zeidler *et al.*, 2013) and ICERrep of 5,156 £/QALY (Knapp *et al.*, 2008), 86,918 CAD/response (Cooper *et al.*, 2008) and 1,329,395 USD/QALY (Lindner *et al.*, 2009). The study conducted by Cooper *et al.* appears twice in the data because of the evaluation of two populations, one previously hospitalized and another never hospitalized before.

Risperidone vs. clozapine

Risperidone and clozapine were concomitantly evaluated by three included studies. In all of them, risperidone was considered less costly and less effective with ICERcalc of 7,860 £/QALY (Knapp *et al.*, 2008), 384,513 MXP/month free of symptoms (Mould-Quevedo *et al.*, 2009) e 58,618 I$/DALY averted (Anh *et al.*, 2015).

Risperidone vs. aripiprazole

Risperidone and aripiprazole were simultaneously evaluated by eight included studies. Risperidone was considered the dominant strategy by six studies (Edwards *et al.*, 2008; Geitona *et al.*, 2008; Furiak *et al.*, 2009; Lindström *et al.*, 2011; Ascher-Svanum *et al.*, 2012; O'day *et al.*, 2013). Risperidone was found to be less costly and less effective than aripiprazole by two studies with ICERcalc of 31,396 EUR/remission (Obradovic *et al.*, 2007) e 361,428 EUR/QALY (Garcia-Ruiz *et al.*, 2012).

Quetiapine vs. ziprasidone

Quetiapine and ziprasidone were concomitantly evaluated by seven included studies. Ziprasidone was dominant over quetiapine in four studies (Obradovic *et al.*, 2007; Furiak *et al.*, 2009; Mcintyre *et al.*, 2010; O'day *et al.*, 2013). Quetiapine was dominant over ziprasidone in two studies (Rosenheck *et al.*, 2006; Edwards *et al.*, 2008). Ziprasidone was found to be less costly and less effective than quetiapine in one study with RCEIcalc of de 3,040 EUR/extra stable day (Geitona *et al.*, 2008).

Quetiapine vs. olanzapine

Quetiapine and olanzapine were simultaneously evaluated by ten included studies. In five of them, olanzapine was dominant over quetiapine (Obradovic *et al.*, 2007; Geitona *et al.*, 2008; Knapp *et al.*, 2008; Furiak *et al.*, 2009; O'day *et al.*, 2013). In one study, quetiapine was found to be dominant over olanzapine (Mcintyre *et al.*, 2010). In two studies, olanzapine was considered to be less costly and less effective than quetiapine with ICERcalc of 224,000 USD/QALY (Rosenheck *et al.*, 2006) and 108,825 EUR/QALY (Zeidler *et al.*, 2013). In two studies, quetiapine was considered less costly and less effective than olanzapine with ICERcalc of 42 USD/extra

stable day (Edwards *et al.*, 2008) e 343.827 RMB/response (Yang *et al.*, 2009).

Quetiapine vs. clozapine

Only one included study evaluated simultaneously quetiapine and clozapine. It found clozapine to be the dominant strategy between the two drugs (Knapp *et al.*, 2008).

Quetiapine vs. aripiprazole

Quetiapine and aripiprazole were concomitantly evaluated by five studies. In two of them, quetiapine was found to be dominant over aripiprazole (Edwards *et al.*, 2008; O'day *et al.*, 2013). In two studies aripiprazole was found to be dominant over quetiapine (Obradovic *et al.*, 2007; Furiak *et al.*, 2009). In one study, aripiprazole was considered less costly and less effective than quetiapine with ICERcalc of 245 EUR/extra stable day (Geitona *et al.*, 2008).

Ziprasidone vs. olanzapine

Ziprasidone and olanzapine were evaluated simultaneously by eight included studies. In five of them, olanzapine was considered the dominant strategy over ziprasidone (Rosenheck *et al.*, 2006; Obradovic *et al.*, 2007; Edwards *et al.*, 2008; Geitona *et al.*, 2008; Furiak *et al.*, 2009). In two of them, ziprasidone was considered the dominant strategy over olanzapine (Mould-Quevedo *et al.*, 2009; Mcintyre *et al.*, 2010). In one study, ziprasidone resulted in lower costs and lower effectiveness than olanzapina with ICERcalc of 6,272 USD/ hospitalization avoided (O'day *et al.*, 2013).

Ziprasidone vs. clozapine

Ziprasidone and clozapine were concomitantly evaluated by one included study that found ziprasidone to be the dominant strategy over clozapine (Mould-Quevedo *et al.*, 2009).

Ziprasidone vs. aripiprazole

Ziprasidone and aripiprazole were simultaneously evaluated by five included studies. Aripiprazole was considered dominant over ziprasidone in one of them (Obradovic *et al.*, 2007) and ziprasidone was considered dominant over aripiprazole in two of them (Geitona *et al.*, 2008; O'day *et al.*, 2013). In two studies, ziprasidone resulted in lower costs and lower effectiveness with ICERcalc of 75 USD/extra stable day (Edwards *et al.*, 2008) e 94,500 USD/QALY (Furiak *et al.*, 2009).

Olanzapine vs. clozapine

Olanzapine and clozapine were simultaneously evaluated by three included studies. Clozapine was considered the dominant strategy over olanzapine in one study (Mould-Quevedo *et al.*, 2009). In one study, clozapine resulted in lower costs and lower effectiveness with ICERrep of 775 £/ QALY (Knapp *et al.*, 2008) and in the other study, olanzapine resulted in lower costs and lower effectiveness with ICERcalc of 21,451 I$/DALY averted (Anh *et al.*, 2015).

Olanzapine vs. aripiprazole

Olanzapine and aripiprazole were concomitantly evaluated by eleven included studies. Aripiprazole was considered the dominant strategy over olanzapine by two studies (Colombo *et al.*, 2008; Treur *et al.*, 2012). Olanzapine was considered the dominant strategy over aripiprazole by eight studies (Edwards *et al.*, 2008; Geitona *et al.*, 2008; Furiak *et al.*, 2009; Ascher-Svanum *et al.*, 2011; Lindström *et al.*, 2011; Ascher-Svanum *et al.*, 2012; Garcia-Ruiz *et al.*, 2012; O'day *et al.*, 2013). In one study, aripiprazole was found to be less costly and less effective than olanzapine with ICERrep of 3,952 EUR/ remission (Obradovic *et al.*, 2007).

Clozapine vs. aripiprazole

Clozapine and aripiprazole were not evaluated simultaneously in any of the included study.

Qualitative synthesis

The trend observed in the pooled studies showed that risperidone, olanzapine and clozapine were the antipsychotics most commonly found to be cost-effective to treat schizophrenia. While olanzapine and risperidone were evaluated in 24 and 20 included studies, respectively, only three included studies evaluated clozapine (Knapp *et al.*, 2008; Mould-Quevedo *et al.*, 2009; Anh *et al.*, 2015). Clozapine was only compared to ziprasidone by one study that found ziprasidone to be dominant (Mould-Quevedo *et al.*, 2009). In this study, however, ziprasidone was considered also dominant over risperidone, olanzapine and haloperidol, a scenario that do not agree with other studies that made these evaluations (Rosenheck *et al.*, 2006; Obradovic *et al.*, 2007; Edwards *et al.*, 2008; Geitona *et al.*, 2008; Furiak *et al.*, 2009; O'day *et al.*, 2013). Aripiprazole and haloperidol were considered comparable to quetiapine or ziprasidone, and less cost-effective than olanzapine and risperidone (Table 2).

Some prospective design-based studies found it difficult to demonstrate a significant difference between the treatment strategies, either with respect to costs or effectiveness. This appears to be related to the small sample sizes and small differences of outcome between drug strategies (Rosenheck *et al.*, 2006; Tunis *et al.*, 2006; De Ridder & De Graeve, 2009). Cohort studies are important for evaluation of effectiveness, but in cohort studies that evaluate drug strategies for schizophrenia, the drugs reserved for refractory patients can produce worse results in Quality of Life scales. Refractory patients are already more difficult to treat and usually have worse scores of Quality of Life. In some algorithms, olanzapine is already reserved for refractory patients, in part because of its metabolic side effects. Olanzapine's evaluation might have

been hindered by this situation in some studies (Colombo *et al.*, 2008; De Ridder & De Graeve, 2009). A cohort study found advantage in cost-effectiveness terms to olanzapine compared to quetiapine and risperidone anyway (Knapp *et al.*, 2008). Additionally, two other cohort studies were evaluated. One of them found results that favor risperidone (Cooper *et al.*, 2008) and the other slightly favors risperidone, but clarifies that no statistical difference was found (De Ridder & De Graeve, 2009). The metabolic side effects of olanzapine are widely known and there is evidence that they are more prevalent with olanzapine than with other drugs (Rosenheck *et al.*, 2003; Mcquade *et al.*, 2004; Breier *et al.*, 2005; Lieberman *et al.*, 2005; Chiu *et al.*, 2006; Fleischhacker *et al.*, 2009; Kane *et al.*, 2009; Alvarez *et al.*, 2012; Ou *et al.*, 2013; Zhang & Lan, 2014). When the developed model depends highly of metabolic effects, olanzapine tend to be in disadvantage when compared to aripiprazole, risperidone and ziprasidone (Colombo *et al.*, 2008; Mcintyre *et al.*, 2010).

Hospitalization and relapses are the main direct medical cost drivers of schizophrenia (Genduso & Haley,

Table 2. ICER-based comparisons

		Strategy 2				
		Haloperidol	**Risperidone**	**Quetiapine**	**Ziprasidone**	**Olanzapine**
Strategy 1	Risperidone	RIS dominant (Bounthavong e Okamoto, 2007; Mould-Quevedo *et al.,* 2009; Lindström *et al.,* 2011; Garcia-Ruiz *et al.,* 2012; Zeidler *et al.,* 2013) 39,890.33 US$/QALY (Lindner *et al.,* 2009) 5,378.77 €/remissão (Obradovic *et al.,* 2007)				
	Quetiapine	HAL dominant (Obradovic *et al.*, 2007) 31,626.67 €/QALY (Zeidler *et al.*, 2013)	RIS dominant (Obradovic *et al.*, 2007; Edwards *et al.*, 2008; Geitona *et al.*, 2008; Furiak *et al.*, 2009; Mcintyre *et al.*, 2010; O'day *et al.*, 2013) 8,785.71 US$/QALY (Rosenheck *et al.*, 2006) 85,747.13 £/QALY (Knapp *et al.*, 2008) 57,540.00 €/QALY (Zeidler *et al.*, 2013)			
	Ziprasidone	HAL dominant (Obradovic *et al.*, 2007) ZIP dominant (Mould-Quevedo *et al.*, 2009)	ZIP dominant (Mould-Quevedo *et al.*, 2009) RIS dominant (Obradovic *et al.*, 2007; Edwards *et al.*, 2008; Geitona *et al.*, 2008; Furiak *et al.*, 2009; O'day *et al.*, 2013) 16,333.33 US$/QALY (Rosenheck *et al.*, 2006) 218,060 C$/QALY (Mcintyre *et al.*, 2010)2010	ZIP dominant (Obradovic *et al.*, 2007; Furiak *et al.*, 2009; Mcintyre *et al.*, 2010; O'day *et al.*, 2013) QUE dominant (Rosenheck *et al.*, 2006; Edwards *et al.*, 2008) 3,040.00 €/extra stable day (Geitona *et al.*, 2008)		

		Strategy 2				
		Haloperidol	**Risperidone**	**Quetiapine**	**Ziprasidone**	**Olanzapine**
Strategy 1	Olanzapine	OLA dominant (Bounthavong e Okamoto, 2007; Mould-Quevedo *et al.*, 2009) 8,008.57 €/remissão (Obradovic *et al.*, 2007) 119,704.24 US$/QALY (Lindner *et al.*, 2009) 41,411.76 SEK/QALY (Lindström *et al.*, 2011) 3,554.55 €/QALY (Zeidler *et al.*, 2013) 23,621 €/QALY (Garcia-Ruiz *et al.*, 2012)	OLA dominant (Rosenheck *et al.*, 2006; Tunis *et al.*, 2006; Geitona *et al.*, 2008; Furiak *et al.*, 2009; Kim e Aas, 2011) RIS dominant (Bounthavong e Okamoto, 2007; Cooper *et al.*, 2008; Mould-Quevedo *et al.*, 2009; Mcintyre *et al.*, 2010; Lindström *et al.*, 2011; Anh *et al.*, 2015) 5,779.15 €/QALY (De Ridder e De Graeve, 2009) 466 US$/extra stable Day (Edwards *et al.*, 2008) 8,911.57 €/remission (Obradovic *et al.*, 2007) 43,466.67 US$/QALY (Ascher-Svanum *et al.*, 2012) 50,652.17 €/QALY(Garcia-Ruiz *et al.*, 2012) 47,922.08 US$/hospitalizarion avoided (O'day *et al.*, 2013) 38,890.91 €/QALY (Zeidler *et al.*, 2013) 5,156 £/QALY (Knapp *et al.*, 2008) 86,918 C$/response (Cooper *et al.*, 2008) 1,329,394.88 US$/QALY (Lindner *et al.*, 2009)	OLA dominant (Obradovic *et al.*, 2007; Geitona *et al.*, 2008; Knapp *et al.*, 2008; Furiak *et al.*, 2009; O'day *et al.*, 2013) QUE dominant (Mcintyre *et al.*, 2010)2010 224,000.00 US$/QALY (Rosenheck *et al.*, 2006) 108,825.00 €/QALY (Zeidler *et al.*, 2013) 42,50 US$/extra stable day (Edwards *et al.*, 2008) 343,826.59 RMB/response (Yang *et al.*, 2009)	OLA dominant (Rosenheck *et al.*, 2006; Obradovic *et al.*, 2007; Edwards *et al.*, 2008; Geitona *et al.*, 2008; Furiak *et al.*, 2009) ZIP dominant (Mould-Quevedo *et al.*, 2009; Mcintyre *et al.*, 2010) 6,271.51 US$/hospitalization avoided (O'day *et al.*, 2013)	
	Clozapine	CLO dominant (Mould-Quevedo *et al.*, 2009)	7,859.78 £/QALY (Knapp *et al.*, 2008) 384,513.48 MEX$/extra month free of symptoms (Mould-Quevedo *et al.*, 2009) 58,618.05 I$/DALY averted (Anh *et al.*, 2015)	CLO dominant (Knapp *et al.*, 2008)	ZIP dominant (Mould-Quevedo *et al.*, 2009)	CLO dominant (Mould-Quevedo *et al.*, 2009) 775 £/QALY(Knapp *et al.*, 2008) 21,451.30 I$/DALY averted(Anh *et al.*, 2015)

		Strategy 2				
		Haloperidol	**Risperidone**	**Quetiapine**	**Ziprasidone**	**Olanzapine**
Strategy 1	Aripiprazole	14,350.23 €/ remission (Obradovic *et al.*, 2007) 315,625.00 SEK/QALY (Lindström *et al.*, 2011) 94,558 €/QALY (Garcia-Ruiz *et al.*, 2012)	RIS dominant(Edwards *et al.*, 2008; Geitona *et al.*, 2008; Furiak *et al.*, 2009; Lindström *et al.*, 2011; Ascher-Svanum *et al.*, 2012; O'day *et al.*, 2013) 31,396.00 €/ remission (Obradovic *et al.*, 2007) 361,428.57 €/ QALY (Garcia-Ruiz *et al.*, 2012)	ARI dominant (Obradovic *et al.*, 2007; Furiak *et al.*, 2009) QUE dominant (Edwards *et al.*, 2008; O'day *et al.*, 2013) 244,76 €/extra stable day (Geitona *et al.*, 2008)	ARI dominant (Obradovic *et al.*, 2007) ZIP dominant(Geitona *et al.*, 2008; O'day *et al.*, 2013) 75.00 US$/extra stable day (Edwards *et al.*, 2008) 94,500.00 US$/QALY (Furiak *et al.*, 2009)	ARI dominant (Colombo *et al.*, 2008; Treur *et al.*, 2012) OLA dominant (Edwards *et al.*, 2008; Geitona *et al.*, 2008; Furiak *et al.*, 2009; Ascher-Svanum *et al.*, 2011; Lindström *et al.*, 2011; Ascher-Svanum *et al.*, 2012; Garcia-Ruiz *et al.*, 2012; O'day *et al.*, 2013) 3,951.72 €/remission (Obradovic *et al.*, 2007)

1997; Jones *et al.*, 2006; Daltio *et al.*, 2007). Drugs that can lower these costs can have a important impact in the costs associated with the disease (Daltio *et al.*, 2007). The capacity of olanzapine in reducing the costs associated with hospitalization more than other antipsychotics can be one of the factors that make it cost-effective in comparison with other drugs. Olanzapine is more expensive than other drugs such as haloperidol and risperidone, nevertheless, it was shown to compensate the price of the drug reducing hospitalization costs (Rosenheck *et al.*, 2006; Bounthavong & Okamoto, 2007; Obradovic *et al.*, 2007; Geitona *et al.*, 2008; Furiak *et al.*, 2009; Mcintyre *et al.*, 2010; Ascher-Svanum *et al.*, 2012; Zeidler *et al.*, 2013).

Sensitivity analysis

After removal of comparisons that had a drug of the study sponsor included, risperidone, olanzapine and clozapine were still considered cost-effective strategies to treat schizophrenia by most studies. Ziprasidone advantage over clozapine disappeared and its cost-effectiveness trend was considered comparable to aripiprazole and quetiapine, as before. Aripiprazole was still considered less cost-effective than olanzapine and risperidone and comparable to quetiapine and ziprasidone by most studies (Table 3). The analysis of only cost-utility studies shows approximately the same results of the other analysis, with a loss of sensitivity related to the drop of eleven articles. The analysis of the pooled studies indicates that risperidone, olanzapine

Table 3. ICER-based comparisons excluding analysis of the sponsored drugs

		Strategy 2				
		Haloperidol	**Risperidone**	**Quetiapine**	**Ziprasidone**	**Olanzapine**
Strategy 1	Risperidone	RIS dominant (Bounthavong e Okamoto, 2007; Mould-Quevedo *et al.*, 2009; Lindström *et al.*, 2011) 39,890.33 US$/QALY (Lindner *et al.*, 2009) 5,378.77 €/remissão (Obradovic *et al.*, 2007)				

		Strategy 2				
		Haloperidol	**Risperidone**	**Quetiapine**	**Ziprasidone**	**Olanzapine**
Strategy 1	Quetiapine	HAL dominant (Obradovic *et al.*, 2007) 31,626.67 €/QALY (Zeidler *et al.*, 2013)	RIS dominant (Obradovic *et al.*, 2007; Furiak *et al.*, 2009; Mcintyre *et al.*, 2010; O'day *et al.*, 2013) 8,785.71 US$/QALY (Rosenheck *et al.*, 2006) 85,747.13 £/QALY (Knapp *et al.*, 2008)			
	Ziprasidone	HAL dominant (Obradovic *et al.*, 2007)	RIS dominant (Obradovic *et al.*, 2007; Furiak *et al.*, 2009; O'day *et al.*, 2013) 16,333.33 US$/ QALY(Rosenheck *et al.*, 2006)	ZIP dominant (Obradovic *et al.*, 2007; Furiak *et al.*, 2009; O'day *et al.*, 2013) QUE dominant (Rosenheck *et al.*, 2006; Edwards *et al.*, 2008) 3,040.00 €/extra stable day (Geitona *et al.*, 2008)		
	Olanzapine	OLA dominant (Bounthavong e Okamoto, 2007; Mould-Quevedo *et al.*, 2009) 8,008.57 €/remissão (Obradovic *et al.*, 2007) 119,704.24 US$/QALY (Lindner *et al.*, 2009) 41,411.76 SEK/QALY (Lindström *et al.*, 2011) 3,554.55 €/QALY (Zeidler *et al.*, 2013) 23,621 €/QALY (Garcia-Ruiz *et al.*, 2012)	OLA dominant (Rosenheck *et al.*, 2006; Kim e Aas, 2011) RIS dominant (Bounthavong e Okamoto, 2007; Mould-Quevedo *et al.*, 2009; Mcintyre *et al.*, 2010; Lindström *et al.*, 2011; Anh *et al.*, 2015) 8,911.57 €/remission (Obradovic *et al.*, 2007) 47,922.08 US$/ hospitalizarion avoided (O'day *et al.*, 2013) 1,329,394.88 US$/QALY (Lindner *et al.*, 2009)	OLA dominant (Obradovic *et al.*, 2007; Geitona *et al.*, 2008; O'day *et al.*, 2013) QUE dominant (Mcintyre *et al.*, 2010) 2010 224,000.00 US$/ QALY (Rosenheck *et al.*, 2006) 108,825.00 €/QALY (Zeidler *et al.*, 2013) 42,50 US$/extra stable day (Edwards *et al.*, 2008) 343,826.59 RMB/ response (Yang *et al.*, 2009)	OLA dominant (Rosenheck *et al.*, 2006; Obradovic *et al.*, 2007; Edwards *et al.*, 2008; Geitona *et al.*, 2008) 6,271.51 US$/ hospitalization avoided (O'day *et al.*, 2013)	
	Clozapine	CLO dominant (Mould-Quevedo *et al.*, 2009)	7,859.78 £/QALY (Knapp *et al.*, 2008) 384,513.48 MEX$/ extra month free of symptoms (Mould-Quevedo *et al.*, 2009) 58,618.05 I$/ DALY averted(Anh *et al.*, 2015)	CLO dominant (Knapp *et al.*, 2008)		CLO dominant (Mould-Quevedo *et al.*, 2009) 21,451.30 I$/DALY averted (Anh *et al.*, 2015)
	Aripiprazole	14,350.23 €/ remission (Obradovic *et al.*, 2007) 315,625.00 SEK/QALY (Lindström *et al.*, 2011) 94,558 €/QALY (Garcia-Ruiz *et al.*, 2012)	RIS dominant (Furiak *et al.*, 2009; Lindström *et al.*, 2011; Ascher-Svanum *et al.*, 2012; O'day *et al.*, 2013) 31,396.00 €/ remission (Obradovic *et al.*, 2007)	ARI dominant (Obradovic *et al.*, 2007; Furiak *et al.*, 2009) QUE dominant (Edwards *et al.*, 2008; O'day *et al.*, 2013) 244,76 €/extra stable day (Geitona *et al.*, 2008)	ARI dominant (Obradovic *et al.*, 2007) ZIP dominant (Geitona *et al.*, 2008; O'day *et al.*, 2013) 75.00 US$/extra stable day (Edwards *et al.*, 2008) 94,500.00 US$/QALY (Furiak *et al.*, 2009)	ARI dominant (Treur *et al.*, 2012) OLA dominant (Edwards *et al.*, 2008; Geitona *et al.*, 2008; Lindström *et al.*, 2011; Garcia-Ruiz *et al.*, 2012; O'day *et al.*, 2013) 3,951.72 €/remission (Obradovic *et al.*, 2007)

RIS = Risperidone; OLA = Olanzapine; QUE = Quetiapine; CLO = Clozapine; ARI = Aripiprazole; ZIP = Ziprasidone.

Table 4. ICER-based comparisons of cost-utility studies

		Strategy 2				
		Haloperidol	**Risperidone**	**Quetiapine**	**Ziprasidone**	**Olanzapine**
Strategy 1	Risperidone	RIS dominant (Lindström *et al.*, 2011; Garcia-Ruiz *et al.*, 2012; Zeidler *et al.*, 2013) 39,890.33 US$/QALY (Lindner *et al.*, 2009)				
	Quetiapine	31,626.67 €/QALY (Zeidler *et al.*, 2013)	RIS dominant (Furiak *et al.*, 2009; Mcintyre *et al.*, 2010) 8,785.71 US$/QALY (Rosenheck *et al.*, 2006) 85,747.13 £/QALY 57,540.00 €/QALY (Zeidler *et al.*, 2013)			
	Ziprasidone		RIS dominant (Furiak *et al.*, 2009) 16,333.33 US$/QALY (Rosenheck *et al.*, 2006) 218,060 C$/QALY (Mcintyre *et al.*, 2010)2010	ZIP dominant (Furiak *et al.*, 2009; Mcintyre *et al.*, 2010) QUE dominant (Rosenheck *et al.*, 2006)		
	Olanzapine	119,704.24 US$/QALY (Lindner *et al.*, 2009) 41,411.76 SEK/QALY (Lindström *et al.*, 2011) 3,554.55 €/QALY (Zeidler *et al.*, 2013) 23,621 €/QALY (Garcia-Ruiz *et al.*, 2012)	OLA dominant (Rosenheck *et al.*, 2006; Furiak *et al.*, 2009) RIS dominant (Mcintyre *et al.*, 2010; Lindström *et al.*, 2011; Anh *et al.*, 2015) 5,779.15 €/QALY (De Ridder e De Graeve, 2009) 43,466.67 US$/QALY (Ascher-Svanum *et al.*, 2012) 50,652.17 €/QALY (Garcia-Ruiz *et al.*, 2012) 38,890.91 €/QALY (Zeidler *et al.*, 2013) 5,156 £/QALY (Knapp *et al.*, 2008) 1,329,394.88 US$/QALY (Lindner *et al.*, 2009)	OLA dominant (Knapp *et al.*, 2008; Furiak *et al.*, 2009) QUE dominant (Mcintyre *et al.*, 2010)2010 224,000.00 US$/QALY (Rosenheck *et al.*, 2006) 108,825.00 €/QALY (Zeidler *et al.*, 2013)	OLA dominant (Rosenheck *et al.*, 2006; Furiak *et al.*, 2009) ZIP dominant (Mcintyre *et al.*, 2010) 2010	
	Clozapine		7,859.78 £/QALY (Knapp *et al.*, 2008) 58,618.05 I$/DALY averted (Anh *et al.*, 2015)	CLO dominant (Knapp *et al.*, 2008)		775 £/QALY (Knapp *et al.*, 2008) 21,451.30 I$/DALY averted (Anh *et al.*, 2015)
	Aripiprazole	315,625.00 SEK/QALY (Lindström *et al.*, 2011) 94,558 €/QALY (Garcia-Ruiz *et al.*, 2012)	RIS dominant (Furiak *et al.*, 2009; Lindström *et al.*, 2011; Ascher-Svanum *et al.*, 2012) 361,428.57 €/QALY (Garcia-Ruiz *et al.*, 2012)	ARI dominant (Furiak *et al.*, 2009)	94,500.00 US$/QALY (Furiak *et al.*, 2009)	ARI dominant (Treur *et al.*, 2012) OLA dominant (Furiak *et al.*, 2009; Ascher-Svanum *et al.*, 2011; Lindström *et al.*, 2011; Ascher-Svanum *et al.*, 2012; Garcia-Ruiz *et al.*, 2012)

RIS = Risperidone; OLA = Olanzapine; QUE = Quetiapine; CLO = Clozapine; ARI = Aripiprazole; ZIP = Ziprasidone.

and clozapine are cost-effective strategies in comparison with aripiprazole, ziprasidone, quetiapine and haloperidol (Table 4).

Quality assessment

In a global evaluation, articles reported in a reasonably clear way the question to be answered by the study. The objectives described permitted to conclude about what was going to be evaluated in the analysis. Some studies did not express the drugs compared or the perspective adopted in the objectives, but these issues were described elsewhere. Only one of the articles included reported data compared to a do-nothing scenario (Anh *et al.*, 2015) to demonstrate the cost-savings of the treatments. All the other studies compared antipsychotics against each other. Most articles briefly described the treatment alternatives, but to be able to make an evaluation of the outcomes and costs included in the analysis, the reader has to have previous knowledge about the drugs and the disease. Three randomized controlled trials and three cohort studies were included in the analysis. The cohort studies have the disadvantage of imposing a higher burden to the drugs that are proven to be efficacious for refractory patients. This effect should not happen in randomized controlled trials. The other 18 articles report data of pharmacoeconomic models. The models *per se* are already an approximation of reality and are only as good as the data that was used to fulfill it. The better the information used to build a model are, better will be its prediction capabilities. The majority of the studies did report the source of data, but not the reasons for doing so. The most part of these sources are specific studies, not systematic reviews for effectiveness, and databases or a collective of isolated cost information put together. Most of the studies considered the main costs of schizophrenia in the analysis: costs of ambulatory treatment, hospitalization, prescription and treatment of adverse events.

The studies that had time horizons over a year reported the discount rates applied. The values varied from 3 to 5%. Eight studies applied a 3% discount rate (Colombo *et al.*, 2008; De Ridder & De Graeve, 2009; Lindner *et al.*, 2009; Yang *et al.*, 2009; Treur *et al.*, 2012; O'day *et al.*, 2013; Zeidler *et al.*, 2013; Anh *et al.*, 2015), one study applied a 4% discount rate (Kim & Aas, 2011) and two studies applied a 5% discount rate (Mcintyre *et al.*, 2010; Lindström *et al.*, 2011). Nine of the model-based evaluations included largely extrapolate the time horizon of the studies available to measure efficacy or effectiveness (Colombo *et al.*, 2008; Lindner *et al.*, 2009; Mcintyre *et al.*, 2010; Kim & Aas, 2011; Lindström *et al.*, 2011; Treur *et al.*, 2012; O'day *et al.*, 2013; Zeidler *et al.*, 2013; Anh *et al.*, 2015). There is no robust evidence that the extrapolation of effectiveness data would reflect the long-term effectiveness of antipsychotic drugs and its impact in a real world setting (Garcia-Ruiz *et al.*, 2012). Most studies included deterministic and/or probabilistic sensitivity analysis to test the robustness of the findings, but did not reach a critical conclusion considering its results. Many studies reported really small differences between the drugs compared, but did not conclude with the doubt that this analysis provide, giving straight answers to complicated scenarios.

Discussion

The analysis of the pooled articles demonstrates a trend of cost-effectiveness favoring clozapine, olanzapine and risperidone for schizophrenia treatment. The sensitivity analysis indicates that the results are robust. It could be argued that the funding of the study is related to the results, because most studies were funded by Eli Lilly and Janssen-Cilag. However, after exclusion of the head-to-head comparisons including sponsored drugs in the pooled analysis, the results remained the same, indicating that this is not the reason for the observed trend. Risperidone, olanzapine and clozapine also showed better cost-effectiveness profile in the utility-based analysis. It cannot be determined, however, that the outcome measure does not alter the result of the studies. Half of the included studies did not exceed one year of time horizon, eleven studies report discount rates within the recommended interval, varying from 3 to 5%. Most of these reported a discount rate of 3% (eight studies). Therefore, the discount rates applied did not vary largely between studies.

Of the 24 included studies, 18 were funded by pharmaceutical companies. Between the studies funded by pharmaceutical companies, 16 (89%) found results that benefits the drug produced by the sponsor of the study, in accordance with the findings of Heres and colleagues (2006). A study funded by Eli Lilly did not demonstrate difference between olanzapine and risperidone (De Ridder & De Graeve, 2009) and a study funded by Pfizer actually showed results that benefit risperidone instead of ziprasidone. Some authors expressed concern that the systematic funding of pharmaceutical companies generate bias in the analysis favoring the companies' new drugs (Lexchin *et al.*, 2003; Bero *et al.*, 2007; Sismondo, 2008). Six non-funded cost-effectiveness studies were included in our final analysis: two favored first-generation antipsychotics (Rosenheck *et al.*, 2006; Lindner *et al.*, 2009) and four favored second-generation antipsychotics (Bounthavong & Okamoto, 2007; Obradovic *et al.*, 2007; Kim & Aas, 2011; Anh *et al.*, 2015). Between the studies that favor second-generation antipsychotics, two favor risperidone (Bounthavong & Okamoto, 2007; Anh *et al.*, 2015) and two favor olanzapine (Obradovic *et al.*, 2007; Kim & Aas, 2011). This way, we cannot confirm the prejudicial effect of the private funding in the evidence, but we also believe that first-generations antipsychotics cost-effectiveness profiles might be affected

by the lack of interest in proving data saying that they are more cost-effective than second-generation antipsychotics.

In a meta-analysis of randomized controlled trials evaluating oral formulations of first- and second-generation antipsychotics, Leucht *et al.* (2009) found that the drugs are very different in terms of efficacy and safety from each other and that some of them (including olanzapine, clozapine and risperidone) were found to be more efficacious than first-generation antipsychotics, in a analysis excluding open-label trials (Leucht *et al.*, 2009). This conclusion, associated with the evidence that the purchase cost of drugs correspond to only a very small part of the costs of schizophrenia (Genduso & Haley, 1997; Jones *et al.*, 2006), indicate that there might be a advantage in terms of cost-effectiveness for some second-generation antipsychotics in comparison to first-generation drugs. Pragmatic trials that include a cost-effectiveness component do not show clear evidence that second-generation antipsychotics are superior to first-generation antipsychotics in terms of cost-effectiveness (Rosenheck *et al.*, 2003; Jones *et al.*, 2006; Rosenheck *et al.*, 2006). Hanrahan *et al.* (2006), in a review of prospective pharmacoeconomic studies of antipsychotics, found that the design of a study is associated to the results. They observed that the efficacy trials show advantage for the second-generation antipsychotics and the effectiveness studies do not, indicating that the real world conditions could be related to the loss of cost-effectiveness of second-generation antipsychotics (Hanrahan *et al.*, 2006). Only three included studies evaluated in our analysis were prospective cost-effectiveness analysis that compared first- and second-generation antipsychotics. These studies do not show that trend: one pragmatic randomized clinical trial-based study favored perphenazine (Rosenheck *et al.*, 2006) over second-generation antipsychotics, one randomized clinical trial-based study favored olanzapine (Tunis *et al.*, 2006) and one cohort-based study also favored olanzapine (Knapp *et al.*, 2008). But it can be argued that the choice of main outcome could favor one class or another. Important pragmatic trials that evaluated first- and second-generation antipsychotic show different results depending on the outcome evaluated (Rosenheck *et al.*, 2003; Lieberman *et al.*, 2005; Jones *et al.*, 2006; Kahn *et al.*, 2008).

Polsky *et al.* (2006) conducted a review of eight randomized clinical trials-based cost-effectiveness analysis of antipsychotics. Most of these suggested that second-generation antipsychotics were considered cost-effective in comparison with first-generation drugs. They evaluated the methods applied to build the cost-effectiveness analysis to discuss the validation of the results and conclude that, even with the results pointing toward the cost-effectiveness of second-generation antipsychotics, the methodological issues found suggested that there were no clear evidence that the second-generation antipsychotics are cost-effective in a comparison with first-generation antipsychotics (Polsky *et al.*, 2006). We found some methodological issues that could influence the results of the evaluations related to the sources of information and the conclusions drawn from really small differences in costs and effects of drugs. However, we included in our analysis randomized controlled trials, observational studies and modeling techniques, industry-sponsored studies and not funded studies and we observed that this subgroups do not show very different results from each other.

The ICERcalc data presented do not intent to be as precise as the ICERrep data. It was only calculated to allow the comparison of all drugs included in a study, not only the results presented, and to provide a trend of cost-effectiveness. A model of cost-effectiveness analysis is just as good as the data that was used to fill the model and the perception of what is the important parameters to consider in the simplification of reality. The analysis of the assumptions taken is important to the internal and external validity of the analysis and represents a possible risk of bias, allowing the benefit of one drug or another. Economic and effectiveness data are difficult to apply from one place to another. They are highly dependent of the healthcare setting and demographic, cultural, available resources and social constructs (Brandão *et al.*, 2012). This study aims to identify a trend of cost-effectiveness worldwide, not to take conclusions from one place to apply to another place. In a systematic review of economic evaluations, the multiplicity of ways to calculate the effectiveness makes comparisons difficult. Therefore, we only described the results of the studies as an estimation of trend of cost-effectiveness, not making direct comparisons between studies or calculating any form of aggregate result. The date restriction was imposed because we would like to evaluate a scenario more representative of the present. With time the technologies' patents end and the efficiency of its use tend to improve. So we chose to evaluate only from 2005. Other databases like EMBASE were not included for lack of access. Also, the parameters to decide for cost-effectiveness, based on the willingness to pay, are usually provisional and arbitrary, and in most cases, are applied to units of outcome adjusted by utility, not being useful for all comparisons. Nevertheless, the knowledge of pharmacoeconomic analysis of other countries can be a good guide for decision making.

We conclude, in the light of the included evidence, that there is a difference in the cost-effectiveness profiles between specific antipsychotic drugs. Risperidone, olanzapine and clozapine seem to be the drugs most considered cost-effective in a pooled analysis. This result was robust to changes in funding. An analysis that consider first- vs. second-generation antipsychotics polled together might be biased by the different profiles of the specific drugs, not considering the heterogeneity of the group of second-generation antipsychotics.

Acknowledgments

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SUPPLEMENTARY MATERIALS

1. SEARCH STRATEGIES

PubMed
((“schizophrenia” [MeSH Terms] OR “schizophrenia” [All Fields]) OR esquizofrenia [All Fields]) AND ((“cost-benefit analysis” [MeSH Terms] OR (“cost-benefit” [All Fields] AND “analysis” [All Fields]) OR “cost-benefit analysis” [All Fields] OR (“cost” [All Fields] AND “effectiveness” [All Fields]) OR “cost effectiveness” [All Fields]) OR custo-efetividade [All Fields] OR (“cost-benefit analysis” [MeSH Terms] OR (“cost-benefit” [All Fields] AND “analysis” [All Fields]) OR “cost-benefit analysis” [All Fields] OR (“cost” [All Fields] AND “benefit” [All Fields]) OR “cost benefit” [All Fields]) OR custo-benefício [All Fields] OR custo-utilidade [All Fields] OR cost-utility [All Fields] OR “economic evaluation” [All Fields] OR (avaliação [All Fields] AND (“Econômica” [Journal] OR “econômica” [All Fields]))))
LILACS
tw:((schizophrenia OR esquizofrenia) AND (cost-effectiveness OR custo-efetividade OR cost-utility OR custo-utilidade OR custo-benefício OR cost-benefit OR “avaliação econômica” OR “economic evaluation”))
PsychINFO
schizophrenia AND (cost-effectiveness OR cost-utility OR cost-benefit)

2. Criteria for quality evaluation of economic analysis (Drummond et al., 2005).

1. Was a well-defined question posed in answerable form?
2. Was a comprehensive description of the competing alternatives given?
3. Was the effectiveness of the programmes or services established?
4. Were all the important and relevant costs and consequences for each alternative identified?
5. Were costs and consequences measured accurately in appropriate physical units?
6. Were costs and consequences valued credibly?
7. Were costs and consequences adjusted for differential timing?
8. Was an incremental analysis of costs and consequences of alternatives performed?
9. Was allowance made for uncertainty in the estimates of costs and consequences?
10. Did the presentation and discussion of study results include all issues of concern to users?

3. Excluded Studies in phase two

ID	Status	Obs	author	title	year
1	Excluded	Study	Geitona, Maria and Kousoulakou, Hara and Ollandezos, Markos and Athanasakis, Kostas and Papanicolaou, Sotiria and Kyriopoulos, Ioannis	“Costs and effects of paliperidone extended release compared with alternative oral antipsychotic agents in patients with schizophrenia in Greece: A cost effectiveness study”: Correction	2009
2	Excluded	Date	Lecomte, Pascal and De Hert, Marc and van Dijk, Marc and Nuijten, Mart and Nuyts, Guy and Persson, Ulf	A 1-Year Cost-Effectiveness Model for the Treatment of Chronic Schizophrenia with Acute Exacerbations in Belgium	2000
3	Excluded	Date	Petit, C. and Maccario, J.	A Bayesian analysis of pharmacoeconomic Date from a clinical trial on schizophrenia	2003
4	Excluded	Perspective	Lubinga, S. J. and Mutamba, B. B. and Nganizi, A. and Babigumira, J. B.	A Cost-effectiveness Analysis of Antipsychotics for Treatment of Schizophrenia in Uganda	2015
5	Excluded	Date	Palmer, C. S. and Revicki, D. A. and Genduso, L. A. and Hamilton, S. H. and Brown, R. E.	A cost-effectiveness clinical decision analysis model for schizophrenia	1998
6	Excluded	Date	Palmer, C. S. and Brunner, E. and Ruiz-Flores, L. G. and Paez-Agraz, F. and Revicki, D. A.	A cost-effectiveness clinical decision analysis model for treatment of Schizophrenia	2002

ID	Status	Obs	author	title	year
7	Excluded	Date	I. Bitter; G. Hoffer; J. Vitrai; L. Porkolab; and P. Alfoldi	Comparative evaluation of the cost-effectiveness of olanzapine treatment to haloperidol treatment with Markov-modeling in Hungary.	2000
8	Excluded	Duplicate	Lindström, Eva and Eberhard, Jonas and Fors, Björn M. and Hansen, Karina and Sapin, Christophe	A pharmacoeconomic analysis of sertindole in the treatment of schizophrenia in Sweden	2011
10	Excluded	Date	Hansen, K. and Francois, C. and Toumi, M. and Lancon, C.	A pharmacoeconomic evaluation of zuclopenthixol compared with haloperidol and risperidone in the treatment of schizophrenia	2002
12	Excluded	Comparator	Davies, Linda M. and Barnes, Thomas R. E. and Jones, Peter B. and Lewis, Shôn and Gaughran, Fiona and Hayhurst, Karen and Markwick, Alison and Lloyd, Helen	A randomized controlled trial of the cost-utility of second-generation antipsychotics in people with psychosis and eligible for clozapine	2008
13	Excluded	Date	Tilden, D. and Aristides, M. and Meddis, D. and Burns, T.	An economic assessment of quetiapine and haloperidol in patients with schizophrenia only partially responsive to conventional antipsychotics	2002
15	Excluded	Population	Vadruccio, Felice and Fazio, Giacobba	Analisi costo/efficacaia dei trattamenti di pazienti psicotici cronici in cura con olanzapina, antipsicotici atipici e neurolettici tradizionali. [Cost/effectiveness analysis of treatments for chronic psychotic patients taking olanzapine, a typical antipsychotic and neuroleptic drug.]	2008
16	Excluded	Intervention	Magnus, A. and Carr, V. and Mihalopoulos, C. and Carter, R. and Vos, T.	Assessing cost-effectiveness of drug interventions for schizophrenia	2005
17	Excluded	Duplicate	Lindner, Leandro Mendonça and Marasciulo, Antonio Carlos and Farias, Mareni Rocha and Grohs, Geder Evandro Motta	Economic evaluation of antipsychotic drugs for schizophrenia treatment within the Brazilian Healthcare System	2009
18	Excluded	Date	Tunis, S. L. and Johnstone, B. M. and Gibson, P. J. and Loosbrock, D. L. and Dulisse, B. K.	Changes in perceived health and functioning as a cost-effectiveness measure for olanzapine versus haloperidol treatment of schizophrenia	1999
21	Excluded	Date	Almond, S. and O'Donnell, O.	Cost analysis of the treatment of schizophrenia in the UK. A simulation model comparing olanzapine, risperidone and haloperidol	2000
22	Excluded	Date	Almond, S. and O'Donnell, O.	Cost analysis of the treatment of schizophrenia in the UK: a comparison of olanzapine and haloperidol	1998
23	Excluded	Date	Meltzer, H. Y. and Cola, P. and Way, L. and Thompson, P. A. and Bastani, B. and Davies, M. A. and Snitz, B.	Cost effectiveness of clozapine in neuroleptic-resistant schizophrenia	1993
24	Excluded	Date	Meltzer, Herbert Y. and Cola, Philip and Thompson, Paul A. and Bastani, Bijan and Davies, Marilyn and Snitz, Beth	Cost effectiveness of clozapine in neuroleptic-resistant schizophrenia. [A neuroleptikum-rezisztens szkizofrenia clozapin-kezelesenek koltsegvonzatai.]	1995
26	Excluded	Comparator	Muser, E. and Kozma, C. M. and Benson, C. J. and Mao, L. and Starr, H. L. and Alphs, L. and Fastenau, J.	Cost effectiveness of paliperidone palmitate versus oral antipsychotics in patients with schizophrenia and a history of criminal justice involvement	2015

ID	Status	Obs	author	title	year
28	Excluded	Comparator	King, D. and Knapp, M. and Thomas, P. and Razzouk, D. and Loze, J. Y. and Kan, H. J. and van Baardewijk, M.	Cost-effectiveness analysis of aripiprazole vs standard-of-care in the management of community-treated patients with schizophrenia: STAR study	2011
30	Excluded	Comparator	Bernardo, M. and Azanza, J. R. and Rubio-Terrés, C. and Rejas, J.	Cost-effectiveness analysis of the prevention of relapse of schizophrenia in the ZEUS longitudinal study Ziprasidone Extended Use in Schizophrenia (ZEUS)	2007
33	Excluded	Comparator	Lachaine, J. and Beauchemin, C. and Mathurin, K. and Gilbert, D. and Beillat, M.	Cost-effectiveness of asenapine in the treatment of schizophrenia in Canada	2014
34	Excluded	Study	Davies, A. and Vardeva, K. and Loze, J. Y. and L'Italien G, J. and Sennfalt, K. and Baardewijk, Mv	Cost-effectiveness of atypical antipsychotics for the management of schizophrenia in the UK	2008
35	Excluded	Duplicate	Davies, Andrew and Vardeva, Kawitha and Loze, Jean-Yves and L'Italien, Gilbert J. and Sennfalt, Karin and van Baardewijk, Marc	Cost-effectiveness of atypical antipsychotics for the management of schizophrenia in the UK	2008
36	Excluded	Date	Karki, Shyam D. and Bellnier, Terrance J. and Patil, Kashinath and Oretega, Tulio	Cost-effectiveness of atypical antipsychotics in severely and persistently mentally ill patients with schizophrenia and schizoaffective disorders	2001
37	Excluded	Date	Aitchison, Katherine J. and Kerwin, Robert W.	Cost-effectiveness of clozapine	1997
38	Excluded	Date	Essock, Susan M. and Frisman, Linda K. and Covell, Nancy H. and Hargreaves, William A.	Cost-effectiveness of clozapine compared with conventional antipsychotic medication for patients in state hospitals	2000
39	Excluded	Date	Revicki, Dennis A. and Luce, Bryan R. and Weschler, Joan M. and Brown, Ruth E. and et al.	Cost-effectiveness of clozapine for treatment-resistant schizophrenic patients	1990
40	Excluded	Date	Rosenheck, Robert and Cramer, Joyce and Allan, Edward and Erdos, Joseph and Frisman, Linda K. and Xu, Weichun and Thomas, Jonathan and Henderson, William and Charney, Dennis	Cost-effectiveness of clozapine in patients with high and low levels of hospital use	1999
41	Excluded	Date	Jonsson, D. and Walinder, J.	Cost-effectiveness of clozapine treatment in therapy-refractory schizophrenia	1995
42	Excluded	Date	Jonsson, Dick and Walinder, J.	Cost-effectiveness of clozapine treatment in therapy-refractory schizophrenia	1995
43	Excluded	Date	Aitchison, K. J. and Kerwin, R. W.	Cost-effectiveness of clozapine. A UK clinic-based study	1997
44	Excluded	Intervention	Gutierrez-Recacha, P. and Chisholm, D. and Haro, J. M. and Salvador-Carulla, L. and Ayuso-Mateos, J. L.	Cost-effectiveness of different clinical interventions for reducing the burden of schizophrenia in Spain	2006
45	Excluded	Intervention	Davies, L. M. and Lewis, S. and Jones, P. B. and Barnes, T. R. E. and Gaughran, F. and Hayhurst, K. and Markwick, A. and Lloyd, H.	Cost-effectiveness of first- v. second-generation antipsychotic drugs: Results from a randomised controlled trial in schizophrenia responding poorly to previous therapy	2007
48	Excluded	Comparator	Furiak, Nicolas M. and Ascher-Svanum, Haya and Klein, Robert W. and Smolen, Lee J. and Lawson, Anthony H. and Montgomery, William and Conley, Robert R.	Cost-effectiveness of olanzapine long-acting injection in the treatment of patients with schizophrenia in the United States: A micro-simulation economic decision model	2011
50	Excluded	Outcomes	Phanthunane, P. and Vos, T. and Whiteford, H. and Bertram, M.	Cost-effectiveness of pharmacological and psychosocial interventions for schizophrenia	2011
51	Excluded	Date	Jerrell, Jeanette M.	Cost-effectiveness of risperidone, olanzapine, and conventional antipsychotic medications	2002

ID	Status	Obs	author	title	year
53	Excluded	Study	Park, T. and Kuntz, K. M.	Cost-effectiveness of second-generation antipsychotics for the treatment of schizophrenia	2014
54	Excluded	Date	Launois, Robert and von der Schulenburg, Matthias Graf and Knapp, Martin and Toumi, Mondher	Cost-effectiveness of sertindole versus olanzapine or haloperidol: A comprehensive model	1998
58	Excluded	Duplicate	Cabello Rangel, Héctor and Díaz Castro, Lina and Arredondo, Armando	Cost effectiveness of interventions for schizophrenia in Mexico	
59	Excluded	Intervention	Cabello Rangel, Héctor and Díaz Castro, Lina and Arredondo, Armando	Costo-efectividad de intervenciones para esquizofrenia en Mexico. [Cost effectiveness of interventions for schizophrenia in Mexico.]	2011
62	Excluded	Duplicate	María del Carmen Lara–Muñoz; Rebeca Robles–García; Ricardo Orozco; Ma. Teresa Saltijeral Méndez; Ma. Elena Medina–Mora; Dan Chishol	Estudio de costo-efectividad del tratamiento de la esquizofrenia en México Cost effectiveness study of schizophrenia a management in Mexico	
63	Excluded	Intervention	María del Carmen Lara–Muñoz; Rebeca Robles–García; Ricardo Orozco; Ma. Teresa Saltijeral Méndez; Ma. Elena Medina–Mora; Dan Chisho	Estudio de costo-efectividad del tratamiento de la esquizofrenia en México. [Cost effectiveness study of schizophrenia management in Mexico.]	2010
64	Excluded	Date	Ganguly, Rahul and Miller, L. Stephen and Martin, Bradley C.	Future employability, a new approach to cost-effectiveness analysis of antipsychotic therapy	2003
66	Excluded	Study	Windmeijer, F. and Kontodimas, S. and Knapp, M. and Brown, J. and Haro, J. M.	Methodological approach for assessing the cost-effectiveness of treatments using longitudinal observational Date: the SOHO study	2006
67	Excluded	Date	Rosenheck, R. and Cramer, J. and Xu, W. and Grabowski, J. and Douyon, R. and Thomas, J. and Henderson, W. and Charney, D.	Multiple outcome assessment in a study of the cost-effectiveness of clozapine in the treatment of refractory schizophrenia. Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia	1998
69	Excluded	Date	Oh, P. I. and Iskedjian, M. and Addis, A. and Lanctot, K. and Einarson, T. R.	Pharmacoeconomic evaluation of clozapine in treatment-resistant schizophrenia: a cost-utility analysis	2001
70	Excluded	Comparator	Jones, P. B. and Barnes, T. R. and Davies, L. and Dunn, G. and Lloyd, H. and Hayhurst, K. P. and Murray, R. M. and Markwick, A. and Lewis, S. W.	Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1)	2006
71	Excluded	Date	Davies, Alison and Langley, Paul C. and Keks, Nicholas A. and Catts, Stanley V. and Lambert, Tim and Schweitzer, Isaac	Risperidone versus haloperidol: II. Cost-effectiveness	1998
73	Excluded	Intervention	Chisholm, D. and Gureje, O. and Saldivia, S. and Villalon Calderon, M. and Wickremasinghe, R. and Mendis, N. and Ayuso-Mateos, J. L. and Saxena, S.	Schizophrenia treatment in the developing world: an interregional and multinational cost-effectiveness analysis	2008
74	Excluded	Intervention	Heeg, Bart and Buskens, Erik and Botteman, Marc and Caleo, Sue and Ingham, Mike and Damen, Joep and de Charro, Frank and van Hout, Ben	The cost-effectiveness of atypicals in the UK	2008

ID	Status	Obs	author	title	year
76	Excluded	Study	Graham, C. N. and Mauskopf, J. A. and Lawson, A. H. and Ascher-Svanum, H. and Bruhn, D.	Updating and confirming an industry-sponsored pharmacoeconomic model: comparing two antipsychotics in the treatment of schizophrenia	2012
77	Excluded	Date	Sacristan, J. A. and Gomez, J. C. and Salvador-Carulla, L.	[Cost effectiveness analysis of olanzapine versus haloperidol in the treatment of schizophrenia++ in Spain]	1997

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