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Economic evaluations on use of aripiprazole for patients with schizophrenia: a systematic review.

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Course Conclusion Paper of the Pharmacy-Biochemistry course of University of São Paulo's Faculty of Pharmaceutical Sciences.

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LIST OF ABBREVIATION

ICER	Incremental Cost-Effectiveness Ratio
ICUR	Incremental Cost-Utility Ratio
PANSS	Positive And Negative Syndrome Scale
CEA	Cost-effectiveness analysis
NHS	National Health Service
LILACS	*Literatura Latino-Americana e do Caribe em Ciências da Saúde*
MeSH	Medical Subject Headings
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
QALY	Quality-Adjusted Life-Year
AOM	Aripiprazole Once-Monthly
PLAI	Paliperidone Long-Acting Injectable
ALAI	Aripiprazole Long-Acting Injectable
ACMTS	*Agence Canadienne des Médicaments et des Technologies de la Santé*
SUS	*Sistema Único de Saúde*
ICD	International Classification of Diseases

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ABSTRACT

HENRIQUE, ICB. **Economic evaluations on use of aripiprazole for patients with schizophrenia: a systematic review**. 2018. 45 p. Course Conclusion Paper of Pharmacy-Biochemistry Course – Faculty of Pharmaceutical Sciences – University of São Paulo, São Paulo, 2018.

Key words: Aripiprazole, Schizophrenia, Systematic Review, Economic Evaluation.

INTRODUCTION: Schizophrenia is a serious mental disorder and is associated with substantial economic and social burden. Cost-effectiveness analyses are important in assessing differences in value between treatment options. However, there is lack of information on the reporting quality of economic evaluations, cost drivers, as well as updated data focused on aripiprazole - antipsychotic drug commonly prescribed for schizophrenia. OBJECTIVE: To elaborate a systematic review to evaluate the full economic evaluations on the use of aripiprazole in schizophrenia, to identify cost drivers and to critically evaluate the reporting quality of the studies. MATERIALS AND METHODS: A literature research was conducted in PubMed, NHS Economic Evaluation Database, CEA Registry, and LILACS databases until March 2018. This review included cost-effectiveness or cost-utility analyses based on decision models, published in English, Portuguese, or Spanish, which evaluated the costs and outcomes of aripiprazole in schizophrenia. The selection of studies, data extraction, and evaluation of the reporting quality of economic evaluations were carried out by two independent authors and the differences were solved by a third author. The reporting quality was evaluated by the CHEERS checklist. RESULTS: The literature search has identified 79 potential studies, from which 17 model-based economic evaluations fully met the eligibility criteria. Of these, 15 were industry-funded studies. A trend favoring olanzapine, lurasidone, and paliperidone could be observed, while aripiprazole was extensively described as a dominated alternative. In addition, 93% of the industry-funded studies presented favorable results to their sponsor; two of them being aripiprazole's manufacturer. With regards to cost drivers, they were usually related to relapse rates/probabilities. The reporting quality of the economic analyses was poor, with most studies got around 12-13 points. CONCLUSION: No consistent conclusion on aripiprazole's cost-effectiveness can be drawn due to due to the context-specific costs, conflicting parameters of effectiveness and safety, and criticism related to industry sponsorship. The most reliable finding that can indeed be drawn from this review were the cost drivers, which was usually related to relapse rates/probabilities, regardless of the study funding. Furthermore, the poor reporting quality of the economic studies requires improvement to ensure greater reliability of the findings.

1. INTRODUCTION

Schizophrenia is a psychotic disorder characterized by abnormalities in one or more of the following five aspects: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behavior (including catatonia) and negative symptoms (APA, 2013). This disease appears to be present worldwide with a prevalence rate of approximately 0.5% (SIMEONE et al., 2015); and is associated with a 40% to 60% higher chance of premature death when compared to the general population (WHO, 2013). In addition, the medical treatment received by patients with schizophrenia is commonly lower in quality (i.e., fewer visits, less likely to receive a detailed physical examination and fewer documented medical problems), which contributes to the increased mortality rate and shows the impact of this disease on the individual's life (TAJIMA-POZO et al., 2015).

In a broad analysis, one can also see the great social and economic burden of schizophrenia. Like other mental disorders, the investigated disease is associated with situations of homelessness and poverty, with its economic burden estimated at US $ 16.3 million between 2011 and 2030 (WHO, 2013). This high cost is due to the direct costs (medications, hospitalizations, outpatient visits, etc.) of the disease itself and to those associated with the comorbidities that the individuals tends to develop (TAJIMA-POZO et al., 2015). Moreover, the indirect costs of schizophrenia (usually loss of productivity of the individual, relatives, or caregivers) are those that contribute to most of the total cost of the disease (about 50% to 85%), according to systematic review regarding economic evaluations conducted from the perspective of society (CHONG et al., 2016).

The treatment of schizophrenia has as therapeutic objectives the induction of remission, the prevention of recurrence and the reestablishment of the behavioral, psychosocial, and cognitive functions in pre-morbid levels. For this, pharmacological and psychotherapeutic approaches are employed, and the success of the treatment depends greatly on each individual and on the characteristics their schizophrenia’s subtype (PORTH, 2005). For example, for the

predominance of positive symptoms, patients usually respond to pharmacotherapy with first (typical) or second generation (atypical) drugs. On the other hand, with regards to the negative symptoms, atypical antipsychotics are related to better responses, although there is no specific therapy for such symptoms (PORTH, 2005; PATEL, 2014).

Among the atypical antipsychotic drugs, aripiprazole is commonly prescribed for schizophrenia. In a recent overview, Ribeiro et al. (2018) summarized the efficacy and safety of this drug for the treatment of patients with schizophrenia. The authors showed that aripiprazole is effective for the reduction in total PANSS (Positive And Negative Syndrome Scale) and has efficacy similar to typical and atypical (with the exception of olanzapine and amisulpride) antipsychotics. In addition, it showed lower weight gain and lower change in glucose and cholesterol levels, in comparison with clozapine, risperidone, or olanzapine; and general extrapyramidal side effects, need for antiparkinsonian medication, and akathisia when compared to risperidone and typical antipsychotics (RIBEIRO et al., 2018).

Given the limited availability of financial resources and the need for greater efficiency in their allocation, decision-making on the incorporation of technologies should consider factors beyond efficacy and safety. Cost, cost-effectiveness and social, legal, ethical, and political impacts are some of them (POSTMA, 2009). In this context, economic evaluations have increasingly played an important role in decisions about the financing of new technologies, based on technical and scientific analyses. Previous systematic review has evaluated full economic evaluations of all antipsychotic drugs used for the treatment of schizophrenia (SANTOS et al., 2017). However, there is a lack of information on the reporting quality of these economic evaluations, cost drivers, as well as updated data focused on the use of aripiprazole in schizophrenia.

2. OBJECTIVE

To elaborate a systematic review to evaluate full economic evaluations on the use of aripiprazole in schizophrenia, identify cost drivers, and critically evaluate the reporting quality of the studies.

3. MATERIALS AND METHODS

3.1. Databases

This systematic review conducted a comprehensive search in the databases PubMed, CEA Registry, NHS Economic Evaluation Database, and LILACS until March 2018. In addition, references to articles found were also evaluated manually to include any potential articles that have not been tracked.

3.2. Search strategy

The standardized search strategy included MeSH terms and disease-related keywords (schizophrenia), intervention (aripiprazole), and type of study (economic evaluation). The complete search strategy for all databases can be seen in Appendix 1.

3.3. Study selection

All of the studies selection process was made by two independent authors (I.C.B.H. and T.M.L), and any disagreement was analyzed and judged by a third reviewer (P.M.A.). After searching for articles, the first step was the studies' grouping by database and elimination of repeated articles by title. Then, the title and abstract were read to verify the studies that did not correspond with the purpose of this review. Sequentially to the exclusion stage of the titles/abstracts that are not related to the review, a consensus was reached by classifying the selected articles in: Yes (enter the review), No (does not enter the review) and Not Sure (doubt on the selected study). After consensus, only studies that received

"Yes" and "Not Sure" remained. The next step was to read the full text of the article. If the articles were not available in the databases, a contact to the corresponding authors via email or Researchgate (www.researchgate.net) could have been done, but this was not an issue once all articles were found.

To be included in this systematic review, the article should: 1) be identified as a full economic evaluation - a study comparing two or more alternatives, examining their costs and consequences, and reporting incremental cost-effectiveness (ICER) or cost-utility (ICUR) ratio (DRUMMOND et al., 2005); 2) be based in an decision analysis model; 3) be published in English, Portuguese, or Spanish; 4) evaluated the use of aripiprazole compared to another drug, the combination of other drugs, or placebo; 5) report the costs and consequences of the alternatives; and 6) included patients with schizophrenia. Conference abstracts, other study types, incomplete economic evaluations, studies lacking an explicit ICER/ICUR (i.e., we have not calculated any additional ICER/ICUR) were excluded.

3.4. Data extraction

After selecting studies, the selected economic evaluation data were extracted into a preformatted worksheet in Microsoft Excel ®. The extraction of these data was performed by two independent reviewers (I.C.B.H. and T.M.L) and any disagreement was resolved by a third evaluator (P.M.A.).

Details of the economic evaluations' methods were extracted, including: type of economic evaluation, population studied, country, payer perspective, reference comparator, time horizon, types of costs, discount rates, economic modeling type, assessed outcomes, study results (i.e., ICER and ICUR), cost drivers, and sources of funding.

The results of economic evaluations (i.e., ICER and ICUR) were presented as: 1) more effective and more costly; 2) more effective and less costly (dominant); 3) less effective and less costly, and 4) less effective and more costly (dominated).

Situations 1 and 3 require judgment and often depend on what the decision maker is willing to pay (COHEN & REYNOLDS, 2008).

3.5. Critical quality evaluation

In order to evaluate the reporting quality of the full economic evaluations, the "Consolidated Health Economic Evaluation Reporting Standards" (CHEERS) was used. This is a tool developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (HUSEREAU et al., 2013).

The CHEERS checklist consists of 24 items that included six areas: 1) title and abstract (two items); 2) introduction (one item); 3) methods (14 items); 4) results (four items); 5) discussion (one item); and 6) other, which is related to funding and conflict of interest (two items). The items were scored as "yes" (only those that clearly included the item in its entirely), "no" (when the evaluator considered the description of the item incomplete, non-existent or doubtful) and "not applicable". The total score was obtained by assigning the score 1 for each answer "yes" and the score 0 for the other answers, varying from the minimum 0 (no item contemplated) to 24 (all items contemplated).

Although the CHEERS checklist is not a scoring tool, the reporting quality of the studies was expressed as the percentage of studies in line with recommendation and items fully met in each article. Two independent reviewers (I.C.B.H. and T.M.L) evaluated the studies and any disagreement were resolved by a third investigator (P.M.A.).

4. RESULTS

4.1. Literature search

The comprehensive literature search has identified 79 potential studies. After removing duplicated entries and subsequently reading of titles and abstracts, 27 articles were left for full-text reading. From these, two were conference abstracts, three were not complete economic evaluations, and five were not based on decision models (Appendix 2). Finally, 17 model-based economic evaluations, all published in English and between 2007 and 2016 (RAJAGOPALAN et al, 2016; DRUAIS et al., 2016; LIN et al., 2016; EINARSON et al., 2015; CITROME et al., 2014; LACHAINE et al., 2014; O'DAY et al., 2013; RAJAGOPALAN et al., 2013; TREUR et al., 2012; GARCÍA-RUIZ et al., 2012; ASCHER-SVANUM et al., 2012; LINDSTRÖM et al., 2011; KASTENG et al., 2011; FURIAK et al., 2009; DAVIES et al., 2008; GEITONA et al., 2008; OBRADOVIC et al., 2007), fully met the eligibility criteria and were selected for this systematic review (Figure 1).

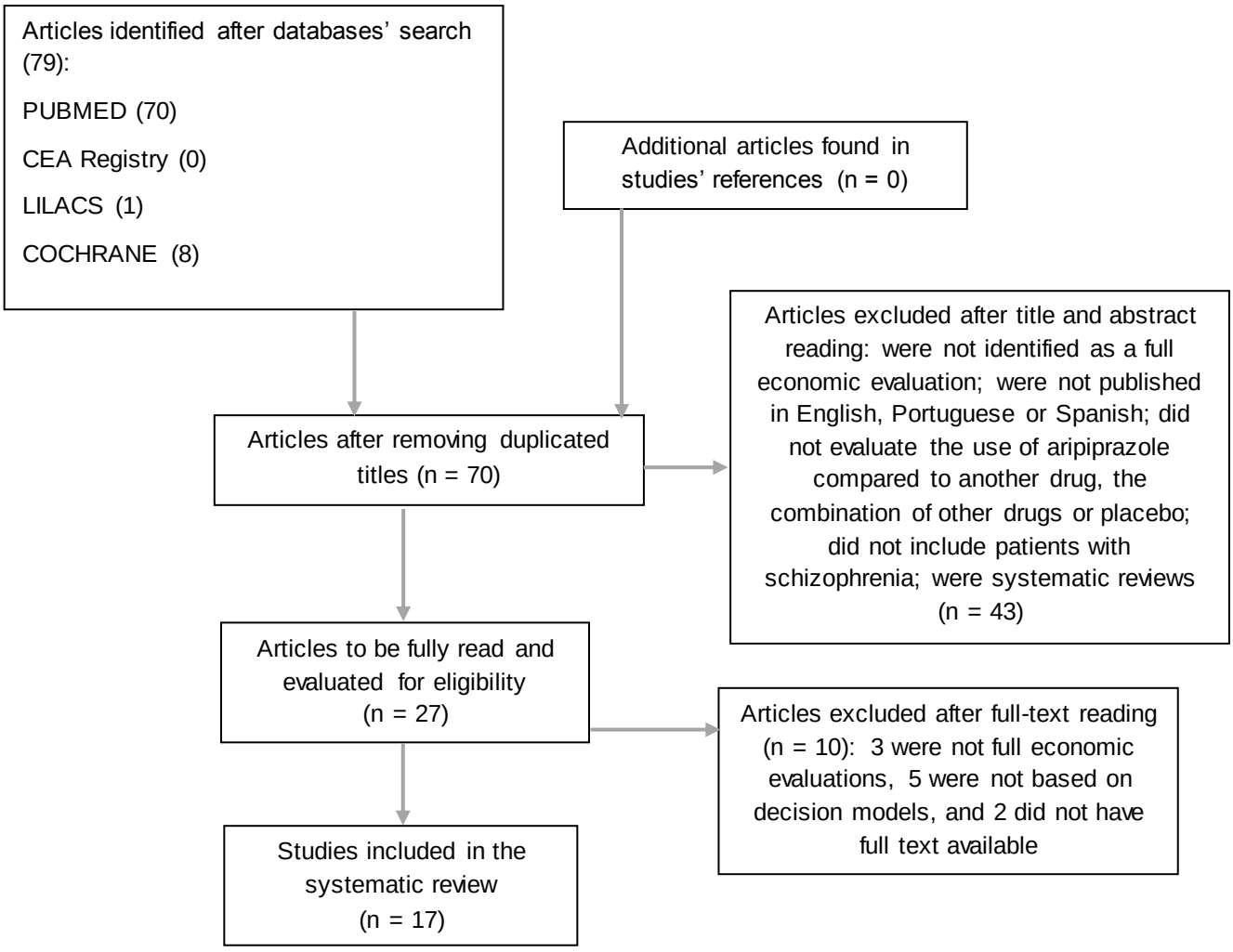

Figure 1: Study selection flowchart.

4.2. Characteristics of the full economic evaluations

The description of the selected studies can be seen at Table 1. Most studies have not established an age group for the target population and four studies did so have focused on adult patients (RAJAGOPALAN et al, 2016; LACHAINE et al., 2014; O'DAY et al., 2013; RAJAGOPALAN et al., 2013). In addition, only one of them has specified the disease's onset age (LACHAINE et al., 2014), and none of them have established the age group's definition (e.g., from 30 years old to 50 years old). Only eight of the articles specified the phase at which patients with schizophrenia entered the study (e.g., remission, acute phase, right after failure of an antipsychotic therapy, hospitalization) (RAJAGOPALAN et al., 2016, DRUAIS et al., 2016, LIN et al., 2016, EINARSON et al., 2015, RAJAGOPALAN et al., 2013, DAVIES et al., 2008, GEITONA et al., 2008; OBRADOVIC et al., 2007).

With regards to the type of economic evaluation, eight studies were cost-utility analysis (LIN et al., 2016; LACHAINE et al., 2014; TREUR et al., 2012; GARCÍA-RUIZ et al., 2012; ASCHER-SVANUM et al., 2012; KASTENG et al., 2011; FURIAK et al., 2009; DAVIES et al., 2008; GEITONA et al., 2008;), five studies were cost-effectiveness (CITROME et al., 2014; O'DAY et al., 2013; RAJAGOPALAN et al., 2013; OBRADOVIC et al., 2007), and four did both analyses (RAJAGOPALAN et al, 2016; DRUAIS et al., 2016; EINARSON et al., 2015; LINDSTRÖM et al., 2011). However, the majority of articles were erroneously describing their type of analysis, using "cost-effectiveness" as a general term (RAJAGOPALAN et al, 2016; DRUAIS et al., 2016; LIN et al., 2016; EINARSON et al., 2015; LACHAINE et al., 2014; TREUR et al., 2012; GARCÍA-RUIZ et al., 2012; ASCHER-SVANUM et al., 2012; LINDSTRÖM et al., 2011; KASTENG et al., 2011; FURIAK et al., 2009; DAVIES et al., 2008).

It is worth noticing that 15 of the 17 articles were funded by a pharmaceutical industry (RAJAGOPALAN et al, 2016; DRUAIS et al., 2016; EINARSON et al., 2015; CITROME et al., 2014; LACHAINE et al., 2014; O'DAY et al., 2013; RAJAGOPALAN et al., 2013; TREUR et al., 2012; GARCÍA-RUIZ et al., 2012; ASCHER-SVANUM et al., 2012; LINDSTRÖM et al., 2011; KASTENG et al., 2011; FURIAK et al., 2009; DAVIES et al., 2008; GEITONA et al., 2008). From the remaining studies, one has declared no funding (OBRADOVIC et al., 2007) and one has not reported the issue (LIN et al., 2016).

The time horizon of the studies ranged from one year (EINARSON et al., 2015; CITROME et al., 2014; GARCÍA-RUIZ et al., 2012; ASCHER-SVANUM et al., 2012; FURIAK et al., 2009; GEITONA et al., 2008; OBRADOVIC et al., 2007) to a life-time horizon (LIN et al., 2016; KASTENG et al., 2011). The eight remaining articles applied either a 5-year period of analysis (DRUAIS et al., 2016; O'DAY et al., 2013; RAJAGOPALAN et al., 2013; TREUR et al., 2012; LINDSTRÖM et al., 2011) or 10 years (RAJAGOPALAN et al, 2016; LACHAINE et al., 2014; DAVIES et al., 2008). It was expected that the highest discount rates would be applied to articles adopting a life-time horizon; however, those were seen mostly for the 10-year and 5-year studies (RAJAGOPALAN et al., 2016; DAVIES et al., 2008; DRUAIS et al., 2016; LACHAINE et al., 2014; LINDSTRÖM et al., 2011).

The analyses that were 1 yearlong used either with Monte-Carlo simulation (ASCHER-SVANUM et al., 2012; FURIAK et al., 2009) or decision tree (EINARSON et al., 2015; CITROME et al., 2014; GARCÍA-RUIZ et al., 2012; GEITONA et al., 2008; OBRADOVIC et al., 2007) to simulate the disease's path and obtain the economic results. The studies adopting longer time horizons used solely Markov model (LIN et al., 2016; O'DAY et al., 2013; RAJAGOPALAN et al., 2013; KASTENG et al., 2011; RAJAGOPALAN et al., 2016; DAVIES et al., 2008; DRUAIS et al., 2016; LINDSTRÖM et al., 2011), except for the work of Lachaine et al. (2014), which used both Markov and decision tree models, and the work of Treur et al., (2012), which was the only article using discrete event simulation.

Finally, with regards to country and study perspective, only two have adopted a societal view, accompanied or not by another perspective's analysis

(LACHAINE et al., 2014; KASTENG et al., 2011). These studies included indirect costs in their analysis, in addition to direct costs. A third full economic evaluation, from Sweden, has also included indirect costs and assumed a public health system perspective (LINDSTRÖM et al., 2011). The United States was the country with the greatest number of studies (O'DAY et al., 2013; RAJAGOPALAN et al., 2013; CITROME et al., 2014; ASCHER-SVANUM et al., 2012; FURIAK et al., 2009), followed by Spain (TREUR et al., 2012; GARCÍA-RUIZ et al., 2012), and Sweden (KASTENG et al, 2011; LINDSTRÖM et al., 2011) tied up.

4.3. Results of full economic analyses

Aripiprazole was compared solely amongst atypical antipsychotics, except in the work of García-Ruiz et al. (2012) and of Obradovic et al. (2007), who included haloperidol in their analyses, as displayed in Table 2. Among the 15 industry-funded studies, 14 (93.3%) found results that benefits the drug produced by the sponsor of the study. Aripiprazole was frequently described as a dominated alternative by other therapies in the selected studies (RAJAGOPALAN et al, 2016; DRUAIS et al., 2016; LIN et al., 2016; EINARSON et al., 2015; O'DAY et al., 2013; RAJAGOPALAN et al., 2013; TREUR et al., 2012; ASCHER-SVANUM et al., 2012; LINDSTRÖM et al., 2011; FURIAK et al., 2009; GEITONA et al., 2008; OBRADOVIC et al., 2007). In addition, both articles that did not declare to be funded by a pharmaceutical industry were not favorable to aripiprazole. While Lin et al. (2016) has concluded olanzapine was the dominant alternative in terms of quality-adjusted life-year (QALY), Obradovic et al. (2007) found the same compound was dominant in terms of patient remission percentage, and that haloperidol decanoate also dominated aripiprazole in its analysis.

The most common cost driver between industry-funded articles was related to relapse rates/probabilities (e.g., length of hospital stay after relapse, relapse due to lack of efficacy, relapse with hospitalization, etc) (RAJAGOPALAN et al, 2016; DRUAIS et al., 2016; LIN et al., 2016; EINARSON et al., 2015; O'DAY et al., 2013; ASCHER-SVANUM et al., 2012; FURIAK et al., 2009), followed by no cost driver

(RAJAGOPALAN et al., 2013; TREUR et al., 2012; LINDSTRÖM et al., 2011; KASTENG et al., 2011; GEITONA et al., 2008; OBRADOVIC et al., 2007). Moreover, cost and relapse probability were the cost drivers specifically for a study not funded by industry (LIN et al., 2016).

Table 1. Characteristics of full economic evaluations on the use of aripiprazole for schizophrenia.

Author, year	Target population	Evaluation type	Decision models	Country; perspective	Time horizon	Discount rate	Sensitivity analysis	Funding
Rajagopalan et al., 2016	Adult patients with acute schizophrenia	Cost-effectiveness and cost-utility	Markov	Scotland and Wales; NHS and social services	10 years	3.5 % (costs and benefits)	Deterministic	Industry
Druais et al., 2016	Stable patients after a schizophrenic episode	Cost-effectiveness and cost-utility	Markov	France; French health insurance	5 years	4% (costs and benefits)	Deterministic and probabilistic	Industry
Lin et al., 2016	Patients with schizophrenia in remission phase	Cost-utility	Markov	Singapore; national healthcare system	Life time	3% (costs and benefits)	Deterministic and probabilistic	NR
Einarson et al., 2015	Patients with chronic schizophrenia	Cost-effectiveness and cost-utility	Decision tree	Finland; Finnish Ministry of Health	1 year	NA	Deterministic and probabilistic	Industry
Citrome et al., 2014	Patients with schizophrenia	Cost-effectiveness	Decision tree	US; payer	1 year	NA	Deterministic	Industry
Lachaine et al., 2014	Patients above 40 years old with moderate to severe schizophrenia	Cost-utility	Decision tree and Markov	Canada; Canadian Ministry of Health and societal	10 years	5% (costs and benefits)	Deterministic and probabilistic	Industry

Author, year	Target population	Evaluation type	Decision models	Country; perspective	Time horizon	Discount rate	Sensitivity analysis	Funding
O'Day et al., 2013	Adult patients with schizophrenia	Cost-effectiveness	Markov	US; payer	5 years	3% (costs and benefits)	Deterministic and probabilistic	Industry
Rajagopalan et al., 2013	Adult patients with schizophrenia who have previously failed on a generic atypical antipsychotic	Cost-effectiveness	Markov	US; payer	5 years	3% (costs and benefits)	Deterministic and probabilistic	Industry
Treur et al., 2012	Patients with schizophrenia	Cost-utility	Discrete event simulation	Spain; payer	5 years	3% (costs and benefits)	Scenario analysis and probabilistic	Industry
García-Ruiz et al., 2012	Patients with schizophrenia	Cost-utility	Decision tree	Spain; national healthcare system	1 year	NA	Deterministic	Industry
Ascher-Svanum et al., 2012	Patients with schizophrenia	Cost-utility	Monte-Carlo micro-simulation	US; third-party payers within the US healthcare system	1 year	NA	Sequential bifurcation and probabilistic	Industry
Lindström et al., 2011	Patients with schizophrenia intolerant to other antipsychotics	Cost-effectiveness and cost-utility	Markov	Sweden; National Health Insurance Board	5 years	5% (costs and benefits)	Scenario analysis	Industry

Author, year	Target population	Evaluation type	Decision models	Country; perspective	Time horizon	Discount rate	Sensitivity analysis	Funding
Kasteng et al., 2011	Patients with schizophrenia	Cost-utility	Markov	Sweden; societal	Life time	3% (costs and benefits)	Deterministic and probabilistic	Industry
Furiak et al., 2009	Patients with schizophrenia	Cost-utility	Monte-Carlo micro-simulation	US; national health care system	1 year	NA	Deterministic and probabilistic	Industry
Davies et al., 2008	Patients with stable schizophrenia	Cost-utility	Markov	UK; NHS	10 years	3.5% (costs and benefits)	Probabilistic	Industry
Geitona et al., 2008	Patients with schizophrenia with acute exacerbation	Cost-effectiveness	Decision tree	Greece; national healthcare system	1 year	NA	Deterministic	Industry
Obradovic et al., 2007	Outpatients with chronic schizophrenia	Cost-effectiveness	Decision tree	Slovenia; national healthcare system	1 year	NA	Deterministic	None

Abbreviations: UK, United Kingdom; US, United States; NHS, National Health Service; NR, not reported; NA, not applicable.

When analyzing the studies that did not consider aripiprazole to be dominated by at least one other alternative (LACHAINE et al., 2014; CITROME et al., 2014; GARCÍA-RUIZ et al., 2012; KASTENG et al., 2011; DAVIES et al., 2008), the relapse factor was a cost driver for two of these studies (GARCÍA-RUIZ et al., 2012; DAVIES et al., 2008), and the index treatment dose was found to be the driver in another study (CITROME et al., 2014). It is worth noticing that 3 out of these 5 studies resulted in ICUR (LACHAINE et al., 2014; GARCÍA-RUIZ et al., 2012; DAVIES et al., 2008), meaning that although aripiprazole was not a dominated option, it was not dominant as well. Rather, the decision maker should rely on its willingness-to-pay when analyzing the alternatives presented. More specifically, aripiprazole was not considered cost-effective by Lachaine et al. (2014), who adopted a willingness to pay of $ 50,000/QALY and found aripirazole had an ICUR of $1,485,625/QALY; and García-Ruiz et al. (2012), who adopted a range of € 30,000-45,000/QALY and concluded aripiprazole had an ICUR of € 94,558/ QALY. On the other hand, Davies et al. (2008) show an ICUR of £ 9,440/QALY for the therapy sequence aripiprazole-risperidone vs risperidone-olanzapine (under the £ 30,000/ QALY limit established), and several scenarios in which aripiprazole-risperidone dominated the alternate sequence.

Besides Davies et al (2008), Kasteng et.al. (2011) and Citrome et al. (2014) have also found aripiprazole dominating another drug, but these conclusions were inconsistent with other economic evaluations. For Kasteng et.al. (2011), aripiprazole has dominated olanzapine, unlike the results of Furiak et al. (2009) and Obradovic et al. (2007). For Citrome et al. (2014), aripiprazole once-monthly (AOM, another name for aripiprazole long-acting injection) has dominated paliperidone long-acting injectable (PLAI), which was contrasting with the findings of Druais et al. (2015) and Einarson et al. (2015).

Most comparisons were made amongst atypical antipsychotics, from which a trend favoring olanzapine (FURIAK et al., 2009; OBRADOVIC et al., 2007; LIN et al., 2016; ASCHER-SVANUM et al., 2012), lurasidone (RAJAGOPALAN et al, 2016; O'DAY et al., 2013; RAJAGOPALAN et al., 2013), and paliperidone (DRUAIS et al., 2016; EINARSON et al., 2015; TREUR et al., 2012; GEITONA et

al., 2008), when in comparison with aripiprazole. Exceptions were seen in the work of Citrome et al. (2014) and Kasteng et al. (2011), as previously described. Also, when aripiprazole was compared with typical antipsychotics, the results were unfavorable to it. While García-Ruiz et al. (2012) obtained an ICUR of € 94,558/QALY for aripiprazole vs haloperidol (value above of the willingness-to-pay threshold), Obradovic et al. (2007) concluded haloperidol decanoate dominated aripiprazole.

Overall, aripiprazole therapy was described as one of the most, if not the most, expensive alternatives for schizophrenia treatment. For instance, Lin et al. (2016) showed that, although the drug had best preventive factors for diabetes, it was associated with higher costs than not taking any treatment. In addition, O'Day et al. (2013), Ascher-Svanum et al. (2012), and Lindström et al. (2011) reported that aripiprazole had the highest total cost amongst the several therapies compared, including olanzapine. These results were only inconsistent to the work of Kasteng et al. (2011), who found aripiprazole was actually the cheapest therapeutic alternative when compared to olanzapine.

It is worth noticing that some economic evaluations reported a poor efficacy and safety profile of aripiprazole included in their decision models. Rajagopalan et al. (2016) and Rajagopalan et al. (2013) have alleged aripiprazole had more adverse events when compared to other antipsychotic drugs. Moreover, relapse rates for the aripiprazole have also been reported to be higher than other drugs (O'DAY et al., 2013; OBRADOVIC et al., 2007).

4.4. Critical quality evaluation

The percentage of full economic evaluations that met the requirements of CHEERS statement was summarized in Table 3. The items "setting and location", "measurement of effectiveness", "assumptions", and "analytical methods" were reported by 100% of the articles in the review, followed by 94.1% who reported "conflict of interest", and 88.2% who reported "estimating resources and costs" and "characterizing uncertainty". The least reported items were "study parameters"

(11.8%), “target population and subgroups” (17.6%), and “discount rate” (29.4%). In addition, none of the studies have reported on choice of health outcomes, failing mostly in describing the outcome measure’s relevance for the type of analysis performed. The criteria “characterizing heterogeneity”, on the other hand, was not applicable for any of the articles, once they have not studied subgroups of patients in their analysis.

In addition, the items fully met in each article can be seen in Appendix 3. Most studies scored 12 (EINARSON et al., 2015; O’DAY et al., 2013; GEITONA et al., 2008) to 13 points (LACHAINE et al., 2014; TREUR et al., 2012; LINDSTRÖM et al., 2011) from the 24 CHEERS’ items. The top scorers were Rajagopalan et al. (2016) with 20 points, followed by Druais et al. (2016) with 18, and then three studies with 17 points (FURIAK et al., 2009; RAJAGOPALAN et al., 2013; LIN et al., 2016). In contrast, the lowest overall amount of points (9) was obtained by the only openly not industry-funded article (OBRADOVIC et al., 2007), followed by the industry-funded Davies et al. (2008), which scored 11.

Table 2. Results of full economic evaluations on the use of aripiprazole for schizophrenia.

Author, year	Comparators	Choice of outcome	Costs included	Currency, year	Willingness to pay	ICER	ICUR	Cost drivers
Rajagopalan et al, 2016	LUR vs. ARI	Life-years, relapse-free days and QALY	Direct (drug therapy, adverse events, switching therapy, outpatient, primary and community care, relapse and residential care)	Sterling pound, 2013/14	£ 20,000-30,000/ QALY	Dominant	Dominant	Relapse rate
Druais et al., 2016	PLAI vs. ALAI	Relapse avoided and QALY	Direct (drug therapy, drug administration, hospitalization, ambulatory visits and adverse events)	Euro, 2014	€ 30,000/ QALY	Dominant	Dominant	ICUR: therapy switch due to drug intolerance and adverse events rate; ICER: treatment interruption and relapse due to lack of efficacy
Lin et al., 2016	OLA vs. ARI	QALY	Direct (drug therapy, relapse, adverse events and treatment	Singapore dollar, 2015	SGD 70,000/ QALY	NA	Dominant	Cost and relapse probability

Author, year	Comparators	Choice of outcome	Costs included	Currency, year	Willingness to pay	ICER	ICUR	Cost drivers
			discontinuation)					
Einarson et al., 2015	PLAI vs. ALAI	QALY, hospitalization rate, relapse (not requiring hospitalization; only treated in the emergency room) rate and days with stable disease	Direct (drug therapy, health professionals and hospitals/facilities)	Euro, 2015	NR	Dominant	Dominant	Rates of adherence, dropouts, relapses, and possibly drug prices
Citrome et al., 2014	AOM vs. PLAI	Relapse avoided	Direct (drug therapy, drug administration, adverse events, and relapses, which included hospitalization and other services costs)	US dollar, 2013	NR	Dominant	NA	Index treatment dose

Author, year	Comparators	Choice of outcome	Costs included	Currency, year	Willingness to pay	ICER	ICUR	Cost drivers
Lachaine et al., 2014	ARI vs. ASE	QALY	Direct (drug therapy, extrapyramidal effects management, costs associated with long-term metabolic complications) and indirect (productivity losses, informal care due to long-term metabolic complications)	Canadian dollar, 2011	$ 50,000/ QALY	NA	$1,485,625 /QALY (Ministry of Health); $1,485,623 / QALY (society)	NR
O'Day et al., 2013	ARI vs. RIS ARI vs. LUR	Avoided hospitalization due to relapse	Direct (drug therapy, psychiatric care, relapse with psychiatric hospitalization, relapse without psychiatric hospitalization, diabetes and cardiovascular events)	US dollar, 2012	$ 50,000/ QALY	Dominated Dominated	NA	Hospitalization rate of RIS and LUR

Author, year	Comparators	Choice of outcome	Costs included	Currency, year	Willingness to pay	ICER	ICUR	Cost drivers
Rajagopalan et al., 2013	LUR vs. ARI	Relapse avoided and avoided hospitalization	Direct (drug therapy, psychiatric hospitalization, emergency room visits, group psychosocial therapy, diabetes and cardiovascular events)	US dollar, 2012	$ 50,000/ QALY	Dominant	NA	None
Treur et al., 2012	PAL ER vs. ARI	QALY	Direct (drug therapy, location costs, side effects and monitoring cost)	Euro, 2010	€ 20,000-30,000/ QALY	NA	Dominant	None
García-Ruiz et al., 2012	ARI vs. HAL	QALY	Direct (drug therapy, inpatient stays due to relapse, outpatient primary and community care costs of treating adverse events and metabolic complications of antipsychotic treatment)	Euro, 2009	€ 30,000-45,000/ QALY	NA	€ 94,558/ QALY	Relapse probability

Author, year	Comparators	Choice of outcome	Costs included	Currency, year	Willingness to pay	ICER	ICUR	Cost drivers
Ascher-Svanum et al., 2012	OLA ODT vs. ARI OLA ODT vs. ARI ODT	QALY	Direct (drug therapy, adverse events, hospitalization, emergency room care)	US dollar, 2010	$ 50,000/ QALY	NA	Dominant Dominant	Relapse rates
Lindström et al., 2011	SER vs. ARI	Time without relapse, QALY	Direct (drug therapy, emergency room and inpatient hospital services, laboratory tests and clinical examinations) and indirect (sick leave per day)	Swedish kroner, 2004	SEK 230,000-344,000/ QALY	Dominant	Dominant	None
Kasteng et al., 2011	ARI vs. OLA	QALY	Direct (drug therapy, monitoring and treatment of metabolic syndrome, diabetes and coronary heart disease) and indirect (loss of productivity)	Swedish kroner, 2009	SEK 500,000/ QALY	NA	Dominant	None

Author, year	Comparators	Choice of outcome	Costs included	Currency, year	Willingness to pay	ICER	ICUR	Cost drivers
Furiak et al., 2009	OLA vs. ARI RIS vs. ARI	QALY	Direct (drug therapy, hospitalization days, day hospital treatment days, emergency room visits, physician visits, mental health clinic visits, home care hours, group intervention hours, nutritionist visits, adverse events)	US dollar, 2007	$ 50,000 - 100,000/ QALY	NA	Dominant Dominant	Treatment adherence end relapse rate
Davies et al., 2008	ARI > RIS vs. RIS > OLA ARI > RIS vs. RIS > ARI ARI > RIS vs. ARI > QTP ARI > RIS vs. QTP > ARI ARI > RIS vs. ARI > OLA ARI > RIS vs. OLA > ARI	QALY	Direct (drug therapy, medical care, relapse, adverse events and diabetes)	Sterling pound, 2006	£ 30,000/ QALY	NA	£ 9,440/ QALY Dominant Dominant Dominant Dominant Dominant	Length of stay in hospital following relapse

Author, year	Comparators	Choice of outcome	Costs included	Currency, year	Willingness to pay	ICER	ICUR	Cost drivers
Geitona et al., 2008	PAL ER vs. ARI	Number of stable days	Direct (drug therapy, physician visits, mental health clinic visits, social/group therapy visits, hours of home care, day hospital visits, nutritionist visits, hospitalization, emergency room visits, adverse events)	Euro, NR	NR	Dominant	NA	None
Obradovic et al., 2007	ARI vs. HAL DEC ARI vs. OLA	Percentage of patients in remission	Direct (drug therapy, adverse events, hospitalization, ambulatory visits)	Euro, 2005	NR	Dominated Dominated	NA	None

Abbreviations: ALAI, aripiprazole long acting injection; ARI, aripiprazole; ARI ODT, aripiprazole Orally Disintegrating Tablets; ASE, asenapine; QALY, quality-adjusted life-year; HAL, haloperidol; HAL DEC, haloperidol decanoate; LUR, lurasidone; NA, not applicable; NR, not reported; OLA, olanzapine; OLA ODT, olanzapine Orally Disintegrating Tablets; PAL ER, paliperidone extended release; PLAI, paliperidona long acting injection; QTP, quetiapine; SER, sertindole; SEK, Swedish krona.

Table 3. Reporting quality assessment of economic evaluation with CHEERS statement checklist.

Section/item	Item No	Recommendation	Studies in line with recommendation n (%)
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	8 (47.0%)
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	7 (41.2%)
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	11 (64.7%)
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analyzed, including why they were chosen.	3 (17.6%)
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	17 (100%)
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	13 (76.5%)
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	13 (76.5%)
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	8 (47.0%)
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	5 (29.4%)
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	0 (0%)

Section/item	Item No	Recommendation	Studies in line with recommendation n (%)
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	17 (100%)
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	12 (70.6%)
Estimating resources and costs	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	15 (88.2%)
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	12 (70.6%)
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	9 (52.6%)
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	17 (100%)
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data;	17 (100%)

Section/item	Item No	Recommendation	Studies in line with recommendation n (%)
		approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	2 (11.8%)
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	10 (58.8%)
Characterizing uncertainty	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	15 (88.2%)
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	11 (64.7%)
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design,	7 (41.2%)

Section/item	Item No	Recommendation	Studies in line with recommendation n (%)
		conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	16 (94.1%)

Abbreviation: NA, not applicable.

5. DISCUSSION

5.1. Main findings

This systematic review has identified 17 model-based full economic evaluations that evaluated the use of aripiprazole compared to another drug, or to the combination of other drugs. In the clear majority of the studies, aripiprazole was shown to be dominated by other alternatives and, therefore, not cost-effective. More specifically, a trend favoring olanzapine, lurasidone, and paliperidone could be detected. Similarly, Santos et al. (2017) have shown in their systematic review a trend of cost-effectiveness favoring olanzapine in schizophrenia treatment. In contrast to the present study, clozapine and risperidone were favored, instead of lurasidone and paliperidone. In addition, this was still seen after exclusion of the head-to-head comparisons including sponsored drugs in the pooled analysis. One factor that may have contributed for these findings was the fact Santos et al. (2017) have included full economic evaluations based on not only decision models, but controlled trials and cohort studies.

The poor safety and efficacy profile utilized in some economic evaluations included in this review (more adverse events and/or more relapse rates), which contrasted with recent overview (RIBEIRO et al, 2018), may have impacted the cost-effectiveness results of aripiprazole. Other important contributor for findings of our review was that most of the studies were funded by industry and there is a known

association between positive results in economic studies and industry sponsorship for their own products (BELL et al., 2006; GARATTINI et al., 2010). Given that only two economic evaluations were funded by the manufacturers of aripiprazole, this may have directly contributed for the unfavorable result for the drug.

Based on these factors, one could argue aripiprazole could still be considered a cost-effective alternative by the findings of articles favoring this compound. For instance, Kasteng et al. (2011) presented a very strong argument when aripiprazole was showed to remain dominant over olanzapine in a scenario in which the price of the latter drug was reduced to one-fourth of its then current price in Sweden. This article, however, was criticized by Lachaine et al. (2015) due to the lack of consideration of non-metabolic adverse events as well as drug switching or discontinuation. Druais et al. (2015) have also criticized Citrome et al (2014), a study that considered ALAI to be dominant over PLAI, because their efficacy and safety parameters were derived from product prescribing information and pivotal trials, which could introduce biases caused by targeted population heterogeneity and lack of adjustment of the treatment on the placebo arms. Therefore, one can critically doubt on both study' types: the ones stating aripiprazole was dominated by other alternative and the others stating it was actually the dominant strategy.

More importantly, because study parameters are invariably different according to the country, no universal conclusion could be drawn from this systematic review with regards to cost-effectiveness results of aripiprazole, even if all studies were of impeccable methodology. In fact, this context-specific nature is translated on the irregular pattern of aripiprazole's free access around the world. While this drug is available free of charge or by co-payment programs in several countries, such as United Kingdom (NHS, 2015), Australia (AUSTRALIA, 2018), and Canada (ACMTS, 2011), other countries have not included it in their public health systems. For instance, in Brazil, aripiprazole has been considered very similar in effectiveness to other antipsychotics in studies of schizophrenia in general, which does not justify their inclusion in the National Health Care System (SUS) (BRAZIL, 2011). In contrast, this drug reached the fifth place on the ranking of most requested medicines by judicialization in Brazil between 2005 and 2008 (DELDUQUE e MARQUES, 2011).

The most consistent finding that can indeed be drawn from this review has to do with the cost drivers. As previously stated, the majority of cost driver between among all

studies (financed or not by industry) was related to relapse rates/probabilities. This finding is in accordance with previous evidence, which indicates that the purchase cost of drugs corresponding to only a small part of schizophrenia's total costs (CHONG et al., 2016). Instead, indirect costs contribute to 50%–85% of the total costs associated this disease (CHONG et al., 2016), but were little explored in economic evaluations included in this systematic review. Only three of the studies have included indirect costs in their analysis (LACHAINE et al., 2014; KASTENG et al., 2011; LINDSTRÖM et al., 2011); however, surprisingly, one of them assumed a public health system perspective (LINDSTRÖM et al., 2011).

5.2. Economic evaluations' quality

Regardless of the results' differences among economic evaluations, their quality according to CHEERS was overall poor. As stated in the results, most studies got around 12-13 points, and none of them got a full score (originally 24 points, but, in this case, 23, once the category "characterizing heterogeneity" was not applicable for any of the articles). Among the articles above the average, one can find the work of Citrome et al. (2014) and Kasteng et al. (2011), both arguing aripiprazole was a dominant alternative over other antipsychotics, with 16 and 15 points, respectively. The best quality economic evaluations (ranging from 17 to 20 points) were all unfavorable to aripiprazole. Rather, they all concluded aripiprazole was dominated either by lurasidone (oral or long-acting injectable), olanzapine, or risperidone.

Despite these findings are useful in pointing topics authors must improve reporting, they did not necessarily skim the most complete and correct evaluations from the set of articles in this review. First, the scoring of multiple-criterium items can lead to grouping different quality articles in the same category. Originally, CHEERS checklist is supposed to be filled with "yes" or "no", or "0" or "1", indicating whether an article succeed in fulfilling a requirement or not. However, some items, like item 2 (abstract), are evaluated in several aspects by CHEERS and, because of it, they end up grouping articles that missed one criterion with those missing all of them in the same "no" or "0" category. Banke-Thomas et al. (2017) and Le et al. (2017) have avoided this issue in their review by either grading the item based on the percentage of criteria met, or by

setting a gradual score (1 for fully met criterion, 0.5 for partially met, and 0 for not met), respectively.

Similarly, items that are not multiple-criterium can lead to the same grouping issue. For instance, item 4 (target population and subgroups) lacks a more precise description of its requirements, listing the relevant characteristics to be considered (e.g. age group, clinical condition, definition of clinical condition). Due to it, an article that reports to have studied adult patients with schizophrenia could get the same “yes” or “1” score as one reporting as population patients between 30-50 years old diagnosed with schizophrenia ICD-10 (International Classification of Disease).

More importantly, poorly described items can lead into the “black box” effect once again, as once mentioned by John-Baptiste et al. (2011). Item 16 (model assumptions), for example, only ask the author to describe “all structural or other assumptions”, which is a very general guidance. There is no distinction, for the person evaluating the article’s quality with CHEERS statement, on what would be a complete description of the model’s assumptions, i.e. the evaluator is forced to assume what was reported was indeed all that had to be reported. In addition, no item was created in the checklist to evaluate if the model’s assumptions are of good quality or if they lead to distorted results.

Another limitation of CHEERS is the lack of relative importance for each item. As reported by Palfreyman & Stone (2015), CHEERS solely gives an indication of how many items have been included or not in an analysis. This means one article could get a good overall amount of points when scoring items like “title” or “setting and location”, although major subjects like “analytic methods” or “characterizing uncertainty” were not fulfilled. This can generate “balancing effect”, where simpler topics offset the most important ones in the article.

5.1. Opportunities for future researches

The first opportunity one can point out for future research is the elaboration of pharmacoeconomic analysis including a more specific population group (i.e., subgroup analysis). Moreover, late adolescence would be an interesting age group to be studied once it is the typicall onset age for the disease (HAFNER et al., 1994). Also, according to Druais et al. (2016), it was noticed in clinical practice that patients with prior relapse

had a greater probability of relapse than stable patients without relapse. Thus, studying the most cost-effective alternative for the beginning of the disease would be a good strategy to avoid a higher relapse rates in the future.

Still about the population characteristics, pharmacoeconomic evaluations reporting the disease's definition adopted (e.g., ICD F20.0, which is paranoid schizophrenia, or ICD F20.2 for catatonic schizophrenia) are needed. None of the articles in this review have described it and, thus, no information was available on whether they only included the broad schizophrenia diagnosis or its related psychoses as well. Alongside this, a more targeted study in terms of schizophrenia type (e.g., negative symptoms predominance) could benefit payers in deciding the most cost-effective alternative for well-established subgroups of patients. This approach could be considered instead of choosing a single answer for all patients, once the inter-individual variation in antipsychotic therapy can lead some patients to low compliance behavior, given the adverse events, or poor response profile (BASILE et al., 2002).

Another opportunity to be considered for future researches is a better description and elaboration of decision models' assumptions. Some articles evaluated have shown great work in this aspect, such as Druais et al. (2016) when differing probabilities of death between stable patients and patients in relapse; Geitona et al. (2008) when defining positive response as at least 30% reduction in PANSS total score; and Lachaine et al. (2014) when extracting the risks for selected complications in the general population who gained weight. However, those were not seen all together in a single study. In addition, many more improvements could be made in studies, for example, justify the choice of health outcomes, report the choice of discount rate used for costs and outcomes and say why appropriate, measure the precision of model parameters, and mean differences between the comparator groups for the main categories of estimated costs and outcomes of interest.

Finally, a small number of non-industry-funded studies were noted in this review. Considering that a rate of 90% of head-to-head antipsychotics comparisons favoring their sponsor has already been verified (HERES et al., 2006), which is close to 93% found in this review, independent studies could provide an unbiased update in data regarding cost-effectiveness of aripiprazole. Additionally, these studies are especially important after patency expiry of drugs in schizophrenia treatment, given that a large

downward in their price is expected after this process, which may influence several pharmacoeconomic parameters, as noticed by Lin et al. (2016).

5.1. Limitations

This systematic review has some limitations worth being noticed. First, it is possible that some studies were missed because they were not indexed in the databases searched or those not written in English, Portuguese, or Spanish. In addition, articles that were not based in decision models or lacking an explicit ICER/ICUR has not been explored in this review. Finally, it is important to note that CHEERS checklist solely gives an indication of how many items have been reported or not in an economic evaluation, which might not reflect the quality of conduct.

6. CONCLUSION

This systematic review has characterized 17 full economic evaluations, from which 15 were funded by pharmaceutical industry. More importantly, 93% of the industry-funded studies presented favorable results to their sponsor; two of them being aripiprazole's manufacturer. While aripiprazole was extensively described as a dominated alternative, a trend favoring olanzapine, lurasidone, and paliperidone could be observed. No reliable conclusion on aripiprazole's cost-effectiveness can be drawn due to the context-specific costs, conflicting parameters of effectiveness and safety, and criticism related to industry sponsorship. The most consistent finding of this review has to do with the cost drivers, which was usually related to relapse rates/probabilities, regardless of the study funding. In addition, the reporting quality of the full economic evaluations was poor, mainly failing to describe the outcome measure's relevance for the type of economic analysis, report of precision measures for all parameters of the model, and describe the characteristics of the base case population (including why they were chosen).

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8. APPENDIXES

Appendix 1: Electronic databases' search strategy.

Electronic databases	Search strategy
Pubmed	((Aripiprazole[MeSH Terms]) OR (Aripiprazole) OR ("OPC 14597") OR ("14597 OPC") OR ("OPC-14597") OR (Abilify)) AND ((Schizophrenia[MeSH Terms]) OR (Schizophrenia*) OR ("Schizophrenic Disorders") OR ("Disorder, Schizophrenic") OR ("Disorders, Schizophrenic")) AND ((costs and cost analysis[MeSH Terms]) OR (cost*) OR ("economic analysis") OR (health care costs[MeSH Terms]) OR (cost-effective*) OR (cost-utility) OR (quality-adjusted life year*))
LILACS	((MH:"apipiprazole") OR (aripiprazole) OR (abilify)) AND ((MH:" Schizophrenia") OR (Schizophrenia$) OR ("Schizophrenic Disorders")) AND ((MH:"health care costs") OR (cost$) OR (economic$) OR (MH:"cost analysis") OR (custo$))
NHS Economic Evaluation Database (via Cochrane Library)	# 1 MeSH descriptor: [Aripiprazole] explode all trees # 2 aripiprazole # 3 "OPC 14597" OR "14597 OPC" OR "OPC-14597" # 4 Abilify # 5 MeSH descriptor: [Schizophrenia] explode all trees # 6 Schizophrenia or Schizophrenias # 7 Schizophrenic Disorders # 8 MeSH descriptor: [Costs and Cost Analysis] explode all trees # 9 MeSH descriptor: [Health Care Costs] explode all trees # 10 cost:ti,ab # 11 economic analysis # 12 cost-effective

	# 13 cost-utility # 14 quality-adjusted life years # 15 (#1 or #2 or #3 or #4) # 16 (#5 or #6 or #7) # 17 (#8 or #9 or #10 or #11 or #12 or #13 or #14) # 18 (#15 and #16 and #17)
CEA Registry	Aripiprazole

Appendix 2: Studies excluded after full text reading.

Reason for exclusion	Author, year	Title	Reference
Incomplete economic evaluation	Pilon et al., 2017	Treatment Patterns, Health Care Resource Utilization, and Spending in Medicaid Beneficiaries Initiating Second-generation Long-acting Injectable Agents Versus Oral Atypical Antipsychotics.	Clinical Therapeutics, Volume 39, Issue 10, 1972 - 1985.e2
Study was not based in a decision model	Sapin et al., 2016	Pharmacoeconomic comparison of aripiprazole once-monthly and paliperidone palmitate from a head-to-head clinical trial in schizophrenia: a US analysis.	Drugs Context. 2016 Sep 23;5:212301. eCollection 2016.
	Wilson et al., 2016	Inpatient resource use and costs associated with switching from oral antipsychotics to aripiprazole once-monthly for the treatment of schizophrenia.	Drugs Context. 2016 Mar 11;5:212273. doi: 10.7573/dic.212273. eCollection 2016.
Abstract	Rajagopalan et al., 2015	Cost-Utility and Budget Impact Analyses Comparing Lurasidone with Aripiprazole in Adults with Schizophrenia in Scotland.	Value in Health, Volume 18, Issue 7, A408 - A409
	Sapin et al., 2014	Aripiprazole Once-Monthly is a Cost-Effective Therapeutic Option in the Maintenance Treatment of Schizophrenia: Results from a Markov Model.	Value in Health, Volume 17, Issue 7, A457 - A458
Study was not based in a decision model	King et al., 2011	Cost-effectiveness analysis of aripiprazole vs standard-of-care in the management of community-treated patients with schizophrenia: STAR study.	Current Medical Research and Opinion, Volume 27: 365-374
	Ascher-Svanum et al., 2011	Cost-effectiveness of olanzapine vs. aripiprazole in the treatment of schizophrenia	Current Medical Research and Opinion, Volume 27: 115-122
	Colombo et al.,	An economic evaluation of aripiprazole vs olanzapine adapted to the Italian	Neuropsychiatric Disease

Reason for exclusion	Author, year	Title	Reference
	2008	setting using outcomes of metabolic syndrome and risk for diabetes in patients with schizophrenia.	and Treatment, Volume 4(5): 967–976
No ICER/ICUR was reported for aripiprazole	Edwards et al., 2008	One-year clinical and economic consequences of oral atypical antipsychotics in the treatment of schizophrenia.	Current Medical Research and Opinion, Volume 24: 3341-3355
	Edwards et al., 2005	Cost effectiveness of long-acting risperidone injection versus alternative antipsychotic agents in patients with schizophrenia in the USA.	Pharmacoeconomics, Volume 23: 75-89

Appendix 3: Reporting quality of full economic evaluations on aripiprazole use in schizophrenia treatment.

	Title and abstract		Intro-duction	Methods														Results				Discus-sion	Other		
Author, year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**Total -S**
Rajagopalan et al, 2016	S	S	S	N	S	S	S	S	S	N	S	S	S	S	S	S	S	N	S	S	NA	S	S	S	20
Druais et al., 2016	S	S	N	S	S	S	S	N	S	N	S	S	S	S	S	S	S	N	S	S	NA	S	N	S	18
Lin et al., 2016	N	N	S	S	S	S	S	S	N	N	S	S	S	N	S	S	S	S	S	S	NA	S	N	S	17
Einarson et al., 2015	N	N	N	N	S	S	S	N	N	N	S	S	S	S	S	S	S	N	N	S	NA	S	N	N	12
Citrome et al., 2014	S	N	N	N	S	S	S	S	S	N	S	NA	S	S	S	S	S	N	S	N	NA	S	S	S	16
Lachaine et al., 2014	N	N	S	N	S	S	S	S	N	N	S	S	N	S	S	S	S	N	S	N	NA	N	N	S	13
O'Day et al., 2013	N	S	S	N	S	S	N	N	N	N	S	NA	S	S	N	S	S	N	N	S	NA	S	N	S	12
Rajagopalan et al., 2013	S	N	S	S	S	S	N	N	N	N	S	NA	S	S	S	S	S	S	S	S	NA	S	S	S	17
Treur et al., 2012	N	N	N	N	S	S	S	N	S	N	S	S	N	S	N	S	S	N	S	S	NA	N	S	S	13
García-Ruiz et al., 2012	N	S	S	N	S	N	S	S	S	N	S	S	S	S	N	S	S	N	N	S	NA	S	S	S	16
Ascher-Svanum et al., 2012	S	N	S	N	S	S	S	N	N	N	S	S	S	S	N	S	S	N	N	S	NA	S	N	S	14
Lindström et al., 2011	N	N	S	N	S	N	S	N	N	N	S	S	S	N	S	S	S	N	S	S	NA	S	N	S	13
Kasteng et al., 2011	S	S	S	N	S	S	N	S	N	N	S	S	S	S	N	S	S	N	S	S	NA	N	N	S	15
Furiak et al., 2009	S	S	S	N	S	S	S	S	N	N	S	S	S	S	S	S	S	N	N	S	NA	S	N	S	17
Davies et al., 2008	N	N	N	N	S	N	S	S	N	N	S	S	S	N	N	S	S	N	N	S	NA	N	S	S	11

	Title and abstract		Intro-duction	Methods														Results				Discus-sion	Other		
Author, year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**Total -S**
Geitona et al., 2008	S	S	S	N	S	S	S	N	N	N	S	NA	S	N	N	S	S	N	N	S	NA	N	N	S	12
Obradovic et al., 2007	N	N	N	N	S	N	N	N	N	N	S	NA	S	N	N	S	S	N	S	S	NA	N	S	S	9

27.09.18

Date and signature of the student

27.09.18

Date and signature of the advisor