A SYSTEMATIC REVIEW OF HEALTH ECONOMIC STUDIES ON BIPOLAR DISORDER TYPE I IN THE UNITED STATES

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INTRODUCTION

- Bipolar disorder (BD) is a recurrent chronic disorder characterized by fluctuations in mood state and energy. Bipolar disorder type I (BD-I) is a chronic and severe mental illness in which depressive episodes are typical, but not necessary for diagnosis.[1]
- Although effective therapies are available, treatment rates remain low maintaining BD among the top 20 leading causes of disability worldwide surpassing asthma, myocardial infarction, dementia and infectious diseases. [2,3]
- Several factors collaborate to increase the personal and economic burden of this illness: early age of onset, high incidence of comorbidities and substance abuse, steep risk of suicide, high relapse rates and poor adherence to treatment.[3]
- The main objective was to identify, describe and critically assess health economic studies in BD-I in the United States during the last ten years and provide recommendations for future researchers.

METHODOLOGY

- The question to be answered was defined as: *How are the economic analyses that evaluate the treatment of patients with BD-I in the United States?*
- Search strings were developed for the following databases: MEDLINE, EMBASE, National Health System Economic Evaluation Database (NHS EED) and the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) database, as shown on Figure 1.
- The search was limited to a 10-year period (2006-2016) and broad keywords were used to identify BD-I and economic evaluations.

Inclusion & Exclusion criteria

- Only budget impact analyses (BIA) or full economic analyses (EA) being cost-effectiveness analyses [CEA]; cost-minimization analyses [CMA] or cost-benefit analyses [CBA] performed in populations with disorder BD-I in the United States (US) were included. Publications were limited to articles or posters that were published in English.
- One reviewer extracted and selected title/abstracts, followed by a full article or poster selection. Two reviewers independently extracted data from the publications using an adapted template from the Centre for Review Dissemination (CRD) guideline. [4]
- The following data were extracted from EA and BIA: study design; main parameters included; modelling techniques; sources, type and quality of clinical and costs data; uncertainty assessment methods and main study results.
- The quality of all EA published as articles was independently evaluated by two reviewers using two quality assessment checklists recommended by the Cochrane Collaboration (Drummond Checklist; Phillips checklist). [5,6] Checklists were answered with either "Yes" or "No" or "NA (not applicable)". Based on a published systematic review [3], all questions were assigned the same weight and a score of 1 and 0 was attributed to the answers respectively (with "NA" answers excluded from the final scoring). Studies fulfilling <50% or 50-80% or >80% of criteria were classified as having high, medium or low risk of bias, respectively. For BIAs quality assessment, due to lack of standardized checklist, the two reviewers used the report from ISPOR Taskforce on Good Practice. [7]

RESULTS

- The search initially retrieved 2353 non-duplicate citations and after careful screening, six publications were included for analysis: 5 full EA (4 complete articles and 1 poster) [8-12] and one BIA [13]. Figure 2 details the PRISMA study flow.
- Among the retrieved EA, four studies used cohort Markov models and one used a decision tree. The analyses were either both cost-effectiveness and cost-utility or only cost-effectiveness. [8-10,12]
- The following effectiveness measures were used: number of episodes avoided [11,12]; euthymic days gained [12] and remission rate.[9]
- A discrete event simulation model was used in the BIA. [13]
- All studies reported direct costs and two studies also included indirect costs (productivity loss). [8,10] Costs were reported as US dollars from the years 2004 [12,13]; 2007 [11]; 2009 [10]; 2014 [9] or 2015. [9] Table 1 details the studies included in this review and the critical analysis performed by the reviewers.
- Quality assessment showed medium-to-high risk of bias, and very weak clinical bases supporting the analyses, as detailed on Table 1.

Figure 1. Question and search strategies for each database

Question regarding economic evaluations on BD-I in the US

How are the economic analyses that evaluate the treatment of patients with BD-I in the United States?

Search strategies

MEDLINE: ((bipolar AND disorder) OR mania OR manic) AND (cost OR cost* OR "economics, pharmaceutical"[MeSH Terms])

EMBASE: 'bipolar disorder'/exp OR mania AND ('economic evaluation'/exp OR 'pharmacoeconomics'/exp OR cost) AND [2006-2016]/py

NHS EED: bipolar disorder OR mania OR manic

ISPOR database: Bipolar Disorder

Figure 2. PRISMA study flow

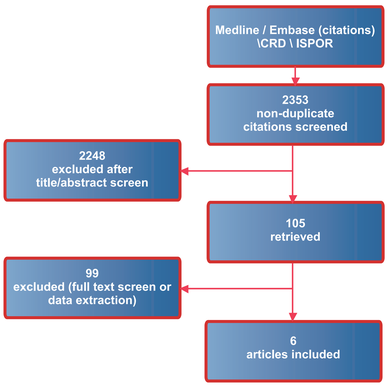

Table 1. Details of included studies

Calvert, 2006 [12]

Type of analysis: CEA/CUA
Intervention vs. Comparators: lamotrigine vs. lithium or olanzapine
Indication: Maintenance treatment for BD-I with recent maniac episodes
Results:
ICER Lamotrigine vs Lithium: $2,400 per episode avoided; $30 per euthymic day gained; $26,000/QALY.
ICER Olanzapine vs Lithium: $7,000 per episode avoided; $200 per euthymic day gained; $374,500/QALY. Lamotrigine dominated olanzapine (all outcomes). All active treatments were dominant compared to "no maintenance".
Risk of bias: high
Critical Assessment:
• Unclear points: objectives (especially choice of comparators and perspective), choice of trials as sources for effectiveness data, source of utilities and parameters for deterministic sensitivity analyses (DSA).
• Simple model structure. Reasonable assumptions. The choice of QALY as benefit measure facilitated result interpretation for decision makers. Methodologically incorrect calculation of transition probabilities (TPs). Lack of probabilistic sensitivity analysis (PSA).

Woodward, 2009 [11]

Type of analysis: CEA/CUA
Intervention vs. Comparators: quetiapine + lithium or divalproex vs. placebo + lithium or divalproex
Indication: BD-I maintenance treatment after a stabilization period
Results:
quetiapine + lithium or divalproex: 46% decrease in acute manic mood episodes; 41% decrease in acute depressive episodes compared with placebo + lithium or divalproex. Quetiapine + lithium or divalproex dominated the comparator.
Risk of bias: Medium to high
Critical Assessment:
• The study combined two pivotal trials (pooled analysis), but the trial selection was not further explained. Choice of comparators was unclear. Assumption of lack of 2nd line treatment questionable. Model was further developed with the addition of a state representing "death".
• Sources for TPs were identified; but they were adjusted based on clinical experts' inputs not further described.
• Only direct costs were included; but indirect costs were reported in the results. In the PSA, no drug costs were varied; the amount of simulation iterations was not stated and no CUA plan was displayed.

Woodward, 2010 [10]

Type of analysis: CEA/CUA
Intervention vs. Comparators: quetiapine XR vs. placebo + lithium or divalproex; no maintenance therapy; lithium monotherapy; lamotrigine monotherapy; olanzapine monotherapy; aripiprazole monotherapy.
Indication: BD-I maintenance treatment
Results:
Quetiapine XR + lithium or divalproex vs placebo + lithium or divalproex: ICER = $22,959/QALY (only direct costs).
Lithium monotherapy: ICER = $100,235/QALY. All other maintenance treatment options dominated (only direct costs).
Quetiapine XR + lithium or divalproex vs lithium monotherapy: ICER = $81,712/QALY. All other maintenance treatment options dominated (direct + indirect costs)
Risk of bias: Medium to high
Critical Assessment:
• The same criticisms on Woodward, 2009 11 apply to time horizon; model structure; cycle length; TPs; sensitivity analyses. The same criticism stated about resource use and utilities in Calvert et al. also apply here.
• There is a lack of description of selected studies and detailing of key opinion leader consultations for selecting and synthetizing efficacy data is presented.
• TP data from RCTs with different follow-up times. No extrapolation methodology for the 2-years' time horizon is mentioned. The number of work loss days considered is not described.

Rajagopalan, 2015 [9]

Type of analysis: CEA
Intervention vs. Comparators: Lurasidone vs. quetiapine XR
Indication: Acute BD-I depression
Results: Difference in cost: $306.00; difference in remission rate: 8.8%; ICER = $3,474/remission gained.
Risk of bias: Medium to high
Critical Assessment:
• No head-to-head analysis available. A simple indirect adjusted comparison was performed, without systematic literature review or heterogeneity assessment. Populations differed considerably. The benefit measure selected (remission rate) is rarely used since it may hinder the comparison of benefits and the decision-making process with other studies.
• Calculation of remission rates for lurasidone used 2 different doses, while cost was calculated using only one (57 mg). Simplistic model. ICER was calculated as value per remission gained, but interpreted by authors as a value spent for 100 patients with remission. No reference for the $5.000/ remission threshold used. PSA used a normal distribution for costs (inappropriate because negative results are impossible).

Bhagvandas, 2016 [8]**

Type of analysis: CEA/CUA
Intervention vs. Comparators: Lurasidone vs. quetiapine + olanzapine
Indication: BD-I depression episode
Results: Monetary net benefits: Lurasidone: $36,744; Quetiapine: $34,485; Olanzapine: $15,865.
Risk of bias: NA*
Critical Assessment:
• Study available only as poster. No references on the text (hampers data tracking). Unclear use of trials in analysis. All trials used placebos as comparators, no head-to-head or indirect comparisons studies were mentioned.
• The time horizon (5 years) was not justified, and the acute mania stage was not included in the analysis, suggesting that patients would experience only acute depression or remission.
• No methodology was described for the DSA graph. No data labels or variation ranges were shown. This is the only study that used a net benefit analysis (NBA) approach.

Caro, 2006 [13]

Type of analysis: BIA
Intervention vs. Comparators: quetiapine + lithium vs. lithium monotherapy; lithium + risperidone or lithium + olanzapine
Indication: Hospitalized patients with acute bipolar mania
Results: reflected that the uptake of quetiapine under a U.S. third-party payer has great cost-saving potential.
Mean cost per patient: $6,912 (5% market share of quetiapine + lithium); $6,277 (40% market share of quetiapine + lithium); $5,525 (100% market share of quetiapine + lithium).
Risk of bias: NA*
Critical Assessment:
• Studies were selected without a systematic review. The strength of this analysis is that the treatment effect simulation over time used a quadratic function of YMRS.
• The model structure was considered appropriate. The study aimed to show interventions benefits and costs but only cost results were reported. Rationale for eligible population calculation is not specified. Short time horizon (100 days) could limit the usefulness of the analysis to the budget holder.

*NA – not applicable; CEA – cost-effectiveness analysis; CUA – cost-utility analysis; BIA – budget impact analysis; XR – extended release. *Checklist not performed due to type of analysis (BIA) or type of publication (poster). **published as poster. The first publication was Calvert et al. 2006 [12] and many studies published afterwards were based on this analysis. [9-11]*

CONCLUSION

- This search found a small number of economic studies on Bipolar Disorder, most with medium-to-high risk of bias. Economic evaluations are essential in the decision-making process for reimbursement of new technologies, but to be truly useful they should be construed with the lowest level of bias possible.

RECOMMENDATIONS

- The following recommendations may serve as the first step to build a robust analysis that will efficiently guide decisions.

Key Points

- The studies found present a very weak clinical basis. To perform a CEA, there should be evidence of added health benefit in relation to the comparators in real-life. The gain in effectiveness should be the basis of the analysis and not its result.
- For an economic evaluation in BD-I it is essential to first understand what are the main comparators used in the real-life setting in the US. Then, the effectiveness evidence of the intervention in relation to its comparators should be established.
- If no head-to-head comparison is available, a systematic review should be performed, possibly followed by a network meta-analysis to establish a comparison of therapies. Arbitrary selection of trials is not recommended.
- The time horizon of the analyses should reflect the chronicity of BD-I, preferentially in a lifetime framework.
- Parameters from previous publications should be used with caution (a critical assessment is necessary). Instead, the use of existing real world data should be considered, for e.g. resource use.
- Existing Markov structure is a good basis and could be further explored (e.g. to reflect the migration to 2nd line treatment). Additionally, the use of individual-level transition models, such as the one performed by Caro et al., should also be considered [13].
- Net benefit analyses (NBA) are a feasible approach: not difficult to interpret and allowing for easier calculation of confidence intervals than with incremental cost-effectiveness ratio (ICER) measure [14,15].

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Disclosures

• Greene is an employee of Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ
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