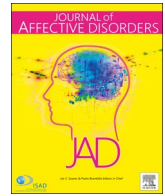


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Review article

Economic evaluations of non-pharmacological interventions and cost-of-illness studies in bipolar disorder: A systematic review

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ABSTRACT

Background Bipolar disorder (BD) is associated with substantial societal burden. Therefore, economic studies in BD are becoming increasingly important. The goal of the current study is three-fold: (1) summarize the evidence regarding economic evaluations (EEs) of non-pharmacological interventions for BD, (2) summarize cost-of-illness studies (COIs) for BD published 2012 or later and (3) assess the quality of the identified studies.

Methods A systematic search was conducted in MedLine, EMBASE and PsycINFO. For both EEs and COIs, quality assessments were conducted and general and methodological characteristics of the studies were extracted. Outcomes included incremental-cost-effectiveness ratios for EEs and direct and indirect costs for COIs.

Results Eight EEs and ten COIs were identified. The included studies revealed high heterogeneity in general and methodological characteristics and study quality. All interventions resulted in improved clinical outcomes. Five studies additionally concluded decreased total costs. For COIs, we found a wide range of direct (\$881-\$27,617) and indirect cost estimates per capita per year (\$1,568-\$116,062).

Limitations High heterogeneity in terms of interventions, study design and outcomes made it difficult to compare results across studies.

Conclusions Interventions improved clinical outcomes in all studies and led to cost-savings in five studies. Findings suggest that non-pharmacological intervention for BD might be cost-effective. Studies on the costs of BD revealed that BD has a substantial economic burden. However, we also found that the number of EEs was relatively low and methodology was heterogenous and therefore encourage future research to widen the body of knowledge in this research field and use standardized methodology.

1. Introduction

Bipolar disorder (BD) is a severe mood disorder characterized by recurrent manic and depressive episodes, often becoming manifest in early adulthood and extending over a lifetime (Goodwin and Jamison, 2007). In general, a distinction is made between bipolar I (BDI) and bipolar II (BDII). In the latter, a person experiences hypomanic and depressive episodes, but never a full-blown manic episode as in BDI (American Psychiatric Association, 2013). The lifetime prevalence of BD has been estimated at 0.6% for BDI and 0.4% for BDII, and the 12-month prevalence has been estimated at 0.4% and 0.3% respectively (Merikangas et al., 2011). Besides emotional distress and the impact on quality of life (Dean et al., 2004), negative social consequences (Calabrese et al., 2003) and high caregiver burden

(Laxman et al., 2008; Miller et al., 2014), BD is also associated with a high economic burden. In 2010, the total costs including all direct and indirect costs (adjusted for purchasing power parity) of BD were estimated at €21.49 billion and the total costs per patient was estimated to be €7183 in Europe (Olesen et al., 2012).

Economic evaluations (EEs) and cost-of-illness studies (COIs) contain important information to inform the healthcare sector about the cost-effectiveness of treatments and economic burden of a disease. The resources of our society are limited, and it is not possible to pay for every available intervention. Policy makers ought to be informed about the potential economic value of a new treatment or intervention. EEs aim to compare at least two treatment alternatives regarding costs and outcomes. Incremental analyses, which put the difference in effects in relation to the difference in costs between two competing interventions,

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are used to express the cost-effectiveness of an intervention towards a comparator. COIs are used to assess the economic impact of a disease and identify the associated costs to inform decision makers about the economic burden of the illness (Stuhldreher et al., 2012).

Summarizing studies regarding the cost-effectiveness of treatments and cost-of-illness of BD would guide policy makers in their decision making of which interventions should be prioritized. These decisions also have an impact on the work of clinicians, since decisions by the policy-makers set the agenda for treatment of mental disorders and determine which interventions are used and applied by clinicians. For academics, this is relevant as it provides an overview of the research field and identifies knowledge gaps. Therefore, it would help to obtain a comprehensive overview of this research field.

One review about EEs of pharmacological treatments has been published recently (Mavranzouli and Lokkerbol, 2017). However, BD is typically treated with a combination of pharmacological and psychological interventions, both during acute episodes and during preventive maintenance treatment of unlimited duration. Psychological interventions thus have an important place in the treatment of people with BD. To our knowledge, the only systematic review on EEs of psychological interventions specifically for BD was conducted by Abdul Pari, Simon, Wolstenholme, Geddes, and Goodwin (2014). For COIs, two reviews on COIs in BD were conducted (Jin and McCrone, 2015; Kleine-Budde et al., 2014). Although the execution of the mentioned reviews was sound, the reviews only comprised studies until 2012 (Abdul Pari et al., 2014; Kleine-Budde et al., 2014) and 2013, respectively (Jin and McCrone, 2015) and an update is needed.

Thus, to our knowledge, no up-to-date comprehensive overview of EEs of non-pharmacological treatments for BD and of COIs exists. Summarizing this knowledge may help policy makers to prioritize interventions and academics to identify knowledge gaps. Therefore, the goal of the present study is three-fold: (1) to summarize the evidence regarding EEs of non-pharmacological interventions for BD in terms of their costs and outcomes, (2) to summarize COIs for BD published 2012 or later and summarize the estimated costs related to BD and (3) to assess the quality of the identified studies.

2. Method

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2015). The review has been registered in PROSPERO, the International Prospective Register of Systematic Reviews (CRD42019124044). Data sharing is not applicable to this article as no new data was created or analysed in this study.

2.1. Search strategy

A literature search was conducted in September 2018 for the period from January 1990 to September 2018 in the following databases: MedLine, EMBASE and PsycINFO. The search was repeated in January 2020 and results were updated. The search strategy was adapted from the search strategy of an earlier review about the cost-effectiveness of interventions for anxiety disorders (Ophuis et al., 2017). Search terms relating to economic studies were used from this earlier search and complemented with terms relating to bipolar disorder, that were derived from earlier reviews that were conducted to develop the Dutch multidisciplinary guidelines for treatment of BD (Kupka et al., 2015). The search strategy was supplemented with Medical Subject Headings (MeSH) for searches in MedLine and Thesaurus terms for searches in PsycINFO. The search string can be found in Appendix A. For EEs, the earlier review by Abdul Pari et al. (2014) was cross-checked. To check whether trials were available that were not identified through our original database search, we cross-checked three clinical trial registers (www.clinicaltrialsregister.eu, www.clinicaltrials.gov, www.isrctn.com) in January 2019 and again in January 2020. Checking trial

registers is not likely to lead to additional studies, but we conducted this as an extra check for our literature search. Although there has been conducted a systematic review on EEs earlier, we decided to provide a complete overview of all EEs in this study, using a consistent quality appraisal tool. We considered it important to use a consistent quality assessment for all EEs, as outcomes of these studies might be especially relevant for policy-makers to prioritize interventions. If we only would have included more recent EEs, it would have been difficult to compare quality of studies with results from the earlier review (Abdul Pari et al., 2014). For COIs, the search was limited from 2012 to 2020, since we merely aimed to provide an update on the literature in this research field. Earlier reviews of COIs were cross-checked (Jin and McCrone, 2015; Kleine-Budde et al., 2014), to avoid including studies in the current review which were already included in an earlier review.

2.2. Selection of studies

All identified articles were screened on title by the first and second author. Remaining abstracts and full-texts were independently screened by the first and second author and ambiguities were discussed until consensus was reached. Consensus was reached in every case, since any ambiguities were discussed until a collective decision could be made. Eligibility criteria were designed to cover the PICO characteristics (population, intervention, comparison and outcome). Both EEs and COIs had to contain a target population of people of any age diagnosed with BD. The target population could either be euthymic (i.e. stable) patients with BD or patients currently in an acute depressive or manic phase. EEs were included if they assessed the effectiveness of any non-pharmacological treatment for BD or any non-pharmacological treatment in combination with pharmacotherapy and conducted a full-economic evaluation. To be included in the review, included interventions should be aimed to elicit changes in individuals' emotions, behaviors or cognitions. Both model-based economic evaluations (MBEES) and trial-based economic evaluations (TBEES) were included. Regarding the control group, it was not relevant which comparator was used in the included studies (e.g. treatment as usual, placebo, waiting-list or pharmacological treatment), as long as the intervention group contained a psychological intervention or a combination of psychological intervention with pharmacotherapy. Cost-utility analyses (CUAs), cost-effectiveness analyses (CEAs) or cost-benefit analyses (CBAs) were seen as full economic evaluations. COIs were included if the article reported the cost impact of BD, thus either direct (e.g. healthcare costs) or indirect (e.g. productivity loss) costs per individual and/or estimated direct or indirect societal costs. Studies needed to be in English, Dutch or German language. Possible COIs were excluded if the study reported the costs of an intervention only or if direct or indirect costs of BD were not reported or could not be derived. For both EEs and COIs, literature reviews, book chapters and studies not published in peer-reviewed journals were excluded. Since studies published in peer-reviewed journals went through quality control by external reviews, we decided to exclude studies not published in peer-reviewed journals to ensure certain quality of studies. Furthermore, conference or dissertation abstracts, editorials, letters, commentaries and notes were excluded, as they did not provide enough details for their methodological quality to be judged.

2.3. Data extraction

For EEs, data was extracted based on an adaptation of a pre-specified data extraction form (Wijnen et al., 2016) and included authors, publication year, country, type of economic evaluation (i.e. TBEE or MBEE), study type, analysis, valuation year, time horizon and funding. The type of perspective chosen by the authors of the papers (i.e. healthcare or societal perspective) was also extracted from the studies (Husereau et al., 2013). If the perspective was not explicitly mentioned, we decided whether a societal or healthcare perspective was chosen

based on whether non-health related (i.e. productivity loss) outcomes were considered or not. Although societal and healthcare perspectives are most likely to be the most common chosen perspectives in economic studies for BD, other perspectives also may be relevant for this review, such as a health insurer perspective, health and social care or public sector perspective. For COIs, diagnostic criteria, approach (i.e. prevalence or incidence-based) and description of costs (i.e. per capita or national) were extracted. In addition, methodological characteristics were extracted for both EEs and COIs, including target population, sample size, comparators, mean age and gender. In case of EEs, the type of effect measurement used was also extracted. Any ambiguities in the data extraction were discussed between the first and second author until uncertainties could be resolved.

2.4. Quality assessment

Quality of included EEs was assessed with the extended Consensus on Health Economic Criteria (CHEC) list (Evers et al., 2005; Odnoletkova et al., 2014), aiming to judge the internal and external validity of EEs. For this review, the CHEC-extended was used (Evers et al., 2005), which consists of the 20 CHEC-items and contains one extra item regarding model-quality (relevant in case of model-based economic evaluations). Item number seven of the CHEC (“Is the actual perspective chosen appropriate?”) was scored with 0 if the chosen perspective was not societal and no argumentation was provided for why a narrower perspective was chosen. We scored this item with 1 if the perspective was societal, or if the choice for a narrower perspective was properly motivated.

Since no standard instrument is available to assess the quality of COIs, included COIs were rated using a checklist provided in a previous systematic review on COIs in eating disorders (Stuhldreher et al., 2012). The checklist was developed based on recommendations by McGhan et al. (2009) and Drummond et al. (2015) and contains items on six different topics: (1) scope, (2) general economic criteria, (3) calculation of costs, (4) study design and analysis, (5) presentation of results and (5) discussion. Items of the CHEC and the quality assessment provided by Stuhldreher et al. (2012) were scored with *Yes* (score 1), *Suboptimal* (score 0.5), *No* (score 0), *NA* (not applicable) or *Uncertain* to obtain a more quantitative ranking. The first and second author independently assessed the quality of the included studies. The second author is a health economist and the first author a psychologist. Disagreements were discussed between the first and second author in consensus meetings until consensus was reached. Items were scored with uncertain only if the information was not clearly described in the article. Authors of the included studies were not contacted to clarify uncertainties.

2.5. Outcomes

Incremental-cost effectiveness ratios (ICERs) were reported as the outcome for the included EEs. ICERs can be expressed as costs per quality-adjusted life year (QALY) gained or costs per any (clinical) outcome gained. If a study did not report an ICER, we presented the result of the EEs narratively. Since ICERs tend to be heterogeneous and are therefore not comparable, we did not pool the results. For COIs, direct, indirect and total costs reported in the studies were described for the BD group and (if applicable) also for a control group. If costs for a control group were also mentioned in the study, we also provided a ratio of costs between BD and the non-clinical group. Costs for the control group were only described if it concerned a non-clinical population. ICERs and costs were converted to 2018 international dollar (INT\$) by using Purchasing Power Parity (PPP) rates to account for varying price levels (Shemilt et al., 2010; World Bank, 2017) and then converted based on the Consumer Price Index provided by the US Bureau of Labor statistics (Bureau of Labor Statistics, 2018) to provide the most recent values adjusted for inflation rates.

3. Results

3.1. Study selection

In total, the search yielded 2363 studies and after removal of duplicates and screening of titles and abstracts, 65 full-texts were assessed for eligibility. Of these full-texts, 18 met inclusion criteria. The main reasons for exclusion of full-texts was that they did not present results specific for BD samples ($n = 17$), were no CEA or COI studies ($n = 17$), were conference papers or conference abstracts ($n = 10$). Of the articles included in the final review, eight studies concerned EEs (Bauer et al., 2006; Camacho et al., 2017; Chisholm et al., 2005; Flood et al., 2006; Kessing et al., 2013; Lam et al., 2005; Scott et al., 2009; Simon et al., 2006) and ten studies were COIs (Broder et al., 2018; Cloutier et al., 2018; Correll et al., 2017; Degli Esposti et al., 2014; Ekman et al., 2013; Mennini et al., 2014; Pan et al., 2019; Parker et al., 2013; Somaiya et al., 2014; Wu et al., 2013). All studies investigating the cost-effectiveness of psychological interventions included in the earlier review on EEs in bipolar disorders (Abdul Pari et al., 2014) were also identified in the current review (Bauer et al., 2006; Chisholm et al., 2005; Lam et al., 2005; Simon et al., 2006). The study selection process is summarized in Fig. 1.

3.2. Overview of included EEs

3.2.1. Main characteristics

The most recent study was published in 2017 (Camacho et al., 2017) and the least recent studies in 2005 (Chisholm et al., 2005; Lam et al., 2005). All studies were published in western countries, namely the United Kingdom ($n = 3$), United States ($n = 2$), Denmark ($n = 1$) and Spain ($n = 1$). One study reported costs and outcomes globally for different regions (Chisholm et al., 2005). All EEs concerned RCTs, except one study which additionally conducted a MBEE to extrapolate results of a RCT (Camacho et al., 2017) and one study which applied a MBEE (Chisholm et al., 2005). Most studies used CEA, while two studies used CUA to investigate the cost-effectiveness of the intervention (Camacho et al., 2017; Chisholm et al., 2005). The perspective chosen by the studies concerned a healthcare perspective in most included studies, while one study explicitly stated that they chose a health and personal social services perspective (Camacho et al., 2017). Time horizon of the included EEs which applied TBEEs varied between 15 months (Flood et al., 2006) and five years (Scott et al., 2009). The only pure MBEE chose a life-time analytical horizon (Chisholm et al., 2005). The studies that reported their source of funding were not funded by industry and one study did not report their source of funding (Chisholm et al., 2005). Main characteristics of included EEs are described in Table 1.

3.2.2. Methodological characteristics

Included effect measurement concerned QALYs in one study (Camacho et al., 2017) and DALYs in one study (Chisholm et al., 2005). Other outcomes included admission to hospital ($n = 2$), time spent in relapse or in any episode or hospitalized ($n = 3$), relapse free years ($n = 1$) and manic or depressive symptoms ($n = 1$). Methodological characteristics of included EEs are summarized in Table 2.

Most studies involved people with a diagnosis of both BDI or BDII, while one study was specifically aimed at patients BDI experiencing frequent relapse currently not fulfilling criteria for a bipolar episode (Lam et al., 2005). One other study included patients with BD discharged from their hospital admission (Kessing et al., 2013). One study included veterans with BD (Bauer et al., 2006) and two studies included euthymic patients (Scott et al., 2009; Camacho et al., 2017), one of them patients at an increased risk for relapse (Camacho et al., 2017). Two studies contained any patients with BD (Chisholm et al., 2005; Flood et al., 2006) and one study patients with any diagnosis of bipolar spectrum disorder (Simon et al., 2006).

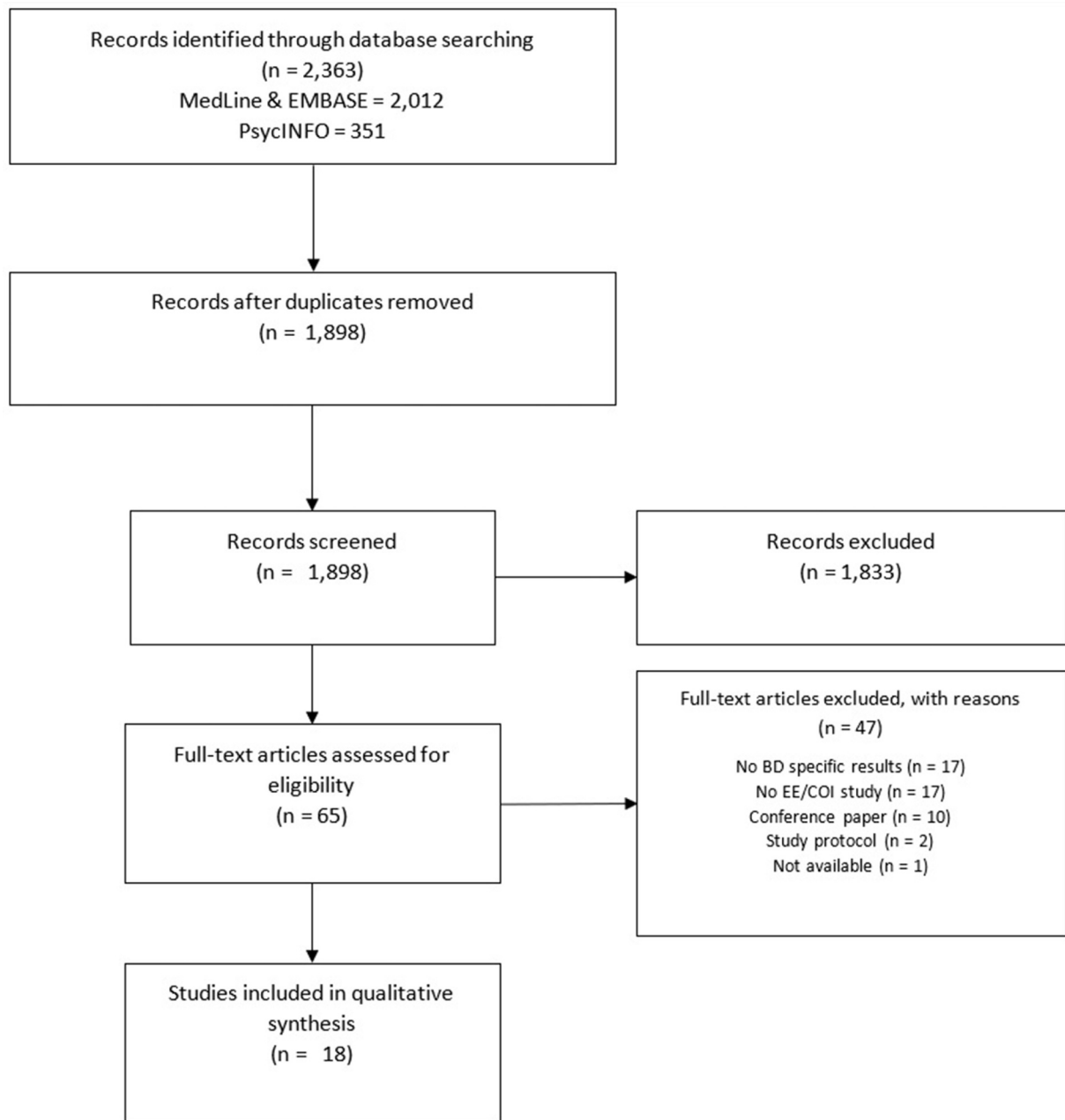


Fig. 1. Flowchart of study selection process.

Table 1
Main characteristics of included EEs.

First author (year)	Country	Economic evaluation	Study type	Analysis	Perspective	Time horizon	Industry funding
Bauer et al. (2006)	USA	TBEE	RCT	CEA	Healthcare	3 years	No
Camacho et al. (2017)	UK	Combined ^a	Combined ^a	CUA	Health and Personal Social Services	96 weeks	No
Chisholm et al. (2005)	Global	MBEE	Population model	CUA	Healthcare	Life-time analytical horizon	NR
Flood et al. (2006)	UK	TBEE	RCT	CEA	Healthcare	15 months	No
Kessing et al. (2013)	Denmark	TBEE	RCT	CEA	Healthcare	2 years	No
Lam et al. (2005)	UK	TBEE	RCT	CEA	Healthcare	30 months	No
Scott et al. (2009)	Spain	TBEE	RCT	CEA	Healthcare	5 years	No
Simon et al. (2006)	USA	TBEE	RCT	CEA	Healthcare	2 years	No

Note. EEs = Economic evaluations, CUA = Cost-Utility Analyses, MBEE = Model-based-economic evaluation, NR = Not reported, RCT = Randomized controlled trial. TBEE = Trial-based-economic evaluation.

^a Both TBEE and MBEE components.

Table 2
Methodological characteristics of included EEs.

First author (year)	Target population	Treatment alternatives (n)	% female	Mean age	Study type	Outcomes	Discount rate	Valuation year, original currency	Description of treatment alternatives
Bauer et al. (2006)	Veterans with BD	I: Bipolar Disorders Program (166), II: TAU (164)	NR	NR	RCT	Weeks in any episode, mental and physical QoL (SF-36)	3.0%	2004, USD	I: Collaborative care program with a specialty team, including the enhancement of self-management via group psychoeducation, evidence-based pharmacotherapy and access to care. II: Patients continued with TAU.
Camacho et al. (2017)	Euthymic patients with BD at increased risk for relapse	I: Bipolar group structured PE + TAU (153), II: Unstructured bipolar group peer-support + TAU (151)	58.0	45.0	RCT	OALYs (EQ-5D-3 L), relapse free years, relapse avoided	NR ^a	2012, pound	I: Weekly (21 sessions) structured bipolar group PE delivered by two healthcare professionals, each session included specific handouts and homework tasks. II: Weekly (21 sessions) unstructured peer-support groups delivered by healthcare professionals and a service-user facilitator, including a short manual.
Chisholm et al. (2005)	Patients with BD	I: Lithium or valproic acid + psychosocial care; lithium or valproic acid alone, II: No treatment	NA	NA	Population model	DALYs	3.0%	2003, INT\$	I: Four treatments are included in the model representing either pharmacotherapy alone or in combination with psychosocial care: Lithium + psychosocial care, valproic acid + psychosocial care, lithium alone and valproic acid alone. II: The comparator is no treatment.
Flood et al. (2006)	Patients with BD	I: Joint crisis plan + TAU (80), II: standardized service information + TAU (80)	53.0	39.1	RCT	Admission to hospital	NR ^b	2001, pound	I: During two sessions a joint crisis plan was developed, which contains a set of statements of what to do in a crisis. The patient was encouraged to bring a friend or advocate to the second meeting to work on the plan together. II: Patients received leaflets about local services and mental health.
Kessing et al. (2013)	Patients with BD, discharged from hospital	I: Specialized mood disorder clinical group (72), II: TAU (86)	42.9	36.3	RCT	Readmission to hospital	NR	2006, EUR	I: Specialized out-patient clinic offering a combined treatment of evidence-based pharmacological treatment and group PE and psychotherapy for 2 years. Participants followed three sequential PE and psychotherapeutic group sessions. II: Patients continued with TAU.
Lam et al. (2005)	Patients with BD and frequent relapse	I: CBT (51), II: TAU (52)	56.5	44.0	RCT	Number of days in bipolar episode	NR	2001, pound	I: Cognitive therapy delivered by clinical psychologists for 12 to 18 individual sessions within 6 months and two additional booster sessions in the second 6 months. II: Patients continued with TAU.
Scott et al. (2009)	Euthymic patients with a lifetime diagnosis of bipolar disorder I or II	I: Structured PE + TAU (60), II: Unstructured PE + TAU (60)	63.3	34.1	RCT	Number of days spent in relapse or hospitalized	NR	2006, EUR	I: Structured group PE (21 sessions, 1.5 h per session) run by two psychologists, aimed at improving illness awareness, treatment compliance, early detection of symptoms and lifestyle. II: Unstructured group meetings with the two psychologists, who tried to not give psychoeducational feedback except for what was necessary.

(continued on next page)

Table 2 (continued)

Simon et al. (2006)	Patients with any diagnosis of bipolar spectrum disorder	I: Systematic care program for BD (212), II: TAU (229)	68.3	44.2	RCT	Manic and depressive symptoms (PSR; SCID interviews)	NR	2000, USD	I: Multicomponent intervention provided by three nurse care managers (24 months), aimed at care planning, structured monthly telephone calls, feedback to the mental health treatment team, structured group PE, as-needed support, education and care coordination. II: Patients continued with TAU.
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Note. BD = Bipolar disorder, = Cognitive Behavioral Therapy, DALYs = Disability-adjusted life-years, EQ-5D-3 L = EuroQol 5D – 3 level version, EUR = Euro, ICERs = Incremental cost-effectiveness ratios, INTd = International dollar, NA = Not applicable, NR = Not Reported, PE = Psychoeducation, PSR = Psychiatric Status Rating, RCT = Randomized controlled trial, SCID = Structured Clinical Interview for DSM, SF-36 = 36-item Short Form Survey, QALYs = Quality-adjusted life years, QoL = Quality of Life, TAU = Treatment as usual, USD = US dollar.

^a Due to the relatively short study period future costs and outcomes were not discounted.

^b Due to a lack of data on the timing of resource costs that occurred after the first 12 months of the trial costs could not be discounted.

Economic evaluations included in this review used an array of different interventions for BD. The Bipolar Disorders Program (Bauer et al., 2006) was described as collaborative care program including for example enhancement of patient skills in self-managing the illness by psychoeducation. The joint crisis plan intervention (Flood et al., 2006) consisted of meetings with healthcare professionals aimed at generating a crisis plan. The systematic care program for BD (Simon et al., 2006) contained, for example, care planning and structured group psychoeducation. One study concerned an intervention program from an outpatient mood disorder clinical group program (Kessing et al., 2013). Two studies examined the effect of structured psycho-education (Scott et al., 2009; Camacho et al., 2017) and one study used Cognitive Behavioral Therapy (CBT; Lam et al., 2005). None of the included articles mentioned that TAU was withheld from the intervention arm or constrained. Therefore it can be assumed that TAU was part of all the interventions included in this review.

Four of the included studies compared the effect of the psychological intervention versus treatment as usual only (TAU) only, while one study used unstructured psycho-education and TAU as comparator (Scott et al., 2009) and another study used unstructured group peer-support and TAU as treatment alternative (Camacho et al., 2017). One study used standardized service information and TAU as treatment alternative (Flood et al., 2006) and one study investigated the effect of pharmacotherapy plus psychosocial care and pharmacotherapy only in comparison with no treatment (Chisholm et al., 2005). The studies that described TAU in their studies outlined it in a similar way, mainly consisting of pharmacotherapy, psychoeducation and supportive sessions.

3.2.3. Outcomes

The main outcomes of included EEs are summarized in Table 3. Of the included EEs, four studies reported an ICER. Of these articles, one study estimated the costs for one additional QALY gained at \$75,106 and one relapse free year at \$13,187 for bipolar group structured psychoeducation and TAU compared to unstructured peer-supported psychoeducation and TAU (Camacho et al., 2017). One other study estimated the cost-effectiveness of joint crisis plans and concluded that the intervention led to less mean total costs per patient and was more effective in reducing admission to hospital compared to standardized service information in addition to TAU in the UK (Flood et al., 2006). Another study from Spain reported fewer total costs for structured psychoeducation and TAU compared with unstructured psychoeducation and TAU for the study period of 5 years. Also, the intervention resulted in less days in relapse and less mean hospital admissions. The intervention thus dominated the control group over the study period of five years (Scott et al., 2009). The Bipolar Disorders Program resulted in less weeks in any episode at higher outpatient costs compared to TAU only in the US. However, mean total costs were lower for the intervention arm over the study period of 3 years (Bauer et al., 2006). Treatment in the mood disorder clinic group resulted in fewer hospital admissions, decreased inpatient costs and lower two-year total treatment costs compared to TAU in Denmark (Kessing et al., 2013). The systematic care program for BD led to less manic symptoms, but not depressive symptoms at higher total costs compared to TAU in the US (Simon et al., 2006). One other intervention in the UK (cognitive behavioral therapy) led to fewer total costs at both 12 and 30 months after baseline. The higher costs of the intervention were offset by lower costs for other services. Cost-effectiveness analyses suggested that, if the value for one bipolar-free day was set at \$21, the probability that the intervention was cost-effective was about 85% for a period of 12 months and about 80% for a period of 30 months (Lam et al., 2005).

The only MBEE included in this review (Chisholm et al., 2005) compared the cost-effectiveness of four different interventions with no treatment; lithium plus psychosocial care, lithium alone, valproic acid plus psychosocial care and valproic acid alone. Compared to no treatment, the additional costs of lithium plus psychosocial care were

Table 3
Outcomes of included EEs (in PPP-INT\$).

First author (year)	Incremental health benefits per patient	Incremental costs per patient	ICER	Description of outcomes
Bauer et al. (2006)	6.2 fewer weeks in any episode; improvement in mental QoL	-\$3879, 95%CI(-\$20,861-\$13,796)	Dominant	Intervention resulted in less weeks in any episode and improved mental functioning at lower 3-year total costs compared to the control group (\$79,901 versus \$83,780); ICER NR.
Camacho et al. (2017)	0.023 QALYs; 0.131 relapse free years; 0.102 Relapse avoided during follow-up	\$1727, 95%CI(\$396-\$3056)	\$75,106/QALY; \$13,187/relapse free year; \$16,931/relapse avoided	Additional costs of \$1727 in healthcare resources used for PE group; QALY gain of 0.023 in the PE group, 0.131 relapse free years and 0.102 relapse avoided; ICER group PE versus control; \$75,106/QALY gained; \$13,187/relapse free year and \$16,931/relapse avoided.
Chisholm et al. (2005)	Fewer disability free days per year ^a ; Li + psy (59.6 - 67.3); Va + Psy (58.4-63.3); Li (54.5-62.1); Va (53.1-60.2)	Costs per treated case, coverage rate of 50%; Hospital-based ^b : Li + psy (\$1091-\$9627); Va + Psy (\$1208-\$9409); Li (\$1068-\$9493); Va (\$1181-\$9235) Community-based ^c : Li + psy (\$719-\$5599); Va + Psy (\$849-\$5531); Li (\$697-\$5465); Va (\$821-\$5344)	Hospital-based ^d : Li + psy (\$4096-\$47,611/DALY); Va + psy (\$5650-\$48,572/DALY); Li (\$4324-\$51,252/DALY); Va (\$5959-\$52,540/DALY) Community-based ^e : Li + psy (\$2894-\$28,245/DALY); Va + psy (\$4212-\$29,779/DALY); Li (\$3028-\$30,110); Va (\$4403-\$31,036)	Hospital-based service model: Lithium + psychosocial care had a lower ICER than valproic acid + psychosocial care compared with no treatment; Community-based service model: Lithium + psychosocial care had a lower ICER than valproic acid + psychosocial care compared with no treatment. Lithium alone had a higher ICER than lithium + psychosocial care compared to no treatment in both models; Valproic acid alone had a higher ICER than valproic acid + psychosocial care compared to no treatment in both models.
Flood et al. (2006)	0.69 fewer hospital admissions	-\$2286, 95%CI(-\$10,445-\$5874)	Dominant; \$273/reduction of 1% of patients admitted to hospital	Decreased mean total costs per patient in the intervention group (\$15,161 versus \$17,448, nonsignificant); intervention was cheaper and more effective; ICER joint crisis plan versus control group, \$273 per 1% reduction in the proportion of patients admitted to hospital. Intervention resulted in fewer hospital readmissions after discharge, decreased inpatient costs (\$18,302 versus \$27,175) and lower two-year total treatment costs (\$32,787 versus \$36,823); ICER NR.
Kessing et al. (2013)	0.61 fewer hospital readmissions after discharge	-\$4036	Dominant	Intervention led to 110 fewer days with bipolar episodes (95.3 versus 201 days) in 30 months at lower total costs (\$21,739 versus \$24,620); if society is willing to pay \$21 per bipolar free day CBT is more cost effective with 85% probability over the study period of 30 months; ICER NR.
Lam et al. (2005)	110 fewer days spent in bipolar episode	-\$2881	Dominant	Intervention resulted in less days in relapse (153.7 versus 586.5), less mean admission to the hospital (0.24 versus 0.59) at higher outpatient but lower total costs (\$29,734 versus \$35,361); Structured PE + TAU dominated the control group over the study period of 5 years.
Scott et al. (2009)	433 fewer days spent in relapse, 0.35 fewer admissions to the hospital	-\$5626, 95%CI(-\$16,538-\$5283)	Dominant; ICER based on outpatient costs: \$6824/relapse free person and \$5882/hospitalization-free person	Intervention resulted in less manic symptoms; no difference was found for depressive symptoms; Intervention group resulted in higher total costs (\$11,396 versus \$9550); ICER NR.
Simon et al. (2006)	Fewer manic symptoms; 5.5 fewer weeks with clinically significant mania symptoms	\$1846, after adjustment for several baseline covariates: \$1774, 95%CI (\$78-\$3470)	NR	Intervention resulted in less manic symptoms; no difference was found for depressive symptoms; Intervention group resulted in higher total costs (\$11,396 versus \$9550); ICER NR.

Note. BD = Bipolar disorder, CI = Confidence Interval, CBT = Cognitive Behavioral Therapy, DALYs = Disability Adjusted Life Years, EEs = Economic evaluations, EQ-5D-3 L = EuroQol 5D - 3 level version, ICER = Incremental cost-effectiveness ratio, Li = Lithium, Li + psy = Lithium plus psychosocial care, NA = Not applicable, NR = Not Reported, PE = Psycho-education, PSR = Psychiatric Status Rating, QALYs = Quality-adjusted life years, QoL = Quality of life, RCT = Randomized controlled trial, SF-36 = 36-item Short Form Survey, Va = Valproic acid, Va + psy = Valproic acid plus psychosocial care. ^aNumbers between brackets represent the range of estimates for different subregions and for the corresponding treatment alternative.

estimated to be \$4096 to \$47,611 per additional DALY averted in a hospital-based service model and at \$2894 to \$28,245 in a community-based service model, depending on the subregion in which the costs are assumed to occur (e.g. developing or non-developing regions). Compared with no treatment, lithium plus psychosocial care had a lower ICER than lithium alone. Valproic acid plus psychosocial compared with no treatment was estimated to lead to \$5650 to \$48,572 additional costs in a hospital-based service model and to \$4212 to \$29,779 in a community-based service model. Valproic acid alone had a higher ICER than treatment with valproic acid and psychosocial care compared with no treatment. Among all treatment alternatives, lithium plus psychosocial care had the lowest ICER compared to no treatment. Furthermore, lithium alone had a lower ICER than valproic acid plus psychosocial care or valproic acid alone compared with no treatment.

3.3. Overview of included COIs

3.3.1. Main characteristics

Seven of the included COIs were conducted in western countries, including United States ($n = 3$), Italy ($n = 2$), Sweden ($n = 1$) and Australia ($n = 1$). One study was conducted in India (Somaiya et al., 2014) and two in Taiwan (Pan et al., 2019; Wu et al., 2013). All articles, except one, reported diagnostic criteria for the target group included in the studies. Seven studies used criteria of the International Classification of Diseases (ICD) and two of the Diagnostic Statistical Manual of Mental Disorders (DSM). The approach to determine the costs of BD was prevalence-based in all of the included studies. Of all included COIs, five studies took a societal perspective and five a healthcare perspective. The perspective chosen was explicitly mentioned in two studies only (Cloutier et al., 2018; Ekman et al., 2013) and took a societal perspective in both cases. Six of the included COIs used national or insurance databases as data source. Two studies used databases from hospitals to estimate costs related with BD (Ekman et al., 2013; Somaiya et al., 2014), of which one study combined it with self-report questionnaire data from patients (Somaiya et al., 2014). Two studies used purely self-report questionnaire data to obtain costs (Mennini et al., 2014; Parker et al., 2013). The description of costs was based on per capita costs in all of the COI studies. One study additionally estimated national costs related with BD. Five of the studies were funded by industry, four studies were not (Pan et al., 2019; Parker et al., 2013; Somaiya et al., 2014; Wu et al., 2013) and one study did not report funding source (Mennini et al., 2014). Main characteristics of included COIs are summarized in Table 4.

3.3.2. Methodological characteristics

Methodological characteristics and outcomes of included COIs are summarized in Table 5. Four studies focused on BDI (Broder et al., 2018; Cloutier et al., 2018; Correll et al., 2017; Mennini et al., 2014). One of these studies (Correll et al., 2017) also included patients with BD and cardiometabolic comorbidities, but for the present review only the estimated costs for patients without cardiometabolic comorbidities were extracted. Five studies included samples with both BDI and BDII (Degli Esposti et al., 2014; Ekman et al., 2013; Pan et al., 2019; Parker et al., 2013; Somaiya et al., 2014). One study included patients with BD and intellectual disabilities and cost estimates for patients with BD only. We used only the latter estimates for this review (Wu et al., 2013). Another study estimated direct costs for two different age groups in Taiwan, namely for people with BDI and BDII aged 18–64 and aged 65 or older (Pan et al., 2019). Direct costs related to BD were estimated in nine of the included COIs, one study merely estimated indirect costs but no direct costs (Mennini et al., 2014). Five studies estimated indirect costs. Total costs (direct and indirect costs combined) were estimated in four studies. In every study estimating direct costs, these costs included the costs of drugs and in six studies also outpatient and inpatient costs (Broder et al., 2018; Cloutier et al., 2018; Ekman et al., 2013; Pan et al., 2019; Parker et al., 2013; Wu et al.,

Table 4
Main characteristics of included COIs.

First author (year)	Country	Diagnostic criteria	Approach	Perspective	Data source	Valuation year, original currency	Description of costs	Industry funding
Broder et al. (2018)	USA	ICD-9, ICD-10	P	Healthcare	Truven Health Analytics MarketScan databases	2016, USD	PC	Yes
Cloutier (2018)	USA	ICD-9, ICD-10	P	Societal	Truven Health Analytics MarketScan databases	2015, USD	PC/NC	Yes
Correll (2017)	USA	ICD-9	P	Healthcare	Premier Perspective Database	2014, USD	PC	Yes
Degli Esposti (2014)	Italy	ICD-10	P	Healthcare	Health-assisted Subjects' Database, Medications Prescription Database, Hospital Discharge Database, Mental Health Information System, Specialist Outpatient Services Database, No Charges Database	2010, EUR	PC	Yes
Ekman (2013)	Sweden	ICD-10	P	Societal	Management system Northern Stockholm Psychiatry, Swedish Prescribed Drug Registry of the National Board of Health and Welfare, Social Insurance Authority	2009, EUR	PC	Yes
Mennini (2014)	Italy	NR	P	Societal	Self-reported data from a longitudinal prospective study	2012, EUR	PC	NR
Pan (2019)	Taiwan	ICD-9	P	Healthcare	National Health Insurance Research Database	2008, NTW	PC	No
Parker (2013)	Australia	DSM-IV	P	Societal	Self-reported questionnaire data ^a	2011, AUD	PC	No
Somaiya (2014)	India	DSM-IV	P	Societal	Hospital statistics, bills, payment slips and self-report	2011, Indian rupee	PC	No
Wu (2013)	Taiwan	ICD-9	P	Healthcare	National Health Insurance Research Database	2007, USD	PC	No

Note. AUD = Australian Dollar, COIs = Cost-of-illness studies, DSM = Diagnostic Statistical Manual of Mental Disorders, EUR = Euro, ICD = International Classification of Diseases, NC = National costs, NTW = New Taiwan Dollar, P = Prevalence-based, PC = Per capita, USD = US Dollar.
^a Participants were only asked at one measurement point.

Table 5
Methodological characteristics and outcomes of included COIs (in PPP-INT\$).

First author (year)	Target population (n)	% female	Mean age	Bipolar disorder			Controls			Ratio
				Direct costs include	Direct costs per annum	Indirect costs include	Indirect costs per annum	Total costs Per annum	Total costs per annum	
Broder et al. (2018)	People with BDI (51,480)	64.0	41.6	Outpatient, Inpatient, Drugs	\$27,617 per capita	-	-	-	-	-
Cloutier (2018)	I: People with BDI (2,477,737) ^a ; II: Healthy US population	66.4	41.4	Outpatient, Inpatient, Drugs Others	\$59,050,087,989 (societal ^b); \$23,832 per capita ^c	Productivity loss	\$154,449,703,726 (societal ^b); \$62,343 per capita ^c	\$213,499,791,715 (societal ^b); \$86,175 per capita ^c	\$86,977,430,290 (societal ^b)	2.5
Correll (2017) Degli Esposti (2014)	People with BDI (61,777) ^d People with BD (5486)	63.0 ^e 59.0	45.4 ^e 52.0	Inpatient, Drugs Inpatient, Drugs, Others	\$7604 per capita ^f \$5118 per capita	-	-	-	-	-
Ekman (2013)	People with BD (1846)	59.0	50.1	Inpatient, Outpatient, Drugs	\$7160 per capita	Productivity loss	\$24,477 per capita	\$31,637 per capita	-	-
Memini (2014)	People with BDI (265)	54.9	50.0	-	-	Productivity loss	\$9056 (low income class); \$17,585 (high income class)	-	-	-
Pan (2009)	I: People with BDI or BDII aged 18–64 (13,105); II: People with BDI or BDII aged ≥ 65 (2149);	I: 60.3, II: 58.8	I: 40.0, II: 74.7	Inpatient, Outpatient, Drugs Emergency attendances	I: 6617 per capita, II: 10,425 per capita	-	-	-	-	-
Parker (2013)	People with BDI (44) or BDII (102)	59.6	35.8	Outpatient, Inpatient, Drugs, Others	\$19,036 (BDI) per capita, \$12,699 (BDII) per capita	Productivity loss Disability pension Others	\$97,026 (BDI); \$55,492 (BDII)	\$116,062 (BDI) per capita; \$68,191 (BDII) per capita	-	-
Somaiya (2014)	People with BD (75)	30.7	34.3	Inpatient, Drugs, Others	\$881 per capita	Productivity loss Others	\$1568 per capita	\$2449 per capita	-	-
Wu (2013)	People with BD (17,355)	58.6	27.2	Inpatient, Outpatient, Drugs, Others	\$9065 per capita	-	-	-	-	-

Note. BD = Bipolar Disorder, COIs = Cost-of-illness studies, SD = Standard Deviation.

^a The adult US BDI population was estimated based on a prevalence of 1.0%.

^b Societal costs = estimated annual costs for the US that is caused by BDI.

^c Costs per capita were not provided in the study and were calculated by dividing the societal costs by the assumed number of individuals with BDI.

^d Actual sample size was larger, but also included people with cardiometabolic comorbidities. For the present study, only costs for patients without cardiometabolic comorbidities were extracted.

^e Based on the whole sample (incl. cardiometabolic comorbidities).

^f Not clear for which time period the costs were calculated.

2013). Three studies assessed costs of inpatient care only, instead of inpatient and outpatient costs (Correll et al., 2017; Degli Esposti et al., 2014; Somaiya et al., 2014). All five studies which estimated indirect costs, included productivity loss in their cost estimation. Three studies also included other indirect costs, for example unemployment and caregiving (Cloutier et al., 2018) or disability pension (Parker et al., 2013). One study included a non-clinical control group to compare the costs associated with BD to a healthy population (Cloutier et al., 2018).

3.3.3. Outcomes

Four studies reported costs for patients with BDI and three of these estimated direct costs, including a range of \$7604 and \$27,617 per capita per year (Broder et al., 2018; Cloutier et al., 2018; Correll et al., 2017). Indirect costs for BDI ranged between \$9065 in Italy (Mennini et al., 2014) and \$62,343 per year per capita in the US (Cloutier et al., 2018). One study also calculated the societal costs for BDI and estimated direct costs of \$59,050,087,989 and indirect costs of \$154,449,703,726 per year in the in the United States. Estimated costs were 2.5 times higher compared to a non-clinical US population (Cloutier et al., 2018). Another study reported the costs for BDI and BDII separately and estimated the direct costs of BDI at \$19,036 and for BDII at \$12,699 and indirect costs for BDI at \$97,026 and for BDII at \$55,492 per year per capita in Australia (Parker et al., 2013). Direct costs for samples including both BDI and BDII ranged between \$881 in India (Somaiya et al., 2014) and \$10,425 in Taiwan for people aged 65 or older (Pan et al., 2019) per capita per year. Indirect costs were estimated at \$1568 in India (Somaiya et al., 2014) and at \$24,477 per capita per year in Sweden (Ekman et al., 2013). The study by Wu et al. (2013) estimated costs for patients with BD with and without intellectual disability and estimated the total direct costs at \$9065 per year per capita in Taiwan for patients with BD without intellectual disability.

3.4. Quality assessment

The quality assessment of included EEs revealed an average study quality of 74%, with a range of 68% to 83%. Across all included studies, the two items on ‘appropriate discounting’ (item 15) and ‘generalizability of results’ (item 18) had the lowest scores. Merely one study appropriately discounted future costs and outcomes and only two studies discussed generalizability of the findings properly. Items regarding the economic study design and the chosen time horizon had the highest scores. These items were considered appropriate for all included EEs.

For included COIs, the average study quality was 70.6%, with the quality of included studies ranging between 41% and 88%. The lowest scores were found for whether a non-diseased comparison group was used and whether a perspective was reported. Merely one study contained a non-clinical control group, while only two studies mentioned the perspective. The highest scores were found for the items on study objective, diagnostic criteria, analysis of costs that accrued from a particular disease, currency, source of healthcare utilization, sample size reported, sample characteristics described, and limitations discussed in detail. These items were rated as sufficient for all included COIs. Results of the quality assessment are summarized in Table 6 and 7.

4. Discussion

In all of the included EEs, the interventions resulted in improved clinical outcomes and five studies additionally concluded decreased total costs (Bauer et al., 2006; Flood et al., 2006; Kessing et al., 2013; Lam et al., 2005; Scott et al., 2009). Thus, in five of the included studies, the intervention dominated its comparator over the study period. Overall, these findings indicate that psychological treatments may reflect a (cost)-effective option for the treatment of BD. However, the results should be interpreted with caution, as the studies used several

different outcomes to assess the (cost)-effectiveness of their interventions, such as admissions to hospital, number of days with BD or symptomatology and also different types of comparators. Furthermore, healthcare costs were retrieved in different ways, for example by self-report questionnaires or computerized pharmacy registration data. This makes it difficult to compare the EEs included in this review and also makes generalizability and transferability to other settings difficult.

Of the included EEs, one study expressed the cost-effectiveness of an intervention as ICER in relation to QALYs (Camacho et al., 2017). In this study, structured group psychoeducation as addition to TAU led to an increase in QALYs compared to TAU in combination with unstructured peer-supported psychoeducation. One additional QALY gained was estimated to cost \$75,106. This is higher than the willingness-to-pay threshold (WTP-T) in the UK (approx. \$25,000-\$40,000), but still within the range of the WTP-T for the Netherlands (\$20,000-\$80,000), for example. The relatively small increase in QALYs could be explained by the included quality of life instrument (EQ-5D) or due to the lack of additional effect of the intervention. It is debatable whether the EQ-5D is sensitive to change in people with mental disorders and assesses all relevant aspects of quality of life for this target group (Brazier, 2010; Longworth et al., 2014). Another included study assessed quality of life with the SF-36, but they did not need to report an ICER (Bauer et al., 2006) as the intervention (Bipolar disorder program) resulted in fewer 3-year costs and a significant improvement in quality of life and thus was dominant compared to TAU.

The only MBEE included in this review estimated the cost-effectiveness of lithium and psychosocial care and valproic acid and psychosocial care compared to no treatment (Chisholm et al., 2005). One additional DALY averted was estimated to cost up to \$47,611 for lithium and psychosocial care compared to no treatment, while the other treatment alternatives (lithium alone, valproic acid plus psychosocial care and valproic acid alone) were estimated to have higher ICERs compared to no treatment. This is also in line with an earlier review on economic evaluations in BD, concluding that combined therapies (pharmacological and psychotherapy) might be important for this target group. Psychotherapy can be effective in enhancing the patients’ awareness, compliance and thereby prevent relapse and hence improve overall treatment outcomes (Abdul Pari et al., 2014).

While the current review was conducted, another systematic review about EEs of psychological interventions for people with BD and/or schizophrenia has been published (Shields et al., 2019). Interestingly, merely two studies that were included as EEs in our study were also included in their study (Camacho et al., 2017; Lam et al., 2005). One of the main reasons why this review has included more studies are the broader eligibility criteria regarding outcomes compared to the study by Shields et al. (2019), in which the authors decided to only include full EEs including an ICER or some measure of net benefit that incorporates health outcomes. Studies also had to include a ‘cost-effectiveness acceptability curve’ (CEAC) or explicitly report probabilities of being cost-effective to allow for an assessment of uncertainty (Shields et al., 2019). In general, however, the conclusions by Shields et al. (2019) were similar to the current study, namely that non-pharmacological interventions for BD might be cost-effective, but that studies remain scarce and that there was also great heterogeneity in study characteristics, which makes it difficult to reach strong conclusions.

One other review about EEs of pharmacological treatments for BD has been conducted recently (Mavranzouli and Lokkerbol, 2017). In general, they concluded that pharmacological interventions are cost effective compared with no treatment. Specifically, antipsychotic drugs in combination with lithium or valproate appear to be most cost effective for acute manic, mixed or depressive phases compared with no treatment. For maintenance treatment, lithium appears to be cost effective compared with no treatment. However, they also note that results are difficult to compare across studies due to high heterogeneity regarding methodological and intervention characteristics, which is in

Table 6
CHEC quality assessment of included EEs.

Item	First author							
	Bauer	Camacho	Chisholm	Flood	Kessing	Lam	Scott	Simon
1. Is the study population clearly described?	1	1	0.5	0.5	1	1	1	1
2. Are competing alternatives clearly described?	1	1	0.5	1	1	0.5	1	1
3. Is a well-defined research question posed in answerable form?	1	1	0.5	1	1	1	1	0.5
4. Is the economic study design appropriate to the stated objective?	1	1	1	1	1	1	1	1
5. Are the structural assumptions and the validation methods of the model properly reported?	NA	0.5	0.5	NA	NA	NA	NA	NA
6. Is the chosen time horizon appropriate in order to include relevant costs and consequences?	1	1	1	1	1	1	1	1
7. Is the actual perspective chosen appropriate?	1	1	1	0	1	0	0	0
8. Are all important and relevant costs for each alternative identified?	1	1	0.5	1	0	1	0.5	0.5
9. Are all costs measured appropriately in physical units?	1	1	0	0.5	1	1	0.5	1
10. Are costs valued appropriately?	1	1	1	1	1	1	1	0.5
11. Are all important and relevant outcomes for each alternative identified?	1	1	1	0	1	1	1	1
12. Are all outcomes measured appropriately?	1	1	1	1	1	1	1	1
13. Are outcomes valued appropriately?	1	1	1	1	1	1	1	1
14. Is an appropriate incremental analysis of costs and outcomes of alternatives performed?	0	1	0.5	1	0	0.5	0	1
15. Are all future costs and outcomes discounted appropriately?	0.5	0	1	0	0	0	0	0
16. Are all important variables, whose values are uncertain, subjected to sensitivity analysis?	0	1	0.5	1	0.5	0.5	0	0
17. Do the conclusions follow from the data reported?	1	1	1	0.5	1	1	1	1
18. Does the study discuss the generalizability of the results to other settings and groups?	0	0	0.5	0	1	0	0	1
19. Does the article indicate that there is no potential conflict of interest?	0	1	1	1	1	1	1	1
20. Are ethical and distributional issues discussed appropriately?	0	0	NA ^a	1	1	0	1	1
Score (%)	69	83	72	71	77	76	68	76

Note. NA = Not applicable.

^a Ethical considerations were not applicable, since this study concerns a MBEE.

line with our findings regarding non-pharmacological interventions. Combining their findings with results from the current review, it can be concluded that both pharmacological interventions and psychological interventions might be cost-effective compared to no treatment.

However, specific conclusion about the cost-effectiveness between psychological and pharmacological treatment cannot be drawn. Although a direct comparison of psychological and pharmacological interventions would be difficult to research in acute phases, future

Table 7
Quality assessment of included COIs.

Item	First author									
	Broder	Cloutier	Corell	Degli Esposti	Ekman	Mennini	Pan	Parker	Somaiya	Wu
1. Is the study objective defined and were hypotheses given?	1	1	1	1	1	1	1	1	1	1
2. Are clear and objective inclusion and exclusion criteria defined?	1	1	1	1	0.5	1	1	1	1	1
3. Are the objective diagnostic criteria reported used to identify eligible participants?	1	1	1	1	1	1	1	1	1	1
4. Does that study analyze costs that accrued from a particular disease?	1	1	1	1	1	1	1	1	1	1
5. Does the study include a non-diseased control group to calculate excess cost or are the costs restricted to the disease of interest?	0	1	0	0	0	0	1	0	0	0
6. Is the currency in which the costs are reported uncontroversial?	1	1	1	1	1	1	1	1	1	1
7. Are all costs valued at the price level of a stated base year (and inflated if necessary)?	1	1	1	0	1	0	1	1	0	0
8. Are the costs analyzed from the perspective of a patient, a payer or the society and was the perspective reported?	0	1	0	0	1	0	1	0	0	0
9. Does the study estimate costs from the utilization of different kinds of health care services?	1	1	0.5	1	1	0	1	1	1	1
10. Is the source of information on healthcare utilization reported?	1	1	1	1	1	1	1	1	1	1
11. If data on healthcare utilization is reported, does the study report the source of unit costs?	0	1	1	1	1	0	0	1	0	0
12. If costs are estimated for a period longer than one year, are the future costs and effects discounted and is the discount rate given?	0	1	0	0	0	0	0	0	NA	0
13. Is the proportion of missing data reported and is the imputation method described?	NA	NA	NA	NA	NA	0	0	0	0	NA
14. Are the statistical methods described and appropriate regarding the characteristics of cost data?	1	0	1	0	1	0	0	1	1	1
15. Are all relevant parameters subjected to sensitivity analyses?	1	1	0	0	0	0	0	0	0	0
16. Is the sample size of each group reported?	1	1	1	1	1	1	1	1	1	1
17. Are the characteristics of the sample described?	1	1	1	1	1	1	1	1	1	1
18. Are the cost estimated presented as arithmetic means?	1	1	1	1	1	1	1	1	1	1
19. Are the standard deviations of cost estimates reported?	0	0	0	0	1	0	1	0	1	1
20. Are the results discussed in relation to other studies on the same topic?	1	1	1	1	1	0	1	1	1	1
21. Are the limitations (particular in calculation of costs) discussed in detail?	1	1	1	1	1	0	1	1	1	1
22. Do the conclusion allow for the uncertainty inherent to the results?	0.5	0.5	0.5	0.5	1	0	1	0	0.5	1
Score (%)	74	88	71	64	83	41	77	68	69	71

Note. NA = Not applicable.

research might address this question for example in maintenance phases of the disorder.

It is notable that all included EEs in the current review used a time horizon of one year or longer to estimate the cost-effectiveness of their intervention. This allows cost-effectiveness to be estimated over a substantial period of time. In prior reviews, for example on EEs in anxiety disorders (Ophuis et al., 2017), the percentage of studies using an appropriate time horizon of at least one year was substantially smaller. The average study quality was 74%, which is comparable to a prior review on EEs in anxiety disorders (Ophuis et al., 2017) and suggests that studies adhered to most of the quality criteria as outlined by the CHEC. However, most studies lacked discounting and a clear discussion of the generalizability of the findings. Therefore, we encourage future research to properly discount the costs and discuss the generalizability of their results.

In total, ten COIs were included in the current review. We found a wide range of direct costs (\$881–\$27,617) and of indirect cost estimates per capita per year (\$1568–\$116,062). These findings coincide with earlier reviews on this topic, which also identified a wide range of cost estimates and heterogeneity in characteristics of the studies (Jin and McCrone, 2015; Kleine-Budde et al., 2014). Compared to the findings of the review by Kleine-Budde et al. (2014), direct cost estimates per capita were relatively comparable for most studies. It is notable that only four out of 27 studies assessed indirect costs per capita in the prior review. Of these four studies, conducted in the US and the Netherlands, indirect cost estimates were considerably lower compared to findings in our review. When comparing our findings regarding COIs with the review by Jin and McCrone (2015), a similar picture emerges. Direct costs identified were comparable, but the authors also note that there has been inconsistency in the way the studies were conducted and limitations in their design. Similar to the review by Kleine-Budde et al. (2014), relatively few studies reported indirect costs. Since five out of nine studies in the current review reported indirect costs, this suggests that the number of studies reporting indirect costs has increased. In our study, the lowest costs were estimated by Somaiya et al. (2014), which might be attributed to the fact that this study was carried out in India, reflecting a different healthcare system compared to other included COIs. Another possible explanation for the wide range of costs might be that some studies assessed costs more comprehensively than others. For example, while some studies assessed outpatient, inpatient, drugs and other costs (e.g. Parker et al., 2013), some studies merely assessed hospitalizations and drugs as direct costs (e.g. Correll et al., 2017). Also, indirect costs were estimated in different detail. Similar to the findings regarding EEs, the heterogeneity in outcomes, specific target group (BDI or BDII), general characteristics, such as country and data source, makes it difficult to compare the results of the included COIs.

One study included in this review estimated the national total costs of BDI in the United States (Cloutier et al., 2018). They estimated the costs at around \$213 billion per year and concluded that BDI leads to 2.5 times higher costs compared to a control population. These findings are higher than in a prior study by Dilsaver (2011), in which the total costs for BDI were estimated at approximately \$60 billion dollar in 2009 in the US. Cloutier et al. (2018) explain this discrepancy by the fact that the study by Dilsaver (2011) used data and assumptions from a study from 1995 (Wyatt and Henter, 1995), not taking into account any of the changes in the clinical management and classifications since then, which might be an explanation for the discrepancy in costs reported in those two studies.

In general, we could identify four additional studies investigating the cost-effectiveness of non-pharmacological interventions in BD since a prior review in this field has been undertaken (Abdul Pari et al., 2014). Also, we could identify ten additional COIs since the prior reviews have been conducted (Jin and McCrone, 2015;

Kleine-Budde et al., 2014). This suggests that research has been conducted in this research field in the past years. However, the methodology of the studies remained heterogenous, which is in line with the earlier reviews. Especially for EEs, the evidence-base remains relatively small. Due to the lack of published studies including EEs of non-pharmacological interventions for BD interpretation of the findings should be done carefully. Our findings suggest that, for example, cognitive behavioral therapy, structured group psychoeducation or a joint crisis plan might be (cost)-effective treatment alternatives that might improve clinical outcomes and also lead to lower costs. However, considering that the eight included EEs only cover a small range of psychological treatment alternatives and revealed high heterogeneity in study characteristics, it is difficult to prioritize interventions and provide general advice for policy makers on which intervention they should choose. This heterogeneity in outcomes and study characteristics also makes it difficult to pool the results. In this context, it is also notable that the cost-effectiveness of interventions based on more novel developments in clinical psychology have not been conducted, such as third-wave cognitive behavioral therapies or recovery-based approaches (Hayes, 2004; Jones et al., 2012, 2015; Rashid, 2015). Although recently published study protocols are promising (e.g. Hanssen et al., 2019; Kraiss et al., 2018), there remains a lack of evidence in this research domain.

4.1. Strengths and limitations

The current study has several strengths. One strength is that we followed the PRISMA-guidelines (Moher et al., 2015), currently reflecting the golden standard for conducting systematic reviews. Moreover, we followed rigorous guidelines for the preparation of our review (Wijnen et al., 2016) and conducted a comprehensive quality assessment (Evers et al., 2005; Stuhldreher et al., 2012).

Our study also has a number of limitations. First, for both COIs and EEs, a high heterogeneity was found for general and methodological characteristics. Therefore, the results are difficult to compare, and no attempt has been made to pool the results. In line with this, all EEs, apart from the study by Chisholm et al. (2005), and most COIs were conducted in western countries, which also limits the generalizability of the results outside western countries. However, the present review still provides a valuable aggregation of the existing evidence in this research field. Second, we merely included COIs explicitly describing the costs related with BD, but not studies that examined health care utilization only and also not government or institutional reports or other gray literature, which might have helped to better understand the burden associated with BD. We also focused on EE literature only, that might have led to the exclusion of studies examining the effect of intervention on, for example, bed days or emergency department use. Third, due to the descriptive nature of this review, we could not check for the presence of publication bias. Since positive results are more likely to be published, the presence of publication bias (especially in EEs) cannot be excluded. Fourth, our search strategy did not contain an extensive list of terms related to COIs (e.g. burden, economic burden or expenditure) and we therefore might have missed studies reporting cost-of-illness in BD (Higgins et al., 2019). Also, other sources of health economic studies were not included in the search (e.g. the European Network of Health Economic Evaluation Databases), although also including them in the search might have led to the identification of additional studies.

4.2. Implications

Several implications and recommendations arise from the current findings. A relatively low number of studies could be identified for EEs. This shows that the evidence in the field of economic evaluations in BD, specifically for non-pharmacological interventions, is sparse. We

therefore encourage future research to investigate the cost-effectiveness of non-pharmacological interventions for BD. Although the quality of the included EEs was comparable to a prior review in anxiety disorders (Ophuis et al., 2017), we still found a high variability in study quality and also in which sections of the quality assessments were conducted properly. Conducting high quality studies improves the validity of research and we therefore encourage future research to take quality assessments, for example the CHEC (Evers et al., 2005), into account when conducting research on cost-effectiveness. This would increase standardization of methodology across studies and thereby making them less heterogeneous. The study by Camacho et al. (2017) can be highlighted as positive example, since it had the highest quality according to our rating. This study can thus be seen as a valid example for future research.

Moreover, we recommend that future research should clearly mention their perspective. In this context, a societal perspective is desirable since indirect costs (e.g. productivity loss) caused by BD are substantial and should therefore not be ignored. However, whether a healthcare or societal perspective should be chosen always depends on the context of the study and the decision-makers involved.

We also encourage future studies to use quality of life measures, for example the EQ-5D or SF-36 and report ICERs in relation to these measures. This would make the results more comparable across different studies and conditions, especially because WTP thresholds are available for QALYs, supporting decision making processes. When using the EQ-5D however, one should keep in mind that the sensitivity to change might be limited, specifically when examining effects of intervention, and may want to use additional, more elaborative, quality of life instruments. Finally, one should be aware that, as with RCTs, EEs are prone to several biases which may threaten internal or external validity. A threat to the internal validity would be the exclusion of relevant cost parameters or an insensitive outcome questionnaire. The external validity may be threatened by differences across populations but also across different (health care) payment / reimbursement systems. In agreement with Abdul Pari et al. (2014) we emphasize the importance of transparent description of comparators, a broad societal perspective (including all relevant costs and effects), use of a suitable multi-attribute utility instrument, and a thorough description for all statistical issues (e.g. imputation of missing data or indexing).

Conclusion

The current study provides a comprehensive overview of the literature on EEs of non-pharmacological interventions and COIs in BD. In all EEs the interventions resulted in improved clinical outcomes and in most cases also in less total costs. This suggests that non-pharmacological interventions might be cost-effective treatment alternatives for people with BD. The fact that all interventions led to improvements in clinical outcomes also indicates that they might be a valuable adjunct to TAU and might be considered by clinicians as addition to pharmacological treatments. However, for both EEs and COIs, studies were identified with a vast variety of general and methodological characteristics and outcomes. This makes it difficult to compare the results across studies. Therefore, we encourage future research to use standardized methodology, aim to widen the body of knowledge in this research domain and consider to investigate the cost-effectiveness of more novel psychological treatment alternatives for BD.

Contributors

JL and BW had the initial idea for the review and designed the review together with JTK. JTK and BW conducted the systematic search, screened and selected the studies and conducted the quality assessment. JTK extracted the data from the studies and drafted the an initial version of the manuscript. BW, RWK, ETB and JL supported interpretation of the data. All authors reviewed and approved the final manuscript.

Declaration of Competing Interest

None of the authors have any conflicts of interest to declare.

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Supplementary materials

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