

Economic evidence for the clinical management of major depressive disorder: a systematic review and quality appraisal of economic evaluations alongside randomised controlled trials

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Aims. The aim of this systematic review of economic evaluations alongside randomised controlled trials (RCTs) was to provide a comprehensive overview of the evidence concerning cost-effectiveness analyses of common treatment options for major depression.

Methods. An existing database was used to identify studies reporting cost-effectiveness results from RCTs. This database has been developed by a systematic literature search in the bibliographic databases of PubMed, PsychINFO, Embase and Cochrane library from database inception to December 2014. We evaluated the quality of economic evaluations using a 10-item short version of the Drummond checklist. Results were synthesised narratively. The risk of bias of the included RCTs was assessed, based on the Cochrane risk of bias assessment tool.

Results. Fourteen RCTs were included from the 5580 articles screened on titles and abstracts. The methodological quality of the health economic evaluations was relatively high and the majority of the included RCTs had low risk of bias in most of Cochrane items except blinding of participants and personnel. Cognitive behavioural therapy was examined in seven trials as part of a variety of treatment protocols and seems cost-effective compared with pharmacotherapy in the long-term. However cost-effectiveness results for the combination of psychotherapy with pharmacotherapy are conflicting and should be interpreted with caution due to limited comparability between the examined trials. For several treatments, only a single economic evaluation was reported as part of a clinical trial. This was the case for comparisons between different classes of antidepressants, for several types of psychotherapy (behavioural activation, occupational therapy, interpersonal psychotherapy, short-term psychotherapy, psychodynamic psychotherapy, rational emotive behavioural therapy, solution focused therapy), and for transcranial magnetic stimulation *v.* electroconvulsive therapy. The limited evidence base for these interventions means generalisations, based on economic evaluation alongside clinical trials, cannot easily be made.

Conclusions. There is some economic evidence underpinning many of the common treatment options for major depression. Wide variability was observed in study outcomes, probably attributable to differences in population, interventions or follow-up periods. For many interventions, only a single economic evaluation alongside clinical trials was identified. Thus, significant economic evidence gaps remain in the area of major depressive disorder.

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Introduction

Major depressive disorder (MDD) is one of the most common conditions worldwide and is associated with high risk of mortality and morbidity. Lifetime depression prevalence ranges from 3% in Japan to 17% in the USA, while the majority of countries fall within the range of 8–12% (Andrade *et al.* 2003; Kessler *et al.* 2005). MDD has severe economic consequences for

individuals and society arising out of increased health-care utilisation, caregiver burden and labour force productivity losses (Cuijpers *et al.* 2012; Lepine & Briley, 2011). Furthermore, MDD is a major cause of disease burden throughout the world and is one of the priority conditions examined under the Research Agenda for Health Economic Evaluation (RAHEE) project implemented by the World Health Organization (WHO) (Tordrup & Bertollini, 2014; Tordrup *et al.* 2015). The objective of the RAHEE project is to identify health economic research priorities based on availability of economic evidence for selected conditions. The present review arose as part of this project.

There is ample evidence for the therapeutic effectiveness of several forms of therapy in treating MDD. For instance, several systematic reviews have examined the effects of pharmacotherapy and psychotherapy and have demonstrated that both therapeutic options are effective in treating depressive disorders in both the short and the long term (Cuijpers *et al.* 2008a, b, 2010; Cuijpers *et al.* 2009; Karyotaki *et al.* 2016). Moreover, research has shown that other treatment alternatives, such as transcranial magnetic stimulation (rTMS), can be effective in treating the symptoms of MDD (Lee *et al.* 2012). Considering the rising health care costs associated with the treatment of MDD, it is important to further examine the cost-effectiveness of common treatment options, however only a few systematic reviews have touched upon this.

Grochtdreis *et al.* (2015) performed a systematic review of studies examining the cost-effectiveness of collaborative care compared with usual care in patients with depression. The authors found studies were inconsistent in their quality and results, and conclusions were ambiguous depending on willingness to pay. Incremental cost per Quality Adjusted Life Year (QALY) ranged from dominance to US\$ 874 562 Purchasing Power Parity (PPP) (Grochtdreis *et al.* 2015). Furthermore, Rabheru (2012) searched for cost-effectiveness evidence of maintenance electroconvulsive therapy (M-ECT) in patients who had responded to ECT but found no trials reporting cost-effectiveness in a maintenance setting since 1997. In the same year, Lee *et al.* (2012) published a review on the clinical and cost-effectiveness evidence of transcranial magnetic stimulation (TMS) in the treatment of resistant MDD. The authors examined four studies, which were in disagreement on the cost-effectiveness of TMS *v.* ECT. To the best of our knowledge, there are no recent (carried out in the past 10 years) systematic reviews on the cost-effectiveness of psychotherapy or the combination of pharmacotherapy and psychotherapy in patients with MDD.

Given the limited evidence on the cost-effectiveness of treatments for major depression in existing reviews,

the present systematic review of randomised controlled trials (RCTs) seeks to provide a comprehensive overview of the cost-effectiveness of the most common treatment options for MDD. We aimed to identify evidence gaps, as well as highlight the methodological challenges inherent in synthesising the available evidence.

Methods

Search strategy

We screened an existing database that was developed to identify all RCTs on cost-effectiveness outcomes in the treatment of common mental disorders (depression and anxiety disorders). This database has been used in a recently submitted paper, reporting a global return on investment analysis on mental health for depression and anxiety disorders (Chisholm *et al.* 2016). We built the database employing a systematic literature search in PubMed, PsychINFO, Embase and Cochrane library from database inception to December 2014. In these searches, various terms covering economic evaluation and common mental disorders were used in different combinations, using both index and free terms. A full search string for PubMed is provided in Appendix A. In total, 6347 references are included in the database and were examined for eligibility in the present review (2203 from PubMed, 321 from PsychINFO, 2046 from Embase and 1777 from the Cochrane library). In addition to this database, we conducted a separate search in PubMed for verification purposes. Resulting titles and abstracts were screened for eligibility and full texts were retrieved and examined for inclusion. Flow chart 1 shows the study selection process.

Inclusion criteria

Participants: individuals with moderate or severe MDD (as defined in individual studies). No age or country restriction was applied.

Intervention: treatment options for MDD – psychotherapy, pharmacotherapy, combined psychotherapy with pharmacotherapy, physical treatments (ECT and transcranial magnetic stimulation).

Comparison: Control comparison conditions (treatment as usual (TAU) or pill placebo); or active comparison conditions (common treatment options for MDD, as described above).

Outcomes: We included full economic evaluations reporting outcomes on cost-benefit, cost-effectiveness and cost-utility. We also considered cost-minimisation studies of interventions with identical effectiveness (a special case of cost-effectiveness), and cost-

consequence studies where one intervention was less costly and more effective (equivalent to a dominant intervention in a cost-effectiveness study).

Study design: RCTs

Exclusion criteria

Studies were excluded if they did not integrate cost- and effectiveness analyses, e.g. cost-consequence or cost-minimisation studies, except as specified above. Moreover, we excluded collaborative care interventions since this topic has already been covered by a recent systematic review (Grochtdreis *et al.* 2015). Modelling studies were excluded due to methodological differences compared with RCT-based economic evaluations. Further, studies were excluded if the language was not English. Finally, we did not search for unpublished data because it was out of the scope of the present systematic review.

Quality assessment of economic evaluations

We assessed the methodological quality of the economic evaluations based on the Drummond 10-item checklist (Drummond, 2005). For each of the 10 items, studies were scored as 'yes', 'no', 'cannot tell' or 'not applicable', the latter being used for items that were not applicable to certain studies. One author (C.B.) completed the checklist and another reviewed it (E.K.). Disagreement was resolved through discussion.

Risk of bias assessment

Furthermore, we assessed the validity of the included studies according to the Cochrane Collaboration's Risk of bias assessment tool (Higgins & Altman, 2011; Higgins & Green, 2011). This tool examines the following domains of possible bias: (a) selection bias: systematic differences between groups in baseline characteristics due to inadequate random sequence generation or allocation concealment, (b) performance bias: systematic differences between the groups in the treatment provided due to the absence of blinding of participants and personnel, (c) detection bias: systematic differences between the groups in how outcomes were assessed and determined due to the absence of blinding of outcome assessors, (d) attrition bias: systematic differences between groups in study dropout (incomplete outcome data), (e) reporting bias: systematic differences between reported and unreported results (selective reporting), (f) other bias: bias due to other issues (Higgins and Altman, 2011; Higgins & Green, 2011).

Data extraction and management

Two authors (E.K. and D.T.) extracted independently the following data: authors' names, study setting, major depression diagnosis status, type and duration of the therapy, type of control groups and economic perspective and outcomes. This information is summarised in Table 1. Data from the included studies are combined narratively and are presented in the following section. This narrative description presents the main characteristics of the economic evidence. All costs were inflated to 2014 US\$ PPP using OECD and World Bank country specific Consumer Price Index statistics and currency conversion rates (OECD, 2016a, b; WB, 2015). 2014 US\$ PPP values are given throughout the paper, with original currencies and values in [brackets].

Results – data synthesis

Study characteristics

Across the 14 included RCTs (Fig. 1), outpatients were recruited mainly through clinical samples ($n=12$), while two studies recruited participants through both community and clinical referrals. The included studies were conducted in six different countries: Finland ($n=1$), Romania ($n=1$), the Netherlands ($n=3$), Japan ($n=1$), the UK ($n=5$) and the USA ($n=3$). Time horizons for economic outcomes were 2–36 months. The included RCTs examined eight types of psychotherapeutic interventions: behavioural activation (BA; $n=1$ study), cognitive behavioural therapy (CBT; $n=7$ studies), interpersonal psychotherapy (IPT; $n=1$ study), occupational therapy (OT; $n=1$ study), psychodynamic psychotherapy (PDT; $n=1$ study), psychoeducation (PEP; $n=2$ studies), rational emotive behavioural therapy (REBT; $n=1$ study) and solution focused therapy (SFT; $n=1$ study), while the included pharmacotherapeutic trials examined mostly antidepressants from the cluster of selective serotonin reuptake inhibitors (SSRIs). Finally, one trial examined the effects of TMS compared with ECT. Studies targeting absolute efficacy used TAU or pill placebo as control comparison condition ($n=8$ studies). Table 1 presents a summary of study characteristics.

Quality assessment of economic evaluations

The overall methodological quality of the economic evaluations was relatively good, but varied among studies. The mean relative value of the methodological quality criteria fulfilled was 9.7 out of 12 (see Table 2). The minimum relative value of criteria fulfilled was 8 (Knapp *et al.* 2008) and the maximum value of criteria

Table 1. Study characteristics

Study	Recruitment	Diagnosis	Interventions	N patients per intervention	FU (months)	Results on cost-effectiveness outcomes	Country	Perspective
Moderate major depressive disorder								
<i>Psychotherapeutic interventions v. other types of psychotherapeutic interventions or control groups</i>								
Schene <i>et al.</i> (2007)	Clinical setting	Moderate MDD (DSM-IV)	<ul style="list-style-type: none"> • OT and TAU • TAU 	<ul style="list-style-type: none"> • 30 • 32 	42	<p>Compared with TAU:</p> <ul style="list-style-type: none"> • OT and TAU did not improve depression outcomes • OT and TAU had a 75.5% probability of being cost-effective (higher net benefit at an average wage value of US\$ 44.74 [US\$ 36.88]) compared with TAU alone • OT and TAU resulted in more hours worked in the first 18 months 	NL	Societal
Shimodera <i>et al.</i> (2012)	Clinical setting	Moderate MDD (DSM-IV)	<ul style="list-style-type: none"> • Maintenance TAU and family PEP • Maintenance TAU 	<ul style="list-style-type: none"> • 24 • 30 	9	<ul style="list-style-type: none"> • The total costs were US\$ 1897 [US\$ 1842] for maintenance TAU and family PEP compared with US\$ 2717 [US\$ 2638] for maintenance TAU group. Differences between groups were not significant ($p = 0.509$) • Maintenance TAU and family PEP had a 90% probability of being cost-effective compared with maintenance TAU alone if the decision maker is willing to pay US\$ 21 [US\$ 20] for 1 additional day free of relapse 	JP	Health system
Stant <i>et al.</i> (2009)	Clinical setting	Moderate MDD (DSM-IV)	<ul style="list-style-type: none"> • CBT-enhanced PEP • PEP • Psychiatrist-enhanced PEP • TAU 	<ul style="list-style-type: none"> • 36 • 97 • 33 • 61 	36	<ul style="list-style-type: none"> • The mean total intervention costs were: <ul style="list-style-type: none"> ◦ CBT-enhanced PEP: US\$ 12 506 [€ 9254] ◦ PEP: US\$ 13 265 [€ 9816] ◦ Psychiatrist-enhanced PEP: US\$ 13 303 [€ 9844] ◦ TAU: US\$ 11 081 [€ 8200] • No significant differences were observed in QALY gains • Up to a willingness-to-pay of US\$ 405 [€ 300] for 1 additional depression free day, TAU was most cost-effective. Above this 	NL	Societal

Table 1. Continued

Study	Recruitment	Diagnosis	Interventions	N patients per intervention	FU (months)	Results on cost-effectiveness outcomes	Country	Perspective
Ekers <i>et al.</i> (2011)	Clinical setting	Moderate Depression (ICD-10)	<ul style="list-style-type: none"> • BA • TAU 	<ul style="list-style-type: none"> • 24 • 23 	3	<p>threshold, CBT-enhanced PEP was most cost-effective closely followed by psychiatrist-enhanced PEP</p> <ul style="list-style-type: none"> • BA yielded significantly higher QALY gain of 0.20 (95% CI 0.01 to 0.39, $p = 0.042$) • ICER of US\$ 8301 [£ 5756] per QALY for BA at 3 months • 97% probability that BA is cost-effective compared to TAU at a threshold value of US\$ 28 843 [£ 20 000] 	UK	Health system
Maljanen <i>et al.</i> (2012)	Clinical setting	Moderate MDD (DSM-IV)	<ul style="list-style-type: none"> • S-PDT • S-SFT 	<ul style="list-style-type: none"> • 101 • 97 	12	<p>No significant differences in costs or outcomes were observed</p> <ul style="list-style-type: none"> • The mean total direct costs in the S-PDT group (US\$ 1946 [€ 1791]) were 16% lower than the mean total direct costs in the S-SFT group (US\$ 2322 [€ 2137]). Differences between groups were not significant ($p > 0.05$) • Symptoms were significantly reduced in both interventions, but with no significant differences between the two 	FI	Societal
Bosmans <i>et al.</i> (2007)	Clinical setting	Moderate MDD (PRIME-MD)	<ul style="list-style-type: none"> • IPT • TAU 	<ul style="list-style-type: none"> • 69 • 74 	12	<p>No significant differences in mean total cost or remission were observed</p> <ul style="list-style-type: none"> • IPT group experienced 6% less remission (MADRS) compared with TAU at 12 months • Total costs (direct and indirect) were on average non-significantly higher (US\$ 1039 [€ 769]) for IPT • This resulted in a negative ICER of US\$ -177 [€ -131] for IPT compared with TAU, 	NL	Societal

Continued

Table 1. Continued

Study	Recruitment	Diagnosis	Interventions	N patients per intervention	FU (months)	Results on cost-effectiveness outcomes	Country	Perspective
						with cost-effect pairs mostly distributed near the origin and in all four quadrants of the cost-effectiveness plane		
<i>Combinations of and comparisons between psychotherapeutic interventions and pharmacotherapy</i>								
Domino et al. (2008); Domino et al. (2009)	Clinical setting	Moderate MDD (DSM-IV)	<ul style="list-style-type: none"> • CBT • ADM (SSRI) • CBT & ADM (SSRI) • Placebo 	<ul style="list-style-type: none"> • 111 • 109 • 107 • 112 	3, 9	<ul style="list-style-type: none"> • ICER's over placebo at 12 weeks: <ul style="list-style-type: none"> ◦ CBT: US\$ 11 866 556 [US\$ 9 210 622] ◦ ADM: US\$ 30 582 [US\$ 23 737] ◦ CBT & ADM: US\$ 158 652 [US\$ 123 143] • CBT & ADM had more than 90% probability (at a threshold of US\$ 128 836 [US\$ 100 000]) of being more cost-effective than ADM alone at 36 weeks • CBT is not likely to be more cost-effective than ADM alone at 36 weeks 	US	Societal
Lynch et al. (2011)	Clinical setting	Moderate MDD (DSM-IV)	<ul style="list-style-type: none"> • SSRI • SSRI and CBT 	<ul style="list-style-type: none"> • 168 • 166 	6	Combined treatment resulted in 8.3 additional depression free days ($p = 0.03$) ICERs: <ul style="list-style-type: none"> • US\$ 221 [US\$ 188] (95%CI US\$ -26 [US\$ -22] to US\$ 1896 [US\$ 1613]) per depression free day • US\$ 167 [US\$ 142] (95%CI US\$ -16 [US\$ -14] to US\$ 2973 [US\$ 2529]) per depression improvement day • US\$ 92 812 [US\$ 78 948] (95%CI US\$ -10 840 [US\$ -9221] to US\$ 796 418 [US\$ 677 448]) per QALY • 61% probability that combined treatment is cost-effective at a willingness to pay of US\$ 117 561/QALY [US\$ 100 000/QALY] 	US	Societal
Byford et al. (2007)	Clinical setting	Moderate MDD (DSM-IV)	<ul style="list-style-type: none"> • CBT and SSRIs • SSRIs 	<ul style="list-style-type: none"> • 105 • 103 	7	No significant differences in cost or QALY effects were observed.	UK	Societal

Table 1. Continued

Study	Recruitment	Diagnosis	Interventions	N patients per intervention	FU (months)	Results on cost-effectiveness outcomes	Country	Perspective
Sava <i>et al.</i> (2009)	Community and Clinical setting	Moderate MDD (DSM-IV)	<ul style="list-style-type: none"> • CBT • REBT • SSRI 	<ul style="list-style-type: none"> • 56 • 57 • 57 	6	<ul style="list-style-type: none"> • For CBT and SSRI compared with SSRI alone, the ICER is US\$ 4687 [£ 2873] per unit increase in HoNOSCA (higher scores indicate worsening of symptoms) • There is only 25% probability that CBT and SSRI is more cost-effective than SSRI alone at a threshold value of US\$ 81 577 [£50 000] • Both CBT and REBT were more cost-effective per depression free day gained per month compared with SSRI: <ul style="list-style-type: none"> ◦ CBT median: US\$ 70.63 [US\$ 26.44] ◦ REBT median: US\$ 63.50 [US\$ 23.77] ◦ SSRI median: US\$ 93.31 [US\$ 34.93] • Both CBT and REBT exhibited better cost-utility compared with SSRIs <ul style="list-style-type: none"> ◦ CBT: US\$ 4375 [US\$ 1638] ◦ REBT: US\$ 4632 [US\$ 1734] ◦ SSRI: US\$ 6109 [US\$ 2287] 	RO	Societal
Revicki <i>et al.</i> (2005)	Clinical setting	Moderate MDD (DSM-IV)	<ul style="list-style-type: none"> • SSRI • CBT • TAU 	<ul style="list-style-type: none"> • 88 • 90 • 89 	12	<ul style="list-style-type: none"> • SSRI resulted in more depression-free days (mean, 39.7; 95% CI, 12.9–66.5) than the CBT group (mean, 25.80; 95% CI, 0.04–51.50) compared with TAU • The outpatient and medication costs were US\$ 32.49 [US\$ 24.65] per additional depression-free day for pharmacotherapy and US\$ 35.64 [US\$ 27.04] for CBT <i>v.</i> TAU. Total cost (incl. inpatient) was approximately double • ICER's including total costs (outpatient + inpatient + medication) were US\$ 39 570/QALY [US\$ 30 023/QALY] for 	US	Health system

Continued

Table 1. Continued

Study	Recruitment	Diagnosis	Interventions	N patients per intervention	FU (months)	Results on cost-effectiveness outcomes	Country	Perspective
						pharmacotherapy and US\$ 49 514 [US\$ 37 568] for CBT		
<i>Direct comparison between antidepressant agents</i>								
Wade et al. (2008)	Clinical setting	Moderate MDD (DSM-IV)	<ul style="list-style-type: none"> • SSRIs • SNRIs 	<ul style="list-style-type: none"> • 144 • 151 	6	<ul style="list-style-type: none"> • Total costs were significantly lower ($p < 0.05$) for the SSRI (US\$ 294 [£ 188]) compared with the SNRI (US\$ 522 [£ 334]) • The SSRI was also more effective in terms of SDS score reduction, with a difference of 2.4 (95% CI 0.4, 4.1) against the SNRI • Mean sick leave duration was significantly shorter with the SSRI (30.7 days <i>v.</i> 62.2 days; $p = 0.007$) 	UK	Societal
<i>Severe and refractory major depressive disorder</i>								
<i>ECT and rTMS</i>								
Knapp et al. (2008)	Clinical setting	Severe MDD (diagnostic interview not specified)	<ul style="list-style-type: none"> • ECT • rTMS 	<ul style="list-style-type: none"> • 22 • 24 	7	<ul style="list-style-type: none"> • ECT was initially more effective than rTMS with 59% <i>v.</i> 17% of patients achieving remission, but no differences were observed after 6 months follow-up ($p = 0.93$). Total costs were lower for ECT than for rTMS ($p = 0.04$) • At a willingness-to-pay of US\$ 826 [£ 500] per unit of symptom improvement (HSRD), there is a 98% probability rTMS is cost-effective compared with ECT. However at a willingness-to-pay of zero per unit of improvement, the probability is 24%. • At a willingness-to-pay of US\$ 49 583 [£ 30 000] per QALY, the probability of rTMS being cost-effective compared with ECT is less than 20% 	UK	Both
<i>Addition of CBT</i>								
Hollingshurst et al. (2014)	Clinical setting	Treatment resistant MDD (ICD-10)	<ul style="list-style-type: none"> • CBT & TAU • TAU 	<ul style="list-style-type: none"> • 234 • 235 	12	<ul style="list-style-type: none"> • CBT & TAU resulted in higher QALY gains of 0.057 (95% CI 0.015–0.099; $p < 0.05$) corresponding to 21 days a year of good health 	UK	Health system

Table 1. Continued

Study	Recruitment	Diagnosis	Interventions	N patients per intervention	FU (months)	Results on cost-effectiveness outcomes	Country	Perspective
						<ul style="list-style-type: none"> The CBT & TAU group compared with TAU incurred a cost per QALY of US\$ 20 817 [£14 911], corresponding to a probability of 74% that the intervention is cost-effective at a threshold value of US\$ 27 922 [£ 20 000] 		

ADM, antidepressant medication; BA, behavioural activation; CI, confidence intervals; DSM, diagnostic and statistical manual of mental disorders; ECT, electroconvulsive therapy; FI, Finland; FU, follow up; HoNOSCA, health of the Nation Outcome Scale for children and adolescents; ICD, international classification of diseases; ICER, incremental cost effectiveness ratio; IPT, interpersonal psychotherapy; MADRS, Montgomery Asberg Depression Scale; MDD, major depressive disorder; *n*, number; OT, occupational therapy; PEP, psychoeducation programme; PRIME-MD, Primary care evaluation of mental disorders; QALY, quality adjusted life years; REBT, rationale emotive behavioral therapy; RO, Romania; rTMS, repetitive transcranial magnetic stimulation; S-PDT, short-term psychodynamic therapy; S-SFT, short-term solution-focused therapy; S-SRI, selective serotonin reuptake inhibitors; TAU, treatment as usual WEB, psychiatric services through webcam.

met was 11 (Domino *et al.* 2008; Lynch *et al.* 2011; Maljanen *et al.* 2012; Hollinghurst *et al.* 2014). All studies included a well-defined research question, reported on the effectiveness of the programme or service concerned, identified all relevant costs and consequences accurately, and valued the cost credibly. All studies except for one (in brackets) included a comprehensive description of the competing alternatives (Wade *et al.* 2008), valued the consequences credibly (Byford *et al.* 2007), performed an incremental analysis of costs and consequences of alternatives (Knapp *et al.* 2008), and included a presentation and discussion of study results that covered all issues of concern to users (Knapp *et al.* 2008). Only three studies reported on adjusting cost and consequences for differential timing (Byford *et al.* 2007; Domino *et al.* 2008; Maljanen *et al.* 2012). Five studies did not make allowances for uncertainty in the estimation of costs (Revicki *et al.* 2005; Bosmans *et al.* 2007; Domino *et al.* 2008; Sava *et al.* 2009; Ekers *et al.* 2011). Only three studies allowed for uncertainty in the estimation of consequences (Domino *et al.* 2008; Lynch *et al.* 2011; Hollinghurst *et al.* 2014).

Risk-of-bias assessment

With regard to risk-of-bias assessment, the majority of the included trials reported an adequate random sequence generation (11/14). The allocation was concealed in 6 out of the 14 included RCTs while the remainder reported inadequate information to permit judgement. Blinding of personnel and participants was possible in only one of the included studies and incomplete outcome data were adequately addressed by 11 included RCTs. Finally the vast majority of the included trials were rated as free from selective outcome reporting bias (13/14) and other sources of bias (14/14) (Fig. 2).

Moderate major depressive disorder

Psychotherapeutic interventions v. other types of psychotherapeutic interventions or control groups

One study examined the cost-effectiveness of psychotherapeutic interventions targeting work related outcomes (e.g. productivity losses). Schene *et al.* (2007) found that adding OT to TAU did not improve depression outcomes, but did result in a significant reduction of workdays lost over 18 months. Net benefit was calculated as the 'value of work' (hourly wages multiplied by time) minus costs of the intervention. Mean net benefit was higher in the OT group with a 76% chance of being cost-effective (higher net benefit) over usual care at a median wage value of US\$ 44.74 [US\$ 36,88] per hour.

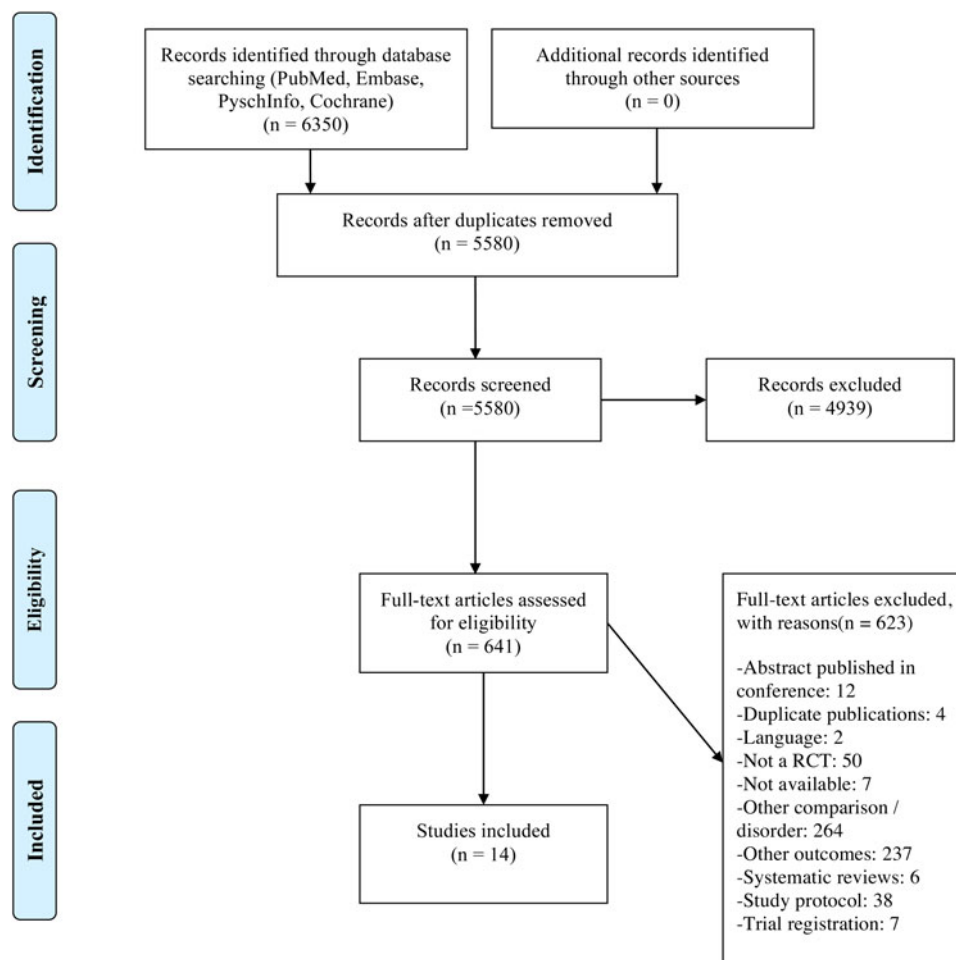


Fig. 1. PRISMA Flow chart of the studies selection process.

Two studies assessed psychoeducation targeting prevention of MDD relapse/recurrence. A Japanese study comparing family psychoeducation maintenance treatment with usual care reported significantly more relapse-free days in the maintenance treatment group. The intervention was considered cost-effective with a probability of almost 100% at a willingness-to-pay (WTP) of US\$ 31 [US\$ 30] per depression-free day. No cost-utility results were reported (Shimodera *et al.* 2012). In contrast, an individual psychoeducation prevention program (PEP) reported by Stant *et al.* (2009) in the Netherlands was more expensive and less effective in terms of depression-free days compared with TAU. If supplemented with psychiatric consultation or CBT, outcomes with PEP were slightly better than TAU, but neither combination was cost-effective. Follow-up duration was shorter in the Japanese study (9 months) than in the Dutch study (36 months).

Ekers *et al.* (2011) conducted a relatively small study ($n=47$ participants) to examine the cost-effectiveness of BA delivered by non-specialist mental health nurses compared with TAU. The authors found a significant

difference between groups in QALY's of 0.20 (95% CI, 0.01–0.39; $p=0.042$) in favour of BA and an incremental cost-utility ratio (ICUR) of US\$ 8301/QALY [£5756/QALY].

Two types of short-term psychotherapy were compared in a Finnish context (PDT and SFT). No significant differences in costs or effects were observed though PDT trended towards lower costs and greater improvements. No cost/QALY was reported (Maljanen *et al.* 2012).

Management of MDD in elderly (55+) people identified through primary care screening was assessed by one study. IPT did not result in significant clinical change compared with TAU over 12 months but did incur non-significantly higher total costs. Uncertainty around the cost-effectiveness estimate suggested that the intervention was unlikely to be cost-effective (Bosmans *et al.* 2007).

Combinations of and comparisons between psychotherapeutic interventions and pharmacotherapy

Eight trials showed conflicting results for the comparison of combination therapy (psychotherapy with

Table 2. Quality assessment with the 10-item Drummond checklist

Checklist											
1. Was a well-defined question posed in answerable form? 2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where and how often)? 3. Was the effectiveness of the programme or services established? 4. Were all the important and relevant costs (a) and consequences (b) for each alternative identified? 5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)? 6. Were the cost (a) and consequences (b) valued credibly? 7. Were costs and consequences adjusted for differential timing? 8. Was an incremental analysis of costs and consequences of alternatives performed? 9. Was allowance made for uncertainty in the estimates of costs (a) and consequences (b)? 10. Did the presentation and discussion of study results include all issues of concern to users?											
Study	1	2	3	4	5	6	7	8	9	10	
				a	b	a	b		a	b	
Bosmans <i>et al.</i> (2007)	✓	✓	✓	✓	✓	✓	✓	0	✓	x	✓
Byford <i>et al.</i> (2007)	✓	✓	✓	✓	✓	✓	0	X*	✓	x	✓
Domino <i>et al.</i> (2008); Domino <i>et al.</i> (2009)	✓	✓	✓	✓	✓	✓	✓	X*	✓	x	✓
Ekers <i>et al.</i> (2011)	✓	✓	✓	✓	✓	✓	✓	0	✓	x	✓
Hollinghurst <i>et al.</i> (2014)	✓	✓	✓	✓	✓	✓	✓	0	✓	✓	✓
Knapp <i>et al.</i> (2008)	✓	✓	✓	✓	✓	✓	✓	0	0	✓	0
Lynch <i>et al.</i> (2011)	✓	✓	✓	✓	✓	✓	✓	0	✓	✓	✓
Maljanen <i>et al.</i> (2012)	✓	✓	✓	✓	✓	✓	✓	X*	✓	✓	✓
Revicki <i>et al.</i> (2005)	✓	✓	✓	✓	✓	✓	✓	0	✓	x	✓
Sava <i>et al.</i> (2009)	✓	✓	✓	✓	✓	✓	✓	0	✓	X	✓
Schene <i>et al.</i> (2007)	✓	✓	✓	✓	✓	✓	✓	0	✓	✓	✓
Shimodera <i>et al.</i> (2012)	✓	✓	✓	✓	✓	✓	✓	0	✓	✓	✓
Stant <i>et al.</i> (2009)	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	✓
Wade <i>et al.</i> (2008)	✓	0	✓	✓	✓	✓	✓	0	✓	✓	✓

Note: yes ✓, no X, explanation is given why costs and consequences are not discounted X*, cannot tell 0.

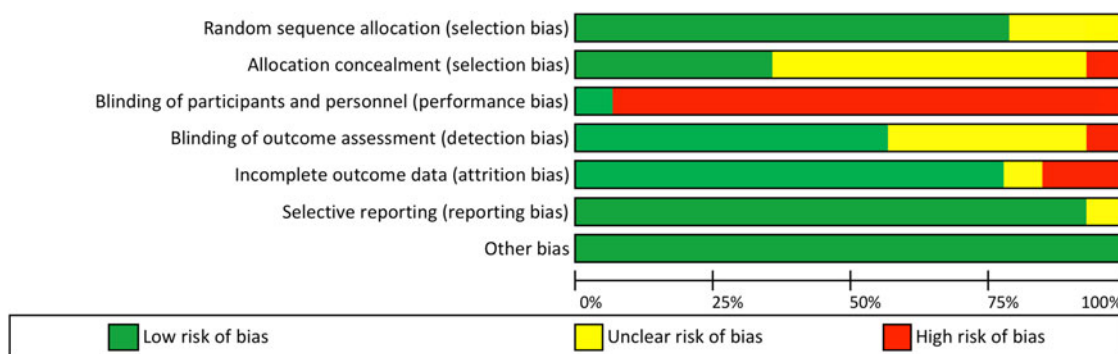


Fig. 2. Risk of bias assessment.

pharmacotherapy) with monotherapy (either pharmacotherapy or psychotherapy alone). Domino *et al.* (2008) compared CBT with fluoxetine (an SSRI) and a combination of both in a sample of American adolescents with MDD. Compared with pill placebo at 12

weeks, fluoxetine alone was more cost-effective (US\$ 30 582/QALY [US\$ 23 737/QALY]) than fluoxetine with CBT (US\$ 158 652/QALY [US\$ 123 143/QALY]). Furthermore, addition of CBT to fluoxetine was not cost-effective compared with fluoxetine alone (US\$

591 121/QALY [US\$ 458 818/QALY]) at 12 weeks. Results from the same trial indicated that the combination of fluoxetine plus CBT became more cost-effective than fluoxetine alone over a longer follow-up of 36 weeks (>90% probability at a threshold of US\$ 128 836 [US\$ 100 000]). The authors concluded combination therapy is both clinically effective and cost-effective (Domino *et al.* 2009).

Byford *et al.* (2007) studied whether CBT in addition to SSRI treatment was cost-effective in UK adolescents attending outpatient mental health clinics, who had not responded to an initial brief intervention. Compared with TAU, at 28 weeks there was no significant difference in costs or clinical outcomes though there was a trend towards higher costs and worse clinical outcomes for combination therapy. Lynch *et al.* (2011) studied CBT as an add-on to medication switch in young people with SSRI-resistant depression. Addition of CBT to medication switch was associated with higher costs but also higher gains in depression-free days at 24 weeks compared with medication switch alone (Incremental Cost Effectiveness Ratio – ICER of US\$ 221 [US\$ 188] per depression-free day or US\$ 92 812/QALY [US\$ 78 948/QALY]).

Sava *et al.* (2009) examined CBT, REBT and fluoxetine individually and followed patients for 6 months after completion of the intervention. The authors did not find significant differences between treatment groups in depression severity, depression-free days or QALYs. Due to lower costs, the psychotherapeutic interventions were more cost-effective than fluoxetine at US\$ 4375/QALY [US\$ 1638/QALY] and US\$ 4632/QALY [US\$ 1734/QALY] for CBT and REBT, respectively, against US\$ 6109/QALY [US\$ 2287/QALY] for fluoxetine (before *v.* after treatment).

Among low-income ethnic minority women with major depression in Washington DC, Revicki *et al.* (2005) compared either pharmacotherapy (paroxetine potentially followed by bupropion) or CBT with 'community' referral, consisting of education about depression and its treatment along with referral to usual providers of mental health care services in the community. At 12-month follow-up, pharmacotherapy was slightly more cost-effective than CBT (US\$ 39 570/QALY [US\$ 30 023/QALY] *v.* US\$ 49 514 [US\$ 37 568/QALY]) compared with community referral.

Direct comparison between antidepressant agents

Only one study examined differences between various antidepressant medications. Wade *et al.* (2008) examined the cost-effectiveness of escitalopram compared with duloxetine in treating patients with MDD. The authors found that treatment with duloxetine was associated with higher cost, higher mean sick leave

and higher depression scores over the 24-week study period (Wade *et al.* 2008).

Severe and refractory major depressive disorder

ECT and repetitive TMS (rTMS)

A small study of people with severe depressive episodes ($n=46$) compared rTMS with ECT. In the 6 months after treatment, total costs for ECT (treatment, services and informal care) were lower than for rTMS, and ECT was more effective (McLoughlin *et al.* 2007; Knapp *et al.* 2008).

Combined CBT plus TAU

A UK study compared addition of CBT to TAU with TAU alone in primary care patients who did not respond to medication for at least 6 weeks. Over 12 months, the costs of health and social care, out-of-pocket expenses and productivity losses did not differ between groups. However, CBT incurred an additional expense of US\$ 1270 [GBP £910] per patient and resulted in improved outcomes within ICUR of US\$ 20 817/QALY [GBP £14 911/QALY] (Hollinghurst *et al.* 2014).

Discussion

Main results

The present systematic review presents a comprehensive overview of health economic evidence for the various treatment modalities for major depression. Several economic evaluations of clinical trials have been conducted in the area of major depression, covering pharmacotherapeutic treatments as well as different types of psychotherapeutic interventions, with some studies comparing both. Only one study evaluated the cost-effectiveness of ECT and transcranial magnetic stimulation.

For moderate MDD, family psychoeducation was considered cost-effective compared with TAU (Shimodera *et al.* 2012). In contrast, Stant *et al.* (2009) found that individual psychoeducation was outperformed by TAU in clinical effectiveness and cost-effectiveness. The difference in the results of psychoeducation could be attributed to differences in treatment format (family *v.* individual) or to differences in follow-up duration (9 *v.* 36 months). Two studies examined CBT alone, but using different methodological approaches. Using a pre-post analysis, Sava *et al.* (2009) found CBT and REBT were more cost-effective than fluoxetine on account of their relative input prices. In contrast, Revicki *et al.* (2005) found CBT was less cost-effective than pharmacotherapy,

compared with community referral. However it is clear that both study design, population and setting (Romania *v.* USA) are likely to play a major role in these differences between findings.

A relatively broad literature examined the effects of monotherapy with SSRIs and CBT, or the combination of both in patients with moderate MDD. Domino *et al.* reported the combination of CBT with SSRIs was clinically effective and cost-effective compared with monotherapy, but only in the longer term (Domino *et al.* 2008, 2009). Lynch *et al.* (2011) showed higher clinical gains as well as higher costs in favour of combined treatment compared with monotherapy with SSRIs. Finally, Byford *et al.* (2007) found no significant differences between combined treatment and monotherapy in cost or clinical effectiveness. It should be noted that the interventions, although similar, had differences. In Lynch *et al.* (2011) trial CBT was added to medication switch, while in Byford *et al.* (2007) trial patients received CBT and started receiving SSRIs at the same time. Thus, results should be interpreted with caution due to limited comparability between the examined trials. Concerning direct comparison between antidepressants, one study found escitalopram dominated duloxetine (Wade *et al.* 2008).

Importantly, for several interventions (behavioural activation, occupational therapy, short-term psychological therapies, IPT) only results from a single study were identified (Bosmans *et al.* 2007; Schene *et al.* 2007; Maljanen *et al.* 2012) limiting the generalisability of conclusions. With regard to severe and refractory MDD, only two clinical studies of different interventions were identified (Knapp *et al.* 2008; Hollinghurst *et al.* 2014), and consequently no generalisations can be made.

Quality of economic evaluations

The overall methodological quality of the included economic evaluations was relatively high. The majority of studies described the methods in a transparent way, reducing possible biases related to methodology of economic outcomes assessment. However, the results of the trial-based economic evaluations rely heavily on the methodology of the RCTs. Thus, we examined the included RCTs for a spectrum of possible sources of bias related to the methodology. The results of the risk-of-bias assessment indicated that the included studies presented overall low risk of bias in most of the items examined except for blinding of personnel and participants, since this type of blinding is inherently difficult or impossible following exposure to active psychotherapeutic interventions. Therefore, the conclusions of the present systematic

review should be interpreted with caution due to high risk of performance bias.

Strengths and limitations

One of the strengths of the present review is the systematic method employed to reduce the risk of bias and to provide reliable findings and conclusions. Moreover, this paper examined the validity of the included studies and presents a detailed quality appraisal. However, the work also has several limitations. A formal meta-analysis could not be conducted due to the high diversity in outcomes across the included studies. Moreover, this heterogeneity of results limited the comparability of the findings and our ability to draw robust conclusions regarding relative cost-effectiveness of interventions. Finally, it should be noted that the cost effectiveness of a particular intervention might differ substantially between countries due to variations in usual care, differences in the way new treatments are introduced, and in costs of inputs such as the salaries of health professionals between countries. Thus, the present findings should be interpreted with caution, and clinicians and policy makers should take into account any national or regional evidence in order to draw conclusions about the cost effectiveness of an intervention for major depression.

Evidence gaps and future research

Little is known about the economics of occupational therapy, short-term psychological therapies, behavioural activation, PDT, REBT and IPT for the treatment of moderate MDD and/or prevention of progression to more severe disease. Additionally, little empirical evidence is available on the cost-effectiveness of treatment options for severe MDD. There are gaps in knowledge regarding which medication is likely to be most cost-effective and for which patient groups, and which psychological therapy is to be preferred. There is also relatively little information on the long-term impact of treatments. No published evidence was identified regarding the cost-effectiveness of self-help programmes delivered through the Internet by therapists or healthcare workers other than qualified psychotherapists. Similar trials are ongoing in this area, such as Internet-delivered treatment for individuals with depressive symptoms (Warmerdam *et al.* 2010), which may provide a cost-effective approach to limiting disease progression with early intervention.

The present review, and earlier draft stages, formed part of the WHO Research Agenda for Health Economic Evaluation project, where priorities for economic research in mental health and nine other subject

areas were discussed by a panel of experts (Tordrup et al. 2015). Suggested research priorities for MDD, based on the limitations of the available evidence, include: economic primary studies of rarely evaluated interventions (e.g. self-help interventions); long-term head-to-head comparisons of well studied treatments (e.g. CBT, CBT in combination with SSRIs) against usual care, using routinely available real-world data; analysis of the disease course to enable prediction of progression, thereby ensuring treatments are targeted at those unlikely to recover naturally; and elucidation of genetic components to treatment response. Importantly, when considering interventions that are supported by extensive evidence and are known to work in treating depression, the next step should be to target patients most likely to respond.

Conclusions

In conclusion, there is some economic evidence underpinning many of the interventions routinely used to treat major depressive disorder. Wide variability was observed in study outcomes, probably attributable to differences in population, interventions or follow-up periods. Significant economic evidence gaps remain in the area of major depressive disorder.

Supplementary Material

The supplementary material for this article can be found at <http://dx.doi.org/10.1017/S2045796016000421>.

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Conflict of interest

The authors have no financial conflicts of interest to declare.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the

relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Availability of Data and Materials

Data supporting the present findings are publicly available. For further details, the reader is encouraged to contact the corresponding authors.

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