Antidepressants and cognitive behavioural therapy interventions for major depressive disorder

Health Technology Assessment Report

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Abbreviations

ACT	Acceptance and Commitment Therapy
ADM	Antidepressant medication
ADRDA	Alzheimer's Disease and Related Disorders Association
AD-SUS	Adult Service Use Schedule
AE	Adverse Effect
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
BA	Behavioural Activation
BCBT	Blended CBT
BDI-II	Beck Depression Inventory-II
BHA	Benefit Harm Assessment
BIA	Budget Impact Analysis
CBASP	Cognitive Behavioural Analysis System of Psychotherapy
CBT	Cognitive Behavioural Therapy
CBTe	CBT with exercise
CBTm	CBT with mindfulness
CCBT	Computerized CBT
CCDAN	Cochrane Collaboration Depression, Anxiety and Neurosis Review Group
CENTRAL	Cochrane Central Register of Controlled Trials
CES-D	Center for Epidemiological Studies-Depression
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHF	Swiss Franc
CI	Confidence Interval
CRD	Centre for Review and Dissemination
CSDD	Cornell Scale for Depression in Dementia
CT	Cognitive Therapy
DBT	Dialectical Behaviour Therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
e.g.	exempli gratia (lat., = for example)
EQ-5D-5L	EuroQoL 5-Dimension 5-Level Questionnaire
HAM-D	Hamilton Rating Scale of Depression
GAF	Global Assessment of Functioning
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HTA	Health Technology Assessment
ICD	International Classification of Diseases
ICER	Incremental Cost Effectiveness Ratio
i.e.	id est (lat., = that is)
IQR	Interquartile Range
ITT	Intention-to-treat
KVG	Swiss health insurance law ("Krankenversicherungsgesetz")
LIFE	Longitudinal Interval Follow-up Evaluation
MADRS	Montgomery–Asberg Depression Rating Scale
MBCL	Mindfulness-Based Compassionate Living
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
NR	Not Reported
OECD	Organization for Economic Co-operation and Development
PHQ-9	Patient Health Questionnaire

PICO	Population, Intervention, Comparator, Outcome
PLC	Placebo
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International prospective register of systematic reviews
PST	Problem Solving Therapy
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
QOLIE-89	Quality of Life in Epilepsy Inventory-89
RCT	Randomized Controlled Trial
REBT	Rational Emotive Behaviour Therapy
REML	Restricted Maximum-Likelihood Estimator
RoB	Risk of Bias
RR	Risk Ratio
SASS	Social Adaptation Self-evaluation Scale
SCBT	Standard CBT
SD	Standard Deviation
SDS	Sheehan Disability Scale
SFOPH	Swiss Federal Office of Public Health
SF-36	Short-Form-36 Questionnaire
SHS	Swiss Hospital Statistics
SFSO	Swiss Federal Statistical Office
SMD	Standardized mean difference
SOC	System Organ Class
ST	Standard Therapy
SwissDRG	Swiss Diagnosis Related Group
TAU	Treatment As Usual
UK	United Kingdom
USA	United States of America
USD	United States Dollars
VAS	Visual Analogue Scale
vs.	versus
WL	Waiting list
WSAS	Work and Social Adjustment Scale

1 Executive Summary

1.1 Summary

Introduction

Major depressive disorder (MDD) is one of the most frequent mental health disorders with a substantial societal and economic burden. MDD is mainly treated by antidepressant medications (ADM) or psychotherapy, of which cognitive behavioural therapy (CBT) is the most frequently used. The choice of initial treatment depends on multiple factors including the severity of depression symptoms, costs, and patient preferences. Treatment is often continued for several months to enhance remission and prevent relapse and maintained up to three years in patients with risk factors for recurrence. The evaluation of the efficacy of the different interventions is largely based on short-term randomized controlled trials (RCTs) encompassing the acute management phase (up to 12 weeks), and longer term efficacy is uncertain. Furthermore, due to the short-term nature of the studies, little is known about the persistence and development of adverse effects (AE). This lack of evidence has so far hindered an adequate evaluation of the risk-benefit ratios of MDD therapies.

Aim

In this Health Technology Assessment (HTA), we aimed at evaluating the clinical efficacy and safety, benefit-harm balance and health economic characteristics of ADM and CBT interventions, alone or in combination, in patients with MDD and receiving these treatments beyond the acute management phase (i.e., >12 weeks) within the context of Switzerland.

Methods

A. PICO

The **population of interest** for this HTA were adults diagnosed with MDD.

We investigated the following **interventions**:

1. Antidepressants
2. Cognitive behavioural therapies

We considered the following **comparator** treatments:

- ADM or CBTs as monotherapy
- Combination of ADM and CBTs
- Control conditions (placebo, waiting list, treatment as usual)

We defined the following **outcomes** of interest:

- Clinical efficacy outcomes:
    - Primary: relapse, recurrence, quality of life (QoL), social functioning

  - Secondary: response, remission
- Safety outcomes:
  - Primary: acceptability (i.e., proportion of participants who withdrew from the study for any reason), worsening of depression, mortality
  - Secondary: specific adverse effects, tolerability (i.e., proportion of participants who withdrew from the study due to adverse effects)
- Health economic outcomes: costs, quality-adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs)

B. Assessment of Clinical Efficacy and Safety

In the assessment of the clinical efficacy and safety of the different MDD treatments, the timeframe was divided into three periods based on the management phases of MDD (i.e., acute phase: ≤12 weeks, continuation phase: 13 to 24 weeks, and maintenance phase: ≥25 weeks). We considered outcomes assessed at >12 weeks to be mid- to long-term. We included evidence from both classical RCTs and discontinuation RCTs (i.e., trials in which participants receive an open label treatment for the acute phase and those responding are subsequently randomly allocated to continue the treatment or to receive placebo or active control).

We conducted a two-step literature search process to identify relevant RCTs. First, we performed a search strategy in the Ovid Medline and Cochrane Library databases for high-quality systematic reviews of MDD interventions published between 2018 and 2020. Three reviewers screened all identified systematic reviews for eligibility and assessed their quality using the "Assessing the Methodological Quality of Systematic Reviews" (AMSTAR)-2 checklist. Second, we conducted follow-up searches using the same search strategies as in the systematic reviews judged to be of high-quality according to AMSTAR-2. We searched Medline, EMBASE, PsycInfo, and the Cochrane Library. Two of three reviewers screened records identified by the follow-up searches for potentially relevant studies for inclusion.

We extracted relevant information related to study design and characteristics, demographics and characteristics of study participants, details on interventions and comparators, and measured outcomes. We assessed the risk of bias (RoB) of the included RCTs on an outcome-basis for the primary clinical and safety outcomes using the RoB 2.0 tool. When possible, we conducted pairwise and network meta-analyses for the different comparisons and outcomes and calculated pooled risk ratios (RRs) with their 95% confidence intervals (CI). The analyses were conducted at the overall treatment modality level (e.g., ADM vs CBT) and for each treatment phase separately. Due to the heterogeneity of the studies in terms of study design (including the lack of blinding in trials evaluating CBT interventions) and participant characteristics which could affect the validity of results of the network meta-analyses, we considered the pairwise meta-anaylses to be the primary analyses and we interpreted our findings accordingly. As our aim was a comparative assessment of ADM and CBT and their combination, we first presented

results of these direct comparisons, followed by the comparison of either ADM or CBT versus placebo, waiting list or treatment as usual. In instances where a meta-analysis was not possible or appropriate due to scarce or heterogeneous data, we narratively synthesized the evidence. Last, we used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to evaluate the certainty of evidence for the primary outcomes in the continuation phase.

C. *Benefit-Harm Assessment (BHA)*

Benefit (reduced risk of relapse) was weighed against harms (all-cause study drop-outs (acceptability) or specific AE, including neurological, respiratory, gastrointestinal, suicidal, psychiatric, and musculoskeletal) to estimate the net clinical benefit of CBT, ADM, or their combinations.

The analysis took into account (i) relative treatment effects (efficacy in terms of risk reduction of relapse and excess risks of AEs), (2) outcome risks as a basis to estimate the magnitude of absolute effects of the treatment interventions in the MDD general population, (iii) preferences as a measure of relative importance of benefit and harm outcomes, and (iv) time horizon of 12 months for estimating the cumulative risk of benefit and harm outcomes, which is equivalent to an average duration of treatment in the maintenance phase.

Assuming constant rates of relapse and all-cause study dropouts and the other harm outcomes over 12 months, the cumulative risks of these outcomes were estimated using an exponential model for a theoretical cohort of 1,000 patients receiving the different interventions of interests. The absolute differences in incidence rates of the outcomes between the interventions were then calculated and subsequently weighted individually based on the patient preferences to provide benefit-harm balance index or net clinical benefit. The analysis was performed stochastically with 100,000 repetitions accounting for the uncertainty of parameter estimates to generate a distribution of the net clinical benefit. From the distribution, we calculated the probability that patients receiving the interventions would experience a clinical net benefit. Probability above 60% was interpreted as net clinical benefit (or more clinical benefit than harms), below 40% were interpreted as net harm (less benefits than harms) or as neither harmful nor beneficial (40 to 60%). In addition, we estimated the absolute net clinical benefit over the 12-month time horizon. Because the BHA is highly dependent on the selection of evidence for the input parameters, we tested sensitivity of the net clinical benefit to different alternative estimates, including longer time horizon (24 months), varying preference weights and varying baseline risk of relapse.

D. Health Economic Literature Review

For the economic systematic review, a search strategy was developed to identify all relevant literature in MEDLINE, EMBASE, and the Centre for Review and Dissemination (CRD) database. The search string was obtained by integrating and combining the search string used in the clinical part of this assessment report, and search strings for health economic analyses. A two-phase process consisting of title/abstract and full text screening was conducted. Data extraction and quality assessment according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 24-item checklist was conducted for all articles reporting a full-scale health economic evaluation study. Population demographics and study characteristics were summarised. Measurement and sources of clinical effectiveness and costs were synthesised. Results of the cost-effectiveness analyses covering different treatments comparisons within one study as well as across studies were numerically adapted to Switzerland. Only cost-effectiveness analyses reporting ICERs in terms of costs per QALY gained were included in the health economic review.

E. Budget Impact Analysis

The budget impact analysis consisted of two main steps. First, the total number of eligible MDD patients in 2020 in Switzerland was estimated. For this purpose, data from the Swiss Health Survey 2017 were combined with Swiss demographic data from 2020. Second, the number of eligible patients was combined with estimated resource use (covering hospitalisations, physician visits, psychotherapy, and ADM) and unit costs. Costs at the national level were estimated from the Swiss healthcare perspective.

Since there was no information on the distribution of different therapies among MDD patients available, several scenarios, including monotherapies (e.g. only psychotherapy or ADM for all treated MDD patients) and combinations (e.g. 10% psychotherapy alone and 90% psychotherapy plus ADM), were analysed. We assumed that patients would be treated for a whole year, without treatment discontinuation nor switches between different treatment strategies.

Results & Discussion

A. Assessment of Clinical Efficacy and Safety

In the first step of our search strategy, we identified 15 eligible systematic reviews. Based on the AMSTAR-2 quality assessment and the comprehensiveness of their scope, two high-quality systematic reviews were selected. In the second step, 43 publications (42 trials) met the eligibility criteria. Eight studies evaluated ADM versus CBT, four studies evaluated ADM versus ADM plus CBT, and one study evaluated CBT versus ADM plus CBT. Additionally, 20 studies assessed either ADM or CBT versus control conditions. Different

types of ADM were evaluated head to head in 16 studies and six studies compared different CBTs. The duration of studies ranged from 13 to 168 weeks. A total of 22 studies assessed any of the clinical or safety outcomes at ≤12 weeks, 29 studies at 13 to 24 weeks and 14 studies at ≥25 weeks. 18 trials, all of which assessed an ADM compared to placebo or another ADM, were sponsored by the pharmaceutical industry.

In this summary of results, we present the results of the pairwise meta-analyes for the primary outcomes during the continuation and maintenance phases.

Only a few trials assessed the efficacy of ADM and CBT in reducing the risk of relapse or recurrence. Three studies assessed outcomes for longer than a year and only one had a three-year follow-up. We judged the risk of bias as high in eight out of nine studies due to methodological limitations (lack of blinding and allocation concealment) and possible selective outcome reporting.

In the continuation phase, only one study evaluated ADM versus CBT and reported a higher non-significant risk of relapse among patients receiving ADM (RR= 2.48, 95% CI= 0.69 to 8.87). Compared to placebo, individuals receiving ADM had a lower risk of relapse with ADM in two studies (pooled anaylsis not possible due to different study designs; RR= 0.49, 95% CI= 0.34 to 0.68 and RR= 0.49, 95% CI= 0.29 to 0.83). In the maintenance phase, the effects of ADM and CBT on relapse appeared comparable in two studies (pooled anaylsis not possible ; RR= 1.19, 95% CI= 0.50 to 2.80 and RR= 0.86, 95% CI= 0.31 to 2.40). A lower, but non-significant, risk of relapse in those receiving ADM plus CBT (66 relapses in 44 patients) compared to ADM alone (80 relapses in 49 patients) was reported in one study. Pooled analysis of studies comparing ADM and placebo in the maintenance phase revealed no difference between the two groups (RR= 0.84, 95% CI= 0.44 to 1.59). One study evaluating CBT and placebo in the maintenance phase reported that participants in the CBT group were less likely to relapse compared to placebo (16% versus 25%, respectively), however the difference was not significant. The quality of evidence for the ADM versus CBT comparison was low due to risk of bias and imprecision and was moderate for ADM versus placebo as judged by GRADE.
Recurrence rates were similar between those receiving ADM or ADM plus CBT combination therapy during the maintenance phase (treatment up to three years) in a single study (RR= 0.99; 95% CI = 0.69 to 1.41).

Data on the impact of mid- to long-term treatment on the QoL and social functioning of patients with MDD was reported in six and seven studies, respectively. There was large heterogeneity across trials regarding the instruments used and the evaluation of specific endpoints. We judged the overall risk of bias of most studies to be high and the certainty around the evidence was low for all comparisons in both outcomes except ADM versus placebo in social functioning (moderate).
For QoL, one study reported that while there was an improvement in QoL over time in both ADM and CBT arms, there was no significant difference between the two during the continuation phase. Authors also reported that the improvement in depression was positively associated with QoL, implying that improvement in QoL over the course of

treatment may be partially accounted for by a reduction in depressive symptoms. No data on QoL was available for combination treatment nor for ADM compared to CBT during the maintenance phase.
Similarly for social functioning, while there were significant improvements in the assessment scores of patients receiving ADM or CBT or their combination during the continuation phase, there was no evidence that either was more effective than the other. On the other hand for the comparison of ADM versus placebo, one study reported that the improvement in social functioning was significantly greater for ADM during the continuation phase. In the maintenance phase, two trials found inconsistent results with only one detecting a significantly better improvement in social functioning from baseline at 9 months in the ADM group. We did not identify any studies assessing social functioning in patients receiving ADM or CBT or their combination during the maintenance phase.
Overall for both QoL and social functioning the effect sizes of the changes in scores were smaller than those of the changes of depressive symptoms, indicating that improvements in both aspects and returning to normal may require a much longer time.

Acceptability was evaluated in 35 studies. In the continuation phase, pooled analyses showed similar acceptability rates between ADM and CBT (RR= 1.57, 95% CI= 0.94 to 2.62). On the other hand, there was better acceptability rates (lower study drop-outs) in ADM plus CBT than in ADM alone (RR= 2.06, 95% CI= 1.31 to 3.25) or CBT alone (RR= 2.12, 95% CI= 1.29 to 3.48). In the maintenance phase, one study reported no difference between ADM and CBT (RR=1.21, 95% CI= 0.87 to 1.81) while another reported lower drop-out rates with ADM compared to CBT (RR=0.62, 95% CI= 0.41 to 0.93). The quality of evidence was low for all comparisons except for ADM versus placebo.

Tolerability was reported in 24 studies. In the continuation phase, one study reported less tolerability (higher drop-outs due to AEs) with ADM compared to CBT (9% versus 0%). Compared to placebo, ADM was less tolerable (RR=3.46, 95% CI= 1.65 to 7.25). There were no studies comparing tolerability of ADM and CBT in the maintenance phase. Regarding adverse effects, reporting of adverse effects was inconsistent across studies and certainly lacking for CBT and ADM plus CBT. Nevertheless, from the available evidence, we found that a high proportion of patients experienced adverse effects in both the continuation and maintenance phases, particularly among those receiving ADM. While the available evidence suggests that ADM alone was not optimal from the perspective of acceptability and tolerability, it is important to note that a comparison of AEs in those receiving ADM versus CBT needs to be done with caution as AEs in CBT trials were often not reported which may lead to a possible underestimation of their harms.

The findings of this review need to be considered in light of some limitations to both the review process and the evidence base. One main limitation relates to the heterogeneity of the included studies which comprised different populations, interventions and comparators. There were also substantial differences in the study designs and conducts, relating mainly to the lack of blinding in CBT trials. These factors may violate the underlying transitivity assumption of our network meta-analyses and the lack of blinding may lead to an overestimation of the efficacy of CBT. Limitations relating to the underlying

evidence base include scarcity of data, especially relating to AEs of CBT. Due to the small number of studies, we could not evaluate whether the impact of the different interventions on relapse and recurrence was differential across the different MDD severity groups. Furthermore, most studies suffered from methodological limitations and were at high risk of bias weakening the validity of the results. Finally, we only included RCTs in our analysis, which generally include highly selected populations who may not be representative of the general population and procedures that do not reflect real-world clinical practice.

B. Benefit-Harm Assessment

When weighing the risk of averted relapse against the excess risk of harm outcomes on the same scale, MDD patients treated with CBT demonstrated a net clinical benefit than those treated with ADM over 12 months. The corresponding probability of net benefit in terms of preventing relapse was 91.8% for CBT compared to ADM taking into account specific harm outcomes and 98.2% when all-cause study dropout was considered as the harm outcome.

Whereas the above results were based on treatment estimates from RCTs with shorter follow up (>12 to <25 weeks), we repeated the analysis with evidence from RCTs with 25 weeks and longer follow-up times, but this time using only all-cause study dropout as a harm endpoint. CBT remained superior to ADM, with a probability for net clinical benefit of 77.1%. This implies a decrease in net benefit over time compared with the above results. However, the combination of CBT and ADM boosted the likelihood of net clinical rate to 96.7% compared to ADM alone and 80% compared to CBT alone.

In absolute terms, the number of relapse-equivalents (i.e., net clinical benefit) that would be prevented over 12 months was 346 in 1000 MDD patients treated with CBT instead of ADM when considering treatment effects from RCTs with shorter follow-up. This diminished to 126 in 1000 patients when evidence only from RCTs with more than 6 months of follow-up was considered. However, the decrease in effect was reversed to a more favourable net clinical benefit with combination therapy of CBT and ADM compared to monotherapy with ADM at the end of 12 months (i.e., 228 relapse equivalents averted in 1000 patients) or CBT (i.e., 126 relapse equivalents averted in 1000 patients).

Several sensitivity analyses reaffirmed the favourability of CBT over ADM and of their combination over monotherapy. This was mainly because CBT was associated with lower relapse rates and lower dropout rate and safety outcomes than ADM. As such, the results were not substantially different, even with changes in patient risks and preference values for relapse and dropout. However, it is worth noting that this assessment is among the first BHAs conducted in the context of MDD interventions, and there is little evidence for comparison.

Our results should be interpreted with caution and need to be considered in light of the limitations of the study. This includes the lack of detail of reported harm outcome data (e.g., estimates for all different types and severity level of AEs), in particular in trials evaluating CBT, which may lead to an underestimation of true harms. However, we did not rely solely on specific AEs as our harm outcome but also alternatively used all-cause study drop-outs which is more consistently reported in studies, with similar results when using either as a harm outcome. Additional limitations include use of RCT data only which may underestimate harm outcome rates in the general population, lack of detailed data on relevant benefit outcomes, such as recovery and recurrence and the use of generic preference weights rather than weights derived from preference studies. Overall, readers should not take the estimated net clinical benefit as definitive as it is difficult to estimate the extent to which these limitations might have an effect on the estimated net clinical benefit. However, we are confident that the relative benefit-harm balance of the different therapies has been captured adequately, especially for the time horizon of 12 months or less. Our analysis can be updated when new data for the input parameters become available.

C. Health Economic Literature Review

Out of 2,689 citations identified from the electronic database searches, 33 were eligible cost-effectiveness analyses: 14 of them assessed ADM as intervention strategy, whereas 19 assessed CBT. The comparators varied across studies. 29 out of the 33 cost-effectiveness analyses included in this review used a time horizon longer than 12 weeks. The majority of the cost-effectiveness analyses of ADMs were sponsored by pharmaceutical companies, whereas all of the cost-effectiveness analyses of CBT were public sector funded.

The majority of the included cost-effectiveness analyses of ADMs were model-based. The most frequently investigated treatments were escitalopram (a SSRI), venlafaxine (SNRI), sertraline (SSRI), duloxetine (SNRI), and SSRIs considered as a group.

Six cost-effectiveness analyses concluded that there was favourable evidence to support the cost-effectiveness of escitalopram versus other ADMs. All these analyses were based on clinical inputs showing that remission or response probabilities were highest for escitalopram relative to all other comparators. In all cost-effectiveness analyses where venlafaxine, sertraline or duloxetine were compared against escitalopram, it was estimated that escitalopram was the dominant strategy (i.e. less expensive and more effective) or highly cost-effective (i.e. had very low ICERs). Also, after numerical adaptation for Switzerland escitalopram resulted in being a dominant strategy in most cases.

Venlafaxine was investigated in six cost-effectiveness analyses as either intervention or comparator. When compared with escitalopram, venlafaxine was in most cases dominated (i.e. was more expensive but less effective) or was found to be less expensive

but less effective. In contrast, when compared to other ADMs (e.g. citalopram, duloxetine, fluoxetine, paroxetine, sertraline), venlafaxine was generally considered a dominant strategy.

Six cost-effectiveness analyses compared sertraline with placebo or a set of anti-depressants. Sertraline was considered a dominant strategy when compared to citalopram (from both healthcare and societal perspectives), whereas it was dominated when compared to escitalopram, venlafaxine, and agomelatine. For all other comparisons, the results were heterogeneous.

Duloxetine was evaluated as a comparator strategy in four cost-effectiveness analyses. In three of them, it was dominated by escitalopram. The comparison with other ADMs showed discordant results.

The three cost-effectiveness analyses considering SSRIs as a group indicated that SSRIs were cost-effective when compared to other ADMs or usual care.
Most of the cost-effectiveness analyses investigating CBT were within-trial analyses. We identified eight cost-effectiveness analyses suggesting that CBT was cost-effective or dominant if compared to usual care or ADM. However, there were also five cost-effectiveness analyses which estimated the opposite (i.e., ADM or usual care were the dominant strategies, or the ICER for CBT versus the comparators was very high, and thus not did not indicate cost-effectiveness).

Our findings need to be carefully interpreted in the presence of several limitations. This includes high heterogeneity across the identified studies relating to different populations, interventions and comparators, time horizons and types of costs, especially for CBT interventions. Furthermore, the majority of the cost-effectiveness analyses of ADMs were sponsored by pharmaceutical companies, which may imply a potential for biases. On the other hand, treatment effects in CBT trials may have been associated with researcher allegiance and could also pose a potential bias. Finally, the limitations of the clinical evidence base are also applicable to the review of the economic literature.

It is important to note that there were some methodological differences between the clinical and economic reviews of this HTA including the inclusion of patients with substantial depressive symptomology in the economic review in contrast to the clinical review which focused on patients diagnosed with MDD. While the clinical part included all international studies, the economic part excluded East Asian countries as they are likely to substantially differ to Switzerland in terms of settings, costs, and perception of quality of life. Furthermore, unlike the clinical systematic review which only included CBT interventions which lasted for more than 12 weeks, we included two cost-effectiveness analyses of CBT that reported a treatment duration potentially below 12 weeks (in these trials the authors reported 6-8 weekly CBT lessons/modules, but did not specify whether the lessons/modules were conducted consecutively in the shortest time possible, or whether they were distributed over a period of time exceeding 12 weeks). In general, it should be emphasized that in many cases the real duration of CBT was not specified in

months, but in number of sessions or modules. The exact distribution of sessions/modules over time was often not reported.

D. Budget Impact Analysis

We estimated the total number of MDD patients treated in Switzerland in 2020 to be 334,835. The total direct medical costs were estimated to range between CHF 5,330 million (assuming that MDD patients would be treated exclusively with the least expensive ADM, without receiving any kind of psychotherapy) and CHF 6,032 million (assuming that all MDD patients would undergo psychotherapy and receive the most expensive ADM). Depending on the distribution of treatments and cost assumptions, hospitalisation costs represented 82% to 92% of the total costs. Physician visit, psychotherapy, and ADM costs seemed to play a relatively minor role. The treatment costs ranged from CHF 84 million (assuming that all treated MDD patients would receive the least expensive ADM only and no psychotherapy) to CHF 800 million (assuming that all MDD patients would receive both psychotherapy and the most expensive ADM). Treatment with psychotherapy alone for all MDD patients was estimated to cost CHF 603 million (assuming 12 sessions per year).

The budget impact estimation required numerous assumptions and thus substantial limitations apply, including possible underestimation of the number of patients eligible for MDD treatment, underestimation of the costs of hospitalisation, and exclusion of costs of diagnostic tests and concomitant medications. We further did not take into account treatment switching or discontinuation. Information concerning differences in productivity loss, depression-related disability or early retirement, and depression related suicides according to different treatment options was not sufficient to perform the analyses from a societal perspective.

Conclusion

This HTA attempted a comprehensive evaluation of the clinical efficacy, safety, benefit-harm balance, and health economic characteristics of ADM and CBT in adult patients with MDD from a mid- to long-term perspective.

Within the available data, we found no evidence of a difference between ADM, CBT and their combination with regards to the primary clinical efficacy outcomes, including QoL and social functioning. However, ADM alone appeared to be non-optimal from the perspective of acceptability and tolerability. Our findings need to be interpreted carefully in light of the limitations such as the large heterogeneity of included studies as well as issues related to the risk of bias arising from the lack of blinding in CBT trials. The benefit-harm assessment –which also took into account outcome risks and preferences– revealed a relatively greater likelihood of mid- to long-term net clinical benefit with CBT than with

ADM, or with the combination of CBT and ADM than with monotherapy. However, the true benefit-harm balance may not be adequately captured given the non- and unreliable reporting of AEs in trials, especially when related to CBT interventions. As such, more systematic and detailed assessments and reporting of mid- to long-term clinical outcomes, specifically QoL, social functioning, and AEs by the RCTs would allow for a better evaluation of the different interventions across these dimensions, as well as the conduct of a more comprehensive BHA. The results of the economic systematic review suggested that escitalopram may be the most cost-effective treatment among the included antidepressants, followed by venlafaxine, sertraline, and duloxetine.

The cost-effectiveness analyses comparing CBT or internet-based CBT with ADMs or usual care led to discordant results. The budget impact analysis suggested that the total direct medical costs of MDD per year may range between CHF 5,330 million and CHF 6,032 million. The main cost drivers were the estimated number of MDD patients being treated and hospitalisations. This finding highlights that hospitalisation due to MDD is an important clinical outcome that, along with other consequences on occupational activity and well-being, should ideally be captured by clinical trials and observational studies to allow a more comprehensive assessment of MDD treatments. The costs of psychotherapy and ADM depended on the assumed treatment distribution. Treatment with psychotherapy alone was estimated to cost CHF 603 million, whereas the costs for combination treatment would range between CHF 687 million and CHF 801 million.

In conclusion, we found that while both ADM and CBT interventions appear to be efficient options in the management of MDD, none appeared to definitively perform better than the other. While our benefit-harm assessment seemed to show that CBT interventions may provide a greater clinical benefit for MDD patients compared to ADM, the systematic review of the cost-effectiveness analyses, adapted to the Swiss context, revealed that CBT may also be more expensive depending on how it is conducted (number of sessions, online vs. face-to-face). These findings need to be carefully interpreted given the methodological shortcomings of the review and the evidence base, as well as the potential limited applicability of findings of controlled trials to real-world clinical settings.

1.2 Zusammenfassung

Einführung

Die Major Depressive Disorder (MDD) ist eine der häufigsten psychischen Erkrankungen, welche eine erhebliche gesellschaftliche und wirtschaftliche Belastung darstellt. MDD wird hauptsächlich mit antidepressiven Medikamenten (antidepressant medication, ADM) oder Psychotherapie behandelt, wobei die kognitive Verhaltenstherapie (cognitive behavioural therapy, CBT) am häufigsten eingesetzt wird. Die Wahl der Erstbehandlung hängt von mehreren Faktoren ab, darunter dem Schweregrad der depressiven Symptome, den Kosten und den Patientenpräferenzen. Die Behandlung erstreckt sich häufig über mehrere Monate, um die Remission zu erreichen und einen Rückfall zu verhindern, und in Patienten mit Risikofaktoren für ein Rezidiv wird die Behandlung bis zu drei Jahren fortgesetzt. Die Bestimmung der Wirksamkeit der verschiedenen Interventionen beruht weitgehend auf kurzfristig randomisierten kontrollierten Studien (randomized controlled trials, RCTs), welche die akute Behandlungsphase (bis zu 12 Wochen) umfassen, und dessen längerfristige Wirksamkeit ist ungewiss. Darüber hinaus ist, aufgrund der kurzen Studiendauer, wenig über das Fortbestehen und die Entwicklung von unerwünschten Wirkungen (adverse effect, AE) bekannt. Dieser Mangel an Evidenz hat bisher eine angemessene Beurteilung des Nutzen-Risiko-Verhältnisses von MDD-Therapien verhindert.

Ziel

Dieses Health Technology Assessment (HTA) zielte darauf ab, die klinische Wirksamkeit und Sicherheit, das Nutzen-Risiko-Verhältnis und die gesundheitsökonomischen Eigenschaften von ADM und CBT Interventionen, allein oder in Kombination, bei Patienten mit MDD in Bezug auf die Schweiz, welche diese Behandlungen über die Akuttherapie hinaus (d.h. >12 Wochen) erhalten, zu bestimmen.

Methoden

A. PICO

Die **Population,** die für dieses HTA von Interesse war**,** waren Erwachsene mit der MDD Diagnose.

Wir untersuchten die folgenden **Interventionen**:

1. Antidepressiva
2. Kognitive Verhaltenstherapien

Wir haben die folgenden **Vergleichsinterventionen** in Betracht gezogen:

- ADM oder CBT als Monotherapie
- Kombination von ADM und CBT
- Kontrollbedingungen (Placebo, Warteliste, übliche Behandlung)

Wir haben die **Ergebnisparameter** wie folgt definiert:

- Ergebnisparameter der klinischen Wirksamkeit:
  - Primär: Rückfall, Rezidiv, Lebensqualität (QoL), soziales Funktionsniveau
  - Sekundär: Ansprechen, Remission
- Ergebnisparameter der Sicherheit:
  - Primär: Akzeptanz (d.h. Anteil der Teilnehmer, die sich aus einem beliebigen Grund von der Studie zurückgezogen haben), Verschlimmerung der Depression, Mortalität
  - Sekundär: spezifisch unerwünschte Wirkungen, Verträglichkeit (d.h. Anteil der Teilnehmer, welche die Studie aufgrund von unerwünschten Wirkungen abgebrochen haben)
- Gesundheitsökonomische Ergebnisparameter: Kosten, qualitätskorrigiertes Lebensjahr (QALYs), inkrementelle Kosten-Effektivitäts-Verhältnisse (ICERs)

B. Beurteilung der klinischen Wirksamkeit und Sicherheit

Bei der Beurteilung der klinischen Wirksamkeit und Sicherheit der verschiedenen MDD-Behandlungen wurde der Zeitrahmen in drei Perioden unterteilt, welche sich an den MDD Behandlungsphasen orientieren (d.h. Akutphase: ≤12 Wochen, Fortsetzungsphase: 13 bis 24 Wochen, und Erhaltungsphase: ≥25 Wochen). Wir betrachteten Ergebnisparameter, die nach >12 Wochen bewertet wurden, als mittel- bis langfristig. Es wurden sowohl klassische RCTs als auch Abbruch-RCTs berücksichtigt (d.h. Studien, bei denen die Teilnehmer eine Open-Label-Behandlung in der Akutphase erhielten und diejenigen, die darauf ansprachen, anschliessend nach dem Zufallsprinzip für die Fortsetzung der Behandlung oder für ein Placebo oder eine aktive Kontrolle zugeordnet wurden).

Wir führten eine zweistufige Literaturrecherche durch, um relevante RCTs zu identifizieren. Im ersten Schritt führten wir eine systematische Literatursuche in den Datenbanken Ovid Medline und Cochrane Library für qualitativ hochwertige, systematische Übersichtsarbeiten bezüglich MDD-Interventionen durch, die zwischen 2018 und 2020 veröffentlicht wurden. Drei Gutachter überprüften unabhängig alle identifizierten systematischen Übersichtsarbeiten auf ihre Eignung und bewerteten ihre Qualität anhand der "Assessing the Methodological Quality of Systematic Reviews" (AMSTAR)-2 Checkliste. Im zweiten Schritt führten wir systematische Literatursuchen durch, wobei wir dieselben Suchstrategien, welche auch von den hochwertigen systematischen Übersichtsarbeiten, gemäss AMSTAR-2, verwendet wurden. Wir durchsuchten die Datenbanken Medline, EMBASE, PsycInfo und Cochrane Library. Zwei von drei Gutachtern überprüften unabhängig die Studien, die in der Folgesuche identifiziert wurden, um sie einzuschliessen.

Wir extrahierten relevante Informationen über Studiendesign und -merkmale, demografische Charakteristika der Studienteilnehmer, Details über die Interventionen und die Vergleichsinterventionen, sowie die evaluierten Endpunkte. Wir bewerteten das Verzerrungsrisiko (Risk of Bias, RoB) der eingeschlossenen RCTs basierend auf den

Ergebnisparametern der primären klinischen Wirksamkeit und Sicherheit mithilfe des RoB 2.0 Tools. Wenn möglich, führten wir paarweise sowie Netzwerk Meta-Analysen für die verschiedenen Vergleiche sowie Ergebnisparametern durch und berechneten aggregierte Risikoverhältnisse (Risk Ratios, RRs) mit ihren 95%-Konfidenzintervallen (CI). Die Analysen wurden auf Ebene der allgemeinen Behandlungsmodalität (z.B. ADM vs. CBT) und für jede Behandlungsphase separat durchgeführt. Aufgrund der Heterogenität der Studien bezüglich der Studiendesigns (einschliesslich der fehlenden Verblindung in Studien, die CBT-Interventionen evaluierten) und Merkmale der Studienteilnehmer, welche die Validität der Ergebnisse der Netzwerk Meta-Analysen beeinträchtigen konnten, betrachteten wir die paarweisen Meta-Analysen als primäre Analysen und interpretierten unsere Ergebnisse entsprechend. Da unser Ziel eine vergleichende Bewertung von ADM und CBT sowie ihrer Kombination war, haben wir zunächst die Ergebnisse dieser direkten Vergleiche dargestellt, gefolgt von dem Vergleich von ADM oder CBT mit Placebo, Warteliste oder übliche Behandlung. In den Fällen, in denen eine Meta-Analyse aufgrund mangelnder oder heterogener Daten nicht möglich oder angemessen war, haben wir die Evidenz narrativ zusammengefasst. Schliesslich wurde die Qualität der Evidenz für jene primären Endpunkte in der Fortsetzungsphase anhand der GRADE-Methodik (Grading of Recommendations Assessment, Development, and Evaluation) bewertet.

C. *Nutzen-Schaden-Abwägung (BHA)*

Der Nutzen (vermindertes Rückfallrisiko) wurde gegen den Schaden (Studienabbruch im Allgemeinen (Akzeptanz) oder spezifische AE, einschliesslich neurologischer, respiratorischer, gastrointestinaler, suizidaler, psychiatrischer und muskuloskelettaler Erkrankungen) abgewogen, um den klinischen Nettonutzen von CBT, ADM oder deren Kombinationen abzuschätzen.

Bei der Analyse wurden folgende Faktoren berücksichtigt: (i) relative Behandlungseffekte (Wirksamkeit in Bezug auf die Verringerung des Rückfallrisikos und das erhöhte Risiko von AE), (ii) das Risiko der Ergebnisparameter als Grundlage für die Schätzung des Ausmasses der absoluten Auswirkungen der Behandlungsmassnahmen in der allgemeinen MDD Population, (iii) Präferenzen als Mass für die relative Wichtigkeit von Nutzen und Schaden und (iv) ein Zeithorizont von 12 Monaten für die Abschätzung des kumulativen Risikos von Nutzen und Schaden, was einer durchschnittlichen Behandlungsdauer in der Erhaltungsphase entspricht.

Unter der Annahme konstanter Raten an Rückfällen und Studienabbrüchen im Allgemeinen sowie andere schädliche Ergebnisse über 12 Monate wurden die kumulativen Risiken dieser Ergebnisparameter mithilfe eines exponentiellen Modells für eine theoretische Kohorte von 1000 Patienten geschätzt, welche die verschiedenen Interventionen erhielten. Die absoluten Unterschiede in den Inzidenzraten der Ergebnisparametern zwischen den Interventionen wurden dann berechnet und anschliessend basierend auf den Patientenpräferenzen individuell gewichtet, um einen

Nutzen-Schaden Balance Index oder einen klinischen Nettonutzen zu erhalten. Die Analyse wurde stochastisch mit 100.000 Wiederholungen durchgeführt, wobei die Unsicherheit der Parameterschätzungen berücksichtigt wurde, um eine Verteilung des klinischen Nettonutzens zu generieren. Anhand dieser Verteilung wurde die Wahrscheinlichkeit berechnet, dass die Patienten, welche die Interventionen erhielten, einen klinischen Nettonutzen erfahren würden. Eine Wahrscheinlichkeit von über 60% wurde als klinischer Nettonutzen (oder mehr klinischer Nutzen als Schaden) interpretiert, während ein Wert von unter 40% als Nettoschaden (weniger Nutzen als Schaden) oder als weder schädlich noch nützlich (40 bis 60%) interpretiert wurde. Darüber hinaus haben wir den absoluten klinischen Nettonutzen über den Zeithorizont von 12 Monaten abgeschätzt. Da das BHA in hohem Masse von der Auswahl der Evidenz für die Eingangsparameter abhängt, testeten wir die Sensitivität des klinischen Nettonutzens für verschiedene alternative Schätzungen, einschliesslich eines längeren Zeithorizonts (24 Monate), unterschiedlicher Präferenzgewichte und eines unterschiedlichen Ausgangsrisikos für einen Rückfall.

D. Gesundheitsökonomische Literaturübersicht

Für die wirtschaftliche systematische Überprüfung wurde eine Suchstrategie entwickelt, um alle relevante Literatur in den verschiedenen Datenbanken, wie MEDLINE, EMBASE und des Centre for Review and Dissemination (CRD) zu ermitteln. Die Suchstrategie wurde durch Integration und Kombination der Suchstrategien, welche im klinischen Teil dieser Übersichtsarbeit verwendet wurden, sowie der Suchstrategien in der gesundheitsökonomischen Analyse, erstellt. Es wurde ein zweistufiger Prozess durchgeführt, der aus einem Titel/Abstract- und einem Volltextscreening bestand. Die Datenextraktion und Qualitätsbewertung wurde für alle Artikel durchgeführt, die eine umfassende gesundheitsökonomische Evaluationsstudie enthielten gemäss der 24 Punkte Checkliste der Consolidated Health Economic Evaluation Reporting Standards (CHEERS). Die demografischen Daten der Bevölkerung und die Studienmerkmale wurden zusammengefasst. Die Messung und die Ursprünge der klinischen Wirksamkeit und der Kosten wurden zusammenfassend dargestellt. Die Ergebnisse der Kosten-Effektivitäts-Analysen, die verschiedene Behandlungen innerhalb einer Studie sowie studienübergreifend verglichen, wurden zahlenmässig der Schweiz angepasst. Nur Kosten-Effektivitäts-Analysen, die ICERs in Form von Kosten pro gewonnenem QALY ausweisen, wurden in die gesundheitsökonomische Übersicht aufgenommen.

E. Budget Impact-Analyse

Die Budget Impact-Analyse bestand aus zwei wesentlichen Schritten. Zunächst wurde die Gesamtzahl der anspruchsberechtigten MDD-Patienten in der Schweiz im Jahr 2020 geschätzt. Zu diesem Zweck wurden die Daten der schweizerischen Gesundheitsbefragung von 2017 mit den demografischen Daten der Schweiz von 2020 kombiniert. Im zweiten Schritt wurde die Zahl der anspruchsberechtigten Patienten mit

der geschätzten Ressourcennutzung (Krankenhausaufenthalte, Arztbesuche, Psychotherapie und ADM umfassend) und die Kosten pro Einheit kombiniert. Die Kosten auf nationaler Ebene wurden aus Sicht des Schweizer Gesundheitswesens geschätzt.

Da keine Informationen über die Verteilung der verschiedenen Therapien auf die MDD-Patienten vorlagen, wurden mehrere Szenarien analysiert, darunter Monotherapien (z.B. nur Psychotherapie oder ADM für alle behandelten MDD-Patienten) und Kombinationen (z.B. 10% nur Psychotherapie und 90% Psychotherapie plus ADM). Wir gingen davon aus, dass die Patienten ein ganzes Jahr lang behandelt wurden, ohne dass die Behandlung abgebrochen oder zwischen den verschiedenen Behandlungsstrategien gewechselt wurde.

Resultate & Diskussion

A. Beurteilung der klinischen Wirksamkeit und Sicherheit

Im ersten Schritt unserer Suchstrategie haben wir 15 potenziell geeignete systematische Übersichtsarbeiten identifiziert. Basierend auf der AMSTAR-2 Qualitätsbeurteilung und der Vollständigkeit ihres Umfangs wurden zwei hochwertige systematische Übersichtsarbeiten ausgewählt. Im zweiten Schritt erfüllten 43 Publikationen (42 Studien) die Zulassungskriterien. Acht Studien untersuchten ADM versus CBT, vier Studien untersuchten ADM versus ADM plus CBT, und eine Studie untersuchte CBT versus ADM plus CBT. Zusätzlich untersuchten 20 Studien entweder ADM oder CBT versus Kontrollbedingungen. In 16 Studien wurden verschiedene ADM-Typen direkt miteinander verglichen, und sechs Studien verglichen verschiedene CBTs untereinander. Die Studiendauer reichte von 13 bis 168 Wochen. Insgesamt 22 Studien bewerteten einen der klinischen oder sicherheitsrelevanten Ergebnisparameter nach ≤12 Wochen, 29 Studien nach 13 bis 24 Wochen und 14 Studien nach ≥25 Wochen. 18 Studien, die alle ein ADM versus Placebo oder einem anderen ADM untersuchten, wurden von der pharmazeutischen Industrie gesponsert.

In dieser Zusammenfassung der Resultate stellen wir die Ergebnisse der paarweisen Meta-Analysen für die primären Endpunkte während der Fortsetzungs- und Erhaltungsphase vor.

Nur wenige Studien untersuchten die Wirksamkeit von ADM und CBT im Hinblick auf die Verringerung des Rückfall- oder Rezidivrisikos. Drei Studien untersuchten die Ergebnisparameter über einen Zeitraum von mehr als einem Jahr, und nur eine Studie wies eine dreijährige Nachbeobachtungszeit auf. Wir stuften das Verzerrungsrisiko in acht von neun Studien als hoch ein, was auf methodische Einschränkungen (fehlende Verblindung und verdeckte Zuteilung (allocation concealment)) und eine mögliche selektive Ergebnisberichterstattung zurückzuführen ist.

In der Fortsetzungsphase untersuchte nur eine Studie ADM versus CBT und berichtete über ein höheres, nicht signifikantes Rückfallrisiko bei Patienten, die ADM erhielten (RR=2.48, 95% CI= 0.69 bis 8.87). Verglichen mit Placebo wiesen Personen, die ADM erhielten, in zwei Studien ein geringeres Rückfallrisiko auf (zusammengefasste Analyse aufgrund unterschiedlicher Studiendesigns nicht möglich; RR= 0.49, 95% CI= 0.34 bis 0.68 und RR= 0.49, 95% CI= 0.29 bis 0.83). In der Erhaltungsphase schienen die Auswirkungen von ADM und CBT auf Rückfälle in zwei Studien vergleichbar zu sein (zusammengefasste Analyse nicht möglich; RR= 1.19, 95% CI= 0.50 bis 2.80 und RR= 0.86, 95% CI= 0.31 bis 2.40). In einer Studie wurde ein geringeres, aber nicht signifikantes Rückfallrisiko bei Patienten, die ADM plus CBT erhielten (66 Rückfälle in 44 Patienten), im Vergleich zu ADM allein (80 Rückfälle in 49 Patienten) berichtet. Eine zusammengefasste Analyse von Studien, die ADM und Placebo in der Erhaltungsphase verglichen, ergab keinen Unterschied zwischen den beiden Gruppen (RR= 0.84, 95% CI= 0.44 bis 1.59). In einer Studie, in der CBT und Placebo in der Erhaltungsphase verglichen wurden, wurde berichtet, dass die Teilnehmer in der CBT-Gruppe im Vergleich zu Placebo seltener einen Rückfall erlitten (16% bzw. 25%), der Unterschied war jedoch nicht signifikant. Die Qualität der Evidenz, gemäss GRADE, für den Vergleich zwischen ADM und CBT war gering, aufgrund des Verzerrungsrisiko und der Ungenauigkeit, und für ADM versus Placebo mässig.
In einer einzigen Studie waren die Rezidivraten der Patienten, die während der Erhaltungsphase (Behandlung bis zu drei Jahren) ADM oder ADM plus CBT erhielten, ähnlich (RR= 0.99; 95% CI = 0.69 bis 1.41).

Daten zu den Auswirkungen einer mittel- bis langfristigen Behandlung auf die QoL und das soziale Funktionsniveau von Patienten mit MDD wurden in sechs bzw. sieben Studien erhoben. Zwischen den Studien bestand eine grosse Heterogenität hinsichtlich der verwendeten Instrumente und der Bewertung spezifischer Endpunkte. Wir bewerteten das gesamte Verzerrungsrisiko bei den meisten Studien als hoch und die Qualität der Evidenz war für alle Vergleiche bei beiden Ergebnisparametern gering, mit Ausnahme von ADM versus Placebo beim sozialen Funktionsniveau (moderat).
In Bezug auf die QoL wurde in einer Studie berichtet, dass sich die QoL im Laufe der Zeit zwar sowohl in der ADM- als auch in der CBT-Gruppe verbesserte, jedoch in der Fortsetzungsphase kein signifikanter Unterschied zwischen den beiden Gruppen bestand. Die Autoren berichteten auch, dass die Verbesserung der Depression positiv mit der QoL verbunden war, was bedeutet, dass die Verbesserung der QoL im Verlauf der Behandlung teilweise auf eine Verringerung der depressiven Symptome zurückzuführen sein könnte. Daten, für die QoL in der Erhaltungsphase, lagen weder für die Kombinationsbehandlung noch für ADM versus CBT vor.
Auch für das soziale Funktionsniveau gab es zwar signifikante Verbesserungen in den Bewertungsergebnissen der Patienten, die während der Fortsetzungsphase ADM oder CBT oder eine Kombination davon erhielten, aber es gab keine Hinweise darauf, dass eine der beiden Methoden wirksamer war als die andere. Für den Vergleich von ADM versus Placebo wurde in einer Studie berichtet, dass die Verbesserung des sozialen Funktionsniveaus in der Fortsetzungsphase unter ADM signifikant grösser war. In der Erhaltungsphase fanden zwei Studien widersprüchliche Ergebnisse, wobei nur in einer

Studie eine signifikant bessere Verbesserung des sozialen Funktionsniveau gegenüber dem Ausgangswert nach 9 Monaten in der ADM-Gruppe festgestellt wurde. Wir haben keine Studien identifiziert, welche das soziale Funktionsniveau von Patienten, die in der Erhaltungsphase ADM, CBT oder dessen Kombination erhielten, untersuchten.

Insgesamt waren sowohl für die QoL als auch für das soziale Funktionsniveau die Veränderung der Effektgrösse in Punktwerte geringer als die der Veränderungen der depressiven Symptome, was darauf hindeutet, dass Verbesserungen in beiden Aspekten und die Rückkehr zur Normalität einen viel längeren Zeitraum erfordern könnten.

Die Akzeptanz wurde in 35 Studien bewertet. In der Fortsetzungsphase zeigten zusammengefasste Analysen ähnliche Akzeptanzraten zwischen ADM und CBT (RR= 1.57, 95% CI= 0.94 bis 2.62). Andererseits waren die Akzeptanzraten (weniger Studienabbrüche) bei ADM plus CBT besser als bei ADM allein (RR= 2.06, 95% CI= 1.31 bis 3.25) oder CBT allein (RR= 2.12, 95% CI= 1.29 bis 3.48). In der Erhaltungsphase berichtete eine Studie über keinen Unterschied zwischen ADM und CBT (RR=1.21, 95% CI= 0.87 bis 1.81), während eine andere Studie über niedrigere Abbruchraten bei ADM im Vergleich zu CBT berichtete (RR=0.62, 95% CI= 0.41 bis 0.93). Die Qualität der Evidenz war für alle Vergleiche gering mit Ausnahme von ADM versus Placebo.

Über die Verträglichkeit wurde in 24 Studien berichtet. In der Fortsetzungsphase berichtete eine Studie über eine geringere Verträglichkeit (mehr Abbrüche aufgrund von AEs) von ADM im Vergleich zu CBT (9% gegenüber 0%). Im Vergleich zu Placebo war ADM weniger gut verträglich (RR= 3.46, 95% CI= 1.65 bis 7.25). Es gab keine Studien zum Vergleich der Verträglichkeit von ADM und CBT in der Erhaltungsphase. Was die unerwünschten Wirkungen betrifft, so waren die Berichte über unerwünschte Wirkungen in den einzelnen Studien inkonsistent, und mangelten eindeutig für CBT und ADM plus CBT. Aus den verfügbaren Daten geht jedoch hervor, dass bei einem hohen Anteil der Patienten sowohl in der Fortsetzungs- als auch in der Erhaltungsphase unerwünschte Wirkungen auftraten, insbesondere bei denjenigen, die ADM erhielten. Während die vorliegenden Daten darauf hindeuten, dass ADM aus der Sicht der Akzeptanz und Verträglichkeit nicht optimal war, muss darauf hingewiesen werden, dass ein Vergleich der AEs zwischen ADM versus CBT mit Vorsicht zu geniessen ist, da von AEs in CBT-Studien häufig nicht berichtet wurde, was zu einer möglichen Unterschätzung ihrer Schäden führen könnte.

Die Untersuchungsergebnisse dieser Übersichtsarbeit müssen unter Berücksichtigung einiger Einschränkungen, in Bezug auf das Überprüfungsverfahren als auch der Evidenzbasis, betrachtet werden. Eine wesentliche Einschränkung betrifft die Heterogenität der eingeschlossenen Studien, die unterschiedliche Populationen, Interventionen und Vergleichsinterventionen umfassten. Ausserdem gab es erhebliche Unterschiede in den Studiendesigns und -durchführungen, die sich hauptsächlich auf die fehlende Verblindung in den CBT-Studien bezogen. Diese Faktoren könnten die Transitivitätsannahme unserer Netzwerk-Metaanalysen verletzen, und die fehlende Verblindung könnte zu einer Überbewertung der CBT Wirksamkeit führen. Die

Einschränkungen bezüglich der Evidenzbasis betreffen den Mangel an Daten, insbesondere in Bezug auf die AEs von CBT. Aufgrund der geringen Studienanzahl konnten wir nicht beurteilen, ob die Auswirkungen der verschiedenen Interventionen auf Rückfall und Rezidiv in den verschiedenen MDD-Schweregradgruppen unterschiedlich waren. Darüber hinaus wiesen die meisten Studien methodische Einschränkungen auf und waren mit einem hohen Verzerrungsrisiko behaftet, was die Validität der Ergebnisse schwächte. Schliesslich haben wir nur RCTs in unsere Analyse einbezogen, die in der Regel sorgfältig ausgewählte Populationen umfassen, die möglicherweise nicht repräsentativ für die Allgemeinbevölkerung sind, und Verfahren, welche nicht die reale klinische Praxis widerspiegeln.

B. Nutzen-Schaden-Abwägung

Bei der Risikoabwägung eines verhinderten Rückfalls gegen das übermässige Risiko schädlicher Ergebnisse auf der gleichen Skala, zeigten MDD-Patienten, welche mit CBT behandelt wurden, über 12 Monate einen klinischen Nettonutzen gegenüber den Patienten, welche mit ADM behandelt wurden. Die entsprechende Wahrscheinlichkeit des Nettonutzens in Bezug auf die Verhinderung eines Rückfalls betrug 91.8% für CBT im Vergleich zu ADM, wenn man die spezifischen Schadensfolgen berücksichtigt, und 98.2%, wenn der allgemeine Studienabbruch als Schadensfolge betrachtet wurde.

Während die obigen Resultate auf Behandlungsschätzungen aus RCTs mit kürzerer Nachbeobachtungszeit (>12 bis <25 Wochen) basierten, wiederholten wir die Analyse mit Daten aus RCTs mit 25 Wochen und längerer Nachbeobachtungszeit, wobei wir dieses Mal nur den allgemeinen Studienabbruch insgesamt als Schadensendpunkt verwendeten. Die CBT blieb der ADM überlegen, mit einer Wahrscheinlichkeit für einen klinischen Nettonutzen von 77.1%. Dies bedeutet, dass der Nettonutzen im Vergleich zu den obigen Ergebnissen im Laufe der Zeit abnimmt. Die Kombination von CBT und ADM steigerte jedoch die Wahrscheinlichkeit eines klinischen Nettonutzens auf 96.7% im Vergleich zu ADM allein und auf 80% im Vergleich zu CBT allein.
In absoluten Zahlen ausgedrückt betrug die Anzahl der Rückfall-Äquivalente (d.h. der klinische Nettonutzen), die über einen Zeitraum von 12 Monaten verhindert würden, 346 von 1000 MDD-Patienten, welche mit CBT anstelle von ADM behandelt wurden, wenn die Behandlungseffekte aus RCTs mit kürzeren Nachbeobachtungszeit berücksichtigt wurden. Dieser Wert verringerte sich auf 126 von 1000 Patienten, wenn nur die Ergebnisse von RCTs mit einer Nachbeobachtungszeit von mehr als 6 Monaten berücksichtigt wurden. Der Rückgang der Wirkung kehrte sich jedoch in einen günstigeren klinischen Nettonutzen der Kombinationstherapie aus CBT und ADM im Vergleich zur Monotherapie mit ADM nach 12 Monaten (d.h. 228 abgewendete Rückfälle bei 1000 Patienten) oder CBT (d.h. 126 abgewendete Rückfälle bei 1000 Patienten) um.

Mehrere Sensitivitätsanalysen bestätigten die Vorzüge von CBT gegenüber von ADM und ihrer Kombination gegenüber der Monotherapie. Dies lag vor allem daran, dass CBT mit niedrigeren Rückfallraten, einer geringeren Abbruchquote und geringeren

sicherheitsrelevanten Ergebnisparameter verbunden war als ADM. Daher unterschieden sich die Ergebnisse nicht wesentlich, selbst wenn sich die Risiken für die Patienten und die Präferenzwerte für Rückfälle und Abbrüche änderten. Es ist jedoch anzumerken, dass es sich bei dieser Bewertung um eine der ersten BHAs handelt, die im Zusammenhang mit MDD-Interventionen durchgeführt wurden, und dass es nur wenige Belege für einen Vergleich gibt.

Unsere Ergebnisse sollten mit Vorsicht interpretiert und müssen unter Berücksichtigung einiger Einschränkungen der Studie betrachtet werden. Dazu gehört die mangelnde Detailliertheit der gemeldeten Schadensdaten (z.B. Schätzungen für alle verschiedenen Arten und Schweregrade von AEs), insbesondere in CBT Studien, was zu einer Unterschätzung der tatsächlichen Schäden führen könnte. Wir haben uns jedoch nicht nur auf spezifische AEs als Schadensergebnis verlassen, sondern alternativ auch Studienabbrüche im Allgemeinen verwendet, über die in den Studien konsistenter berichtet wurde, mit ähnlichen Ergebnissen bei Verwendung beider Ergebnisse als Schadensergebnis. Zu den weiteren Einschränkungen gehören die ausschliessliche Verwendung von RCT-Daten, wodurch die Raten der Schadensergebnisse in der Allgemeinbevölkerung möglicherweise unterschätzt werden, das Fehlen detaillierter Daten zu relevanten Nutzenergebnissen wie Genesung und Rezidiv sowie die Verwendung allgemeiner Präferenzgewichtungen anstelle von Gewichtungen, die aus Präferenzstudien abgeleitet wurden. Insgesamt sollten die Leser den geschätzten klinischen Nettonutzen nicht als endgültig ansehen, da es schwierig ist, das Ausmass abzuschätzen, in dem sich diese Einschränkungen auf den geschätzten klinischen Nettonutzen auswirken könnten. Wir sind jedoch zuversichtlich, dass das relative Nutzen-Schaden-Verhältnis der verschiedenen Therapien angemessen erfasst wurde, insbesondere für den Zeithorizont von 12 Monaten oder weniger. Unsere Analyse kann aktualisiert werden, wenn neue Daten zu den Eingangsparametern verfügbar sind.

C. Gesundheitsökonomische Literaturübersicht

Von den 2689 Zitierungen, die bei der elektronischen Datenbankrecherche ermittelt wurden, kamen 33 Kosten-Wirksamkeit-Analysen in Frage: 14 von ihnen bewerteten ADM als Interventionsstrategie, während 19 CBT bewerteten. Die Vergleichsinterventionen variierten von Studie zu Studie. 29 der 33 in diese Untersuchung einbezogenen Kosten-Wirksamkeits-Analysen verwendeten einen Zeithorizont von mehr als 12 Wochen. Die meisten Kosten-Wirksamkeits-Analysen zu ADM wurden von Pharmaunternehmen gesponsert, während alle Kosten-Wirksamkeits-Analysen zu CBT vom öffentlichen Sektor finanziert wurden.

Die meisten der eingeschlossenen Kosten-Wirksamkeits-Analysen von ADMs waren modellbasiert. Die am häufigsten untersuchten Behandlungen waren Escitalopram (ein SSRI), Venlafaxine (SNRI), Sertraline (SSRI), Duloxetine (SNRI) und die SSRIs als Gruppe.

Sechs Kosten-Wirksamkeits-Analysen kamen zu dem Schluss, dass die Kosten-Wirksamkeit von Escitalopram im Vergleich zu anderen ADMs günstiger belegt war. Alle diese Analysen basierten auf klinischen Daten, die zeigten, dass die Wahrscheinlichkeit einer Remission oder eines Ansprechens für Escitalopram im Vergleich zu allen anderen Vergleichsinterventionen am höchsten war. In allen Kosten-Wirksamkeits-Analysen, in denen Venlafaxine, Sertraline oder Duloxetine mit Escitalopram verglichen wurden, wurde geschätzt, dass Escitalopram die dominante Strategie (d.h. kostengünstiger und wirksamer) oder sehr kosteneffektiv (d.h. mit sehr niedrigen ICERs) war. Auch nach der zahlenmässigen Anpassung für die Schweiz erwies sich Escitalopram in den meisten Fällen als dominante Strategie.

Venlafaxine wurde in sechs Kosten-Wirksamkeits-Analysen entweder als Intervention oder als Vergleichsinterventionen untersucht. Beim Vergleich mit Escitalopram wurde Venlafaxine in den meisten Fällen dominiert (d.h. es war teurer, aber weniger wirksam) oder es wurde als weniger teuer, aber weniger wirksam eingestuft. Im Gegensatz dazu wurde Venlafaxine im Vergleich zu anderen ADMs (z.B. Citalopram, Duloxetine, Fluoxetine, Paroxetine, Sertraline) im Allgemeinen als dominante Strategie angesehen.

In sechs Kosten-Nutzen-Analysen wurde Sertraline mit Placebo oder einer Reihe von Antidepressiva verglichen. Sertraline wurde im Vergleich zu Citalopram als dominante Strategie angesehen (sowohl aus gesundheitlicher als auch aus gesellschaftlicher Sicht), während es im Vergleich zu Escitalopram, Venlafaxine und Agomelatine dominierte. Bei allen anderen Vergleichen waren die Ergebnisse uneinheitlich.

Duloxetine wurde in vier Kosten-Wirksamkeits-Analysen als Vergleichsinterventionen bewertet. In drei von ihnen wurde es von Escitalopram dominiert. Der Vergleich mit anderen ADMs ergab widersprüchliche Ergebnisse.

Die drei Kosten-Wirksamkeits-Analysen, in denen SSRI als Gruppe betrachtet wurden, ergaben, dass SSRI im Vergleich zu anderen ADM oder der üblichen Behandlung kosteneffektiv waren.
Bei den meisten Kosten-Wirksamkeits-Analysen, die CBT untersuchten, handelte es sich um Analysen innerhalb einer Studie. Wir haben acht Kosten-Wirksamkeits-Analysen identifiziert, die darauf hindeuten, dass die CBT kosteneffektiv oder dominant war, wenn sie mit der üblichen Behandlung oder ADM verglichen wurde. Es gab jedoch auch fünf Kosten-Wirksamkeits-Analysen, die das Gegenteil ergaben (d.h. ADM oder die übliche Behandlung waren die dominanten Strategien, oder die ICER für CBT war im Vergleich zu den Vergleichsinterventionen sehr hoch, so dass sie nicht auf eine Kosten- Wirksamkeit hindeuteten).

Unsere Ergebnisse müssen angesichts mehrerer Einschränkungen sorgfältig interpretiert werden. Dazu gehört die grosse Heterogenität der identifizierten Studien in Bezug auf unterschiedliche Populationen, Interventionen und Vergleichsinterventionen, Zeitrahmen und Kostenarten, insbesondere für CBT-Interventionen. Darüber hinaus wurde die Mehrzahl der Kosten-Wirksamkeits-Analysen von ADM von

Pharmaunternehmen gesponsert, was potenziell zu Verzerrungen führen kann. Andererseits könnten die Behandlungseffekte in CBT-Studien mit der Loyalität der Forscher zusammenhängen, was ebenfalls eine mögliche Verzerrung darstellen könnte. Schliesslich gelten die Einschränkungen der klinischen Evidenzbasis auch für die gesundheitsökonomische Literaturübersicht.

Es ist wichtig zu erwähnen, dass es einige methodische Unterschiede zwischen der klinischen und der ökonomischen Überprüfung dieses HTA gab, darunter die Einbeziehung von Patienten mit erheblicher depressiver Symptomatik in der gesundheitsökonomische Literaturübersicht im Gegensatz zur klinischen Literaturübersicht, die sich auf Patienten mit diagnostizierter MDD konzentrierte. Während im klinischen Teil alle internationalen Studien berücksichtigt wurden, wurden im ökonomischen Teil ostasiatische Länder ausgeschlossen, da sie sich in Bezug auf die Rahmenbedingungen, die Kosten und die Wahrnehmung der Lebensqualität wahrscheinlich erheblich von der Schweiz unterscheiden. Im Gegensatz zur klinischen systematischen Übersichtsarbeit, die nur CBT-Interventionen mit einer Dauer von mehr als 12 Wochen einschloss, haben wir zudem zwei Kosten-Wirksamkeits-Analysen zu CBT einbezogen, die eine Behandlungsdauer von möglicherweise weniger als 12 Wochen angaben (in diesen Studien berichteten die Autoren über 6 – 8 wöchentliche CBT-Lektionen/Module, gaben aber nicht an, ob die Lektionen/Module in möglichst kurzer Zeit aufeinanderfolgend durchgeführt wurden oder ob sie über einen Zeitraum von mehr als 12 Wochen verteilt waren). Generell ist zu betonen, dass in vielen Fällen die tatsächliche Dauer von CBT nicht in Monaten, sondern in der Anzahl der Sitzungen oder Module angegeben wurde. Die genaue Verteilung der Sitzungen/Module über die Zeit wurde oft nicht angegeben.

D. Budget Impact-Analyse

Wir schätzten die Gesamtzahl, der in der Schweiz im Jahr 2020 behandelten MDD-Patienten, auf 334'835. Die direkten medizinischen Gesamtkosten wurden zwischen 5.330 Mio. CHF (unter der Annahme, dass MDD-Patienten ausschliesslich mit dem günstigsten ADM behandelt wurden und keine Psychotherapie erhielten) und 6.032 Mio. CHF (unter der Annahme, dass alle MDD-Patienten eine Psychotherapie erhielten und mit dem teuersten ADM behandelt wurden) geschätzt. Je nach Verteilung der Behandlungen und Kostenannahmen machten die Krankenhauskosten 82% bis 92% der Gesamtkosten aus. Die Kosten für Arztbesuche, Psychotherapie und ADM schienen eine relativ geringe Rolle zu spielen. Die Behandlungskosten reichten von 84 Millionen CHF (unter der Annahme, dass alle behandelten MDD-Patienten nur das kostengünstigste ADM und keine Psychotherapie erhielten) bis zu 800 Millionen CHF (unter der Annahme, dass alle MDD-Patienten sowohl Psychotherapie als auch das teuerste ADM erhielten). Die Kosten für eine alleinige psychotherapeutische Behandlung aller MDD-Patienten wurden auf 603 Mio. CHF geschätzt (unter der Annahme von 12 Sitzungen pro Jahr).

Die Budget Impact Schätzung erforderte zahlreiche Annahmen und ist daher mit erheblichen Einschränkungen verbunden. Dazu gehören eine mögliche Unterschätzung der Zahl der Patienten, die für eine MDD-Behandlung in Frage kommen, eine Unterschätzung der Krankenhauskosten und die Nichtberücksichtigung der Kosten für diagnostische Tests und begleitende Medikamente. Ausserdem haben wir den Wechsel oder den Abbruch von Behandlungen nicht berücksichtigt. Die Informationen über die Unterschiede in Bezug auf Produktivitätsverluste, depressionsbedingte Arbeitsunfähigkeit oder vorzeitige Pensionierung und depressionsbedingte Selbstmorde in Abhängigkeit von den verschiedenen Behandlungsoptionen reichten nicht aus, um die Analysen aus gesellschaftlicher Sicht durchzuführen.

Schlussfolgerung

Dieses HTA versuchte eine umfassende Bewertung der klinischen Wirksamkeit, der Sicherheit, der Nutzen-Schaden-Abwägung und der gesundheitsökonomischen Charakteristika von ADM und CBT bei erwachsenen Patienten mit MDD aus einer mittel- bis langfristigen Perspektive zu untersuchen.

Innerhalb der verfügbaren Daten fanden wir keine Hinweise auf einen Unterschied zwischen ADM, CBT und ihrer Kombination in Bezug auf die primären klinischen Wirksamkeitsresultate, einschliesslich QoL und soziales Funktionsniveau. Allerdings schien ADM allein aus der Perspektive der Akzeptanz und Verträglichkeit nicht optimal zu sein. Unsere Ergebnisse müssen angesichts der Einschränkungen, wie der grossen Heterogenität der eingeschlossenen Studien sowie des Verzerrungsrisikos aufgrund der fehlenden Verblindung in CBT-Studien sorgfältig interpretiert werden. Die Nutzen-Schaden-Abwägung, welche sowohl das Risiko von Ergebnisparametern als auch Präferenzen berücksichtigte, ergab eine relativ grössere Wahrscheinlichkeit eines mittel- bis langfristigen klinischen Nettonutzens für CBT als für ADM oder für die Kombination von CBT und ADM als für die Monotherapie. Die tatsächliche Nutzen-Schaden-Abwägung wird jedoch möglicherweise nicht angemessen erfasst, da in den Studien keine oder nur unzuverlässige Berichte über AEs vorgelegt wurden, insbesondere im Zusammenhang mit CBT-Interventionen. Systematischere und detailliertere Beurteilung und Berichte über mittel- bis langfristige klinische Ergebnisse, insbesondere QoL, soziales Funktionsniveau und AEs in den RCTs würden eine bessere Bewertung der verschiedenen Interventionen in diesen Bereichen sowie die Durchführung einer umfassenderen BHA ermöglichen. Die Ergebnisse der ökonomischen systematischen Literaturübersicht legen nahe, dass Escitalopram die kosteneffektivste Behandlung unter den eingeschlossenen Antidepressiva sein könnte, gefolgt von Venlafaxine, Sertraline und Duloxetine.

Die Kosten-Wirksamkeits-Analysen, die CBT oder internetbasierte CBT mit ADM oder übliche Behandlung verglichen, führten zu widersprüchlichen Ergebnissen. Die Budget Impact-Analyse deutet darauf hin, dass die direkten medizinischen Gesamtkosten von MDD pro Jahr zwischen CHF 5.330 Millionen und CHF 6.032 Millionen liegen könnten. Die

wichtigsten Kostentreiber waren die geschätzte Anzahl behandelter MDD-Patienten und die Krankenhausaufenthalte. Dieses Ergebnis unterstreicht, dass Krankenhausaufenthalte aufgrund von MDD ein wichtiges klinisches Ergebnis sind, das zusammen mit anderen Auswirkungen auf die berufliche Tätigkeit und das Wohlbefinden idealerweise durch klinische Studien und Beobachtungsstudien erfasst werden sollte, um eine umfassendere Bewertung von MDD-Behandlungen zu ermöglichen. Die Kosten für Psychotherapie und ADM hingen von der angenommenen Behandlungsverteilung ab. Die Kosten für eine alleinige Psychotherapie wurden auf 603 Mio. CHF geschätzt, während die Kosten für eine Kombinationsbehandlung zwischen 687 Mio. CHF und 801 Mio. CHF liegen würden.

Zusammenfassend stellten wir fest, dass sowohl ADM- als auch CBT-Interventionen effiziente Optionen für die Behandlung von MDD zu sein scheinen, wobei keine der beiden definitiv besser abschneidet als die andere. Während unsere Nutzen-Schaden-Abwägung schien darauf hinzudeuten, dass CBT-Interventionen einen grösseren klinischen Nutzen für MDD-Patienten bieten als ADM, zeigte die systematische Übersichtsarbeit der Kosten-Wirksamkeits-Analysen, angepasst an den Schweizer Kontext, dass CBT auch teurer sein kann, je nachdem, wie sie durchgeführt wird (Anzahl der Sitzungen, online vs. face-to-face). Diese Ergebnisse müssen angesichts der methodischen Unzulänglichkeit der Übersichtsarbeit und der Evidenzbasis sowie der potenziell begrenzten Übertragbarkeit der Ergebnisse kontrollierter Studien auf reale klinische Situationen sorgfältig interpretiert werden.

1.3 Résumé

Introduction

Le Major Depressive Disorder (MDD) est l'un des troubles de santé mentale les plus courants et représente un enjeu considérable tant sur le plan sociétal et économique. Le MDD est principalement traité par des médicaments antidépresseurs (antidepressant medications, ADM) ou par la psychothérapie, dont la thérapie cognitivo-comportementale (cognitive behavioural therapy, CBT) est la thérapie utilisé le plus souvant. Le choix du traitement initial dépend de plusieurs facteurs, tels que la gravité des symptômes de la dépression, les coûts ou les préférences du patient. Le traitement est souvent poursuivi pendant plusieurs mois afin d'obtenir une rémission et prévenir les rechutes, et chez les patients présentant des facteurs de risque de récidive le traitement est poursuivi jusqu'à trois ans. La détermination de l'efficacité des différentes interventions est largement basée sur des essais contrôlés randomisés (randomized controlled trials, RCTs) à court terme couvrant la phase de traitement aigu (jusqu'à 12 semaines). L'efficacité à plus long terme est incertaine. En outre, en raison de la durée courte des études, on sait peu sur la persistance et le développement des effets indésirables (adverse effects, AE). Jusqu'à présent ce manque de preuves a empêché une évaluation adéquate du rapport risque-bénéfice des thérapies du MDD.

Objectif

Le but de cette Health Technology Assessment (HTA), est d'évaluer l'efficacité et la sécurité cliniques, l'équilibre bénéfices-inconvénients et les caractéristiques économiques de santé des interventions ADM et CBT, administrées seules ou en combinaison, chez les patients souffrant de MDD et recevant ces traitements au-delà de la phase de traitement aigu (c'est-à-dire, >12 semaines) en Suisse.

Méthodes

A. PICO

La **population concernée par** cette HTA est constituée d'adultes souffrant de MDD.

Nous avons étudié les **interventions** suivantes :

1. Antidépresseurs
2. Thérapies cognitivo-comportementales

Nous avons considéré les traitements de **comparaison** suivants :

- ADM ou CBT en monothérapie
- Combinaison de l'ADM et des CBT
- Conditions de contrôle (placebo, liste d'attente, traitement habituel)

Nous avons défini les **paramètres de résultat** suivants :

- Paramètres de résultat de l'efficacité clinique :
  - Primaire : rechute, récidive, qualité de vie (QoL), fonctionnement social.
  - Secondaire : réponse, rémission
- Paramètres de résultat de sécurité :
  - Primaire : acceptabilité (c'est-à-dire proportion de participants qui se sont retirés de l'étude pour une raison quelconque), aggravation de la dépression, mortalité.
  - Secondaire : effets indésirables spécifiques, tolérance (c'est-à-dire la proportion de participants qui se sont retirés de l'étude en raison d'effets indésirables).
- Paramètres de résultat économiques de santé : coûts, années de vie ajustées à la qualité de vie (QALY), rapports coût-efficacité incrémentiels (ICER).

B. Évaluation de l'efficacité et de la sécurité cliniques

Dans l'évaluation de l'efficacité et de la sécurité cliniques des différents traitements du MDD, le délai a été divisé en trois périodes basées sur les phases de prise en charge du MDD (c'est-à-dire, la phase de traitement aigu : ≤12 semaines, la phase de continuation : 13 à 24 semaines, et la phase de maintien : ≥25 semaines). Nous avons considéré les paramètres de résultat, évalués à >12 semaines comme étant à moyen ou long terme. Les ECR classiques ainsi que les ECR de discontinuation ont été inclus (c'est-à-dire les essais dans lesquels les participants ont reçu un traitement ouvert dans la phase de traitment aigu et ceux qui ont répondu ont ensuite été assignés de manière aléatoire à la poursuite du traitement soit à un placebo soit un contrôle actif).

Afin d'identifier les RCT pertinents nous avons effectué un stratégie de recherche en deux étapes. D'abord, nous avons effectué une recherche documentaire systématique avec les bases de données Ovid Medline et Cochrane Library, pour trouver des revues systématiques de haute qualité sur les interventions de MDD publiées entre 2018 et 2020. Trois évaluateur ont examiné toutes les revues systématiques de manière indépendante pour vérifier leur pertinence et ont évalué leur qualité à l'aide de la liste de contrôle "Assessing the Methodological Quality of Systematic Reviews" (AMSTAR)-2. Deuxièmement, nous avons effectué des recherches systématiques de littérature en utilisant les mêmes stratégies de recherche que dans les revues systématiques jugées de haute qualité selon AMSTAR-2. Nous avons effectué des recherches dans Medline, EMBASE, PsycInfo et la Cochrane Library. Deux des trois examinateurs ont passé en revue de manière indépendant les enregistrements identifiés par les recherches systématique de littérature afin de trouver des études potentiellement pertinentes à inclure.

Nous avons extrait les informations pertinentes sur la conception et aux caractéristiques de l'étude, les caractéristiques démographiques des participants à l'étude , les détails sur les interventions et les résultats de l'étude, et les interventions de comparaison, ainsi que les paramètres évalués. Nous avons évalué le risque de biais (RoB) des RCT inclus sur la

base des paramètres de résultat de l'efficacité clinique primaire et de sécurité en utilisant l'outil RoB 2.0. Dans la mesure du possible, nous avons effectué des méta-analyses par paires et en réseau pour les différentes comparaisons et les différents paramètres de résultats, puis nous avons calculé des rapports de risque (Risk Ratio, RR) agrégés avec leurs intervalles de confiance (IC) à 95%. Les analyses ont été menées au niveau de la modalité de traitement général (par exemple, ADM vs CBT) et séparément pour chaque phase de traitement. En raison de l'hétérogénéité des études en termes de conception (y compris l'absence d'aveugle dans les études évaluant les interventions de CBT) et de caractéristiques des participants, ce qui pourrait affecter la validité des résultats des méta-analyses en réseau, nous avons considéré les méta-analyses par paires comme les analyses primaires et nous avons interprété nos résultats en conséquence. Puisque l'objectif de cette étude était de faire une évaluation comparative de l'ADM et de la CBT et de leur combinaison, nous avons d'abord présenté les résultats de ces comparaisons directes, puis la comparaison de l'ADM ou de la CBT par rapport au placebo, à la liste d'attente ou au traitement habituel. Dans les cas où une méta-analyse n'était pas possible ou appropriée en raison du manque de données ou de l'hétérogénéité des données, nous avons résumé les preuves de manière narrative. Enfin, la qualité des preuves pour ces résultats primaires a été évaluée dans la phase de continuation en utilisant la méthodologie GRADE (Grading of Recommendations Assessment, Development, and Evaluation).

C. *Évaluation des avantages et des inconvénients (BHA)*

Les avantages (réduction du risque de rechute) ont été mis en balance avec les inconvénients (abandons de l'étude en général (acceptabilité) ou AE spécifiques, notamment neurologiques, respiratoires, gastro-intestinaux, suicidaires, psychiatriques et musculo-squelettiques) pour estimer le bénéfice clinique net de la CBT, de l'ADM ou de leurs combinaisons.

L'analyse a pris en compte : (i) les effets relatifs du traitement (efficacité en termes de réduction du risque de rechute et le risque accru d'AE), (ii) les risques liés aux paramètres de résultats comme base pour estimer l'ampleur de l'impact absolu des interventions de traitement dans la population générale du MDD, (iii) les préférences comme mesure de l'importance relative des résultats bénéfiques et inconvénients, et (iv) un horizon temporel de 12 mois pour l'estimation de risque cumulatif des résultats bénéfiques et inconvénients, ce qui équivaut à une durée moyenne de traitement dans la phase d'entretien.

En supposant des taux constants de rechute et d'abandons de l'étude en général, et d'autres effets indésirables sur 12 mois, les risques cumulatifs de ces effets ont été estimés avec un modèle exponentiel pour une cohorte théorique de 1000 patients recevant les différentes interventions. Ensuite les différences absolues dans les taux d'incidence des paramètres de résultats entre les interventions ont été calculées, puis pondérées individuellement en fonction des préférences des patients afin d'obtenir un indice

d'équilibre avantages-inconvénients ou un bénéfice clinique net. L'analyse a été effectuée de manière stochastique avec 100 000 répétitions tenant compte de l'incertitude des estimations des paramètres afin de générer une distribution du bénéfice clinique net. Cette distribution a été utilisée pour calculer la probabilité que les patients recevant les interventions, obtiennent un bénéfice clinique net. Une probabilité supérieure à 60% a été interprétée comme un bénéfice clinique net (ou plus de bénéfices cliniques que d'inconvénients), tandis qu'une valeur inférieure à 40 % a été interprétée comme un inconvénient net (moins de bénéfices que d'inconvénients) ou comme n'étant ni inconvénient ni bénéfique (40 à 60%). En outre, nous avons estimé le bénéfice clinique net absolu sur l'horizon temporel de 12 mois. Comme la BHA dépend fortement du choix de l'évidence des preuves pour les paramètres d'entrée, nous avons testé la sensibilité du bénéfice clinique net à différentes estimations alternatives, y compris un horizon temporel plus long (24 mois), des pondérations de préférence variables et un risque de rechute différent au départ.

D. Recherche de la littérature sur l'économie de la santé

Pour l'analyse économique systématique, une stratégie de recherche a été élaborée afin d'identifier toute la littérature pertinente dans les différentes bases de données, telles que MEDLINE, EMBASE et la base de données du Centre for Review and Dissemination (CRD). La chaîne de recherche a été obtenue en intégrant et en combinant la chaîne de recherche utilisée dans la partie clinique dans la partie clinique de cette evaluation, et les chaînes de recherche utilisées dans l'analyse économique de santé. Un processus en deux phases a été mené, consistant en un tri des titres/résumés et un tri du texte intégral.
L'extraction des données et l'évaluation de la qualité ont été effectuées pour tous les articles contenant une étude complète d'évaluation économique de la santé selon la liste de contrôle en 24 points des Consolidated Health Economic Evaluation Reporting Standards (CHEERS). Les données démographiques de la population et les caractéristiques de l'étude ont été résumées. Les mesures et les sources de l'efficacité clinique et des coûts ont été synthétisées. Les résultats des analyses coût-efficacité, couvrant différentes comparaisons de traitements au sein d'une même étude ainsi qu'entre plusieurs études, ont été adaptés numériquement à la Suisse. Seules les analyses coût-efficacité qui rapportent les ICER en termes de coûts par QALY gagnée ont été incluses dans l'examen économique de la santé.

E. Analyse de l'impact budgétaire

L'analyse de l'impact budgétaire a été réalisée en deux étapes principales. Tout d'abord, le nombre total de patients MDD éligibles en 2020 en Suisse a été estimé. À cette fin, les données de l'Enquête suisse sur la santé 2017 ont été combinées avec les données démographiques suisses de 2020. Deuxièmement, le nombre de patients éligibles a été combiné avec l'utilisation des ressources estimée (couvrant les hospitalisations, les

visites chez le médecin, la psychothérapie et le AMD) et les coûts par unit. Les coûts au niveau national ont été estimés du point de vue du système de santé suisse.

En l'absence d'informations sur la distribution des différentes thérapies parmi les patients souffrant de MDD, plusieurs scénarios ont été analysés, y compris les monothérapies (par exemple, seulement la psychothérapie ou seulement l'ADM pour tous les patients souffrant de MDD traités) et les combinaisons (par exemple, 10% seulement de psychothérapie et 90% de psychothérapie plus ADM). Nous avons supposé, que les patients seraient traités pendant une année entière, sans arrêter le traitement ni des changement entre les différentes stratégies de traitement.

Résultats et discussion

A. Évaluation de l'efficacité et de la sécurité cliniques

Dans la première étape de notre stratégie de recherche, nous avons identifié 15 revues systématiques potentiellement appropriées. Sur la base de l'évaluation de la qualité AMSTAR-2 et de l'exhaustivité de leur champ d'application, deux revues systématiques de haute qualité ont été sélectionnées. Dans la deuxième étape, 43 publications (42 études) ont répondu aux critères d'éligibilité. Huit études ont évalué l'ADM par rapport à la CBT, quatre études ont évalué l'ADM par rapport à l'ADM plus la CBT, et une étude a évalué la CBT par rapport à l'ADM plus la CBT. En outre, 20 études ont évalué soit l'ADM soit la CBT par rapport à des conditions de contrôle. Seize études ont directement comparé différents types d'ADM, et six études ont comparé différentes types de CBT . La durée des études était comprise entre 13 et 168 semaines. Au total, 22 études ont évalué l'un des paramètres de résultats cliniques ou de sécurité à ≤12 semaines, 29 études à 13 à 24 semaines et 14 études à ≥25 semaines. 18 études, qui ont tous évalué un ADM par rapport à un placebo ou à un autre ADM, ont été parrainés par l'industrie pharmaceutique.

Dans ce résumé des résultats, nous présentons les résultats des méta-analyses par paires pour les critères d'évaluation primaires pendant les phases de continuation et de maintien.

Peu d'études ont examiné l'efficacité de l'ADM et de la CBT pour réduire le risque de rechute ou de récidive. Trois études ont évalué les paramètres de résultats sur une période de plus d'un an et une seule étude a eu une période de suivi de trois ans. Nous avons évalué le risque de biais comme étant élevé dans huit des neuf études en raison de limitations méthodologiques (absence d'aveugle et de dissimulation de l'allocation) et d'une possible présentation sélective des résultats.

Dans la phase de continuation, une seule étude a évalué l'ADM par rapport à la CBT et a rapporté un risque de rechute plus élevé, mais non significatif, chez les patients recevant l'ADM (RR= 2,48, IC à 95%= 0,69 à 8,87). Deux études ont montré que, comparativement

au placebo, les personnes recevant l'ADM présentaient un risque de rechute plus faible (analyse groupée impossible en raison des différents modèles d'étude ; RR= 0,49, IC à 95 % = 0,34 à 0,68 et RR= 0,49, IC à 95 % = 0,29 à 0,83). Dans deux études successives, il a été montré que dans la phase d'entretien les effets de l'ADM et de la CBT semblaient être comparables (analyse groupée impossible ; RR= 1,19, IC 95 % = 0,50 à 2,80 et RR= 0,86, IC 95 % = 0,31 à 2,40). Une étude a rapporté un risque de rechute plus faible, mais non significatif, chez les patients recevant ADM plus la CBT (66 rechutes chez 44 patients) par rapport à l'administration seule de l'ADM (80 rechutes chez 49 patients). L'analyse groupée des études comparant l'ADM et le placebo dans la phase d'entretien n'a révélé aucune différence entre les deux groupes (RR= 0,84, IC 95 %= 0,44 à 1,59). Dans une étude comparant la CBT et le placebo dans la phase d'entretien, il a été rapporté que les participants du groupe CBT étaient moins susceptibles de rechuter que ceux du groupe de placebo (16 % contre 25 %, respectivement), mais la différence n'était pas significative. La qualité des preuves, selon le système GRADE, pour la comparaison entre l'ADM et la CBT était faible, en raison du risque de biais et d'imprécision, et était modérée pour l'ADM contre le placebo.
Seulement une étude a rapporté, que les taux de rechute étaient similaires entre les personnes recevant seulement ADM ou ADM plus CBT pendant la phase d'entretien (traitement jusqu'à trois ans) (RR= 0,99 ; IC 95 % = 0,69 à 1,41).

Des données sur les effets d'un traitement à moyen et à long terme sur la QoL et le niveau de fonctionnement social des patients souffrant de MDD ont été rapportées dans six et sept études, respectivement. En ce qui concerne les instruments utilisés et l'évaluation des critères d'évaluation spécifiques, il y avait une hétérogénéité considérable entre les études. Nous avons évalué que le risque global de biais de la plupart des études était élevé et que la qualité des preuves était faible pour toutes les comparaisons dans les deux paramètres de résultats, à l'exception de l'ADM contre placebo dans le niveau de fonctionnement social (modéré).
En ce qui concerne la QoL, une étude a rapporté que, bien qu'il y ait eu une amélioration de la QoL au fil du temps dans les deux bras ADM et CBT, il n'y avait pas de différence significative entre les deux pendant la phase de continuation. Les auteurs ont également constaté que l'amélioration de la dépression était positivement associée à la QoL, ce qui implique que l'amélioration de la QoL au cours du traitement peut être expliquée partiellement par une réduction des symptômes dépressifs. Aucune donnée sur la QoL n'était disponible, ni pour le traitement combiné ni pour l'ADM comparé à la CBT pendant la phase de maintien.
De même, pour les niveaux de fonctionnement social, bien qu'il y ait eu des améliorations significatives dans les valeurs d'évaluation des patients recevant l'ADM ou la CBT ou une combinaison des deux pendant la phase de continuation, il n'y avait aucune preuve que l'un était plus efficace que l'autre. Par contre, pour la comparaison entre l'ADM et le placebo, une étude a rapporté que l'amélioration du niveau de fonctionnement social était significativement plus importante sous l'ADM pendant la phase de continuation. Dans la phase d'entretien, deux études ont présenté des résultats contradictoires, une seule étude ayant rapporté une amélioration significativement plus importante du niveau de fonctionnement social par rapport au niveau de base à 9 mois dans le groupe ADM. Nous

n'avons identifié aucune études évaluant le niveau de fonctionnement des patients recevant l'ADM ou la CBT ou une combinaison des deux pendant la phase de maintien.
Par ailleurs, tant pour la QoL que pour le niveveau de fonctionnement social, le changement de l'ampleur de l'effet dans les valeurs ponctuelles était plus faible que le changement des symptômes dépressifs, ce qui suggère que l'amélioration des deux aspects et le retour à la normalité peuvent nécessiter une période beaucoup plus longue.

L'acceptabilité a été évaluée dans 35 études. Dans la phase de continuation, les analyses sommaires ont montré des taux d'acceptabilité similaires entre l'ADM et la CBT (RR= 1,57, IC 95 % = 0,94 à 2,62). Par ailleurs, les taux d'acceptabilité (moins d'abandons de l'étude) étaient meilleurs avec le AMD plus CBT qu'avec seulement l'AMD (RR= 2,06, IC à 95 %= 1,31 à 3,25) ou seulement de la CBT (RR= 2,12, IC à 95 %= 1,29 à 3,48). Dans la phase d'entretien, une étude n'a signalé aucune différence entre l'ADM et la CBT (RR=1,21, IC 95 %= 0,87 à 1,81), tandis qu'une autre a fait état de taux d'abandon plus faibles avec l'ADM par rapport à la CBT (RR=0,62, IC 95 %= 0,41 à 0,93). La qualité des preuves était faible pour toutes les comparaisons, sauf pour l'ADM par rapport au placebo.

La tolérance a été rapportée dans 24 études. Dans la phase de continuation, une étude a rapporté une tolérance moindre (abandons plus élevés en raison d'AE) avec ADM par rapport à CBT (9% contre 0%). L'ADM était moins tolérable, comparativement au placebo (RR=3,46, IC 95 %= 1,65 à 7,25). Aucune étude n'a comparé la tolérance de l'ADM et de la CBT dans la phase d'entretien. En ce qui concerne les effets indésirables, les rapports sur les effets indésirables n'étaient pas cohérents d'une étude à l'autre et manquaient certainement pour la CBT et l'association ADM-CBT. Néanmoins, à partir des preuves disponibles, nous avons constaté qu'une proportion élevée de patients ont subi des effets indésirables dans les phases de continuation et d'entretien, en particulier parmi ceux qui recevaient l'ADM. Bien que les données disponibles suggèrent que seulement l'ADM n'était pas optimal du point de vue de l'acceptabilité et de la tolérance, il est important de noter qu'il faut toutefois rester prudent en effectuant une comparaison des effets indésirables chez les patients recevant l'ADM par rapport à ceux recevant la CBT , car les effets indésirables dans les études de CBT n'étaient souvent pas signalés, ce qui pourrait être cause d'une possible sous-estimation de leurs inconvénients.

Il faut considerer que les résultats de cette analyse sont soumises aux certaines limites, tant en ce qui concerne le processus d'examen que la base de données probantes. Une limitation majeure concerne l'hétérogénéité des études incluses, qui comprenaient différentes populations, interventions et interventions comparateurs. Également il y avait des différences substantielles dans la conception et la mise en œuvre des études, liées principalement à l'absence d'aveuglement dans les études de CBT. Ces facteurs pourraient violer l'hypothèse de transitivité sous-jacente de nos méta-analyses en réseau et l'absence d'aveugle pourrait être cause d'une surestimation de l'efficacité de la CBT. Les limites liées à la base de données probantes sont liées au manque de données, notamment en ce qui concerne les effets indésirables de la CBT. En raison du petit nombre d'études, nous n'avons pas pu évaluer si les effets des différentes interventions sur la rechute et la récidive différaient selon les différents groupes de gravité du MDD. En outre, la plupart

des études présentaient des limites méthodologiques et un risque élevé de biais, ce qui affaiblissait la validité des résultats. Nous n'avons enfin inclus que des RCT dans notre analyse, qui en générale incluent des populations soigneusement sélectionnées qui peuvent ne pas être représentatives de la population générale et des procédures qui ne reflètent pas la pratique clinique réelle.

B. Évaluation des avantages et des inconvénients

Lorsque l'on met en balance, sur la même échelle, le risque de rechute évitée et le risque excédentaire d'effets néfastes, les patients souffrant de MDD traités par CBT ont démontré un bénéfice clinique net par rapport à ceux traités par ADM sur 12 mois. La probabilité correspondante de bénéfice net en termes de prévention des rechutes était de 91,8 % pour la CBT par rapport à l'ADM en tenant compte des résultats négatifs spécifiques et de 98,2 % lorsque l'abandon de l'étude, toutes causes confondues, était considéré comme le résultat négatif.

Alors que les résultats ci-dessus étaient basés sur des estimations de traitement provenant d'RCT avec un suivi plus court (>12 à <25 semaines), nous avons répété l'analyse avec des preuves provenant d'RCT avec 25 semaines et des durées de suivi plus longues, où, cette fois, nous n'avons utilisé que l'abandon de l'étude, toutes causes confondues, comme critère de préjudice. La CBT reste supérieure à l'ADM, avec une probabilité de bénéfice clinique net de 77,1%. Cela implique une diminution du bénéfice net dans le temps par rapport aux résultats précédents. Cependant, la combinaison de la CBT et de l'ADM a fait grimper la probabilité d'un bénéfice clinique net à 96,7 % par rapport à l'ADM seul et à 80 % par rapport à la CBT seule.

En termes absolus, le nombre d'équivalents de rechute (c.-à-d. le bénéfice clinique net) qui seraient évités sur 12 mois était de 346 sur 1000 patients souffrant de MDD et traités par CBT au lieu d'ADM, lorsque l'on considère les effets du traitement provenant des RCT avec un suivi plus court. Cette valeur a diminué à 126 sur 1000 patients lorsque seuls les résultats des RCT avec une durée de suivi de plus de 6 mois ont été pris en compte. Cependant, la réduction de l'effet s'est inversée en un bénéfice clinique net plus favorable avec le traitement combiné de la CBT et de l'ADM par rapport à la monothérapie avec l'ADM au bout de 12 mois (soit 228 rechutes évitées sur 1000 patients) ou la CBT (soit 126 rechutes évitées sur 1000 patients).

Plusieurs analyses de sensibilité ont confirmé le caractère favorable de la CBT par rapport à l'ADM et de la combinaison entre les deux par rapport à la monothérapie. Cela s'explique principalement par le fait que la CBT était associée à des taux de rechute et d'abandon plus faibles et à des paramètres de résultats liés à la sécurité plus faibles que l'ADM. Par conséquent, même si les risques pour les patients et les valeurs de préférence pour la rechute et l'abandon ont changé, les résultats n'ont pas différé de manière significative. Toutefois, il convient de noter que cette évaluation est l'une des premières BHA menées

dans le contexte des interventions sur le MDD, et que les preuves de comparaison sont limitées.

Nos résultats doivent être interprétés avec prudence et il faut se comte tenu des limites de l'étude. Notamment, il s'agit du manque de détails dans les données sur les dommages rapportés (par exemple, les estimations pour tous les différents types et niveaux de gravité des AE), en particulier dans les études évaluant la CBT, ce qui pourrait être cause d'une possible sous-estimation des préjudices réels. Cependant, nous ne nous sommes pas basés uniquement sur les AE spécifiques comme critère des préjudices, mais nous avons également utilisé les abandons d'étude, toutes causes confondues, qui ont été rapportés de manière plus cohérente dans les études, avec des résultats similaires lorsque les deux critères sont utilisés comme critère de préjudice. Parmi les autres limites, citons l'utilisation des données d' RCT uniquement, ce qui peut sous-estimer les taux d'effets néfastes dans la population générale, le manque de données détaillées sur les effets bénéfiques pertinents, tels que la guérison et la rechute, et l'utilisation de pondérations de préférence générales plutôt que de pondérations dérivées d'études de préférence. Dans l'ensemble, il ne faut pas considérer l'estimation du bénéfice clinique net comme définitive, car il est difficile d'estimer l'étendue de l'effet de ces limites sur l'estimation du bénéfice clinique net. Nous somme , cependant, convaincus le rapport relatif bénéfices-inconvénients des différentes thérapies a été correctement saisi, en particulier pour l'horizon temporel de 12 mois ou moins. Notre analyse pourra être mise à jour lorsque de nouvelles données pour les paramètres d'entrée seront disponibles.

C. Analyse documentaire sur l'économie de la santé

Sur les 2 689 citations identifiées lors de la recherche dans les bases de données électroniques, 33 étaient éligibles pour les analyses coût-efficacité admissibles : 14 d'entre elles ont évalué l'ADM comme stratégie d'intervention, tandis que 19 ont évalué la CBT. Les interventions comparateurs variaient selon les études. 29 des 33 analyses coût-efficacité incluses dans cette revue ont utilisé un horizon temporel supérieur à 12 semaines. La majorité des analyses coût-efficacité des AMD étaient parrainées par des sociétés pharmaceutiques, tandis que toutes les analyses coût-efficacité de la CBT étaient financées par le secteur public.

La majorité des analyses coût-efficacité des AMD incluses étaient basé sur un modèle. Les traitements les plus couramment étudiés étaient l'Escitalopram (un SSRI), la Venlafaxine (un SNRI), la Sertraline (un SSRI), la Duloxétine (un SNRI) et les SSRI en tant que groupe.

Six analyses du rapport coût-efficacité ont conclu que les preuves du rapport coût-efficacité de l'Escitalopram étaient plus favorables que celles des autres AMD. Toutes ces analyses étaient fondées sur des données cliniques montrant que les probabilités de rémission ou de réponse étaient les plus élevées pour l'Escitalopram par rapport à tous les autres interventions comparateurs. Dans toutes les analyses coût-efficacité où la Venlafaxine, la Sertraline ou la Duloxétine étaient comparées à l'Escitalopram, il a été

estimé que l'Escitalopram était la stratégie dominante (c'est-à-dire moins chère et plus efficace) ou très rentable (c'est-à-dire avec des RCED très bas). De plus, après adaptation numérique pour la Suisse, l'Escitalopram s'est avéré être une stratégie dominante dans la plupart des cas.

La venlafaxine a été étudiée dans six analyses coût-efficacité, soit comme intervention, soit comme intervention comparateur. Par rapport à l'escitalopram, à la plupart des cas la venlafaxine a été dominée (c'est-à-dire qu'elle était plus chère mais moins efficace) ou bien elle s'est avérée moins chère mais moins efficace. La venlafaxine, au contraire, comparée à d'autres AMD (par exemple, le citalopram, la duloxétine, Fluoxetine, Paroxetine, Sertraline) était généralement considérée comme la stratégie dominante.

Six analyses coût-efficacité ont comparé la Sertraline à un placebo ou à un ensemble d'antidépresseurs. La Sertraline était considérée comme la stratégie dominante lorsqu'elle était comparée au Citalopram (tant du point de vue de la santé que du point de vue de la société), alors qu'elle était dominée lorsqu'elle était comparée à l'Escitalopram, à la Venlafaxine et à l'Agomélatine. Pour toutes les autres comparaisons, les résultats étaient hétérogènes.

La Duloxétine a été évaluée comme intervention comparatives dans quatre analyses coût-efficacité. Dans trois d'entre elles, elle était dominée par l'Escitalopram. La comparaison avec d'autres AMD a donné des résultats contradictoires.

Les trois analyses coût-efficacité dans lesquelles les SSRI ont été considérés comme un groupe, les SSRI étaient rentables par rapport aux autres AMD ou aux traitment habituels. La plupart des analyses coût-efficacité portant sur la CBT, étaient des analyses intra-étude. Nous avons identifié huit analyses coût-efficacité indiquant que la CBT était rentable ou dominante par rapport aux traitments habituels ou à l'ADM. Cependant, cinq analyses de coût-efficacité ont également conclu le contraire (c'est-à-dire que l'ADM ou les traitments habituels étaient les stratégies dominantes, ou que le RCED pour la CBT par rapport aux interventions comparateurs était très élevé, de sorte qu'elles n'étaient pas indicatives de coût-efficacité).

Les résultats de cette évaluation doivent être interprétés soigneusement compte tenu de plusieurs limitations. Il s'agit notamment d'une forte hétérogénéité entre les études identifiées concernant différentes populations, interventions et interventions comparateurs, horizons temporels et types de coûts, en particulier pour les interventions de CBT. En outre, la majorité des analyses coût-efficacité des AMD étaient parrainées par des sociétés pharmaceutiques, ce qui peut impliquer un risque de biais. D'autre part, les effets du traitement dans les études de CBT ont pu être associés à l'allégeance des chercheurs et pourraient également constituer un biais potentiel. Enfin, les limites de la base de preuves cliniques s'appliquent également à la recherche de la littérature économique.

Il est important de noter qu'il y a eu quelques différences méthodologiques entre les examens cliniques et économiques de cette HTA. Notamment, l'inclusion de patients présentant une symptomatologie dépressive importante dans l'examen de la documentation économique, contrairement à l'examen de la documentation clinique qui s'est concentrée sur les patients diagnostiqués comme souffrant de MDD. Si toutes les études internationales ont été prises en compte dans la partie clinique, les pays d'Asie de l'Est ont été exclus dans la partie économique, car ils sont susceptibles de différer sensiblement de la Suisse en termes de conditions cadres, de coûts et de perception de la QoL. De plus, contrairement à la revue systématique clinique qui n'incluait que les interventions de CBT qui duraient plus de 12 semaines, nous avons également inclus deux analyses coût-efficacité de la CBT qui rapportaient une durée de traitement potentiellement inférieure à 12 semaines (dans ces études, les auteurs ont rapporté 6 à 8 leçons/modules de CBT hebdomadaires, mais n'ont pas précisé si les leçons/modules étaient menées consécutivement dans le temps le plus court possible, ou si elles étaient réparties sur une période de temps supérieure à 12 semaines). En général, il faut souligner que dans de nombreux cas, la durée réelle de la CBT n'était pas spécifiée en mois, mais en nombre de sessions ou de modules. La distribution exacte des sessions/modules dans le temps n'a souvent pas été rapportée.

D. Analyse de l'impact budgétaire

Nous avons estimé le nombre total de patients souffrant de MDD traités en Suisse en 2020 à 334 835. Les coûts médicaux directs totaux ont été estimés entre 5 330 millions de francs suisses (en supposant que les patients souffrant de MDD seraient traités exclusivement avec l'AMD le moins cher, sans recevoir aucune sorte de psychothérapie) et 6 032 millions de francs suisses (en supposant que tous les patients souffrant de MDD suivraient une psychothérapie et recevraient l'AMD le plus cher). Selon la répartition des traitements et les hypothèses de coûts, les coûts d'hospitalisation représentaient 82% à 92% des coûts totaux. Les coûts des visites chez le médecin, de la psychothérapie et du AMD ne jouent qu'un rôle de second plan. Les coûts des traitements variaient de 84 millions de francs suisses (en supposant que tous les patients souffrant de MDD traités recevraient uniquement le AMD le moins cher et aucune psychothérapie) à 800 millions de francs suisses (en supposant que tous les patients souffrant de MDD recevraient à la fois une psychothérapie et le AMD le plus cher). Le coût du traitement seulement par psychothérapie pour tous les patients souffrant de MDD a été estimé à 603 millions de francs suisses (en supposant 12 séances par an).

L'estimation de l'impact budgétaire a nécessité de nombreuses hypothèses et et est donc soumise à des limitations importantes. Il s'agit notamment d'une possible sous-estimation du nombre de patients pouvant bénéficier d'un traitement contre le MDD, d'une sous-estimation des coûts d'hospitalisation et de l'exclusion des coûts pour les services suivants les tests de diagnostic et les médicaments concomitants. De plus, nous n'avons pas pris en compte le changement ou l'abandon de traitement. Les informations concernant les différences de perte de productivité, d'invalidité ou de retraite anticipée

liées à la dépression, et de suicides liés à la dépression selon les différentes options de traitement n'étaient pas suffisantes pour effectuer les analyses d'un point de vue sociétal.

Conclusion

Cette HTA a tenté une évaluation globale de l'efficacité clinique, de la sécurité, de l'équilibre avantages-inconvénients et des caractéristiques économiques de l'ADM et de la CBT chez les patients adultes souffrant de MDD dans une perspective de moyen à long terme.

Parmi les données disponibles, nous n'avons trouvé aucune preuve d'une différence entre l'ADM, la CBT et leur combinaison en ce qui concerne les résultats d'efficacité clinique primaire, y compris la QoL et le niveau de fonctionnement social. Cependant, l'ADM seul ne semble pas être optimal du point de vue de l'acceptabilité et de la tolérance. Nos résultats doivent être interprétés avec précaution, donné les limitations telles que la grande hétérogénéité des études incluses ainsi que le risque de biais dû à l'absence d'aveugle dans les études sur la CBT. L'évaluation des avantages et des inconvénients - qui tenait également compte des risques et des préférences en matière de résultats - a révélé une probabilité relativement plus grande d'avantages cliniques nets à moyen et à long terme avec la CBT qu'avec l'ADM, ou avec l'association CBT et ADM qu'avec la monothérapie. Cependant, le véritable équilibre entre les avantages et les inconvénients ne peut pas être correctement saisi dû au manque de fiabilité des rapports sur les effets indésirables dans les essais, en particulier lorsqu'ils sont liés aux interventions de CBT. Ainsi, des évaluations et des rapports plus systématiques et détaillés des résultats cliniques à moyen et à long terme, en particulier de la qualité de vie, du fonctionnement social et des effets indésirables dans les RCT, permettraient de mieux évaluer les différentes interventions en fonction de ces dimensions, et de mener une analyse économique systématique plus complète. Les résultats de l'examen systématique économique suggèrent que l'escitalopram pourrait être le traitement le plus rentable parmi les antidépresseurs inclus, suivi par la venlafaxine, la sertraline et la duloxétine.

Les analyses coût-efficacité comparant la CBT ou la CBT par Internet aux AMD ou aux soins habituels ont donné des résultats discordants. L'analyse d'impact budgétaire a suggéré que le total des coûts médicaux directs du MDD par an pourrait se situer entre 5 330 millions et 6 032 millions de francs suisses. Les principaux facteurs de coût étaient le nombre estimé de patients traités pour le MDD et les hospitalisations. Ce résultat souligne que l'hospitalisation due au MDD est un résultat clinique important qui, avec d'autres conséquences sur l'activité professionnelle et le bien-être, devrait idéalement être pris en compte par les essais cliniques et les études d'observation pour permettre une évaluation plus complète des traitements du MDD. Les coûts de la psychothérapie et du AMD dépendaient de la répartition supposée des traitements. Le traitement par psychothérapie seule a été estimé à 603 millions de francs suisses, tandis que les coûts du traitement combiné se situeraient entre 687 millions et 801 millions de francs suisses.

Avec cette étude nous avons constaté que si les interventions ADM et CBT semblent être des options efficaces dans la gestion du MDD, aucune ne semble être définitivement plus performante que l'autre. Alors que notre évaluation des avantages et des inconvénients semble montrer que les interventions de CBT peuvent apporter un plus grand bénéfice clinique aux patients souffrant de MDD par rapport à l'ADM, l'examen systématique des analyses coût-efficacité, adaptées au contexte suisse, a révélé que la CBT peut également être plus coûteuse selon la manière dont elle est menée (nombre de séances, en ligne ou en face à face). Ces résultats doivent être interprétés avec prudence étant donné les lacunes méthodologiques de l'examen et de la base de données probantes, ainsi que l'applicabilité limitée potentielle des résultats des essais contrôlés aux contextes cliniques réels.

2 Introduction

Major depressive disorder is one of the most commonly diagnosed mental health disorders and a significant cause of disability worldwide (1–3). Over a life course, MDD affects more than one in five people (4–6) and often has a recurrent and fluctuating course (7,8). Apart from the subjective experiences of negative symptoms, MDD imposes a considerable functional and social burden on individuals and their families and is associated with high socio-economic costs (3,9–12).

In Switzerland, depression is among the most frequently treated mental health disorders and its prevalence appears to be increasing (13). According to the Swiss Health Survey, the percentage of Swiss population above 15 years of age that suffered from moderate to severe MDD increased from 6.5% in 2012 to 8.6% in 2017 (14). In addition, suicide, a possible consequence of MDD, remains the most common cause of death among 19-34 year olds (13). Not only does MDD lead to negative health outcomes, but also leaves individuals, societies and health systems with substantial financial costs. Tomonaga et al. estimated the economic burden associated with depression be around €8 billion per year, related mainly to hospitalisation costs and workdays lost (15).

Numerous treatment strategies for MDD exist, including antidepressants or psychotherapies (most commonly cognitive behavioural therapies). The choice of initial treatment depends on multiple factors (e.g., patient preferences, costs, anticipated side effects, severity of symptoms). The aim is to achieve symptom remission, restore a normal level of psychosocial functioning, and prevent relapse in the longer term. In any treatment modality, the management of MDD is generally divided into three phases (Figure 1) (16–19). A minimum of 6 to 12 weeks of initial treatment is recommended during which the treatment goal is symptom improvement until remission has been achieved (i.e., acute phase). This is followed by 4 to 9 months of continued treatment to prevent relapse (i.e., continuation phase) and maintenance treatment for longer than a year and in some high-risk cases continued indefinitely to prevent recurrence or chronic depression (i.e., maintenance phase).

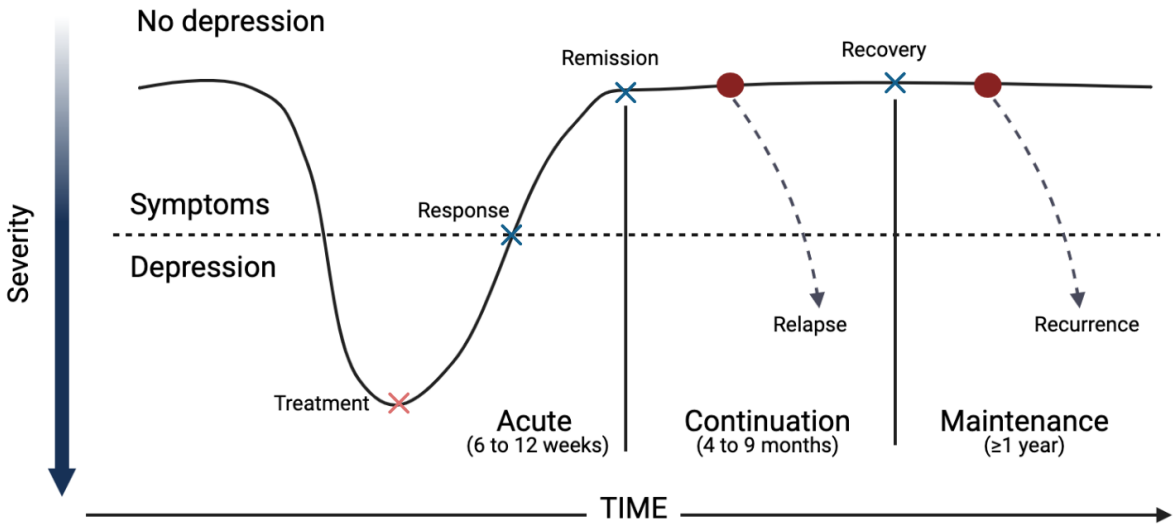


Figure 1. Management phases of MDD.
Recreated from Kupfer et al (Kupfer et al 1999).

For more than 60 years, the mainstay of MDD management has been antidepressants. Current guidelines recommend psychotherapy as initial treatment in those with mild to moderate depression and the combination of antidepressants and psychotherapy in those with moderate to severe symptoms (16–22). This is based on results from hundreds of randomized controlled trials demonstrating the efficacy of antidepressants and psychotherapies in reducing symptoms of depression (23–27). However, despite the recommended long-term duration of these treatments, the assessment of their efficacy has been largely based on short-term RCTs spanning 4 to 12 weeks and evidence on their benefit beyond 12 weeks is scarce and conflicting (26,28–33). Furthermore, due to the short-term nature of study follow-ups, the assessment of harms of treatments is limited and may have been neglected sometimes (34,35). While some of the commonly experienced adverse effects, such as nausea and headache with ADMs, are often transient and self-resolving in the short term (36), little is known about whether long-term use of ADM or CBT is associated with the persistence or development of other adverse effects. This lack of evidence has thus so far hindered an adequate evaluation of the risk-benefit ratios of MDD therapies.

As such, in this Health Technology Assessment, we aimed at evaluating the clinical efficacy, safety, benefit-harm balance and cost-effectiveness of ADMs and cognitive behavioural therapy interventions, alone or in combination, beyond the acute management phase in patients with MDD in Switzerland.

3 Objective

The overall aim of this HTA was to provide an assessment of ADM and CBT, alone or in combination, beyond the acute management phase in adults with MDD. Specifically, we address the clinical efficacy, adverse effects, the cost-effectiveness and the budget impact as well as the benefit-harm balance of the different treatment options when given for longer than 12 weeks.

4 Decision Context (PICO)

In this chapter, we describe the population, intervention, comparators, and outcomes (PICO) for the current HTA. A brief summary is provided in Table 1.

Table 1. Summary description of the population, intervention, comparators, and outcomes (PICO)

			Description
Population		Adult patients (≥18 years) diagnosed with major depressive disorder	
Intervention	I.	ADM	Escitalopram, citalopram, paroxetine, fluvoxamine, fluoxetine, sertraline, duloxetine, reboxetine, venlafaxine, clomipramine, amitriptyline, trimipramine, doxepin, mirtazapine , agomelatine, bupropion, moclobemide, vortioxetine, trazodone, and mianserin.
	II.	CBT interventions	BA, CT, REBT, DBT, ACT, CBASP, MBCL, CBT, and PST.
Comparators	I.	ADM monotherapy	Any of those listed above
	II.	CBT monotherapy	Any of those listed above
	III.	Control conditions	Placebo, treatment as usual, or waiting list
Outcomes	I.	Clinical efficacy	
		Primary	Relapse Recurrence Quality of life Social functioning
		Secondary	Response Remission Recovery
	II.	Safety	
		Primary	Acceptability Worsening of depression symptoms Mortality
		Secondary	Specific adverse effects Tolerability
	III.	Health economic	Costs Quality-adjusted life years Incremental cost-effectiveness ratios

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy intervention; BA: behavioural activation; CT: cognitive therapy; REBT: rational emotive behaviour therapy; DBT: dialectical behaviour therapy; ACT: acceptance and commitment therapy; CBASP: cognitive behavioural analysis system of psychotherapy; MBCL: mindfulness-based compassionate living; PST: problem solving therapy.

4.1 Population

The primary target population of this HTA was adult individuals (18 years or older) diagnosed with MDD using validated diagnostic instruments (e.g. *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-3, DSM-4, and DSM-5 or the International Classification of Diseases (ICD)-10). Individuals with treatment resistant depression,

persistent depressive disorders, seasonal affective disorders, bipolar depression, psychotic depression, substance/medication induced depressive disorder, and perinatal depression were not considered part of the target population as they constitute categories of depression that are distinct from major depressive disorder and need their own treatment approaches. In cases where studies included mixed populations of these other depression types with MDD, we included studies if the MDD cases covered at least 90% of the participants. We excluded studies that focused exclusively on patients with MDD with a specific comorbid mental disorder as the type of intervention studied would be targeting the comorbid mental disorder rather than MDD alone.

4.2 Interventions

We included the following interventions when administered for more than 12 weeks:

1. **Antidepressants:**

We included antidepressants which are available in Switzerland, according to the Swiss "Spezialitätenliste". This included escitalopram (ESC), citalopram (CIT), paroxetine (PAR), fluvoxamine (FLV), fluoxetine (FXT), sertraline (SER), duloxetine (DXT), reboxetine (REB), venlafaxine (VEN), clomipramine (CMI), amitriptyline (AMI), trimipramine, doxepin, mirtazapine (MIR), agomelatine (AGM), bupropion (BUP), moclobemide, vortioxetine, trazodone, and mianserin. A full list of available antidepressants with their corresponding active ingredients and medication class can be found in Appendix 11.1.1.1

2. **CBT interventions**

We used the classification of CBT interventions according to the Cochrane Collaboration Depression, Anxiety and Neurosis Review Group (CCDAN) classification system and categorized CBT interventions into standard CBT and 3rd wave CBT classes (Appendix 11.1.1.2). This included behavioural activation (BA), cognitive therapy (CT), rational-emotive behaviour therapy (REBT), dialectical behaviour therapy (DBT), acceptance and commitment therapy (ACT), cognitive behavioural analysis system of psychotherapy (CBASP), mindfulness-based compassionate living (MBCL), CBT (which included blended (BCBT), standard (SCBT), CBT with exercise (CBTe), or CBT with mindfulness (CBTm)), and problem solving therapy (PST).

4.3 Comparators

The main comparators included combination of ADM plus CBT or either as monotherapy. Addition comparators were control conditions (i.e., placebo, waiting list (WL), and treatment as usual (TAU)).

4.4 Outcomes

4.4.1 Clinical efficacy outcomes

1.4.1.1. Primary outcomes

We defined the following as primary clinical efficacy outcomes:

- Relapse, measured as the proportion of patients experiencing depression relapse during the continuation/maintenance phases, as defined by each of the studies
- Recurrence, measured as the proportion of patients experiencing recurrent depressive episodes during the continuation/maintenance phases, as defined by each of the studies
- Improvement in QoL
- Improvement in social functioning or daily life activities

For QoL and social functioning, we considered differences in absolute scores at different timepoints of follow-up and changes in scores from baseline within treatments, as well as differences in absolute scores or change in scores between treatments.

1.4.1.2. Secondary outcomes

Secondary clinical efficacy outcomes were the following:

- Response, measured as the proportion of participants responding to treatment which is typically defined as a 50% improvement between baseline and the follow-up timepoint using standardized scales (e.g., Hamilton Rating Scale of Depression (HDRS or HAM-D), Montgomery–Asberg Depression Rating Scale (MADRS))
- Remission, measured as the proportion of participants with remission, as defined by authors

4.4.2 Safety outcomes

4.4.2.1. Primary outcomes

- Acceptability, measured as the proportion of participants who left the trial for any reason prior to the end of the study
- Worsening of depression symptoms
- Mortality (all-cause death)

4.4.2.2. Secondary outcomes

- Specific AEs. We included all available data on AEs and classified them by organ system, in accordance with the "System Organ Class (SOC)" Medical dictionary for regulatory activities (MedDRA) classification of the European Medicines Agency (EMA) (Appendix 11.1.1.3).

- Tolerability, measured as the proportion of participants who left the study due to AEs.

The clinical efficacy, safety, and cost effectiveness outcomes were agreed on in consultation with the experts and stakeholders during the scoping process. The primary clinical and safety outcomes were chosen based on what is commonly assessed in trials evaluating the mid-long term treatment of MDD (e.g., relapse) and what is possibly relevant to both clinicians and patients (e.g., quality of life) when deciding on the treatment options. This was done in in consultation with an external clinical expert. The decision was based on the importance of the outcomes in clinical practice and their relation to the goals of longer term treatment.

4.4.3 Health economic outcomes

The economic systematic review and cost effectiveness analysis focused on costs, QALYs, and ICERs, while the budget impact analysis focused on costs only.

4.5 Timeframe

In the assessment of the clinical efficacy and safety of the different MDD treatments, we divided the follow-up time in studies into three periods, based on the management phases of MDD as previously described, being ≤12 weeks (i.e., acute phase, referred to as T1), 13 to 24 weeks (i.e., continuation phase) and ≥25 weeks (i.e., maintenance phase,). We considered outcomes assessed at >12 weeks to be mid- to long-term. In cases where a study provided estimates at multiple timepoints within each period, we gave preference to the latest one. Primary and secondary outcomes were assessed in each timeframe as available and applicable.

4.6 Study Designs

For the evaluation of the clinical efficacy and safety of ADM and CBT, we included evidence from RCTs, including multi-arm and multistage trials. We identified three types of study designs (Figure 2). The first design (classic RCTs and hereafter referred to as Design I) are two- or multi-arm parallel RCTs, in which participants are assigned to an intervention or comparator arm and are followed up for a long period of time. In the second (known as enrichment or discontinuation trials and referred to in this report as Design II), participants receive an open label treatment for the acute phase (usually with ADM) and those responding are subsequently randomly allocated to continue the treatment or to receive the comparator (placebo or active control) and followed up. The third study design (Design III) is similar to Design I but only participants responding to the acute phase treatment are maintained on treatment and followed up.

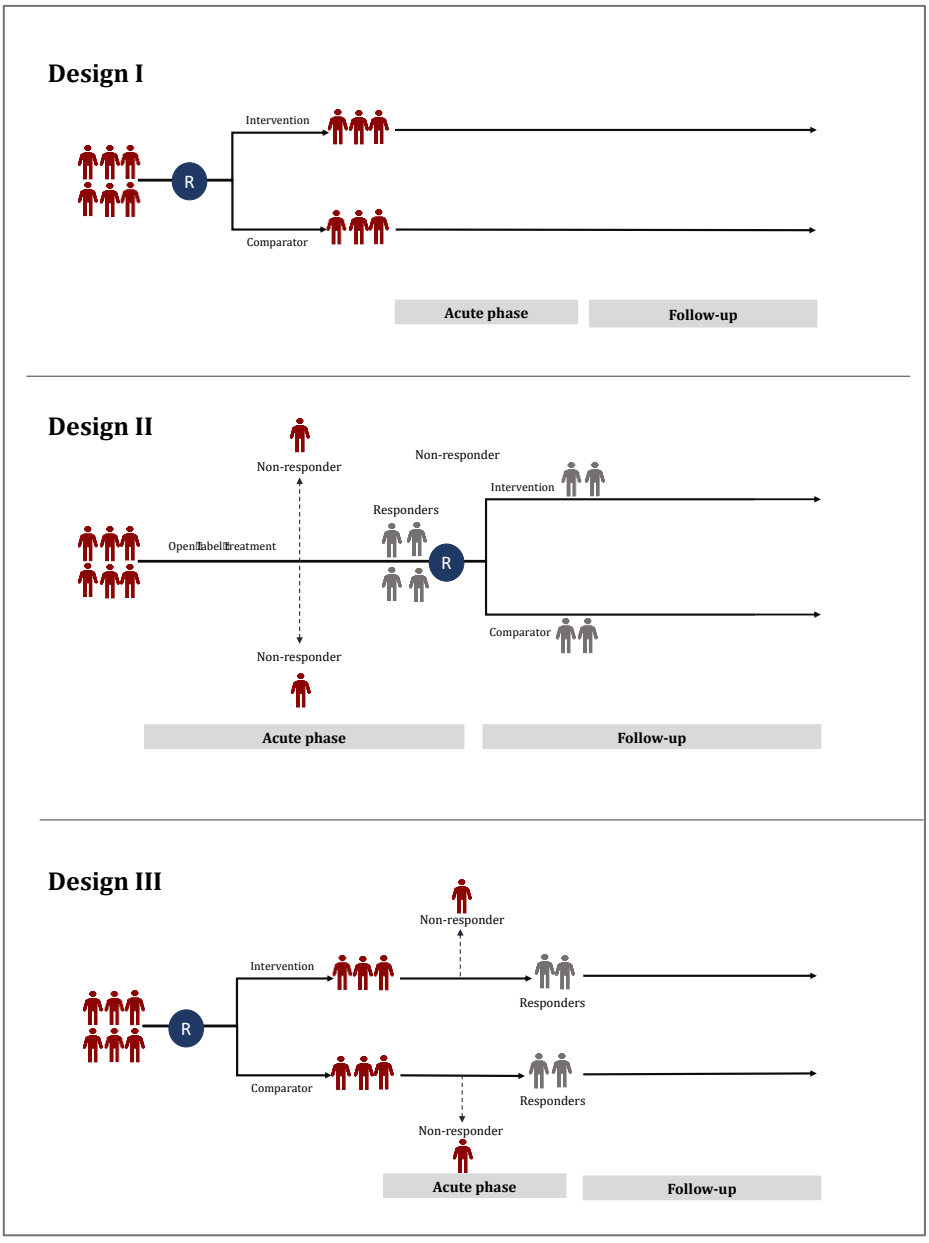


Figure 2. Different trial designs.
R: randomization

5 Assessment of Clinical Efficacy and Safety

5.1 Methods

The systematic review for the clinical evaluation was performed on the basis of the scoping document for the present HTA, as well as according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and its extension for network meta-analyses (37,38). The research protocol for the systematic review was registered a priori on PROSPERO (CRD42020190819).

5.1.1 Systematic Review

Several systematic reviews of ADM and CBT interventions have already been published. Thus, we expected that potentially eligible RCTs for our aim would be identified reliably by the most recently published high-quality systematic reviews. As such, we used the following two-step approach for the identification of relevant RCTs (39,40) (Figure 3):

(i) In the first step, we conducted a systematic search in Ovid Medline and Cochrane Library databases for systemic reviews on MDD interventions published between 2018 and 2020. Search terms for ADM included "antidepressant", "antidepressant drug therapy", “antidepressant pharmacologic therapy” as well as individual generic names and broad terms related to antidepressants in conjunction with "systematic reviews", "meta-analysis" and "network meta-analysis". For the CBT interventions, terms such as "cognitive therapy" and "cognitive-behavioural therapy" were used (see Appendix 11.1.2.1). Two of three reviewers (TB, AR, HY) independently screened the titles and abstracts of the identified systematic reviews for eligibility. We then evaluated the eligibility of the systematic reviews based on full-text and assessed their quality using the AMSTAR-2 checklist (41). We focused on the AMSTAR-2 criteria that were deemed relevant for our aim, i.e. those relating to the PICO, the quality of the literature search (comprehensiveness, selection, extraction strategies) and the risk of bias assessment (AMSTAR-2 criteria 1, and 4 - 9). Systematic reviews meeting these criteria were considered to be of high quality and were used for the extraction of potentially eligible RCTs.

(ii) In the second step, we performed a follow-up search of the published literature with the same search strategies used in the selected systematic reviews to ensure consistency (Appendix 11.1.2.2). We conducted the follow-up searches in Medline (PubMed), EMBASE, PsycInfo and Cochrane Library. We excluded studies that were conducted prior to 1 January 1995. We chose this date based on the date of introduction of the last major class of antidepressants into the market. We considered that it is likely that the landscape of MDD treatment before 1995 differed from what it is now with no major changes in MDD management since then. In addition, bibliographies of the included studies were searched for additional studies. No language restrictions to the search were applied.

5.1.2 Study selection and data management

The review and selection process of eligible RCTs are shown in Figure 3. Individual RCTs that were identified from the high-quality systematic reviews and follow-up search were reviewed in full text by two of three independent reviewers (TB, AR, HY) to determine their eligibility. Disagreements between the three reviewers were by consensus and by the involvement of an experienced senior reviewer (MP). We used CADIMA (https://www.cadima.info)– an online platform– for conducting the study screening and data extraction. The extracted data was exported to an excel which was later used for analysis in R.

5.1.3 Data collection

From all eligible RCTs, we extracted data in duplicate regarding study information (setting, design, blinding, year of publication, sample size, inclusion criteria), demographic and other characteristics of study participants (age, severity of disease), details of the intervention and comparators (type, dose, mode of delivery), and measured outcomes. We extracted data reported based on the intention-to-treat (ITT) assignment in trials. In cases where the trial assessed different dosages of an ADM, we extracted data from the arm using the current recommended dosage. When estimates were not reported by trials but were available in graphs, we used a digitization software (Webplotdigitizer: https://apps.automeris.io/wpd/) to extract these estimates.

5.1.4 Risk of Bias Assessment

We assessed the RoB in the included RCTs using RoB 2.0 (42). RoB was assessed independently and in duplicate by two of the three reviewers (TB, AR, HY) according to the following domains: (i) randomisation process, (ii) deviations from intended interventions, (iii) missing outcome data, (iv) measurement of the outcome, and (v) selection of the reported results. Each of these domains is composed of multiple detailed criteria, all of which contribute to the overall risk of bias assessment for the RCTs. We assessed the criteria on an outcome basis for the primary clinical and safety outcomes.

5.1.5 Data Synthesis

We summarized population demographics and main study characteristics using descriptive statistics. We conducted pairwise and network meta-analyses for the different comparisons and outcomes when possible. The analyses were conducted for each time period separately. When studies had multiple intervention groups, we combined the common intervention or control groups into a single group to avoid double counting (43). As the primary focus of this assessment is the mid- to long-term efficacy and safety of MDD treatment, the main analyses were those conducted in the continuation and maintenance phases. The primary analyses were done by treatment modality (e.g., ADM versus CBT or ADM versus CBT plus ADM). Due to the heterogeneity of the studies in terms of study design and participant characteristics potentially affecting the validity of results of the network meta-analyses, we considered the pairwise meta-anaylses to be the

primary analyses and we interpreted our findings accordingly. As our aim was a comparative assessment of ADM and CBT and their combination, we first presented the results of these direct comparisons, followed by the comparison of either ADM or CBT versus placebo, waiting list or treatment-as-usual. Secondary analyses included class and individual drug level analyses. When conducting a meta-analysis was not possible due to scarcity of studies, we narratively summarized the evidence.

5.1.5.1 Pairwise Meta-Analysis and Network Meta-Analysis

We performed random-effects pairwise meta-analyses and frequentist multivariable random-effects network meta-analyses and using the restricted maximum-likelihood estimator (REML) to estimate the heterogeneity variance. We obtained risk ratios (RR) for dichotomous outcomes and standardized mean differences (SMD, Cohen's d) for continuous outcomes with their 95% confidence intervals (CI). Zero events, occurring in particular in the assessment of AEs, were replaced by 0.5 to enable calculations (continuity correction). Heterogeneity was statistically quantified using the I^2 statistic with its 95% CI and interpreted as following: 0% – 40%: low, 30% – 60%: moderate, 50% – 90%: substantial and 75% – 100%: considerable, while taking into account the magnitude and consistency of estimates across studies (43). Additionally, we conducted sensitivity analyses of the meta-analyses to assess heterogeneity based on MDD severity and population characteristics (e.g., selective population). We also calculated RR for single study estimates. We assessed the transitivity assumption predominantly with respect to epidemiological and clinical plausibility based on the distributions of potential effect modifiers across comparisons. We excluded studies evaluating MDD in patients with specific co-morbid conditions in the network meta-analysis. Furthermore, as we expected that participants in the different study designs are dissimilar, the analyses were performed separately for each study design ensuring that the transitivity assumption is not violated. We also explored the presence of inconsistency between direct and indirect estimates in the available data, where applicable. We further conducted a sensitivity analysis by excluding first ("older") generation from the network analysis. We were not able to assess publication bias using funnel plots due to the low number of studies (43).

All statistical analyses were performed using R (version 4.0.2).

5.1.6 GRADE Assessment

We assessed the quality of evidence or confidence in the estimates from the analyses of the continuation phase (TB, AR). For the direct estimates from the pairwise meta-analysis for the primary clinical outcomes, we used the standard GRADE approach which is based on the five domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias (44–51). For the network estimates, we used the GRADE approach with the extension for network meta-analysis (52,53).

5.1.7 Subgroups

We were unable to conduct the pre-planned subgroup analyses (i.e., for age groups, MDD severity, country settings (industrialized versus non-industrialized), dosing schedule of antidepressants, delivery format of CBT, and treatment setting) due to sparsity of stratified data reported in relevant RCTs.

5.2 Results

5.2.1 Search results

In the first step of our search strategy, we screened a total of 1,028 references in title and abstract and evaluated 50 references in full text for eligibility. We identified 15 systematic reviews meeting our eligibility criteria. Based on the AMSTAR-2 quality assessment and the comprehensiveness of their scope, two high-quality systematic reviews were selected (23,25) through which we identified 623 RCTs. In the second step, we identified 7,799 records through the follow-up search, as well as six additional studies from the reference screening of retrieved RCTs and systematic reviews. Out of these, 43 publications fulfilled the eligibility criteria and provided results. These 43 publications corresponded to 42 trials with a 2 phase trial contributing results to two separate publications (54,55). The list of excluded reviews and studies with reasons for exclusion can be found in Appendix 11.1.3.

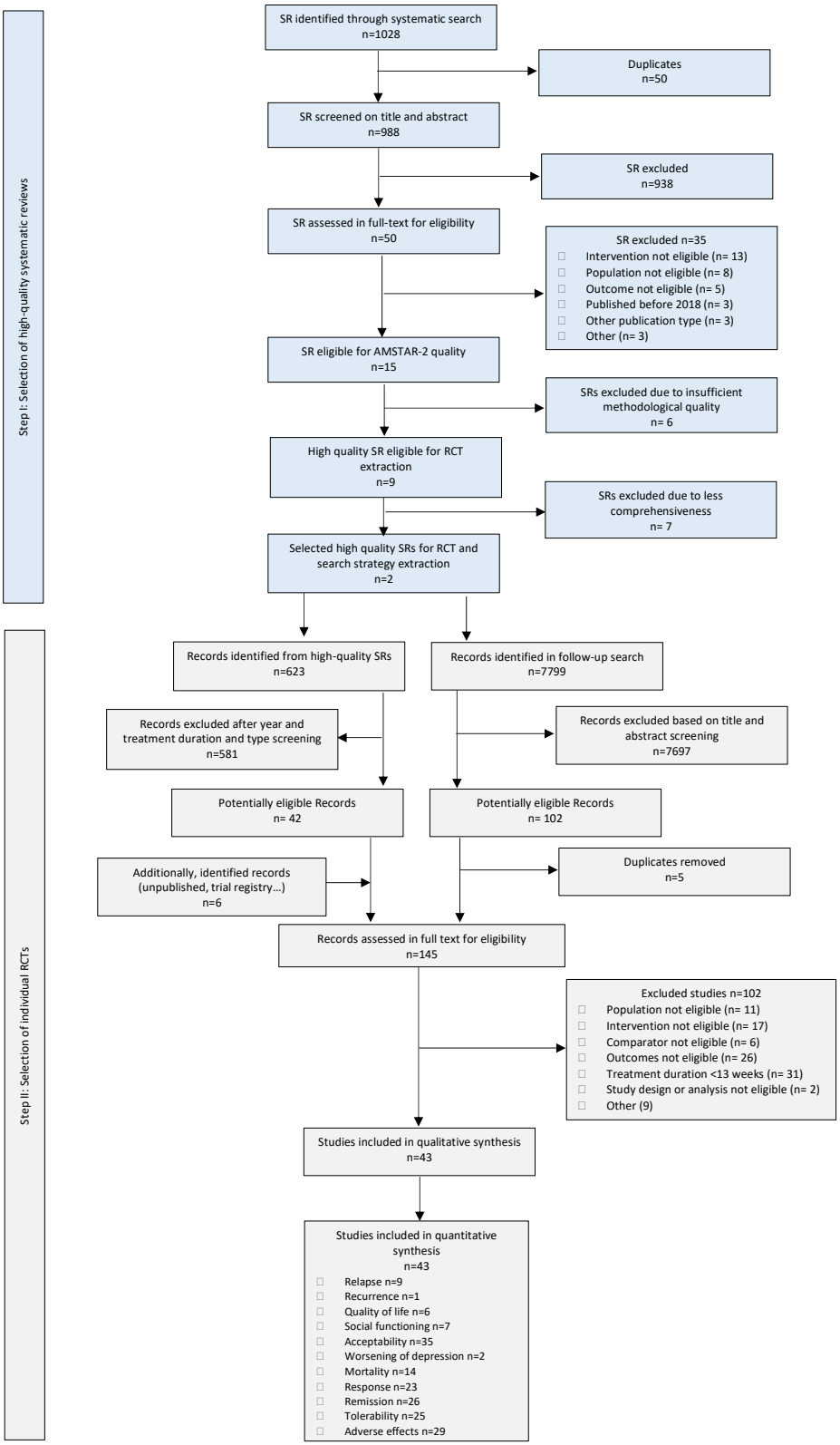


Figure 3. Flowchart of the systematic review and study selection process.
SR: systematic review; RCT: randomized controlled trial

5.2.2 Study Characteristics

A detailed summary of the characteristics of included studies is shown in Appendix 11.1.3.2.

We included eight studies evaluating ADM versus CBT, four studies evaluating ADM versus ADM plus CBT, and one study evaluating CBT versus ADM plus CBT. Additionally, 20 studies assessed either ADM versus placebo (n= 16), CBT versus placebo (n= 2), ADM versus TAU (n= 2), CBT versus TAU (n= 1), or CBT versus waiting list (n= 1). Different types of ADM were evaluated head to head in 16 studies and six studies compared different CBTs. The most frequently used classes of ADM were SSRIs and atypicals and the most frequently assessed CBT was CT. The duration of studies ranged from 13 to 168 weeks and 13 studies had an extension/continuation phase for 12 up to 32 weeks. 22 studies assessed any of the outcomes at ≤12 weeks, 29 studies at 13 to 24 weeks and 14 studies at ≥25 weeks.

Sample sizes of participants ranged from 30 to 1088. As defined by the authors, 16 publications were aimed at adults with any severity level of MDD, four with mild to moderate MDD, 22 with moderate to severe MDD and two publications with severe MDD. Three studies were specific for elderly adults (56–58) and seven studies included participants with a specific co-morbid medical condition (diabetes mellitus (59), end stage renal disease on haemodialysis (60), heart failure (61), acute coronary syndrome (62), multiple sclerosis (63), Alzheimer's disease (64), and epilepsy (65)). 18 trials, all of which assessed an ADM compared to placebo or another ADM, were sponsored by the pharmaceutical industry.

5.2.3 Primary Outcomes

5.2.3.1 Relapse

Nine studies assessed relapse during continuation or maintenance phases (54,66–73). Table 2 provides a brief summary of the different studies and comparisons assessing relapse at different timepoints.

Table 2. Characteristics of studies assessing relapse

Study	Design	Comparison	Population and MDD severity	Mean (SD) MDD severity[1]	Definition of relapse	Timepoint
Blackburn & Moore	I	ADM vs CBT *(ADM versus CT)*	18-65 year old with MDD *(moderate to severe)*	I: 20.3 (4.3) C: 19.2 (3.6)	HAM-D= 14-15 on follow-up	≥25 weeks
CL3-20098-022	III	ADM vs ADM *(AGM vs FXT)* ADM vs PLC *(AGM or FXT vs PLC)*	18-59 year old with MDD (*moderate to severe)*	I: 27.6 (2.9) C: (FXT): 27.5 (NR) C (PLC): 28.0 (3.6)	NR	13 - 24 weeks
CL3-20098-021	II	ADM vs PLC *(AGM vs PLC)*	18-59 year old with MDD *(moderate to severe)*	I: NR C: NR	HAM-D ≥16 or suicide or attempted suicide	≥25 weeks
CL3-20098-041	II	ADM vs PLC *(AGM vs PLC)*	18-59 year old with MDD *(moderate to severe)*	I: 27.0 (NR) C: NR	HAM-D ≥16 or suicide or attempted suicide or withdrawal for lack of efficacy	13 - 24 weeks
David	I	ADM vs CBT *(REBT or CT versus FXT)*	Adults with MDD *(all severities)*	I: 21.4 (8.0) C (REBT): 22.9 (7.0) C (CT): 23.1 (7.6)	MDD on follow up	13 - 24 weeks
Hollon	I	ADM vs ADM plus CBT *(ADM vs ADM plus CT)*	Adults with MDD *(all severities)*	I: 22.2 (4.4) C: 21.9 (4.0)	HAM-D ≥16 or LIFE ≥5 for 2 weeks	≥25 weeks
Jarrett	II	CBT vs ADM *(CT vs FXT)* CBT vs PLC *(CT vs PLC)* ADM vs PLC *(FXT vs PLC)*	Adults with MDD *(all severities)*	I: NR C (ADM): NR C (PLC): NR	Score of 5–6 on a weekly psychiatric status rating of DSM-IV for ≥ 2 weeks	≥25 weeks
Keller	I	ADM vs ADM *(VEN vs FXT)*	Adults with MDD *(moderate to severe)*	I: 22.6 (3.1) C: 23.0 (3.2)	HAM-D ≥12 and ≤50% reduction from baseline and met DSM criteria for MDD at two consecutive visits	≥25 weeks
Thase	I	CBT vs CBT *(SCBT vs CCBT)*	Adults with MDD *(all severities)*	I: 19.6 (3.8) C: 19.8 (3.5)	Remitted patient fits criteria for MDD again	≥25 weeks

[1] assessed by HAM-D unless stated otherwise

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; MDD: major depressive disorder; NR: not reported; CT: cognitive therapy; REBT: rational emotive behavioural therapy; SCBT: standard CBT; CCBT: computerized CBT; SD: standard deviation; I: intervention; C: comparator; PLC: placebo; HAM-D: Hamilton Depression Rating Scale; DSM: Diagnostic and Statistical Manual of Mental Disorders; LIFE: Longitudinal Interval Follow-up Evaluation

Risk of bias

We judged the evidence from eight out of the nine studies to be at a high overall risk of bias and we had some concerns about one study (Figure 4). All but two of the included studies evaluated the efficacy of the interventions based on assignment to the intervention (i.e., ITT). Only four studies reported allocation concealment and none of the studies reported whether the trial analysis was done in accordance with a prespecified protocol.

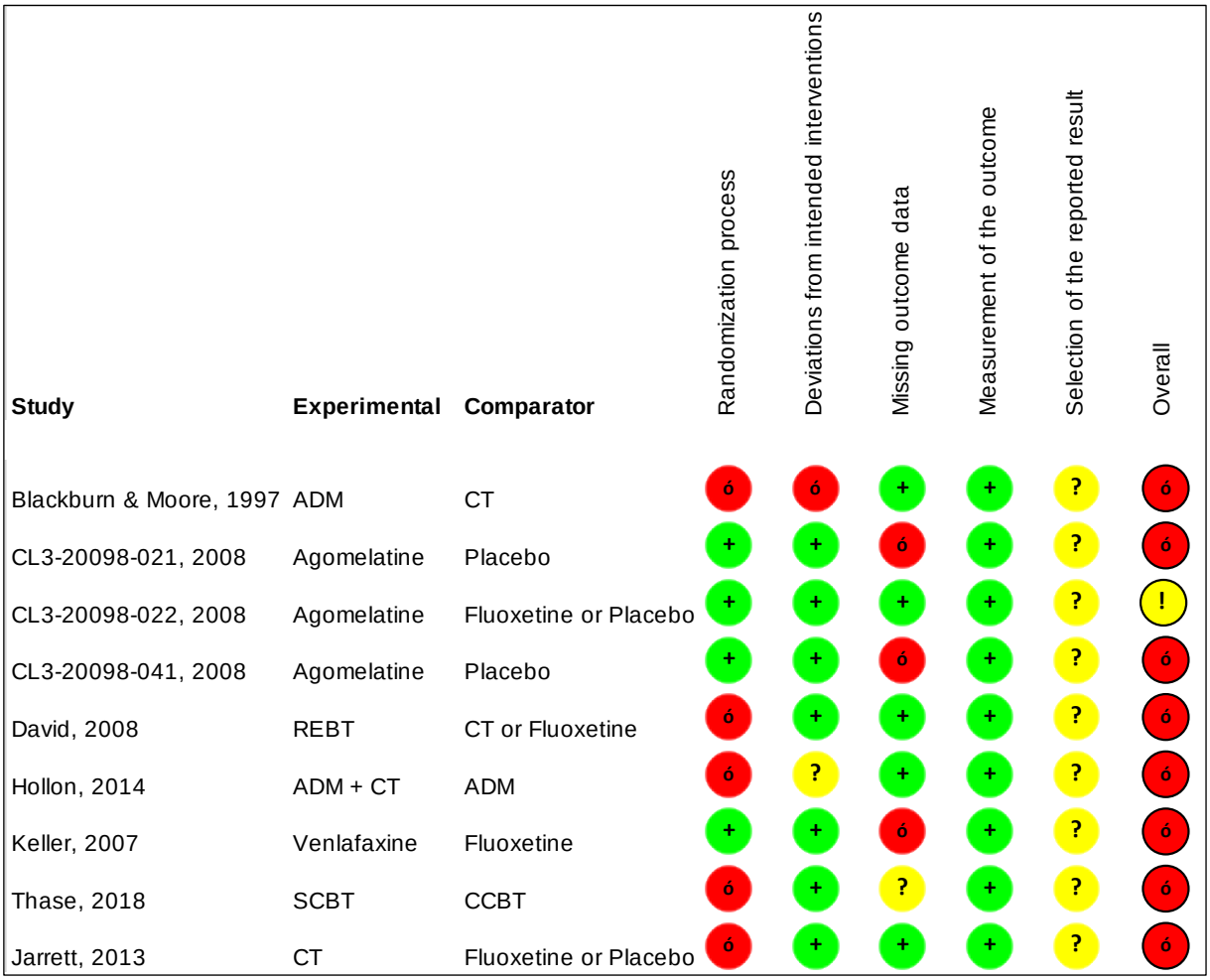


Figure 4. Risk of bias of studies for relapse outcome (based on RoB 2.0).
Legend: ADM: antidepressant medication; CT: cognitive therapy; REBT: rational emotive behavioural therapy; SCBT: standard cognitive behavioural therapy; CCBT: computerized cognitive behavioural therapy

Data Synthesis

In almost all comparisons except for ADM versus placebo, a pairwise meta-analysis was not possible due to the heterogeneity of studies (i.e., due to different study designs) and scarcity of data. As such, the results from the studies are presented narratively. In the

main analysis, results are presented on an overall treatment modality level. Individual drug and class level estimates can be found in Appendix 11.1.6.1.

ADM versus CBT

5.2.3.1.1.1.1 Continuation phase (13 to 24 weeks)

Only one study assessed the effect of ADM versus CBT on relapse between 13 and 24 weeks. David et al. compared the effect of two different CBTs (REBT and CT) and ADM (FXT) on the risk of relapse (67). After receiving 14 weeks of treatment, participants in the ADM arm continued the same treatment up to 24 weeks after randomization while participants in both CBT arms received booster sessions over the follow-up period. Authors reported that the number of relapsed patients was higher in the group receiving ADM (n= 5/57) than either CBT groups (REBT n =1/57 and CT n= 3/56) at 24 weeks. When comparing ADM versus either CBT (REBT or CT), we found a higher but non-significant risk of relapse among those receiving ADM (RR = 2.48, 95% CI= 0.69 to 8.87).

5.2.3.1.1.1.2 Maintenance phase (≥25 weeks)

Two studies assessed the efficacy of ADM compared to CBT on relapse for ≥25 weeks (66,68). The two studies had different designs and thus, a pairwise meta-analysis could not be done. Blackburn and Moore compared the effect of maintaining individuals on ADM or CBT (CT) after the acute treatment (66). At 96 weeks, authors found no difference in the proportion of individuals with relapse in those receiving ADM (n= 8/26, 31%) compared to CBT (n= 7/27, 26%) (RR= 1.19 , 95% CI = 0.50 to 2.80). Similarly, Jarrett et al reported comparable relapse among participants receiving ADM (FXT) (n = 12/86, 20%) and CBT (CT) (n = 14/86, 26%) at 44 weeks after randomization (68) (RR= 0.86, 95% CI = 0.31 to 2.40).

ADM versus ADM plus CBT

5.2.3.1.1.1.3 Continuation phase (13 to 24 weeks)

We did not find any studies evaluating ADM versus ADM plus CBT at 13 to 24 weeks post randomization.

5.2.3.1.1.1.4 Maintenance phase (≥25 weeks)

One study evaluated the efficacy of ADM alone compared to the combination of ADM and CBT (54). Authors found that patients in the ADM plus CBT (ADM plus CT) group had fewer relapses than patients in the ADM-alone group at month 18 (66 relapses in 44 patients versus 80 relapses in 49 patients, respectively), but this difference was not significant.

CBT versus ADM plus CBT

We did not find any studies evaluating the effect of CBT alone versus ADM plus CBT on relapses in both the continuation and maintenance phases.

ADM versus placebo

5.2.3.1.1.1.5 Continuation phase (13 to 24 weeks)

Two studies assessed the effect of ADM versus placebo on the risk of relapse (72,73). Due to the different designs of the studies, we synthesize the evidence from these studies narratively.

In CL3-20098-041, all patients with recurrent MDD received ADM (AGM) during an open label period after which they were randomized to continue the ADM or to receive placebo (73). The effect of ADM in reducing the risk of relapse was then assessed. Authors found a lower risk of relapse in the ADM group compared to placebo (21% versus 41%, respectively) at 24 weeks after randomization (RR= 0.49, 95% CI= 0.34 to 0.68). In a subgroup of patients with HAMD-D ≥25 (severe MDD), similar results were found (22% versus 45%) (RR= 0.49, 95% CI= 0.33 to 0.71).

In CL3-20098-022, patients with single or recurrent MDD were randomized to receive ADM (AGM or FXT) or placebo for six weeks followed by an optional extension period for responders for a total of 18 weeks (72). Among those who had responded to treatment in the acute phase, a lower proportion of relapse was found among the ADM groups (14% in AGM and 18% in FXT groups) compared to placebo (33%) (72). When we compared the risk of relapse in either ADM (AGM or FXT) versus placebo, we found a significantly lower risk of relapse among those receiving ADM (RR 0.49, 95% CI= 0.29 to 0.83).

5.2.3.1.1.1.6 Maintenance phase (≥25 weeks)

The results of the pairwise meta-analysis of two studies evaluating relapse in ADM versus placebo in the maintenance phase is shown in Figure 5 (68,71) . We found no difference in the risk of relapse between the ADM and placebo groups (RR= 0.84, 95% CI= 0.44 to 1.59). However, the estimates from these two studies were inconsistent and there was substantial heterogeneity (I^2= 66%, 95% CI= 0.0% to 92.3%; Q= 2.94, p= 0.09). This heterogeneity could possibly be related to the different populations included in the two studies. In CL3-20098-21, participants 18-59 years with moderate to severe MDD were included (71). On the other hand, there were no age or MDD severity restrictions for inclusion into the trial by Jarrett et al (68). We were not able to assess differences in the baseline mean MDD severity between these studies since baseline values were not reported in either study. A post-hoc analysis conducted in CL3-20098-21 in the group of more severe patients (with HAM-D > 25 and CGI-S≥5) showed a lower proportion of relapse among the ADM group compared to placebo (21% versus 31%) (71).

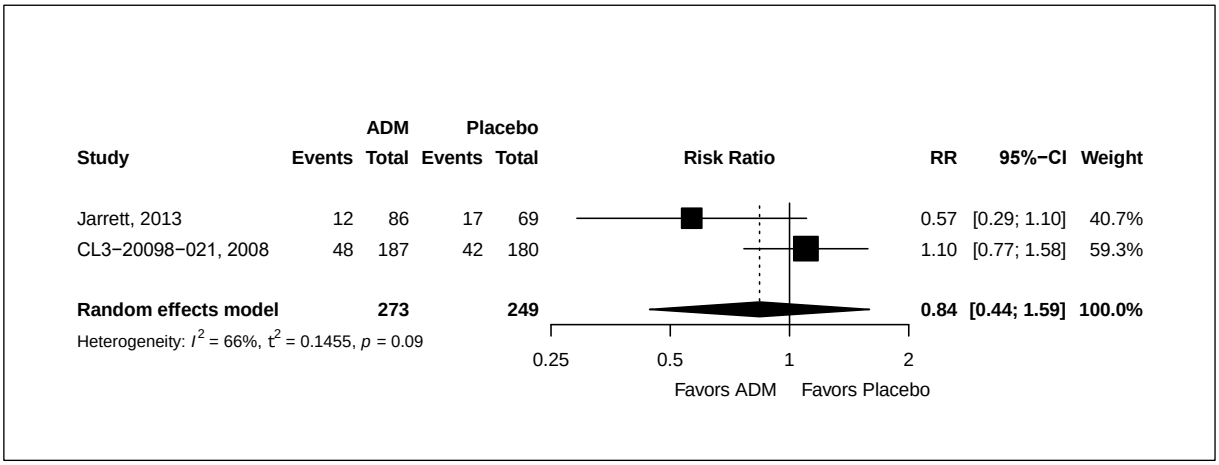


Figure 5. Pairwise meta-analysis for relapse of ADM versus placebo in the maintenance phase
Legend: ADM: antidepressant medication; RR: risk ratio; CI: confidence interval

CBT versus placebo

5.2.3.1.1.1.7 Continuation phase (13 to 24 weeks)
We did not find any studies evaluating CBT versus placebo at 13 to 24 weeks post randomization.

5.2.3.1.1.1.8 Maintenance phase (≥25 weeks)
We found only one study evaluating the effect of CBT versus placebo on reducing relapse (68). Jarrett et al. found that participants in the CBT group (CT) (n= 14/86, 16%) were less likely to relapse compared to placebo (n = 17/69, 25%) after 44 weeks of treatment; however the difference was not significant.

We did not find any studies at either treatment phase assessing CBT or ADM versus waiting list or treatment as usual. Estimates from the individual drug and class level pairwise analysis are presented in Appendix 11.1.6.1.

Network meta-analysis and ranking of treatment

We synthesized data from available comparisons for the maintenance phase for studies with design I and II separately (Figure 6) . We did not find any difference in the effects of any of the treatments in either design. In studies with design II, we examined the consistency of the network using the loop-specific approach and design by treatment interaction and found no evidence of inconsistency. There was substantial heterogeneity (I^2= 66%, 95% CI= 0.0% to 92.3%; Q=2.94, p= 0.09). Estimates from the individual drug and class level analysis in the maintenance phase are presented in Appendix 11.1.6.1 with no significant differences between the different classes. The p-score analyses are shown

in Table 3. Using studies with design I, CBT ranked first followed by ADM plus CBT ranking second and ADM ranking third. In studies with design II, CBT also ranked first followed by ADM and placebo ranking second and third, respectively (Appendix 11.1.6.1).

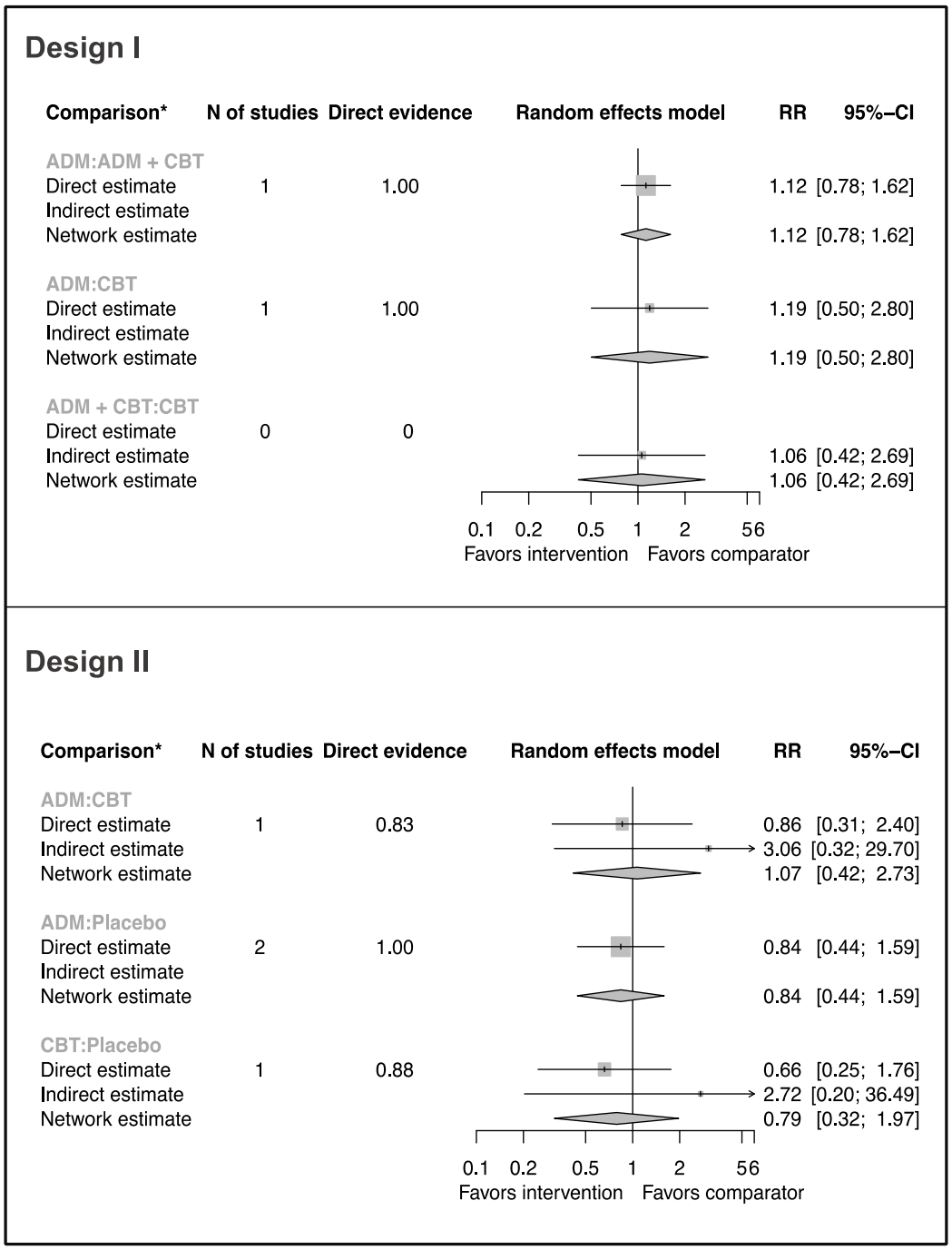


Figure 6. Direct and indirect estimates from the network meta-analysis of relapse outcome in the maintenance phase of treatment

*intervention on the left side and comparator on the right side of the comparison
Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; RR: risk ratio; CI: confidence interval

Table 3. Results of the P-score analyses. The P-score shows the probability of a treatment being the best treatment, derived from the posterior distributions of all treatment estimates.

Rank	P-Score (Design I)	
1	CBT	0.60
2	ADM plus CBT	0.60
3	ADM	0.31
Rank	**P-Score (Design II)**	
1	CBT	0.63
2	ADM	0.58
3	Placebo	0.30

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy

GRADE Assessment

The results of the GRADE assessment for the different comparisons regarding relapse in the continuation phase is shown in Table 4 (detailed GRADE assessment can be found in Appendix 11.1.5). We judged the quality of the evidence as low for ADM vs CBT and moderate for ADM vs placebo. The rating for the ADM versus CBT comparison was downgraded by one point due to risk of bias and one point due to the imprecision relating to small sample sizes. The rating for ADM versus placebo was downgraded by one point due to the overall risk of bias of the studies.

Table 4. Summary of findings table with GRADE assessment for the primary outcomes

The efficacy of ADM and CBTs in the treatment of MDD beyond the acute phase
Patient or population: adult patients with MDD
Intervention: ADM or CBT
Comparison: ADM plus CBT, ADM or CBT as monotherapy, control conditions (placebo, WL, TAU)

Outcomes	Anticipated absolute effects (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Relapse	**ADM vs CBT**	**RR** 2.48 (0.69 to 8.8) (favours CBT)	170	⨁⨁◯◯	Only one study contributing to the results
	52 more per 1,000 (from 11 fewer to 279 more)		1 RCT	LOW[a,b]	
	ADM vs Placebo	not estimable	536	⨁⨁⨁◯	Different design for each study
	-		2 RCTs	MODERATE[a]	
	ADM vs ADM plus CBT	not estimable	-	-	-
	-				
	CBT vs ADM plus CBT	not estimable	-	-	-
	-				
	CBT vs Placebo	not estimable	-	-	-
	-				
	ADM vs TAU	not estimable	-	-	-
	-				
	ADM vs WL	not estimable	-	-	-
	-				
	CBT vs TAU	not estimable	-	-	-
	-				
	CBT vs WL	not estimable	-	-	-
	-				
Recurrence	**ADM vs CBT**	not estimable	-	-	-
	-				
	ADM vs Placebo	not estimable	-	-	-
	-				
	ADM vs ADM plus CBT	not estimable	-	-	-
	-				
	CBT vs ADM plus CBT	not estimable	-	-	-
	-				
	CBT vs Placebo	not estimable	-	-	-

	-				
	ADM vs TAU	not estimable	-	-	-
	-				
	ADM vs WL	not estimable	-	-	-
	-				
	CBT vs TAU	not estimable	-	-	-
	-				
	CBT vs WL	not estimable	-	-	-
	-				
QoL	**ADM vs CBT**	**SMD** 3.10 (-2.89 to 9.09) (favours ADM)	140 1 RCT	⊕◯◯◯[a,b,c] VERY LOW	Only one study contributing to the results
	-				
	ADM vs Placebo	not estimable	-	-	-
	-				
	ADM vs ADM plus CBT	not estimable	-	-	-
	-				
	CBT vs ADM plus CBT	not estimable	-	-	-
	-				
	CBT vs Placebo	not estimable	-	-	-
	-				
	ADM vs TAU	**SMD** 24.0 (23.88 to 24.12) (favours ADM)	160 1 RCT	⊕◯◯◯[a,b,c] VERY LOW	Only one study contributing to the results
	-				
	ADM vs WL	not estimable	-	-	-
	-				
	CBT vs TAU	not estimable	-	-	-
	-				
	CBT vs WL	not estimable	-	-	-
	-				
Social functioning	**ADM vs CBT**	**SMD** 0.14 (-0.30 to 0.58) (favours CBT)	90 1 RCT	⊕◯◯◯[a,b,c] VERY LOW	Only one study contributing to the results
	-				
	ADM vs Placebo	**SMD** -0.76 (-1.0 to -0.52) (favours ADM)	278 1 RCT	⊕⊕⊕◯[b] MODERATE	Only one study contributing to the results
	-				
	ADM vs ADM plus CBT	**SMD** -0.28 (-0.64 to 0.08) (favours ADM)	120 1 RCT	⊕◯◯◯[a,b,c] VERY LOW	Only one study contributing to the results
	-				
	CBT vs ADM plus CBT	**SMD** -0.60 (-1.05 to -0.16) (favours CBT)	90 1 RCT	⊕◯◯◯[a,b,c] VERY LOW	Only one study contributing to the results
	-				
	CBT vs Placebo	not estimable	-	-	-
	-				
	ADM vs TAU	not estimable	-	-	-

	-				
	ADM vs WL	not estimable	-	-	-
	-				
	CBT vs TAU	**SMD** -0.18 (-0.68 to 0.33) (favours CBT)	60 1 RCT	⊕◯◯◯[a,b,c] VERY LOW	Only one study contributing to the results
	-				
	CBT vs WL	not estimable	-	-	-
	-				
Worsening of depression	**ADM vs CBT**	**RR** 1.13 (0.36 to 3.54) (favours CBT)	140 1 RCT	⊕⊕◯◯[a,c] LOW	Only one study contributing to the results
	10 more per 1,000 (from 47 fewer to 187 more)				
	ADM vs Placebo	not estimable	-	-	-
	-				
	ADM vs ADM plus CBT	not estimable	-	-	-
	-				
	CBT vs ADM plus CBT	not estimable	-	-	-
	-				
	CBT vs Placebo	not estimable	-	-	-
	-				
	ADM vs TAU	not estimable	-	-	-
	-				
	ADM vs WL	not estimable	-	-	-
	-				
	CBT vs TAU	not estimable	-	-	-
	-				
	CBT vs WL	**RR** 0.86 (0.27 to 2.76) (favours CBT)	174 1 RCT	⊕⊕⊕◯[b] MODERATE	Only one study contributing to the results
	-				
Mortality	**ADM vs CBT**	not estimable	140 1 RCT	⊕⊕◯◯[b,c] LOW	Only one study contributing to the results
	-				
	ADM vs Placebo	not estimable	530 3 RCTs	⊕⊕◯◯[d] LOW	Different populations and study designs
	-				
	ADM vs ADM plus CBT	not estimable	-	-	-
	-				
	CBT vs ADM plus CBT	not estimable	-	-	-
	-				
	CBT vs Placebo	not estimable	-	-	-
	-				
	ADM vs TAU	not estimable	-	-	-
	-				
	ADM vs WL	not estimable	-	-	-

	-				
	CBT vs TAU	not estimable	-	-	-
	-				
	CBT vs WL	not estimable	-	-	-
	-				

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; TAU: treatment as usual; WL: waiting list; RR: risk ratio; SMD: standardized mean difference; CI: confidence interval; RCT: randomized controlled trial

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Downgraded one point as majority of studies judged as of overall poor quality regarding risk of bias.

b. Downgraded one point due to imprecision (defined as wide confidence intervals including no effect or low overall sample size (defined as <400 participants for continuous outcomes or below optimal information size for dichotomous outcomes)).

c. Downgraded one point due to indirectness related to the population of interest.

d. Downgraded two points due to indirectness related to the population of interest and the different designs of the RCTs.

5.2.3.2 Recurrence

Only one study assessed recurrence during continuation or maintenance phases (55) (Table 5). As no meta-analysis was possible, we present a narrative summary of the findings of this study.

Table 5. Characteristics of studies assessing recurrence

Study	Design	Comparison	Population and MDD severity	Mean (SD) MDD severity[1]	Definition of recurrence	Timepoint
DeRubeis	I	ADM plus CBT vs ADM	Adults with MDD *(all severities)*	I: 5.8 (4.0) C: 5.4 (4.0)	LIFE ratings of 5 or 6 for 2 consecutive weeks at any time after the first 8 weeks of phase 2	≥25 weeks

[1]assessed by HAM-D unless stated otherwise

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; MDD: major depressive disorder; I: intervention; C: comparator; SD: standard deviation; LIFE: Longitudinal Interval Follow-up Evaluation

Risk of bias

We judged the evidence from the study to be at a high overall risk of bias due to missing outcome data (Figure 7).

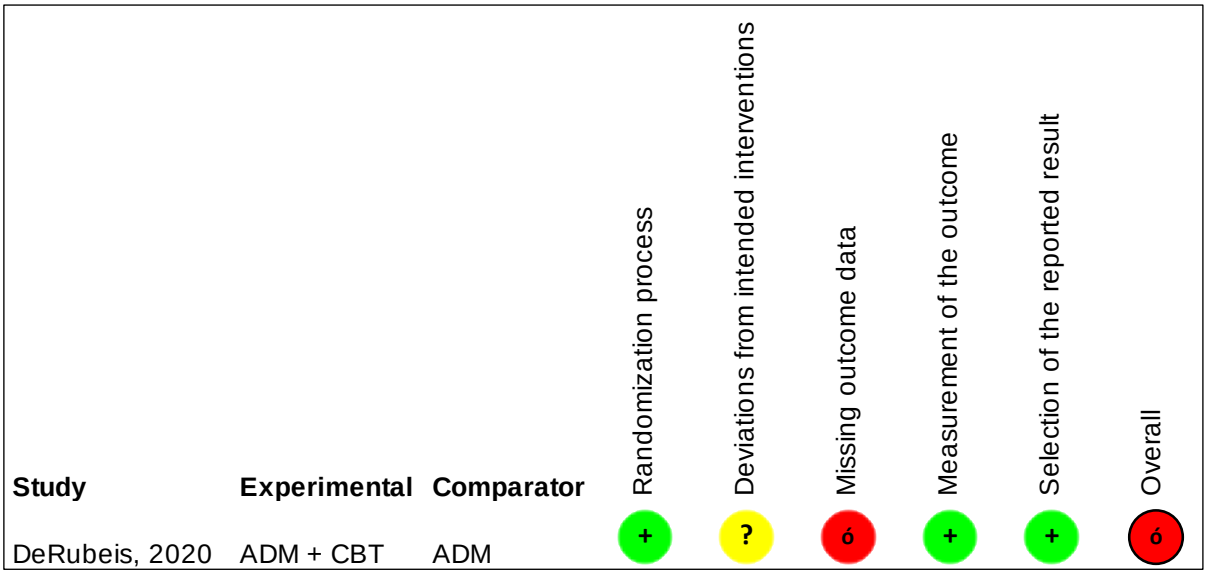


Figure 7. Risk of bias of studies for recurrence outcome (based on RoB 2.0).
ADM: antidepressant medication; CBT: cognitive behavioural therapy

Data synthesis

ADM versus ADM plus CBT in the maintenance phase

In a phase two randomized controlled trial of ADM monotherapy versus ADM plus CBT combination therapy, DeRubeis et al evaluated whether the provision of CBT in addition to ADM provided protection against future recurrences (55). In phase 1 of the trial, patients were randomized to ADM monotherapy or ADM plus CBT (54). Those who achieved recovery in phase 1 were randomized to receive either maintenance or withdrawal of ADM with a 3-year follow-up. As our comparison is the maintenance of ADM versus ADM plus CBT, we extracted the relevant estimates and disregarded data on patients who were not maintained on treatment. Overall, there was no difference in recurrence between the ADM monotherapy and ADM plus CBT groups at three years (RR= 0.99, 95% = CI 0.69 to 1.41).

We found no studies evaluating recurrnce in any of the remaining comparisons.

GRADE Assessment

We could not perform a GRADE assessment as we did not find any studies assessing the effect of any of the comparisons on the risk of recurrence in the continuation phase.

5.2.3.3 QoL

QoL was evaluated by seven studies (59,65,74–77) (Table 6) and the full extracted data from these studies is presented in Appendix 11.1.6.2. Due to the large heterogeneity between the publications regarding the instruments used and the evaluation of specific QoL-related endpoints between publications, a meta-analysis was not possible based on the available data. As such, we present a narrative review of the evidence.

Table 6. Characteristics of studies assessing quality of life outcome

Study	Design	Comparison	Population and MDD severity	Mean (SD) MDD severity[1]	Scale	Timepoint
A-Tjak	I	CBT vs CBT *(ACT vs CBT)*	18-65 year old with MDD *(all severities)*	I: 19.3 (5.3) C: 17.7 (8.1)	EUROHIS	≥ 25 weeks
CL3-20098-062	I	ADM vs ADM *(AGM vs DLX)*	18-65 year old with MDD *(moderate to severe)*	I: 26.2 (NR) C: 26.3 (NR)	VAS and EQ5D	13 - 24 weeks
Corruble	III	ADM vs ADM *(AGM vs ESC)*	18-70 year old with MDD *(moderate to severe)*	I: 26.8 (3.1) C: 26.6 (2.5)	VAS feeling good	≤12 weeks 13 - 24 weeks
Gilliam	I	ADM vs CBT *(SRT vs SCBT)*	21-75 year old with epilepsy and MDD *(all severities)*	I: 24.2 (8.4)* C: 26.9 (10.5)	QOLIE-89	13 - 24 weeks
Kumar	I	ADM vs TAU *(SRT vs TAU)*	18-70 year old with MDD *(moderate to severe)*	I: 15.7 (0.4)** C: 15.4 (0.5)	WHO-5	≤12 weeks 13 - 24 weeks
Kooistra	I	CBT vs CBT *(BCBT vs SCBT)*	Adults with MDD *(moderate to severe)*	I: 45.2 (12.2)*** C: 41.5 (11.6)	EQ5D3L	≤12 weeks 13 - 24 weeks ≥25 weeks

[1] assessed by HAM-D unless stated otherwise: *BDI-II, **PHQ-9, ***IDS-SR

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; MDD: major depressive disorder; I: intervention; C: comparator; SD: standard deviation; TAU: treatment as usual; BCBT: blended CBT; SCBT: standard CBT; VAS: visual analogue scale; NR: not reported; QOLIE-89: Quality of Life in Epilepsy Inventory-89

Risk of bias

We judged the evidence from three studies to be at a high overall risk of bias and we had some concerns about three studies (Figure 8). All but one of the included studies evaluated the efficacy of the interventions based on ITT effects. Four studies reported allocation concealment and one did not provide any information. Blinding was not possible in three of the studies and there was no information on whether the analyses were done as prespecified in three studies as well.

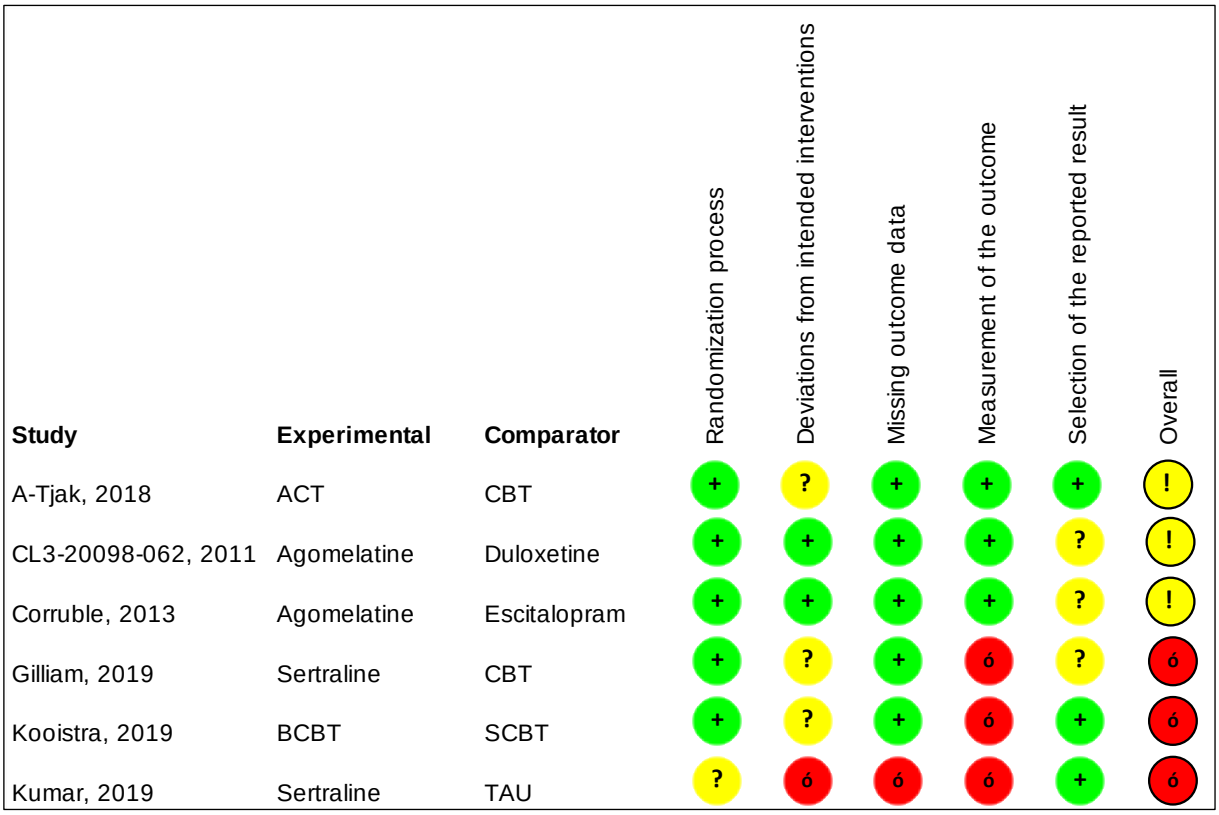


Figure 8. Risk of bias of studies for QoL (based on RoB 2.0).
Legend: ACT: Acceptance and commitment therapy; CBT: cognitive behavioural therapy; SCBT: standard CBT; BCBT: blended CBT; TAU: treatment as usual

Data synthesis

ADM versus CBT

5.2.3.3.1.1.1 Acute phase (≤12 weeks)

We found no studies assesing QoL during the acute phase in patients receiving ADM and CBT.

5.2.3.3.1.1.2 Continuation phase (13-24 weeks)

We identified only one study assessing QoL in patients with MDD and receiving ADM compared to CBT during the continuation phase (65). This RCT randomized adults with

epilepsy and MDD to ADM (SRT) or CBT (CBT) for 16 weeks and assessed their QoL using the Quality of Life in Epilepsy Inventory-89 (QOLIE-89). Authors found that while the total QOLIE-89 scores improved from baseline to the follow-up timepoint in both groups (ADM= 51±14.9 to 66.1±17.7 and CBT= 50.1 ±13.6 to 63.0 ±18.4), there was no significant difference in the scores between the two groups.

5.2.3.3.1.1.3 Maintenance phase (≥24 weeks)

We found no studies assesing QoL during the maintenance phase in patients receiving ADM and CBT.

ADM versus TAU

5.2.3.3.1.1.4 Acute phase (≤12 weeks)

One study evaluated QoL in patients receiving ADM versus those receiving TAU up to 12 weeks (59). In this trial, patients with type 2 diabetes mellitus and moderate to severe MDD were randomized to receive ADM (SRT) or TAU (diabetes only medications) for six months. QoL was evaluated at three and six months using the WHO-5 (wellbeing index). At three months, both groups showed an improvement in the WHO-5 scores, where the mean scores increased from 43.5±0.54 at baseline to 64±0.22 at the follow up in the ADM group and from 43.8±0.58 to 56±0.39 in the TAU group. However, there was no significant difference between the two arms.

5.2.3.3.1.1.5 Continuation phase (13-24 weeks)

On the other hand, at six months, Kumar et al observed a significant improvement in those receiving ADM compared to TAU (88.0±0.26 versus 64±0.48) (59).

5.2.3.3.1.1.6 Maintenance phase (≥24 weeks)

We found no studies assesing QoL during the maintenance phase in patients receiving ADM and TAU.

For all the remaining comparisons, we did not identify any studies at any of the timepoints.

GRADE Assessment

The results of the GRADE assessment for the different comparisons regarding QoL in the continuation phase is shown in Table 4. We judged the quality of the evidence as very low for ADM vs CBT and ADM vs TAU. The rating for both comparisons was downgraded due to risk of bias, the indirectness of the evidence (as both trials were conducted in selected populations) and one point due to the imprecision relating to small sample sizes.

5.2.3.4 Improvement in social functioning

Improvement in social functioning was evaluated by seven studies (75,77–80). A short summary of the studies assessing this outcome is presented in Table 7.

Table 7. Characteristics of studies assessing social functioning

Study	Design	Comparison	Population and MDD severity	Mean MDD (SD) severity[1]	Scale	Timepoint
CL3-20098-062	I	ADM vs ADM *(AGM vs DLX)*	18-65 year old with MDD *(moderate to severe)*	I: 26.2 (NR) C: 26.3 (NR)	SDS	13 - 24 weeks
Corruble	III	ADM vs ADM *(AGM vs ESC)*	18-70 year old with MDD *(moderate to severe)*	I: 26.8 (3.1) C: 26.6 (2.5)	GAF	≤ 12 weeks 13 - 24 weeks
Kennedy	III	ADM vs PLC *(DLX vs PLC)*	18-65 year old with MDD *(moderate to severe)*	I: 26.7 (2.9) C: 26.6 (2.6)	SDS	13 - 24 weeks
Oakes a	I	ADM vs PLC *(DLX vs PLC)*	18-65 year old with MDD *(moderate to severe)*	I: 22.9 (4.3) C: 22.8 (3.7)	SASS and SDS	≤12 weeks ≥25 weeks
Oakes b	I	ADM vs PLC *(DLX vs PLC)*	18-65 year old with MDD *(moderate to severe)*	I: 22.8 (4.5) C: 22.9 (4.9)	SASS and SDS	≤12 weeks ≥25 weeks
Study 043	I	ADM vs ADM *(CIT vs RBX)*	18-70 year old with MDD *(severe)*	I: 27.4 (3.9) C: 27.4 (3.5)	SASS	≤ 12 weeks 13 - 24 weeks
Zu	I	ADM vs CBT *(ADM vs SCBT)* ADM vs ADM plus CBT *(ADM vs ADM plus SCBT)* CBT vs ADM plus CBT *(SCBT vs ADM plus SCBT)* ADM vs TAU CBT vs TAU *(SCBT vs TAU)*	17-60 year old with MDD *(moderate to severe)*	I: 23.2 (5.3) C (SCBT): 19.6 (3.8) C (ADM+SCBT): 25.1 (6.0) C (TAU): 21.6 (5.1)	WSAS	≤ 12 weeks 13 - 24 weeks

[1] assessed by HAM-D unless stated otherwise

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; MDD: major depressive disorder; SASS: Social Adaptation Self-evaluation Scale; SDS: Sheehan Disability Scale; WSAS: Work and Social Adjustment Scale; GAF: Global Assessment of Functioning ; SD: standard deviation; NR: not reported; TAU: treatment as usual; SCBT: standard CBT

Risk of bias

We evaluated two studies to be at an overall high risk of bias and we had some concerns about the evidence in five studies (Figure 9). The main reasons for the risk of bias in these studies were the unavailability of a prespecified analysis plan and missing outcome data for some participants.

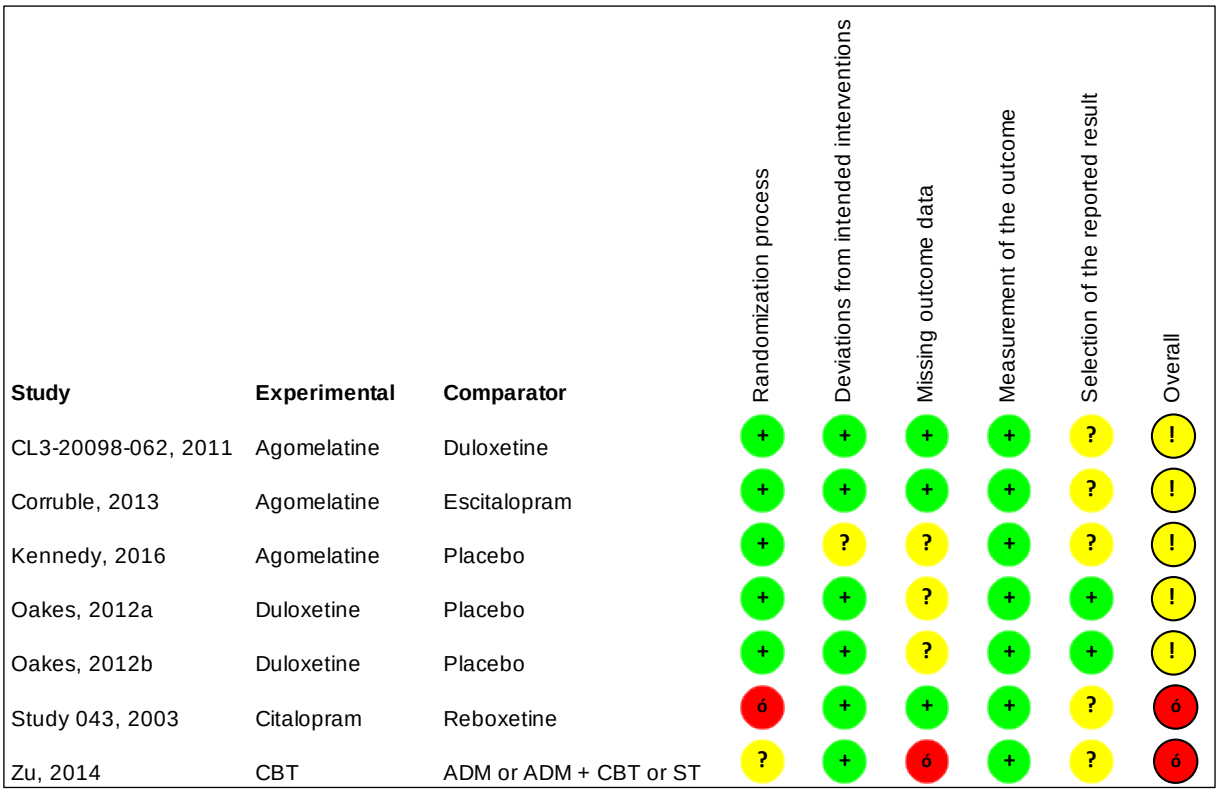


Figure 9. Risk of bias of studies for improvement in social function (based on RoB 2.0).

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; ST: standard therapy

Data synthesis

ADM versus CBT

5.2.3.4.1.1.1 Acute phase (≤12 weeks)

Zu et al evaluated the effect of ADM and CBT on social functioning in patients with moderate to severe MDD (80). Treatments were administered for six months and social functioning was evaluated using the Work and Social Adjustment Scale (WSAS) at three and six month follow-up. At three months, the authors did not find any significant differences between the two groups in score changes of WSAS from baseline (ADM: change from 23.3±9.6 to 13.1±11.1 at 3 months

5.2.3.4.1.1.2 Continuation phase (13-24 weeks)

Similarly at six months, Zu et al did not find any significant differences between the two groups in score changes of WSAS from baseline (ADM: change from 23.3±9.6 to 9.9±9.4 at 6 months; CBT: 19.1±9.4 to 8.6±8.7 at 6 months) (80).

5.2.3.4.1.1.3 Maintenance phase (≥24 weeks)

We found no studies assesing social functioning during the maintenance phase in patients receiving ADM and CBT.

ADM versus ADM plus CBT

5.2.3.4.1.1.4 Acute phase (≤12 weeks)

The effect of ADM versus ADM plus CBT on social functioning using WSAS was also evaluated by Zu et al (80). At month 3, there were no differences between the two groups in score changes of WSAS from baseline (ADM: change from 23.3±9.6 to 13.1±11.1 at month 3; ADM plus CBT: 24.6±7.0 to 15.6±9.8 at month 3).

5.2.3.4.1.1.5 Continuation phase (13-24 weeks)

Similar findings were reported by Zu et al. at six months (ADM: change from 23.3±9.6 to 9.9±9.4 at month 6; ADM plus CBT: 24.6±7.0 to 11.1±2.0 at month 6) (80).

5.2.3.4.1.1.6 Maintenance phase (≥24 weeks)

We found no studies assesing social functioning during the maintenance phase in patients receiving ADM compared to ADM plus CBT.

CBT versus ADM plus CBT

5.2.3.4.1.1.7 Acute phase (≤12 weeks)

Zu et al also evaluated CBT versus ADM plus CBT on social functioning at month 3 and month 6 of treatment (80). At both follow-ups, there were no differences between the two groups in score changes of WSAS from baseline (CBT: change from 19.1±9.4 to 12±8.4 at month 3 and 8.6±8.7 at month 6; ADM plus CBT: 24.6±7.0 to 15.6±9.8 at month 3 and 11.1±2.0 at month 6).

5.2.3.4.1.1.8 Continuation phase (13-24 weeks)

No differences regarding social functioning at 6 months of treatment between CBT versus ADM plus CBT were reported in Zu at al. (CBT: change from 19.1±9.4 to 8.6±8.7 at month 6; ADM plus CBT: 24.6±7.0 to 11.1±2.0 at month 6) (80).

5.2.3.4.1.1.9 Maintenance phase (≥24 weeks)

We found no studies assesing social functioning during the maintenance phase in patients receiving CBT compared to ADM plus CBT.

ADM versus placebo

5.2.3.4.1.1.10 Acute phase (≤12 weeks)

Oakes et al presented data from two studies (trial I and II) evaluating the efficacy of ADM (DLX) versus placebo on the functional impairment of patients with moderate to severe MDD (78). The outcome was measured using the HAMD work/activities item and two patient rated scales: Social Adjustment Scale (SASS) with an increase in the outcome measurement signifying improvement and Sheehan Disability Scale (SDS) where a decrease in the score means less functional impairment.

With regard to the HAMD work/activities item, the two trials yielded inconsistent results, with only trial II finding a difference between the two groups at week 12. In both trials however, the majority of participants still had depressive symptoms related to social functioning. In both trials, treatment with ADM was associated with significant improvement on the SASS total score at week 12 (mean change of ADM versus placebo-trial I: 7.18±0.62 vs 3.40±0.99, p=0.001; trial II: 7.54±0.61 versus 4.52±0.92, p=0.006). Furthermore, the mean SASS scores in the ADM groups of both trials were ≥35 which indicated that the patients achieved normal social functioning, while the placebo groups fell short of the cut-off score. Regarding SDS scores, only Oakes trial II found a significant difference in the scores between the two groups (mean change of ADM versus placebo-trial I: -8.32±0.53 vs -6.84±0.87, p=0.142; trial II: -7.70±0.52 vs -4.94±0.84, p=0.005).

5.2.3.4.1.1.11 Continuation phase (13 to 24 weeks)

Only one study compared the effects of ADM versus placebo on social functioning at 13 to 24 weeks of treatment in patients with moderate to severe MDD (81). After receiving ADM (AGM) or placebo in the acute phase, only responders entered the extension period and social functioning was assessed at week 24 using SDS. Authors found that the mean decreases in the total SDS score (improvement in social functioning) were significantly greater in the ADM group than in the placebo group, with mean differences reaching 7.25±1.14 points. Furthermore, within the scale, decreases in all the sub-scores (i.e., work/school, social life, family life/home responsibilities) were more pronounced in the ADM group compared to the placebo group. Using the threshold cut-off total score of ≤6 for functional remission, 53% of individuals receiving ADM achieved functional remission compared to 28% in the placebo group. Similar findings were also found in the subgroup of individuals with severe MDD.

5.2.3.4.1.1.12 Maintenance phase (≥25 weeks)

Oakes et al also evaluated the efficacy of ADM (DLX) versus placebo in terms of reducing the functional impairment of patients with moderate to severe MDD at 9 months. There were no differences in the score changes of the HAMD work/activities item and SDS between ADM and placebo for both trials at 9 months. Only trial II detected a significantly better improvement in the SASS scores at month 9 from baseline in the ADM group compared to placebo (13.81±1.04 vs 9.28±1.92, p=0.04).

CBT versus TAU

5.2.3.4.1.1.13 Acute phase (≤12 weeks)

A comparison of the effects of CBT and TAU in Zu et al on social functioning revealed no differences between the two groups at both acute and continuation phase endpoints (CBT: change in WSAS score from 19.1±9.4 to 12±8.4 at month 3 and 8.6±8.7 at month 6; TAU: 21.9±11.5 to 13.1±9.3 at month 3 and 10.3±10.3 at month 6) (80).

5.2.3.4.1.1.14 Continuation phase (13 to 24 weeks)

No difference between CBT and TAU at the continuation phase endpoint was observed by Zu et al. (CBT: change in WSAS score from 19.1±9.4 8.6±8.7 at month 6; TAU: 21.9±11.5 to 10.3±10.3 at month 6) (80).

5.2.3.4.1.1.15 Maintenance phase (≥24 weeks)

We found no studies assesing social functioning during the maintenance phase in patients receiving CBT compared to TAU.

We did not find any studies at any of timepoints assessing ADM or CBT versus waiting list or treatment as usual.

GRADE Assessment

The results of the GRADE assessment for the different comparisons regarding social functioning in the continuation phase is shown in Table 4. We judged the quality of the evidence as very low for ADM vs CBT, ADM vs ADM plus CBT, CBT vs ADM plus CBT, and CBT vs TAU. The rating for these comparisons was downgraded due to risk of bias and imprecision relating to no effects and small sample sizes, as well as the indirectness of the evidence relating to the population (Chinese patients). We judged the quality of the evidence for ADM vs placebo as moderate. We downgraded it by one point due to the small sample size.

5.2.3.5 Acceptability

Acceptability was evaluated in 35 studies (54,55,68,70–75,77–79,56,80–89,57,90,91,58–60,63,64,67). A brief summary of the characteristics of these trials is listed in Table 8. We did not evaluate the risk of bias for this outcome as we deemed most of the domains of the bias assessment not applicable to it.

Table 8. Characteristics of the studies reporting on acceptability (drop-outs for any reason)

Study	Design	Comparison	Population and MDD severity	Mean MDD (SD) severity[1]	Timepoint
A-Tjak	I	CBT vs CBT *(ACT vs CBT)*	18-65 year old with MDD *(all severities)*	I: 19.3 (5.3) C: 17.7 (8.1)	≥ 25 weeks
Barber	I	ADM vs PLC *(SRT vs PLC)*	18-70 year old with MDD *(all severities)*	I: 19 (3.4) C: 19.3 (3.8)	13 - 24 weeks
Banerjee	I	ADM vs ADM *(SRT vs MIR)* ADM vs PLC *(SRT or MIR vs PLC)*	Adults, fulfilling ADRDA criteria for Alzheimer's disease with MDD *(all severities)*	I: 12.8 (3.6)* C (MIR): 12.5 (3.7) C (PLC): 13.6 (5.2)	≥ 25 weeks
CL3-20098-022	III	ADM vs ADM *(AGM vs FXT)* ADM vs PLC *(AGM or FXT vs PLC)*	18-59 year old with MDD *(moderate to severe)*	I: 27.6 (2.9) C (FXT): 27.5 (NR) C (PLC): 28 (3.6)	13 - 24 weeks
CL3-20098-048	I	ADM vs ADM *(AGM vs PAR)*	≥ 60 year old with MDD *(moderate to severe)*	I: 26.3 (NR) C: 26.2 (NR)	≤ 12 weeks 13 - 24 weeks
CL3-20098-062	I	ADM vs ADM *(AGM vs DLX)*	18-65 year old with MDD *(moderate to severe)*	I: 26.2 (NR) C: 26.3 (NR)	≤ 12 weeks 13 - 24 weeks ≥ 25 weeks
CL3-20098-070	III	ADM vs PLC *(AGM vs PLC)*	≥65 year old with MDD *(moderate to severe)*	I: 26.8 (NR) C: 26.7 (NR)	≤ 12 weeks 13 - 24 weeks
CL3-20098-021	II	ADM vs PLC *(AGM vs PLC)*	18-59 year old with MDD *(moderate to severe)*	I: NR C: NR	≥25 weeks
CL3-20098-041	II	ADM vs PLC *(AGM vs PLC)*	18-59 year old with MDD *(moderate to severe)*	I: 27.0 (NR) C: NR	13 - 24 weeks
Corruble	III	ADM vs ADM *(AGM vs ESC)*	18-70 year old with MDD *(moderate to severe)*	I: 26.8 (3.1) C: 26.6 (2.5)	≤ 12 weeks 13 - 24 weeks
David	I	ADM vs CBT *(REBT or CT versus FXT)*	Adults with MDD *(all severities)*	I: 21.4 (8.0) C (REBT): 22.9 (7.0) C (CT): 23.1 (7.6)	≤ 12 weeks 13 - 24 weeks
DeRubeis	I	ADM vs ADM +CBT	Adults with MDD *(all severities)*	I: 5.8 (4.0) C: 5.4 (4.0)	≥25 weeks

Dimidjian	I	ADM vs CBT *(PAR vs BA or CT)* ADM vs PLC *(PAR vs PLC)* CBT vs PLC *(CT or BA vs PLC)*	18-60 year old with MDD *(all severities)*	I: 20.8 (NR) C (BA): NR C (CT): NR C (PLC): 21.2 (NR)	13 - 24 weeks
Friedli	I	ADM vs PLC *(SRT vs PLC)*	Adults with MDD *(mild to moderate),* on haemodialysis for ≥3 months	I: 24.5 (4.5)** C: 25.3 (4.2)	13 - 24 weeks
Grunebaum	III	ADM vs ADM *(BUP vs PAR)*	18-75 year old with MDD *(moderate to severe)* with past suicide attempt	I: 17.6 (5.2) C: 16.9 (5.8)	≤ 12 weeks 13 - 24 weeks
Hashimoto	I	ADM vs ADM *(MIR vs SRT vs SSRI vs PAR)*	20-75 year old with MDD *(all severities)*	I: 23.0 (1.2) C (SRT): 23.1 (0.9) C (SSRI): 23.2 (1.1) C (PAR): 22.9 (1.5)	13 - 24 weeks
Hollon	I	ADM vs ADM plus CBT *(ADM vs ADM plus CT)*	Adults with MDD *(all severities)*	I: 22.2 (4.4) C: 21.9 (4.0)	≤12 weeks ≥25 weeks
Jarrett	II	CBT vs ADM *(CT vs FXT)* CBT vs PLC *(CT vs PLC)* ADM vs PLC *(FXT vs PLC)*	Adults with MDD *(all severities)*	I: NR C (ADM): NR C (PLC): NR	≥25 weeks
Kavoussi	I	ADM vs ADM *(BUP vs SRT)*	Adults with MDD *(moderate to severe)*	I: NR C: NR	13 - 24 weeks
Kennedy	III	ADM vs PLC *(DLX vs PLC)*	18-65 year old with MDD *(moderate to severe)*	I: 26.7 (2.9) C: 26.6 (2.6)	13 - 24 weeks
Kishi	I	ADM vs ADM *(ESC vs PAR)*	20-70 year old with MDD	I: 23.7 (3.6) C: 23.2 (3.8)	13 - 24 weeks
Kumar	I	ADM vs TAU	18-70 year old with type II diabetes mellitus and MDD *(moderate to severe)*	I: 15.7 (0.4) *** C: 15.4 (0.5)	13 - 24 weeks
Lecrubier	I	ADM vs PLC *(VEN or IMI vs PLC)*	18-65 year old with MDD *(mild to moderate)*	I: 24.9 (NR)** C: 24.2 (NR) C: 24.4 (NR)	13 - 24 weeks
Mohr	I	CBT vs ADM *(SCBT vs SRT)*	Adults with multiple sclerosis & MDD *(moderate)*	I: 21.0 (3.4) C: 20.5 (3.5)	13 - 24 weeks
Oakes a	I	ADM vs PLC *(DLX vs PLC)*	18-65 year old with MDD *(moderate to severe)*	I: 22.9 (4.3) C: 22.8 (3.7)	≤12 weeks ≥25 weeks
Oakes b	I	ADM vs PLC *(DLX vs PLC)*	18-65 year old with MDD *(moderate to severe)*	I: 22.8 (4.5) C: 22.9 (4.9)	≤12 weeks ≥25 weeks

Quera-Salva	III	ADM vs ADM *(AGM vs ESC)*	18-60 year old with MDD *(moderate to severe)*	I: 26.1 (2.3) C: 26.1 (2.9)	13 - 24 weeks
Quigley	I	CBT vs ADM *(SCBT vs ADM)*	18-65 year old with MDD *(all severities)*	I: 16.8 (5.0) C: 16.4 (5.3)	13 - 24 weeks
Robinson	I	ADM vs PLC *(DLX vs PLC)*	≥65 year old with MDD *(moderate to severe)*	I: 19.4 (5.6) C: 19.3 (5.8)	13 - 24 weeks
Rush	I	ADM vs ADM *(BUP vs SRT)*	Adults with MDD *(moderate to severe)*	I: 24.8 (4.6) C: 24.8 (4.6)	13 - 24 weeks
Study 043	I	ADM vs ADM (CIT vs RBX)	18-70 year old with MDD *(severe)*	I: 27.4 (3.9) C: 27.4 (3.5)	13 - 24 weeks
Thase	I	CBT vs CBT *(SCBT vs CCBT)*	Adults with MDD *(all severities)*	I: 19.6 (3.8) C: 19.8 (3.5)	13 - 24 weeks
Zu	I	ADM vs CBT *(ADM vs SCBT)* ADM vs ADM plus CBT *(ADM vs ADM plus SCBT)* CBT vs ADM plus CBT *(SCBT vs ADM vs SCBT)* ADM vs TAU *(ADM vs TAU)* CBT vs TAU *(SCBT vs TAU)*	17-60 year old with MDD *(moderate to severe)*	I: 23.2 (5.3) C (SCBT): 19.6 (3.8) C (ADM+SCBT): 25.1 (6.0) C (TAU): 21.6 (5.1)	13 - 24 weeks

[1] assessed by HAM-D unless stated otherwise: *CSDD, ** MADRS,***PHQ-9

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; PLC: placebo; MDD: major depressive disorder; SD: standard deviation; NR: not reported; I: intervention; C: comparator; TAU: treatment as usual; SCBT: standard CBT; CCBT: computerized CBT; REBT: rational emotive behaviour therapy; CT: cognitive therapy; BA: behavioural activation; ADRDA: Alzheimer's Disease and Related Disorders Association

Data synthesis

ADM versus CBT

5.2.3.5.1.1.1 Acute phase (≤12 weeks)

Two studies evaluated ADM versus CBT up to 12 weeks of treatment (Figure 10) (66,67). In the pairwise meta-analysis, we did not find any evidence of a difference between ADM and CBT (RR= 1.17, 95% CI = 0.49 to 2.80).

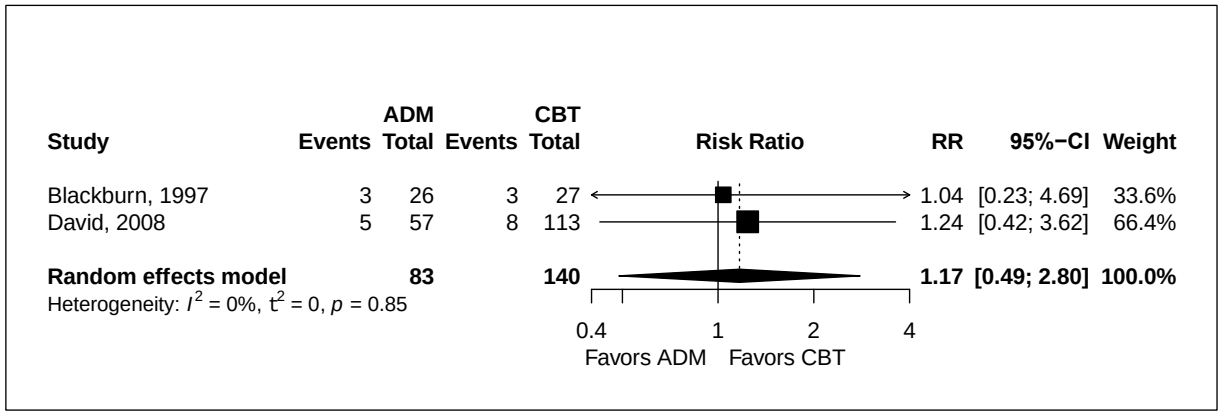


Figure 10. Pooled analysis of acceptability outcome of ADM versus CBT in the acute phase

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; RR: risk ratio; CI: confidence interval

5.2.3.5.1.1.2 Continuation phase (13 to 24 weeks)

We found six studies evaluating the acceptability of ADM versus CBT in the continuation phase (63,66,67,80,83,90). Only one study found evidence of a higher acceptability rate among the CBT group (83) (RR = 3.30, 95% CI= 1.52 to 7.18). Figure 11 shows the results of the pooled meta-analysis for acceptability rates with no evidence of an overall difference between the two groups (RR= 1.57, 95% CI= 0.94 to 2.62). Heterogeneity was substantial with I^2 of 52% (95% CI= 0.0% to 82.4%; Q=10.52, p= 0.062) and was reduced to 0% (Q= 0.68 , p=0.41) when restricting the analysis to studies including patients with only moderate to severe MDD (Figure 11).

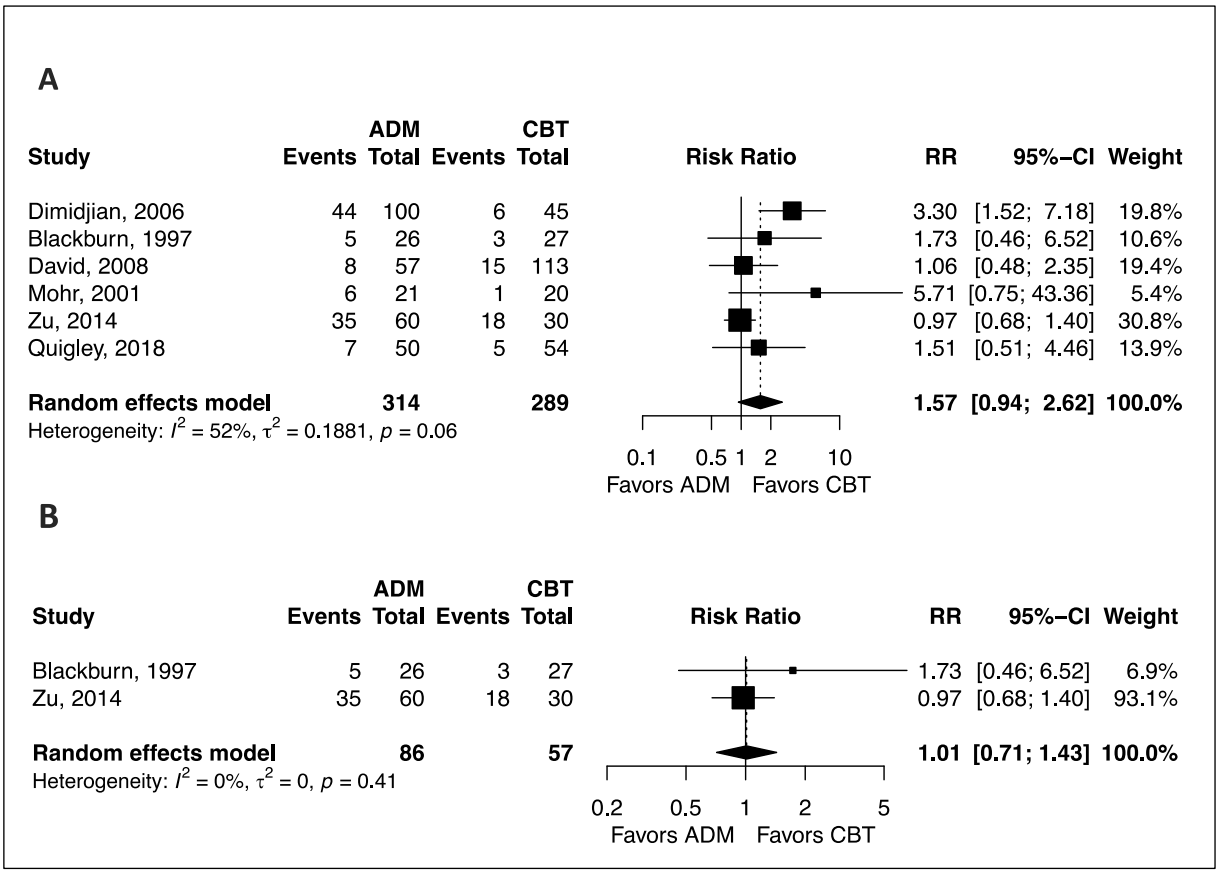


Figure 11.Pairwise meta-analysis of acceptability outcome in ADM versus CBT in the continuation phase. Panel A: Primary analysis including all studies; Panel B: Sensitivity analysis excluding studies with participants with any MDD severity level

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; RR: risk ratio; CI: confidence interval

5.2.3.5.1.1.3 Maintenance phase (≥25 weeks)

Acceptability rates in the maintenance phase between ADM and CBT were reported by two studies (66,68). In Blackburn & Moore there was no difference between the drop-out rates in the two groups by 96 weeks (66) (RR= 1.21, 95 % CI= 0.87 to 1.68) while in Jarret et al, a lower proportion of individuals in the ADM group had dropped out of the study at compared to the CBT group at 44 weeks (68) (RR= 0.62, 95 % CI= 0.41 to 0.93). We could not pool the evidence as the studies had different designs.

ADM versus ADM plus CBT

5.2.3.5.1.1.4 Acute phase (≤12 weeks)

We identified one study evaluating ADM vs ADM plus CBT and reporting on drop-out rates with no difference between the two groups up to 12 weeks of treatment (54) (RR=1.22, 95% CI= 0.77 to 1.92).

5.2.3.5.1.1.5 Continuation phase (13 to 24 weeks)

Zu et al reported the drop-out rates up to 24 weeks of treatment which were significantly higher in the ADM group compared to the ADM plus CBT group (80) (58% vs 28%, RR= 2.06, 95 % CI= 1.31 to 3.25).

5.2.3.5.1.1.6 Maintenance phase (≥25 weeks)

Figure 12 shows the pooled analysis of acceptability of ADM vs ADM plus CBT for longer than 24 weeks with no difference between the two groups (RR= 1.23, 95 % CI: 0.92 to 1.65).

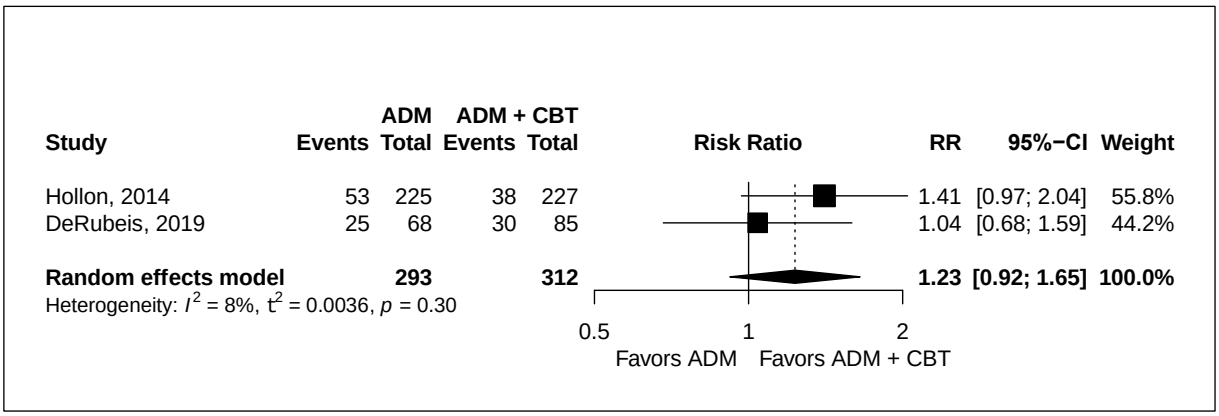


Figure 12. Pairwise meta-analysis of acceptability outcome of ADM versus ADM plus CBT in the maintenance phase

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; RR: risk ratio; CI: confidence interval

CBT versus ADM plus CBT

5.2.3.5.1.1.7 Acute phase (≤12 weeks)

We found no studies assessing the acceptability of CBT versus ADM plus CBT during the acute phase.

5.2.3.5.1.1.8 Continuation phase (13 to 24 weeks)

A higher acceptability of ADM plus CBT was reported in the study by Zu et al compared to CBT alone at 24 weeks (80) (60% vs 28%; RR= 2.12, 95 % CI= 1.29 to 3.48).

5.2.3.5.1.1.9 Maintenance phase (≥25 weeks)

We found no studies assessing the acceptability of CBT versus ADM plus CBT during the maintenance phase.

ADM versus placebo

5.2.3.5.1.1.10 Acute phase (≤12 weeks)

Four studies evaluated acceptability of ADM versus placebo in the acute phase (56,58,78). Only one study found evidence of a significantly higher acceptability rate among the ADM group (56) (RR= 0.58, 95% CI= 0.35 to 0.96). Figure 13 shows the results of the pooled analysis for acceptability rates with evidence of an overall higher acceptability rate among the ADM group (RR= 0.79, 95% CI = 0.67 to 0.94). Results were consistent across studies with no heterogeneity (I^2=0%, Q=1.80, p=0.62).

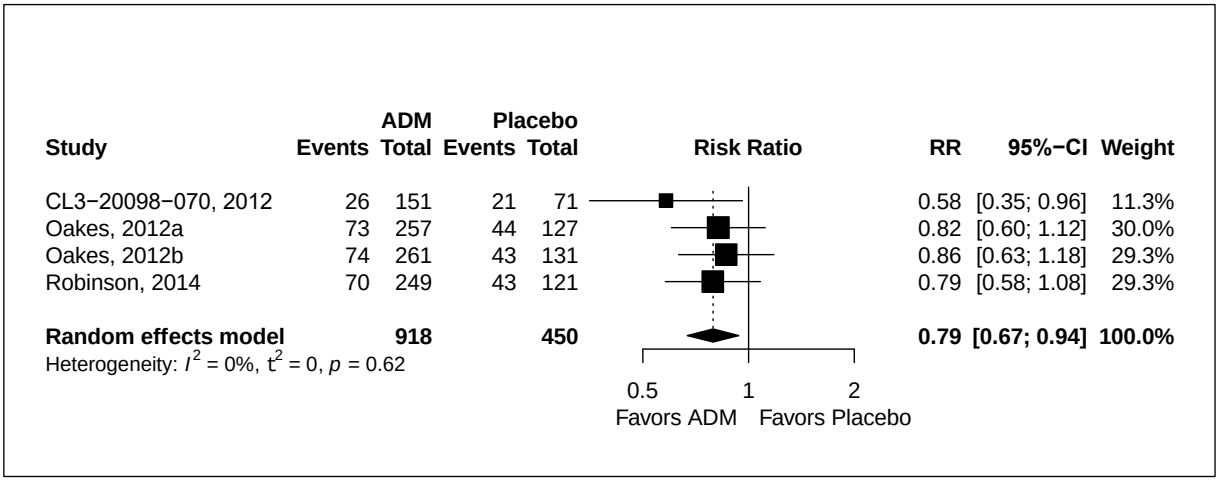


Figure 13. Pairwise meta-analysis of acceptability outcome of ADM versus placebo in the acute phase

Legend: ADM: antidepressant medication; RR: risk ratio; CI: confidence interval

5.2.3.5.1.1.11 Continuation phase (13 to 24 weeks)

Eight studies reported on drop-out rates between 13 and 24 weeks, of which five studies had study design I (58,60,82,83,88), one design II (73) and two had design III (56,81). We synthesized the evidence across the studies with a similar design.

There was no significant difference concerning acceptability between ADM and placebo across all studies with design I with a pooled estimate of RR=1.41 (95%= 0.93 to 2.14) and moderate heterogeneity (I^2=54%, 95% CI 0.0% to 83.2%; Q=8.77, p=0.067) (Figure 14). When omitting Robinson et al which was the only study that included only older participants (≥65 years), we found better acceptability in those receiving placebo (RR= 1.69, 95% CI= 1.07 to 2.69) and the heterogeneity was reduced to 20% (95% CI= 0.0% to 87.8%; Q= 3.76, p=0.29) (Figure 14).

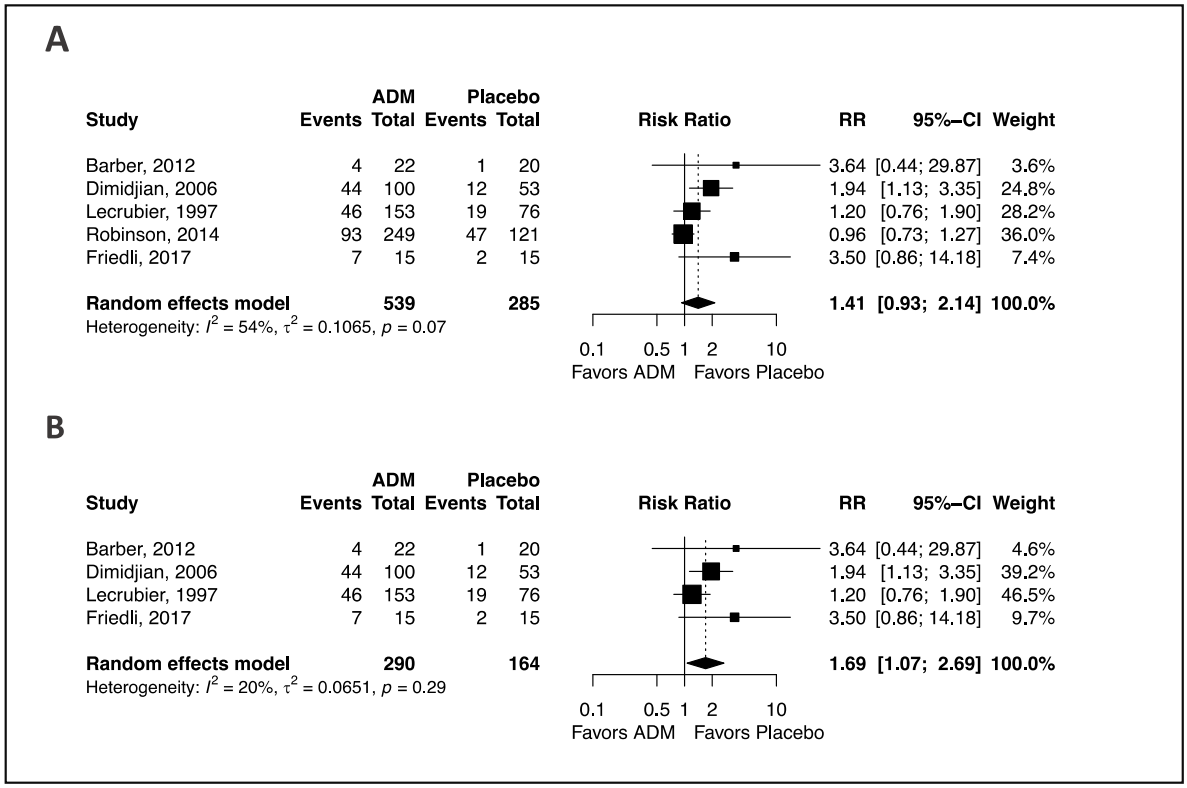


Figure 14. Pairwise meta-analysis of acceptability outcome in ADM versus placebo in the continuation phase. Panel A: Primary analysis including all studies; Panel B: Sensitivity analysis excluding the study by Robinson et al.

Legend: ADM: antidepressant medication; RR: risk ratio; CI: confidence interval

In the pooled analysis of studies with design III, we found better acceptability among those receiving ADM compared to placebo (RR= 0.71, 95% CI= 0.57 to 0.89) (Figure 15). Estimates were similar in the two studies and no heterogeneity was found (I^2=0%, Q=0.16, p=0.69).

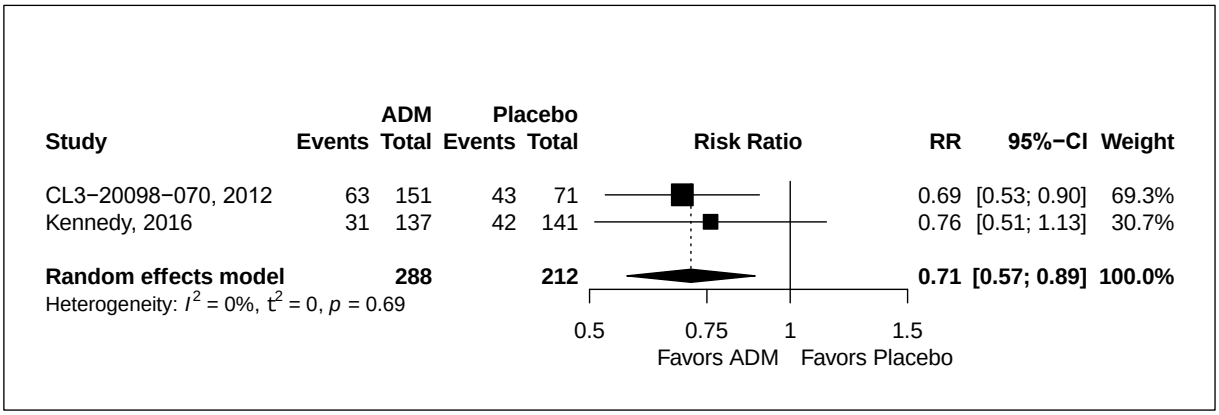


Figure 15. Pairwise meta-analysis of acceptability outcome of ADM versus placebo in studies with design III in the continuation phase

Legend: ADM: antidepressant medication; RR: risk ratio; CI: confidence interval

5.2.3.5.1.1.12 Maintenance phase

Six studies reported on drop-out rates at 25 weeks or longer, with three studies with design I (64,78) and two with design II (68,71). We synthesized the evidence across studies with a similar design.

Of the studies with design I, three reported on the acceptability outcome with no difference between the ADM and placebo groups with a pooled RR estimate= 0.96 (95 % CI= 0.85 to 1.07) and some heterogeneity (I^2= 28%, 95 % CI= 0.0% to 92.5%; Q= 2.76, p=0.25). While results from the two trials published by Oakes were consistent with each other (78), those from Banerjee et al were not (64). This could potentially be due to the selective (patients with Alzheimer's disease) and older population (as reflected by mean age of participants) included by Banerjee et al. Figure 16 shows the pooled analysis after omitting the study by Banerjee et al. Similar results were found with no heterogeneity (I^2= 0%, Q= 0.05, p=0.83).

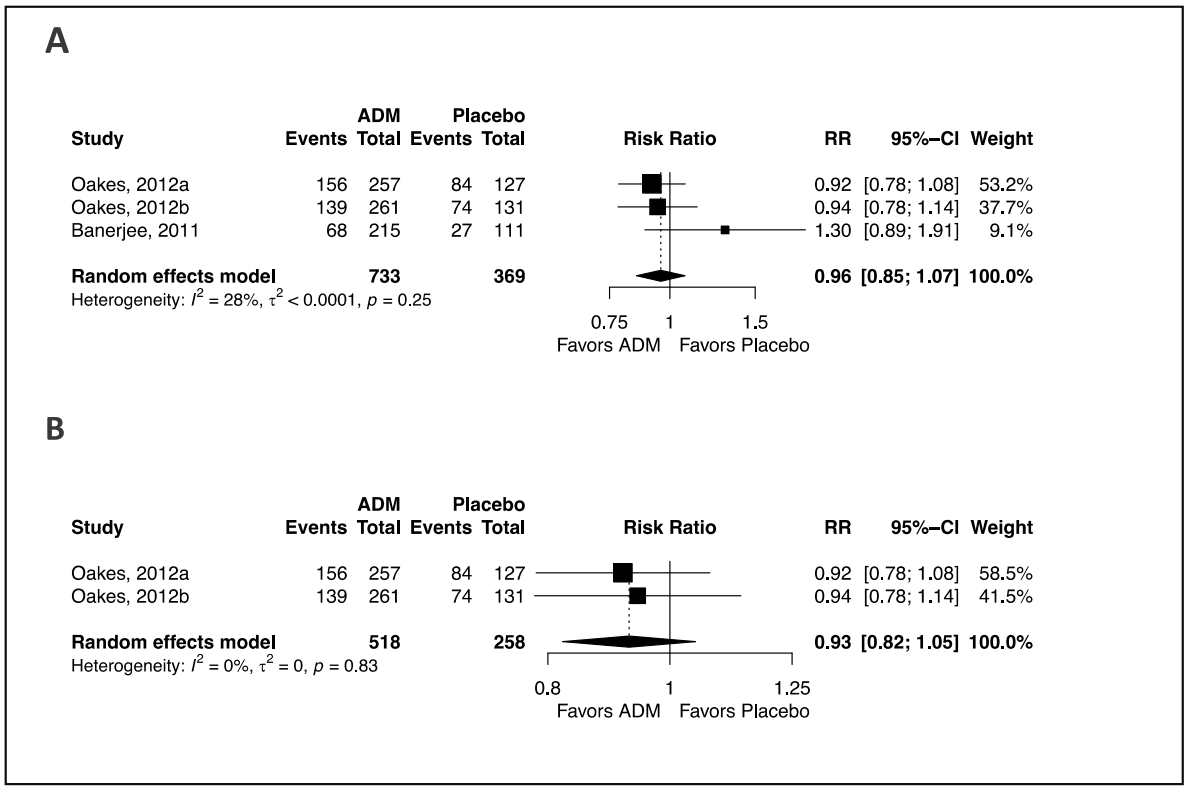


Figure 16. Pairwise meta-analysis of acceptability outcome in ADM versus placebo in the maintenance phase. Panel A: Primary analysis including all studies; Panel B: Sensitivity analysis excluding the study by Banerjee et al.

Legend: ADM: antidepressant medication; RR: risk ratio; CI: confidence interval

In the design II studies, participants in the placebo group in Jarrett et al had a higher drop-out rate than the ADM group (RR= 0.52, 95% CI= 0.35 to 0.78) while in in CL3-20098-021, there was no difference between the two groups (RR= 0.95, 95 % CI= 0.72 to 1.26). The

overall pooled estimate of the two studies showed no difference between the two groups (RR= 0.72, 95% CI= 0.40 to 1.29) (Figure 17). However, there was substantial heterogeneity (I^2 = 82%, 95% CI= 26.0% to 95.8%; Q=5.68, p=0.02) which could possibly be related to the different treatments given in the open label phase of the two studies (CBT in Jarrett et al and ADM in CL3-20098-021), as well as the different efficacy and side effects of the two ADMs used in the trials (AGM and FXT).

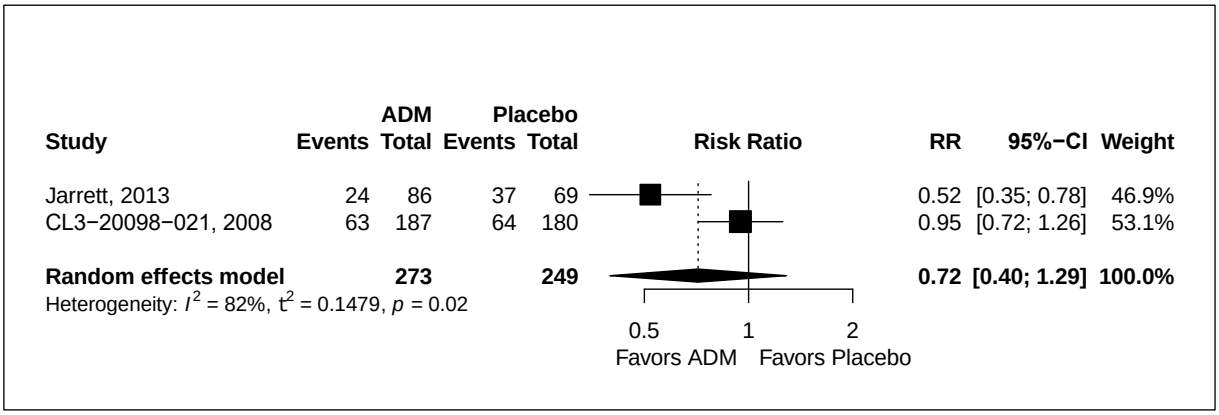


Figure 17. Pairwise meta-analysis of acceptability outcome of ADM versus placebo in studies with design II in the maintenance phase
Legend: ADM: antidepressant medication; RR: risk ratio; CI: confidence interval

CBT versus placebo

5.2.3.5.1.1.13 Acute phase (≤12 weeks)

We found no studies assessing the acceptability of CBT versus placebo during the acute phase.

5.2.3.5.1.1.14 Continuation phase (13 to 24 weeks)

In the one trial we identified with a CBT vs placebo comparison (83), there was no evidence of a difference in acceptability rates between individuals in the two groups at 16 weeks (15% versus 22%; RR= 0.65, 95 % CI= 0.32 to 1.32).

5.2.3.5.1.1.15 Maintenance phase

We found no studies assessing the acceptability of CBT versus placebo during the maintenance phase.

CBT versus TAU

5.2.3.5.1.1.16 Acute phase (≤12 weeks)

We found no studies assessing the acceptability of CBT versus TAU during the acute phase.

5.2.3.5.1.1.17 Continuation phase (13 to 24 weeks)

There was no difference in the acceptability rates between individuals in the CBT and TAU groups at the 24 week follow-up in Zu et al (80) (RR= 1.29, 95% CI= 0.80 to 2.08).

5.2.3.5.1.1.18 Maintenance phase

We found no studies assessing the acceptability of CBT versus TAU during the maintenance phase.

ADM versus TAU

5.2.3.5.1.1.19 Acute phase (≤12 weeks)

We found no studies assessing the acceptability of ADM versus TAU during the acute phase.

5.2.3.5.1.1.20 Continuation phase (13 to 24 weeks)

We did not find evidence of any difference in the drop-out rates in the study assessing ADM and TAU at week 24 of treatment (80) (RR= 1.11, 95 % CI = 0.78 to 1.60, I^2= 0%).

5.2.3.5.1.1.21 Maintenance phase

We found no studies assessing the acceptability of ADM versus TAU during the maintenance phase.

We did not find any studies providing data on drop-out rates in ADM or CBT compared to WL.

Network meta-analysis and treatment ranking

We synthesized data from available comparisons in a network meta-analysis when possible. In the acute phase, acceptability was only significantly better for ADM compared to placebo (RR= 0.79, 95 % CI= 0.67 to 0.94). In the continuation phase, acceptability was less for ADM group compared to CBT (RR= 1.41, 95% CI= 0.90 to 2.21) and CBT plus ADM (RR= 2.45, 95% CI= 1.12 to 5.35). No significant differences were found between any of the comparisons in the maintenance phase. There was evidence of inconsistency in one of the seven loops in the continuation phase network of studies with design I. There was no evidence of inconsistency in the maintenance phase networks. The complete direct and indirect evidence as well as estimates from the individual drug and class level analysis as well as the results of the sensitivity analysis (excluding older generation ADM) are found in Appendix 11.1.6.3. In the continuation phase of studies with Design I, agomelatine and paroxetine had significantly higher drop-out rates compared to placebo. On the other

hand, the different CBT interventions had lower drop-out rates ranging from an RR of 0.68 (for CT) to 0.86 (for REBT) compared to placebo as well as compared to ADM (RR ranging from 0.15 to 0.80). In the class level analysis, standard CBT and 3rd wave CBT were comparable to each other and both had lower drop-out rates than SSRI and NARI classes. Treatment rankings across the different treatment phases are presented in Appendix 11.1.6.3. In the acute phase, ADM plus CBT ranked first, followed by CBT as second, ADM as third and placebo as fourth. In the continuation phase, ADM plus CBT also ranked first, with TAU, CBT, placebo and ADM ranking from second to fifth, respectively. In the maintenance phase of studies with design I, ADM plus CBT ranked first followed by CBT in the second rank, ADM in the third and placebo in the fourth rank. In studies with design II; ADM ranked first, CBT second and placebo third.

GRADE Assessment

The results of the GRADE assessment for the different comparisons regarding acceptability in the continuation phase is shown in Table 9. We judged the quality of the evidence as low for all comparisons except for ADM vs placebo. The ratings for these comparisons were downgraded due to indirectness and imprecision of the direct and indirect estimates. The indirect estimates for CBT vs ADM plus CBT, ADM vs placebo and CBT vs TAU were downgraded due to inconsistency with the direct estimates.

Table 9. GRADE assessment for acceptability across different comparisons

Comparison	Direct Estimate		Indirect Estimate		NMA Estimate	
	RR (95%CI)	Rating	RR (95%CI)	Rating	RR (95%CI)	Rating
ADM vs CBT	1.44 [0.91; 2.27]	LOW[a,b]	0.72 [0.05; 10.22]	LOW[b,c]	1.41 [0.90; 2.21]	LOW
ADM vs ADM plus CBT	2.06 [0.89; 4.76]	LOW[a,b*]	7.66 [0.89; 65.94]	LOW[b,c]	2.45 [1.12; 5.35]	LOW
CBT vs ADM plus CBT	2.12 [0.89; 5.00]	LOW[a,b*]	0.65 [0.09; 4.55]	VERY LOW[a,b,c]	1.75 [0.78; 3.85]	LOW
ADM vs placebo	1.32 [0.83; 2.10]	MODERATE[a]	0.14 [0.01; 1.91]	VERY LOW[a,b,c]	1.23 [0.78; 1.95]	MODERATE
ADM vs TAU	1.25 [0.55; 2.87]	LOW[a,b*]	4.52 [0.55; 36.94]	LOW[b,c]	1.49 [0.69; 3.22]	LOW
CBT vs placebo	0.65 [0.24; 1.77]	LOW[a,b*]	1.04 [0.49; 2.24]	LOW[b,c]	0.88 [0.48; 1.61]	LOW
CBT vs TAU	1.29 [0.55; 3.02]	LOW[a,b*]	0.39 [0.06; 2.66]	VERY LOW[a,b,c]	1.06 [0.48; 2.30]	LOW

Downgrading due to:, a = Indirectness because of questionable comparability of some of the trial populations to the target population, b = Imprecision due to wide confidence intervals including no effect or low overall sample size, c = Inconsistency
** only one study contributed to the estimate*

5.2.3.6 Worsening of depression symptoms

Worsening of depression symptoms as an adverse effect of treatment was reported by two studies (65,92) (Table 10). We could not perform a meta-analysis due to the low number of studies. We, therefore, present a narrative summary of the findings from these studies.

Table 10. Characteristics of the studies assessing worsening of depression symptoms outcome

Study	Design	Comparison	Population and MDD severity	Mean MDD (SD) severity[1]	Timepoint
Gilliam	I	ADM vs CBT *(SRT vs SCBT)*	21-75 year old with epilepsy & MDD *(all severities*	I: 24.2 (8.4)* C: 26.9 (10.5)	13 - 24 weeks
Rief	I	CBT vs CBT *(CBASP vs CBTe vs CBTm)* CBT vs WL *(CBASP or CBTe or CBTm vs WL)*	Adults with MDD *(all severities)*	I: 28.1 (8.1) C (CBTe): 30.5 (8.6) C (CBTm): 29.2 (8.3) C (WL): 28.3(10.1)	13 - 24 weeks

[1] assessed by HAM-D unless stated otherwise: *BDI-II

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; MDD: major depressive disorder; SD: standard deviation; I: intervention; C: comparator; WL: waiting list; CBASP: cognitive behavioural analysis system of psychotherapy; SCBT: standard CBT; CBTe: CBT with exercise; CBTm: CBT with mindfulness

Risk of bias

The risk of bias assessment for the outcome of worsening of depression symptoms is shown in Figure 18 with some concerns overall regarding the evidence from the two included studies.

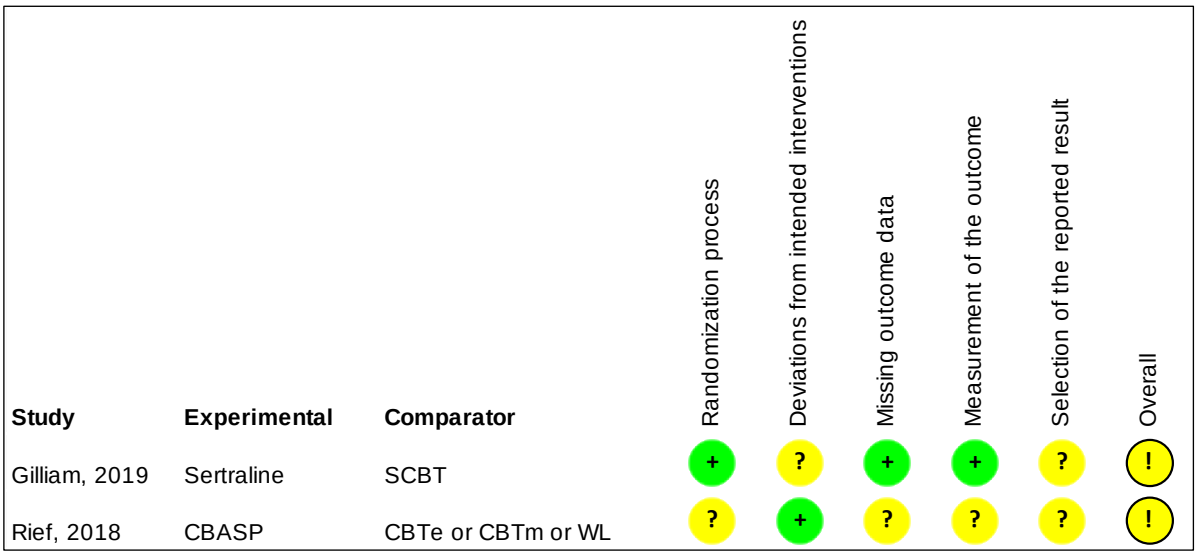


Figure 18. Risk of bias of studies for worsening of depression symptoms (based on RoB 2.0).

Legend: SCBT: standard cognitive behavioural therapy; WL: waiting list; CBASP: cognitive behavioural analysis system of psychotherapy; CBTe: CBT with exercise; CBTm: CBT with mindfulness

Data synthesis

ADM versus CBT

5.2.3.6.1.1.1 Acute phase (≤12 weeks)

We found no studies assessing worsening of symptoms in individuals receiving ADM versus CBT during the acute phase.

5.2.3.6.1.1.2 Continuation phase (13 to 24 weeks)

Gilliam et al presented data on the comparison of ADM (SRT) vs CBT (SCBT) regarding individuals experiencing worsening of depression symptoms with similar proportions (7% in ADM versus 8% in CBT, RR= 1.13, 95% CI= 0.36 to 3.54) across the two groups at week 16 (65).

5.2.3.6.1.1.3 Maintenance phase

We found no studies assessing worsening of symptoms in individuals receiving ADM versus CBT during the maintenance phase.

CBT versus WL

5.2.3.6.1.1.4 Acute phase (≤12 weeks)

We found no studies assessing worsening of symptoms in individuals receiving CBT versus WL during the acute phase.

5.2.3.6.1.1.5 Continuation phase (13 to 24 weeks)

In a study by Rief et al., there was no difference in the proportion of patients experiencing worsening of depression in participants receiving CBT compared to WL at week 16 (92) (8% versus 9%, respectively; RR= 0.86, 95% CI= 0.27 to 2.76).

5.2.3.6.1.1.6 Maintenance phase

We found no studies assessing worsening of symptoms in individuals receiving CBT versus WL during the maintenance phase.

For the remaining comparisons (i.e., assessing ADM or CBT versus ADM plus CBT, CBT versus placebo or TAU, or ADM versus any of the control conditions), we did not identify any studies at any of the timepoints. Estimates from individual drug and class level assessments for the continuation phase are presented in Appendix 11.1.6.4.

GRADE Assessment

The results of the GRADE assessment for the different comparisons regarding worsening of symptoms in the continuation phase is shown in Table 4. We judged the quality of the evidence as low for ADM vs CBT and moderate for CBT vs WL. The rating for these two comparisons was downgraded by one point due to small sample sizes. The rating for ADM vs CBT was additionally downgraded by one point due to the indirectness of the evidence as the trial was conducted in a selected population of individuals with epilepsy.

5.2.3.7 Mortality

Mortality was described in 14 studies, summarized in Table 11.

Table 11. Characteristics of studies reporting on all-cause mortality

Study	Design	Comparison	Population and MDD severity	Mean (SD) MDD severity[1]	Timepoint
Banerjee	I	ADM vs ADM *(SRT vs MIR)* ADM vs PLC *(SRT or MIR vs PLC)*	Adults, fulfilling ADRDA criteria for Alzheimer's disease with MDD *(all severities)*	I: 12.8 (3.6)* C (MIR): 12.5 (3.7) C (PLC): 13.6 (5.2)	≥ 25 weeks
CL3-20098-048	I	ADM vs ADM *(AGM vs PAR)*	≥ 60 year old with MDD *(moderate to severe)*	I: 26.3 (NR) C: 26.2 (NR)	13 - 24 weeks
CL3-20098-062	I	ADM vs ADM *(AGM vs DLX)*	18-65 year old with MDD *(moderate to severe)*	I: 26.2 (NR) C: 26.3 (NR)	≥ 25 weeks
CL3-20098-070	III	ADM vs PLC *(AGM vs PLC)*	≥65 year old with MDD *(moderate to severe)*	I: 26.8 (NR) C: 26.7 (NR)	13 - 24 weeks
Corruble	III	ADM vs ADM *(AGM vs ESC)*	18-70 year old with MDD *(moderate to severe)*	I: 26.8 (3.1) C: 26.6 (2.5)	13 - 24 weeks
Friedli	I	ADM vs PLC *(SRT vs PLC)*	Adults with MDD *(mild to moderate),* on haemodialysis for ≥3 months (end stage renal disease)	I: 24.5 (4.5)** C: 25.3 (4.2)	13 - 24 weeks
Gilliam	I	ADM vs CBT *(SRT vs SCBT)*	21-75 year old with epilepsy & MDD *(all severities*)	I: 24.2 (8.4)*** C: 26.9 (10.5)	13 - 24 weeks
Hashimoto	I	ADM vs ADM *(MIR vs SRT vs SSRI vs PAR)*	20-75 year old with MDD *(all severities)*	I: 23.0 (1.2) C (SRT): 23.1 (0.9) C (SSRI): 23.2 (1.1) C (PAR): 22.9 (1.5)	13 - 24 weeks
Kishi	I	ADM vs ADM *(ESC vs PAR)*	20-70 year old with MDD	I: 23.7 (3.6) C: 23.2 (3.8)	13 - 24 weeks
Keller	I	ADM vs ADM *(VEN vs FXT)*	Adults with MDD *(moderate to severe)*	I: 22.6 (3.1) C: 23.0 (3.2)	≤12 weeks ≥25 weeks
Kennedy	III	ADM vs PLC *(DLX vs PLC)*	18-65 year old with MDD *(moderate to severe)*	I: 26.7 (2.9) C: 26.6 (2.6)	13 - 24 weeks
Kooistra	I	CBT vs CBT *(BCBT vs SCBT)*	Adult with MDD *(moderate to severe)*	I: 45.2 (12.2)**** C: 41.5 (11.6)	≤12 weeks 13 - 24 weeks ≥ 25 weeks
Oakes b	I	ADM vs PLC *(DLX vs PLC)*	18-65 year old with MDD *(moderate to severe)*	I: 22.8 (4.5) C: 22.9 (4.9)	≤12 weeks
Thase	I	CBT vs CBT *(SCBT vs CCBT)*	Adults with MDD *(all severities)*	I: 19.6 (3.8) C: 19.8 (3.5)	13 - 24 weeks

[1] assessed by HAM-D unless stated otherwise: *CSDD,**MADRS, ***BDI-II, ****IDS-SR

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; MDD: major depressive disorder; NR: not reported; PLC: placebo; SD: standard deviation; I: intervention; C: comparator; SCBT: standard CBT; BCBT: blended CBT; ADRDA: Alzheimer's Disease and Related Disorders Association

Risk of bias

We judged three studies to have an overall high risk of bias for the mortality outcome (Figure 19). We had some concerns for the remaining studies. All but three studies evaluated intervention efficacy based on ITT effects. Main reasons for the risk of bias in these studies included lack of a prespecified analysis plan and non-blinding of participants or physicians.

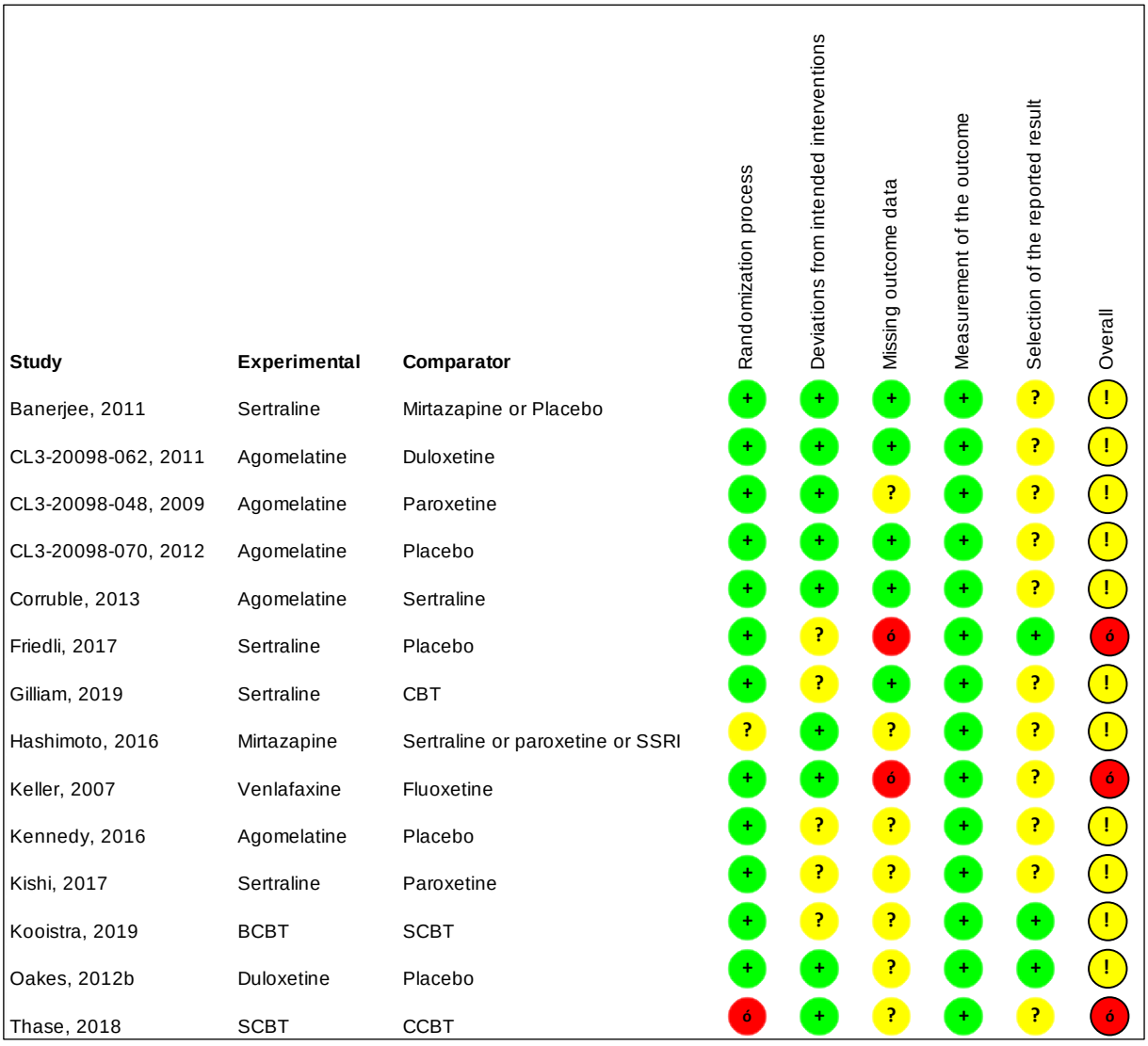


Figure 19. Risk of bias of studies for mortality outcome (based on RoB 2.0).
Legend: CBT: cognitive behavioural therapy; SCBT: standard CBT; CCBT: computerized CBT; BCBT: blended CBT

Data synthesis

ADM versus CBT

5.2.3.7.1.1.1 Acute phase (≤12 weeks)

We found no studies assessing mortality in individuals receiving ADM versus CBT during the acute phase.

5.2.3.7.1.1.2 Continuation phase (13 to 24 weeks)

Only one study assessed mortality in those receiving ADM compared to CBT (65). In this trial, only one death occurred in the study at up to 16 weeks of treatment, presumably unrelated to the treatment (sudden unexpected death in epilepsy).

5.2.3.7.1.1.3 Maintenance phase

We found no studies evaluating mortality in individuals receiving ADM versus CBT during the maintenance phase.

ADM versus placebo

5.2.3.7.1.1.4 Acute phase (≤12 weeks)

In one of the trials by Oakes et al, two deaths occurred during the acute phase (78). One was a completed suicide in the placebo group and the other was a ruptured cerebral aneurysm. The events were not considered by the authors and trial investigators to be related to the procedures or treatments received.

5.2.3.7.1.1.5 Continuation phase (13 to 24 weeks)

Three studies reported on any deaths occurring in ADM versus placebo groups (56,60,81). In both CL3-20098-070 and Friedli et al., no deaths occurred in either group at 24 weeks of follow-up (56,60). In Kennedy et al, one patient in the ADM group died of cardiac arrest after taking one tablet of the medication (81). According to the authors, this death may have been possibly related to the medication.

5.2.3.7.1.1.6 Maintenance phase (≥25 weeks)

In the trial by Banerjee et al, a higher number of events was observed in the ADM group compared to placebo (10 versus 5 deaths by week 39) (64). Authors did not provide information possible causes of these deaths or whether they were related to the treatment.

At any of the timepoints, we did not find any studies assessing ADM or CBT versus ADM plus CBT, CBT versus any of the control conditions, or ADM versus TAU or WL.

GRADE Assessment

The results of the GRADE assessment for the different comparisons regarding mortality in the continuation phase is shown in Table 4. We judged the quality of the evidence as low for ADM vs CBT and ADM vs placebo. The rating for ADM vs CBT was downgraded for indirectness of the evidence due to the selected population and for the small sample size. We downgraded the rating for ADM vs placebo by two points due to the different populations as well as the designs of each of the trials.

5.2.4 Secondary Outcomes

For secondary outcomes, we briefly report only on the estimates for ADM versus CBT, ADM plus CBT or placebo. The full analysis for these outcomes across all comparisons is reported in Appendix 11.1.6.5 - 11.1.6.8

5.2.4.1 Response

Response to treatment was evaluated in 23 studies (Appendix 11.1.3.2, Table 12).

Table 12. Characteristics of studies reporting on response

Study	Comparison	Definition of response	Timepoint
Barber	ADM vs PLC (SRT vs PLC)	HAM-D score ≤ 12 or a 50% reduction from baseline HAMD7 score	≤12 weeks 13 - 24 weeks
Blackburn	ADM vs CBT (ADM vs CT)	HSRD 7-14 (partial response)	≥ 25 weeks
Boulenger	ADM vs ADM (ESC vs PAR)	MADRS ≥50% reduction	13 - 24 weeks
CL3-20098-022	ADM vs ADM vs PLC (AGM vs FLX vs PLC)	HAM-D ≥ 50% reduction	≤12 weeks
CL3-20098-048	ADM vs ADM (AGM vs PAR)	HAM-D ≥ 50% reduction	≤12 weeks
CL3-20098-062	ADM vs ADM (AGM vs DLX)	HAM-D ≥ 50% reduction	≤12 weeks 13 – 24 weeks
CL3-20098-070	ADM vs PLC (AGM vs PLC)	HAM-D ≥ 50% reduction	≤12 weeks 13 – 24 weeks
Corruble	ADM vs ADM (AGM vs ESC)	HAM-D ≥ 50% reduction	≤12 weeks 13 – 24 weeks
David	ADM vs CBT vs CBT (REBT vs CT vs FLX)	HAM-D ≤12	≤12 weeks 13 – 24 weeks
Dimidjian	ADM vs CBT vs CBT vs PLC (PAR vs BA vs CT vs PLC)	HAM-D ≥ 50% reduction	13 – 24 weeks
Grunebaum	ADM vs ADM (BUP vs PAR)	HAM-D ≥ 50% reduction	≤12 weeks
Hollon	ADM vs ADM plus CBT (ADM vs ADM plus CT)	4 weeks of of HAM-D score ≤12 or LIFE ≤3	≥ 25 weeks
Kato	ADM vs ADM (SRT vs MIR)	PHQ-9 ≥ 50% reduction	≤12 weeks

Keller	ADM vs ADM (VEN vs FLX)	HAM-D ≥ 50% reduction or total score ≤12	≤12 weeks ≥ 25 weeks
Kennedy	ADM vs PLC (AGM vs PLC)	HAM-D ≥ 50% reduction	13 – 24 weeks
Lecrubier	ADM vs ADM vs PLC (VEN vs IMI vs PLC)	MADRS ≥ 50% reduction	≤12 weeks 13 – 24 weeks
Mohr	ADM vs CBT (SRT vs SCBT)	HAM-D ≥ 50% reduction	13 – 24 weeks
Oakesa	ADM vs PLC (DLX vs PLC)	HAM-D ≥ 50% reduction	≤12 weeks
Oakesb	ADM vs PLC (DLX vs PLC)	HAM-D ≥ 50% reduction	≤12 weeks
Quera-Salva	ADM vs ADM (AGM vs ESC)	HAM-D ≥ 50% reduction	≤12 weeks 13 – 24 weeks
Rief	CBT vs CBT vs WL (CBASP vs CBTe vs CBTm vs WL)	BDI score ≥ 50% reduction	13 – 24 weeks
Rush	ADM vs ADM (BUP vs SER)	HAM-D ≥ 50% reduction	≤12 weeks 13 – 24 weeks
Study 043	ADM vs ADM (CIT vs REB)	HAM-D ≥ 50% reduction	≤12 weeks 13 – 24 weeks

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; PLC: placebo; CT: cognitive therapy; BA: behaivoral activation; REBT: rational emotive behaviour therapy; SCBT: standard CBT; CBASP: cognitive behaivoural analysis system of psychotherapy; CBTe: CBT with exercise; CBTm: CBT with mindfulness; WL: waiting list

Data synthesis

ADM versus CBT

We found no studies assessing response in individuals receiving ADM versus CBT during the acute phase.

5.2.4.1.1.1.1 Continuation phase (13 to 24 weeks)

Pooled analysis of response comparing ADM and CBT at 13 to 24 weeks resulted in an RR of 0.79 (95% CI= 0.65 to 0.95) favouring CBT (Figure 20).

5.2.4.1.1.1.2 Maintenance phase

At ≥25 weeks, only one study evaluated response with no difference was between the two groups (RR= 1.27, 95% CI= 0.63 to 2.55) (66).

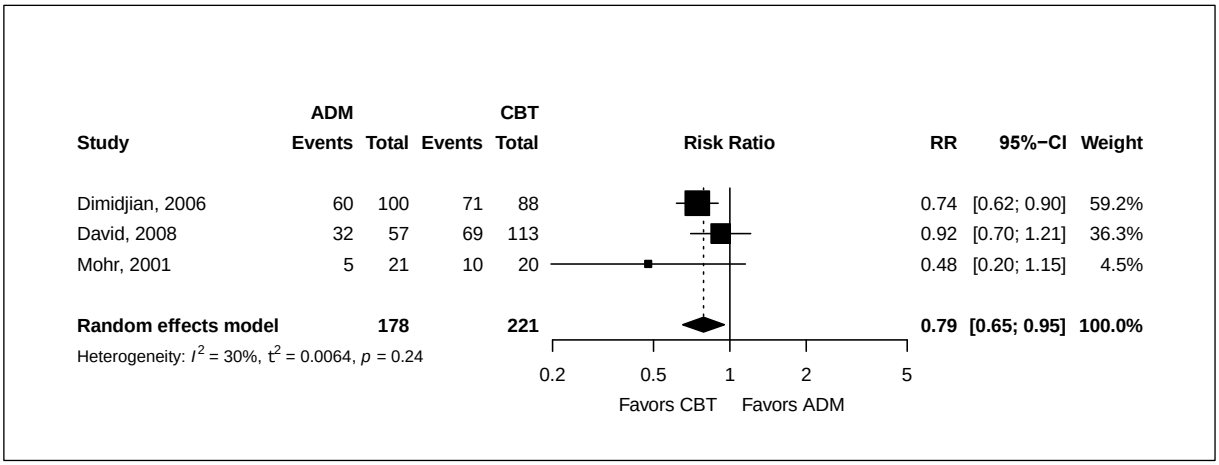


Figure 20. Pairwise meta-analysis of response outcome of ADM versus CBT in continuation phase

Legend: ADM: antidepressant; CBT: cognitive behavioural therapy; RR: risk ratio; CI: confidence interval

ADM versus placebo

5.2.4.1.1.1.3 Acute phase (≤12 weeks)

At 12 weeks or less, pooled analysis showed better response in patients treated with ADM compared to the placebo arm (RR= 1.24, 95% CI= 1.00 to 1.54) (Figure 21). Heterogeneity was substantial with an I^2 of 80% (95% CI= 57.8%; 91.0%; Q= 25.59, p<0.01). After omitting two studies with lower baseline MDD severity, the RR from the pooled analysis of the remaining four studies was 1.44 (95% CI= 1.23 to 1.70) favouring ADM and heterogeneity was reduced to 52% (95% CI= 0.0% to 84.0%; Q= 6.21, p=0.10) (Appendix 11.1.6.3).

5.2.4.1.1.1.4 Continuation phase (13 to 24 weeks)

Similarly, between 13 and 24 weeks, we found evidence of better response with ADM compared to placebo in both design I (RR= 1.57, 95% CI= 0.94 to 2.62) and design III (RR= 1.65, 95% CI= 1.27 to 2.14) studies (Figure 21).

5.2.4.1.1.1.5 Maintenance phase

We found no studies assessing response in individuals receiving ADM versus placebo in the maintenance phase of treatment.

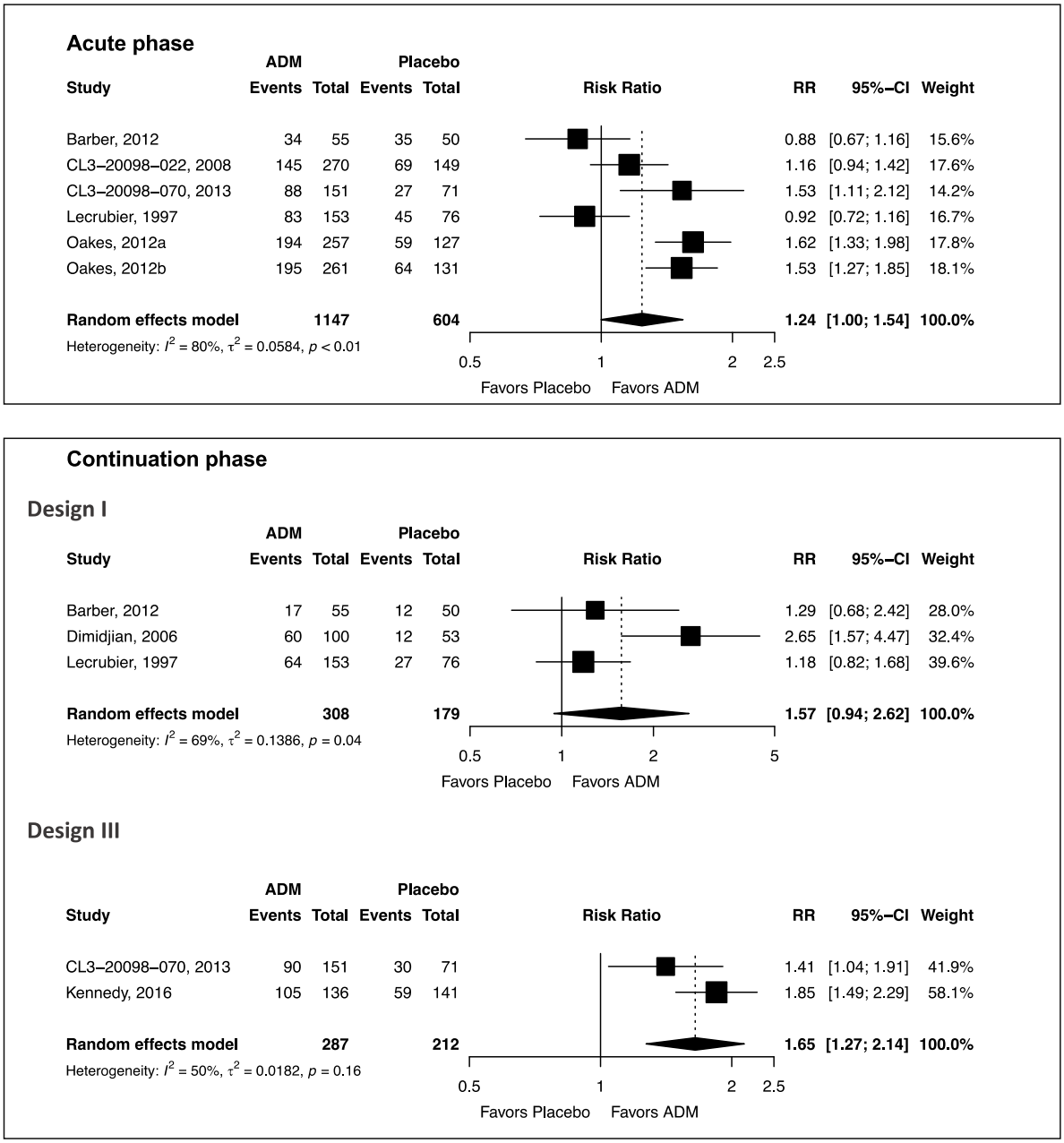


Figure 21. Pairwise meta-analyses of response outcome of ADM compared to placebo in the acute and continuation phase

Legend: ADM: antidepressant; RR: risk ratio; CI: confidence interval

Network meta-analysis

In the continuation phase, response was better for CBT compared to ADM (RR= 0.75, 95% CI= 0.52 to 1.08), but it was not significant. Response was also better for ADM (RR= 1.60, 95% CI= 1.08 to 2.36) and CBT compared to placebo (RR= 2.13, 95% CI= 1.30 to 2.47) (Figure 22). Similar findings were found in the individual drug level analysis with significantly better response for both BA and CT compared to ADMs. In the class level analysis, we found evidence of better response with standard CBT compared to TCA and atypical ADMs. We did not find any differences between CBT and 3rd wave CBT. Regarding the maintenance phase, we did not find any difference between any of the comparisons. Treatment rankings across in the continuation and maintenance phases are presented in Appendix 11.1.6.5. In the continuation phase, CBT ranked first, followed by ADM as second, placebo as third and waiting list as fourth. In the maintenance phase, ADM plus CBT ranked first, with ADM and CBT ranking second and third, respectively. The full analyses from the individual drug and class level analysis are presented in Appendix 11.1.6.5.

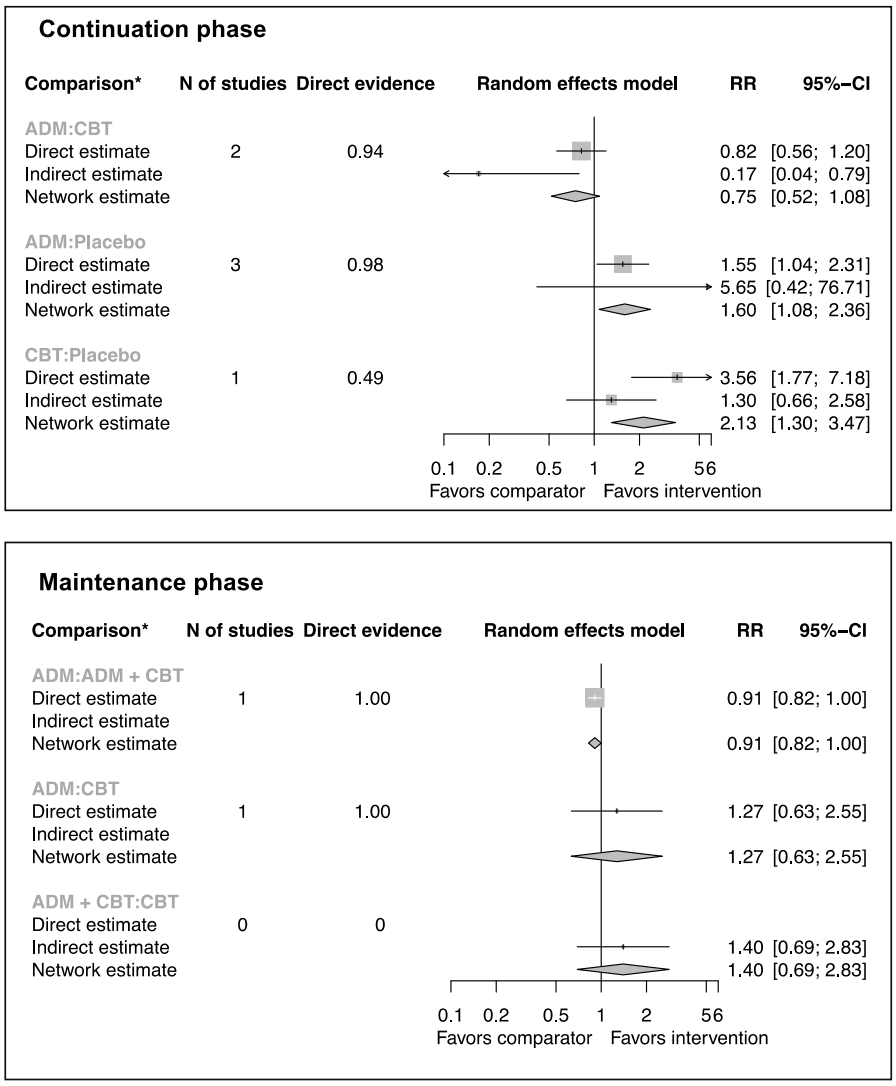


Figure 22. Network meta-analyses estimates for the response outcome in the continuation and maintenance phases

*intervention on the left side and comparator on the right side of the comparison

Legend: ADM: antidepressant; RR: risk ratio; CI: confidence interval

5.2.4.2 Remission

A total of 26 studies reported on remission between the different interventions and comparators (Appendix 11.1.3.2, Table 13).

Tabelle 13. Characteristics of studies reporting remission

Study	Comparison	Definition of response	Timepoint
Barber	ADM vs PLC (SRT vs PLC)	HAM-D < 8 and no longer meeting criteria of MDD	≤12 weeks 13 - 24 weeks
Blackburn	ADM vs CBT (ADM vs CT)	HAM-D ≤ 6	≥ 25 weeks
Boulenger	ADM vs ADM (ESC vs PAR)	MADRS ≤ 12	≤12 weeks 13 - 24 weeks
CL3-20098-022	ADM vs ADM vs PLC (AGM vs FLX vs PLC)	HAM-D ≤ 6	≤12 weeks
CL3-20098-048	ADM vs ADM (AGM VS PAR)	HAM-D ≤ 6	≤12 weeks
CL3-20098-062	ADM vs ADM (AGM vs DLX)	HAM-D ≤ 6	≤12 weeks 13 - 24 weeks
CL3-20098-070	ADM vs PLC (AGM vs PLC)	HAM-D ≤ 6	≤12 weeks 13 - 24 weeks
Corruble	ADM vs ADM (AGM vs ESC)	HAM-D ≤ 7	≤12 weeks 13 - 24 weeks
David	CBT vs CBT vs ADM (REBT vs CT vs FLX)	HAM-D <7 and no MDD	≤12 weeks 13 - 24 weeks
Dimidjian	ADM vs CBT vs CBT vs PLC (PAR vs BA vs CT vs PLC)	HAM-D ≤ 7	13 - 24 weeks
Gilliam	ADM vs CBT (SRT vs SCBT)	Achieved remission based on MINI	13 - 24 weeks
Hollon	ADM vs ADM plus CBT (ADM vs ADM plus CT)	HRSD ≤8 and LIFE ≤2 for 4 consecutive weeks	≥ 25 weeks
Kato	ADM vs ADM (SRT vs MIR)	PHQ-9 ≤4	≤12 weeks ≥ 25 weeks
Keller	ADM vs ADM (VEN vs FLX)	HAM-D ≤ 6	≤12 weeks ≥ 25 weeks
Kennedy	ADM vs PLC (AGM vs PLC)	HAM-D ≤ 6	13 – 24 weeks
Lynch	ADM plus CBT vs ADM (ADM plus DBT vs ADM)	HAM-D ≤ 7 or BDI ≤9	13 – 24 weeks
Mohr	ADM vs CBT (SRT vs SCBT)	No MDD	13 – 24 weeks
Oakesa	ADM vs PLC (DLX vs PLC)	HAM-D ≤ 7	≤12 weeks
Oakesb	ADM vs PLC (DLX vs PLC)	HAM-D ≤ 7	≤12 weeks
Quera-Salva	ADM vs ADM (AGM vs ESC)	HAM-D ≤ 7	13 – 24 weeks
Robinson	ADM vs PLC (DLX vs PLC)	HAM-D ≤ 7 and ≤ 10	≤12 weeks 13 – 24 weeks
Rush	ADM vs ADM (BUP vs SER)	HAM-D ≤ 8	≤12 weeks 13 – 24 weeks
Study 043	ADM vs ADM (CIT vs REB)	MADRS ≤ 12	≤12 weeks 13 – 24 weeks
Thase	CBT vs CBT (SCBT vs CCBT)	HAM-D ≤ 7	13 – 24 weeks
Zu	ADM vs CBT vs ADM plus CBT vs TAU	C-QIDS-SR <5	13 - 24 weeks

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; PLC: placebo; CT: cognitive therapy; BA: behaivoral activation; REBT: rational emotive behaviour therapy; SCBT: standard CBT; CBASP: cognitive behaivoural analysis system of psychotherapy; CBTe: CBT with exercise; CBTm: CBT with mindfulness; WL: waiting list

Data synthesis

ADM versus CBT

5.2.4.2.1.1.1 Acute phase (≤12 weeks)

We found no studies assessing remissions in individuals receiving ADM versus CBT during the acute phase of treatment.

5.2.4.2.1.1.2 Continuation phase (13 to 24 weeks)

Pooled analysis of remission between ADM and CBT at 13 to 24 weeks resulted in an RR of 0.76 (95% CI= 0.59 to 0.98) favouring CBT (66).

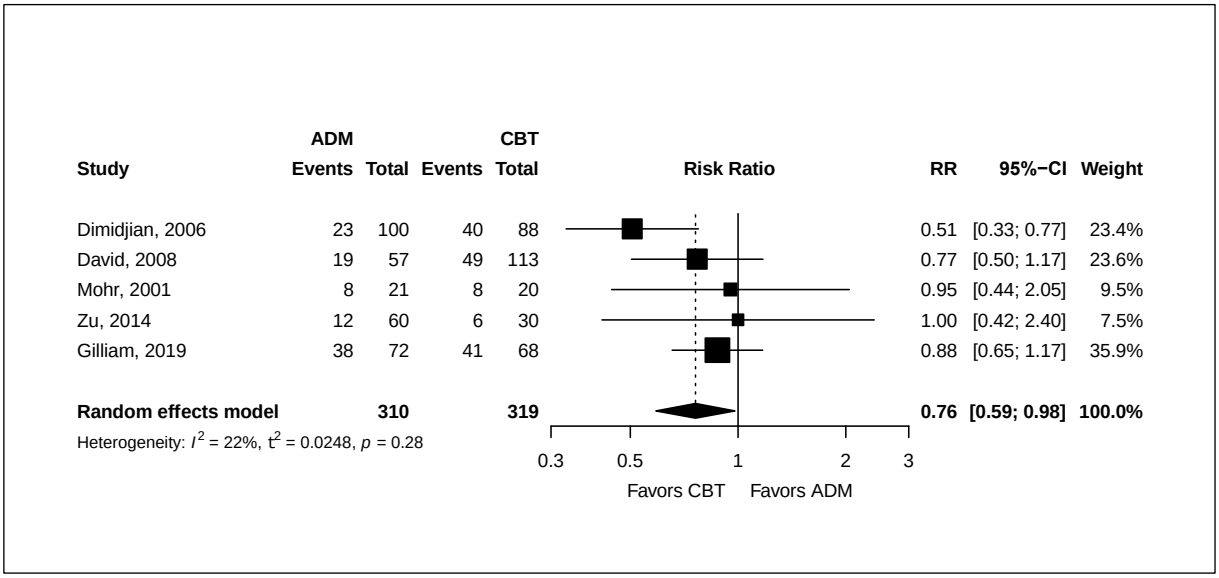


Figure 23. Pairwise meta-analysis of remission outcome in ADM compared to CBT in continuation phase

Legend: ADM: antidepressant; CBT: cognitive behavioural therapy; RR: risk ratio; CI: confidence interval

5.2.4.2.1.1.3 Maintenance phase

At ≥25 weeks, only one study evaluated remission with similar results favouring CBT, however the difference was not significant (RR= 0.69, 95% CI= 0.29 to 1.67) (66).

ADM versus ADM plus CBT

5.2.4.2.1.1.4 Acute phase (≤12 weeks)

We found no studies assessing remissions in individuals receiving ADM versus ADM plus during the acute phase of treatment.

5.2.4.2.1.1.5 Continuation phase (13 to 24 weeks)

We identified two studies reporting on remission in ADM monotherapy compared to the combination of ADM and CBT during the continuation phase (80,93) with the pooled analysis favoruing ADM plus CBT (RR=0.40, 95% CI= 0.40 to 0.92) (Figure 24).

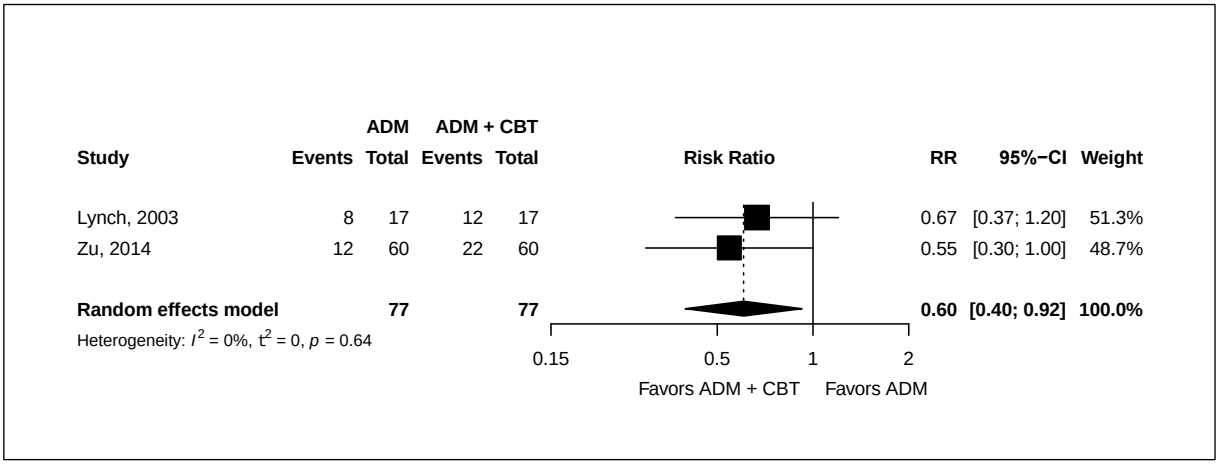


Figure 24. Pairwise meta-analyses of remission outcome of ADM plus CBT compared to ADM alone in the continuation phase

5.2.4.2.1.1.6 Maintenance phase

We identified only one study evaluating remission in individuals receiving ADM plus CBT compared to ADM alone in the maintenance phase with authors reporing no difference between ADM and ADM plus CBT at 1 year (54) (77% vs 81%; RR= 0.95, 95% CI= 0.87 to 1.05).

ADM versus placebo

5.2.4.2.1.1.7 Acute phase (≤12 weeks)

At 12 weeks or less, pooled analysis of remission between ADM and placebo resulted in an RR of 1.52 (95% CI= 1.34 to 1.72) favouring ADM (Figure 25). Heterogeneity was moderate with an I^2 of 34.4% (95% CI= 0.0% to 73.7%; Q= 7.62, p=0.17).

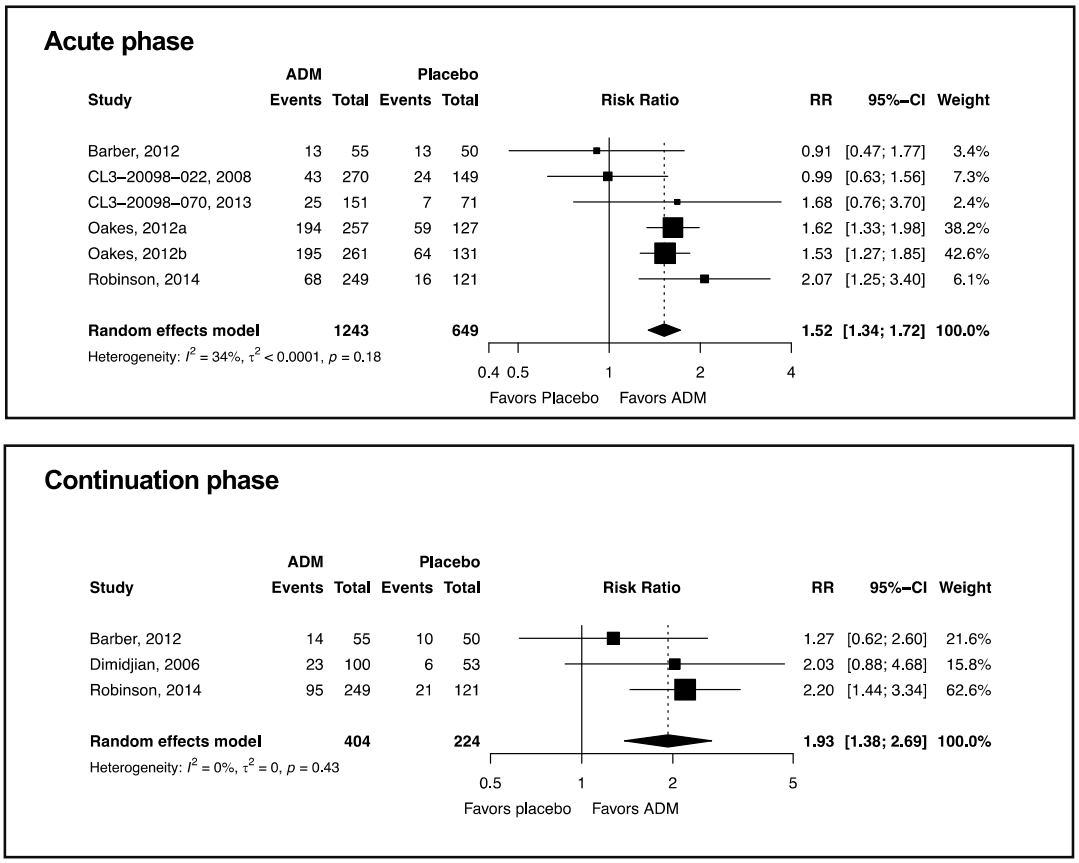


Figure 25. Pairwise meta-analyses of remission outcome of ADM compared to placebo in the acute and continuation phases
Legend: ADM: antidepressant; RR: risk ratio; CI: confidence interval

5.2.4.2.1.1.8 Continuation phase (13 to 24 weeks)

We found evidence of better remission with ADM compared to placebo during the continuation phase (RR= 1.93, 95% CI= 1.38 to 2.69). Heterogeneity was low (I^2= 0%, 95% CI= 0.0% to 87.7%; Q=1.68, p=0.43).

5.2.4.2.1.1.9 Maintenance phase

We found no studies assessing remission in individuals receiving ADM versus placebo during the maintenance phase.

Network meta-analysis

In the continuation phase, remission was significantly better for the combination of ADM and CBT (RR=0.55, 95% CI= 0.36 to 0.84) and CBT compared to ADM (RR= 0.66, 95% CI= 0.49 to 0.89), and for ADM (RR= 1.98, 95% CI= 1.39 to 2.82) and CBT compared to placebo (RR= 3.01, 95% CI= 1.95 to 4.67). We did not find any difference between any of the comparisons in the maintenance phase. The results of the network meta-analyses,

treatment ranking and additional estimates from the individual drug and class level analysis are presented in Appendix 11.1.6.6.

5.2.4.3 Tolerability

Drop-outs due to adverse effects were reported in 25 studies and ranged from 5.3% for placebo to 7.7% for ADM in the acute phase, 0.8% for CBT to 9.2% for ADM in the continuation phase, and 7.1% for placebo to 9.6% for ADM in the maintenance phase. The full results of the analyses are shown in Appendix 0. Only one study comparing ADM and CBT reported on the drop-outs due to side effects (83). In Dimidjian et al, CBT was more tolerated than ADM where 9% of the participants dropped out of the study due to side effects compared to 0% in the CBT group by week 16 (83).

Results from the pairwise meta-analyses for tolerability of ADM versus placebo are shown in Figure 26 with no difference between the two groups in the acute and maintenance phase. In the continuation phase, ADM was less tolerable than placebo (RR= 3.46, 95% CI= 1.65 to 7.25).

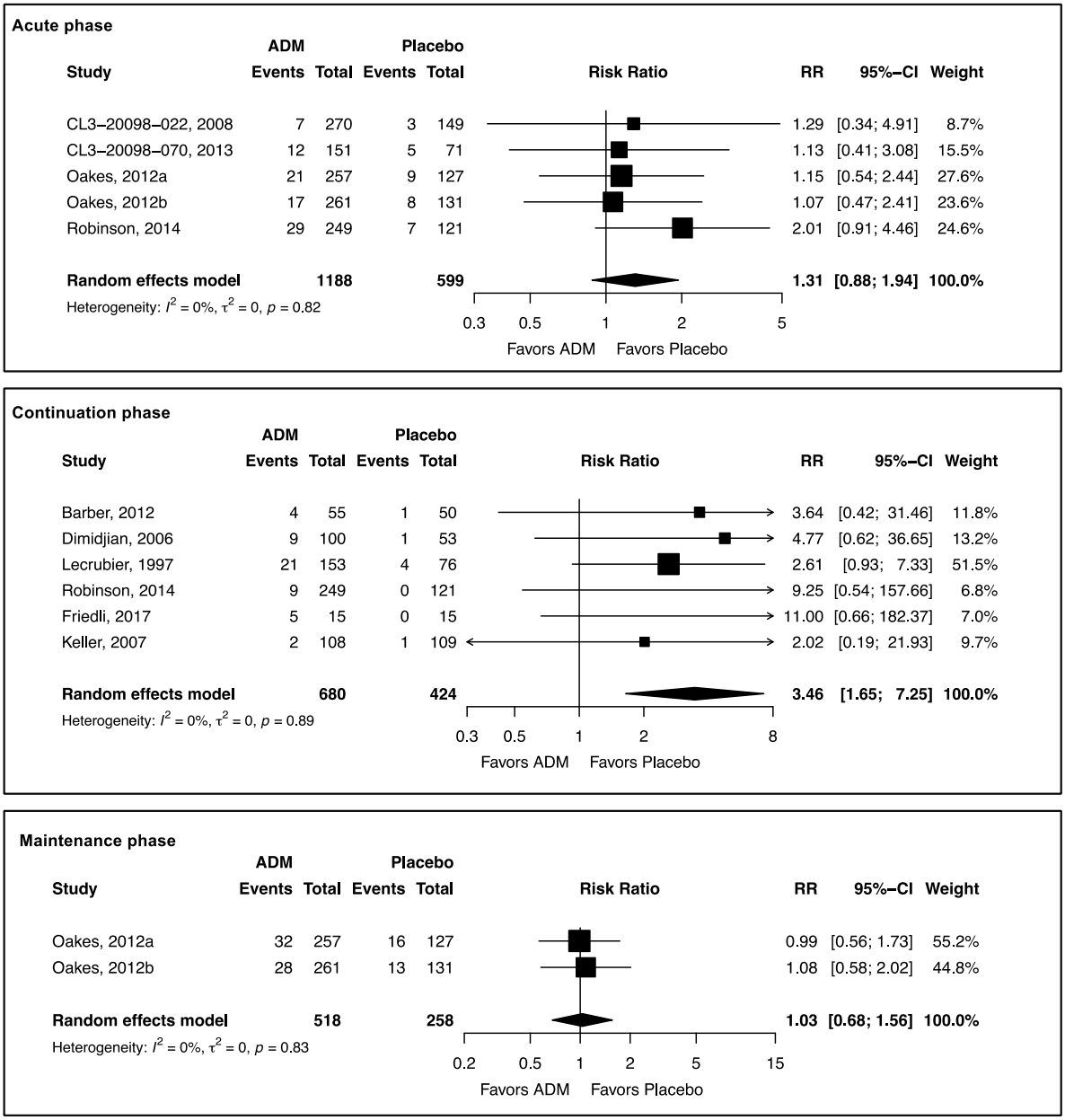


Figure 26. Pairwise meta-analyses of tolerability of ADM versus placebo
Legend: ADM: antidepressant medication; RR: risk ratio; CI: confidence interval

5.2.4.4 Adverse effects

Assessment and reporting of adverse effects was inconsistent across studies and data regarding adverse effects, in particular those related to CBT and ADM plus CBT, was scarce. Table 13 summarizes the proportions of experienced adverse effects (as grouped using the MEDRA classification). Among those receiving ADM, gastrointestinal and nervous system AEs were the most frequently reported in the acute phase (34% and 18%) followed by general and psychiatric (12% and 6%) AEs. In the continuation phase, gastrointestinal and nervous system AEs were also the most frequently experienced (32%

and 31%) followed by general (12%), psychiatric (12%) and cardiac (9%) AEs. On the other hand, the most frequently reported adverse effects in the maintenance phase were reproductive (21%), gastrointestinal (20%) nervous system (19%) and cardiac (13%) AEs. Adverse effects in participants receiving CBT were less frequently described in the studies and were reported mostly in the continuation phase with nervous system, general and musculoskeletal AEs being the most common (21%, 12% and 10%, respectively).

Appendix 11.1.6.8 shows the RR estimates of different AEs across the different comparisons. Most estimates were single studies, and we were not able to conduct meta-analyses except in very few instances. There was a significantly higher risk of any adverse effects (as reported by studies) in ADMs compared to placebo and CBT. There were no differences between the groups with regards to serious adverse effects. Compared to CBT, ADMs increased the risk of gastrointestinal and nervous system AEs in the continuation phase. Similarly, there was a higher risk of gastrointestinal and nervous system AEs with ADMs compared to placebo in both the acute and continuation phases.

Table 13. Proportions (95% confidence intervals) of adverse effects across treatments

Adverse effect	Timepoint	ADM	CBT	Placebo	ADM plus CBT
Any side effects	Acute	47.2% (43.2% to 51.4%)	-	36.6% (26.4% to 48.2%)	-
	Continuation	61.7% (59.5% to 63.9%)	1.3% (0.3% to 5.5%)	33.3% (27.1% to 40.2%)	-
	Maintenance	39.7% (37.4% to 42.0%)	-	46.8% (41.3% to 52.5%)	18.1% (13.6% to 23.6%)
Serious side effects	Acute	-	-	-	-
	Continuation	4.4% (3.6% to 5.4%)	9.7% (5.8% to 15.6%)	5.0% (3.4% to 7.2%)	-
	Maintenance	7.9% (6.0% to 10.3%)	1.2% (0.2% to 6.3%)	1.4% (0.3% to 7.8%)	22.4% (14.8% to 32.3%)
Blood and lymphatic system	Acute	-	-	-	-
	Continuation	-	-	-	-
	Maintenance	5.4% (2.9% to 9.6%)	-	4.2% (2.1% to 8.1%)	-
Cardiac	Acute	0.4% (0.1% to 1.4%)	-	-	-
	Continuation	8.6% (7.1% to 10.5%)	-	9.2% (5.8% to 14.3%)	-
	Maintenance	13.2% (11.3% to 15.3%)	-	0.5% (0.1% to 2.0%)	-
Endocrine	Acute	-	-	-	-
	Continuation	6.3% (4.3% to 9.1%)	-	-	-
	Maintenance	5.7% (3.9% to 8.4%)	-	-	-
Gastrointestinal	Acute	33.8% (31.1% to 36.5%)	-	25.1% (21.0% to 29.7%)	-
	Continuation	31.7% (29.9% to 33.6%)	7.4% (3.2% to 16.1%)	8.7% (6.5% to 11.5%)	-
	Maintenance	19.9% (18.2% to 21.8%)	-	5.6% (3.6% to 8.9%)	-
General	Acute	11.8% (9.3% to 14.8%)	-	6.2% (3.9% to 9.8%)	-
	Continuation	14.6% (13.2% to 16.2%)	11.8% (6.1% to 21.5%)	1.9% (0.9% to 4.3%)	-
	Maintenance	6.1% (4.9% to 7.6%)	-	11.1% (7.3% to 16.3%)	-
Hepato-biliary	Acute	-	-	-	-
	Continuation	1.7% (1.0% to 2.7%)	-	0%	-
	Maintenance	3.8% (2.4% to 6.1%)	-	-	-
Metabolic and nutrition	Acute	0.5% (0.1% to 1.5%)	-	0.6% (0.1% to 2.5%)	-
	Continuation	3.4% (2.2% to 5.3%)	-	-	-
	Maintenance	2.3% (1.7% to 3.0%)	-	0.6% (0.1% to 2.5%)	-
	Acute	-	-	-	-

Musculoskeletal and connective tissue	Continuation	5.6% (3.0% to 9.9%)	10.3% (5.1% to 19.8%)	1.8% (0.5% to 6.4%)	-
	Maintenance	-	-	-	-
Nervous system	Acute	18% (16% to 20.1%)	-	17.3% (14.1% to 21.1%)	-
	Continuation	30.7% (28.9% to 32.5%)	20.2% (15% to 26.6%)	9.5% (7.2% to 12.4%)	-
	Maintenance	18.6% (16.8% to 20.5%)	-	7.2% (3.7% to 13.6%)	-
Psychiatric	Acute	6.0% (3.2% to 10.9%)	-	1.4% (0.2% to 7.6%)	-
	Continuation	11.7% (10.2% to 13.4%)	5.4% (3.4% to 8.6%)	1.4% (0.4% to 5-0%)	-
	Maintenance	6.1% (5.1% to 7.4%)	-	9.0% (5.0% to 15.8%)	-
Renal and urinary	Acute	-	-	-	-
	Continuation	7.0% (5.8% to 8.5%)	-	-	-
	Maintenance	-	-	-	-
Reproductive system and breast	Acute	-	-	-	-
	Continuation	7.0% (5.8% to 8.5%)	-	1.5% (0.5 to 4.9%)	-
	Maintenance	20.9% (18.9% to 23%)	-	-	-
Respiratory, thoracic and mediastinal	Acute	-	-	-	-
	Continuation	6.4% (5.1% to 8.0%)	-	1.3% (0.5% to 4.9%)	-
	Maintenance	2.8% (2.1% to 3.8%)	-	3.1% (1.6% to 6.0%)	-
Suicidal behaviour	Acute	0.4% (0.2% to 0.9%)	-	0.6% (0.1% to 2.5%)	-
	Continuation	1.2% (0.6% to 2.2%)	4.4% (1.5% to 12.2%)	0%	-
	Maintenance	0.9% (0.5% to 1.6%)	-	-	0.4% (0.1% to 2.5%)
Vascular	Acute	-	-	-	-
	Continuation	3.0% (2.0% to 4.5%)	-	5.5% (2.5% to 11.5%)	-
	Maintenance	-	-	-	-

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy

5.3 Discussion

5.3.1 Main findings in context

This review was based on 43 studies evaluating the clinical efficacy of antidepressants or CBTs when administered for longer than 12 weeks, of which 29 studies provided data on the continuation and 14 on the maintenance treatment phases. Most studies evaluated ADM versus placebo and only few studies compared ADM to CBT or either monotherapy to combination therapy. As the focus of this review was to provide evidence on the longer term outcomes of the different treatments in depression, strict criteria for inclusion of studies (i.e., treatment duration ≥13 weeks) were applied and we thus did not adequately evaluate the acute phase efficacy of the different treatments. Nevertheless, our findings of significantly better response and remission in patients receiving ADM compared to those on placebo up to 12 weeks of treatment are largely consistent with the literature (23,25,94–96). The most comprehensive systematic review to date on the efficacy and acceptability of antidepressants in adults with MDD, by Cipriani et al., includes a network meta-analysis of 522 placebo-controlled and head-to-head trials (23). Similar to other reviews (25,94–96), the authors found that antidepressants overall were more efficacious than placebo during the acute treatment phase (23). In terms of acceptability (i.e., study drop-outs for any reason) and tolerability (i.e., study drop-outs due to side effects) during the acute phase, we found varying rates of acceptability and worse tolerability rates of antidepressant use compared to placebo use, similar as reported by Cipriani et al (23).

Below, we summarize and discuss the different findings related to the continuation and maintenance phases of MDD treatment.

The efficacy of ADM or CBT during the continuation and maintenance phases on relapse was evaluated in eight studies and on recurrence in only one study. A small number of trials contributed to each comparison and there was large uncertainty surrounding the estimates. The studies additionally suffered from several methodological shortcomings, with most studies being at high risk of bias in several domains. This included possible selective outcome reporting and lack of blinding and allocation concealment. In the six CBT trials (54,55,66–68,70) where double blinding was not possible, only two trials (55,70) reported blinding of outcome assessors. Furthermore, because of the resulting high risk of bias, our GRADE assessment showed that the quality of evidence of studies which included a comparison of ADM and CBT needs to be regarded as low. Insufficient blinding in these trials may have biased the estimates in favour of CBT. Our assessment of these mid- to long-term outcomes was further limited by the duration of trials. Very few trials assessed patients for longer than a year and only one had a three year follow-up.

We found only one study evaluating ADM versus CBT in the continuation phase, in which authors reported a higher non-significant risk of relapse among those receiving ADM (67). In the maintenance phase, the effects of ADM and CBT on relapse appeared comparable (66,68). On the other hand, a lower, albeit non-significant, risk of relapse in those receiving ADM plus CBT compared to ADM alone was reported (54). In a single study, recurrence rates were similar between those receiving ADM or ADM plus CBT combination therapy up to three years (55).

While some findings from other reviews are in line with our findings, others are conflicting (97–102). Similar to our results, a meta-analysis of 13 randomized trials by Biesheuvel-Leliefeld et al. comparing psychotherapy (including CBT) to ADM found comparable efficacy between the two treatments in reducing the risk of relapse or recurrence up to 90 weeks (102). Vittengel et al also found that while CBT did not significantly reduce relapse or recurrence compared to ADM, the effect was nevertheless in the expected direction where patients treated with continuation CBT had a 56% chance of a better outcome (101).

In contrast to our findings of no difference in relapse or recurrence among those receiving ADM monotherapy or combination therapy during the continuation or maintenance phases, other reviews found that relapse or recurrence were less likely to occur with combination treatment than ADM alone (100,102–104). However, these reviews also included other types of psychotherapy and defined their main efficacy outcomes differently. For example, Karyotaki et al used any positive outcome, including response, remission or being free of relapse or recurrence (100). In that context, it is hard to directly compare findings. In addition, we could only include fewer studies which may have underpowered our analyses to detect any differenes. We did nevertheless similarly find response and remission estimates favouring ADM plus CBT in the continuation and maintenance phases. This is similar to findings from a recent meta-analysis where authors found that combined treatment was more efficient than pharmacotherapy alone and psychotherapy alone at 6 to 12 months of follow-up (25). It is also noteworthy to mention that while there is a clear distinction in depression treatment between relapse and recurrence (where the aim of continuation treatment is to prevent relapse and that of maintenance treatment to prevent recurrence), this was less well defined in some studies. In these, relapse was also often assessed in the maintenance phase. While current guidelines support the continuation of treatment for six months and up to three years in high risk patients, the evidence in support of either ADM or CBT is limited, in particular as a maintenance treatment.

When compared to placebo, we found a lower risk of relapse with ADM in the continuation phase, including in those with severe MDD (72,73). On the other hand, there was no difference between ADM and placebo in the maintenance phase (68,71). One study evaluating CBT and placebo in the maintenance phase reported that participants in the

CBT group were less likely to relapse compared to placebo, however the difference was not significant (68). Similar to our findings, a pooled analysis of nine trials comparing ADM and placebo found that relapse occurred less frequently in patients who received ADM in the continuation phase (97). But after six months of treatment, Borges et al found that the relapse rate difference between ADM and placebo became less and the two arms appeared to become comparable (98). A recent meta-analysis of 40 trials found similar results (105). Any clinical interpretation of these results should be done with caution. The designs of the trials included in these reviews (and of some trials included in ours) necessitated that some patients were withdrawn from active treatment after an open label treatment phase and switched to placebo. Therefore, the risk of relapse might be increased due to the withdrawal of the drug per se rather than due to MDD. It has also been observed that after sustained remission, the risk of relapse falls. It might therefore be expected that the duration of the open label phase and subsequently the duration in which a patient sustains response before randomization plays a role for the risk of relapse (99). We did not explore this in our analysis, but if there is such an effect, the efficacy of ADM in the continuation therapy may have been overestimated. We were also unable to take into account the number of patients' previous depressive episodes, which is a known predictor of relapse (106).

Very few trials assessed the impact of longer term treatment on the quality of life and social functioning of patients with MDD. We found only one study comparing the quality of life outcome of patients with ADM and CBT (65) and most comparisons for improvement in social functioning were derived from one study (80). Gilliam et al compared QoL between ADM and CBT and reported that while there was an improvement over time in both arms at 16 weeks of treatment, there was no significant difference between the two. Furthermore, the authors also observed that the improvement in depression was positively associated with changes in QoL (65). This is somewhat consistent with previous research showing that improvement in QoL over the course of treatment was partially accounted for by a reduction in depressive symptoms (107). Nevertheless, the certainty of evidence surrounding this study is very low. It included a specific population of epilepsy patients and thus the findings may not be applicable to the broader population of patients with MDD.

Similarly for social functioning, Zu et al found significant improvements in the functioning of patients with moderate to severe MDD receiving ADM or CBT or the combination of either up to six months. However, there was no evidence supporting that either was more efficient than the other. Overall, the effect size of the change in social functioning was smaller than that of the reduction of depressive symptoms. This finding is in line with other research that indicate that contrary to depression symptoms which may improve within weeks, improvements in social functioning as well as quality of life (and ultimately returning to normal) require much longer (108–110). Others have also suggested that worsening in social functioning in the continuation phase could precede relapse or

recurrence of MDD episodes (111), highlighting the importance of clinical screening for and identifying areas of psychosocial deterioration. Future studies with comprehensive and longer-term assessments that also incorporate mediation analyses would provide valuable data on examining the relation between QoL, social functioning and in depression symptoms.

Acceptability, defined on the basis of study drop-out for any reason, was higher in ADM plus CBT than in ADM or CBT alone, and in CBT than in ADM in the continuation phase. Acceptability of ADM may be lower (i.e., higher study drop-outs) due to side effects or because of patient preferences. Besides, as it includes drop-outs for any reason, there is the possibility that patients dropped out due to the inefficacy of treatment, with possible overlap between relapse/recurrence and acceptability. Drop-outs due to adverse effects (tolerability) were less consistently reported compared to all-cause drop-outs, with higher risk of drop-outs in ADM arms than CBT or placebo. For a comprehensive assessment of the harms of all treatments, we extracted all available data on adverse effects from trials. Overall, we found that a high proportion of patients experienced adverse effects, particularly among those receiving ADM. However, reporting of adverse effects was inconsistent across studies and certainly lacking for CBT and combination of ADM and CBT, which may lead to a biased knowledge base and may not allow an adequate direct comparison of the harms of CBT and ADM. Nevertheless, taken together, the available evidence indicates that ADM alone was not optimal from the perspective of acceptability and tolerability. Such a finding needs to be incorporated in treatment decisions.

5.3.2 Strengths and Limitations

Our review has several strengths. We conducted a comprehensive search process in multiple databases and used two of the largest reviews on antidepressants and cognitive behavioural therapy to identify relevant studies (23,25). We used the same search strategies as used by the authors of the two reviews to ensure consistency, accepting that some of the search terms were incomplete (e.g., LU AA 21004 was not contained as a vortioxetine search term). While we are confident that our search strategy captured relevant studies well, we cannot exclude that some may have remained unidentified. We did not apply any language restrictions in our search process, thereby avoiding language bias. Furthermore and importantly, in addition to our primary analyses we covered topics which are also relevant in clinical practice and decision making such as adverse effects, quality of life and social functioning. Last, we included and evaluated the different outcomes across all types of trial designs. Previous reviews have focused primarily on discontinuation trials, which can be difficult to interpret and may tend to overestimate the effects of treatments.

Some limitations to both the review process and the evidence base should be mentioned.

5.3.2.1 Limitations of the review process

First, both pairwise and network meta-analyses assume that the included trials are drawn from the same population. While we only included adults with MDD, our dataset still included some populations with different age groups and specific medical comorbidities. Nevertheless, we tried to ensure homogeneity by excluding trials focusing on specific populations in the network meta-analyses and by performing sensitivity analyses on the pairwise meta-analyses. Network meta-analyses also assume that the interventions provided across the different studies are similar in terms of conduct and rationale. However, there were different classes of ADMs and a wide range of CBTs included in the studies, and the group of TAU may have merged different treatments (in terms of nature and intensity). This may violate the underlying transitivity assumption of our network and comprise the validity of our results. Along the same line, there were substantial differences in the study designs and conducts. While double-blinded placebo-controlled trials are usually employed for the evaluation of ADM, it is not possible to employ the same design in CBT (psychotherapy, in general) trials. It is essentially impossible to blind clinicians and patients to CBT. The inclusion of non-blinded trials in our network may affect the robustness of the estimates and the clinical benefit of CBT may be overestimated. Additionally, the choice of a true placebo in CBT trials is tricky and consequently other control groups are often used, such as waiting list and treatment as usual. It has been suggested that different control conditions in CBT trials lead to substantially different estimates and waiting list control groups could overestimate the effect of CBT (112). Furthermore, placebo effects of both ADM and CBT are well reported in the literature. While it is possible to estimate the placebo effect of ADM, it is hard to dismantle the true CBT effect from placebo as well as other non-specific factors such as patient expectancies, patient-doctor relationship and therapeutic alliance (112–119). Unfortunately, we could not explore the impact of placebo or nocebo effects of the different treatments on study estimates.

Second, by performing the analyses at an overall treatment modality level, any possible differences within treatment modalities may have been obscured, with possible underestimation of the efficacy of certain interventions. Even though, when possible, we did perform the analyses on an individual drug and class level, the focus of this report was the treatment modality level, and we thus did not interpret any differences between individual drugs or classes. We additionally did not evaluate the adequacy of the dosing of antidepressants or the CBT sessions in the trials. It is worth noting that some studies showed that acute phase CBT may have an enduring effect even after the discontinuation of acute phase treatment (26,101). This is important as patients are usually maintained on ADM for several months for the prevention of relapse and recurrence. A comparison

of the long-lasting effects of both CBT and ADM (in their presence and absence) would allow for better decision making by patients and clinicians on the initial treatment. However, we did not address this aspect in this review as we only included studies where participants were maintained beyond 12 weeks, on either treatment.

Third, we only included studies that provided data on at least one of the outcomes for at least 13 weeks and thus our comparative assessment of the "acute phase" is limited as we have certainly excluded hundreds of studies. Fourth, we analysed only average treatment outcomes on a study-level, and we could not assess potential effect modification by certain demographic and clinical factors such as age and MDD severity, as would have been possible by individual patient data meta-analyses. Fifth, due to time constraints, as well as to ensure homogeneity of the analyses to the extent possible, we restricted our inclusion criteria and did not include other patient populations (e.g., patients with dysthymia or treatment resistant depression) or data from observational studies which could have provided more evidence, particularly on safety outcomes. In addition, we were unable to contact authors of studies if there was missing or unclear information. We also did not search for grey or unpublished literature. However, we are fairly certain that our search through the Cochrane database captured RCTs in trial registries well.

A substantial proportion of the ADM trials included were sponsored by industry which could possibly imply an increased risk of bias (120–123). Estimates in CBT trials on the other hand may be associated with researcher allegiance as suggested by the literature (124–126). We could not investigate the impact of either on our estimates. Furthermore, we included studies that were conducted between 1995 and 2020 and there may be differences between past and current practices in conducting and evaluating the CBT interventions. Along the same line, clinicians rendering the interventions in the different studies may have had different training or experiences. Thus, the applicability of our findings may be limited. Future work might evaluate the impact of such differences on treatment effects.

The efficacy of ADMs has been reported to be overestimated because of publication bias and selective outcome reporting (127,128). This may occur due to several factors including reluctance of authors or sponsors to report and journals to publish null findings, especially in the early 2000s before trial registration was enforced (129). Similarly for psychotherapy trials, there is a growing body of evidence that the clinical benefit of psychotherapies reported in meta-analyses may also be overestimated because of publication bias (128,130,131). However, we were unable to assess the extent of publication bias and selective outcome reporting due to the small number of trials included and both biases remain likely for both ADM and CBT and both efficacies may have been overestimated.

5.3.2.2 Limitations of the evidence base

Several limitations that characterize the body of evidence presented in this review should be noted.

First, for our primary, longer term clinical outcomes, i.e. relapse and recurrence, data was scarce. We often were only able to synthesize the evidence narratively and were unable to conduct any of the pre-specified subgroup analyses. Importantly, the data offers no insights on how treatments might differ based on patients' severity of depression. This limits the interpretation of our findings in the context of current clinical guidelines where the recommended initial and maintained treatment strategies are based on severity of depression symptoms.

Second, when enough data was present to obtain pooled results, interpretation of the findings was often limited by small sample sizes and methodological limitations. Across our primary outcomes, we judged most of the studies to be at high risk of bias and none to be at a low risk. The potential bias in these studies, especially in those assessing CBT, was due to to limitations (mainly driven by the nature of CBT) and flaws in the design and outcome measurements weakening the validity of results where high risk bias trials may tend to overestimate the benefits and underestimate the harms. Consequently, the quality of the evidence base drawn from these studies was too low to draw any firm conclusions.

Third, we only included RCTs in our analysis. RCTs generally include highly selected populations, and include patients from secondary or tertiary care settings who may have higher levels of depression severity and be at a higher risk of relapse than the general population. Notably, studies often had an enrichment design where patients were expected to have responded favourably to prior treatment. Such designs as well as procedures applied in clinical trials do not necessarily reflect real world practice. Thus, how these findings apply to the broader clinical population, including patients with milder MDD forms and who were underrepresented in such trials, is unclear.

A fourth limitation is the lack of or inadequate assessment of the adverse effects of treatments, particularly relating to CBT. This inconsistent reporting of AEs in CBT trials may lead to an underestimation of their harms. The methods of evaluating adverse effects across studies were heterogeneous and rarely described in detail and objective, structured instruments were very rarely used. While some authors reported all occurring adverse effects, others only reported those occurring above a certain frequency threshold (e.g., above 5% or 10%). Similar limitations should be taken into consideration when interpreting findings on quality of life and social functioning. Measurement of these two outcomes focused on changes between baseline and endpoints and the differences between intervention and comparator and results were almost never analysed or interpreted in the context of detecting a minimally important difference. More robust

assessments of such outcomes within and across subgroups of patients with MMD should be integrated into clinical trials. Finally, we were unable to perform any of the planned subgroup analyses due to the limited evidence, and thus we were unable to assess whether any of the treatments is less or more efficacious for certain populations.

5.4 Conclusion

The evidence regarding the comparative clinical efficacy and safety of antidepressants and cognitive behavioural therapy on the mid- to long-term remains largely inconsistent and inconclusive. While we found no statistically significant difference between ADM and CBT on our primary efficacy outcomes, we are unable to make a clear statement regarding the usefulness of either given the scarcity and uncertainty of the available evidence. For a more adequate judgment of the relative long-term efficacy of treatments, our findings encourage additional, well-designed and larger trials, conducted over longer periods, with vigorous assessments of clinically relevant outcomes, that encompass both benefits and harms and extend beyond those that are typically assessed in the acute phase.

6 Benefit-Harm Assessment

6.1 Methods

We followed the recommendations of the PROTECT Group for the conduct of the benefit-harm assessment (132). This approach consisted of five stages: planning, evidence selection and data preparation, analysis, exploration and sensitivity analysis, discussion and interpretation.

6.1.1 Population

The target population for the BHA was adults with a diagnosis of MDD. Populations with other distinct depressive disorders, such as treatment-resistant depression, persistent depressive disorders, seasonal affective disorders, bipolar depression, psychotic depression, substance/medication-induced depressive disorder, and perinatal depression were not subject to inference for the BHA.

6.1.2 Interventions

We chose treatment comparisons for the BHA based on the availability of evidence from the clinical assessment for the different benefit and harm endpoints. Accordingly, CBT versus ADM as well as combination therapy with CBT plus ADM versus monotherapy were considered. When possible, the BHA additionally assessed the different comparisons at a treatment class level.

6.1.3 Outcomes

The following outcomes were considered for the BHA:

- **Benefit Outcome**: Risk reduction in relapse – or symptomatic exacerbation occurring after remission– was considered to inform the mid- to long-term efficacy of interventions for MDD following acute phase treatment (see Figure 1). Recovery (i.e., sustained period of remission representing resolution of the index episode) and recurrence (i.e., new episode of depressive illness following recovery) would also be important long-term outcome measures beyond the continuation phase therapy of MDD, but the evidence on these outcomes in the available RCTs was limited (133).

- **Harm Outcomes**: We extracted all reported AEs that were related to CBT, ADM or their combinations. We grouped the AEs into system organ classes to inform the BHA assessment, according to MedDRA (see appendix for the list of AEs under each class) (134). The groups of AEs comprised suicidal behaviour, nervous system, musculoskeletal and connective tissue, respiratory and mediastinal, psychiatric,

gastrointestinal, and general AEs. In addition to these classes of AEs, we also considered all-cause dropout (i.e., treatment discontinuation for any reason) in a separate model as a good indicator for measure of the overall acceptability of treatments. However, while drop-outs occurs mostly due to AEs, it should be noted that other reasons, such as lack of efficacy, cannot be excluded.

6.1.4 Data Inputs for the Benefit-Harm Assessment

(a) Treatment Effects: efficacy of interventions

The relative treatment estimates of MDD interventions regarding the benefits (i.e., efficacy in terms of risk reduction of relapse) and harms (i.e., excess risks of harm outcomes) were based on the results of the pairwise meta-analysis in the clinical evaluation presented in section 5. Summary estimates are shown in Table 14).

(b) Outcome Risks: incidence rates

We considered risks of relapse as well as harm outcomes in comparators as a basis to estimate the magnitude of absolute effects of the treatment interventions in the MDD general population. Due to unavailability of valid and reliable population-based studies or registries, RCTs were used to retrieve the baseline incidence of benefit and harms outcomes (Table 14; see sensitivity analysis further below for additional basis risks considered in the analysis).

(c) Preference Weights

The preference weights represent the relative importance (or seriousness) of the outcomes, where a higher value means that patients have a stronger preference to avoid the outcome. Empirically determined preference weights, for example by preference-elicitation surveys, were not available for the specified outcomes. We therefore used generic values on a scale of 0 to 1.0 that have been applied in other decision contexts (135,136); i.e., a preference weight of 1.0 for death, 0.75 for life-threatening outcomes, 0.5 for severe outcomes, 0.25 for moderate, and 0.1 for mild outcomes (Table 14). On the bases of these generic values, three members of the research team assigned independent values and consensus values were taken for the BHA analysis. Preferences were assigned at the MedDRA system organ class level. Some of the adverse effects are serious and some are only mild. For example, stroke belongs to the neurologic class of AEs, but many other AEs that are mild and more frequent were also grouped within the same class. We therefore took into account the number of outcomes, frequency, severity and prognosis of the outcomes within a class when assigning preferences.

Moreover, additional ranges of preference weights were used for the benefit and harm outcomes (see sensitivity analyses).

Table 14. Input parameters for benefit-harm assessment model: Relative treatment estimates, outcome risks, and preference weights

	MDD interventions	Relapse	Acceptability (all-cause dropout)	Suicide (attempt, thought or complete)	Neurological AEs	Musculoskeletal AEs	Respiratory AEs	Psychiatric AEs	Gastrointestinal AEs	General AEs	All-cause mortality†
Treatment effect estimates, RR (95% CI)	ADM vs. CBT (estimates from RCTs followed for >13 weeks to <25 weeks)(63,65–67,80,83,90)	2.45 (0.72–8.33)	1.44 (1.09–1.90)	0.16 (0.01–3.09)	1.81 (1.42–2.29)	1.21 (0.48–3.08)	0.63 (0.19–2.13)	2.82 (1.15–6.94)	4.72 (1.86–11.98)	3.54 (1.32–9.52)	
	ADM vs. CBT (estimates from RCTs followed for ≥25 weeks) (66,68)	1.27 (0.38–4.21)	1.21 (0.84–1.75)								
	ADM vs. CBT plus ADM(54,55,80)	1.16 (0.73–1.83)	2.40 1.56–3.69)								
	CBT vs. CBT plus ADM(80)	1.10 (0.30–3.95)	1.67 (1.08–2.56)								
	CT/REBT vs. SSRI*(67)	0.44 (0.14–1.39)	0.48 (0.32–0.72)		0.50 (0.25–1.00)			0.35 (0.14–0.86)			
Outcome risks per 1000- months (95% CI)	CBT	27 (9–78)	100 (64–155)	11 (4–34)	8 (1–76)	26 (13–55)	22 (10–49)	13 (6–27)	18 (8–44)	30 (15–60)	3 (1–9)
Alternative outcome risks per 1000- months (95% CI)	CBT	Risk spectrum (4 to 58 per 1000 person-months, which are equivalent to 5% to 50% in one year									
Preference weights, 0 to 1.0 scale§§		0.5	0.375	1.0	0.29	0.1	0.1	0.1	0.1	0.12	
Alternative preferences weights, 0 to 1.0 scale		0.05 to 1.0 values	0.05 to 1.0 values								

MDD: Major Depressive Disorder. CBT: Cognitive Behavioural Therapy. ADM: Antidepressant Medicine. CT/REBT: Cognitive Therapy/Rational Emotive Behaviour Therapy. RR: Relative risk. AE: Adverse effects. AE: Adverse events † All-cause mortality was considered as a competing risk in the benefit-harm assessment. * class-level estimate.
See Appendix 11.1.1.3 for list of AEs in each class.

§§ Specific adverse effects were first grouped into system organ classes according to the Medical Dictionary for Regulatory Activities, a clinically validated international medical terminologies (MedDRA). Preferences were assigned at the class level. Some of the adverse effects are serious and some are only mild. For example, stroke belongs to the neurologic class, but many other AEs that are mild and more frequent were also grouped within the same class. We therefore took into account the number of outcomes, frequency, severity and prognosis of the outcomes within a class when assigning preferences.

6.1.5 Time horizon

We used a 12-month time horizon to estimate the cumulative risk of the benefit and harm outcomes, which is equivalent to an average-duration maintenance-phase therapy.

6.1.6 Analysis

We used a modification of the approach by Gail. et al. This model is based on an estimation of the expected absolute difference in the occurrence of each type of benefit and harm event between the intervention groups over a defined time horizon. It thus combines evidence on the outcome risks of patients with evidence on relative treatment effects, as well as patient preferences. The model allows to quantitatively combine all expected events of benefit and harm endpoints on the same scale in order to assess whether the benefits outweigh the harms or vice versa. This approach has been applied in benefit-harm assessments of various preventive and therapeutic treatments (135,137–140).

First, the cumulative risk (p_i) of relapse and the risk of harm outcomes were calculated using an exponential model for a theoretical fixed cohort of 1000 MDD patients treated with CBT with the following model. $p_i = pap \times \frac{I_i}{I_i+M_i} \times (1 - e^{-(I_i+M_i)\times t})$; where pap is population at risk, I_i is the risk of benefit and harm outcomes with CBT alone, M_i is competing risk, and t is time horizon. The model assumes the risk of relapse and the harm outcomes remain constant over the time horizon of 12 months.

Second, the risk of the outcomes (p_j) was calculated for the groups receiving ADM or dual therapy with CBT and ADM using the same exponential model, but this time incorporated the relative treatment effect as $p_i = pap \times \frac{I_i \times rr_i}{I_i \times rr_i + M_i} \times (1 - e^{-(I_i \times rr_i + M_i)\times t})$; where rr_i is the relative treatment estimates of the different outcomes.

Third, the absolute difference in incidence rates of the outcomes was estimated from the above two models. Fourth, the absolute differences were then weighted individually based on the respective preference weights to the benefit and harm outcomes; i.e., $(p_i - p_j) \times w_i$. This calculation was carried out simultaneously for relapse as well as harm outcomes and added up to a benefit-harm balance index (hereafter net clinical benefit) as $\sum_i^n (p_i - p_j) \times w_i$; where n is the number of benefit and harm outcomes considered in the model. The index for net clinical benefit shows whether the benefits outweighed the harms (positive index) or vice versa (negative index), or whether benefits equal harms (index equals zero).

Finally, the analysis was performed stochastically with 100,000 repetitions accounting for the uncertainty of parameter estimates to generate a distribution of the net clinical benefit. From the distribution, we calculated the probability that patients receiving the treatment interventions would experience a clinical benefit overall. A probability above 60% was interpreted as net clinical benefit (i.e., more clinical benefits than harms), below

40% was interpreted as net clinical harm (less benefits than harms). Probabilities between 40% and 60% were interpreted as neither harmful nor beneficial.

In addition, we estimated the absolute net clinical benefit as well as the expected cumulative events of individual benefit and harm outcomes over 12 months with the model. The net clinical benefit was expressed as total "death-equivalents" avoided by the intervention without experiencing any AEs. When necessary, we converted the net clinical benefit to relapse-equivalents by dividing the index by the preference weight for relapse. We calculated a 95% uncertainty around the expected events with the 2.5% and the 97.5% centile of the distributions of the calculated net clinical benefit.

6.1.7 Sensitivity Analysis

BHA is often dependent on the selection of evidence on the input parameters, particularly relative treatment estimates, outcome risks, and patient preferences (141). Additional sensitivity analyses were thus performed to assess the net clinical benefit taking into account alternative assumptions for the input parameters.

The duration of follow-up times of the RCTs that were analysed to estimate relative treatment effects were mostly less than 6 months and some were from RCTs with a follow-up period somewhat longer than 6 months. Therefore, it may be difficult to extrapolate such effects to a longer time horizon beyond 12 months, but we performed a sensitivity analysis of the BHA at 24 months.

Furthermore, although an average relapse rate was used for the main model, we extended the analysis by alternatively considering a spectrum of relapse risks ranging from 5% to 50% over one year that would likely encompass most patients with MDD. We also tested the influence of patient perceptions towards the benefit and harm outcomes on the net clinical benefit, with preference weights varying from 0.05 to 1.0 (in steps of 0.05) for both relapse and dropout simultaneously.

The BHA focused primarily on overall ADM compared to CBT or the combination of both, as no class-level mid- to long-term treatment estimates for relapse, recovery, or recurrence were available, other than little data for CT/REBT compared to SSRIs. We performed the BHA for this class-level contrast, however the results should be interpreted with caution as the estimates of relapse and harm outcomes were based on one study.

6.2 Results

6.2.1 Benefit-Harm Balance: Probability of Net Clinical Benefit

Figure 27 shows the distribution of the benefit-harm balance index, from which the probabilities for a net clinical benefit were estimated. When weighing the risk of averted relapse against the excess risk of harm outcomes on the same scale, MDD patients treated with CBT demonstrated a net clinical benefit over 12 months compared to their counterparts treated with ADM. The corresponding probability of net benefit in terms of preventing relapse was 91.8% for CBT compared to ADM taking into account specific harm outcomes and 98.2% when all-cause dropout was considered as the harm outcome.

Whereas the above results were based on treatment estimates from short-term RCTs (with >12 to <25 weeks of follow up), we repeated the analysis with evidence from longer RCTs (with ≥25 weeks or longer), but this time using only all-cause dropout as a harm endpoint. CBT was still superior to ADM, with a probability for net clinical benefit of 77.1%. This showed a decrease in net benefit over time compared with the benefit using estimates from RCTs with shorter follow-up periods. However, the combination of CBT and ADM boosted the net clinical index. That is, the combination of CBT plus ADM showed a higher net clinical benefit compared to monotherapy with ADM (probability, 96.7%), but an only slightly higher one when compared to CBT (80.3%).

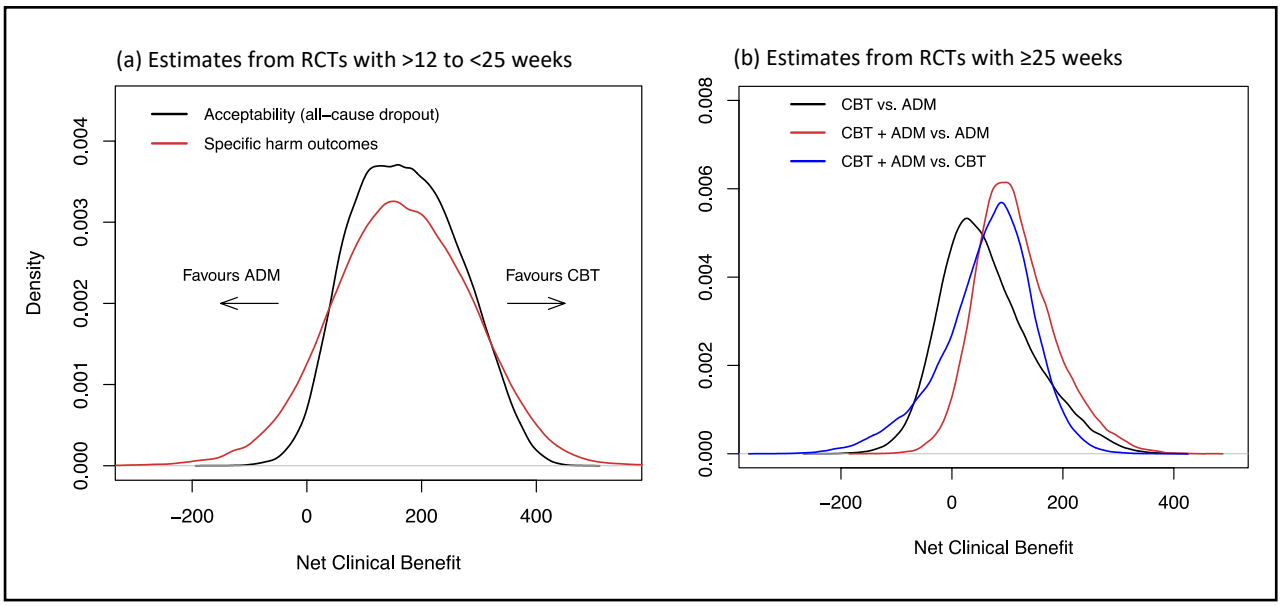


Figure 27. Distribution of net clinical benefit for MDD interventions over 12 months

a) CBT vs. ADM. Benefits: risk reduction in relapse; harms: excess risk of specific harm outcomes as well as acceptability (all-cause dropout). The treatment estimates for these outcomes were retrieved from randomized clinical trials with >12 to ≤25 weeks of follow up. (b) Benefits: risk reduction in relapse; harms: acceptability (all-cause dropout). Treatment estimates retrieved from randomized clinical trials with ≥25 weeks of follow up.

6.2.2 Benefit-Harm Balance: Absolute Expected Events

The probability of a net benefit (defined as a probability of 60% or more) is indicative of benefits outweighing harms but does not show the extent of additional absolute benefit of one intervention over the other. We thus further estimated the absolute net clinical benefit, calculated as an overall measure of preference-adjusted net clinical benefit. It is important to note that the overall net clinical benefit is a composite of both the reduction in relapse and the increase in harm outcomes with additional adjustment by preference weights. The net clinical benefit can be interpreted as number of death-equivalents averted without experiencing any harm events or converted to averted relapse-equivalents by dividing the net index by the preference weight of relapse (i.e., 0.5) (Table 15).

Using the treatment effects observed in RCTs with follow-up times of <6 months, the number of relapse-equivalents (i.e., net clinical benefit) that would be avoided over 12 months was 346 in 1000 MDD patients treated with CBT compared to ADM. This was reduced to 126 in 1000 patients when only evidence from RCTs with more than 6 months of follow-up was considered. However, the decrease in effect was reversed to a more favourable net clinical benefit with combination therapy of CBT plus ADM. The number of relapse equivalents averted with CBT plus ADM compared to monotherapy with ADM at the end of 12 months was 228 in 1000 patients). Compared with CBT, it was 126 relapse equivalents averted in 1000 patients.

Table 15. Net clinical benefit and expected events of benefit and harm outcomes over 12 months.

			Expected events per 1000 patients in 12 months								
Treatment contrasts	**Pr. net clinical benefit in 12 months, %**	**Net clinical benefit per 1000 patients in 12 months (2.5th, 97.5th centiles)**	**Relapse with CBT/ADM**	**Acceptability with CBT/ADM**	**Suicide with CBT/ADM**	**Neurological AE with CBT/ADM**	**Musculoskeletal AE with CBT/ADM**	**Respiratory AE with CBT/ADM**	**General AE with CBT/ADM**	**Psychiatric AEs with CBT/ADM**	**Gastrointestinal AEs with CBT/ADM**
CBT vs. ADM	91.8§	166 (-72 to 399)	292/550	–	136/37	137/217	275/336	242/182	308/694	149/378	197/633
	98.2†	173 (8 to 353)	292/550	685/802							
	77.1§§	63 (-76 to 248)	293/372	685/747							
CBT plus ADM vs. ADM	96.7	114 (-7 to 275)	293/345	685/918							
CBT plus ADM vs. CBT	72.0	42 (-158 to 190)	293/341	507/685							

§ In this model, specific harms were considered, rather than acceptability. † This model considered all-cause dropout as harm outcome §§ Evidence from RCTs with follow-up times of 25 weeks or longer. MDD: Major Depressive Disorder. CBT: Cognitive behavioural Therapy. ADM: Antidepressant Medicine. AE: Adverse events

Net clinical benefit was interpreted as the death-equivalents averted by an intervention. When necessary, the net clinical benefit can be converted to relapse-equivalents by dividing the net index by the preference weight of relapse (i.e., 0.5). For example, the net benefit interpreted as death-equivalents of CBT was 166 in 1000 patients as the end of 12 months compared with those treated with ADM. The net relapse-equivalents averted by CBT would be 166/0.5=332 in 1000 patients.

6.2.3 Sensitivity Analyses

Longer time horizon

We repeated the benefit-harm analysis over a longer time horizon of 24 months taking into account relapse and all-cause dropout as benefit and harm endpoints, respectively. Our results at 24 months revealed higher cumulative risks for relapse and dropout for MDD patients treated with CBT and ADM, but the risk differences between the interventions were slightly smaller compared to those at 12 months and, therefore, was the net clinical benefit. Regardless of the decrease in net clinical benefit, the probabilities at this longer time horizon still exceeded the 60% threshold probability for a net benefit and thus CBT and dual therapy with CBT plus ADM remained superior over the counterparts. That is, the probabilities of net clinical benefit were 70% (95.5% when considering RCTs with follow-up < 6 months) for CBT compared with ADM and 74% for CBT plus ADM compared with CBT. CBT plus ADM also showed a favourable net clinical benefit compared to ADM alone, with a probability of 77.6%, implying larger deviation from the 12 month result of 96.7% (Table 16, Figure 28)

Table 16. Net clinical benefit and expected events of benefit and harm outcomes over 24 months

			Expected events per 1000 patients in 24 months	
Treatment contrasts	**Pr. net clinical benefit in 24 months, %**	**Net clinical benefit per 1000 patients in 24 months (2.5th, 97.5th centiles)**	**Relapse with CBT/ADM**	**Acceptability with CBT/ADM**
CBT vs. ADM	95.5††	155 (-24 to 307)	473/728	877/938
	70.1	51 (-117 to 227)	473/550	877/910
CBT plus ADM vs. ADM	77.6	63 (-86 to 223)	473/524	877/977
CBT plus ADM vs. CBT	74	61 (-139 to 241)	473/460	877/731

†† Treatment estimates from RCTs with follow up period of less than 6 months. MDD: Major Depressive Disorder. MDD: Major Depressive Disorder. CBT: Cognitive behavioural Therapy. ADM: Antidepressant Medicine. AE: Adverse events

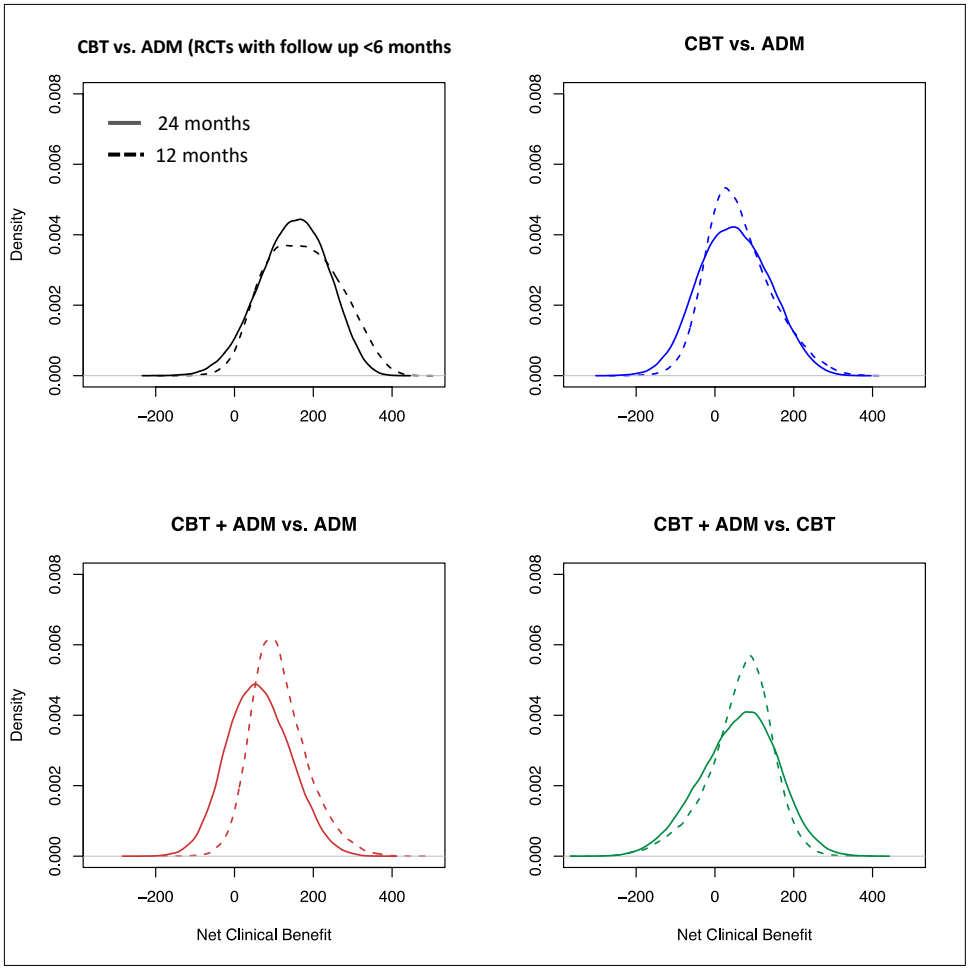


Figure 28. Distribution of net clinical benefit for MDD interventions at 24 months. The distribution at 12 months (dashed line) is also included for contrast.

Baseline risk rates of relapse

We further assessed the sensitivity of net clinical benefit to the use of alternative assumptions on the baseline risk for the main benefit outcome, namely relapse, due to the fact that treatment indication for MDD treatments may depend on patients' level of risk. Given that both relative rates of relapse and dropout were higher in MDD patients treated with ADM than with CBT, the results revealed CBT was superior at all relapse risk levels, with only a marginal increase in net clinical benefit as risk increases. The likelihood of net benefit ranged from 84.0% to 92% for relapse risks of 5% (or 4/1000 person-months) and 50% risk over one year (58/1000 person-months), respectively (Figure 29 and Table 17). The results were similar when the different specific harms were substituted for all-cause dropout in the model (data not shown).

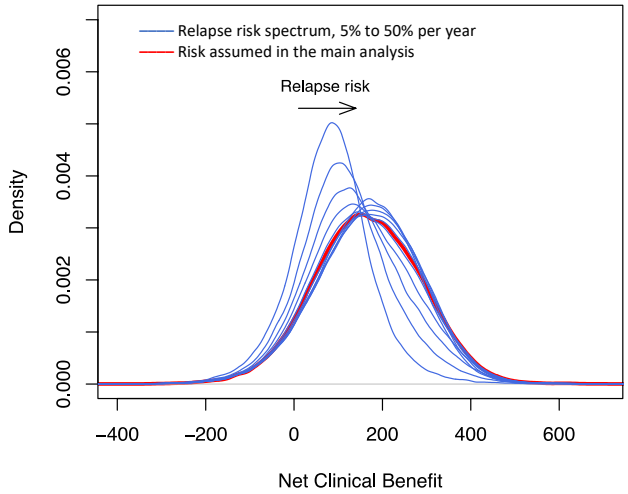


Figure 29. Distribution of net clinical benefit for CBT compared to ADM at 12 months for risk spectrum of relapse.

Table 17. Net clinical benefit of CBT compared to ADM for the treatment of MDD patients at different risk for relapse

Risk of relapse over one year	Pr. net clinical benefit in 24 months, %	Net clinical benefit per 1000 patients in 24 months (2.5th, 97.5th centiles)
5%	84.0	84 (-106 to 278)
10%	88.0	116 (-91 to 348)
15%	89.7	138 (-82 to 380)
20%	90.9	153 (-76 to 393)
25%	91.5	163 (-73 to 399)
30%	92.0	169 (-72 to 399)
35%	92.2	171 (-72 to 396)
40%	92.2	171 (-72 to 292)
45%	92.2	168 (-74 to 386)
50%	92.0	164 (-76 to 378)

Preferences weights of relapse and acceptability (all-cause dropout)

The impact of varying preference weights on net clinical benefit was assessed for the outcomes of relapse and dropout. The results demonstrated a net clinical benefit for CBT compared with ADM, regardless of any preference weights for both outcomes, which was because CBT was protective for both relapse and dropouts compared with ADM. However, the probabilities of net benefit and absolute net clinical benefit increased as the preference weights for the outcomes increased. The net clinical benefit of CBT compared to ADM was larger in patients with higher preference weights for one or both outcomes, whereas the benefit was less with lower preference weights (Figure 30).

Preference weights of acceptabilility (all-cause dropout)

Preference weights of relapse	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95	1.00
0.05	19 (69)	24 (76)	30 (81)	36 (85)	42 (88)	48 (88)	54 (92)	60 (94)	65 (95)	71 (95)	77 (96)	83 (97)	89 (97)	95 (97)	101 (98)	107 (98)	112 (98)	118 (98)	124 (98)	130 (99)
0.10	31 (79)	37 (84)	43 (88)	49 (91)	55 (93)	61 (93)	67 (96)	72 (97)	78 (97)	84 (98)	90 (98)	96 (98)	102 (99)	108 (99)	113 (99)	119 (99)	125 (99)	131 (99)	137 (99)	143 (99)
0.15	44 (85)	50 (89)	56 (92)	62 (95)	68 (96)	74 (96)	79 (98)	85 (98)	91 (99)	97 (99)	103 (99)	109 (99)	115 (99)	120 (99)	126 (99)	132 (99)	138 (100)	144 (100)	150 (100)	156 (100)
0.20	57 (89)	63 (92)	69 (95)	75 (96)	80 (97)	86 (97)	92 (99)	98 (99)	104 (99)	110 (99)	116 (99)	122 (99)	127 (100)	133 (100)	139 (100)	145 (100)	151 (100)	157 (100)	163 (100)	168 (100)
0.25	70 (91)	76 (94)	82 (96)	87 (97)	93 (98)	99 (98)	105 (99)	111 (99)	117 (99)	123 (99)	128 (99)	134 (100)	140 (100)	146 (100)	152 (100)	158 (100)	164 (100)	169 (100)	175 (100)	181 (100)
0.30	83 (92)	88 (94)	94 (96)	100 (97)	106 (98)	112 (98)	118 (99)	124 (99)	130 (99)	135 (99)	141 (99)	147 (99)	153 (100)	159 (100)	165 (100)	171 (100)	176 (100)	182 (100)	188 (100)	194 (100)
0.35	95 (93)	101 (94)	107 (96)	113 (97)	119 (97)	125 (97)	131 (98)	136 (99)	142 (99)	148 (99)	154 (99)	160 (99)	166 (99)	172 (100)	178 (100)	183 (100)	189 (100)	195 (100)	201 (100)	207 (100)
0.40	108 (93)	114 (94)	120 (96)	126 (97)	132 (97)	138 (97)	143 (98)	149 (98)	155 (99)	161 (99)	167 (99)	173 (99)	179 (99)	184 (99)	190 (99)	196 (100)	202 (100)	208 (100)	214 (100)	220 (100)
0.45	121 (93)	127 (94)	133 (95)	139 (96)	145 (97)	150 (97)	156 (98)	162 (98)	168 (99)	174 (99)	180 (99)	186 (99)	191 (99)	197 (99)	203 (99)	209 (99)	215 (100)	221 (100)	227 (100)	232 (100)
0.50	134 (93)	140 (94)	146 (95)	151 (96)	157 (97)	163 (97)	169 (98)	175 (98)	181 (98)	187 (99)	192 (99)	198 (99)	204 (99)	210 (99)	216 (99)	222 (99)	228 (99)	234 (99)	239 (100)	245 (100)
0.55	147 (93)	153 (94)	158 (95)	164 (96)	170 (96)	176 (96)	182 (97)	188 (98)	194 (98)	199 (98)	205 (99)	211 (99)	217 (99)	223 (99)	229 (99)	235 (99)	240 (99)	246 (99)	252 (99)	258 (99)
0.60	159 (93)	165 (94)	171 (95)	177 (96)	183 (96)	189 (96)	195 (97)	201 (98)	206 (98)	212 (98)	218 (98)	224 (99)	230 (99)	236 (99)	242 (99)	247 (99)	253 (99)	259 (99)	265 (99)	271 (99)
0.65	172 (93)	178 (94)	184 (95)	190 (95)	196 (96)	202 (96)	207 (97)	213 (97)	219 (98)	225 (98)	231 (98)	237 (98)	243 (99)	249 (99)	254 (99)	260 (99)	266 (99)	272 (99)	278 (99)	284 (99)
0.70	185 (93)	191 (94)	197 (95)	203 (95)	209 (96)	214 (96)	220 (97)	226 (97)	232 (98)	238 (98)	244 (98)	250 (98)	255 (98)	261 (99)	267 (99)	273 (99)	279 (99)	285 (99)	291 (99)	296 (99)
0.75	198 (93)	204 (94)	210 (95)	216 (95)	221 (96)	227 (96)	233 (97)	239 (97)	245 (97)	251 (98)	257 (98)	262 (98)	268 (98)	274 (98)	280 (99)	286 (99)	292 (99)	298 (99)	303 (99)	309 (99)
0.80	211 (93)	217 (94)	222 (94)	228 (95)	234 (96)	240 (96)	246 (96)	252 (97)	258 (97)	263 (97)	269 (98)	275 (98)	281 (98)	287 (98)	293 (99)	299 (99)	305 (99)	310 (99)	316 (99)	322 (99)
0.85	224 (93)	229 (94)	235 (94)	241 (95)	247 (95)	253 (95)	259 (96)	265 (97)	270 (97)	276 (97)	282 (98)	288 (98)	294 (98)	300 (98)	306 (98)	311 (99)	317 (99)	323 (99)	329 (99)	335 (99)
0.90	236 (93)	242 (94)	248 (94)	254 (95)	260 (95)	266 (95)	272 (96)	277 (97)	283 (97)	289 (97)	295 (97)	301 (98)	307 (98)	313 (98)	318 (98)	324 (98)	330 (99)	336 (99)	342 (99)	348 (99)
0.95	249 (93)	255 (94)	261 (94)	267 (95)	273 (95)	278 (95)	284 (96)	290 (96)	296 (97)	302 (97)	308 (97)	314 (98)	320 (98)	325 (98)	331 (98)	337 (98)	343 (98)	349 (98)	355 (99)	361 (99)
1.00	262 (93)	268 (94)	274 (94)	280 (95)	285 (95)	291 (95)	297 (96)	303 (96)	309 97	315 (97)	321 (97)	326 (97)	332 (98)	338 (98)	344 (98)	350 (98)	356 (98)	362 (98)	367 (99)	373 (99)

Favourable Net Clinical Benefit

Figure 30. Net clinical benefit and probability of net benefit for different preference weights of benefit and harm outcomes.

The results show the absolute net clinical benefit in 1000 patients treated with CBT compared to ADM, as well as the probability of net benefit in parentheses. In the sensitivity analysis, preference weights from 0.05 to 1.00 were used simultaneously for relapse and all-cause dropout.

Class level benefit-harm assessment

ADM or CBT class-level estimates of input parameter values for BHA were sparse. The BHA was conducted for CT/REBT vs. SSRIs for which estimates of benefit and harm outcomes were available from one study. The analysis showed that CT/REBT was more likely to provide greater net clinical benefit than SSRIs, with probabilities of 98.8% and 99.4% for models considering specific harms and dropout, respectively (Appendix 11.2).

6.3 Discussion

A quantitative BHA was conducted for CBT and ADM treatments for MDD. We considered benefits in terms of relapses and harms in terms of all-cause dropouts avoided, as well as specific harm outcomes. The results indicated CBT to be a more favourable intervention, 91.8% (and 98.2% when all-cause dropout was considered) likely to provide more net clinical benefit at 12 months than ADM. In subsequent analyses in which only RCTs with longer follow-up times were considered, the net clinical benefit decreased slightly (probability, 77.1%), but when combination therapy with CBT plus ADM was assessed, the probability of a net clinical benefit increased to 96.7%. Sensitivity analyses reaffirmed the superiority of CBT over ADM for long term use, regardless of patient risks for relapse and perceived severity toward the benefit and harm outcomes considered.

There are a few studies of MDD in special populations, e.g. assessing the benefit-risk of specific drug treatments during pregnancy and in the elderly population (142,143). However, we did not identify any mid-to long-term studies in the general adult population with MDD. As a result, comparing our results to published evidence is difficult.

The decision context and the quality and validity of the evidence for the input parameters must be taken into account in the interpretation of BHA results. Although long-term outcomes of interventions for MDD are ideally best measured by recovery or recurrence rates, we were unable to find RCTs reporting such outcomes. In our analysis we considered relapse risk reduction as a benefit outcome defined as a symptomatic exacerbation occurring after remission but before recovery. In light of this, our estimates of long-term net clinical benefit should not be overinterpreted, because relapse reflects a recurrence of the index episode of depression that is likely to occur more frequently before recovery or sustained remissions (133). Therefore, we are confident that the overall net clinical benefit reflects the quality of the continuation-phase therapy, often at 6 months but less so thereafter. Although we found no evidence on recovery or recurrence rates, we divided the evidence on relapse into that from RCTs with a follow-up period between 3 and 6 months or more than 6 months. Based on the data for more than 6 months, relative performance still favoured CBT over ADM and combination therapy with CBT plus ADM over monotherapy, but the net clinical benefit showed a decline over time. Moreover, the extra benefit of adding ADM to CBT for mid- to long-term use was not substantial. This suggests that a well-adhered, protocolized CBT intervention might yield non-inferior net clinical benefit compared to combination therapies. Indeed, treatment burden could play a negative role in the overall performance of the multiple therapies, although our analysis did not capture this factor.

Most medical decisions are generally sensitive to risks and preferences of patients, but our BHA analysis showed that CBT remains more effective in achieving net clinical benefit over 12 months than ADM, similarly for patients at low and high risk of relapse. Additionally, preference weights had little effect on, and did not reverse, the benefit-harm

balance of CBT compared to ADM, because relative relapse rates and dropouts were lower in CBT than ADM. However, it should be noted that the absolute net clinical benefit is greater in patients at high risk of relapse and among those who perceive relapse or dropouts to be more important to them.

In our BHA analysis, all-cause study dropout was deemed a measure of treatment acceptability. However, it could be argued that dropouts could also be due to lack of efficacy in addition to adverse effects (23). While this should be tested in other studies, we found in our analysis that the net clinical benefit was similar for both scenarios –if only dropouts or specific harm end points were taken into account– which may imply that dropouts may mostly be due to harm outcomes. In the present comparison of pharmacological and non-pharmacological interventions, individuals may also be predisposed to report more on adverse effects attributed to drugs and less on those attributed to behavioural therapies. If so, dropouts may more neutrally reflect the overall negative effects of the intervention causing discontinuation.

6.3.1 Limitations

There are several limitations that need to be considered when interpreting our BHA results. Given that this study is the first BHA undertaken for MDD interventions, the most appropriate model to quantitatively assess the benefit-harm balance is not known and is likely to be highly dependent on the context and choice of treatments. One important determinant for model choice is the availability of individual-participant data (144). We used the approach by Gail et al. as our experiences have shown it to be a highly flexible approach that is useful for judging the benefit-harm balance across a wide variety of contexts (135,137–140).

Readers should not take the estimated net clinical benefit as definitive, as the analysis was underpinned by several assumptions. For example, it was assumed that benefit and risks would be evenly distributed across the time horizon of 12 months, population treated, or the use of specific types of ADM or CBT and doses. Moreover, we used data from RCTs only for the conduct of the BHA. According to the evidence selection framework by Fain et al. (141), observational evidence may be ideal to estimate baseline incidence rates for both benefit and harm outcomes, as RCT populations may not be fully representative of real-world patient populations. However, we did not find any recent, applicable, high-quality observational study that could have served as a sufficiently reliable data source for the BHA. Thus, we had to rely on data from the included RCTs, which may underestimate harm outcome rates in the general population due to selective recruitment (lower-risk population) or selective recording of harm events. Additionally, as reported in the clinical review, a serious limitation of the evidence base on treatment relates to inconsistent AE reporting, particularly in trials evaluating CBT, which may lead to an underestimation of its true harms. As such, we did not rely solely on specific AEs as

our harm outcome but also alternatively used all-cause study drop-outs which is more consistently reported in studies, with similar results when using either harm outcome.

Furthermore, we used generic preference weights for the benefit and harm outcomes. Ideally, preference weights would be derived from preference studies targeted at informing BHA. While there were few preference studies on MDD patients (145,146), we found the contents and estimates not suitable for our purpose. We thus used generic preference weights that have also been applied in previous assessments in other contexts (135,136). Nevertheless, average empirical preference weights are not always useful, especially for clinical decision making, because preferences are mostly highly variable between individuals (147–149). However, in our study, the BHA results were not substantially dependent on the preference weights use, as demonstrated in sensitivity analysis Therefore, other empirical-based preference values would not have materially altered the benefit-harm profile of the interventions.

Of note, mid- to long-term BHA for specific ADM or CBT is beyond the scope of this report. There was only one study that reported relapse and harm outcomes for SSRI and CT/REBT, which are considered effective and safer treatment classes than others. The BHA based on this study showed that CT/REBT was likely to provide greater net clinical benefit than SSRI, which was consistent with the results of the global ADM and CBT. However, this cannot be taken for granted in the face of limited input data.

Overall, it is difficult to estimate the extent to which these limitations might have an effect on the estimated net clinical benefit, as well as the likelihood of a net benefit from the different treatments. However, we are confident that the relative benefit-harm balance of the different therapies has been captured correctly, especially for the time horizon of 12 months or less. Our analysis can be updated when new data for the input parameters become available.

6.4 Conclusion

The quantitative BHA revealed a relevant difference in the benefit-harm balance of the MDD interventions. We found a relatively high probability for a mid- to long-term net clinical benefit with CBT compared to ADM, or dual therapy with CBT plus ADM compared to a monotherapy. Obtaining more detailed data on relevant outcomes, such as recovery and recurrence, and harm outcomes would allow to better explore the mid- to long-term benefit-harm balance of interventions for MDD.

7 Health Economic Assessment

7.1 Methods

The health economic assessment consisted of a systematic review of the currently published literature, an adaptation of the cost-effectiveness results for Switzerland, and a budget impact analysis. In the scoping, options considered included a *de novo* cost-effectiveness analysis or a cost analysis with a potentially short time horizon, depending on data availability. Given the large amount of published literature, including several studies from European countries, a new cost-effectiveness analysis was considered redundant.

7.1.1 Literature search strategy and screening of search results

We carried out a systematic review of cost-effectiveness studies. The eligible population was people with a major depressive disorder (i.e. depression, diagnosed using a valid diagnostic tool). We excluded cost-effectiveness studies of populations with other types of depression; namely treatment-resistant depression, persistent depressive disorders, seasonal affective disorders, bipolar depression, psychotic depression, substance/medication induced depressive disorder and perinatal depression. Eligible interventions were any single or multi-component interventions which included an ADM administered for at least 12 weeks (i.e. escitalopram, citalopram, paroxetine, fluvoxamine, fluoxetine, sertraline, duloxetine, reboxetine, venlafaxine, clomipramine, amitriptyline, trimipramine, doxepin, mirtazapine , agomelatine, bupropion, moclobemide, vortioxetine, trazodone, mianserin), or CBT administered for at least 4 weeks. The eligible comparators were a different ADM to the intervention, a non-CBT-based psychological intervention, or unspecific control (e.g. usual care). Eligible outcomes were incremental cost per QALY gained, incremental cost per DALY avoided, net monetary benefit based on QALYs or DALYs, or dominant/dominated outcomes based on QALYs/DALYs. Eligible study designs were cost-effectiveness/cost-utility analyses in which costs and QALY/DALYs were explicitly compared (e.g. presented in a ratio). Only English, French, German, and Italian language studies were considered. Moreover, only studies published in the last 15 years (i.e. from 2006 onwards) were included in the final synthesis. Conference proceedings were excluded. Cost-effectiveness analyses for low- and middle-income country settings or from Asian countries (e.g. China, South Korea, Japan, Singapore) were excluded. Cost-effectiveness analyses of populations with depression co-morbid with another disease (e.g. diabetes, dementia, post-stroke, self-harm) were excluded.

There were several methodological differences between the health economic systematic review and the clinical systematic review. In the health economic systematic review, we included populations with substantial depressive symptomology as measured by a questionnaire such as the PHQ-9 (Patient Health Questionnaire 9 item) or the CES-D (Center for Epidemiologic Studies Depression Scale), which have been shown to have

high sensitivity and specificity for MDD. This was done to avoid the exclusion of relevant material. We excluded cost-effectiveness analyses considering patients with MDD co-morbid with other diseases (e.g. dementia, generalised anxiety disorder). Moreover, we excluded studies conducted in East Asian countries due to expected lack of comparability, and cost-effectiveness analyses published from 1995 to 2005. CBT interventions were included if they lasted for at least four weeks.

The databases we searched were EMBASE OVID, MEDLINE OVID, and York Centre for Reviews and Dissemination (CRD). We searched these databases from 1st January 1995 to 30th June 2020. However, due to the high volume of studies that we identified, in the final study selection we only included cost-effectiveness analyses published from 2006 to 2020.

Clinical keywords were based on the terms used for the search of clinical studies in this report. For economic keywords, we used the terms from a study by Pillai et al. (150). Detailed search strategies are provided in the appendices.

Titles and abstracts were screened by one reviewer; 10% (randomly selected) were also screened by an additional reviewer. Following this, full texts were screened to identify the final selection, by one reviewer. Then, data extraction was completed for all included studies, by one reviewer. Discrepancies between reviewers identified in the title and abstract screening, were resolved by the two reviewers meeting and achieving consensus. One discrepancy was identified from this screening.

7.1.2 Data extraction and quality assessment

Data extraction was conducted to obtain the following information:

- Authors
- Year
- Title of the article
- Country
- Type of study
- Intervention
- Comparator
- Modelling approach
- Time horizon
- Population
- Mean intervention costs per person
- Mean comparator costs per person
- Mean intervention effect per person
- Mean comparator effect per person
- Incremental cost-effectiveness ratio (ICER)
- Currency
- Annual discount rate (for both costs and effects)
- Cost-effectiveness threshold (country-specific)
- Sensitivity analysis

- (Types of) sources of effectiveness estimates (e.g. meta-analysis of RCTs, single RCT/within-trial, observational data)
- (Types of) sources of cost estimates
- Cost types considered
- Perspective of cost assessment

Quality of reporting was assessed though the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 24-item checklist, recommended by the ISPOR Health Economic Evaluations Publication Guidelines Task Force. For each study, each item of the checklist received a score of either “0”, “0.5”, “1” or “not applicable" ("NA”), depending on the level of transparency of reporting.
Selected CHEERS criteria were defined which needed to be met in order to make a study transferable and thus suitable for numerical adaptation of ICER results to Switzerland (see next section). Of note, it was expected that CHEERS criteria 4 (population), 7 (intervention / comparator[s]) and 10 (outcome measures) would be met by all studies assessed because studies failing any of these criteria would not have met the eligibility criteria.

7.1.3 Assessment of transferability

International cost-effectiveness studies were expected to be potentially 'qualitatively transferable' to Switzerland. A variety of authors have worked on criteria for assessing such transferability between jurisdictions (151). Relevant, related aspects have been published early by O'Brien et al. (152). Welte at al. and Drummond et al. have suggested related multistep procedure (153,154). In the present study, we perform a modified approach as described below. One key reason for using this modified approach is that we did not have available any of the original models underlying the eligible cost-effectiveness studies. Therefore, actual model recalculations on the basis of localized input parameters such as e.g. unit costs, were not possible.

- The most top-level criteria are covered by the eligibility criteria. Essentially, this step excluded studies which were not full-scale health economic evaluation studies assessing incremental cost-effectiveness, did not meet the 'PIC' of the PICO, or were performed for countries very different from Switzerland in terms of socioeconomic characteristics. All remaining studies had to meet CHEERS criteria 4, 7 and 10.
- Studies not meeting CHEERS items 5, 6, 8, 13, 14 and 19 were regarded as not transferable due to lack of key information. In relation to item 19, the availability of costs and outcomes of interest for both the intervention and comparator strategies was considered fundamental. Where articles only reported resulting ICERs, the underlying study was considered non-transferable.
- The remaining studies were considered qualitatively transferable, and underwent approximate, numerical adaptation of cost results, and hence of cost-effectiveness results, if scrutiny of transferability factors taken from O'Brien et al. and Welte et

al. did not preclude this for a specific reason (152,153). In all other cases, the results of the scrutiny of transferability factors were used qualitatively.

The following transferability factors were considered:

Methodological characteristics:

- Perspective of cost assessment
- Discount rate
- Approach to assessment of medical costs
- Approach to assessment of costs of lost productivity (for studies using a societal perspective)

Healthcare system characteristics:

- Prices in healthcare
- Clinical practice variation; differences in resource use, incentives and regulations for health-care providers
- Technology availability

Population characteristics:

- Demography
- Disease incidence and prevalence
- Case-mix
- Life expectancy
- Health-status preferences
- Acceptance, compliance, incentives to the patients
- Lost productivity and work time

For most cost-effectiveness studies meeting the general eligibility criteria we did not expect severe transferability problems since methodological and population characteristic were expected to be similar to those expected for Switzerland. Regarding healthcare system characteristics, we do not expect major differences in availability of technology. Absolute prices in healthcare were adapted numerically (see next section).

7.1.4 Adaptation of cost-effectiveness results to Switzerland

The adaptation of cost data for Switzerland was performed in three distinct steps: correction for different levels of resource utilisation, for different prices of healthcare services, and for change in level of resource utilisation and prices over time. Subsequently, adapted ICERs were calculated. This process cannot be interpreted as achieving realistic ICERs for Switzerland but has intended to achieve a certain approximation of cost-effectiveness levels to be expected for Switzerland. It has certainly made the results of international cost-effectiveness studies, reported for different countries and in different currencies, more comparable.

1. *Resource utilisation:* The types and quantities of resource utilisation differ between countries. For the same disease, patients in Switzerland often receive more medical treatments than in other countries (i.e. they are treated more intensively for an equivalent diagnosis). Therefore a “quantity correction" is necessary. The quantity correction was based on the Organization for Economic Co-operation and Development (OECD) statistics of healthcare expenses per capita, corrected for purchasing power. A correction for differences in resource utilisation levels (unaffected by price levels) was thus achieved (155).
2. *Prices of healthcare services:* The price for the same healthcare service or treatment is often different across countries. A “price correction” was achieved by applying correction factors provided by the OECD. Such purchasing power parities represent the proportional costs for identical products in two countries (156).
3. *Change in costs over time:* Healthcare costs change over time. For eligible cost-effectiveness studies performed in countries other than Switzerland, the two steps described above achieved an adaptation of reported costs. However, the resulting estimates are valid for the same cost year as in the original study. Additional correction for the development of costs over time was necessary. In the case of a specific disease and set of treatment strategies, costs may change over time due to mere price changes but no changes in resource utilisation, or resource utilisation for the treatment of the disease of interest may also change. In our 'base case' approach, we assumed the latter, and that changes in resource utilisation would occur with the same cost impact as at the level of total Swiss health care expenditures. The resulting correction was based on the yearly growth rates of total Swiss healthcare expenditures, as reported by the Swiss Federal Office of Statistics (157).

7.1.5 Synthesis of findings

The resulting different pieces of information were synthesized. This necessarily involved an element of interpretation, but it was an explicit aim to make all related assumptions transparent. Comparisons of the assumptions and of the data used by different cost-effectiveness analyses were made. The discussion was complemented with a critical review of possible sources of uncertainty.

7.2 Results

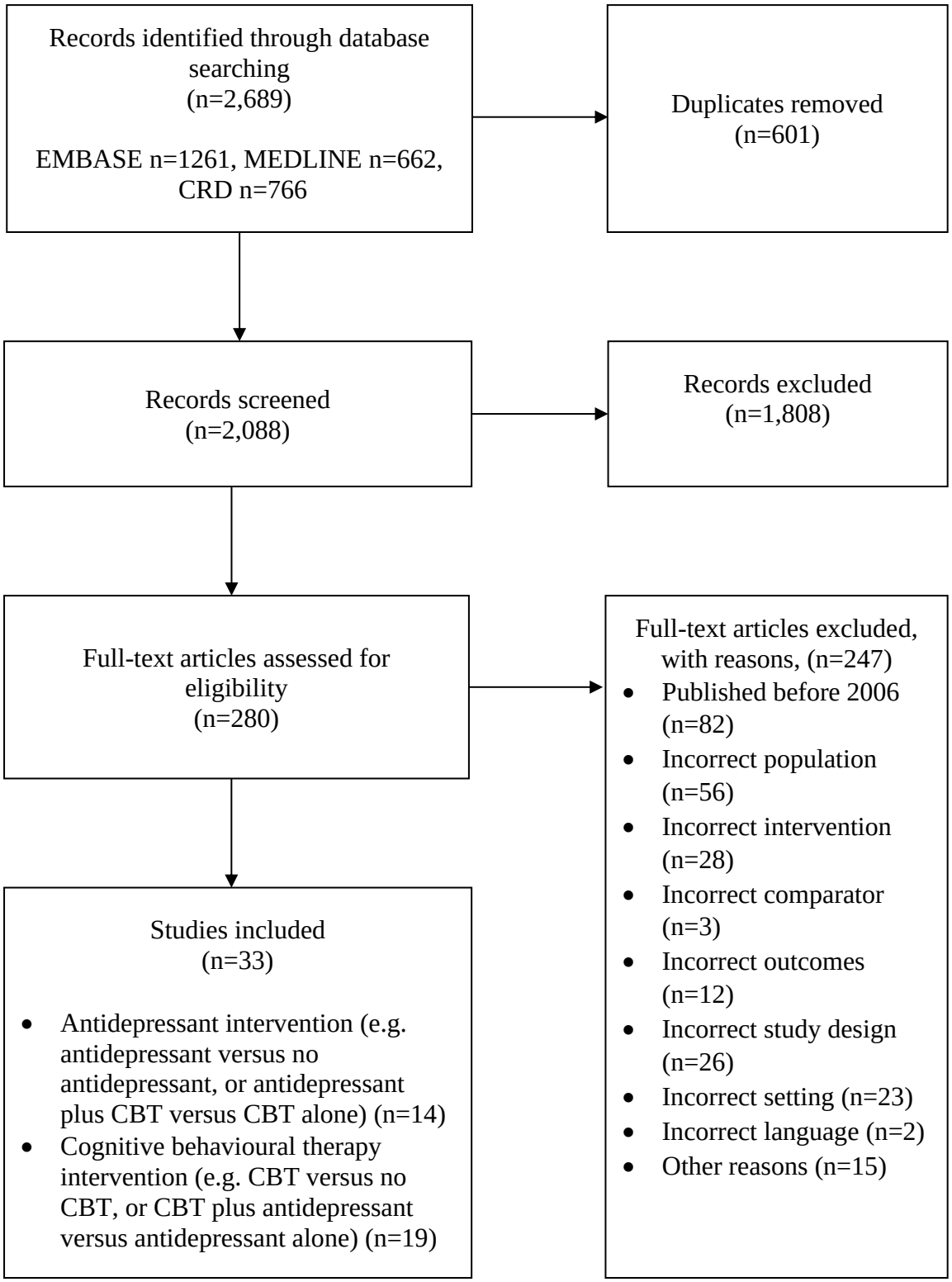
7.2.1 Study selection

A total of 2,689 citations were identified from the searched electronic databases. Following the removal of duplicates, 2,088 full citations were reviewed (Figure 31). Based on title and abstract, the two investigators excluded 1,808 citations due to inappropriate comparator, non-comparative design, character of a review or commentary piece, inappropriate outcome measure, or not a cost-effectiveness / cost-utility analysis. A total of 280 citations were included for full-text review.

Of these 280 citations, 33 were cost-effectiveness analyses which met the inclusion criteria for the review. The remaining 247 studies were excluded due to inappropriate PICO or other reasons (see Figure 31).

The 33 articles fulfilling the inclusion criteria were included in the systematic review and assessed using the CHEERS checklist and the algorithm for transferability assessment described in the methods section. A total of 29 articles fulfilled the transferability criteria, which was needed to make a study qualitatively transferable and thus suitable for numerical adaptation of ICER results to Switzerland.

Figure 31. PRISMA flow chart



7.2.2 Synthesis of characteristics of the identified cost-effectiveness analyses

A total of 33 cost-effectiveness analyses published between 2006 and 2019 were finally included in the systematic review (158–190): 14 of them assessed ADMs as the intervention strategy, whereas 19 cost-effectiveness analyses assessed CBT as the intervention strategy. Table 18 summarizes the study characteristics. The cost-effectiveness analyses were most often carried out for the UK (n=13), Sweden (n=5) and the Netherlands (n=5). Two of the included cost-effectiveness analyses looked at populations with recurrent depression (166,180), and the other 31 cost-effectiveness analyses looked at populations with depression, or substantial depressive symptomology.

The comparators varied across studies. Out of the 14 cost-effectiveness analyses evaluating ADM(s) as an intervention strategy, the comparator was a different type of ADM in 10 studies and was placebo/supportive care/active monitoring in the other four. Among the 19 cost-effectiveness analyses evaluating CBT as an intervention strategy, the comparator was a form of usual care in 12 studies and ADM in five studies. Only two studies used, respectively, behavioural activation or website information for patients as the comparator.

Of the included studies, 16 cost-effectiveness analyses were within-trial analyses and 17 were model-based. The time horizons adopted in the cost-effectiveness analyses, ranged from six weeks to 60 months.

Discounting was reported in nine cost-effectiveness analyses. The remaining articles did not mention it or reported that discounting was not required considering the time horizon of their analyses. Discount rates ranged between 3% and 3.5% for both costs and QALYs and were selected according to the jurisdiction the cost-effectiveness analysis was performed for. Most cost-effectiveness analyses reported carrying out a probabilistic sensitivity analysis.

Table 18: Characteristics of the identified studies

ANTIDEPRESSANT MEDICATIONS (ADMs)					
	Population	**Intervention**	**Comparator(s)**	**Perspective Cost types considered Cost year**	**Modelling approach Time horizon Discounting**
Annemans et al. 2014 Belgium	First-line treatment of MDD	Escitalopram	Citalopram fluoxetine, paroxetine, sertraline, duloxetine, venlafaxine, mirtazapine	Healthcare and societal Direct and indirect costs 2011	Decision tree 12 months NR
Armstrong et al. 2007 USA	MDD	Escitalopram	Sertraline	Managed care organisation Direct costs Presumably 2005	Decision tree 6 months NR
Benedict et al. 2010 Scotland	Moderate to severe MDD in primary care (>= 19 on the Hamilton Depression Scale (HAMD-17))	Duloxetine	Venlafaxine, mirtazapine, and SSRIs (as a group).	Healthcare Direct costs 2007	Markov model 12 months NR
Hollingworth et al. 2019 UK	Eligible participants aged between 18 and 74 were identified in primary care with depression or low mood during the past 2 years and had not received antidepressant or anti-anxiety medication in the previous 8 weeks.	Sertraline	Placebo	Healthcare and societal Direct and indirect costs 2017/2018	Within-trial analysis ~ 3 months (12 weeks) NR
Kendrick et al. 2009 UK	Patients diagnosed with new episodes of depression, were potentially in need of treatment, and had at least one somatic symptom on the Bradford Somatic Inventory	Selective serotonin reuptake inhibitor (SSRI) treatment plus supportive care. The SSRI initially prescribed was either fluvoxamine, sertraline, paroxetine, citalopram or escitalopram.	Supportive care alone	Healthcare Direct costs 2006/2007	Within-trial analysis 6 months NR
Kendrick et al. 2006 UK	Adults diagnosed with depression by their GP and accepting antidepressant treatment.	Fluoxetine, paroxetine or sertraline (SSRIs)	Amitriptyline, dothiepin or imipramine (tricyclic antidepressants)	Healthcare Direct costs 2001/2002	Within-trial analysis 12 months NR
Lenox-Smith et al. 2009 UK	Acute MDD	First line venlafaxine; second line fluoxetine	Various combinations of venlafaxine, fluoxetine and amitriptyline; administered in different orders (first-line/second-line)	Healthcare Direct costs 2006	Decision tree6 months 6 months NR

Maniadakis et al. 2013 Greece	MDD	Agomelatine	Branded and generic venlafaxine, escitalopram, fluoxetine and sertraline.	Societal Direct and indirect costs 2012	Markov model 24 months 3.5%
Mencacci et al. 2013 Italy	Patients with a first diagnosis of MDD receiving an antidepressant for the first time	Escitalopram	Citalopram, sertraline, paroxetine, fluoxetine, fluvoxamine, duloxetine, or venlafaxine	Healthcare Direct costs 2013	Decision tree 12 months NR
Nordstrom et al. 2012 Sweden	Adult patients (18-65 years) with moderate to severe MDD seeking treatment in a primary care setting	Escitalopram	Generic venlafaxine	Societal Direct and indirect costs 2009	Decision tree 6 months NR
Nuijten et al. 2012 Netherlands	MDD	Escitalopram	Venlafaxine, citalopram.	Direct and indirect costs 2010	Decision tree 6 months NR
Ramsberg et al. 2012 Sweden	MDD in primary care which is not yet treated	Escitalopram	Citalopram, duloxetine, fluoxetine, fluvoxamine mirtazapine, paroxetine, reboxetine, sertraline and venlafaxine	Healthcare and societal Direct and indirect costs 2009	Decision tree 12 months NR
Rubio-Valera et al. 2019 Spain	Adult patients with a new episode of MDD.	Antidepressants (SSRIs)	Active monitoring (monitoring the patient over 10-12 weeks through a recommended 6-8 follow-up visits)	Healthcare Direct costs 2015	Within-trial analysis 12 months NR
Sobocki et al. 2008 Sweden	Recurrent MDD. At least 2 MDD episodes in past 5 years. Received venlafaxine XR for 6 months prior to randomisation and responded to this.	Maintenance treatment with venlafaxine for two years	Placebo	Societal Direct and indirect costs 2005	Markov model 24 months 3.0%
CBT					
Study Country	**Population**	**Intervention**	**Comparator(s)**	**Perspective Cost types considered Cost year**	**Modelling approach Time horizon Discounting**
Duarte et al. 2017 UK	Presenting with depression according to a self-report questionnaire [score of ⩾10 on the Patient Health Questionnaire (PHQ-9) depression severity instrument]	Internet-based CBT Free-to-use computerized CBT programme (MoodGYM). Five, 1 h-long modules, usually taken weekly.	Usual GP care alone	Healthcare Direct costs 2011/2012	Within-trial analysis 24 months 3.5%
Evans-Lacko et al. 2016 Germany	Employed adults with mild (F32.0, F33.0), moderate (F32.1, F33.1) or severe MDD (F32.2/F32.3,	CBT	Pharmacotherapy (citalopram)	Healthcare Direct costs 2013	Decision tree 27 months 3.4%

	F33.2/F33.3) based on ICD-10 diagnoses	3 months acute treatment, 12 months maintenance treatment, and 12 months follow-up.			
Geraedts et al. 2015 Netherlands	Employees with elevated depressive symptoms (i.e., scoring 16 or higher on the Center for Epidemiologic Studies Depression Scale [CES-D]), average CES-D score of samples was between 25.7 and 26.1.	Internet-based CBT Happy@Work: internet intervention with minimal support, partly comprising of problem-solving treatment cognitive therapy. 6 weekly lessons and optional 1-week extra time in case of delay.	CAU group only received an e-mail with the randomization outcome and were advised to consult their (occupational) physician or a psychologist if they wanted treatment for their depressive symptoms.	Employer and societal Direct and indirect costs 2012	Within-trial analysis 12 months NR
Gerhards et al. 2010 Netherlands	At least mild to moderate depressive complaints (diagnosed by BDI-II score >=16) for at least 3 months	Internet-based CBT Unsupported online program "Colour Your Life" consisting of 8 weekly sessions plus a ninth booster session.	Usual care	Societal Direct and indirect costs 2007	Within-trial analysis 12 months NR
Health Quality Ontario 2019 Canada	Adults with mild to moderate MDD	Internet-based CBT Guided by a therapist, 8-10 weekly sessions	Usual care	Societal Direct and indirect costs 2018	Decision tree 12 months NR
Hollinghurst et al. 2010 UK	Patients aged 18-75 with a new ICD-10 diagnosis of depression	Internet-based CBT Up to 10 sessions of 55 minutes, to be completed within 4 months.	Usual care	Healthcare Direct costs 2007	Within-trial analysis 8 months NR
Holst et al. 2018 Sweden	All patients aged ≥18 years with a probable diagnosis of mild to moderate depression (Montgomery Åsberg Depression Rating Scale—self rating version (MADRS-S) score <35)	Internet-based CBT Commercially available program consisting in 7 modules accessible for 12 weeks.	Usual care	Societal Direct and indirect costs 2013	Within-trial analysis 12 months NR
Kaltenthaler et al. 2006 UK	Patients with depression in a primary care setting	Internet-based CBT Program "Beating the blues" consisting in 15-minute introductory video and eight 1-hour interactive computer sessions.	Usual care for 2 months	Healthcare Direct costs NR	Decision tree 18 months 3.5%
Koeser et al. 2015 UK	Adults with moderate or severe MDD	CBT 16 sessions during the acute treatment phase and two additional 'booster' sessions after that.	Pharmacotherapy (assumed to be 20 mg daily dose of citalopram over 15 months)	Healthcare Direct costs 2012	Decision tree 27 months 3.5%
Kraepelien et al. 2018 Sweden	Aged 18–67 years; and present with ≥10 on the Patient Health Questionnaire (PHQ-9)	Internet-based CBT Individually tailored CBT for 12 weeks.	Usual care	Healthcare and societal Direct and indirect costs 2012	Within-trial analysis 3 months NR

Kuyken et al. 2015 UK	Recurrent MDD, currently on anti-depressants, and had 3 or more previous MDD episodes	CBT Mindfulness-based cognitive therapy (MBCT) in which participants learn mindfulness practices and cognitive-behavioural skills. The programme consists of eight 2·25 h group sessions, normally over consecutive weeks, and four refresher sessions offered roughly every 3 months for the following year.	Patients in a maintenance antidepressant group, who received support from their GPs to maintain a therapeutic level of ADM for the 2-year follow-up period	Healthcare and societal Direct and indirect costs 2011/2012	Within-trial analysis 24 months 3.5%
Phillips et al. 2014 UK	Employees aged over 18 years and met the following criterion: on the Patient Health Questionnaire-9 (PHQ-9), the employee scored 2 or more on five of the nine items, including 2 or more on item 1 (little interest in doing things) or item 2 (feeling hopeless). To be eligible the employee also had to confirm that at least one of the items identified as a problem for them made it difficult to work, take care of things at home, or get along with other people.	Internet-based CBT Free-to-use computerized CBT programme (MoodGYM). Five, 1 h-long modules, usually taken weekly.	Website links sent weekly to participants in the control arm	Societal Direct and indirect costs NR	Within-trial analysis ~ 1.5 months (6 weeks) NR
Richards et al. 2016 UK	MDD adults	CBT Maximum of 20 face-to-face 1-hour sessions over 16 weeks (NB: in the article it was the comparator)	Behavioural activation (BA) (NB: in the article it was the intervention)	Healthcare Direct costs 2013/2014	Within-trial analysis 18 months 3.5%
Romero-Sanchiz et al. 2017 Spain	18-65 years, BDI-II score of 14-28 (indicating mild/moderate symptoms); symptoms lasting longer than 2 weeks	CBT Low-intensity therapist-guided program called “Smiling is fun” consisting of 10 modules.	Usual care	Societal Direct and indirect costs 2014	Within-trial analysis 12 months NR
Ross et al. 2019 USA	Adults with newly diagnosed MDD.	CBT NB: Intervention details were not described.	Second-generation antidepressant (SGA)	Healthcare and societal Direct and indirect costs 2014	Markov model 12 and 60 months 3.0%
Simon et al. 2006 UK	Moderate and severe depression in secondary care.	CBT plus Fluoxetine	Pharmacotherapy (3 months of daily 40 mg fluoxetine)	Healthcare Direct costs 2002/2003	Decision tree 15 months NR
Solomon et al. 2015 Australia	Mild to moderate depression	Internet-based CBT	Usual care, in this case drug treatment with a prescribed antidepressant for an acute	Healthcare Direct costs 2013/2014	Decision tree ~ 6.5 months (28 weeks) NR

		16 sessions of 50 minutes. 3 months acute treatment, 12 months follow-up, no maintenance therapy.	depressive episode, plus a 21-week maintenance phase of drug therapy after remission of symptoms		
Stant et al. 2009 Netherlands	Patients diagnosed with a current, or only very recently in partial remission, DSM-IV major depression	CBT Brief CBT followed by Psychoeducational Prevention Program (PEP) (CBT-Enhanced PEP). Patients had to attend 10 to 12 individual 45 minute sessions.	Usual care	Societal Direct and indirect costs 2003	Within-trial analysis 36 months 0%
Warmerdam et al. 2010 Netherlands	Center of Epidemiologic Studies Depression scale (CES-D) >= 16 (mean score of participants at baseline = 31.7)	CBT 8 weekly lessons followed by a booster session after 12 weeks.	Usual care	Societal Direct and indirect costs 2007	Within-trial analysis ~ 3 months (12 weeks) NR

Abbreviations: CBT=cognitive behavioural therapy; CES-D=Center for Epidemiological Studies-Depression; NR= not reported; MDD= major depressive disorder; PHQ-9= Patient health questionnaire depression module

7.2.3 Synthesis of the main results of the identified cost-effectiveness analyses

This chapter summarises the main results of the identified cost-effectiveness analyses by treatment group (ADMs or CBT). Further detail is provided in the appendices. Summary tables of cost-effectiveness results adapted for Switzerland for the different comparisons, are provided later in the section on adapted results for Switzerland.

7.2.3.1 Antidepressants

We identified 14 cost-effectiveness analyses of ADMs published between 2006 and 2019. The time horizons used were mainly 12 months or less. Only in the cost-effectiveness analysis by Maniadakis et al. a Markov model was created to project costs and QALYs over a two year period (168). Five studies were set in the United Kingdom (UK), three in Sweden, five in other European countries, and one was set in the USA.

The most frequently investigated treatments were escitalopram (a SSRI), venlafaxine (SNRI), sertraline (SSRI), duloxetine (SNRI), and SSRIs considered as a group. The next chapters briefly summarize the results for these antidepressant groups.

Escitalopram

Six cost-effectiveness analyses specifically evaluated the cost-effectiveness of escitalopram, relative to another ADM or set of anti-depressants (158,159,169,171,172,174). The comparators in these studies were either: reboxetine, mirtazapine, fluoxetine mirtazapine combination, citalopram, sertraline, paroxetine, fluoxetine, fluvoxamine, duloxetine, or venlafaxine. All six cost-effectiveness analyses were model-based.

Full data extractions tables specifying the mean costs and QALYs for the intervention and comparator strategies for each cost-effectiveness analysis, are presented in the appendix.

Four out of six studies investigating escitalopram were funded by Lundbeck SAS (pharmaceutical company), one was funded by Forest Laboratories (pharmaceutical company), and one was investigator-funded.

All six cost-effectiveness analyses found that escitalopram was either dominant (i.e. escitalopram generated lower costs and higher QALYs relative to the comparator) or produced a very low ICER (i.e. it was highly cost-effective). All six cost-effectiveness analyses indicated that escitalopram was cost-effective for the respective jurisdictions.

Escitalopram was evaluated as a specific comparator strategy in one cost-effectiveness analysis published by Maniadakis et al. (168). In this study, escitalopram was dominated by agomelatine (i.e. escitalopram was estimated to generate higher costs and lower QALYs). The cost-effectiveness analysis was conducted using the assumption that the remission rates for agomelatine, escitalopram, and venlafaxine, were equivalent, and this assumption was made due to a lack of relevant data.

Venlafaxine

Two cost-effectiveness analyses evaluated the cost-effectiveness of venlafaxine as intervention strategy. Of these, the cost-effectiveness analysis by Lenox-Smith et al. evaluated venlafaxine as a first-line treatment for acute MDD (followed by second-line fluoxetine) (167), whereas the other cost-effectiveness analysis by Sobocki et al. evaluated venlafaxine as a maintenance treatment for patients with recurrent MDD who had previously responded successfully to venlafaxine treatment (180). Both cost-effectiveness analyses indicated that venlafaxine was cost-effective, with Lenox-Smith et al. estimating an ICER for venlafaxine for acute MDD of Great British Pounds (£) 7,215 per QALY gained or better depending on the comparator. Comparators were various combinations of venlafaxine, fluoxetine and amitriptyline; administered in different orders (first-line/second-line). Sobocki et al. estimating an ICER for venlafaxine compared to placebo for recurrent MDD in Sweden, of United States Dollars ($) 18,548 per QALY gained.

In seven studies, an ADM other than venlafaxine was evaluated as an intervention strategy, with venlafaxine being evaluated as a comparator strategy. Out of these studies, four cost-effectiveness analyses funded by Lundbeck SAS (pharmaceutical company) indicated that escitalopram was more cost-effective than venlafaxine (with very low or dominance for escitalopram), one non-industry funded cost-effectiveness analysis indicated that escitalopram was more cost-effective than venlafaxine (with an ICER for escitalopram of € 3,723 per QALY gained being estimated) (174), one cost-effectiveness analysis indicated that duloxetine was more cost-effective than venlafaxine (with duloxetine estimated to be dominant over venlafaxine) (170), and one cost-effectiveness analysis indicated that agomelatine was more cost-effective than generic venlafaxine (with an ICER for agomelatine of € 1,446 per QALY gained being estimated) (168).

Sertraline

A government-funded cost-effectiveness analysis by Hollingworth et al. evaluated sertraline relative to placebo in the UK (190), and estimated that sertraline was dominant. Sertraline was evaluated as a specific comparator strategy in five other cost-effectiveness analyses. Four of them estimated that sertraline was dominated by escitalopram (158,159,169,174), whereas one cost-effectiveness analysis concluded that sertraline was dominated by agomelatine (168).

Duloxetine

A pharmaceutical industry-funded cost-effectiveness analysis by Benedict et al. evaluated duloxetine relative to other ADMs (venlafaxine, mirtazapine, or SSRIs as a group). in the UK. Depending on the comparator, the estimated ICERs for duloxetine were £6,304 per QALY gained or better (i.e. lower), indicating that duloxetine is cost-effective (170). Duloxetine was evaluated as a comparator strategy in three cost-effectiveness analyses

(158,169,174). In all of them, duloxetine was dominated by escitalopram (i.e. duloxetine was estimated to generate higher costs and lower QALYs).

Selective serotonin reuptake inhibitors (SSRIs) considered as a group

Three cost-effectiveness analyses published by Rubio-Valera et al. (178), Kendrick et al. (162) and Kendrick et al. (163) evaluated the cost-effectiveness of SSRIs versus tricyclic ADMs or usual care. All three were within-trial cost-effectiveness analyses which adopted a healthcare perspective and were funded by the government sector. All analyses suggested that SSRIs were cost-effective relative to the comparators.

Kendrick et al. (2009) conducted a cost-effectiveness analysis based on a 26 week UK trial (identifier: ISRCTN84854789) of 200 participants with depression and at least one somatic symptom (163). The cost-effectiveness analysis compared SSRIs (fluvoxamine, sertraline, paroxetine, citalopram or escitalopram) in combination with supportive care, with supportive care alone (i.e. usual care), and estimated an ICER of £14,854 per QALY gained.

The analyses conducted by Kendrick et al. (2006) were based on the AHEAD trial in the UK, a 12-month trial including 327 patients with depression (162). The study compared SSRIs (fluoxetine, paroxetine or sertraline), with tricyclic ADMs (amitriptyline, dothiepin or imipramine), estimating an ICER of £2,692 per QALY gained.

The cost-effectiveness analysis published by Rubio-Valera et al. was based on the INFAP trial in Spain (178), which was a 12 month trial including 263 patients with major depression. The analysis compared SSRIs with active monitoring and estimated an ICER of €6,142 per QALY gained.

Other ADMs

A pharmaceutical industry-funded cost-effectiveness analysis by Maniadakis et al. evaluated agomelatine compared to other ADMs (escitalopram, branded and generic venlafaxine, fluoxetine, or sertraline.) in Greece (168). Depending on the comparator, estimated ICERs for agomelatine were €3,303 per QALY gained or better (i.e. lower). The cost-effectiveness analysis was conducted using the assumption that the remission rates for agomelatine, escitalopram, and venlafaxine were equivalent (this assumption was made due to a lack of relevant data).

Various other ADMs were evaluated as comparator strategies across the cost-effectiveness analyses (e.g. paroxetine, mirtazapine, fluoxetine, citalopram, amitriptyline, fluvoxamine, reboxetine). In most cases these anti-depressants were indicated as having an unfavourable cost-effectiveness profile relative to another antidepressant (e.g. escitalopram, venlafaxine, duloxetine, sertraline, or agomelatine).

7.2.3.2 Cognitive behavioural therapy (CBT)

We identified 19 cost-effectiveness analyses for CBT published between 2006 and 2019. All 19 cost-effectiveness analyses were funded by a public sector organisation (usually a government agency). Eight cost-effectiveness analyses were from the UK, four were from Netherlands, and seven were conducted in other countries.

Methodological characteristics of the CBT-based cost-effectiveness analyses

Twelve cost-effectiveness analyses were within-trial analyses, whereas seven were model-based studies. All 12 within-trial cost-effectiveness analyses were based on a different underlying trial, with the sample sizes of the trials ranging from 90 participants in the cost-effectiveness analysis by Holst et al. (160), to 945 participants in the cost-effectiveness analysis by Kraepelien et al. (165).

The time horizon of the CBT-based cost-effectiveness analyses varied substantially; from six weeks for the cost-effectiveness analysis by Phillips et al. (also, this cost-effectiveness analysis only provided very partial reporting of items from the CHEERS checklist) (173), to 36 months in a within-trial cost-effectiveness analysis published by Stant et al. (183).

For 11 cost-effectiveness analyses, a public sector perspective (e.g. healthcare or government perspective) was adopted for the analysis. Six studies adopted a societal perspective (186). An employer perspective was adopted for one cost-effectiveness analysis. The perspective adopted for the cost-effectiveness analysis published by Evans-Lacko was unclear (but according to the reported costs it was presumably a healthcare perspective).

Populations for the CBT-based cost-effectiveness analyses

The populations of the CBT-based cost-effectiveness analyses were judged to either have clinical depression or substantial depressive symptomology. The criteria for diagnosis of depression varied between the studies: the patient health questionnaire (PHQ-9), the BDI-II, DSM-IV, MADRS-S and the CES-D were among to criteria used across the different cost-effectiveness studies/underlying trials.

Five cost-effectiveness analyses were specifically for populations with mild to moderate depression (160,176,182,187,188), two were specifically for populations with moderate to severe depression (164,179), and one within-trial cost-effectiveness analysis by Kuyken et al. was specifically for a population with recurrent MDD (in this study, participants at baseline had to have had three or more previous MDD episodes) (166).

Interventions and comparators used for the CBT-based cost-effectiveness analyses

For 11 cost-effectiveness analyses, the form of CBT that was evaluated was digital or computerised CBT (internet-based CBT), whereas for the remaining cost-effectiveness analyses the form of CBT was either unspecified or was face-to-face CBT. The number of CBT sessions assumed to be offered to participants was variable: in one within-trial cost-

effectiveness analysis, trial participants in the CBT group underwent five CBT sessions (173); in another, model-based study, participants were assumed to each undertake 18 CBT sessions (164). Two within-trial cost-effectiveness analyses by Geraedts et al. (186) and Phillips et al. (173) were for workplace-based CBT for employees with substantial depression symptomology, measured using the CES-D in the cost-effectiveness analysis by Geraedts et al. and using the PHQ-9 in the cost-effectiveness analysis by Phillips et al. Study comparators varied across CBT-based studies. Usual care was described as the comparator for 12 cost-effectiveness analyses, an antidepressant was the comparator for five cost-effectiveness analyses, and a non-CBT-based psychological intervention was the comparator for two analyses.

Cost-effectiveness results of the CBT-based cost-effectiveness analyses

Of the 19 CBT-based studies, eight cost-effectiveness analyses indicated that CBT was cost-effective, five within-trial cost-effectiveness analyses indicated that CBT was dominated from the comparator. In six cost-effectiveness analyses the results were considered uncertain or neutral (i.e. CBT was not cost-effective relative to the comparator). Cost-effectiveness results for CBT were favourable in three out of the six CBT-based analyses using a societal perspective, and in four out of the 11 CBT-based analyses adopting a healthcare system perspective.

7.2.4 Measurement of costs and data sources

This chapter summarises the main cost assumptions and cost-related data sources of the identified cost-effectiveness analyses. More details for each included study are provided in the appendices.

7.2.4.1 ADMs

Medication costs and outpatient healthcare costs were estimated and included in all 14 cost-effectiveness analyses evaluating ADMs. Inpatient costs were also included in the majority of the analyses: only in the cost-effectiveness analysis by Armstrong et al. (159) inpatient costs were not included, whereas in the cost-effectiveness analysis by Sobocki et al. it was not clear whether or not inpatient costs were included (180). Costs of specific laboratory tests were explicitly included in four cost-effectiveness analyses (167,168,172,178).

Of the six cost-effectiveness analyses of ADMs which adopted a societal perspective (168,171,172,180), all included productivity costs, and none included out-of-pocket costs to patients.

In terms of methods to estimate healthcare resource costs, six cost-effectiveness analyses obtained estimates from the published literature which generally appeared to be relevant to the setting of the study, four cost-effectiveness analyses obtained estimates from expert(s), two within-trial cost-effectiveness analyses undertook primary resource use data collection using a version of the Client Services Receipt Inventory and combined this

data with medical records (163,178), and two other within-trial cost-effectiveness analyses obtained resource use data by combining patient self-reporting and medical practice records (162,190).

7.2.4.2 CBT

CBT intervention costs were estimated and included in 16 out of 19 cost-effectiveness analyses included in this review. In two cost-effectiveness analyses it was unclear whether or not CBT intervention costs were included (173,185): in one case, the form of CBT (internet-based or face-to-face) was not stated, (185) in the other case, the form of CBT was internet-based) (173). In the cost-effectiveness analysis assessing an internet-based CBT intervention published by Romero-Sanchiz et al. (176), CBT intervention costs were not included. The authors reported that using internet-based CBT provided no additional costs.

Outpatient costs appeared to be included in all cost-effectiveness analyses of CBT, medication costs were included in all but two cost-effectiveness analyses (165,186), and inpatient costs appeared to be included in all but seven cost-effectiveness analyses of CBT. In the two CBT-based cost-effectiveness analyses that did not include medication costs (165,186), medication costs may be relevant components of the comparator strategies (which were treatment as usual).

Of the eight cost-effectiveness analyses of CBT adopting a societal perspective, seven clearly stated that productivity costs were included (only in Kaltenthaler et al. it was unclear whether productivity loss was considered or not), and four additionally included out-of-pocket costs to patients.

Among the 12 within-trial cost-effectiveness analyses of CBT, three cost-effectiveness analyses used the Trimbos and iMTA Questionnaire on Costs Associated with Psychiatric Illness (TIC-P) to estimate healthcare resource use (165,184,186), two cost-effectiveness analyses used the Adult Service Use Schedule (AD-SUS) (166,175), and two cost-effectiveness analyses used the Client Service Receipt Inventory (173,176). Among the seven model-based cost-effectiveness analyses of CBT, four cost-effectiveness analyses used resource use estimates based on the published literature (164,177,179,182). The remaining three cost-effectiveness analyses defined resource use estimates by combining data from the published literature with a range of assumptions (161,185,188).

7.2.5 Measurement and sources of clinical effectiveness and health related quality of life

This chapter summarises the main effectiveness assumptions and related data sources of the identified cost-effectiveness analyses. QALY differences in the included model-based cost-effectiveness analyses were driven by different times spent in health states (e.g. mild/moderate/severe depression state or remission status state) or quality of life differences measured at different time points from baseline. Most cost-effectiveness analyses appeared to assume no mortality difference between intervention and comparator. Only the cost-effectiveness analysis by Sobocki et al. (2008) accounted for

the substantially elevated risk of death for someone having a depressive episode (180). More details for each included study are provided in the appendices.

7.2.5.1 Clinical inputs for ADMs

Six cost-effectiveness analyses of ADMs estimated that remission or response probabilities were highest for escitalopram relative to all comparators evaluated in the cost-effectiveness analyses. Consequently, these cost-effectiveness analyses suggested that there was favourable evidence to support the cost-effectiveness of escitalopram (158,159,169,171,172,174). The effectiveness estimates were based on a systematic review/meta-analysis in three studies (158,172,174). In three other studies the effectiveness assumptions were based on a review (169), on individual clinical trials (159), and on a pooled analysis of two RCTs (171), respectively.

One cost-effectiveness analysis by Maniadakis et al. funded by Servier Hellas (168), assumed that the remission rates for agomelatine, escitalopram, and venlafaxine were equivalent (they made this assumption due to a lack of relevant data). They acknowledged that this assumption may be considered a limitation of their analysis.

In the cost-effectiveness analysis published by Benedict et al. and funded by Eli Lilly and Boehringer Ingelheim (170), the clinical probabilities for response and remission were estimated to be higher for duloxetine and venlafaxine, whereas they were relatively lower for SSRIs (as a group) and for mirtazapine. The estimates for clinical probabilities were obtained from a broad range of Eli Lilly trials and meta-analysis studies.

7.2.5.2 Clinical inputs for CBT

In four out of seven model-based cost-effectiveness analyses, the clinical probabilities were clearly more favourable for CBT relative to the comparator (164,177,179,185). In the cost-effectiveness analysis by Solomon et al. (182), effect sizes appeared to be more favourable for CBT relative to antidepressants, with effect sizes for CBT obtained from the RCT of the specific form of CBT that was being evaluated ("myCompass"). Similarly, in the cost-effectiveness analysis by Kaltenthaler et al. the transition probabilities between depression health states generally appeared to be more favourable for CBT relative to treatment as usual; with the effect sizes obtained from the trial of the specific form of CBT that was being evaluated by the authors ("Beating the Blues") (161). In the cost-effectiveness analysis by Health Quality Ontario (2019) for guided CBT compared to usual care, the probability of response was slightly higher for guided CBT (0.73 versus 0.70 in usual care which were obtained from an external systematic review), but the probability of recovery was lower for guided CBT (0.48 as obtained from a previously published meta-analysis, versus 0.62 in usual care) (188).

7.2.5.3 Utility inputs for ADMs

As described earlier, we identified 14 cost-effectiveness analyses evaluating an ADM or a combination of ADMs as the intervention.

In the model-based cost-effectiveness analyses of ADMs, there was considerable heterogeneity in terms of the sources used to obtain utility estimates for the health states. The most commonly reported main source of utility estimates were the Swedish HEADIS study, used in two cost-effectiveness analyses in Sweden, (171,180) and an observational study by Sobocki et al. (2006), which was used as the main source for utility estimates in two other cost-effectiveness analyses (158,174). The remaining model-based cost-effectiveness analyses of ADMs used health state utility estimates from a variety of sources which included Nordstrom et al. (2009), an expert panel, Sullivan et al. (2004), Revicki and Wood (1998), or clinical trial data from Eli Lilly.

Utility estimates for people with depression before remission ranged from 0.49 in the cost-effectiveness analysis by Mencacci et al. , which used an expert panel to estimate it (169), to 0.59 in the cost-effectiveness analysis by Lenox-Smith et al., which used the average of six studies to estimate it (unfortunately, the exact sources in Lenox-Smith et al. were not referenced) (167).

Utility estimates for people with remitted depression ranged from 0.79 in a cost-effectiveness analysis published by Benedict et al. (estimated directly from the duloxetine drug trials, and assuming that the utility increased to 0.86 if the remission was sustained without requiring further treatment based on a published study) (170), to 1.00 in the cost-effectiveness analysis by Lenox-Smith et al., which was the assumed utility for a non-depressed subject (167).

In four cost-effectiveness analyses of ADMs, utility decrement estimates for adverse events were obtained from a study by Sullivan et al. (109,159,171,172). Other model-based cost-effectiveness analyses of ADMs did not explicitly consider disutility due to adverse events and may have instead implicitly assumed it to be covered by the utilities for the main health states.

In three out of four within-trial cost-effectiveness analyses, utility estimates were based on EQ-5D questionnaires completed by the study participants (162,178,190). Similarly, in Kendrick et al. the patients were invited to complete the SF-36 questionnaire (163).

7.2.5.4 Utility inputs for CBT

For all 12 within-trial cost-effectiveness analyses of CBT, the EQ-5D instrument was administered to trial participants in order to estimate QALYs.

In four model-based cost-effectiveness analyses of CBT, utilities were assigned to health states which were primarily defined according to severity of depression (161,179,182,188). In the study conducted by Health Quality Ontario, a utility increment was applied to patients who received CBT treatment based on published utility or cost-effectiveness studies for depression (an increment from 0.79 to 0.84 was assumed for patients who received guided CBT (guided CBT is CBT guided by a therapist, clinician or coach) (188). In the two cost-effectiveness analyses investigating CBT among patients with severe depression, utilities ranged from 0.30 in the cost-effectiveness analysis by Simon et al., obtained from an external utility study of 70 patients with MDD/dysthymia

(179), to 0.38 in the cost-effectiveness analysis by Kaltenthaler et al. (161), obtained from an external study of the EQ-5D scores of 62 patients.
In three model-based cost-effectiveness analyses of CBT, utilities were assigned to health states which were primarily defined according to remission status (164,177,185). The utility values were not clearly stated in the cost-effectiveness analysis by Evans-Lacko et al. (185). The utility values in the cost-effectiveness analysis of newly diagnosed MDD patients used by Ross et al. were estimated at 0.85 for MDD patients in remission, 0.72 for MDD patients with response, and 0.58 for patients without response (177), and were derived from a prospective study of treated MDD patients by Sapin et al. (191). Similarly, the utility values in a cost-effectiveness analysis of moderate or severe MDD patients by Koeser et al. were estimated at 0.80 for remitters, 0.62 for responders, and 0.48 for non-responders (Koeser at el. used data from a trial by Kuyken et al. for patients with recurrent depression) (164).

7.2.6 Assessment of quality and transferability

The quality of reporting according to the CHEERS checklist was generally high, with 27 out of 33 articles reporting information for more than 80% of the checklist items, and six studies reporting information for 60-79% of the checklist items (Phillips (173), Lenox-Smith (167), Armstrong (159), Nuijten (172), Mencacci (169), Rubio-Valera (178)).
Only four study were considered as not qualitatively transferable to Switzerland since they did not report fundamental information like costing year, study perspective, or detailed cost and utility results for both intervention and comparator (Phillips (173), Rubio- Valera (178), Kaltenthaler (161), Sobocki (180)).

7.2.7 Adaptation of economic evaluations results to Switzerland and differences observed between studies

In this chapter the results of the identified cost-effectiveness analyses that were considered transferable are presented after adapting them for Switzerland. The adaptation included a correction for different levels of resource utilisation, for different prices of healthcare services, and for change in level of resource utilisation and prices over time. Subsequently, adapted ICERs were calculated. As already mentioned, this process cannot be interpreted as achieving realistic ICERs for Switzerland but intends to achieve a certain approximation of cost-effectiveness levels to be expected for Switzerland and improve the comparability of studies from different countries.

7.2.7.1 Antidepressants

Escitalopram

Six cost-effectiveness analyses compared escitalopram with another ADM or set of anti-depressants (158,159,169,171,172,174). After cost adaptation, the costs of escitalopram ranged from CHF 1,336 in Armstrong et al. (time horizon 6 months) to CHF 5,963 in Mencacci et al. (time horizon 12 months) from a healthcare perspective. From a societal

perspective, the costs ranged from CHF 2,144 in Nordstrom et al. (time horizon 12 months) to CHF 40,290 in Nuijten et al. (time horizon 26 weeks). The treatment with escitalopram resulted to be cost saving in all comparisons except two (cost savings ranged between CHF 3 and CHF 4,634). In Annemans et al. escitalopram was more expensive (cost difference CHF 40) and more effective (QALY difference 0.003) than venlafaxine (ICER CHF 13,477 per QALY gained, 12-month time horizon, healthcare perspective). Similarly, in Ramsberg et al. it was more expensive (cost difference CHF 4) and more effective (QALY difference 0.0036) than venlafaxine (ICER CHF 1,130 per QALY gained, 12-month time horizon, societal perspective). Table 20 summarizes the results of the cost adaptation for escitalopram versus other antidepressants and resulting cost-effectiveness estimates. In both studies providing results using both healthcare and societal perspective, the cost difference in favour of escitalopram was more pronounced using a societal perspective (158,174)

Venlafaxine

Table 21 summarises the results of the cost adaptation for venlafaxine. Venlafaxine was investigated in seven cost-effectiveness analyses as either intervention or comparator (Annemans, Benedict, Lenox-Smith, Maniadakis, Mencacci, Nordstrom Ramsberg). When compared with escitalopram, venlafaxine was in most cases dominated (i.e. was more expensive but less effective), or less expensive but less effective (see ICERs in the Table of escitalopram versus other ADMs). In contrast, when compared to other ADMs (e.g. citalopram, duloxetine, fluoxetine, paroxetine, sertraline), venlafaxine was generally considered a dominant strategy. In Lenox-Smith et al. a treatment strategy with venlafaxine followed by fluoxetine had an ICER of CHF 2,801 per QALY gained if compared to a strategy with fluoxetine followed by venlafaxine, while it was a dominant strategy if compared to other treatment combinations (from a healthcare perspective). In Benedict et al. venlafaxine had ICERs of CHF 31,601 per QALY gained when compared to mirtazapine and of CHF 58,296 per QALY gained when compared to SSRIs.

Sertraline

Six cost-effectiveness analyses compared sertraline with placebo or a set of anti-depressants(158,159,168,169,174,190). Sertraline was considered a dominant strategy when compared to citalopram (from both healthcare and societal perspectives). According to Mencacci et al. and Hollingworth et al., it was also the dominant strategy when compared to fluvoxamine and placebo, respectively (healthcare perspective). The comparisons with paroxetine or fluoxetine led to discordant results (in some cases sertraline was dominant, in other cases it was the opposite). If compared to duloxetine, sertraline was often less expensive but also less effective (only in one case it was dominated by duloxetine). Finally, sertraline was dominated when compared to escitalopram, venlafaxine, and agomelatine (from both healthcare and societal perspectives).

Duloxetine

Duloxetine was evaluated as a comparator strategy in four cost-effectiveness analyses. In three studies duloxetine was dominated by escitalopram (from both healthcare and societal perspectives) (158,169,174). Concerning the comparison with venlafaxine, there were discordant results: according to Annemans et al., Ramsberg et al., and Mencacci et al., duloxetine was dominated by venlafaxine (from both healthcare and societal perspectives). In contrast, according to Benedict et al., duloxetine was less expensive and more effective than venlafaxine (from a healthcare perspective). If compared to citalopram, duloxetine had ICERs ranging from CHF 484 to CHF 13,031 per QALY gained from a healthcare perspective. Using a societal perspective, it was considered a dominant strategy (in Ramsberg et al.) or had a ICER of CHF 7,581 per QALY gained. Comparison with other ADMs (e.g. mirtazapine, paroxetine, or sertraline) are reported in Table 23.

Other antidepressants

Table 24 summarizes the results of two studies investigating SSRIs as a whole group as well as the results from Maniadakis et al. (comparing agomelatine with other ADMs). According to Benedict et al., SSRIs were dominant if compared to mirtazapine and had ICERs of CHF 26,106 and CHF 58,296 per QALY gained when compared to duloxetine and venlafaxine, respectively (healthcare perspective). In Maniadakis et al. agomelatine was estimated to be the dominant strategy when combined with sertraline, escitalopram, fluoxetine (societal perspective with non-generic prices). If compared to venlafaxine, the ICER was CHF 3,244 per QALY gained. If assuming a threshold of CHF 100,000 per QALY gained, based on the results of the three studies SSRIs as a whole group, as well as agomelatine, appear to be cost-effective in Switzerland.

Table 19. Summary of adapted cost-effectiveness results calculated for Switzerland

INTERVENTION	COMPARATOR	NUMBER OF ADAPTED COST-EFFECTIVENESS ICER RESULTS FOR SWITZERLAND	NUMBER OF ICERs WHICH INDICATE INTERVENTION IS MORE CLINICALLY EFFECTIVE, AND MAY BE COST-EFFECTIVE (ICER BELOW CHF 100,000 per QALY/DOMINANT)
Escitalopram	Citalopram	6	6
	Duloxetine	5	5
	Fluoxetine	5	5
	Fluvoxamine	1	1
	Mirtazapine	4	4
	Paroxetine	5	5
	Sertraline	6	6
	Venlafaxine	7	7
Venlafaxine	Agomelatine	1	0
	Amitriptyline	2	2
	Citalopram	5	5
	Duloxetine	6	5
	Escitalopram	7	0
	Fluoxetine	8	8
	Fluvoxamine	1	1

	Mirtazapine	5	1
	Paroxetine	6	6
	Sertraline	6	6
	SSRIs	1	1
Duloxetine	Citalopram	5	5
	Escitalopram	5	0
	Fluoxetine	5	2
	Mirtazapine	5	3
	Paroxetine	5	4
	Sertraline	5	3
	SSRIs	1	1
	Venlafaxine	6	1
SSRIs	Duloxetine	1	1
	Venlafaxine	1	1
	Mirtazapine	1	1
	Usual care	1	1
	Tricyclic antidepressant	1	1
Agomelatine	Venlafaxine	1	1
	Sertraline	1	1

	Escitalopram	1	1
	Fluoxetine	1	1
Sertraline	Agomelatine	1	0
	Citalopram	5	5
	Duloxetine	5	0
	Escitalopram	7	0
	Fluoxetine	6	5
	Fluvoxamine	1	1
	Mirtazapine	4	0
	Paroxetine	5	3
	Placebo	2	2
	Venlafaxine	6	0
CBT+AD	ADM alone	3	3
Internet-based CBT	Usual care	11	8
CBT (face-to-face implied)	Behavioural activation	1	0
	Usual care	1	0
	Antidepressants	8	4

Interpretation example 1: there were five studies comparing escitalopram with duloxetine (as either intervention or comparator), and all of them suggested that escitalopram was the dominant option or was cost-effective if compared to duloxetine.
Interpretation example 2: there were 11 studies comparing internet-based CBT with usual care. Eight of them suggested that internet-based CBT was the dominant option or was cost-effective if compared to usual care.
Abbreviations: ADM= antidepressant medication; CBT= cognitive behavioural therapy; ICER= incremental cost-effectiveness ratio

Table 20. Cost adaptation of escitalopram versus other antidepressant medications (ADMs) and resulting ICERs, ordered by perspective and comparator.

Author	Intervention	Intervention costs (CHF)	Intervention QALY	Comparator	Comparator costs (CHF)	Comparator QALY	Cost difference	QALY difference	ICER (CHF per QALY gained)	Time Horizon	Perspective
Annemans et al. 2014	Escitalopram	2853	0.701	Citalopram	3151	0.686	-298	0.015	Escitalopram dominates	12 months	Healthcare
Mencacci et al. 2013	Escitalopram	5963	0.732	Citalopram	6203	0.720	-240	0.012	Escitalopram dominates	12 months	Healthcare
Ramsberg et al. 2012	Escitalopram	1479	0.698	Citalopram	1522	0.686	-43	0.012	Escitalopram dominates	12 months	Healthcare
Annemans et al. 2014	Escitalopram	2853	0.701	Duloxetine	3176	0.695	-323	0.006	Escitalopram dominates	12 months	Healthcare
Mencacci et al. 2013	Escitalopram	5963	0.732	Duloxetine	6295	0.727	-331	0.005	Escitalopram dominates	12 months	Healthcare
Ramsberg et al. 2012	Escitalopram	1479	0.698	Duloxetine	1525	0.693	-46	0.004	Escitalopram dominates	12 months	Healthcare
Annemans et al. 2014	Escitalopram	2853	0.701	Fluoxetine	3116	0.685	-263	0.016	Escitalopram dominates	12 months	Healthcare
Mencacci et al. 2013	Escitalopram	5963	0.732	Fluoxetine	6221	0.719	-258	0.013	Escitalopram dominates	12 months	Healthcare
Ramsberg et al. 2012	Escitalopram	1479	0.698	Fluoxetine	1531	0.685	-52	0.013	Escitalopram dominates	12 months	Healthcare
Mencacci et al. 2013	Escitalopram	5963	0.732	Fluvoxamine	7130	0.697	-1167	0.035	Escitalopram dominates	12 months	Healthcare
Annemans et al. 2014	Escitalopram	2853	0.701	Mirtazapine	2866	0.697	-13	0.004	Escitalopram dominates	12 months	Healthcare
Ramsberg et al. 2012	Escitalopram	1479	0.698	Mirtazapine	1482	0.693	-3	0.005	Escitalopram dominates	12 months	Healthcare
Annemans et al. 2014	Escitalopram	2853	0.701	Paroxetine	2979	0.692	-126	0.009	Escitalopram dominates	12 months	Healthcare
Mencacci et al. 2013	Escitalopram	5963	0.732	Paroxetine	6100	0.724	-136	0.008	Escitalopram dominates	12 months	Healthcare
Ramsberg et al. 2012	Escitalopram	1479	0.698	Paroxetine	1495	0.691	-16	0.007	Escitalopram dominates	12 months	Healthcare
Annemans et al. 2014	Escitalopram	2853	0.701	Sertraline	2947	0.693	-93	0.008	Escitalopram dominates	12 months	Healthcare
Armstrong 2007	Escitalopram	1336	0.403	Sertraline	1718	0.393	-382	0.010	Escitalopram dominates	6 months	Healthcare
Mencacci et al. 2013	Escitalopram	5963	0.732	Sertraline	6029	0.724	-65	0.008	Escitalopram dominates	12 months	Healthcare

Ramsberg et al. 2012	Escitalopram	1479	0.698	Sertraline	1502	0.689	-23	0.009	Escitalopram dominates	12 months	Healthcare
Annemans et al. 2014	Escitalopram	2853	0.701	Venlafaxine	2813	0.698	40	0.003	13477	12 months	Healthcare
Ramsberg et al. 2012	Escitalopram	1479	0.698	Venlafaxine	1475	0.694	4	0.004	1130	12 months	Healthcare
Mencacci et al. 2013	Escitalopram	5963	0.732	Venlafaxine	6033	0.729	-69	0.003	Escitalopram dominates	12 months	Healthcare
Annemans et al. 2014	Escitalopram	33470	0.701	Citalopram	37491	0.686	-4020	0.015	Escitalopram dominates	12 months	Societal
Nuijten et al. 2012	Escitalopram	40290	0.324	Citalopram	44923	0.307	-4634	0.017	Escitalopram dominates	26 weeks	Societal
Ramsberg et al. 2012	Escitalopram	4289	0.698	Citalopram	4460	0.686	-171	0.012	Escitalopram dominates	12 months	Societal
Annemans et al. 2014	Escitalopram	33470	0.701	Duloxetine	37559	0.695	-4089	0.006	Escitalopram dominates	12 months	Societal
Ramsberg et al. 2012	Escitalopram	4289	0.698	Duloxetine	4384	0.693	-95	0.004	Escitalopram dominates	12 months	Societal
Annemans et al. 2014	Escitalopram	33470	0.701	Fluoxetine	35750	0.685	-2279	0.016	Escitalopram dominates	12 months	Societal
Ramsberg et al. 2012	Escitalopram	4289	0.698	Fluoxetine	4484	0.685	-196	0.013	Escitalopram dominates	12 months	Societal
Annemans et al. 2014	Escitalopram	33470	0.701	Mirtazapine	34448	0.697	-978	0.004	Escitalopram dominates	12 months	Societal
Ramsberg et al. 2012	Escitalopram	4289	0.698	Mirtazapine	4349	0.693	-60	0.005	Escitalopram dominates	12 months	Societal
Annemans et al. 2014	Escitalopram	33470	0.701	Paroxetine	35601	0.692	-2130	0.009	Escitalopram dominates	12 months	Societal
Ramsberg et al. 2012	Escitalopram	4289	0.698	Paroxetine	4383	0.691	-94	0.007	Escitalopram dominates	12 months	Societal
Annemans et al. 2014	Escitalopram	33470	0.701	Sertraline	35565	0.693	-2095	0.008	Escitalopram dominates	12 months	Societal
Ramsberg et al. 2012	Escitalopram	4289	0.698	Sertraline	4406	0.689	-117	0.009	Escitalopram dominates	12 months	Societal
Annemans et al. 2014	Escitalopram	33470	0.701	Venlafaxine	34122	0.698	-652	0.003	Escitalopram dominates	12 months	Societal
Nuijten et al. 2012	Escitalopram	40290	0.324	Venlafaxine	40901	0.318	-612	0.006	Escitalopram dominates	26 weeks	Societal
Ramsberg et al. 2012	Escitalopram	4289	0.698	Venlafaxine	4325	0.694	-36	0.004	Escitalopram dominates	12 months	Societal

Nordstrom et al. 2012	Escitalopram	2144	0.315	Venlafaxine	2194	0.307	-49	0.009	Escitalopram dominates	6 months	Societal

Table 21. Cost adaptation of venlafaxine versus other antidepressant medications (ADMs) and resulting ICERs, ordered by perspective and comparator

Author	Intervention	Intervention costs (CHF)	Intervention QALY	Comparator	Comparator costs (CHF)	Comparator QALY	Cost difference	QALY difference	ICER (CHF per QALY gained)	Time Horizon	Perspective
Lenox-Smith et al. 2009	Venlafaxine (Fluoxetine)	6735	0.098	Amitriptyline (Fluoxetine)	6925	0.084	-191	0.014	Venlafaxine dominates	24 weeks	Healthcare
Lenox-Smith et al. 2009	Venlafaxine (Fluoxetine)	6735	0.098	Amitriptyline (Venlafaxine)	6764	0.087	-30	0.012	Venlafaxine dominates	24 weeks	Healthcare
Annemans et al. 2014	Venlafaxine	2813	0.698	Citalopram	3151	0.686	-339	0.012	Venlafaxine dominates	12 months	Healthcare
Mencacci et al. 2013	Venlafaxine	6033	0.729	Citalopram	6203	0.720	-171	0.009	Venlafaxine dominates	12 months	Healthcare
Ramsberg et al. 2012	Venlafaxine	1475	0.694	Citalopram	1522	0.686	-47	0.008	Venlafaxine dominates	12 months	Healthcare
Annemans et al. 2014	Venlafaxine	2813	0.698	Duloxetine	3176	0.695	-364	0.003	Venlafaxine dominates	12 months	Healthcare
Benedict et al. 2010	Venlafaxine	2411	0.663	Duloxetine	2238	0.665	173	-0.002	Duloxetine dominates	12 months	Healthcare
Mencacci et al. 2013	Venlafaxine	6033	0.729	Duloxetine	6295	0.727	-262	0.002	Venlafaxine dominates	12 months	Healthcare
Ramsberg et al.2012	Venlafaxine	1475	0.694	Duloxetine	1525	0.693	-50	0.001	Venlafaxine dominates	12 months	Healthcare
Annemans et al. 2014	Venlafaxine	2813	0.698	Escitalopram	2853	0.701	-40	-0.003	Venlafaxine less expensive but less effective	12 months	Healthcare
Mencacci et al. 2013	Venlafaxine	6033	0.729	Escitalopram	5963	0.732	69	-0.003	Escitalopram dominates	12 months	Healthcare
Ramsberg et al. 2012	Venlafaxine	1475	0.694	Escitalopram	1479	0.698	-4	-0.004	Venlafaxine less expensive but less effective	12 months	Healthcare

Annemans et al. 2014	Venlafaxine	2813	0.698	Fluoxetine	3116	0.685	-303	0.013	Venlafaxine dominates	12 months	Healthcare
Mencacci et al. 2013	Venlafaxine	6033	0.729	Fluoxetine	6221	0.719	-189	0.010	Venlafaxine dominates	12 months	Healthcare
Ramsberg et al. 2012	Venlafaxine	1475	0.694	Fluoxetine	1531	0.685	-56	0.010	Venlafaxine dominates	12 months	Healthcare
Lenox-Smith et al. 2009	Venlafaxine (Fluoxetine)	6735	0.098	Fluoxetine (Amitriptyline)	6807	0.088	-73	0.010	Venlafaxine dominates	24 weeks	Healthcare
Lenox-Smith et al. 2009	Venlafaxine (Fluoxetine)	6735	0.098	Fluoxetine (Venlafaxine)	6715	0.091	19	0.007	2,801	24 weeks	Healthcare
Mencacci et al. 2013	Venlafaxine	6033	0.729	Fluvoxamine	7130	0.697	-1097	0.032	Venlafaxine dominates	12 months	Healthcare
Annemans et al. 2014	Venlafaxine	2813	0.698	Mirtazapine	2866	0.697	-53	0.001	Venlafaxine dominates	12 months	Healthcare
Benedict et al. 2010	Venlafaxine	2411	0.663	Mirtazapine	2127	0.654	284	0.009	31,601	12 months	Healthcare
Ramsberg et al. 2012	Venlafaxine	1475	0.694	Mirtazapine	1482	0.693	-7	0.002	Venlafaxine dominates	12 months	Healthcare
Annemans et al. 2014	Venlafaxine	2813	0.698	Paroxetine	2979	0.692	-167	0.006	Venlafaxine dominates	12 months	Healthcare
Mencacci et al. 2013	Venlafaxine	6033	0.729	Paroxetine	6100	0.724	-67	0.005	Venlafaxine dominates	12 months	Healthcare
Ramsberg et al. 2012	Venlafaxine	1475	0.694	Paroxetine	1495	0.691	-20	0.004	Venlafaxine dominates	12 months	Healthcare
Annemans et al. 2014	Venlafaxine	2813	0.698	Sertraline	2947	0.693	-134	0.005	Venlafaxine dominates	12 months	Healthcare
Mencacci et al. 2013	Venlafaxine	6033	0.729	Sertraline	6029	0.724	4	0.005	840	12 months	Healthcare
Ramsberg et al. 2012	Venlafaxine	1475	0.694	Sertraline	1502	0.689	-27	0.005	Venlafaxine dominates	12 months	Healthcare
Benedict et al. 2010	Venlafaxine	2411	0.663	SSRIs	2003	0.656	408	0.007	58,296	12 months	Healthcare
Maniadakis et al. 2013	Venlafaxine	31397	1.436	Agomelatine	31478	1.461	-81	-0.025	Venlafaxine less expensive but less effective	24 months	Societal
Annemans et al. 2014	Venlafaxine	34122	0.698	Citalopram	37491	0.686	-3369	0.012	Venlafaxine dominates	12 months	Societal
Ramsberg et al. 2012	Venlafaxine	4325	0.694	Citalopram	4460	0.686	-135	0.008	Venlafaxine dominates	12 months	Societal

Annemans et al. 2014	Venlafaxine	34122	0.698	Duloxetine	37559	0.695	-3437	0.003	Venlafaxine dominates	12 months	Societal
Ramsberg et al. 2012	Venlafaxine	4325	0.694	Duloxetine	4384	0.693	-59	0.001	Venlafaxine dominates	12 months	Societal
Annemans et al. 2014	Venlafaxine	34122	0.698	Escitalopram	33470	0.701	652	-0.003	Escitalopram dominates	12 months	Societal
Maniadakis et al. 2013	Venlafaxine	31397	1.436	Escitalopram	31641	1.447	-243	-0.011	Venlafaxine less expensive but less effective	24 months	Societal
Nordstrom et al. 2012	Venlafaxine	2194	0.307	Escitalopram	2144	0.315	49	-0.009	Escitalopram dominates	6 months	Societal
Ramsberg et al. 2012	Venlafaxine	4325	0.694	Escitalopram	4289	0.698	36	-0.004	Venlafaxine more expensive but less effective	12 months	Societal
Annemans et al. 2014	Venlafaxine	34122	0.698	Fluoxetine	35750	0.685	-1627	0.013	Venlafaxine dominates	12 months	Societal
Maniadakis et al. 2013	Venlafaxine	31397	1.436	Fluoxetine	32226	1.431	-828	0.005	Venlafaxine dominates	24 months	Societal
Ramsberg et al. 2012	Venlafaxine	4325	0.694	Fluoxetine	4484	0.685	-160	0.010	Venlafaxine dominates	12 months	Societal
Annemans et al. 2014	Venlafaxine	34122	0.698	Mirtazapine	34448	0.697	-326	0.001	Venlafaxine dominates	12 months	Societal
Ramsberg et al. 2012	Venlafaxine	4325	0.694	Mirtazapine	4349	0.693	-24	0.002	Venlafaxine dominates	12 months	Societal
Annemans et al. 2014	Venlafaxine	34122	0.698	Paroxetine	35601	0.692	-1478	0.006	Venlafaxine dominates	12 months	Societal
Ramsberg et al. 2012	Venlafaxine	4325	0.694	Paroxetine	4383	0.691	-59	0.004	Venlafaxine dominates	12 months	Societal
Annemans et al. 2014	Venlafaxine	34122	0.698	Sertraline	35565	0.693	-1443	0.005	Venlafaxine dominates	12 months	Societal
Maniadakis et al. 2013	Venlafaxine	31397	1.436	Sertraline	32730	1.427	-1332	0.009	Venlafaxine dominates	24 months	Societal
Ramsberg et al. 2012	Venlafaxine	4325	0.694	Sertraline	4406	0.689	-82	0.005	Venlafaxine dominates	12 months	Societal
Ramsberg et al. 2012	Venlafaxine	4325	0.694	Paroxetine	4383	0.691	-59	0.004	Venlafaxine dominates	12 months	Societal

Table 22. Cost adaptation of sertraline versus placebo or other antidepressant medications (ADMs) and resulting ICERs, ordered by perspective and comparator

Author	Intervention	Intervention costs (CHF)	Intervention QALY	Comparator	Comparator costs (CHF)	Comparator QALY	Cost difference	QALY difference	ICER (CHF per QALY gained)	Time Horizon	Perspective
Annemans et al. 2014	Sertraline	2947	0.693	Citalopram	3151	0.686	-205	0.007	Sertraline dominates	12 months	Healthcare
Mencacci et al. 2013	Sertraline	6029	0.724	Citalopram	6203	0.720	-175	0.004	Sertraline dominates	12 months	Healthcare
Ramsberg et al. 2012	Sertraline	1502	0.689	Citalopram	1522	0.686	-20	0.003	Sertraline dominates	12 months	Healthcare
Annemans et al. 2014	Sertraline	2947	0.693	Duloxetine	3176	0.695	-230	-0.002	Sertraline less expensive but less effective	12 months	Healthcare
Mencacci et al. 2013	Sertraline	6029	0.724	Duloxetine	6295	0.727	-266	-0.003	Sertraline less expensive but less effective	12 months	Healthcare
Ramsberg et al. 2012	Sertraline	1502	0.689	Duloxetine	1525	0.693	-23	-0.004	Sertraline less expensive but less effective	12 months	Healthcare
Annemans et al. 2014	Sertraline	2947	0.693	Escitalopram	2853	0.701	93	-0.008	Escitalopram dominates	12 months	Healthcare
Armstrong 2007	Sertraline	1718	0.393	Escitalopram	1336	0.403	382	-0.010	Escitalopram dominates	6 months	Healthcare
Mencacci et al. 2013	Sertraline	6029	0.724	Escitalopram	5963	0.732	65	-0.008	Escitalopram dominates	12 months	Healthcare
Ramsberg et al. 2012	Sertraline	1502	0.689	Escitalopram	1479	0.698	23	-0.009	Escitalopram dominates	12 months	Healthcare
Annemans et al. 2014	Sertraline	2947	0.693	Fluoxetine	3116	0.685	-169	0.008	Sertraline dominates	12 months	Healthcare
Mencacci et al. 2013	Sertraline	6029	0.724	Fluoxetine	6221	0.719	-193	0.005	Sertraline dominates	12 months	Healthcare
Ramsberg et al. 2012	Sertraline	1502	0.689	Fluoxetine	1531	0.685	-29	0.005	Sertraline dominates	12 months	Healthcare

Mencacci et al. 2013	Sertraline	6029	0.724	Fluvoxamine	7130	0.697	-1102	0.027	Sertraline dominates	12 months	Healthcare
Annemans et al. 2014	Sertraline	2947	0.693	Mirtazapine	2866	0.697	81	-0.004	Mirtazapine dominates	12 months	Healthcare
Ramsberg et al. 2012	Sertraline	1502	0.689	Mirtazapine	1482	0.693	20	-0.003	Mirtazapine dominates	12 months	Healthcare
Annemans et al. 2014	Sertraline	2947	0.693	Paroxetine	2979	0.692	-33	0.001	Sertraline dominates	12 months	Healthcare
Mencacci et al. 2013	Sertraline	6029	0.724	Paroxetine	6100	0.724	-71	0.000	Sertraline dominates	12 months	Healthcare
Ramsberg et al. 2012	Sertraline	1502	0.689	Paroxetine	1495	0.691	7	-0.001	Paroxetine dominates	12 months	Healthcare
Hollingworth et al. 2019	Sertraline	445	0.182	Placebo	510	0.177	-65	0.005	Sertraline dominates	12 weeks	Healthcare
Annemans et al. 2014	Sertraline	2947	0.693	Venlafaxine	2813	0.698	134	-0.005	Venlafaxine dominates	12 months	Healthcare
Ramsberg et al. 2012	Sertraline	1502	0.689	Venlafaxine	1475	0.694	27	-0.005	Venlafaxine dominates	12 months	Healthcare
Mencacci et al. 2013	Sertraline	6029	0.724	Venlafaxine XR	6033	0.729	-4	-0.005	Venlafaxine dominates	12 months	Healthcare
Maniadakis et al. 2013	Sertraline	32730	1.427	Agomelatine	31478	1.461	1251	-0.034	Agomelatine dominates	24 months	Societal
Annemans et al. 2014	Sertraline	35565	0.693	Citalopram	37491	0.686	-1926	0.007	Sertraline dominates	12 months	Societal
Ramsberg et al. 2012	Sertraline	4406	0.689	Citalopram	4460	0.686	-53	0.003	Sertraline dominates	12 months	Societal
Annemans 2028	Sertraline	35565	0.693	Duloxetine	37559	0.695	-1994	-0.002	Sertraline less expensive but less effective	12 months	Societal
Ramsberg et al. 2012	Sertraline	4406	0.689	Duloxetine	4384	0.693	22	-0.004	Duloxetine dominates	12 months	Societal
Annemans et al. 2014	Sertraline	35565	0.693	Escitalopram	33470	0.701	2095	-0.008	Escitalopram dominates	12 months	Societal
Maniadakis et al. 2013	Sertraline	32730	1.427	Escitalopram	31641	1.447	1089	-0.020	Escitalopram dominates	24 months	Societal
Ramsberg et al. 2012	Sertraline	4406	0.689	Escitalopram	4289	0.698	117	-0.009	Escitalopram dominates	12 months	Societal
Annemans et al. 2014	Sertraline	35565	0.693	Fluoxetine	35750	0.685	-184	0.008	Sertraline dominates	12 months	Societal

Maniadakis et al. 2013	Sertraline	32730	1.427	Fluoxetine	32226	1.431	504	-0.004	Fluoxetine dominates	24 months	Societal
Ramsberg et al. 2012	Sertraline	4406	0.689	Fluoxetine	4484	0.685	-78	0.005	Sertraline dominates	12 months	Societal
Annemans et al. 2014	Sertraline	35565	0.693	Mirtazapine	34448	0.697	1117	-0.004	Mirtazapine dominates	12 months	Societal
Ramsberg et al. 2012	Sertraline	4406	0.689	Mirtazapine	4349	0.693	58	-0.003	Mirtazapine dominates	12 months	Societal
Annemans et al. 2014	Sertraline	35565	0.693	Paroxetine	35601	0.692	-35	0.001	Sertraline dominates	12 months	Societal
Ramsberg et al. 2012	Sertraline	4406	0.689	Paroxetine	4383	0.691	23	-0.001	Paroxetine dominates	12 months	Societal
Hollingworth et al. 2019	Sertraline	833	0.182	Placebo	852	0.177	-18	0.005	Sertraline dominates	12 weeks	Societal
Annemans et al. 2014	Sertraline	35565	0.693	Venlafaxine	34122	0.698	1443	-0.005	Venlafaxine dominates	12 months	Societal
Maniadakis et al. 2013	Sertraline	32730	1.427	Venlafaxine	31397	1.436	1332	-0.009	Venlafaxine dominates	24 months	Societal
Ramsberg et al. 2012	Sertraline	4406	0.689	Venlafaxine	4325	0.694	82	-0.005	Venlafaxine dominates	12 months	Societal

Table 23. Cost adaptation of duloxetine versus placebo or other antidepressant medications (ADMs) and resulting ICERs, ordered by perspective and comparator

Author	Intervention	Intervention costs (CHF)	Intervention QALY	Comparator	Comparator costs (CHF)	Comparator QALY	Cost difference	QALY difference	ICER (CHF per QALY gained)	Time Horizon	Perspective
Annemans et al. 2014	Duloxetine	3176	0.695	Citalopram	3151	0.686	25	0.009	2,808	12 months	Healthcare
Mencacci et al. 2013	Duloxetine	6295	0.727	Citalopram	6203	0.720	91	0.007	13,031	12 months	Healthcare
Ramsberg et al. 2012	Duloxetine	1525	0.693	Citalopram	1522	0.686	3	0.007	484	12 months	Healthcare
Annemans et al. 2014	Duloxetine	3176	0.695	Escitalopram	2853	0.701	323	-0.006	Escitalopram dominates	12 months	Healthcare
Mencacci et al. 2013	Duloxetine	6295	0.727	Escitalopram	5963	0.732	331	-0.005	Escitalopram dominates	12 months	Healthcare
Ramsberg et al. 2012	Duloxetine	1525	0.693	Escitalopram	1479	0.698	46	-0.004	Escitalopram dominates	12 months	Healthcare

Annemans et al. 2014	Duloxetine	3176	0.695	Fluoxetine	3116	0.685	61	0.010	6,065	12 months	Healthcare
Mencacci et al. 2013	Duloxetine	6295	0.727	Fluoxetine	6221	0.719	73	0.008	9,160	12 months	Healthcare
Ramsberg et al. 2012	Duloxetine	1525	0.693	Fluoxetine	1531	0.685	-6	0.009	Duloxetine dominates	12 months	Healthcare
Mencacci et al. 2013	Duloxetine	6295	0.727	Fluvoxamine	7130	0.697	-835	0.030	Duloxetine dominates	12 months	Healthcare
Annemans et al. 2014	Duloxetine	3176	0.695	Mirtazapine	2866	0.697	311	-0.002	Mirtazapine dominates	12 months	Healthcare
Benedict et al. 2010	Duloxetine	2238	0.665	Mirtazapine	2127	0.654	111	0.011	10,117	12 months	Healthcare
Ramsberg et al. 2012	Duloxetine	1525	0.693	Mirtazapine	1482	0.693	43	0.001	61,456	12 months	Healthcare
Annemans et al. 2014	Duloxetine	3176	0.695	Paroxetine	2979	0.692	197	0.003	65,703	12 months	Healthcare
Mencacci et al. 2013	Duloxetine	6295	0.727	Paroxetine	6100	0.724	195	0.003	65,012	12 months	Healthcare
Ramsberg et al. 2012	Duloxetine	1525	0.693	Paroxetine	1495	0.691	30	0.003	11,196	12 months	Healthcare
Annemans et al. 2014	Duloxetine	3176	0.695	Sertraline	2947	0.693	230	0.002	114,979	12 months	Healthcare
Mencacci et al. 2013	Duloxetine	6295	0.727	Sertraline	6029	0.724	266	0.003	88,676	12 months	Healthcare
Ramsberg et al. 2012	Duloxetine	1525	0.693	Sertraline	1502	0.689	23	0.004	5,672	12 months	Healthcare
Benedict et al. 2010	Duloxetine	2238	0.665	SSRIs	2003	0.656	235	0.009	26,106	12 months	Healthcare
Annemans et al. 2014	Duloxetine	3176	0.695	Venlafaxine	2813	0.698	364	-0.003	Venlafaxine dominates	12 months	Healthcare
Ramsberg et al. 2012	Duloxetine	1525	0.693	Venlafaxine	1475	0.694	50	-0.001	Venlafaxine dominates	12 months	Healthcare
Benedict et al. 2010	Duloxetine	2238	0.665	Venlafaxine	2411	0.663	-173	0.002	Duloxetine dominates	12 months	Healthcare
Mencacci et al. 2013	Duloxetine	6295	0.727	Venlafaxine	6033	0.729	262	-0.002	Venlafaxine dominates	12 months	Healthcare
Annemans et al. 2014	Duloxetine	37559	0.695	Citalopram	37491	0.686	68	0.009	7,581	12 months	Societal
Ramsberg et al. 2012	Duloxetine	4384	0.693	Citalopram	4460	0.686	-76	0.007	Duloxetine dominates	12 months	Societal

Annemans et al. 2014	Duloxetine	37559	0.695	Escitalopram	33470	0.701	4089	-0.006	Escitalopram dominates	12 months	Societal
Ramsberg et al. 2012	Duloxetine	4384	0.693	Escitalopram	4289	0.698	95	-0.004	Escitalopram dominates	12 months	Societal
Annemans et al. 2014	Duloxetine	37559	0.695	Fluoxetine	35750	0.685	1809	0.010	180,935	12 months	Societal
Ramsberg et al. 2012	Duloxetine	4384	0.693	Fluoxetine	4484	0.685	-101	0.009	Duloxetine dominates	12 months	Societal
Annemans et al. 2014	Duloxetine	37559	0.695	Mirtazapine	34448	0.697	3111	-0.002	Mirtazapine dominates	12 months	Societal
Ramsberg et al. 2012	Duloxetine	4384	0.693	Mirtazapine	4349	0.693	35	0.001	50,245	12 months	Societal
Annemans et al. 2014	Duloxetine	37559	0.695	Paroxetine	35601	0.692	1958	0.003	652,813	12 months	Societal
Ramsberg et al. 2012	Duloxetine	4384	0.693	Paroxetine	4383	0.691	1	0.003	215	12 months	Societal
Annemans et al. 2014	Duloxetine	37559	0.695	Sertraline	35565	0.693	1994	0.002	996,909	12 months	Societal
Ramsberg et al. 2012	Duloxetine	4384	0.693	Sertraline	4406	0.689	-22	0.004	Duloxetine dominates	12 months	Societal
Annemans et al. 2014	Duloxetine	37559	0.695	Venlafaxine	34122	0.698	3437	-0.003	Venlafaxine dominates	12 months	Societal
Ramsberg et al. 2012	Duloxetine	4384	0.693	Venlafaxine	4325	0.694	59	-0.001	Venlafaxine dominates	12 months	Societal

Table 24. Cost adaptation of SSRIs or agomelatine versus other ADMs and resulting ICERs, ordered by perspective and comparator

Author	Intervention	Intervention costs (CHF)	Intervention QALY	Comparator	Comparator costs (CHF)	Comparator QALY	Cost difference	QALY difference	ICER (CHF per QALY gained)	Time Horizon	Perspective
Benedict et al. 2010	SSRIs	2003	0.656	Duloxetine	2238	0.665	-235	-0.009	26,106	12 months	Healthcare
Benedict et al. 2010	SSRIs	2003	0.656	Venlafaxine XR	2411	0.663	-408	-0.007	58,296	12 months	Healthcare
Benedict et al. 2010	SSRIs	2003	0.656	Mirtazapine	2127	0.654	-124	0.002	SSRIs dominate	12 months	Healthcare
Kendrick et al. 2009	SSRIs	3129	0.331	Usual care	2593	0.318	536	0.013	41,539	6 months	Healthcare
Kendrick et al. 2006	SSRIs	4798	0.590	TCA	4181	0.550	617	0.040	15,414	12 months	Healthcare
Maniadakis et al. 2013	Agomelatine	31478	1.461	Venlafaxine	31397	1.436	81	0.025	3,244	24 months	Societal
Maniadakis et al. 2013	Agomelatine	31478	1.461	Sertraline	32730	1.427	-1251	0.034	Agomelatine dominates	24 months	Societal
Maniadakis et al. 2013	Agomelatine	31478	1.461	Escitalopram	31641	1.447	-162	0.014	Agomelatine dominates	24 months	Societal
Maniadakis et al. 2013	Agomelatine	31478	1.461	Fluoxetine	32226	1.431	-747	0.030	Agomelatine dominates	24 months	Societal
Maniadakis et al. 2013	Agomelatine	31478	1.461	Generic Venlafaxine	31264	1.436	214	0.025	8,573	24 months	Societal
Maniadakis et al. 2013	Agomelatine	31478	1.461	Generic Sertraline	32440	1.427	-962	0.034	Agomelatine dominates	24 months	Societal
Maniadakis et al. 2013	Agomelatine	31478	1.461	Generic Escitalopram	31200	1.448	278	0.013	21,389	24 months	Societal
Maniadakis et al. 2013	Agomelatine	31478	1.461	Generic Fluoxetine	31907	1.431	-429	0.030	Agomelatine dominates	24 months	Societal

7.2.7.2 Cognitive behavioural therapy (CBT)

A total of 18 out of 19 studies investigating CBT versus other treatments or usual care provided enough information for a cost adaptation. As already mentioned, the design as well as the results of the identified studies were very heterogeneous. In this section, besides providing costs adapted for Switzerland, we aimed to present the results according to different types of interventions (normal CBT, internet-based CBT, CBT in combination with ADM), comparators, treatment durations, and perspectives. It should be noted that in some cases the duration of CBT was not accurately described (for example it was not clear whether 12 weekly sessions were distributed over 12 weeks or more).

CBT versus ADM

Four studies compared CBT with ADM (Evans-Lacko (185), Koeser (164), Kukyen (166), Ross (177)). According to Kuyken et al., CBT prescribed over 12 months (8 weekly sessions plus 4 sessions every 3 months) was dominated by ADM from both the societal and healthcare system perspective. In contrast, according to the analyses of Evans-Lacko et al. and Koeser et al., CBT compared to ADM had ICERs around CHF 50,000 – CHF 70,000 per QALY gained (in Evans-Lacko et al. CBT duration was 15 months, whereas in Koeser et al. it was 3 months). Finally, in Ross et al. CBT compared to ADM had ICERs above CHF 100,000 per QALY gained using a time horizon and treatment duration of 12 months, while it was considered a dominant strategy with a time horizon and treatment duration of 60 months (from both healthcare and societal perspectives).

CBT plus ADM versus ADM

Two studies compared the combination of CBT and ADM with ADM alone (Evans-Lacko, Simon) from a healthcare perspective. According to Evans-Lacko et al. (185), CBT plus AD prescribed over 15 months led to an ICER of CHF 94,049 per QALY gained (time horizon 27 months). In Simon et al., assuming a treatment duration of 3 months and a time horizon of 15 months, the ICERs were CHF 69,351 per QALY gained for patients with moderate depression and CHF 31,523 per QALY gained for patients with severe depression.

CBT versus usual care or behavioural activation

Only one study compared CBT with usual care (Stant et al. (183)). Assuming 10-12 CBT sessions and using a time horizon of 36 months, Stant et al. concluded that CBT was dominated by usual care from a societal perspective. In Richards et al. 20 sessions of CBT over 16 weeks were compared to behavioural activation, defined as a "simple psychological treatment for depression that can be conducted by junior mental health workers with no professional training in psychological therapy". Using a time horizon of

18 months and a healthcare perspective, the authors concluded that behavioural activation was the dominant strategy.

Internet-based CBT versus usual care

The previous paragraphs refer to CBT which appeared to be face-to-face CBT. In addition, a total of 10 studies compared internet-based CBT with usual care (Duarte (181), Gerhards 2010 (187), Geraedts 2015 (186), Health Quality Ontario (188), Hollinghurst (189), Holst (160), Kraepelien (165), Solomon (182), Warmerdam (184), Romero-Sanchiz (176)), reporting very discordant results. Three out of 10 studies concluded that internet-based CBT may be a dominant strategy when compared to usual care (Geraedts 2015 (186), Solomon (182), Romero-Sanchiz (176)). In Geraedts et al. internet-based CBT consisted of only 6 weekly lessons, in Romero-Sanchiz et al. self-guided internet-based CBT consisted of 10 modules (with a duration of "at least one week per module"), and in Solomon et al. internet-based CBT was distributed over 12 weeks (all three used a time horizon of 12 months and a societal perspective).
In five studies internet-based CBT was estimated to be more expensive and more effective than usual care, with ICERs ranging between CHF 2,224 and CHF 71,599 per QALY gained (Health Quality Ontario (188), Hollinghurst (189), Kraepelien (165), Warmerdam (184), Romero-Sanchiz (176)). As in the previous cases, across studies there was a considerable variation in the assumed treatment duration (from 6-8 weekly modules to 12 weeks) and time horizon (from 3 to 12 months).
Two studies concluded that internet-based CBT was less expensive but also less effective than usual care (Gerhards 2010 (187), Holst (160)), while only one study suggested that usual care was the dominant strategy (Duarte (181)).

Time horizon and treatment duration

The time horizons of the analyses ranged from 3 to 60 months, and the treatment durations ranged from 2 to 60 months. Independently from the adopted perspective (healthcare or societal), it was not possible to identify any specific trend according to time horizon or treatment duration (i.e. CBT or the comparators were not more frequently dominant or cost-effective for a specific time horizon or treatment duration).

Table 25. Cost adaptation of CBT or CBT plus ADM versus usual care or ADM alone and resulting ICERs, ordered by intervention and perspective.

Author	Intervention	Intervention costs	Intervention QALY	Comparator	Comparator costs	Comparator QALY	Cost difference	QALY difference	ICER	Time Horizon	Treatment duration / details	Perspective
Koeser et al. 2015	CBT	14725	1.274	ADM	12149	1.236	2576	0.038	67,801	27 months	3 months acute treatment phase	Healthcare
Richards et al. 2016	CBT	10495	0.935	Behavioural activation	8383	0.985	2112	-0.050	Behavioural activation dominates	18 months	4 months (20 sessions over 16 weeks)	Healthcare
Ross et al. 2019	CBT	8485	0.715	ADM	7637	0.708	849	0.007	121,221	12 months	12 months	Healthcare
Kuyken et al. 2015	CBT	8279	1.490	ADM	7866	1.530	413	-0.040	ADM dominates	24 months	12 months (8 weekly session plus 4 session every 3 months)	Healthcare
Evans-Lacko et al. 2016	CBT	70072	1.300	ADM	68088	1.260	1984	0.040	49,602	27 months	15 months	Healthcare
Ross et al. 2019	CBT	52233	3.293	ADM	53930	3.238	-1697	0.055	CBT dominates	60 months	60 months	Healthcare
Stant et al. 2009	CBT	28686	2.270	Usual care	25419	2.310	3267	-0.040	Usual care dominates	36 months	3 months (10-12 sessions)	Societal
Ross et al. 2019	CBT	15180	0.715	ADM	13765	0.708	1414	0.007	202,035	12 months	12 months	Societal
Kuyken et al. 2015	CBT	10679	1.490	ADM	9182	1.530	1497	-0.040	ADM dominates	24 months	12 months (8 weekly session plus 4 session every 3 months)	Societal

Ross et al. 2019	CBT	82592	3.293	ADM	84949	3.238	-2357	0.055	CBT dominates	60 months	60 months	Societal
Duarte 2017	CBT (i)	3660	1.356	Usual care	3400	1.388	260	-0.032	Usual care dominates	24 months	24 months	Healthcare
Health Quality Ontario 2019	CBT (i)	2237	0.826	Usual care	550	0.787	1687	0.039	43,262	12 months	2 months (6-8 weekly modules)	Societal
Hollinghurst et al. 2010	CBT (i)	3149	0.522	Usual care	1216	0.495	1933	0.027	71,599	8 months	4 months (10 sessions in max 4 months)	Healthcare
Solomon et al. 2015	CBT (i)	470	0.260	Usual care	736	0.240	-266	0.020	CBT dominates	6 months	6 months (28 weeks)	Healthcare
Geraedts et al. 2015	CBT (i)	48399	0.790	Usual care	49939	0.780	-1540	0.010	CBT dominates	12 months	2 months (6 weekly lessons)	Societal
Gerhards et al. 2010	CBT (i)	23583	0.710	Usual care	25329	0.720	-1746	-0.010	CBT less expensive and less effective	12 months	2-3 months (8 weekly session plus 1 booster session)	Societal
Holst et al. 2018	CBT (i)	10030	0.740	Usual care	10590	0.790	-560	-0.050	CBT less expensive but also less effective	12 months	3 months (12 weeks)	Societal
Kraepelien et al. 2018	CBT (i)	653	0.691	Usual care	551	0.657	102	0.034	3,005	12 months	3 months (12 weeks)	Societal
Warmerdam et al. 2010	CBT (i)	7299	0.160	Usual care	6635	0.150	664	0.010	66,402	3 months	3 months (8 lessons in 8 weeks plus booster lesson after 12 weeks)	Societal
Romero et al. 2017	CBT (i, self-guided)	5884	0.785	Usual care	7725	0.705	-1841	0.080	CBT dominates	12 months	3 months (10 modules, at least one	Societal

											weak per module)	
Romero et al. 2017	CBT (i, therapist guided)	7910	0.788	Usual care	7725	0.705	185	0.083	2,224	12 months	3 months (10 modules, at least one weak per module)	Societal
Evans-Lacko et al. 2016	CBT plus ADM	72791	1.310	ADM	68088	1.260	4702	0.050	94,049	27 months	15 months	Healthcare
Simon et al. 2006	CBT plus ADM (moderate depression)	7060	0.890	ADM (moderate depression)	3593	0.840	3468	0.050	69,351	15 months	3 months	Healthcare
Simon et al. 2006	CBT plus ADM (severe depression)	7060	0.630	ADM (severe depression)	3593	0.520	3468	0.110	31,523	15 months	3 months	Healthcare

7.3 Discussion

A summary of the adapted cost-effectiveness results calculated for Switzerland is provided in Table 19. The majority of the cost-effectiveness analyses of ADMs included in this systematic review were model-based. Six cost-effectiveness analyses concluded that there was favourable evidence to support the cost-effectiveness of escitalopram versus other ADMs. All these analyses were based on clinical inputs showing that remission or response probabilities were highest for escitalopram relative to all other comparators. In all cost-effectiveness analyses where venlafaxine, sertraline or duloxetine were compared against escitalopram, it was estimated that escitalopram was the dominant strategy (i.e. less expensive and more effective) or highly cost-effective (i.e., had very low ICERs). Also, after numerical adaptation for Switzerland escitalopram resulted in being a dominant strategy in most cases. Two studies estimated that escitalopram was more expensive and more effective than venlafaxine from a healthcare perspective, with ICERs estimated to be below CHF 15,000 per QALY gained(158,174). When using a societal perspective, the same authors concluded that escitalopram was a dominant strategy if compared to venlafaxine. Only the cost-effectiveness analysis published by Maniadakis et al. estimated that agomelatine was a dominant strategy if compared to escitalopram (168). It should be noted that in this study, due to a lack of relevant data, the authors assumed that remission rates for agomelatine and escitalopram were equivalent. Additional data showing differences in remission rates between the two treatments might easily change the results of this analysis. It should also be noted that five out of six cost-effectiveness analyses evaluating escitalopram were funded by a pharmaceutical company which produces escitalopram. Although across these studies there were methodological differences (e.g. in terms of sources of clinical inputs that were used, and the varying quality of these sources ranging from the use of individual RCTs to the use of combined estimates from meta-analyses), all of them concluded that escitalopram was highly cost-effective.

Venlafaxine was investigated in seven cost-effectiveness analyses as either intervention or comparator (Annemans, Benedict, Lenox-Smith, Maniadakis, Mencacci, Nordstrom Ramsberg). When compared with escitalopram, venlafaxine was in most cases dominated (i.e. was more expensive but less effective) or resulted being less expensive but less effective (see ICERs in the table of escitalopram versus other anti-depressants). In contrast, when compared to other anti-depressants (e.g. citalopram, duloxetine, fluoxetine, paroxetine, sertraline), venlafaxine was generally considered a dominant strategy.

Six cost-effectiveness analyses compared sertraline with placebo or a set of anti-depressants (Annemans, Armstrong, Hollingworth, Maniadakis, Mencacci, Ramsberg). Sertraline was considered a dominant strategy when compared to citalopram (from both healthcare and societal perspectives), whereas it was dominated when compared to escitalopram, venlafaxine, and agomelatine. For all other comparisons, the results were heterogenous.

Duloxetine was evaluated as a comparator strategy in four cost-effectiveness analyses. In three of them, it was dominated by escitalopram. The comparison with other ADMs showed discordant results.

The three cost-effectiveness analyses considering SSRIs as a group indicated that SSRIs are cost-effective when compared to other ADMs or usual care.

Most of the cost-effectiveness analyses investigating CBT were within-trial analyses. Overall, our review suggests that it is uncertain as to whether CBT is cost-effective or not. We identified eight cost-effectiveness analyses suggesting that CBT was cost-effective or dominant if compared to usual care or ADM. However, there were also five cost-effectiveness analyses which estimated the opposite (i.e. ADM or usual care were the dominant strategies, or the ICER for CBT versus the comparators was very high, and thus not did not indicate cost-effectiveness). Of the cost-effectiveness analyses which appeared to assess face-to-face CBT, about half reported that CBT was the dominant strategy or was cost-effective (i.e. the ICER, after cost-adaptation for Switzerland, was below CHF 100,000 per QALY gained), whereas the other half indicated the opposite. Of the cost-effectiveness analyses which evaluated internet-based CBT, seven produced ICERs below CHF 100,000 per QALY or dominant results in favour of internet-based CBT, while one study indicated the opposite, and two studies indicated that internet -based CBT was less expensive but also less effective than the comparator.

A previous systematic review of cost-effectiveness analyses of CBT for MDD published by Brettschneider et al. in 2015, reported that the majority of the identified studies showed acceptable ICERs (192). Notably, there were several methodological differences in the review by Brettschneider et al. compared with this review. The review by Brettschneider et al. included adolescent MDD populations, and did not exclude studies based on geographical location, date of publication, or comparator.

In another systematic review published in 2012 and investigating model-based cost-effectiveness analyses of MDD interventions (including antidepressant drugs), it was found that the resource use estimates used for most model-based cost-effectiveness analyses were obtained from expert opinion (193). In our systematic review, four of the model-based cost-effectiveness analyses of ADMs we identified obtained resource use estimates from expert opinion, whereas six model-based cost-effectiveness analyses of ADMs obtained resource use estimates from the published literature.

It is important to note was that there were several methodological differences between the economic systematic review and the clinical systematic review performed in this HTA. The clinical systematic review only focused on MDD populations. In contrast, the review of cost-effectiveness analyses also included populations with substantial depressive symptomology as measured by a questionnaire such as the PHQ-9 (Patient Health Questionnaire 9 item) or the CES-D (Center for Epidemiologic Studies Depression Scale), which have been shown to have high sensitivity and specificity for MDD. This is because having substantial depressive symptomology may be considered to be equivalent to having MDD by some clinicians. We excluded East Asian countries from the economics review, as these countries are likely to substantially differ to Switzerland in terms of

settings, costs, and perception of quality of life. We excluded cost-effectiveness analyses of MDD co-morbid with another disease (e.g. dementia, generalised anxiety disorder). Costs and effects might differ due to the presence of such comorbidities. We excluded cost-effectiveness analyses published from 1995 to 2005, as costs reported during this period may be outdated. Unlike the clinical systematic review which only included CBT interventions which lasted for at least 12 weeks, we included two cost-effectiveness analyses of CBT that reported a treatment duration potentially below 12 weeks (the authors reported 6-8 weekly CBT lessons/modules, but did not specify whether the lessons/modules were conducted consecutively in the shortest time possible, or whether they were distributed over a period of time exceeding 12 weeks). In general, it should be emphasized that in many cases the real duration of CBT was not specified in months, but in number of sessions or modules. The exact distribution of sessions/modules over time was often not reported. One of these studies concluded that CBT had an ICER of CHF 43,262 per QALY gained (188), and one suggested that CBT was a dominant strategy (186).
It should also be mentioned that certain ADMs that were evaluated in the clinical systematic review were not identified as an intervention or comparator in our review of cost-effectiveness analyses (e.g. bupropion).

One major strengths of this economic systematic review are the broad spectrum of interventions and comparators included. The review provides a comprehensive overview of the economic literature investigating the cost-effectiveness of ADMs and CBT among depressive patients. Another strength is the adaptation of the costs of the international literature for Switzerland. As already mentioned, this process cannot be interpreted as achieving realistic ICERs for Switzerland but may have achieved a certain approximation of cost-effectiveness levels to be expected for Switzerland. It has certainly made the results of international cost-effectiveness studies, reported for different countries and in different currencies, more comparable.

One main limitation affecting the interpretability of the available cost-effectiveness results concerns the high heterogeneity across the identified studies, which included different populations (from patients with symptoms related to depression to patients with severe MDD), different interventions and comparators, different time horizons, as well as different types of costs. Especially for CBT interventions there were significant differences across the identified studies. For example, in the cost-effectiveness analyses published by Gerhards et al. the intervention consisted of 9 lessons only, whereas in Richards et al., there were 20 sessions over 16 weeks. In other cases, the treatment schedule was not clearly reported. Several limitations concern the time horizons and treatment durations of the identified cost-effectiveness analyses. As previously reported, the time horizons of the analyses ranged from six weeks to 60 months, with most of the studies opting for a 12 to 24-month time horizon.

On one side, the short-term analyses were presumably focusing on the acute treatment phase and may thus diverge from the scoping of this project (which aimed to investigate the MDD treatment beyond the acute maintenance phase). On the other side, in the studies using a longer time horizon it was generally not possible to discern whether the analyses were based on long-term clinical data, of whether (and how) short-term effectiveness assumptions were extrapolated/adapted for long-term calculations. Unfortunately, none of the studies using a long-time horizon reported costs and QALY gained according to the treatment phase (i.e. acute treatment vs. maintenance phase).29 out of the 33 cost-effectiveness analyses included in this review used a time horizon of longer than 12 weeks; therefore suggesting that costs and QALYs were estimated beyond the acute management phase of MDD in these cost-effectiveness analyses.

Another limitation is that the majority of the cost-effectiveness analyses of ADMs were sponsored by pharmaceutical companies. This may have an influence on the effectiveness/cost assumptions used in the calculations, leading to potential biases. On the other hand, it is well known that treatment effects in CBT trials are often associated with researcher allegiance, implying a potential for bias (124–126). Furthermore, the limitations of the clinical evidence base (as discussed in the clinical part of this report), are also applicable to the review of the economic literature. The limited duration of some treatments (particularly for CBT) and limited time horizons of the cost-effectiveness models (as well as of the underlying clinical studies), are further limitations of the economic evidence presented in this report.

7.4 Conclusion

The results of the economic systematic review suggest that escitalopram may be the most cost-effective treatment among the included ADMs, followed by venlafaxine, sertraline, and duloxetine. The cost-effectiveness analyses comparing CBT or internet-based CBT with ADMs or usual care led to discordant results. Two studies investigating CBT in combination with ADM versus ADM alone reported ICERs ranging between CHF 30,000 and CHF 95,000 per QALY gained (i.e. below a hypothetical threshold of CHF 100,000 per QALY gained). The high heterogeneity in the results of the CBT studies suggest that the cost-effectiveness of this intervention may depend on how CBT is provided (e.g. number of sessions, treatment duration, setting).

8 Budget impact analysis

The budget impact analysis consisted of two main steps. First, the total number of eligible patients per year in Switzerland was estimated. This included an estimation of the total number of MDD in Switzerland as well as an estimation of the number of MDD patients being treated (since not all patients with a suspected/diagnosed MDD are treated). Second, the estimated number of eligible patients was combined with resource use and unit cost estimates extracted from the literature to approximate the total costs at a national level.
The costs were calculated for a time period of one year using a healthcare perspective.
Since the cost-effectiveness analyses identified in the systematic review did not provide any/enough information about potential differences in hospitalisation rates, hospitalisation durations, and number of physician visits between different treatment options, the costs of hospitalisations and physician visits were assumed to remain the same for all treatments. In contrast, treatment costs varied according to the treatment distribution assumptions (i.e. psychotherapy, ADM, or a combination of both) and type of ADM.

8.1 Methods

8.1.1 Number of eligible cases

The main source to estimate the number of eligible cases was the Swiss Health Survey conducted in 2017 (Schweizerische Gesundheitsbefragung 2017) (194). Prevalence estimates of MDD in Switzerland were provided by age, gender, and disease severity (195). MDD severity was assessed using the Patient Health Questionnaire (PHQ-9) (194).

In addition to assessing mental health, Swiss Health Survey participants were asked if they had been treated for a mental health problem in the last 12 months (196). Moreover, information on the consumption of ADMs in the last seven days (with or without sedatives/narcoleptics) was also collected (197).
Unfortunately, detailed information on the treatment for psychiatric problems or ADM consumptions according to MDD severity was not available. Therefore, three alternative assumptions were considered to estimate the number of eligible patients:

- Assumption 1: All patients with a MDD in the last 12 months according to the Swiss Health Survey 2017 are considered eligible.

  Advantage: the cost calculations can be performed taking into account the disease severity.
  Disadvantage: not all subjects estimated having a MDD require/request a treatment. Therefore, the total costs may be overestimated.

- Assumption 2: Only patients that reported being treated for a mental health problem are considered eligible.

  Advantage: this assumption may provide a more realistic estimation of the total number of eligible patients.
  Disadvantages: detailed information of disease severity distribution among subjects reporting being treated for mental health problems is not available. Moreover, mental health problems also include other disorders (e.g. bipolar disorder, anxiety, etc.).

- Assumption 3: Only patients that reported consuming ADMs (with or without sedatives/narcoleptics) are considered eligible.

  Advantage: patients' selection is restricted to those who are effectively treated for depression (assuming that ADM are mainly prescribed to depressive patients).
  Disadvantages: detailed information of disease severity distribution is not available. Not all MDD patients are treated with ADMs (before starting ADM, psychotherapy is usually advised). Therefore, the total number of eligible patients may be underestimated.

Although it could not provide information on severity distribution, we considered the results of Assumption 3 as the most plausible for the current project. Based on estimations previously published by Kessler et al. and Birnbaum et al., we assumed that among the patients taking ADM the majority had a severe MDD (50%) or a moderate MDD (40%), while only a minority had a mild MDD (10%) (198,199).
The probabilities reported in the Swiss Health survey were applied to the Swiss population in 2020 (according to age and gender distributions).

8.1.2 Budget impact of depression treatment

For each eligible case, the costs over a period of one year were calculated from a healthcare perspective. The costs included hospitalisations, physician visits, psychotherapy, and ADM. Costs related to laboratory tests, additional medications, or productivity loss (in terms of disability or workdays lost) were not included. Reference year for the cost calculations was 2020.

8.1.2.1 Hospitalisations and hospitalisation costs

Hospitalisation rates and durations were estimated based on a study published in 2013 by Tomonaga et al. (15). Overall, it was estimated that 31.9% of the MDD patients may require a hospitalisation, with a mean duration of 18.4 days. For mild, moderate, and

severe MDD, the estimated hospitalisation rates were 9.2%, 30.8%, and 49.1%, respectively. The mean length of stay in hospital was 3.1 days for mild MDD, 16.9 days for moderate MDD, and 31.1 days for severe MDD.

Estimating the unit costs per hospitalisation day in Switzerland is challenging. In January 2018 a new tariff system for inpatient psychiatry (Tarifstruktur für die stationäre Psychiatrie, TARPSY) was introduced. In this system, different costs weights are assigned according to disease type and duration of hospitalisation (200). For example, for depressive or bipolar depressive disorders among subjects older than 17 years of age, the cost weight for a 3-day-long hospitalisation is 1.384 per day. To estimate the hospitalisations costs for a MDD patients hospitalised for three days, the cost weight must be multiplied with the hospitalisation duration and a "hospitalisation daily base price". The daily base price can differ across different types of hospitals and regions. According to estimates of the Federal Office of Statistics, the mean daily base price in Switzerland in 2018 was CHF 681.20. Using this mean daily base price, the estimated costs for a MDD patient hospitalised for 3 days would be CHF 2,828 (i.e. 1.384 x 3 x 681.2). Table 26 illustrates few examples of cost calculations according to different lengths of stay.

Table 26: Estimated hospitalisation costs of depressive disorders according to the length of stay.

Length of stay	Cost weight	Daily base price (CHF)	Total cost (CHF)	Costs per day (CHF)
1	1.424	681	970	970
3	1.384	681	2,828	942
5	1.272	681	4,332	866
10	1.081	681	7,364	736
15	0.999	681	10,208	681
20	0.989	681	13,474	674
30	0.968	681	19,782	659
>37	0.954	681	24,045*	650

* Total costs calculated for a hospital stay of 37 days. For longer stays the total costs will be higher, whereas the costs per day should remain stable at CHF 650.

According to the duration of hospitalisation estimated in Tomonaga et al. (15), we assumed daily hospitalisation costs of CHF 2,923 for mild MDD (3.1 days x CHF 942/day), CHF 11,454 for moderate MDD (16.9 days x CHF 678/day), and CHF 20,211 for severe MDD (31.1 days x CHF 650/day).

8.1.2.2 Physician visits

The estimated number of physician visits was estimated based on a study published in 2013 by Tomonaga et al. (15). Subjects with mild, moderate, or severe MDD were assumed to have 5.81, 6.52, and 7.39 physician visits per year.

The costs for a single visit may vary depending on its duration, on the performed controls (e.g. blood test), on the involved staff, and other aspects. We conservatively assumed costs of CHF 100 per physician visit. This resulted in mean costs for a physician visits of CHF 581 for mild MDD, CHF 652 for moderate MDD, and CHF 739 for severe MDD.

8.1.2.3 Psychotherapy and ADM

According to the study published by Tomonaga et al., most of the patients (87.5%) suffering from MDD undergo psychotherapy. In contrast, the use of ADMs was less frequent (e.g. 52.2% for SSRIs, 36.8% for SNRIs, or 21.1% for mirtazapine).

Considering that the treatment for MDD may consist in psychotherapy alone, ADM alone, or a combination of both, we investigated several possible scenarios. We assumed that all eligible patients would be treated. Table 27 summarizes the investigated scenarios.

Table 27. Treatment distributions according to several scenarios.

	Psychotherapy alone	Antidepressant treatment alone	Psychotherapy and antidepressant treatment
Scenario 1	100%	0%	0%
Scenario 2	0%	100%	0%
Scenario 3	0%	0%	100%
Scenario 4	10%	0%	90%
Scenario 5	20%	0%	80%
Scenario 6	50%	0%	50%
Scenario 7	25%	25%	50%

According to several sources, the costs of psychotherapy may range between CHF 100 and CHF 250 per session of 45-60 minutes (201,202). In the main analyses we assumed costs of CHF 150 per session. We also assumed that patients undergoing psychotherapy would have 12 sessions per years. This estimation was comparable with the assumptions made in several cost-effectiveness analyses included in the economic systematic review.
The costs for ADMs were extracted from compendium.ch (203). For all investigated ADMs, several products with different characteristics (e.g. pieces per pack, dosage, producer, and costs) were available. The costs per dose was calculated for each product, and mean costs per dose were calculated across all available products providing the same antidepressant substance. In order to perform sensitivity analyses, the costs of the less and of the most expensive products (in terms of costs per dose) were also extracted. Costs per dose were then multiplied by 365 to estimate the treatment costs per year. Table 28 provides a summary of the mean, minimum and maximum yearly costs for ADMs, assuming that the patients were treated for an entire year.
To better evaluate the potential budget impact of different ADMs, the total costs were calculated under the assumption that all patients would receive the same drug.

Table 28. Antidepressant treatment costs per year (according to drug prices as per 24. March 2021).

	Mean (CHF)	Minimum (CHF)	Maximum (CHF)
SSRI			
Citalopram	420	248	690
Escitalopram	339	175	664
Fluoxetine	252	193	449
Fluvoxamine	336	230	442
Paroxetine	358	259	544
Sertraline	591	318	1091
SNRI			
Venlafaxine	442	219	1110
Duloxetine	548	245	1168
Others			
Mirtazapine	438	172	606
Agomelatine	533	442	646

8.1.3 Sensitivity analyses

In a first sensitivity analysis, the percentage of the population that may be eligible for MDD treatment in Switzerland was varied by ±30%. Second, we varied the estimated mean lengths of stay for mild, moderate, and severe MDD by ±30%. Third, the estimated number of physician visits were also varied by ±30%. In a fourth sensitivity analysis, the costs for a single psychotherapy session were varied from CHF 100 to CHF 250. In a sixth sensitivity analysis, the number of psychotherapy sessions was changed, ranging from a minimum of 6 sessions to a maximum of 40 sessions per year). Finally, the total costs of antidepressant treatment were calculated used the lowest as well as the highest market prices (per dose).

8.2 Results

8.2.1 Estimated number of eligible cases

The estimated number of eligible cases based on three different assumptions as described above, is provided in the following tables. Table 29 summarises the estimated number of MDD cases in Switzerland in 2020 (Assumption 1), and Table 30 illustrates the estimated number of patients that reported being treated for mental health problems (Assumption 2) as well the estimated number of patients that reported consuming ADMs (Assumption 3).

According to the data collected through the Swiss Health Survey in 2017, one third of the Swiss population aged 15 years or more may suffer from MDD (25.9% mild MDD, 5.9% moderate MDD, and 2.8% severe MDD). The great majority of the cases (75%) have a mild form of MDD, while moderate and severe MDD are considerably less frequent (17% and 8%, respectively).

If only subjects reporting being treated for mental health problems or reporting taking ADMs are considered, the estimated number of eligible cases is much lower (from more than 2.5 million cases in Assumption 1 to 449,555 cases in Assumption 2 and 334,835 cases in Assumption 3).

Table 29. Estimated number of major depressive disorder (MDD) cases in Switzerland in 2020, by gender and disease severity.

	Mild MDD	Moderate MDD	Severe MDD	All MDD
Males	819,121	180,964	103,513	1,103,598
Females	1,102,296	253,704	100,874	1,456,874
Total	1,918,786	434,012	204,424	2,557,222

* Assessed using the PHQ-9 questionnaire, which evaluate the patient health over the last two weeks. NB: In the Swiss Health Survey the selected participants, representative for the Swiss population, are recruited uniformly through an entire year (i.e. every month the same number of interviews are conducted). Rationale behind this is that the health state and behaviour of the participants may be subjected to seasonal changes. Although the PHQ-9 questionnaire evaluates the patient health over a period of only two weeks, it is assumed that the percentage of subjects showing MDD symptoms in the Swiss Health Survey represent a good approximation of the yearly MDD prevalence in Switzerland.

Table 30. Estimated number of patients treated for mental health problem (in the last 12 months) and estimated number of patients treated with antidepressants (in the last seven days).

	Cases treated for mental health problems	Cases treated with antidepressants
Males	162,131	121,361
Females	288,104	213,677
Total	449,555	334,835

As already mentioned in the methods section, we considered the estimation based on Assumption 3 as the most plausible for our purpose. To estimate the costs of MDD, the total number of cases treated with ADMs was allocated to mild, moderate, or severe MDD according to published estimates. The resulting distribution of patients is summarized in Table 31.

Table 31. Severity distribution of major depressive disorder (MDD) cases treated with antidepressant medications (ADMs) according to Kessler et al. and Birnbaum et al.

	Mild MDD	Moderate MDD	Severe MDD	All MDD
Number of cases	33,483	133,934	167,417	334,835

8.2.2 Budget impact of depression treatment

8.2.2.1 Hospitalisation and physician visits costs

As mentioned in the methods, the cost-effectiveness analyses identified in the systematic review did not provide any/enough information about potential differences in hospitalisation rates, hospitalisation durations, or number of physician visits between different treatment options. Therefore, the costs of hospitalisations and physician visits were assumed to remain the same for all treatments, independently of the chosen treatment option (i.e. psychotherapy, ADM, or both) and ADM (e.g. SSRIs, SNRIs, etc.).

Table 32 summarizes the estimated total costs for hospitalisations and physician visits due to MDD in Switzerland in 2020. The total costs due to hospitalisations and physician visits were estimated to reach CHF 5,016 million and CHF 230 million, respectively. Two third of the total costs were due to severe, 31% to moderate, and only 2% to mild MDD.

Table 32. Estimated total costs for hospitalisations and physician visits due to major depressive disorder (MDD) in Switzerland in 2020 (in million Swiss Francs (mio CHF)).

	Mild MDD	Moderate MDD	Severe MDD	All MDD
Hospitalisation costs (mio CHF)	97.87	1,534.08	3,383.67	5,015.62
Physician visits costs (mio CHF)	19.45	87.32	123.72	230.50
Total	117.33	1,621.40	3,507.39	5,246.12

8.2.2.2 Psychotherapy and ADM costs

To estimate the costs of psychotherapy and ADM, several scenarios with different treatment distributions, as described above, were investigated. Considering that the review of the cost-effectiveness analyses published so far suggested that escitalopram may be the most cost-effective antidepressant among the investigated drugs, for the main analyses we assumed that all patients receiving ADM received escitalopram (the potential economic impact of other antidepressant is illustrated at the end of this section).

The treatment costs ranged from CHF 114 million in Scenario 2 (assuming that all treated MDD patients would receive ADM only) to CHF 716 million in Scenario 3 (assuming that all MDD patients would receive both psychotherapy and ADM) (Table 33).

Table 33. Psychotherapy and ADM costs (in million Swiss Francs (mio CHF)) for major depressive disorder (MDD) according to several scenarios.

	Mild MDD (mio CHF)	Moderate MDD (mio CHF)	Severe MDD (mio CHF)	All MDD (mio CHF)
Scenario 1 (100% Psy)	60.27	241.08	301.35	602.70
Scenario 2 (100% AD)	11.37	45.46	56.83	113.66
Scenario 3 (100% Psy+AD)	71.64	286.54	358.18	716.36
Scenario 4 (10% Psy & 90% Psy+AD)	70.50	282.00	352.50	705.00
Scenario 5 (20% Psy & 80% Psy+AD)	69.36	277.45	346.82	693.63
Scenario 6 (50% Psy & 50% Psy+AD)	65.95	263.81	329.77	659.53
Scenario 7 (25% Psy, 25% AD, & 50% Psy+AD)	53.73	214.91	268.64	537.27

To better evaluate the potential budget impact of different ADMs, the total medication costs were calculated assuming that all patients would receive the same drug. As illustrated in Table 34, the total costs assuming that only one type of ADM would be prescribed to all eligible patients ranged from CHF 84 million (for fluoxetine) to CHF 198 million (for sertraline).

Table 34. Antidepressant treatment costs (in million Swiss Francs (mio CHF)) for major depressive disorder (MDD) per year (according to drug prices as per 24. March 2021).

	Mild MDD (mio CHF)	Moderate MDD (mio CHF)	Severe MDD (mio CHF)	All MDD (mio CHF)
SSRI				
Citalopram	14.05	56.22	70.27	140.55
Escitalopram	11.37	45.46	56.83	113.66
Fluoxetine	8.43	33.73	42.16	84.33
Fluvoxamine	11.24	44.97	56.22	112.44
Paroxetine	11.98	47.91	59.89	119.77
Sertraline	19.80	79.20	98.99	197.99
SNRI				
Venlafaxine	14.79	59.15	73.94	147.88
Duloxetine	18.33	73.33	91.66	183.32
Others				
Mirtazapine	14.67	58.66	73.33	146.66
Agomelatine	17.84	71.37	89.22	178.43

8.2.2.3 Total direct medical costs of MDD

Based on the above, the direct medical costs of MDD in Switzerland were estimated to range between CHF 5,330 million (assuming that MDD patients are treated exclusively with the less expensive ADM, without receiving any kind of psychotherapy) to CHF 6,032 million (assuming that all MDD patients undergo psychotherapy and receive the most expensive ADM).
Hospitalisation costs accounted for more than 80% of the total direct medical costs (ranged from 82% to 92% depending on the psychotherapy and ADMs assumptions).

8.2.2.4 Sensitivity analyses

In the first sensitivity analysis, the percentage of the population that may be eligible for MDD treatment in Switzerland was varied by ±30%. The total number of eligible cases ranged from 234,384 to 435,285. The estimated total costs of MDD ranged from CHF 3,731 million to CHF 7,842 million (Table 35).

In the second sensitivity analyses the estimated mean lengths of stay for mild, moderate, and severe MDD were varied by ±30%. The results were comparable to those of the first sensitivity analysis (resulting range CHF 3,826 to CHF 7,552 million), emphasizing that hospitalisations are the main cost driver in MDD patients.
The results of the third and fourth sensitivity analyses suggested that the number of physician visits and the costs per psychotherapy session have a relatively small impact on the total costs of MDD.
In the sixth sensitivity analysis, the number of psychotherapy sessions was changed, ranging from a minimum of 6 sessions to a maximum of 40 sessions per year. The total costs assuming only six psychotherapy sessions per year were similar to those in the base case (assuming 12 sessions per year). In contrast, assuming 40 sessions per year, the estimated total costs were estimated to range from CHF 5,330 million to CHF 7,438 million.

Table 35. Results of the sensitivity analyses

	Estimated total costs (Mio. CHF)
Base case	5,330 – 6,032
Percentage of eligible cases +30%	6,930 – 7,842
Percentage of eligible cases -30%	3,731 – 4,223
Length of stay +30%	6,835 – 7,552
Length of stay -30%	3.826 – 4,542
Physician visits +30%	5,400 – 6,116
Physician visits -30%	5,261 – 5,978
Psychotherapy costs (CHF 100 per session)	5,330 – 5,831
Psychotherapy costs (CHF 250 per session)	5,330 – 6,434
Psychotherapy sessions (6 x 150 CHF)	5,330 – 5,731
Psychotherapy sessions (40 x 150 CHF)	5,330 – 7,438

*: The less expensive scenario assumed that MDD patients are treated exclusively with the less expensive antidepressant medication, without receiving any psychotherapy. Therefore, minimal costs remained identical to the base case.

In the last sensitivity analysis, the total costs of ADM were calculated using the lowest as well as the highest market prices (per dose). The potential total costs for each ADM are reported in Table 36. When we assumed that only the least expensive products on the market would be used, the estimated costs decreased significantly for all ADMs. Percentage cost reductions were particularly high for escitalopram (-48%), sertraline (-46%) venlafaxine (-50%), duloxetine (-55%), and mirtazapine (-55%). On the other side, the use of the most expensive products led to higher medication costs. Cost increases were higher than 50% for all antidepressants except fluvoxamine

Table 36. Estimated minimal and maximal costs of antidepressant medication (ADM) (assuming that all major depressive disorder (MDD) patients would be treated with the same drug).

	Mean (Mio. CHF)	Minimum (Mio. CHF)	Change in %	Maximum (Mio. CHF)	Change in %
SSRI					
Citalopram	140.55	83.11	-41%	230.99	+64%
Escitalopram	113.66	58.66	-48%	222.43	+96%
Fluoxetine	84.33	64.77	-23%	150.32	+78%
Fluvoxamine	112.44	77.00	-32%	147.88	+32%
Paroxetine	119.77	86.77	-28%	182.10	+52%
Sertraline	197.99	106.33	-46%	365.42	+85%
SNRI					
Venlafaxine	147.88	73.33	-50%	371.53	+151%
Duloxetine	183.32	81.88	-55%	391.09	+113%
Others					
Mirtazapine	146.66	57.44	-61%	202.88	+38%
Agomelatine	178.43	147.88	-17%	216.32	+21%

8.3 Discussion

The budget impact analysis estimated the costs of different combinations of MDD treatments in Switzerland in 2020, using a healthcare perspective (i.e. considering direct medical costs only). The relative magnitudes of antidepressant and psychotherapy costs on the one hand, and hospitalisation and physician visit costs on the other, were also assessed.
The estimated number of subjects suffering from MDD in Switzerland was estimated to be approximatively 2.6 million. However, according to data collected in the Swiss Health Survey 2017, the number of patients being treated was much lower. It was estimated that in 2020 there were 334,835 patients being actively treated for MDD.
The total costs of MDD were estimated to range between CHF 5,330 million (assuming that MDD patients would be treated exclusively with the least expensive ADM, without receiving any kind of psychotherapy) to CHF 6,032 million (assuming that all MDD patients would undergo psychotherapy and receive the most expensive ADM). Depending on the distribution of treatments and cost assumptions, hospitalisation costs represented 82% to 92% of the total costs. Physician visits, psychotherapy, and ADM costs seemed to play a relatively minor role. The treatment costs for psychotherapy and depression treatment ranged from CHF 84 million (assuming that all treated MDD patients would receive the least expensive ADM only) to CHF 800 million (assuming that all MDD patients would receive both psychotherapy and the most expensive ADM). Treatment with psychotherapy alone for all MDD patients was estimated to costs CHF 603 million (assuming 12 sessions per year). The conducted sensitivity analyses emphasised that number of eligible patients and the length of stay in hospital were the factors that influenced the total costs most.

One of the major strengths of the budget impact analysis was the use of Swiss data to estimate the total number of eligible cases (Swiss Health Survey) and to estimate medical resource use according to MDD severity (study on the economic burden of depression in Switzerland published in 2013 by Tomonaga et al. (15)). Unit costs for a single hospitalisation were updated using the recently introduced Swiss tariff system for inpatient psychiatry (Tarifstruktur für die stationäre Psychiatrie, TARPSY) (200). Similarly, unit costs for ADMs were estimated by extracting cost information for all relevant products on the Swiss market (according to compendium.ch).

The budget impact estimation required numerous assumptions. Therefore, substantial limitations apply. First, for the estimation of the number of eligible patients we decided to base the calculation on data concerning antidepressant consumption collected in the Swiss Health Survey 2017. Considering that not all patients treated for MDD may use an ADM, the estimated number of eligible cases may represent an underestimation of the reality. The Swiss Health Survey also provided estimations of the total number of subjects suffering from MDD (approximately 2.5 million persons) and of the total number of

subjects treated for a mental health problem (approximately 427,000 persons). Regarding the first estimate, we considered it as unrealistic that so many subjects (close to a third of the population) would be treated for MDD. The second was also considered an overestimation since mental health problems also include disorders other than MDD (e.g. bipolar disorder, anxiety, etc.). A second limitation concerns the MDD severity distribution across eligible cases. The data of the Swiss Health Survey on severity distribution suggested that the majority of MDD patients have mild disease (1.8 million, 75%), followed by moderate (413,000, 17%) and severe (194,000, 8%) forms. Since it is reasonable to assume that subjects suffering from more severe MDD are more often treated, we decided to not apply this severity distribution to the number of treated cases. As in the study previously published by Tomonaga et al., we used severity distributions of two published studies (198,199). In Kessler et al., the results of a study from the National Comorbidity Survey Replication (NCS-R) including 9,090 participants 18 years of age or older in the US, the depression prevalence for a 12-month period was 6.6 %, with 10.4 % of cases of depression classified as mild, 38.6 % as moderate and 50.9 % as severe or very severe. Similarly, Birnbaum et al. reported that in a sample of 539 US workforce respondents with depression, 13.8 % were classified as mild, 38.5 % as moderate and 47.7 % as severe. As a second limitation, detailed information on the current treatment of MDD patients in Switzerland was not available. Such information would include, for example, the number of MDD patients undergoing psychotherapy, the type and intensity of psychotherapy (face-to-face vs. internet-based; personal vs. group therapy; monthly vs. weekly sessions; short vs. long sessions, etc.), the type and intensity of ADMs, the purchased/prescribed antidepressant products (for all ADMs there are several producers, different dosages, different pack-sizes, and different prices available). Third, estimates of hospitalisation rates and length of stay were based on a study investigating the costs of depression in the first 12 months after diagnosis (15). It is possible that hospitalisation rates during the first months after diagnosis, especially in the case of severe MDD, may be higher than later on, with a longer length of stay and, consequently, higher direct costs. Fourth, in the cost calculations we assumed that the same ADM would be taken for a whole year. Therefore, treatment switch to other drugs or treatment discontinuation were not considered. Another limitation concerns the exclusion of costs of diagnostic tests and concomitant medications. Considering that the identified cost-effectiveness analyses did not report enough information on potential differences in diagnostic tests and concomitant medication between psychotherapy, ADM, or combination treatment, the present budget impact estimation was based on hospitalisation, physician visits, psychotherapy, and anti-depressants treatment costs only. Similarly, information concerning differences in productivity loss (for patients as well as caregivers), depression-related disability or early retirement, and depression related suicides according to different treatment options was not sufficient to perform the analyses from a societal perspective. Nevertheless, it should be emphasized that the total burden of MDD in Switzerland (from a healthcare and societal perspective) may be much higher (especially from a societal perspective including the costs of loss productivity). For

example, in a study on the costs non-communicable in Switzerland published in 2014, the direct and indirect costs related to mental health disorders were estimated to reach, respectively, CHF 6,349 million and CHF 10,638 (204).

8.4 Conclusion

The results of the budget impact analysis suggested that the total direct costs of MDD may range between CHF 5,330 million and CHF 6,032 million. The main cost drivers were the estimated number of MDD patients being treated and the hospitalisations. Physician visits, psychotherapy and ADM costs covered less than 20% of the total costs. The costs of psychotherapy and ADM depended on the assumed treatment distribution. For example, treatment based on psychotherapy alone was estimated to cost CHF 603 million, whereas treatment based on ADM alone was considerably less expensive (e.g. CHF 113 million for escitalopram or CHF 148 million for venlafaxine). If all MDD patients underwent psychotherapy and take ADMs, the costs for these two treatment modalities would range between CHF 687 million and CHF 801 million.

9 Overall Conclusion

This HTA attempted a comprehensive evaluation of the clinical efficacy, safety, benefit-harm balance and health economic characteristics of ADM and CBT as a mid- to long-term treatment in patients with MDD in Switzerland.

In the assessment of the clinical efficacy and safety, the available evidence suggested that both ADM and CBT are effective in reducing the risk of relapse and recurrence. However, there was no statistical evidence of the superiority of one treatment over the other. In terms of QoL, we found that while there was an improvement in QoL over time with both ADM and CBT, there was no significant difference between the two. Similarly, there were improvements in the social functioning of patients receiving ADM, CBT or their combination. However, there was no evidence that either was more effective than the other. Regarding the safety of the treatments, we found that CBT and ADM plus CBT were generally more accepted and tolerated by patients compared to ADM alone. Furthermore, we found that reporting of AEs was inconsistent across trials, and was especially scarce in those evaluating CBT. Among RCTs who reported AEs, a high proportion of patients experienced adverse effects, particularly among those receiving ADM. Our findings need to be interpreted carefully in light of the limitations such as the large heterogeneity of included studies as well as issues related to the risk of bias arising from the lack of blinding in CBT trials.

The available evidence on relative treatment effects, outcomes and preferences showed a favourable benefit-harm balance for CBT over ADM and for the combination of CBT and ADM over either monotherapy. The results remained consistent when using alternative assumptions about baseline risk or preferences for relapse or harms (specific AEs and study drop-outs). However, detailed data on mid- to long-term outcomes (e.g., recovery and recurrence rather than relapse) and harm outcomes relating to both ADM and CBT interventions, as well as preferences elicited from patients, would allow a better evaluation of the different interventions and the conduct of a more detailed BHA.

The cost-effectiveness analyses comparing CBT or internet-based CBT with ADMs or usual care led to discordant results. Although the clinical review indicated that CBT is clinically efficient, interventions that are clinically efficient may not necessarily be cost-effective, and the discordant results from the economics review indicate there is uncertainty as to whether CBT is cost-effective or not. Two studies investigating CBT in combination with antidepressants versus ADM alone reported ICERs ranging between CHF 30,000 and CHF 95,000 per QALY gained. The high heterogeneity in the results of the CBT studies suggested that the cost-effectiveness of this is intervention may depend on how CBT is provided (e.g. number of sessions, treatment duration, setting).

The budget impact analysis suggested that the total direct medical costs of MDD per year may range between CHF 5,330 million and CHF 6,032 million. The main cost drivers were the estimated number of MDD patients being treated and hospitalisations. Physician visits, psychotherapy and ADM costs covered less than 20% of the total costs. This finding highlights that hospitalisation due to MDD is an important clinical outcome that, along with other consequences for occupational activity and well-being, should ideally be captured by clinical trials and observational studies to allow for a more comprehensive assessment of MDD treatments. The costs of psychotherapy and ADM depended on the assumed treatment distribution. For example, treatment based on psychotherapy alone was estimated to cost CHF 603 million, whereas treatment based on ADM alone was considerably less expensive (e.g. CHF 113 million for escitalopram or CHF 148 million for venlafaxine). If all MDD patients underwent psychotherapy and take ADMs, the costs for these two treatment modalities would range between CHF 687 million and CHF 801 million.

In conclusion, we found that while both ADM and CBT interventions appear to be efficient options in the management of MDD, none appeared to definitively perform better than the other. While our benefit-harm assessment seemed to show that CBT interventions may provide a greater clinical benefit for MDD patients compared to ADM (due to lower reported adverse effects in CBT), our cost-effectiveness analysis, adapted to the Swiss context, revealed that CBT may also be more expensive depending on how it is conducted (number of sessions, online vs. face-to-face). However, these findings need to be carefully interpreted given the methodological shortcomings of the review and the evidence base, as well as the potential limited applicability of findings of controlled trials to real-world clinical settings.

10 References

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11 Appendix

11.1 Clinical Effectiveness Appendix

11.1.1 Additional information

11.1.1.1 List of available antidepressants by class and drug in Switzerland*

Class	Drug	Brand name (Company)
SSRI	Escitalopram	Cipralex (Lundbeck)
	Citalopram	Citalopram Helvepharm (Helvepharm) Citalopram Mepha (Mepha Pharma) Citalopram Sandoz (Sandoz Pharmaceuticals) Citalopram Streuli (Streuli Pharma) Claropram (Axapharm) Claropram Spirig HC (Spirig HealthCare) Seropram (Lundbeck)
	Paroxetine	Deroxat (GlaxoSmithKline) Paronex ((Sandoz Pharmaceuticals)) Paroxetin Helvepharm (Helvepharm) Paroxetin Mepha (Mepha Pharma) Paroxetin Spirig (Spirig HealthCare)
	Fluvoxamine	Floxyfral (Mylan Pharma)
	Fluoxetine	Fluctine (Eli Lilly) Fluoxetin Axapharm(Axapharm) Fluoxetin Helvepharm (Helvepharm) Fluoxetin Mepha (Mepha Pharma) Fluoxetin Sandoz (Sandoz Pharmaceuticals) Fluoxetin Spirig (Spirig HealthCare)
	Sertraline	Seralin Mepha ((Mepha Pharma)) Sertragen (Streuli Pharma) Sertralin Helvepharm (Helvepharm) Sertralin Pfizer (Pfizer) Sertralin Sandoz eco (Sandoz Pharmaceuticals) Sertralin Spirig HC (Spirig HealthCare) Zoloft (Pfizer)
SNRI	Duloxetine	Cymbalta (Eli Lilly) Duloxetin Axapharm (Axapharm) Duloxetin Mepha (Mepha Pharma) Duloxetin NOBEL (NOBEL Pharma) Duloxetin Sandoz (Sandoz Pharmaceuticals) Duloxetin Zentiva (Helvepharm) Duloxetin Spirig HC (Spirig HealthCare)
	Venlafaxine	Efexor ER (Pfizer) Venlafaxin ER Sandoz (Sandoz Pharmaceuticals) Venlafaxin Mepha ER (Mepha Pharma) Venlafaxin Pfizer ER (Pfizer) Venlafaxin (Helvepharm) Venlafaxin Spirig HC (Spirig HealthCare) Venlax ER (Drossapharm)
TCA	Clomipramine	Anafranil (Novartis)
	Amitriptyline	Saroten (Lundbeck)
	Doxepin	Sinquan (Pfizer)
	Trimipramine	Surmontil (Sanofi-Aventis) Trimipramin Sandoz (Sandoz Pharmaceuticals) Trimipramine Zentiva (Helvepharm)
Atypical antidepressants	Mirtazapine	Mirtazapin Helvepharm (Helvepharm) Mirtazapin Mepha (Mepha Pharma) Mirtazapin Sandoz eco (Sandoz Pharmaceuticals) Mirtazapin Spirig HC (Spirig HealthCare) Mirtazapin Streuli (Streuli Pharma) Remeron (MSD Merck Sharp & Dohme)
	Agomelatine	Valdoxan (Servier)
	Bupropion	Wellbutrin X, Zyban (GlaxoSmithKline)
MAOIs	Moclobemide	Aurorix (MEDA Pharma)
SARI	Trazodone	Trazodon Sandoz (Sandoz Pharmaceuticals)

		Trittico and trittico retard (OM Pharma Suisse AG)
Tetracyclic antidepressant	Mianserin	Mianserin Mepha 30 (Mepha Pharma)
NARI	Reboxetine	Edronax (Pfizer)
Other antidepressants	Vortioxetine	Brintellix (Lundbeck)

SSRI: Selective serotonin reuptake inhibitors, SNRI: Serotonin-norepinephrine reuptake inhibitors, TCA: Tricyclic antidepressants, MAOI: Monoamine oxidase inhibitors; NARI: noradrenaline reuptake inhibitor, SARI: Serotonin Antagonists and Reuptake Inhibitor
*as listed on http://www.xn--spezialittenliste-yqb.ch/

11.1.1.2 Classification of different CBT according to the Cochrane Collaboration Depression, Anxiety and Neurosis Review Group (CCDAN) classification system

Standard CBT	Third wave therapies
○ Cognitive therapy ○ Problem-solving therapy ○ Rational-emotive behaviour therapy ○ Standard cognitive behaviour therapy (including face-to-face and computerized/internet based CBT) ○ CBT with mindfulness ○ CBT with exercise	○ Behavioural activation ○ Mindfulness-based compassionate living ○ Acceptance and commitment therapy ○ Dialectical behaviour therapy ○ Cognitive behavioural analysis system of psychotherapy

11.1.1.3 Categorization of different adverse effects using the MedDRA SOC classification

Category	Adverse effect
Respiratory, thoracic and mediastinal disorders	Influenza like symptoms
	Upper respiratory tract infection
	Rhinitis
Gastrointestinal disorders	Any Gastrointestinal side effect
	Gastroenteritis
	Abdominal pain
	Nausea
	Vomiting
	Diarrhoea
	Constipation
	Dyspepsia
	Dry mouth
Hepato-biliary disorders	Hepatotoxicity
	Liver function abnormalities
Renal and urinary disorders	Renal function abnormalities
	Any genitourinary side effects
	Micturition abnormalities
Cardiac disorders	Any cardiac side effects
	Any new ECG abnormalities
	Qtc prolongation
	Arrythmia
	Increased heart rate
	Decreased heart rate
Vascular disorders	Hypertension
	Postural hypotension
	Flushing
	Vasodilation
Metabolism and nutrition disorders	Anorexia
	Increased appetite

	Decreased appetite
	Weight loss
	Weight gain
	Hyponatremia
	Any biochemical lab abnormalities
Nervous system disorders	Any neurological
	Headache
	Dizziness
	Drowsiness
	Increased sleep
	Decreased sleep
	Brain haemorrhage
	Seizure
	Stroke
	Insomnia
	Tremor
	Memory difficulty
Reproductive system and breast disorders	Any Sexual dysfunction
	Increased libido
	Decreased libido
	Orgasmic dysfunction
	Anorgasmia
	Ejaculation disorder
	Premature ejaculation
	Delayed ejaculation
	Erectile dysfunction
	Impotence
Endocrine disorders	Diabetes
	Triglyceride/cholesterol abnormalities
Blood and lymphatic system disorders	Bleeding
Musculoskeletal and connective tissue disorders	Bone fractures
	Muscle pain
	Twitching
Psychiatric disorders	Any psychological side effects
	Deterioration/Worsening depression
	Emergence of new depression symptoms
	Anxiety
	Panic
	Negative wellbeing
	Mania/psychosis
	Dependency
	Restlessness
	Anger/crying
	Changes in family relations
	Strains in family relations
	Emotional disturbances during sessions
	Akathisia
	Irritability
	Increased dream activity
	Agitation
Suicidal behaviour	Suicidal thoughts
	Attempted suicides
	Completed suicides
Mortality	Death from any cause
General	Any anticholinergic side effect
	Serotonin syndrome symptoms
	Any infections
	Weakness or fatigue
	Blurred vision
	Sweating
Eye disorders	Cataracts

11.1.2 Search strategies

11.1.2.1 Search strategies for step I

Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Depression] explode all trees	11921
#2	MeSH descriptor: [Depressive Disorder] explode all trees	11990
#3	depress*	103427
#4	#1 or #2 or #3	103469
#5	(antidepress* or anti-depress* or "anti depress*" or MAOI* or RIMA* or “monoamine oxidase inhibit*” or ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) NEAR (uptake or reuptake or re-uptake or "re uptake")) or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic* or pharmacotherap* or psychotropic* or "drug therapy”)	396344
#6	MeSH descriptor: [Antidepressive Agents] explode all trees	5696
#7	MeSH descriptor: [Serotonin and Noradrenaline Reuptake Inhibitors] explode all trees	54
#8	MeSH descriptor: [Monoamine Oxidase Inhibitors] explode all trees	385
#9	MeSH descriptor: [Antidepressive Agents, Tricyclic] explode all trees	968
#10	MeSH descriptor: [Antidepressive Agents, Second-Generation] explode all trees	1328
#11	(Agomelatine or Amitriptylin*or Buproprion or Amfebutamone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Desvenlafaxine or Duloxetine or Doxepin or Escitalopram or Fluoxetine or Fluvoxamine or Imipramin or (Lu AA21004 or Vortioxetine) or Mianserin or Mirtazapine or Moclobemide or Paroxetine or Reboxetine or Sertraline or Trazodone or Trimipramine or Vortioxetine or Venlafaxine)	16591
#12	#5 or #6 or #7 or #8 or #9 or #10 or #11	401707
#13	CBT	8291
#14	(cognitive NEAR behav* NEAR (therap* or theor* or intervention* or train* or treat* or psychotherap* or program* or method* or approach*))	20685
#15	MeSH descriptor: [Cognitive Behavioral Therapy] explode all trees	8693
#16	mindfulness or (acceptance and commitment)	6044
#17	(problem-solving or problem solving) NEAR (therap* or theor* or intervention* or train* or treat* or psychotherap* or program* or method* or approach*)	7993
#18	(meta-cognitive or metacognitive) NEAR (therap* or theor* or intervention* or train* or treat* or psychotherap* or program* or method* or approach*)	415
#19	(third-wave or third wave) NEAR (therap* or theor* or intervention* or train* or treat* or psychotherap* or program* or method* or approach*)	12637
#20	(rational-emotive or rational emotive) NEAR (therap* or theor* or intervention* or train* or treat* or psychotherap* or program* or method* or approach*)	1457
#21	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20	46397
#22	#4 and (#12 or #21)	50089
#23	MeSH descriptor: [Meta-Analysis as Topic] explode all trees	301
#24	MeSH descriptor: [Systematic Reviews as Topic] explode all trees	16
#25	((systematic or literature or umbrella) NEAR (review* or overview*))	25557

#26	meta-analy* or metaanaly* or meta analy*	25181
#27	#23 or #24 or #25 or #26	35863
#28	#22 and #27 with Publication Year from 2018 to 2020, in Trials	**292**

OVID MEDLINE

ID	Search	Hits
#1	exp depressive disorder, major/ or exp depressive disorder/ or exp depression/	215357
#2	depress*.ti.	146407
#3	1 or 2	252246
#4	(antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or serotonin modulator*).mp.	176212
#5	exp Antidepressive Agents/	148399
#6	exp Neurotransmitter Uptake Inhibitors/	146303
#7	exp Monoamine Oxidase Inhibitors/	21659
#8	(Agomelatine or Amitriptylin*or Buproprion or Amfebutamone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Desvenlafaxine or Duloxetine or Doxepin or Escitalopram or Fluoxetine or Fluvoxamine or Imipramin or (Lu AA21004 or Vortioxetine) or Mianserin or Mirtazapine or Moclobemide or Paroxetine or Reboxetine or Sertraline or Trazodone or Trimipramine or Vortioxetine or Venlafaxine).mp.	44878
#9	4 or 5 or 6 or 7 or 8	325093
#10	CBT.mp.	10605
#11	exp Cognitive Therapy/	28386
#12	(cognitive adj2 behavio?ral adj3 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	33641
#13	mindfulness.mp.	7547
#14	(acceptance and commitment).mp.	1750
#15	((problem-solving or problem solving) adj2 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	2197
#16	((meta-cognitive or metacognitive) adj2 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	496
#17	((rational-emotive or rational emotive) adj2 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	292
#18	((third-wave or third wave) adj2 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	87
#19	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	46113
#20	3 and (9 or 19)	61613
#21	(((systematic or literature or umbrella) adj2 (review* or overview*)) or meta-analy* or metaanaly*).ti,ab.	406505

#22	exp meta-analysis as topic/	19586
#23	exp systematic review as topic/	3550
#24	exp Review Literature as Topic/	13963
#25	(meta-analysis or systematic review).pt.	192894
#26	21 or 22 or 23 or 24 or 25	441913
#27	20 and 26	3709
#28	limit 27 to yr="2018 -Current"	736

11.1.2.2 Search strategies for step II

Review 1 (Cuijpers et al)

R1. Cochrane

ID	Search	Hits
#1	MeSH descriptor: [Depressive Disorder] explode all trees	11990
#2	depress*	103436
#3	#1 or #2	103478
#4	major depressive disorder	12657
#5	#3 or #4	103478
#6	mood disorder	8129
#7	affective disorder	4225
#8	#6 or #7	10906
#9	#5 or #8	106332
#10	CBT	8294
#11	Cognitive Behav* therap*	25149
#12	acceptance commitment	1205
#13	mindfulness	5186
#14	metacognitive therap*	393
#15	self control training	10619
#16	#10 or #11 or #12 or #13 or #14 or #15	39123
#17	Randomized Controlled Trial'':ti,ab,kw	694841
#18	#9 and #16 and #17	9771
#19	#18 in Trials	9029
	Limit Year: 2018-2020	2228

R1. Embase

ID	Search	Hits
#20	#19 AND (2018:py OR 2019:py OR 2020:py)	**1486**
#19	#7 AND #18	8294
#18	#10 NOT #17	3804030
#17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	3240629
#16	'random field*':ti,ab OR (('random cluster' NEAR/4 sampl*):ti,ab) OR (review:ab AND review:it NOT trial:ti) OR ('we searched':ab AND (review:ti OR review:it)) OR 'update review':ab OR ((databases NEAR/5 searched):ab) OR ((rat:ti OR rats:ti OR mouse:ti OR mice:ti OR swine:ti OR porcine:ti OR murine:ti OR sheep:ti OR lambs:ti OR pigs:ti OR piglets:ti OR rabbit:ti OR rabbits:ti OR cat:ti OR cats:ti OR dog:ti OR dogs:ti OR cattle:ti OR bovine:ti OR monkey:ti OR monkeys:ti OR trout:ti OR marmoset*:ti) AND 'animal experiment'/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))	3135937
#15	nonrandom*:ti,ab NOT random*:ti,ab	16164
#14	'systematic review':ti NOT (trial:ti OR study:ti)	145239
#13	'case control*':ti,ab AND random*:ti,ab NOT ('randomised controlled':ti,ab OR 'randomized controlled':ti,ab)	16660
#12	'cross-sectional study' NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab OR 'randomized controlled':ti,ab OR 'control group':ti,ab OR 'control groups':ti,ab)	91
#11	((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database OR databases)):ti,ab) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab OR 'randomized controlled':ti,ab OR 'randomly assigned':ti,ab)	2491
#10	#9 NOT #8	4278244
#9	random*:ti,ab OR 'intermethod comparison'/de OR placebo:ti,ab OR compare:ti OR compared:ti OR comparison:ti OR ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)) OR ((open NEXT/1 label):ti,ab) OR (((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab) OR 'double blind procedure'/de OR ((parallel NEXT/1 group*):ti,ab) OR crossover:ti,ab OR 'cross over':ti,ab OR (((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab) OR assigned:ti,ab OR allocated:ti,ab OR ((controlled NEAR/8 (study OR design OR trial)):ti,ab) OR volunteer:ti,ab OR volunteers:ti,ab OR 'human experiment'/de OR trial:ti	4915979
#8	'randomized controlled trial'/de OR 'controlled clinical study'/de	780874
#7	#5 AND #6	56064
#6	'depressive disorder'/exp OR 'depression'/exp OR 'major depression'/exp OR 'major depressive disorder'/exp OR 'depression' OR 'depressions' OR 'depressive' OR 'dysthymic disorder'/exp OR 'dysthymic disorder' OR 'dysthymia'/exp OR 'dysthymic' OR 'mood disorder'/exp OR 'affective disorder'/exp OR 'affective disorder' OR 'affective disorders' OR 'mood disorder' OR 'mood disorders'	793332
#5	#1 OR #4	434246
#4	#2 AND #3	778
#3	'therapies' OR 'therapy' OR 'therapeutics' OR 'therapist' OR 'treatment' OR 'treatments'	12032736
#2	'compassion-focused' OR 'compassion-focussed' OR 'compassion focused' OR 'compassion focussed' OR 'constructivist' OR 'constructivists'	2619

#1	((((('psychotherapy'/exp OR 'psychotherapy' OR 'psychotherapies' OR 'psychotherapeutics' OR 'psychotherapeutical' OR 'cognitive therapy'/exp OR 'cognitive behavior therapy'/exp OR 'behavior therapy'/exp OR´cbt) AND´ OR´cognitive) AND behavioural AND therapy AND´ OR´cognitive) AND behavioural AND therapies AND´ OR cognitive) AND behavioral AND therapy AND´ OR 'cognitive behavioral therapies' OR 'behavior therapy' OR 'behavior therapies' OR 'behaviour therapy' OR 'behaviour therapies' OR 'cognition therapy' OR 'cognitive therapies' OR 'cognitive therapy' OR 'cognitive therapeutic' OR 'cognitive therapeutics' OR 'cognitive therapeutical' OR 'cognitive therapeutist' OR 'cognitive therapeutists' OR 'cognitive treatment' OR 'cognitive treatments' OR 'cognitive restructuring' OR 'cognition therapies' OR 'cognition therapie' OR 'cognition therapeutical' OR 'cognition therapeutic' OR 'cognition therapeutics' OR 'cognition therapeutist' OR 'cognition therapeutists' OR 'cognition treatment' OR 'cognition treatments' OR 'behavior therapeutic' OR 'behavior therapeutical' OR 'behavior therapeutics' OR 'behavior therapeutist' OR 'behavior therapeutists' OR 'behavior treatment' OR 'behavior treatments' OR 'behaviors therapies' OR 'behaviors therapy' OR 'behaviors therapeutics' OR 'behaviors therapeutic' OR 'behaviors therapeutical' OR 'behaviors therapeutist' OR 'behaviors therapeutists' OR 'behaviors treatment' OR 'behaviors treatments' OR 'behavioral therapies' OR 'behavioral therapy' OR 'behavioral therapeutics' OR 'behavioral therapeutic' OR 'behavioral therapeutical' OR 'behavioral therapeutist' OR 'behavioral therapeutists' OR 'behavioral treatment' OR 'behavioral treatments' OR 'behaviour therapeutic' OR 'behaviour therapeutical' OR 'behaviour therapeutics' OR 'behaviour therapeutist' OR 'behaviour therapeutists' OR 'behaviour treatment' OR 'behaviour treatments' OR 'behaviours therapies' OR 'behaviours therapy' OR 'behaviours therapeutics' OR 'behaviours therapeutic' OR 'behaviours therapeutical' OR 'behaviours therapeutist' OR 'behaviours therapeutists' OR 'behaviours treatment' OR 'behaviours treatments' OR 'behavioural therapies' OR 'behavioural therapy' OR 'behavioural therapeutics' OR 'behavioural therapeutic' OR 'behavioural therapeutical' OR 'behavioural therapeutist' OR 'behavioural therapeutists' OR 'behavioural treatment' OR 'behavioural treatments' OR 'behavior activation' OR 'behaviors activation' OR 'behavioral activation' OR 'behaviour activation' OR 'behaviours activation' OR 'behavioural activation' OR 'psychoanalytic therapy'/exp OR 'psychodynamic' OR 'psychodynamical' OR 'psychoanalysis' OR 'psychoanalytical' OR 'counselling'/exp OR 'counseling'/exp OR 'counselling' OR 'counseling' OR 'problem-solving' OR 'problem solving' OR 'supportive therapy' OR 'metacognitive therapy' OR 'metacognitive therapies' OR 'metacognitive therapeutic' OR 'metacognitive therapeutics' OR 'metacognitive therapeutical' OR 'metacognitive therapeutist' OR 'metacognitive therapeutists' OR 'metacognitive treatment' OR 'metacognitive treatments' OR 'meta-cognitive therapy' OR 'meta-cognitive therapies' OR 'meta-cognitive therapeutic' OR 'meta-cognitive therapeutics' OR 'meta-cognitive therapeutical' OR 'meta-cognitive therapeutist' OR 'meta-cognitive therapeutists' OR 'meta-cognitive treatment' OR 'meta-cognitive treatments' OR 'solution-focused therapies' OR 'solution-focussed therapies' OR 'solution focused therapies' OR 'solution-focused therapy' OR 'solution-focussed therapy' OR 'solution focused therapy' OR 'solution-focused therapeutic' OR 'solution focused therapeutic' OR 'solution-focussed therapeutic' OR 'solution focussed therapeutic' OR 'solution-focused therapeutics' OR 'solution-focussed therapeutics' OR 'solution focused therapeutics' OR 'solution-focused therapeutical' OR 'solution-focussed therapeutical' OR 'solution focused therapeutical' OR 'self-control therapies' OR 'self control therapies' OR 'self-control therapy' OR 'self control therapy' OR 'self-control therapeutics' OR 'self control therapeutics' OR 'self-control therapeutical' OR 'self control therapeutical' OR 'self-control therapeutic' OR 'self control therapeutic' OR 'self-control training' OR 'self control training' OR 'self control trainings' OR 'self-control trainings' OR 'mindfulness' OR 'acceptance commitment' OR 'acceptance and commitment' OR 'assertiveness training'	433645

R1. PsycInfo

ID	Search	Hits
#1	(DE "Behavior Therapy" OR DE "Cognitive Behavior Therapy" OR "CBT" OR "behavior therapies" OR "behavior therapy" OR "behavior therapeutic" OR "behavior therapeutical" OR "behavior therapeutics" OR "behavior therapeutist" OR "behavior therapeutists" OR "behavior treatment" OR "behavior treatments" OR "behaviors therapies" OR "behaviors therapy" OR "behaviors therapeutics" OR "behaviors therapeutic" OR "behaviors therapeutical" OR "behaviors therapeutist" OR "behaviors therapeutists" OR "behaviors treatment" OR "behaviors treatments" OR "behavioral therapies" OR "behavioral therapy" OR "behavioral therapeutics" OR "behavioral therapeutic" OR "behavioral	12667

	therapeutical" OR "behavioral therapeutist" OR "behavioral therapeutists" OR "behavioral treatment" OR "behavioral treatments" OR "behaviour therapies" OR "behaviour therapy" OR "behaviour therapeutic" OR "behaviour therapeutical" OR "behaviour therapeutics" OR "behaviour therapeutist" OR "behaviour therapeutists" OR "behaviour treatment" OR "behaviour treatments" OR "behaviours therapies" OR "behaviours therapy" OR "behaviours therapeutics" OR "behaviours therapeutic" OR "behaviours therapeutical" OR "behaviours therapeutist" OR "behaviours therapeutists" OR "behaviours treatment" OR "behaviours treatments" OR "behavioural therapies" OR "behavioural therapy" OR "behavioural therapeutics" OR "behavioural therapeutic" OR "behavioural therapeutical" OR "behavioural therapeutist" OR "behavioural therapeutists" OR "behavioural treatment" OR "behavioural treatments" OR"cognition therapies" OR "cognition therapie" OR "cognition therapy" OR "cognition therapeutical" OR "cognition therapeutic" OR "cognition therapeutics" OR "cognition therapeutist" OR "cognition therapeutists" OR "cognition treatment" OR "cognition treatments" OR "cognitive therapies" OR "cognitive therapy" OR "cognitive therapeutic" OR "cognitive therapeutics" OR "cognitive therapeutical" OR "cognitive therapeutist" OR "cognitive therapeutists" OR "cognitive treatment" OR "cognitive treatments" OR "cognitive restructuring" OR DE "Emotion Focused Therapy" OR "mindfulness" OR ("acceptance" AND "commitment") OR "metacognitive therapies" OR "metacognitive therapy" OR "metacognitive therapeutic" OR "metacognitive therapeutics" OR "metacognitive therapeutical" OR "metacognitive therapeutist" OR "metacognitive therapeutists" OR "metacognitive treatment" OR "metacognitive treatments" OR "meta-cognitive therapies" OR "meta-cognitive therapy" OR "meta-cognitive therapeutic" OR "meta-cognitive therapeutics" OR "meta-cognitive therapeutical" OR "meta-cognitive therapeutist" OR "meta-cognitive therapeutists" OR "meta-cognitive treatment" OR "meta-cognitive treatments" OR "self-control therapies" OR "self-control therapy" OR "self-control therapeutics" OR "self-control therapeutical" OR "self-control therapeutic" OR "self-control training" OR "self-control trainings" OR "self control therapies" OR "self control therapy" OR "self control therapeutics" OR "self control therapeutical" OR "self control therapeutic" OR "self control training" OR "self control trainings" OR ("constructivist" AND ("therapies" OR "therapy" OR "therapie" OR "therapist" OR "therapists" OR "therapeut" OR "treatment" OR "treatments")))	
#2	(DE "Depression (Emotion)" "depressive disorder" OR "depression" OR "depressions" OR "depressive" OR DE "Major Depression" OR "major depression" OR "major depressive disorder" OR DE "Affective Disorders" OR "Affective Disorder" OR "affective disorders" OR "Mood Disorder" OR "Mood disorders")	43,732
#3	SU.EXACT("Treatment Effectiveness Evaluation") OR SU.EXACT.EXPLODE("Treatment Outcomes") OR SU.EXACT("Placebo") OR SU.EXACT("Followup Studies") OR placebo* OR random* OR "comparative stud*" OR clinical N3 trial* OR research N3 design OR evaluat* N3 stud* OR prospectiv* N3 stud* OR (singl* OR doubl* OR trebl* OR tripl*) N3 (blind* OR mask*)	52557
#4	#1 and #2 and #3	9410
	Limit Year: 2018-2020	1745

R1. PubMed

ID	Search	Hits
	((cbt[All Fields] OR "behavior therapies"[All Fields] OR "behavior therapy"[All Fields] OR "behavior therapeutic"[All Fields] OR "behavior therapeutical"[All Fields] OR "behavior therapeutics"[All Fields] OR "behavior therapeutist"[all Fields] OR "behavior therapeutists"[All Fields] OR "behavior treatment"[All Fields] OR "behavior treatments"[All Fields] OR "behaviors therapies"[All Fields] OR "behaviors therapy"[All Fields] OR "behaviors therapeutics"[All Fields] OR "behaviors therapeutic"[All Fields] OR "behaviors therapeutical"[All Fields] OR "behaviors therapeutist"[All Fields] OR "behaviors therapeutists"[All Fields] OR "behaviors treatment"[All Fields] OR "behaviors treatments"[All Fields] OR "behavioral therapies"[All Fields] OR "behavioral therapy"[All Fields] OR "behavioral therapeutics"[All Fields] OR "behavioral therapeutic"[All Fields] OR "behavioral therapeutical"[All Fields] OR "behavioral therapeutist"[All Fields] OR "behavioral therapeutists"[All Fields] OR "behavioral treatment"[All Fields] OR "behavioral treatments"[All Fields] OR "behaviour therapies"[All Fields] OR "behaviour therapy"[All Fields] OR "behaviour therapeutic"[All Fields] OR "behaviour therapeutical"[All Fields] OR "behaviour therapeutics"[All Fields] OR "behaviour therapeutist"[all Fields] OR "behaviour therapeutists"[All Fields] OR "behaviour treatment"[All Fields] OR "behaviour treatments"[All Fields] OR "behaviours therapies"[All Fields] OR "behaviours therapy"[All Fields] OR "behaviours therapeutics"[All Fields] OR "behaviours therapeutic"[All Fields] OR "behaviours therapeutical"[All Fields] OR "behaviours	6531

	therapeutist"[All Fields] OR "behaviours therapeutists"[All Fields] OR "behaviours treatment"[All Fields] OR "behaviours treatments"[All Fields] OR "behavioural therapies"[All Fields] OR "behavioural therapy"[All Fields] OR "behavioural therapeutics"[All Fields] OR "behavioural therapeutic"[All Fields] OR "behavioural therapeutical"[All Fields] OR "behavioural therapeutist"[All Fields] OR "behavioural therapeutists"[All Fields] OR "behavioural treatment"[All Fields] OR "behavioural treatments"[All Fields] OR "cognition therapies"[All Fields] OR "cognition therapie"[All Fields] OR "cognition therapy"[All Fields] OR "cognition therapeutical"[All Fields] OR "cognition therapeutic"[All Fields] OR "cognition therapeutics"[All Fields] OR "cognition therapeutist"[All Fields] OR "cognition therapeutists"[All Fields] OR "cognition treatment"[All Fields] OR "cognition treatments"[All Fields] OR mindfulness[All Fields] OR (acceptance[All Fields] AND commitment[All Fields] OR "cognitive therapies"[All Fields] OR "cognitive therapy"[All Fields] OR "cognitive therapeutic"[All Fields] OR "cognitive therapeutics"[All Fields] OR "cognitive therapeutical"[All Fields] OR "cognitive therapeutist"[All Fields] OR "cognitive therapeutists"[All Fields] OR "cognitive treatment"[All Fields] OR "cognitive treatments"[All Fields] OR "cognitive restructuring"[All Fields] OR "metacognitive therapies"[All Fields] OR "metacognitive therapy"[All Fields] OR "metacognitive therapeutic"[All Fields] OR "metacognitive therapeutics"[All Fields] OR "metacognitive therapeutical"[All Fields] OR "metacognitive therapeutist"[All Fields] OR "metacognitive therapeutists"[All Fields] OR"metacognitive treatment"[All Fields] OR "metacognitive treatments"[All Fields] OR "meta-cognitive therapies"[All Fields] OR "meta-cognitive therapy"[All Fields] OR "meta-cognitive therapeutic"[All Fields] OR "meta-cognitive therapeutics"[All Fields] OR "meta-cognitive therapeutical"[All Fields] OR "meta-cognitive therapeutist"[All Fields] OR "meta-cognitive therapeutists"[All Fields] OR "meta-cognitive treatment"[All Fields] OR "meta-cognitive treatments"[All Fields] OR"self-control therapies"[All Fields] OR "self-control therapy"[All Fields] OR "self-control therapeutics"[All Fields] OR "self-control therapeutical"[All Fields] OR "self-control therapeutic"[All Fields] OR "self-control training"[All Fields] OR "self-control trainings"[All Fields] OR "self control therapies"[All Fields] OR "self control therapy"[All Fields] OR "self control therapeutics"[All Fields] OR "self control therapeutical"[All Fields] OR "self control therapeutic"[All Fields] OR "self control training"[All Fields] OR "self control trainings"[All Fields]) AND (((Depressive Disorder[MH] OR Depression[MH] OR "affective disorder"[All Fields] OR "affective disorders"[All Fields] OR "mood disorder"[All Fields] OR "mood disorders"[All Fields] OR depression*[AllFields] OR depressive*[All Fields])))) AND (((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR randomly [tiab]))) NOT ((animals[mh] NOT (animals[mh] AND humans [mh]))))	
	Filters: from 2018 - 2020	1542

Review 2 (Cipriani et al)

R2.Cochrane

ID	Search	Hits
#1	MeSH descriptor: [Depressive Disorder] explode all trees	11990
#2	MeSH descriptor: [Depressive Disorder, Major] explode all trees	4815
#3	MeSH descriptor: [Mood Disorders] explode all trees	12672
#4	MeSH descriptor: [Affective Symptoms] explode all trees	448
#5	(depress* or "mood disorder" or "mood disorders" or "affective disorder" or "affective symptoms"):ti,ab,kw	85441
#6	#1 or #2 or #3 or #4 or #5	85469
#7	MeSH descriptor: [Amitriptyline] explode all trees	1178
#8	MeSH descriptor: [Bupropion] explode all trees	810
#9	MeSH descriptor: [Citalopram] explode all trees	1443
#10	MeSH descriptor: [Clomipramine] explode all trees	413
#11	MeSH descriptor: [Desvenlafaxine Succinate] explode all trees	107
#12	MeSH descriptor: [Duloxetine Hydrochloride] explode all trees	540

#13	MeSH descriptor: [Fluoxetine] explode all trees	1436
#14	MeSH descriptor: [Fluvoxamine] explode all trees	391
#15	MeSH descriptor: [Paroxetine] explode all trees	988
#16	MeSH descriptor: [Sertraline] explode all trees	1009
#17	MeSH descriptor: [Trazodone] explode all trees	220
#18	MeSH descriptor: [Venlafaxine Hydrochloride] explode all trees	673
#19	((agomelatine or amitriptyline or bupropion or citalopram or clomipramine or desvenlafaxine or duloxetine or escitalopram or fluoxetine or fluvoxamine or mirtazapine or paroxetine or reboxetine or sertraline or trazodone or venlafaxine or vortioxetine)):ti,ab,kw	18144
#20	#7 or #9 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19	18144
#21	#6 and #20 in Trials	9983
#22	Limit year 2016-2020	**1471**

R2. Embase

ID	Search	Hits
#24	#23 AND (2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py)	2349
#23	#22 NOT #21	17289
#22	#3 AND #6 AND #17	17334
#21	#18 NOT #20	7056128
#20	#18 AND #19	22217952
#19	'human'/exp OR 'normal human'/exp OR 'human cell'/exp	22217952
#18	'animals'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/exp	29274080
#17	#7 OR #8 OR #9 OR #10 OR #12 OR #13 OR #14 OR #15 OR #16	2281784
#16	'randomization'/exp	87095
#15	'single blind procedure'/exp	39320
#14	'crossover procedure'/exp	63425
#13	'double blind procedure'/exp	173879
#12	'randomized controlled trial'/exp	610311
#11	crossover	114685
#10	randomi*	1229217
#9	random* NEAR/5 (assign* OR allocat*)	192586
#8	(singl* OR doubl* OR trebl* OR tripl*) AND near AND (blind* OR mask*)	3044
#7	clin* NEAR/2 trial	1579426
#6	#4 OR #5	151857
#5	agomelatine:ti,ab,kw OR amitriptyline:ti,ab,kw OR bupropion:ti,ab,kw OR citalopram:ti,ab,kw OR clomipramine:ti,ab,kw OR desvenlafaxine:ti,ab,kw OR duloxetine:ti,ab,kw OR escitalopram:ti,ab,kw OR fluoxetine:ti,ab,kw OR fluvoxamine:ti,ab,kw OR mirtazapine:ti,ab,kw OR paroxetine:ti,ab,kw OR reboxetine:ti,ab,kw OR sertraline:ti,ab,kw OR trazodone:ti,ab,kw OR venlafaxine:ti,ab,kw OR vortioxetine:ti,ab,kw	63714
#4	'agomelatine'/exp OR 'amitriptyline'/exp OR 'amfebutamone'/exp OR 'citalopram'/exp OR 'clomipramine'/exp OR 'desvenlafaxine'/exp OR 'duloxetine'/exp OR 'escitalopram'/exp OR 'fluoxetine'/exp OR 'fluvoxamine'/exp OR 'mirtazapine'/exp OR 'paroxetine'/exp OR	148326

	'reboxetine'/exp OR 'sertraline'/exp OR 'trazodone'/exp OR 'venlafaxine'/exp OR 'vortioxetine'/exp	
#3	#1 OR #2	479642
#2	(depress* OR mood) AND disorder* OR 'affective disorder' OR 'affective symptoms':ti,ab,kw	360585
#1	(major AND 'depression'/exp OR mood) AND 'disorder'/exp	318877

R2. PsycInfo

ID	Search	Hits
#1	MA major depression or affective disorders	7624
#2	TX depress* or mood disorder* or "affective disorder" or "affective symptoms"	406,202
#3	#1 or #2	406,759
#4	MA AMITRIPTYLINE or BUPROPION or CITALOPRAM or FLUOXETINE or FLUVOXAMINE or PAROXETINE or SERTRALINE or TRAZODONE or VENLAFAXINE	12,349
#5	TX agomelatine or amitriptyline or bupropion or citalopram or clomipramine or desvenlafaxine or duloxetine or escitalopram or fluoxetine or fluvoxamine or mirtazapine or paroxetine or reboxetine or sertraline or trazodone or venlafaxine or vortioxetine	25,613
#6	#4 or #5	25,613
#7	TX ((singl* or doubl* or trebl* or tripl*) n1 (blind* or mask*))	33,909
#8	TX random* n5 (assign* or allocat*)	52,317
#9	TX randomi*	90,921
#10	TX crossover	7,616
#11	or/7-10	148,925
#12	#11 and #6 and #3	1088
	Limit Year: 2016-2020	**174**

R2. Medline

ID	Search	Hits
1	depressive disorder/ or depressive disorder, major/ or Mood Disorders/ or Affective Symptoms/	126399
2	(depress* or mood disorder* or "affective disorder" or "affective symptoms").tw,kw,kf.	466142
3	1 or 2	498825
4	Amitriptyline/ or Bupropion/ or Citalopram/ or CLOMIPRAMINE/ or Desvenlafaxine Succinate/ or Duloxetine Hydrochloride/ or Citalopram/ or FLUOXETINE/ or Fluvoxamine/ or PAROXETINE/ or SERTRALINE/ or TRAZODONE/ or Venlafaxine Hydrochloride/	35763
5	(agomelatine or amitriptyline or bupropion or citalopram or clomipramine or desvenlafaxine or duloxetine or escitalopram or fluoxetine or fluvoxamine or mirtazapine or paroxetine or reboxetine or sertraline or trazodone or venlafaxine or vortioxetine).tw,kw,kf.	44261
6	4 or 5	51947
7	exp clinical trial/	864629

8	exp randomized controlled trials/	137741
9	exp double-blind method/	158834
10	exp single-blind method/	28814
11	exp cross-over studies/	48164
12	randomized controlled trial.pt.	509745
13	clinical trial.pt.	523759
14	controlled clinical trial.pt.	93762
15	(clinic* adj2 trial).mp.	719893
16	(random* adj5 control* adj5 trial*).mp.	727242
17	(crossover or cross-over).mp.	95340
18	((singl* or double* or trebl* or tripl*) adj (blind* or mask*)).mp.	235839
19	randomi*.mp.	881495
20	(random* adj5 (assign* or allocat* or assort* or reciev*)).mp.	243098
21	or/7-20	1425135
22	3 and 6 and 21	7596
23	animals/ not humans/	4685421
24	22 not 23	7425
25	limit 24 to yr="2016 - 2020"	**908**

11.1.3 Excluded reviews and studies

11.1.3.1 Excluded reviews due to low AMSTAR-2 rating and uncomprehensiveness (Step I of the search strategy)

Title	Author, year	AMSTAR-2 rating
Pharmacological and non-pharmacological treatments for major depressive disorder in adults: A systematic review and network meta-analysis	Chen, 2019	Low
Effectiveness and Acceptability of Cognitive Behavior Therapy Delivery Formats in Adults With Depression: A Network Meta-analysis	Cuijpers, 2019	Moderate
A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression	Cuijpers, 2020	Moderate
No benefit from flexible titration above minimum licensed dose in prescribing antidepressants for major depression: systematic review	Furukawa, 2020	Moderate
Long-Term Acute-Phase Treatment With Antidepressants, 8 Weeks and Beyond: A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials	Henssler, 2018	Moderate
Psychotherapy or medication for depression? Using individual symptom meta-analyses to derive a Symptom-Oriented Therapy (SOrT) metric for a personalised psychiatry	Kappelmann, 2020	Low
The process and delivery of CBT for depression in adults: a systematic review and network meta-analysis	Lopez-Lopez, 2019	Moderate
The comparative evidence basis for the efficacy of second-generation antidepressants in the treatment of depression in the US: A Bayesian meta-analysis of Food and Drug Administration reviews	Monden, 2018	Low
Cognitive behaviour therapy for depression in primary care: systematic review and meta-analysis	Santoft, 2019	Low
Towards personalising treatment: a systematic review and meta-analysis of face-to-face efficacy moderators of cognitive-behavioral therapy and interpersonal psychotherapy for major depressive disorder	Whiston, 2019	Low
Cognitive behavioral therapy for primary care depression and anxiety: a secondary meta-analytic review using robust variance estimation in meta-regression	Zhang, 2019	Low
The effectiveness of four empirically supported psychotherapies for primary care depression and anxiety: A systematic review and meta-analysis	Zhang, 2019	Low

The effect of CBT and its modifications for relapse prevention in major depressive disorder: a systematic review and meta-analysis	Zhang, 2019	Moderate

11.1.3.2 Excluded studies (identified in step II of the search strategy)

Excluded studies from the two reviews by Cipriani and Cuijpers

First author	Year	Title
Treatment duration <13 weeks		
Aberg-Wisted	2000	Sertraline versus paroxetine in major depression: clinical outcome after six months of continuous therapy
Ahmadpanah	2016	Influence of adjuvant detached mindfulness and stress management training compared to pharmacologic treatment in primiparae with postpartum depression
AK1102365	unpublished	Study In Patients With Depression Not Responding to Selective Serotonin Re-uptake Inhibitors
Alexopoulos	2004	A placebo-controlled trial of escitalopram and sertraline in the treatment of major depressive disorder
Allard	2004	Efficacy and tolerability of venlafaxine in geriatric outpatients with major depression: a double-blind, randomised 6-month comparative trial with citalopram
Alvarez	2012	A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder
Alves	1999	Efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression
Amini	2005	Comparison of mirtazapine and fluoxetine in the treatment of major depressive disorder: a double-blind, randomized trial
Appleby	1997	A controlled study of fluoxetine and cognitive-behavioural counselling in the treatment of postnatal depression
Armitage	1997	A multicenter, double-blind comparison of the effects of nefazodone and fluoxetine on sleep architecture and quality of sleep in depressed outpatients
Ashouri	2013	Effectiveness of meta-cognitive and cognitive-behavioral therapy in patients with major depressive disorder
Asnis	2013	Efficacy and safety of levomilnacipran sustained release 40 mg, 80 mg, or 120 mg in major depressive disorder: a phase 3, randomized, double-blind, placebo-controlled study
Bakish	1997	Effects of selective serotonin reuptake inhibitors on platelet serotonin parameters in major depressive disorder
Bakish	2014	Levomilnacipran ER 40 mg and 80 mg in patients with major depressive disorder: a phase III, randomized, double-blind, fixed-dose, placebo-controlled study
Baldwin	1996	A multicenter double-blind comparison of nefazodone and paroxetine in the treatment of outpatients with moderate-to-severe depression
Baldwin	2012	Vortioxetine (Lu AA21004) in the long-term open-label treatment of major depressive disorder
Baldwin a	2006	Resolution of sexual dysfunction during double-blind treatment of major depression with reboxetine or paroxetine
Baldwin b	2006	A double-blind, randomized, parallel-group, flexible-dose study to evaluate the tolerability, efficacy and effects of treatment discontinuation with escitalopram and paroxetine in patients with major depressive disorder
Ban	1998	Clinical efficacy of reboxetine: a comparative study with desipramine, with methodological considerations
Bedi	2000	Assessing effectiveness of treatment of depression in primary care. Partially randomised preference trial
Behnke	2003	Mirtazapine orally disintegrating tablet versus sertraline: a prospective onset of action study
Benkert	2000	Mirtazapine compared with paroxetine in major depression
Benkert	2006	Mirtazapine orally disintegrating tablets versus venlafaxine extended release: a double-blind, randomized multicenter trial comparing the onset of antidepressant response in patients with major depressive disorder
Bennie	1995	A double-blind multicenter trial comparing sertraline and fluoxetine in outpatients with major depression
Berlanga	1997	A double-blind comparison of nefazodone and fluoxetine in the treatment of depressed outpatients
Berlanga	2006	Different gender response to serotonergic and noradrenergic antidepressants. A comparative study of the efficacy of citalopram and reboxetine
Bielski	2004	A double-blind comparison of escitalopram and venlafaxine extended release in the treatment of major depressive disorder
Binnemann	2008	A 6-week randomized, placebo-controlled trial of CP-316,311 (a selective CRH1 antagonist) in the treatment of major depression
Bjerkenstedt	2005	Hypericum extract LI 160 and fluoxetine in mild to moderate depression: a randomized, placebo-controlled multi-center study in outpatients
Bosc a	1997	Noradrenaline-selective versus serotonin-selective antidepressant therapy: differential effects on social functioning
Bosc b	1997	Do noradrenaline and serotonin differentially affect social motivation and behaviour?
Bose	unpublished	Escitalopram in the acute treatment of depressed patients aged 60 years or older
Bougerol	1997	Citalopram and Fluoxetine in Major Depression
Boulenger	2014	Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder

Boyer	2008	Efficacy, safety, and tolerability of fixed-dose desvenlafaxine 50 and 100 mg/day for major depressive disorder in a placebo-controlled trial
Bremner	1995	A double-blind comparison of Org 3770, amitriptyline, and placebo in major depression
Brunoni	2012	The Sertraline vs Electrical Current Therapy for Treating Depression Clinical Study Results From a Factorial, Randomized, Controlled Trial
Buchsbaum	1997	Effect of sertraline on regional metabolic rate in patients with affective disorder
Bueno	1997	Estudo duplo-cego comparativo da eficacia e seguranca da nefazodona e amitriptilina
Burke	2002	Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients
CAGO178A2303	unpublished	A Placebo- and Paroxetine-controlled Study of the Efficacy, Safety and Tolerability of Agomelatine (25 or 50 mg) in the Treatment of Major Depressive Disorder (MDD)
Caligiuri	2003	A quantitative neuromotor predictor of antidepressant non-response in patients with major depression
Casabona	2002	A randomized, double blind, comparison of venlafaxine ER and paroxetine in outpatients with moderate to severe major depression
Cassano	2002	Efficacy and safety of amisulpride 50 mg versus paroxetine 20 mg in major depression: a randomized, double-blind, parallel group study
Chang	2015	Association between ABCB1 Polymorphisms and Antidepressant Treatment Response in Taiwanese Major Depressive Patients
Chouinard	1999	A Canadian multicenter, double-blind study of paroxetine and fluoxetine in major depressive disorder
Christiansen	1996	Paroxetine and amitriptyline in the treatment of depression in general practice
Claghorn	1995	A double-blind placebo-controlled study of Org 3770 in depressed outpatients
Claghorn	1996	Fluvoxamine maleate in the treatment of depression: a single-center, double-blind, placebo-controlled comparison with imipramine in outpatients
Clayton	2003	Lack of sexual dysfunction with the selective noradrenaline reuptake inhibitor reboxetine during treatment for major depressive disorder
Clayton	2013	Efficacy and safety of desvenlafaxine 50 mg/d in a randomized, placebo-controlled study of perimenopausal and postmenopausal women with major depressive disorder
Clayton	2015	Desvenlafaxine 50 and 100 mg/d versus placebo for the treatment of major depressive disorder: a phase 4, randomized controlled trial
Clayton a	2006	Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies
Clayton b	2006	Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies
Clerc	2001	Antidepressant efficacy and tolerability of milnacipran, a dual serotonin and noradrenaline reuptake inhibitor: a comparison with fluvoxamine
CN104-002	unpublished	Psychiatric Diagnosis and Clinical Trial Completion Rates: Analysis of the FDA SBA Reports - http://digitalcommons.ohsu.edu/fdadrug/23/
CN104-045	unpublished	Psychiatric Diagnosis and Clinical Trial Completion Rates: Analysis of the FDA SBA Reports - http://digitalcommons.ohsu.edu/fdadrug/23/
CN104-054	unpublished	Psychiatric Diagnosis and Clinical Trial Completion Rates: Analysis of the FDA SBA Reports - http://digitalcommons.ohsu.edu/fdadrug/23/
Cohn	2006	Relapse of Major Depression During Pregnancy in Women Who Maintain or Discontinue Antidepressant Treatment
Coleman	1999	Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment
Coleman	2001	A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine
Colonna	2005	A randomized, double-blind, 24-week study of escitalopram (10 mg/day) versus citalopram (20 mg/day) in primary care patients with major depressive disorder
Corrigan	2000	Comparison of pramipexole, fluoxetine, and placebo in patients with major depression
Costa e Silva	1998	Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression
Croft	1999	A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline
Croft	2014	Efficacy and safety of vilazodone in major depressive disorder: a randomized, double-blind, placebo-controlled trial
Cunningham	1997	Once-Daily Venlafaxine Extended Release (XR) and Venlafaxine Immediate Release (IR) in Outpatients with Major Depression
Cutler	2009	Extended release quetiapine fumarate monotherapy in major depressive disorder: a placebo- and duloxetine-controlled study
Dalery	2003	Fluvoxamine versus fluoxetine in major depressive episode: a double-blind randomised comparison
Davidson	2002	Characterizing the effects of sertraline in post-traumatic stress disorder.
Debonnel	2009	Mirtazapine and paroxetine in major depression: a comparison of monotherapy versus their combination from treatment initiation
DeMartinis	2007	A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder
Demyttenaere	1998	Compliance in depressed patients treated with fluoxetine or amitriptyline. Belgian Compliance Study Group
DeRubeis	2005	Cognitive therapy vs medications in the treatment of moderate to severe depression
Detke	2004	Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial
Detke a	2002	Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial

Detke b	2002	Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression
Deushle	2003	Antidepressive treatment with amitriptyline and paroxetine: effects on saliva cortisol concentrations
Dierick	1996	A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients
Dube	2010	A study of the effects of LY2216684, a selective norepinephrine reuptake inhibitor, in the treatment of major depression
Dunlop	2011	Symptomatic and functional improvement in employed depressed patients: a double-blind clinical trial of desvenlafaxine versus placebo.
Dunlop	2012	Depression beliefs, treatment preference, and outcomes in a randomized trial for major depressive disorder2012
Dunlop	2017	Effects of patient preferences on outcomes in the Predictors of Remission in Depression to Individual and Combined Treatments (PReDICT) study.
E-1569	unpublished	Bupropion, Mirtazapin und Reboxetin bei der Behandlung der Depression
Eisendrath	2016	A randomized controlled trial of mindfulness-based cognitive therapy for treatment-resistant depression
Ekselius	1997	A double-blind multicenter trial comparing sertraline and citalopram in patients with major depression treated in general practice
Fabre	1995	Sertraline in major depression: double-blind comparison with placebo
Fabre	1996	Fluvoxamine vs imipramine and placebo: a double-blind comparison in depressed patients
Fang	1997	Fluoxetine vs amitriptyline in treating 105 patients with depressive disorder with a double-blind study
Faramarzi	2008	Treatment of depression and anxiety in infertile women: cognitive behavioral therapy versus fluoxetine
Fava	1998	A double-blind study of paroxetine, fluoxetine, and placebo in outpatients with major depression.
Fava	2002	Acute efficacy of fluoxetine versus sertraline and paroxetine in major depressive disorder including effects of baseline insomnia
Fava	2005	A Double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder.
Feiger	1996	Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction
Feighner	1998	A double-blind, placebo-controlled trial of nefazodone in the treatment of patients hospitalized for major depression
Feighner	1999	Multicenter, placebo-controlled, fixed-dose study of citalopram in moderate-to-severe depression
Frank	2004	Clinical response augments NK cell activity independent of treatment modality: a randomized double-blind placebo controlled antidepressant trial
Gastpar	2006	Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: a double-blind, randomised, multicentre, placebo-controlled study
Gentil	2000	Double-blind comparison of venlafaxine and amitriptyline in outpatients with major depression with or without melancholia
Geretsegger	1995	Multicenter double blind study of paroxetine and amitriptyline in elderly depressed inpatients
Gillin	1997	A comparison of nefazodone and fluoxetine on mood and on objective, subjective, and clinician-rated measures of sleep in depressed patients: a double-blind, 8-week clinical trial
Golden a	2002	Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression
Golden b	2002	Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression
Goldstein	2002	Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial
Goldstein a	2004	Duloxetine Versus Placebo and Paroxetine in the Acute Treatment of Major Depression, Study Group A
Goldstein b	2004	Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine
Gommoll	2014	A randomized, double-blind, placebo-controlled study of flexible doses of levomilnacipran ER (40–120 mg/day) in patients with major de- pressive disorder
Goodarzi	2015	Comparison of therapeutic effects of mirtazapine and citalopram on out-patients with major depressive disorder with anxiety symptoms
Gorman	2002	Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: pooled analysis of placebo-controlled trials
Griebel a	2012	The vasopressin V(1b) receptor antagonist SSR149415 in the treatment of major depressive and generalized anxiety disorders: results from 4 randomized, double-blind, placebo-controlled studies
Griebel b	2012	The vasopressin V(1b) receptor antagonist SSR149415 in the treatment of major depressive and generalized anxiety disorders: results from 4 randomized, double-blind, placebo-controlled studies
GSK14	unpublished	http://www.gsk-clinicalstudyregister.com/study/14#rs
Guelfi	1995	Effectiveness of venlafaxine in pa- tients hospitalized for major depression and melancholia
Guelfi	1998	A double-blind comparison of the efficacy and safety of milnacipran and fluoxetine in depressed inpatients
Hackett	1998	A randomized, double-blind, parallel-group comparison of venlafaxine and clomipramine in outpatients with major depression
Halikas	1995	A Placebo Controlled Trial in De- pressed Elderly Patients
Hao	2014	Duloxetine reduces pain after Total hip arthroplasty: a prospective, randomized controlled study
Hautzinger	1996	Efficacy of cognitive behavior therapy, pharmacotherapy, and the combination of both in non-melancholic, unipolar depression
Hegerl	2010	Effects of pharmacotherapy and psychotherapy in depressed primary-care patients: a randomized, controlled trial including a patients' choice arm

Henigsberg	2012	A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder.
Heun	2013	Agomelatine Study Group. The efficacy of agomelatine in elderly patients with recurrent major depressive disorder: a placebo-controlled study
Hewett	2009	Eight-week, placebo-controlled, double-blind comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR
Hewett a	2010	Eight-week, placebo-controlled, double-blind comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR
Hewett b	2010	Double-blind, placebo-controlled comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR
Higuchi	2014	A randomized, double-blinded, placebo-controlled study to evaluate the efficacy and safety of venlafaxine extended release and a long-term extension study for patients with major depressive disorder in Japan
Higuchi	2011	Paroxetine controlled-release formulation in the treatment of major depressive disorder: a randomized, double-blind, placebo- controlled study in Japan and Korea
Higuchi	2009	Clinical evaluation of duloxetine in the treatment of major depressive disorder
Hirayasu a	2011	A dose-response study of escitalopram in patients with major depressive disorder: a placebo-controlled, double-blind study
Hirayasu b	2011	A dose-response and non-inferiority study evaluating the efficacy and safety of escitalopram in patients with major depressive disorder
Hong	2003	A double-blind, randomized, group- comparative study of the tolerability and efficacy of 6 weeks' treatment with mirtazapine or fluoxetine in depressed Chinese patients
Hosseini	2015	Double-Blind Randomized Clinical Trial of the Efficacy of Venlafaxine Versus Citalopram in the Treatment of the Acute Phase of Major Depressive Disorder
Hoyberg	1996	A double-blind multicentre comparison of mirtazapine and amitriptyline in elderly depressed patients
Hsu	2011	Faster onset of antidepressant effects of citalopram compared with sertraline in drug-naïve first-episode major depressive disorder in a Chinese population: a 6-week double-blind, randomized comparative study
Hu	2009	Escitalopram vs citalopram for depression: a randomized, double- blind, double-dummy, multicentre, parallel controlled study
Hunter a	2010	Antidepressant response trajectories and quantitative electroencephalography (QEEG) biomarkers in major depressive disorder (Study 1)
Hunter b	2010	Antidepressant response trajectories and quantitative electroencephalography (QEEG) biomarkers in major depressive disorder. (Study 2)
Hunter c	2010	Antidepressant response trajectories and quantitative electroencephalography (QEEG) biomarkers in major depressive disorder (Study 3)
Husain	2017	Treatment of maternal depression in urban slums of Karachi, Pakistan: a randomized controlled trial (RCT) of an integrated maternal psychological and early child development intervention
Iwata	2013	Efficacy and safety of desvenlafaxine 25 and 50mg/day in a randomized, placebo-controlled study of depressed outpatients.
Jacobsen	2015	A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with major depressive disorder
Jain	2013	A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder.
Jarrett	1999	Treatment of atypical depression with cognitive therapy or phenelzine: a double-blind, placebo-controlled trial
Jefferson	2000	A double-blind, placebo controlled, fixed-dosage study comparing the efficacy and tolerability of paroxetine CR and citalopram to placebo in the treatment of Major Depressive Disorder with anxiety
Jefferson	2006	Extended-release bupropion for patients with major depressive disorder presenting with symptoms of reduced energy, pleasure, and interest: findings from a randomized, double-blind, placebo-controlled study.
Jiang	2009	A comparative study on escitalopram and citalopram hydrobromide in the treatment of depression
Kamijima	2013	Double-blind, comparative study of milnacipran and paroxetine in Japanese patients with major depression
Kasper	2012	Combining escitalopram with gaboxadol provides no additional benefit in the treatment of patients with severe major depressive disorde
Kasper a	2005	Escitalopram in the treatment of depressed elderly patients.
Kasper b	2005	A comparative, randomised, double-blind study of trazodone prolonged-release and paroxetine in the treatment of patients with major depressive disorder
Katona	2012	A randomized, double-blind, placebo-controlled, duloxetine- referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder
Katz	2004	Onset and early behavioral effects of pharmacologically different antidepressants and placebo in depression
Keller	2007	The Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) Study: Outcomes from the 2- year and combined maintenance phases
Keller	2000	A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression
Keller a	2006	Lack of efficacy of the substance p (neurokinin1 receptor) antagonist aprepitant in the treatment of major depressive disorder
Keller b	2006	Lack of efficacy of the substance p (neurokinin1 receptor) antagonist aprepitant in the treatment of major depressive disorder
Keller c	2006	Lack of efficacy of the substance p (neurokinin1 receptor) antagonist aprepitant in the treatment of major depressive disorder
Kennedy	2005	A pooled analysis of selective serotonin reuptake inhibitors and venlafaxine

Kennedy	2006	Placebo-controlled trial of agomelatine in the treatment of major depressive disorder
Kennedy	2014	Agomelatine Study Group. A placebo-controlled study of three agomelatine dose regimens (10 mg, 25 mg, 25-50 mg) in patients with major depressive disorder
Khan	1998	The use of venlafaxine in the treatment of major depression and major depression associated with anxiety: a dose-response study. Venlafaxine Investigator Study Group
Khan	2007	Study of Escitalopram in Adult Patients With Major Depressive Disorder
Khan	2011	A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder
Kiev	1997	A double-blind comparison of fluvoxamine and paroxetine in the treatment of depressed outpatients
Kinoshita	2009	A double-blind, placebo controlled study of a new antidepressant, mirtazapine, in depressed patients
Koshino	2013	Efficacy and safety of bupropion sustained-release formulation for the treatment of major depressive disorder: a multi-center, randomized, double-blind, placebo-controlled study in Asian patients
Kramer	1998	Distinct mechanism for antidepressant activity by blockade of central substance P receptors
Kyle	1998	Comparison of the tolerability and efficacy of citalopram and amitriptyline in elderly depressed patients treated in general practice
Lalit	2004	Escitalopram Versus Citalopram and Sertraline: A Double-Blind Controlled, Multi-centric Trial in Indian Patients with Unipolar Major Depression
Lam	2013	Effects of combined pharmacotherapy and psychotherapy for improving work functioning in major depressive disorder
Lam	1995	Multicenter, placebo-controlled study of fluoxetine in seasonal affective disorder
Learned a	2012	Efficacy, safety, and tolerability of a triple reuptake inhibitor GSK372475 in the treatment of patients with major depressive disorder: two randomized, placebo- and active-controlled clinical trials (Study 1)
Learned b	2012	Efficacy, safety, and tolerability of a triple reuptake inhibitor GSK372475 in the treatment of patients with major depressive disorder: two randomized, placebo- and active-controlled clinical trials (Study 2)
Lee	2007	Once-daily duloxetine 60 mg in the treatment of major depressive disorder: multicenter, double-blind, randomized, paroxetine-controlled, non-inferiority trial in China, Korea, Taiwan and Brazil
Leinonen	1999	Efficacy and tolerability of mirtazapine versus citalopram: a double-blind, randomized study in patients with major depressive disorder.
Lepine	2000	A double-blind study of the efficacy and safety of sertraline and clomipramine in outpatients with severe major depression
Lepola	2001	Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression inprimary care
Li	2006	The Effectiveness and Safety of Escitalopram in the Treatment of Depression: A Randomized Double-blind Active-drug Controlled Trial
Li	2010	Clinical Research on Escitalopram Oxalate Tablets in Treatment of Depression. Pharmaceutical and Clinical Research
Lieberman a	2008	A pooled analysis of two placebo-controlled trials of desvenlafaxine in major depressive disorder
Lieberman b	2008	A pooled analysis of two placebo-controlled trials of desvenlafaxine in major depressive disorder
Liebowitz	2008	Efficacy, safety, and tolerability of desvenlafaxine 50 mg/day and 100 mg/day in outpatients with major depressive disorder
Liebowitz	2013	A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/day in adult outpatients with major depressive disorder
Loo	2002	Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT(2C) antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study
Lv	2013	A randomized double-blind study of escitalopram and citalopram in treating major depression
Lydiard	1997	A double-blind, placebo-controlled study comparing the effects of sertraline versus amitriptyline in the treatment of major depression
M/2020/0046	unpublished	Reboxetine, Placebo, and Paroxetine Comparison in Patients With Major Depressive Disorder (Study 046)
M/2020/0047	unpublished	Reboxetine, Placebo, and Paroxetine Comparison in Patients With Major Depressive Disorder (Study 047)
Macaskill	1996	Rational-emotive therapy plus pharmacotherapy versus pharmacotherapy alone in the treatment of high cognitive dysfunction depression
Mahableshwarkar	2013	A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder.
Mahableshwarkar a	2015	A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD.
Mahableshwarkar b	2015	A randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of vortioxetine in adults with major depressive disorder
Mahableshwarkar c	2015	A Randomized, Placebo- Controlled, Active-Reference, Double-Blind, Flexible-Dose Study of the Efficacy of Vortioxetine on Cognitive Function in Major Depressive Disorder
Mao	2008	Escitalopram in major depressive disorder: a multicenter, randomized, double-blind, fixed-dose, parallel trial in a Chinese population
Mao	2015	Rhodiola rosea versus sertraline for major depressive disorder: A randomized placebo-controlled trial
Marchesi	1998	Is Anxious-Agitated Major Depression Responsive to Fluoxetine? A Double-Blind Comparison with Amitriptyline
Mathews	2015	Efficacy and safety of vilazodone 20 and 40 mg in major depressive disorder: a randomized, double-blind, placebo-controlled trial

McGrath	2000	A placebo-controlled study of fluoxetine versus imipramine in the acute treatment of atypical depression
McIntyre	2014	A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults
McPartlin	1998	A comparison of once daily venlafaxine xr and paroxetine in depressed outpatients treated in general practice
MDF/29060/III/070/88/MC	unpublished	A multicentre, double-blind, parallel group, randomised dose study comparing the efficacy of paroxetine 20mg increasing to 30mg daily if there is insufficient response and clomipramine 60mg increasing to 75mg daily, in outpatients (age >60 years) with moderate depression according to...
MDUK/26090/III/83/007	unpublished	A Double-Blind Placebo Controlled Study to Compare Paroxetine with Maprotiline in the Treatment of Depression
Mehtonen	2000	Randomized, Double-Blind Comparison of Venlafaxine and Sertraline in Outpatients With Major Depressive Disorder
Mendels	1995	A double-blind, placebo- controlled trial of two dose ranges of nefazodone in the treatment of depressed outpatients
Mendels	1999	Double blind comparison of citalopram and placebo in depressed outpatients with melancholia
Milgrom	2015	Treatment of postnatal depression with cognitive behavioural therapy, sertraline and combination therapy: a randomised controlled trial
MIR 003-003 (FDA)	unpublished	http://digitalcommons.ohsu.edu/fdadrug/20/
MIR 003-020 (FDA)	unpublished	http://digitalcommons.ohsu.edu/fdadrug/20/
MIR 003-021 (FDA)	unpublished	http://digitalcommons.ohsu.edu/fdadrug/20/
MIR 84062 (FDA)	unpublished	http://digitalcommons.ohsu.edu/fdadrug/20/
Mischoulon	2014	A Double-Blind, Randomized, Placebo-Controlled Clinical Trial of S-Adenosyl-l-Methionine (SAMe) Versus Escitalopram in Major Depressive Disorder
Misri	2004	The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial
Miura	2000	Clinical evaluation of paroxetine HCl, a selective serotonin reuptake inhibitor, in the treatment of depression or depressive spisodes: Double-blind, parallel group study with amitriptyline HCl.
Moller	1998	Double-Blind, Multicenter Comparative Study of Sertraline and Amitriptyline in Hospitalized Patients with Major Depression
Moller	2000	Double-blind, multicenter comparative study of sertraline versus amitriptyline in outpatients with major depression
Montgomery	unpublished	http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020822a.cfm
Montgomery	2013	Efficacy and safety of levomilnacipran sustained release in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled, proof-of-concept study
Montgomery a	2004	A Randomised Study Comparing Escitalopram with Venlafaxine XR in Primary Care Patients with Major Depressive Disorder
Montgomery b	2004	Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: A randomized, double-blind, placebo-controlled discontinuation study
Moore	2005	Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder.
Moradveisi	2013	Behavioural activation v. antidepressant medication for treating depression in Iran: randomised trial
Moreno	2005	Hypericum perforatum versus fluoxetine in the treatment of mild to moderate depression: a randomized double-blind trial in a Brazilian sample.
Moscovitch	2004	International Collaborative Group on Sertraline in the Treatment of Outpatients with Seasonal Affective Disorders. A placebo-controlled study of sertraline in the treatment of outpatients with seasonal affective disorder
Mullin	1996	A multicentre, double-blind, amitriptyline-controlled study of mirtazapine in patients with major depression
Mundt	2012	Vocal acoustic biomarkers of depression severity and treatment response
Munizza	2006	A comparative, randomized, double-blind study of trazodone prolonged-release and sertraline in the treatment of major depressive disorder
Murasaki	1998	Clinical evaluation of SME3110 (fluvoxamine maleate) in the treatment of depression and depressive state: A double-blind, comparative study with amitriptyline.
Murasaki a	2010	Comparison of efficacy and safety of mirtazapine versus fluvoxamine in Japanese and Caucasian patients with major depressive disorder
Murasaki b	2010	Comparison of efficacy and safety of mirtazapine versus fluvoxamine in Japanese and Caucasian patients with major depressive disorder
MY-1008/BRL-029060/2/CPMS-076	unpublished	The Effects of Paroxetine Versus Those of Maprotiline and Placebo on Fundamental Cognitive Functions, Perceptual-Motor Skills and Eye Movements in Depressed Patients
MY-1042/BRL-029060/CPMS-251	unpublished	A Double-Blind, Randomized Trial of Paroxetine Versus Placebo In Patients With Depression Accompanied by Anxiety
MY-1043/BRL-029060/115	unpublished	A multicenter, randomized, double-blind, placebo-controlled comparison of paroxetine and fluoxetine in the treatment of major depressive disorder.
MY-1045/BRL-029060/1 (PAR 128)	unpublished	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Comparison of Paroxetine and Fluoxetine in the Treatment of Major Depressive Disorder
Mynors-Wallis	1995	Randomised controlled trial comparing problem solving treatment with amitriptyline and placebo for major depression in primary care
Naeem	2011	Preliminary evaluation of culturally sensitive CBT for depression in Pakistan: findings from Developing Culturally-Sensitive CBT Project (DCCP)

NCT00822744 (EudraCT Number2008-001718-26)	unpublished	An Eight-week Study of SSR411298 as Treatment for Major Depressive Disorder in Elderly Patients (FIDELIO)
NCT01020799	unpublished	AZD7268 Safety and Tolerability Study
NCT01145755	unpublished	6-week Study Treatment to Evaluate the Safety and Effectiveness of AZD2066 in Patients With Major Depressive Disorder
NCT01254305	unpublished	Safety and Efficacy of Levomilnacipran ER (F2695 SR) in Adults With Fatigue Associated With Major Depressive Disorder
NCT01255787	unpublished	Efficacy and Safety Study of Vortioxetine (Lu AA21004) for Treatment of Major Depressive Disorder
NCT01355081	unpublished	Efficacy Study of Vortioxetine (Lu AA21004) for Treatment of Major Depressive Disorder
NCT01808612	unpublished	A Study of Fluoxetine in Major Depressive Disorder (MDD) Short-Term Dosing
Nemeroff	1995	Double-blind multicenter comparison of fluvoxamine versus sertraline in the treatment of depressed outpatients.
Nemeroff	2007	A double-blind, placebo-controlled comparison of venlafaxine and fluoxetine treatment in depressed outpatients
Newhouse	2000	A double-blind comparison of sertraline and fluoxetine in depressed elderly patients
Nierenberg	2007	Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study
Ninan	unpublished	www.ncbi.nlm.nih.gov/pubmedhealth/PMH0016624/bin/app17c_et6.pdf
NKD20006	unpublished	A Study Of A New Medicine (GW597599B) For The Treatment Of Major Depressive Disorder
Olie	1997	A double-blind placebo-controlled multicentre study of sertraline in the acute and continuation treatment of major depression
Olie	2007	Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5-HT2C antagonistic properties, in major depressive disorder.
Ontiveros Sanchez	1998	Estudio doble-ciego sobre fluoxetina vs amitriptilina en los síntomas depresivos y de ansiedad, y calidad de vida de los adultos con depresión mayor
Ottevanger	1995	Fluvoxamine and clomipramine in depressed hospitalised patients: Results from a randomised, double-blind study
Ou	2010	Efficacy and safety of escitalopram versus citalopram in major depressive disorder: a 6-week, multicenter, randomized, double-blind, flexible-dose study
PAR 279 MDUK	unpublished	A Placebo-controlled, single-dose, five-period crossover evaluation of the pharmacokinetic properties of paroxetine when administered by the oral route
PAR 29060.308 (HP/81/74A)	unpublished	Early clinical evaluation of a new antidepressant: A double-blind parallel study comparing paroxetine 30mg daily with amitriptyline 150mg daily
PAR 29060.310 (HP 81/85A)	unpublished	Early Clinical Evaluation of a New Antidepressant: Double-Blind Parallel Study Comparing Paroxetine 30mg Daily with Amitriptyline 150mg Daily
PAR 29060.314 (HP 82/134)	unpublished	Double Blind Parallel Study Comparing Paroxetine, 30mg Daily, and Amitriptyline, 150mg Daily, in Depressed Patients
PAR 29060.316 (HP/82/47A)	unpublished	Early Clinical Evaluation of a New Antidepressant: A Double-Blind Parallel Study Comparing Paroxetine 30mg Daily with Amitriptyline 150mg Daily
PAR 29060.318 (HP/82/64A)	unpublished	Early Clinical Evaluation of a New Antidepressant: A Double-Blind Parallel Study Comparing Paroxetine 30mg Daily with Amitriptyline 150mg Daily
PAR 29060/281	unpublished	A trial to assess the effectiveness and tolerance of paroxetine by double-blind comparison with amitriptyline in the treatment of depressed patients in General Practice
PAR MDUK 032	unpublished	A Double Blind Study to Compare the Efficacy and Tolerability of Paroxetine and Amitriptyline in a Multi-Centre General Practice Study in Depressed Patients
Parker	2013	The superiority of antidepressant medication to cognitive behavior therapy in melancholic depressed patients: a 12-week single-blind randomized study
Patris	1996	Citalopram versus fluoxetine: A double-blind, controlled, multicentre, phase III trial in patients with unipolar major depression treated in general practice.
Perahia	2006	Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial
Perahia a	2008	A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder.
Perahia b	2008	A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder
Petrak	2015	Cognitive behavioral therapy versus sertraline in patients with depression and poorly controlled diabetes: the Diabetes and Depression (DAD) study: a randomized controlled multicenter trial
Pomara	2013	Efficacy and Safety of Vilazodone in Major Depressive Disorder: A Randomized, Double-blind, Placebo-controlled Trial
PZ/109	unpublished	Consistent superiority of selective serotonin reuptake inhibitors over placebo in reducing depressed mood in patients with major depression
PZ/111	unpublished	Consistent superiority of selective serotonin reuptake inhibitors over placebo in reducing depressed mood in patients with major depression.
Quilty	2014	Cognitive structure and processing during cognitive behavioral therapy vs. pharmacotherapy for depression.
Rapaport	1996	A Comparison of Fluvoxamine and Fluoxetine in the Treatment of Major Depression
Rapaport	2003	Efficacy of controlled-release paroxetine in the treatment of late-life depression
Rapaport	2009	Low doses of controlled-release paroxetine in the treatment of late-life depression: a randomized, placebo-controlled trial
Raskin	2007	Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial

Ravindran	1995	The impact of sertraline, desipramine, and placebo on psychomotor functioning in depression.
Ravindran	1999	Treatment of primary dysthymia with group cognitive therapy and pharmacotherapy: clinical symptoms and functional impairments
Ravindran	1997	A double-blind, multicenter study in primary care comparing paroxetine and clomipramine in subjects with depression and associated anxiety
Reimherr	1998	A multicenter evaluation of the efficacy and safety of 150 and 300 mg/d sustained-release bupropion tabletsversus placebo in depressed outpatients
Rickels	1995	Nefazodone: aspects of efficacy
Rickels	2009	Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled trial
Roose	2004	Old-Old Depression Study Group. Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo-controlled trial.
Rossini	2005	Sertraline Versus Fluvoxamine in the Treatment of Elderly Patients With Major Depression
Rudolph	1999	A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (xr) and fluoxetine for the treatment of depression
Rudolph	1998	A randomized, placebo- controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression
Rush	1998	Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder
Sacchetti	2002	Paroxetine versus amitriptyline in patients with recurrent major depression: A double-blind trial
Sambunaris	2014	A phase III, double- blind, placebo-controlled, flexible-dose study of levomilnacipran extended-release in patients with major depressive disorder
Samuelian	1998	A Randomized, Double-Blind, Parallel-Group Comparison of Venlafaxine and Clomipramine in Outpatients With Major Depression
Sauer	2003	Efficacy and safety of venlafaxine ER vs. amitriptyline ER in patients with major depression of moderate severity
Schatzberg	2002	Mirtazapine vs. Paroxetine Study Group. Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients
Schatzberg	2006	A double-blind, placebo-controlled study of venlafaxine and fluoxetine in geriatric outpatients with major depressio
Schneider	2003	Sertraline Elderly Depression Study Group. An 8-week multicenter, parallel-group, double-blind, placebo- controlled study of sertraline in elderly outpatients with major depression
Schwartz	2002	Reboxetine versus venlafaxine in severe major depression
SCT-MD-09	unpublished	Double-blind comparison of the effects of lu 26-054 (escitalopram) and fluoxetine on sleep in depressed patients
SCT-MD-49	unpublished	Escitalopram in Adult Patients With Major Depressive Disorder
Sechter	1999	A double-blind comparison of sertraline and fluoxetine in the treatment of major depressive episode in outpatients
Sechter	2004	A comparative study of milnacipran and paroxetine in outpatients with major depression
SER 101 (FDA)	unpublished	http://digitalcommons.ohsu.edu/fdadrug/27/
SER 310 (FDA)	unpublished	http://digitalcommons.ohsu.edu/fdadrug/27/
SER 315 (FDA)	unpublished	http://digitalcommons.ohsu.edu/fdadrug/27/
SER-CHN-1	unpublished	Antidepressant efficacy and safety of paroxetine; a double blind amitriptyline controlled multicenter comparison study in depressive patients.
Settle	1999	Safety profile of sustained-release bupropion in depression: results of three clinical trials
Shamsaei	2008	Efficacy of pharmacotherapy and cognitive therapy, alone and in combination in major depressive disorder
Sheehan a	2009	Placebo-controlled inpatient comparison of venlafaxine and fluoxetine for the treatment of major depression with melancholic features
Sheehan b	2009	Extended-release Trazodone in Major Depressive Disorder: A Randomized, Double-blind, Placebo-controlled Study
Shelton	2006	Neuropsychological assessment and EEG sleep in affective disorders
Shu	2014	Comparable efficacy and safety of 8 weeks treatment with agomelatine 25-50mg or fluoxetine 20-40mg in Asian out-patients with major depressive disorder
Silverstone	1999	Once-daily venlafaxine extended release (xr) compared with fluoxetine in outpatients with depression and anxiety
Sir	2005	Randomized trial of sertraline versus venlafaxine XR in major depression: efficacy and discontinuation symptom
Smeraldi	1998	Double-blind, randomized study of venlafaxine, clomipramine, and trazodone in geriatric patients with major depression
Sramek	1995	Placebo-controlled study of ABT-200 versus fluoxetine in the treatment of major depressive disorder
Stahl	2000	Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline
Stahl	2010	Agomelatine in the treatment of major depressive disorder: an 8-week, multicenter, randomized, placebo-controlled trial
Staner	1995	A double blind randomised trial comparing the effects on sleep of paroxetine 30mg daily and amitriptyline 150mg daily in patients with major depression.
Studie 049	unpublished	Reboxetine (PNU-155950E) Versus Placebo in the Treatment of Major Depressive Disorders
Studie009	unpublished	Phase II controlled study of the activity and tolerability of reboxetine in comparison with placebo in patients hospitalizied for major depressive disorders
Studie032	unpublished	REBOXETINE (PNU-155950E) VS FLUOXETINE IN A DOUBLE-BLIND STUDY FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDERS IN TAIWAN.
Study 015	unpublished	Multicentre, multinational bouble-blind study of the activity and tolerability of reboxetine vs imipramine and placebo in patinets suffering from major depressive episodes
Study 032a	unpublished	Double-blind activity and tolerability study of reboxetine vs placebo in elderly patinets with depressive disorders

Study 045	unpublished	Comparison of Placebo and Three Fixed Doses of Reboxetine in a Population of Patients with Major Depression.
Study 19	unpublished	Efficacy of fluoxetine in outpatients with major depression
Study 205	unpublished	http://digitalcommons.ohsu.edu/fdadrug/21/
Study 25	unpublished	Fluoxetine in major depression: A controlled study
Study 62a	unpublished	Pattern analysis shows beneficial effect of fluoxetine treatment in mild depression
Study 62b	unpublished	http://digitalcommons.ohsu.edu/fdadrug/22/
Study 89306	unpublished	http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020822a_medr_P2.pdf
Study F1J-MC-HMAQ - Study Group B	unpublished	http://www.lillytrials.com/results/Cymbalta.pdf
Szegedi	2006	Mirtazapine orally disintegrating tablets versus venlafaxine extended release: a double-blind, randomized multicenter trial comparing the onset of antidepressant response in patients with major depressive disorder
Thase	1997	Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression
Thase	2006	A double-blind comparison between bupropion XL and venlafaxine XR: sexual functioning, antidepressant efficacy, and tolerability
Tollefson	1995	A double-blind, placebo- controlled clinical trial of fluoxetine in geriatric patients with major depression
Tomarken	2004	Assessing the effects of bupropion SR on mood dimensions of depression
Tourian	2009	Desvenlafaxine 50 and 100 mg/d in the Treatment of Major Depressive Disorder: An 8-Week, Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial and a Post Hoc Pooled Analysis of Three Studies
Trivedi	2004	Effectiveness of low doses of paroxetine controlled release in the treatment of major depressive disorder
Tsutsui	2000	Clinical evaluation of paroxetine HCl, a selective serotonin reuptake inhibitor, in the treatment of depression or depressive episodes: Double-blind, parallel group study with trazodone HCl
Tylee	1997	A double-blind, randomized, 12-week comparison study of the safety and efficacy of venlafaxine and fluoxetine in moderate to severe major depression in general practice
Tzanakaki	2000	Increased remission rates with venlafaxine compared with fluoxetine in hospitalized patients with major depression and melancholia
Van Moffaert a	1995	A controlled comparison of sertraline and fluoxetine in acute and continuation treatment of major depression
Van Moffaert b	1995	Mirtazapine is more effective than trazodone: a double-blind controlled study in hospitalized patients with major depression
VEN 600A-303	unpublished	http://digitalcommons.ohsu.edu/fdadrug/24/
VEN 600A-313	unpublished	http://digitalcommons.ohsu.edu/fdadrug/24/
VEN XR 367	unpublished	http://digitalcommons.ohsu.edu/fdadrug/25/
Ventura	2007	Escitalopram versus sertraline in the treatment of major depressive disorder: A randomized clinical trial Current Medical Research and Opinion
Versiani	1999	Fluoxetine versus amitriptyline in the treatment of major depression with associated anxiety (anxious depression): A double-blind comparison
Versiani	2000	Double-blind, placebo-controlled study with reboxetine in inpatients with severe major depressive disorder
Versiani	2005	Comparative Efficacy Antidepressants Study Group. Comparison of the effects of mirtazapine and fluoxetine in severely depressed patients
Wade	2002	Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care
Wade	2003	A randomized, double-blind, 24-week study comparing the efficacy and tolerability of mirtazapine and paroxetine in depressed patients in primary care
Wade	2007	A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder
Walczak	1996	The oral dose-effect relationship for fluvoxamine: a fixed-dose comparison against placebo in depressed outpatients
Wang	2014	A randomized, double-blind study of the efficacy and tolerability of extended-release quetiapine fumarate (quetiapine XR) monotherapy in patients with major depressive disorder
Wang	2015	Comparison of vortioxetine versus venlafaxine XR in adults in Asia with major depressive disorder: a randomized, double-blind study
WELL 029	unpublished	http://digitalcommons.ohsu.edu/fdadrug/21/
WELL AK140016	unpublished	https://www.gsk-clinicalstudyregister.com/study/AK140016#rs
WELL AK1A4006	unpublished	http://digitalcommons.ohsu.edu/fdadrug/21/
Wellbutrin 06	unpublished	http://digitalcommons.ohsu.edu/fdadrug/21/
Wellbutrin 25	unpublished	http://digitalcommons.ohsu.edu/fdadrug/21/
Wheatley	1998	Mirtazapine: efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe major depressive disorder. Mirtazapine-Fluoxetine Study Group
Winokur	2003	Comparative effects of mirtazapine and fluoxetine on sleep physiology measures in patients with major depression and insomnia

Yang	2003	Milnacipran vs Sertraline in Major Depressive Disorder: A double-blind randomised comparative study on the treatment effect and β-adrenergic receptor responsiveness.
Yevtushenko	2007	Efficacy and tolerability of escitalopram versus citalopram in major depressive disorder: a 6-week, multicenter, prospective, randomized, double-blind, active-controlled study in adult outpatients
Zajecka	2010	Efficacy and safety of agomelatine in the treatment of major depressive disorder
Zhang	2014	Efficacy and safety of prolonged-release trazodone in major depressive disorder
Zivkov	1995	Org 3770 versus amitriptyline: A 6-week randomized double-blind multicentre trial in hospitalized depressed patients
845	unpublished	http://digitalcommons.ohsu.edu/fdadrug/21/
003-008 (FDA)	unpublished	http://digitalcommons.ohsu.edu/fdadrug/20/
003-042	unpublished	http://digitalcommons.ohsu.edu/fdadrug/20/
003-048	unpublished	http://digitalcommons.ohsu.edu/fdadrug/20/
030A2-0004/030A2-0005 (FDA)	unpublished	http://digitalcommons.ohsu.edu/fdadrug/23/
03A0A-004A (FDA)	unpublished	http://digitalcommons.ohsu.edu/fdadrug/23/
0600A-326	unpublished	A randomised, double-blind, parallel group comparison of venlafaxine and clomipramine in outpatients with major depression
0600A-332	unpublished	A randomized double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression: final report
0600A-347	unpublished	A double-blind randomization study of the safety and efficacy of two regimens of venlafaxine compared with one regimen of fluvoxamine: final report
0600A-349	unpublished	A double-blind, randomized 8-week, comparative study of the safety and efficacy of venlafaxine and paroxetine: final report
0600A-626	unpublished	A randomised double-blind parallel-group comparison of the efficacy and safety of venlaflaxine versus fluoxetine in the treatment of moderately depressed outpatients
0600A-654	unpublished	A double-blind, randomized 12-week study of the safety and eficacy of oral venlaflaxine up to 75 mg bid compared with oral fluoxetine up to 20 mg bid in patients with moderate and severe major depression
0600A1-300	unpublished	A randomized, double-blind comparison of venlafaxine, amitriptyline, and placebo capsules in inpatients with major depression: final report
0600A1-372	unpublished	A double-blnd, placebocontrolled, parallelgroup, comparative study of venlafaxine and fluoxetine in depressed outpatients to measure onset of clinical activity: final report
0600B1-367	unpublished	A randomized, double-blind, placebo controlled, fixed-dose study of the efficacy and safety of venlafaxine extended release and paroxetine in depressed outpatients: final report
0600B1-384	unpublished	A double-blind, placebo-controlled, comparative study of an extended release formulation of venlafaxine and imipramine on the time of onset of anti-depressant response in patients with severe major depression: final report
0600B1-402	unpublished	A double-blind, placebo-controlled, comparative efficacy study of venlafaxine ER and sertraline in producing remission in outpatients with major depressive disorder: final report
244 (EMD 68 843-009)	unpublished	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022567Orig1s000MedR.pdf
245 (EMD 68 843-010)	unpublished	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022567Orig1s000MedR.pdf
246 (SB 659746-003)	unpublished	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022567Orig1s000MedR.pdf
247 (SB 659746-014)	unpublished	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022567Orig1s000MedR.pdf
248 (SB 659746-002)	unpublished	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022567Orig1s000MedR.pdf
29060 07 001	unpublished	http://www.gsk-clinicalstudyregister.com/study/29060/07/001#rs
29060/299	unpublished	A Double-Blind Study Comparing The Efficacy and Tolerability of Paroxetine and Amitriptyline In Patients With Severe Depression
29060/356	unpublished	A double-blind, multicentre study to compare paroxetine and fluoxetine in the treatment of patients with major depressive disorder with regard to antidepressant efficacy, effects on associated anxiety and tolerability.

First author	Year	Title
Published before 1995		
Aguglia	1993	Double-blind study of the efficacy and safety of sertraline versus fluoxetine in major depression.
Altamura	1989	Clinical activity and tolerability of trazodone, mianserin, and amitriptyline in elderly subjects with major depression: a controlled multicenter trial
Amin	1984	ANTIDEPRESSANT EFFECTS CONFIRMED IN A PLACEBO-CONTROLLED INTERNATIONAL STUDY
Amsterdam	1986	A double-blind comparative trial of zimelidine, amitriptyline, and placebo in patients with mixed anxiety and depression
Andersen	1986	Citalopram: Clinical effect profile in comparison with clomipramine. A controlled multicenter study
Ansseau	1991	Interest of a loading dose of milnacipran in endogenous depressive inpatients. Comparison with the standard regimen and with fluvoxamine
Ansseau a	1989	Controlled comparison of two doses of milnacipran (F 2207) and amitriptyline in major depressive inpatients
Ansseau a	1994	Controlled comparison of paroxetine and fluvoxamine in major depression
Ansseau b	1989	Controlled comparison of milnacipran (F2207) 200 mg and amitriptyline in endogenous depressive inpatients
Ansseau b	1994	Controlled comparison of milnacipran and fluoxetine in major depression
Ansseau c	1994	Controlled comparison of nefazodone and amitriptyline in major depressive inpatients
Bakish	1992	A double-blind placebo-controlled comparison of moclobemide and amitriptyline in the treatment of depression
Battegay	1985	Double-blind comparative study of paroxetine and amitriptyline in depressed patients of a university psychiatric outpatient clinic (pilot study)
Beasley	1991	Fluoxetine versus trazodone: efficacy and activating-sedating effects
Beck	1985	Treatment of depression with cognitive therapy and amitriptyline
Bellack	1981	Social skills training compared with pharmacotherapy and psychotherapy in the treatment of unipolar depression
Bersani	1994	A double-blind comparative study of sertraline and amitriptyline in outpatients with major depressive episodes
Bhatia	1991	Platelet alpha-2 adrenoreceptor activity pre-treatment and post-treatment in major depressive disorder with melancholia
Bignamini	1992	A double-blind multicentre study of paroxetine and amitriptyline in depressed outpatients. Italian Paroxetine Study Group
Blackburn	1981	The efficacy of cognitive therapy in depression: a treatment trial using cognitive therapy and pharmacotherapy, each alone and in combination
Blacker	1988	The drug treatment of depression in general practice: a comparison of nocte administration of trazodone with mianserin, dothiepin and amitriptyline
Brown	1986	Pituitary-adrenocortical hyperfunction and intolerance to fluvoxamine, a selective serotonin uptake inhibitor.
Byerley	1988	Fluoxetine, a selective serotonin uptake inhibitor, for the treatment of outpatients with major depression
Carman	1991	A controlled study of mianserin in moderately to severely depressed outpatients.
Cassano	1986	Use of a standardized documentation system (BLIPS/BDP) in the conduct of a multicenter international trial comparing fluvoxamine, imipramine, and placebo
Chouinard	1983	Bupropion and amitriptyline in the treatment of depressed patients
Chouinard	1985	A double-blind controlled clinical trial of fluoxetine and amitriptyline in the treatment of outpatients with major depressive disorder
Claghorn	1983	Zimeldine tolerability in comparison to amitriptyline and placebo: findings from a multicentre trial
Clerc	1994	A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. The Venlafaxine French Inpatient Study Group
Cohn	1985	A comparison of fluoxetine, imipramine, and placebo in patients with major depressive disorder
Cohn	1990	Double-blind, multicenter comparison of sertraline and amitriptyline in elderly depressed patients
Covi	1987	Cognitive behavioral group psychotherapy combined with imipramine in major depression
Cunningham	1994	A comparison of venlafaxine, trazodone, and placebo in major depression
D'Amico	1990	Placebo-controlled dose-ranging trial designs in phase II development of nefazodone
Debus	1988	Fluoxetine versus trazodone in the treatment of outpatients with major depression
DeRonchi	1988	Fluoxetine and amitriptyline in elderly depressed patients. A 10-week, double-blind study on course of neurocognitive adverse events and depressive symptoms
DeWilde a	1983	Clinical trials of fluvoxamine vs chlorimipramine with single and three times daily dosing
DeWilde b	1983	A double-blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients
Dominguez	1985	A double-blind placebo-controlled study of fluvoxamine and imipramine in depression
Doogan	1994	A double-blind, placebo-controlled comparison of sertraline and dothiepin in the treatment of major depression in general practice
DUAG	1990	Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study.
Dunbar a	1993	The safety and efficacy of paroxetine compared with placebo in a double-blind trial of depressed outpatients

Dunbar b	1993	A comparison of paroxetine and placebo in depressed outpatients. Acta Psychiatr Scand
Dunbar c	1993	A placebo-controlled trial of paroxetine in the treatment of major depression
Dunbar d	1993	A double-blind, placebo-controlled study of paroxetine in depressed outpatients. J Clin Psychiatry
Dunn	1979	Cognitive modification with depression-prone psychiatric patients
Dunner	1992	Optimal dose regimen for paroxetine
Edwards	1989	Placebo-controlled trial of paroxetine in depressive illness
Elkin	1989	National Institute of Mental Health Treatment of Depression Collaborative Research Program
Fabre	1979	Trazodone efficacy in depression: a double-blind comparison with imipramine and placebo in day-hospital type patients
Falk	1989	Fluoxetine Versus Trazodone in Depressed Geriatric Patients
Fawcett	1989	Fluoxetine versus amitriptyline in adult outpatients with major depression
Feighner	1979	A placebo-controlled multicenter trial of Limbitrol versus its components (amitriptyline and chlordiazepoxide) in the symptomatic treatment of depressive illness.
Feighner	1980	Trazodone, a triazolopyridine derivative, in primary depressive disorder
Feighner	1984	A double-blind study of bupropion and placebo in depression
Feighner	1991	Double-blind comparison of bupropion and fluoxetine in depressed outpatients
Feighner a	1989	A double-blind comparison of fluoxetine, imipramine and placebo in outpatients with major depression
Feighner a	1993	Paroxetine in the treatment of depression: a comparison with imipramine and placebo
Feighner b	1989	A placebo-controlled inpatient comparison of fluvoxamine maleate and imipramine in major depression
Feighner b	1993	Paroxetine in major depression: a double-blind trial with imipramine and placebo
Feighner c	1993	A comparison of paroxetine, imipramine and placebo in depressed out-patients
Feighner d	1993	A double-blind comparison of paroxetine, imipramine and placebo in major depression
Feighner e	1993	A study comparing paroxetine placebo and imipramine in depressed patients
Feighner f	1993	A 6-week, double-blind trial of paroxetine, imipramine, and placebo in depressed outpatients
Fontaine	1994	A double-blind comparison of nefazodone, imipramine, and placebo in major depression
Fudge	1990	A comparison of the effect of fluoxetine and trazodone on the cognitive functioning of depressed outpatients
Gagiano	1993	A double blind comparison of paroxetine and fluoxetine in patients with major depression
Gelenberg	1990	Clovox- amine in the treatment of depressed outpatients: a double-blind, parallel-group comparison against amitriptyline and placebo
Georgotas	1982	Controlled trial of zimelidine, a 5-HT reuptake inhibitor, for treatment of depression
Gerner	1980	Treatment of geriatric depression with tra- zodone, imipramine, and placebo: a double-blind study
Ginestet	1989	Fluoxetine in endogenous depression and melancholia versus clomipramine
Guillibert	1989	A double-blind, multicentre study of paroxetine versus clomipramine in depressed elderly patients
Harris	1991	Fluvoxamine versus amitriptyline in depressed hospital out-patients: a multicentre double-blind comparative trial
Heiligenstein	1994	Latency to rapid eye movement sleep as a predictor of treatment response to fluoxetine and placebo in nonpsychotic depressed outpatients
Hicks	1988	Comparison of adinazolam, amitriptyline, and placebo in the treatment of melancholic depression
Hollon	1992	Cognitive therapy and pharmacotherapy for depression
Hormazabal	1985	Cianopramine and amitriptyline in the treatment of depressed patients--a placebo-controlled study
Hutchinson	1992	Paroxetine in the treatment of elderly depressed patients in general practice: a double-blind comparison with amitriptyline
Itil	1983	A double-blind placebo-controlled study of fluvoxamine and imipramine in out-patients with primary depression
Judd	1993	A multicentre double blind trial of fluoxetine versus amitriptyline in the treatment of depressive illness
Kane	1983	Safety and efficacy of bupropion in elderly patients: preliminary observations. J Clin Psychiatry
Katz a	1993	A clinical test of noradrenergic involvement in the therapeutic mode of action of an experimental antidepressant
Katz b	1993	A clinical test of noradrenergic involvement in the therapeutic mode of action of an experimental antidepressant
Keegan	1991	A comparison of fluoxetine and amitriptyline in the treatment of major depression. Int Clin Psychopharmaco
Kellams	1979	Trazodone, a new antidepressant: efficacy and safety in endogenous depression
Kerkhofs	1990	Fluoxetine in major depression: efficacy, safety and effects on sleep polygraphic variables.
Kerr	1984	A comparative clinical and predictive study
Kuhs	1989	A double-blind study of the comparative antidepressant effect of paroxetine and amitriptyline
Kusalic	1993	Thyroid functioning during treatment for depression

Laakman	1988	Fluoxetine vs amitriptyline in the treatment of depressed out-patients
Langlois	1985	High incidence of multisystemic reactions to zimeldine
Lapierre	1980	Differential antidepressant properties of trazodone and amitriptyline in agitated and retarded depression
Lapierre	1987	Treatment of major affective disorder with fluvoxamine
Larsen	1989	Moclobemide and clomipramine in reactive depression. A placebo-controlled randomized clinical trial
Lineberry	1990	A fixed-dose (300 mg) efficacy study of bupropion and placebo in depressed outpatients
Lydiard	1989	Fluvoxamine, imipramine, and placebo in the treatment of depressed outpatients: effects on depression.
Maldonado	1982	Terapia de conducta y depresión: un análisis experimental de los modelos conductual y cognitivo
Maldonado	1984	Un modelo de terapia cognitiva desde la perspectiva de la psicología del aprendizaje
Mann	1981	A controlled study of trazodone, imipramine, and placebo in outpatients with endogenous depression
Manna	1989	Double-blind controlled study on the clinical efficacy and safety of fluoxetine vs clomipramine in the treatment of major depressive disorders
March	1990	A double-blind, placebo-controlled trial of fluvoxamine versus imipramine in outpatients with major depression
Masco	1985	Double-blind comparison of Fluoxetine and Amitripyline in the treatment of Major Depressive Illness. Advances in Therapy
McKnight	1992	Dexamethasone suppression test and response to cognitive therapy and antidepressant medication
McLean	1979	Clinical depression: comparative efficacy of outpatient treatments.
Miller	1989	A double-blind comparison of paroxetine and placebo in the treatment of depressed patients in a psychiatric outpatient clinic
Moises	1981	Trazodone and amitriptyline in treatment of depressed inpatients. A double-blind study
Moller	1993	Double-blind multicenter study of paroxetine and amitriptyline in depressed inpatients
Moon	1994	A double-blind comparison of sertraline and clomipramine in the treatment of major depressive disorder and associated anxiety in general practice.
Murphy	1984	Cognitive therapy and pharmacotherapy. Singly and together in the treatment of depression
Noguera	1991	Fluoxetine vs. clomipramine in depressed patients: a controlled multicentre trial.
Norton	1984	A double-blind comparison of fluvoxamine, imipramine and placebo in depressed patients
Ontiveros	1994	A double-blind, comparative study of paroxetine and fluoxetine in out-patients with depression
PAR 01 001	1989	http://digitalcommons.ohsu.edu/fdadrug/26/
Paykel	1988	Predictors of therapeutic benefit from amitriptyline in mild depression: a general practice placebo-controlled trial
Pélicier	1993	Multicenter double-blind study comparing the efficacy and tolerance of paroxetine and clomipramine in reactive depression in the elderly patient
Preskorn	1991	Antidepressant Response and Plasma Concentrations of Fluoxetine
Raft	1981	Relationship between response to phenelzine and MAO inhibition in a clinical trial of phenelzine, amitriptyline and placebo
Reimherr	1990	Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression
Remick	1994	Comparison of fluvoxamine and amitriptyline in depressed outpatients. Current Therapeutic Research.
Rickels	1982	Trazodone in depressed outpatients
Rickels	1985	Alprazolam, amitriptyline, doxepin, and placebo in the treatment of depression
Rickels	1994	Nefazodone and imipramine in major depression: a placebo-controlled trial
Roffman	1982	A Double-blind comparative study of oxaprotiline with amitriptyline and placebo in moderate depression.
Ropert	1989	Fluoxetine versus clomipramine in major depressive disorders
Roth	1990	A double-blind comparison of fluvoxamine, desipramine and placebo in outpatients with depression
Roth	1982	A comparison of self-control therapy and combined self-control therapy and antidepressant medication in the treatment of depression
Rouillon	1991	A double-blind, multicentre study comparing increasing doses of paroxetine (20-50mg) and clomipramine (50-150mg) in elderly patients with major depression.
Rowan	1980	Comparative effects of phenelzine and amitriptyline: a placebo controlled trial.
Rush	1977	Comparative efficacy of cognitive therapy and pharmacotherapy in the treatment of depressed outpatients.
Rush	1981	Group versus individual cognitive therapy: a pilot study
Schiffer	1990	Antidepressant pharmacotherapy of depression associated with multiple sclerosis
Schoene	1993	A double-blind study of paroxetine compared with fluoxetine in geriatric patients with major depression
Schweizer	1994	Comparison of venlafaxine and imipramine in the acute treatment of major depression in outpatients
Scott	1992	Edinburgh primary care depression study: treatment outcome, patient satisfaction, and cost after 16 weeks
Shaw	1986	A comparison of the antidepressant action of citalopram and amitriptyline
Shipley	1981	Neuropsychological assessment and EEG sleep in affective disorders

Smith	1990	Mirtazapine vs Amitriptyline vs Placebo in the treatment of major depressive disorder
Stark	1985	A review of multicenter controlled studies of fluoxetine vs. imipramine and placebo in outpatients with major depressive disorder
Stratas	1894	A review of multicenter controlled studies of fluoxetine vs. imipramine and placebo in outpatients with major depressive disorder.
Stravynski	1994	The treatment of depression with group behavioural-cognitive therapy and imipramine
Targ	1994	Structured group therapy and fluoxetine to treat depression in HIV-positive persons
Thomson	1982	The treatment of depression in general practice: a comparison of L-tryptophan, amitriptyline, and a combination of L- tryptophan and amitriptyline with placebo
Tignol	1993	A double-blind, randomized, fluoxetine-controlled, multicenter study of paroxetine in the treatment of depression
Timmerman	1993	Efficacy and tolerability of citalopram in comparison with fluvoxamine in depressed outpatients: a double-blind, multicentre study
Upward	1988	Comparative effects of fluoxetine and amitriptyline on cardiac function
Van de Merwe	1984	A double-blind non-crossover placebo-controlled study between group comparison of trazodone and amitriptyline on cardiovascular function in major depressive disorder.
Vartiainen	1994	Double-blind study of mirtazapine and placebo in hospitalized patients with major depression
Weisler	1994	Comparison of bupropion and trazodone for the treatment of major depression
Weissman	1979	The efficacy of drugs and psychotherapy in the treatment of acute depressive episodes
Wilcox	1994	A double- blind, placebo-controlled study comparing mianserin and amitriptyline in moderately depressed outpatients. Int Clin Psychopharmacol
Wilson	1982	Combined pharmacological and behavioural treatment of depression
Young	1987	A controlled comparison of fluoxetine and amitriptyline in depressed out-patients

First author	**Year**	**Title**
Intervention not eligible		
Altamura	2017	Comparing interpersonal counseling and antidepressant treatment in primary care patients with anxious and nonanxious major depression disorder: a randomized control trial.
Barber	2012	Short-term dynamic psychotherapy versus pharmacotherapy for major depressive disorder: a randomized, placebo-controlled trial.
Barrett	2012	Treatment of dysthymia and minor depression in primary care: a randomized trial in patients aged 18 to 59 years
Bellino	2007	Combined therapy of major depression with concomitant borderline personality disorder: comparison of interpersonal and cognitive psychotherapy.
Bloch	2012	The effect of sertraline add-on to brief dynamic psychotherapy for the treatment of postpartum depression: a randomized, double-blind, placebo-controlled study
Blom	2015	Internet treatment addressing either insomnia or depression, for patients with both diagnoses: a randomized trial
Browne	2002	Sertraline and/or interpersonal psychotherapy for patients with dysthymic disorder in primary care: 6-month comparison with longitudinal 2-year follow-up of effectiveness and costs
Burnand	2002	Psychodynamic psychotherapy and clomipramine in the treatment of major depression
Chibanda	2014	Group problem-solving therapy for postnatal depression among HIV-positive and HIV-negative mothers in Zimbabwe.
Corruble	2016	Telephone-administered psychotherapy in combination with antidepressant medication for the acute treatment of major depressive disorder
De Jonghe	2001	Combining psychotherapy and antidepressants in the treatment of depression
De Jonghe	2004	Psychotherapy alone and combined with pharmacotherapy in the treatment of depression
De Mello	2001	A randomized controlled trial comparing moclobemide and moclobemide plus interpersonal psychotherapy in the treatment of dysthymic disorder
Dekker	2008	Speed of action: the relative efficacy of short psychodynamic supportive psychotherapy and pharmacotherapy in the first 8 weeks of a treatment algorithm for depression
Denton	2012	Augmenting antidepressant medication treatment of depressed women with emotionally focused therapy for couples: a randomized pilot study.
Finkenzeller	2009	Interpersonal psychotherapy and pharmacotherapy for post-stroke depression
Frank	2011	Predictors and moderators of time to remission of major depression with interpersonal psychotherapy and SSRI pharmacotherapy
Gater	2010	Social intervention for British Pakistani women with depression: randomised controlled trial
Gaudiano	2015	Acceptance-based behavior therapy for depression with psychosis: results from a pilot feasibility randomized controlled trial
Hellerstein	2001	Adding group psychotherapy to medication treatment in dysthymia: a randomized prospective pilot study
Hsiao	2011	The long-term effects of psychotherapy added to pharmacotherapy on morning to evening diurnal cortisol patterns in outpatients with major depression
Leinonen	1997	Long-term efficacy and safety of milnacipran compared to clomipramine in patients with major depression
Lesperance	2007	Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial
Maina	2010	No effect of adding brief dynamic therapy to pharmacotherapy in the treatment of obsessive-compulsive disorder with concurrent major depression

Markowitz	1998	Treatment of depressive symptoms in human immunodeficiency virus-positive patients
Markowitz	2005	A comparative trial of psychotherapy and pharmacotherapy for "pure" dysthymic patients
Martin	2001	Brain blood flow changes in depressed patients treated with interpersonal psychotherapy or venlafaxine hydrochloride: preliminary findings
Menchetti	2014	Moderators of remission with interpersonal counselling or drug treatment in primary care patients with depression: randomised controlled trial.
Mitchell	2009	Brief psychosocial-behavioral intervention with antidepressant reduces poststroke depression significantly more than usual care with antidepressant living well with stroke: randomized, controlled trial
Murphy	1995	Cognitive behavior therapy, relaxation training, and tricyclic antidepressant medication in the treatment of depression
Mynors-Wallis	1995	Randomised controlled trial comparing problem solving treatment with amitriptyline and placebo for major depression in primary care
Mynors-Wallis	2000	Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care
Reynolds	1999	Treatment of bereavement-related major depressive episodes in later life: a controlled study of acute and continuation treatment with nortriptyline and interpersonal psychotherapy
RodrÌguez Vega	2011	Combined therapy versus usual care for the treatment of depression in oncologic patients: a randomized controlled trial
Salminen	2008	Short-term psychodynamic psychotherapy and fluoxetine in major depressive disorder: a randomized comparative study
Schulberg	1996	Treating major depression in primary care practice. Eight-month clinical outcomes
Sharp	2010	A pragmatic randomised controlled trial to compare antidepressants with a community-based psychosocial intervention for the treatment of women with postnatal depression: the RESPOND trial.
Souza	2016	Interpersonal psychotherapy as add-on for treatment-resistant depression: a pragmatic randomized controlled trial
Williams	2000	Treatment of dysthymia and minor depression in primary care: a randomized controlled trial in older adults
Zisook	1998	Treatment of major depression in HIV-seropositive men

Excluded studies from the updated search (based on full-text screening)

First author	Year	Title
Population not eligible		
Borrellli	2019	Prospective Study of the Effectiveness of Paroxetine on the Onset of Posttraumatic Stress Disorder, Depression, and Health and Functional Outcomes After Trauma
Dunner	1996	Cognitive therapy versus fluoxetine in the treatment of dysthymic disorder. Depression
Guo	2020	Effect of a WeChat-Based Intervention (Run4Love) on Depressive Symptoms Among People Living With HIV in China: a Randomized Controlled Trial
Huijbers	2016	Discontinuation of antidepressant medication after mindfulness-based cognitive therapy for recurrent depression: Randomised controlled non-inferiority trial
Kim	2016	Influences of the Big Five personality traits on the treatment response and longitudinal course of depression in patients with acute coronary syndrome: A randomised controlled trial
Kladnitski	2020	Transdiagnostic internet-delivered CBT and mindfulness-based treatment for depression and anxiety: A randomised controlled trial
Rana	2017	Assessment of automatic thoughts in patients with depressive illness at a tertiary hospital in Nepal
Rollman	2017	Effectiveness of Online Collaborative Care for Treating Mood and Anxiety Disorders in Primary CareA Randomized Clinical Trial
Wiles	2007	A Randomized Controlled Trial of Cognitive Behavioural Therapy as an Adjunct to Pharmacotherapy in Primary Care Based Patients with Treatment Resistant Depression: A Pilot Study
Wiles	2013	Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial
Zuidersma	2019	Sertraline and Mirtazapine Versus Placebo in Subgroups of Depression in Dementia: Findings From the HTA-SADD Randomized Controlled Trial
Intervention not eligible		
Bruijniks	2020	Direct effects of cognitive therapy skill acquisition on cognitive therapy skill use, idiosyncratic dysfunctional beliefs and emotions in distressed individuals: An experimental study
Bruijniks	2020	The effects of once- versus twice-weekly sessions on psychotherapy outcomes in depressed patients
D'Elia	2020	Feasibility of behavioral activation group therapy in reducing depressive symptoms and improving quality of life in patients with depression: the BRAVE pilot trial

Gili	2020	Efficacy of Three Low-Intensity, Internet-Based Psychological Interventions for the Treatment of Depression in Primary Care: Randomized Controlled Trial.
Grosse	2019	A randomized-controlled trial of cognitive-behavioral therapy for depression with integrated techniques from emotion-focused and exposure therapies.
Hicks	2002	Comparison of adinazolam, amitriptyline, and placebo in the treatment of melancholic depression
Kheirabadi	2017	Comparison of citalopram and metacognitive therapy on depression in patients with major depressive disorder
Kroska	2020	How much is enough in brief Acceptance and Commitment Therapy? A randomized trial
Lavretsky	2020	A Randomized Double-Blind Placebo-Controlled Trial of Combined Escitalopram and Memantine for Older Adults With Major Depression and Subjective Memory Complaints
Löbner	2018	Computerized cognitive behavior therapy for patients with mild to moderately severe depression in primary care: A pragmatic cluster randomized controlled trial (@ktiv)
McIntyre	2017	Efficacy of vortioxetine on cognitive functioning in working patients with major depressive disorder
Mohr	2019	A randomized noninferiority trial evaluating remotely-delivered stepped care for depression using internet cognitive behavioral therapy (CBT) and telephone CBT
Ostacoli	2018	Comparison of eye movement desensitization reprocessing and cognitive behavioral therapy as adjunctive treatments for recurrent depression: The European Depression EMDR Network (EDEN) randomized controlled trial
Rush	2011	Combining Medications to Enhance Depression Outcomes (CO-MED): Acute and Long-Term Outcomes of a Single-Blind Randomized Study
Schramm	2015	Cognitive behavioral analysis system of psychotherapy versus escitalopram in chronic major depression
Vrijsen	2018	Cognitive bias modification as an add-on treatment in clinical depression: Results from a placebo-controlled, single-blinded randomized control trial
Yan	2019	Efficacy of vortioxetine combined cognitive behaviour intervention therapy on brain-derived neurotrophic factor level on depressive patients
Comparator not eligible		
Dikaios	2020	Continuation Sessions of Mindfulness-Based Cognitive Therapy (MBCT-C) vs. Treatment as Usual in Late-Life Depression and Anxiety: An Open-Label Extension Study
Dunlop	2019	Benefits of Sequentially Adding Cognitive-Behavioral Therapy or Antidepressant Medication for Adults With Nonremitting Depression
Inoue	2018	Randomized, 8-week, double-blind, placebo-controlled trial of vortioxetine in Japanese adults with major depressive disorder, followed by a 52-week open-label extension trial
Jarrett	2016	Quantifying and Qualifying the Preventive Effects of Acute-Phase Cognitive Therapy: Pathways to Personalizing Care
Perry	2020	Change in defense mechanisms and depression in a pilot study of antidepressive medications plus 20 sessions of psychotherapy for recurrent major depression
Zhitkova	2017	Comparison of Different Doses of Escitalopram in the Prophylaxis of Dementia in Patients with Depression and Moderate Cognitive Dysfunction in Chronic Cerebral Ischemia
Outcome not eligible		
Beresnevaitė	2020	Changes in heart rate variability during cognitive behavior therapy in depressed post-cardiac surgery patients: randomized controlled study
Callesen	2020	Metacognitive Therapy versus Cognitive Behaviour Therapy in Adults with Major Depression: A Parallel Single-Blind Randomised Trial.
Dos Santos	2020	Long-term effectiveness of two models of brief psychotherapy for depression: A three-year follow-up randomized clinical trial
Dozois	2014	Changes in core beliefs (early mala daptive schemas) and selfrepresentation in cognitive therapy and pharma cotherapy for depression.
Heller	2009	Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation
Jacob	2020	A novel study design for investigating relapse prevention in major depressive disorder: Preliminary data from the open-label period of a phase 4 vortioxetine study
Jahoda	2018	Behavioural activation versus guided self-help for depression in adults with learning disabilities: the BeatIt RCT.
Jha a	2018	Do baseline sub-threshold hypomanic symptoms affect acute-phase antidepressant outcome in outpatients with major depressive disorder? Preliminary findings from the randomized CO-MED trial
Jha b	2018	Validating pre-treatment body mass index as moderator of antidepressant treatment outcomes: Findings from CO-MED trial
Jha c	2016	Early normalization of Quality of Life predicts later remission in depression: Findings from the CO-MED trial
Kang	2017	Effects of Escitalopram on Anxiety in Patients with Acute Coronary Syndrome: A Randomized Controlled Trial
Kang	2016	Associations between Serotonergic Genes and Escitalopram Treatment Responses in Patients with Depressive Disorder and Acute Coronary Syndrome: The EsDEPACS Study
Kao	2018	5-HTT mRNA level as a potential biomarker of treatment response in patients with major depression in a clinical trial
Kennedy	2007	Differences in Brain Glucose Metabolism Between Responders to CBT and Venlafaxine in a 16-Week Randomized Controlled Trial
Kim a	2018	Social support deficit and depression treatment outcomes in patients with acute coronary syndrome: Findings from the EsDEPACS study

Kim b	2018	Effect of Escitalopram vs Placebo Treatment for Depression on Long-term Cardiac Outcomes in Patients With Acute Coronary Syndrome A Randomized Clinical Trial
Lutes	2018	COMRADE: A randomized trial of an individually tailored integrated care intervention for uncontrolled type 2 diabetes with depression and/or distress in the rural southeastern US
Quitasol	2018	Changes in psychological need fulfillment over the course of treatment for major depressive disorder
Sherwood	2017	Effects of Exercise and Sertraline on Measures of Coronary Heart Disease Risk in Patients with Major Depression: Results from the SMILE-II Randomized Clinical Trial
Smagula	2019	Moderators of Response to Cognitive Behavior Therapy for Major Depression in Patients With Heart Failure
Tajika	2019	Trajectory of criterion symptoms of major depression under newly started antidepressant treatment: sleep disturbances and anergia linger on while suicidal ideas and psychomotor symptoms disappear early
Thiruchselvam	2019	The role of outcome expectancy in therapeutic change across psychotherapy versus pharmacotherapy for depression
Vittengl	2019	Do comorbid social and other anxiety disorders predict outcomes during and after cognitive therapy for depression?
Vittengl	2017	Longitudinal Social-Interpersonal Functioning among Higher-risk Responders to Acute-phase Cognitive Therapy for Recurrent Major Depressive Disorder
Watanabe	2017	Long-term function and psychosocial outcomes with venlafaxine extended release 75–225 mg/day versus placebo in the PREVENT study
Yoon	2018	Social support deficit and depression treatment outcomes in patients with acute coronary syndrome: Findings from the EsDEPACS study
Treatment duration <13 weeks		
Bockting	2018	Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive relapse or recurrence (DRD study): a three-group, multicentre, randomised controlled trial
Brouwer	2019	Dysfunctional attitudes or extreme response style as predictors of depressive relapse and recurrence after mobile cognitive therapy for recurrent depression
Chokka	2019	Long-term functioning outcomes are predicted by cognitive symptoms in working patients with major depressive disorder treated with vortioxetine: results from the AtWoRC study
CL3-20098-023	2001	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report /human/000915/WC500046226.pdf
CL3-20098-024	2002	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report /human/000916/WC500038315.pdf
CL3-20098-026	2001	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report /human/000916/WC500038315.pdf
De Jong	2018	A Randomized Controlled Pilot Study on Mindfulness-Based Cognitive Therapy for Unipolar Depression in Patients With Chronic Pain
Dobkin	2020	Telephone-based cognitive behavioral therapy for depression in Parkinson disease: A randomized controlled trial
Hale	2010	Superior antidepressant efficacy results of agomelatine versus fluoxetine in severe MDD patients: a randomized, double-blind study
Higuchi	2016	A randomized, double-blinded, placebo-controlled study to evaluate the efficacy and safety of venlafaxine extended release and a long-term extension study for patients with major depressive disorder in Japan
Hopwood	2019	Effect of agomelatine 25-50 mg on social functioning over 6 months in adults and elderly patients with major depressive disorder
Jelinek	2020	Brief web-based intervention for depression: Randomized controlled trial on behavioral activation
Kheirabadi	2020	Citalopram and metacognitive therapy for depressive symptoms and cognitive emotion regulation in patients with major depressive disorder: A randomized controlled trial.
Klein	2018	No sustainable effects of an internet-based relapse prevention program over 24 months in recurrent depression: Primary outcomes of a randomized controlled trial
Lee	2018	Differences in Therapeutic Responses and Factors Affecting Post-Stroke Depression at a Later Stage According to Baseline Depression
Lemoine	2007	Improvement in Subjective Sleep in Major Depressive Disorder With a Novel Antidepressant, Agomelatine: Randomized, Double-Blind Comparison With Venlafaxine
Mahajan	2019	Comparative Efficacy and Safety of Escitalopram versus Desvenlafaxine in Postmenopausal Women with Depression and Anxiety: A Randomized, Open-Label, Comparative Trial.
Marshall	2008	Self-criticism predicts differential response to treatment for major depression
Mergl	2018	One-year follow-up of a randomized controlled trial of sertraline and cognitive behavior group therapy in depressed primary care patients (MIND study)
Miranda	2003	Treating Depression in Predominantly Low-Income Young Minority Women A Randomized Controlled Trial
Msetfi	2016	SSRI enhances sensitivity to background outcomes and modulates response rates: A randomized double blind study of instrumental action and depression
Nissen	2020	Internet-delivered mindfulness-based cognitive therapy for anxiety and depression in cancer survivors: A randomized controlled trial
Pumar	2019	Cognitive behavioural therapy (CBT) for patients with chronic lung disease and psychological comorbidities undergoing pulmonary rehabilitation
Rodgers	2019	Modified mindfulness-based cognitive therapy for depressive symptoms in Parkinson's disease: A pilot trial

Schaub	2018	Efficacy of extended clinical management, group CBT, and group plus individual CBT for major depression: Results of a two-year follow-up study
Senders	2019	Impact of mindfulness-based stress reduction for people with multiple sclerosis at 8 weeks and 12 months: A randomized clinical trial.
Serfaty	2019	Effectiveness of cognitive–behavioural therapy for depression in advanced cancer: CanTalk randomised controlled trial
Shah	2018	Audio and computer cognitive behavioral therapy for depressive symptoms in older adults: A pilot randomized controlled trial
Strand	2018	Metacognitive therapy for depression reduces interpersonal problems: Results from a randomized controlled trial
Thompson	2001	Comparison of Desipramine and Cognitive/Behavioral Therapy in the Treatment of Elderly Outpatients With Mild-to-Moderate Depression
Watanabe	2018	Factors impacting the efficacy of venlafaxine extended release 75–225 mg/day in patients with major depressive disorder: Exploratory post hoc subgroup analyses of a randomized, double-blind, placebo-controlled study in Japan
First author	**Year**	**Title**
Study design or analysis not eligible		
Murphy	2019	Randomised controlled trial of internet-delivered cognitive behaviour therapy for clinical depression and/or anxiety in cancer survivors (iCanADAPT Early)
Schuling	2020	Recovery from recurrent depression: Randomized controlled trial of the efficacy of mindfulness-based compassionate living compared with treatment-as-usual on depressive symptoms and its consolidation at longer term follow-up
Other		
CL3-20098-036	unpublished	Unpublished data provided from Servier upon request.
Dobi	2019	Venlafaxin vs escitalopram in treatment of depression in Parkinson's disease patient
Goodwin	2017	Effect of agomelatine and escitalopram on emotional experiences in outpatients suffering from major depressive disorder
Kasckow	2017	Problem solving therapy improves social problem solving skills in older adults with depression and low back pain
Lopez-Rodriguez	2004	Estudio doble ciego con antidepressivo, psicoterapia breve y placebo en pacientes con depression leve a moderada
Mangin	2016	Effectiveness of maintenance SSRI treatment in primary care depression to prevent recurrence Randomized controlled trial
Nikbakhsh	2019	Depression, anxiety, and quality of life in breast cancer patients with depression receiving citalopram and supportive group psychotherapy: A six-month longitudinal study
Quinn	2018	Selective serotonin reuptake inhibitors and bleeding risk in anticoagulated patients with atrial fibrillation: An analysis from the ROCKET AF trial
Thase	2019	Efficacy and safety of vortioxetine (5, 10, and 20 mg) in relapse prevention: Results of a randomized, double-blind, placebo-controlled, phase 4 study in adults with major depressive disorder (MDD)
Duplicates		
Bockting	2018	Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive relapse or recurrence (DRD study): a three-group, multicentre, randomised control
DeRubeis	2019	Prevention of Recurrence after Recovery from a Major Depressive Episode with Antidepressant Medication Alone or in Combination with Cognitive Behavioral Therapy: a Phase 2 Randomized Clinical Trial
Gilliam	2019	A Trial of Sertraline or Cognitive Behavior Therapy for Depression in Epilepsy
Hashimoto	2016	Effect of mirtazapine versus selective serotonin reuptake inhibitors on benzodiazepine use in patients with major depressive disorder: a pragmatic, multicenter, open-label, randomized, active-controlled, 24-week trial
Kennedy	2016	Sustained efficacy of agomelatine 10 mg, 25 mg, and 25-50 mg on depressive symptoms and functional outcomes in patients with major depressive disorder. A placebo-controlled study over 6 months

11.1.4 Study characteristics

Trial	Study design	Pharmaceutical industry funding	Population characteristics	Comparison	Comparison details	Number of participants	Age (mean (SD))	Female sex (%)	Baseline severity scale	Baseline severity (mean (SD))	Treatment duration (weeks)	Extension phase (weeks)
Angermann, 2016	Design I; DB; MC; Europe	Yes	Adults with heart failure and MDD (DSM-IV) All MDD severities Outpatients; 3ry care	ESC	10-20 mg, flexible dosing	186	62.2 (12)	24%	PHQ9	14.7 (3.8)	96	-
				PLC	0-0 mg	190	62.3 (11.9)	25%		14.6 (3.5)		
A-Tjak, 2018	Design I; RB; SC; Europe	No	18-65 year olds with MDD (DSM-IV) All MDD severities Outpatients; 1ry and 2ry care	ACT	20 sessions (45-55 mins each), face to face	49	42.52 (12.21)	52%	HAMD17	19.3 (5.3)	30	-
				CBT	20 sessions (45-55 mins each), face to face	50	40.45 (12.55)	50%		17.7 (8.1)		
Banerjee, 2011	Design I; DB; MC; Europe	No	Patients fulfilling ADRDA criteria for Alzheimer's disease & depression for ≥4 weeks and CSDD score ≥8 All MDD severities Outpatients; 2ry care	SRT	Flexible dosage	107	80 (8.4)	68%	CSDD	12.8 (3.6)	39	-
				MIR	Flexible dosage	108	79 (8.4)	71%		12.5 (3.7)		
				PLC	Flexible dosage	111	79 (8.8)	64%		13.6 (5.2)		
Barber, 2011	Design I, DB, MC; North America	No	18-70 year olds with MDD (DSM-IV) and HAMD17 ≥14 All MDD severities Outpatients; 2ry and 3ry care	SRT	50-200 mg, fixed dosing	55	38 (12.5)	30%	HAMD17	19 (3.4)	16	-
				PLC	0-0 mg	50	38.3 (12)	31%	HAMD17	19.3 (3.8)		
Blackburn, 1997	Design I; OL; MC; Europe	No	18-65 year old with MDD (RDS), at least second episode of depression and HAMD ≥16 Moderate to severe MDD Outpatients; 2ry and 3ry care	ADM	-	26	40.1 (12.7)	65%	HAMD17	20.3 (4.3)	16	-
				CT	three sessions in the 1st month, then twice in the second month and monthly after	27	39.6 (12)	52%		19.2 (3.6)		
Boulenger, 2006	Design I; DB; MC; Europe	Yes	18-75 year olds with MDD (DSM-IV), MADRS ≥30, duration of episode more than 2 weeks but less than 1 year Severe MDD Outpatients; 2ry and 3ry care	ESC	20-20 mg, fixed dosing	232	43.8 (12.5)	67%	HAMD17	24.7 (4.8)	24	-
				PAR	40-40 mg, fixed dosing	227	44.7 (13)	70%	HAMD17	24.3 (5.0)		
CL3-20098-022, 2008	Design III; DB; MC; Europe	Yes	18-59 year olds with MDD (DSM-IV), HAMD total score ≥22 and CGI score ≥4 Moderate to severe MDD In-and outpatients; 2ry and 3ry care	AGM	25-25 mg, fixed dosing	133	41 (9.7)	67%	HAMD17	27.6 (2.9)	24	18
				FXT	20-20 mg, fixed dosing	137	42.9 (11.3)	67%	HAMD17	27.5 (NA)		
				PLC	0-0 mg	149	43 (9.5)	67%	HAMD17	28 (3.6)		
CL3-20098-048, 2009	Design I; DB; MC; cross-continental	Yes	≥60 year olds , recurrent episode of MDD (DSM-IV), lasting ≥4 weeks and for ≥ 6 months, with HAMD17 score ≥22 and CGI score ≥ 4. Moderate to severe MDD Outpatients; 1ry care	AGM	25-50 mg, flexible dosing	213	68.6 (6.2)	71%	HAMD17	26.3 (NA)	24	12
				PAR	20-30 mg, flexible dosing	199	68.3 (6.2)	75%	HAMD17	26.2 (NA)		
CL3-20098-062, 2011	Design I; DB; MC; cross-continental	Yes	18-65 years with MDD (DSM-IV), HAMD17 ≥22 and HAD score ≥11 at selectionm no more than a 20% decrease in HAMD score at inclusion and CGI score ≥ 4 Moderate to severe MDD Outpatients; 1ry care	AGM	25-50 mg, flexible dosing	202	43 (12.3)	NA	HAMD17	26.2 (NA)	24	-
				DLX	60-60 mg, fixed dosing	216	42.5 (11.9)	NA		26.3 (NA)		
CL3-20098-070, 2012	Design III; DB; MC; cross-continental	Yes	≥65 year olds with recurrent MDD (DSM-IV) and HAMD17 score ≥ 22, CGI score≥ 4, HAD depression sub-score ≥ 11 and MMSE score ≥ 27 Moderate to severe MDD Outpatients; 1ry care	AGM	25-50 mg, flexible dosing	151	71.9 (5.1)	NA	HAMD17	26.8 (NA)	24	16
				PLC	0-0 mg	71	71.7 (4.8)	NA		26.7 (NA)		
CL3-20098-021, 2008	Design II; OL then DB; MC; Europe	Yes	18-59 years olds with recurrent MDD (DSM-IV) and HAMD score ≥22 Moderate to severe MDD In- and outpatients; 2ry and 3ry care	AGM	25-50 mg, fixed dosing	187	45.7*	78%*	HAMD17	NA	52	18
				PLC	0-0mg	180	-	-		NA		
CL3-20098-041, 2008	Design II; OL then DB; MC; Cross-Continental	Yes	18-59 year olds with recurrent MDD (DSM-IV), HAMD score ≥22, a CGI-S score≥ 4, and HAD depression sub-score ≥11 Moderate to severe MDD In- and outpatients; 2ry and 3ry care	AGM	25-50 mg, fixed dosing	165	43.3*	74%*	HAMD17	27.0 (NA)	44	20
				PLC	0-0mg	174	-	-		NA		
Corruble, 2013	Design III; DB; MC; cross-continental	Yes	18-70 year olds with MDD (DSM-IV), HAMD17 ≥22; CGI-S ≥4; HAD ≥11 and decrease in HAMD17 score <20% between selection and inclusion	AGM	25-50 mg, flexible dosing	164	43.6 (12.9)	73%	HAMD17	26.8 (3.1)	24	12

			Moderate to severe MDD Outpatients; 1ry care	ESC	10-20 mg, flexible dosing	160	42.8 (11.8)	69%		26.6 (2.5)	
David, 2008	Design I; OL; MC; Europe	No	MDD (DSM-IV) with ≥ 20 on BDI and ≥14 on HAMD17 All MDD severities Outpatients; 2ry care	REBT	20 sessions (50 mins each), face to face	57	35 (13)	65%	HAMD17	22.9 (7.0)	14	-
				CT	20 sessions (50 mins each), face to face	56	39 (10)	68%		23.1 (7.6)		
				FXT	Flexible dosage, 1 week =20mg/d, 2-14 weeks = 40mg/d, mas dosage during allowed 1-12 week =60-80mg/d; one weekly session with a psychatrist (30-50min)	57	37 (2)	67%		21.4 (8.0)		
DeRubeis, 2020	Design I; RB; MC; North America	No	≥18 year old outpatients with recurrent MDD and HAMD17≥14, and had recovered in the first phase of the trial (Hollon) Outpatients; 1ry care	CBT plus ADM	50 mins at least monthly during continuation	85	45.6(13)	56%	HAMD17	5.8 (4.0)	36	-
				ADM	Flexible dosage	68	45.3 (12.6)	57%		5.4 (4.0)		
Dimidjian, 2006	Design I; TB then SB; SC; North America	No	18-60 year olds with MDD (DSM-IV), BDI-II score ≥20 and HAMD17 ≥ 14 All MDD severities Outpatients; 2ry and 3ry care	PAR	Up to 50 mg, flexible	100	39.9 (NA)	68%	HAMD17	20.9 (NA)	16	-
				BA	24 sessions (each sessions 50 mins)	43	NA	47%		NA		
				CT	24 sessions (each sessions 50 mins)	45	NA	73%		NA		
				PLC	0-0 mg	53	39.9 (NA)	72%		21.2 (NA)		
Friedli, 2017	Design I; DB; MC; Europe	No	≥18 year olds, on hemodialysis for ≥3 months (end stage renal disease) with MDD, BDI-II ≥ 16 on screening Mild to moderate MDD Outpatients; 2ry care	SRT	50-100 mg, flexible dosing	15	61.7 (13.2)	27%	MADRS	24.5 (4.5)	24	-
				PLC	0-0 mg	15	56.4 (14.4)	20%		25.3 (4.2)		
Gilliam, 2019	Design I; OL; MC; North America	No	21-75 year olds with epilepsy, MDD (MINI) and score of >14 on CES-D All MDD severities Outpatients; 2ry care	SRT	50-200 mg, flexible dosing	72	40.1 (10.7)	50%	BDI-II	24.2 (8.4)	16	-
				SCBT	16 sessions (one hour per week), face to face	68	39.1 (12.1)	60%		26.9 (10.5)		
Grunebaum, 2011	Design III; DB; SC; North America	No	18-75 year olds with MDD (DSM-IV), HAMD score ≥16 and reported past suicide attempt or current suicial ideation Moderate to severe MDD In-and outpatients; 2ry and 3ry care	BUP	300-450 mg, flexible dosing	40	37.9 (11.9)	55%	HAMD17	17.6 (5.2)	24	16
				PAR	37.5-50 mg, flexible dosing	38	35.2 (12.8)	58%		16.9 (5.8)		
Hashimoto, 2016	Design I; OL; MC; Asia	No	20–75 year olds with MDD (DSM-IV) and HAMD17 ≥12 All MDD severities Outpatients; 2ry and 3ry care	MIR	15-45 mg	27	38.9 (10.5)	33%	HAMD	23 (1.2)	24	-
				SSRI	-	50	40.4 (13.8)	36%		23.1 (0.9)		
				SRT	25-100 mg	32	39.7 (13.3)	38%		23.2 (1.1)		
				PAR	10-40 mg	18	41.7 (14.9)	33%		22.9 (1.5)		
Hollon, 2014	Design I; OL; MC; North America	No	≥18 year olds with chronic/recurrent MDD (DSM-IV) and HAMD17 ≥14 All MDD severities Outpatients; Other	ADM	Flexible dosage	225	43(13.4)	60%	HAMD17	22.2 (4.4)	168	-
				ADM plus CT	50 mins twice weekly for the first 2 weeks then at least weekly during acute treatment and then at least monthly during continuation	227	43.3 (12.9)	57%		21.9 (4.0)		
Jarret, 2013	Design II; OL; MC; North America	No	Individuals with recurrent MDD, history of remission between depressive episodes and HAMD17 ≥ 14 All MDD severities Outpatients; 1ry and 2ry care	CT	NA	86	43.1 (11.5)	73%	HRSD17	NA	44	32
				FXT	10-40 mg, fixed-flexible	86	41.6 (11.8)	66%		NA		
				PLC	0-0 mg	69	43.6 (12.3)	61%		NA		
Kato, 2018	Design I; OL; MC; Asia	No	25-75 year olds with MDD (PRIME-MD) All MDD severities In- and outpatients; 2ry and 3ry care	SRT	50-100 mg, flexible dosing	551	41.5 (11.6)	53%	PHQ9	12.8 (5.2)	25	-
				MIR	7.5-45 mg, flexible dosing	537	41.4(11.4)	50%		12.8 (5.2)		
Kavoussi, 1997	Design I; DB; MC; North America	Yes	≥18 years with MDD (DSM-IV), current episode for ≥ 4 weeks but ≤ 24 months Moderate to severe MDD Outpatients; Unclear	BUP	100-300 mg, flexible dosing	122	39.2 (10.3)	48%	HAMD	NA	16	-
				SRT	50-200 mg, flexible dosing	126	40 (10.5)	48%		NA		

Keller, 2007	Design I; DB; MC; North America	Yes	≥18 years old with recurrent MDD with depressive symptoms for ≥1 month, a HAMD17 score ≥20 at screening and ≥18 at randomization Moderate to severe MDD Unclear; Unclear	VEN	75-300; flexible dosing	781	39.6 (12.2)	65%	HAMD17	22.6 (3.1)	34	24
				FXT	20-60; flexible dosing	266	40 (11.6)	61%		23.0 (3.2)		
Kennedy, 2016	Design III; DB; MC; Cross-continental	No	18-65 year olds , physically healthy, with MDD (DSM-IV), with HAMD17 ≥22, CGI item 1 score ≥ 4 and HAD ≥ 11 Moderate to severe MDD Outpatients; Unclear	AGM	25-50 mg, flexible dosing	137	43.1 (12.6)	72%	HAMD17	26.7 (2.9)	24	18
				PLC	0-0 mg	141	45.0 (13.0)	77%		26.6 (2.6)		
Kim, 2015	Design I; DB; SC; Asia	Yes	Patients with acute coronary syndrome and MDD (DSM-IV) All MDD severity groups Outpatients; 3ry care	ESC	20-50 mg; flexible dosing schedule	108	60.1 (10.9)	38%	HAM-D	17.8 (5.2)	24	-
				PLC	0-0mg	109	58.5 (10.6)	42%		16.7 (4.8)		
Kishi, 2017	Design I; RB; MC; Asia	No	20-70 year olds with HAMD17 ≥20, no neurologic or systemic diseases, no history of ECT, no addictive substance use within the past 6 month Moderate to severe MDD In- and outpatients; 2ry and 3ry care	ESC	5-20 mg, flexible dosing	43	38.9±12.4	42%	HAMD17	23.7 (3.6)	24	-
				PAR	12.5-50 mg, flexible dosing	45	42.5±14.2	36%		23.2 (3.8)		
Kooistra, 2019	Design I; RB; MC; Europe	No	≥18 years with MDD (DSM-IV) Moderate to severe MDD Outpatients; 2ry and 3ry care	BCBT	19 sessions (10 face to face and 9 web based)	53	39.3 (11.3)	66%	IDS-SR	45.2 (12.2)	30	-
				SCBT	15-20 sessions (face to face)	49	38.1 (10.6)	60%		41.5 (11.6)		
Kumar, 2019	Design I; OL; SC; Asia	No	Individuals with type II diabetes mellitus, aged 18–70 yrs, diagnosed with comorbid depression and PHQ-9 score of ≥10 Moderate to severe MDD Outpatients; 2ry care	SRT	50-100 mg, flexible dosing	80	49.12 (1.04)	45%	PHQ9	15.7 (0.4)	24	-
				TAU	Only diabetes medications	80	50.02 (1.73)	32%		15.4 (0.5)		
Lecrubier, 1997	Design I; DB; MC; Europe	Unclear	18-65 years with MDD (RDS) Mild to moderate MDD Outpatients; Unclear	VEN	75-150 mg, flexible dosing	78	38.3 (*)	71%	MADRS	24.9 (NA)	13	-
				PLC	0-0 mg	76	40.5 (*)	63%		24.2 (NA)		
				IMI	75-150 mg, flexible dosing	75	40.7	68%		24.4 (NA)		
Lynch, 2003	Design I; OL; SC; North America	No	≥60 year olds with MDD (DSM-IV) and ≥18 on HAMD17 or ≥19 on BDI Moderate to severe MDD Outpatients; 1ry and 2ry care	ADM plus DBT	Flexible dosage,weekly group session for 2 hours and individual session for half an hour	17	66 (5)***	85%*	HAMD17	20.9 (3.6)	24	-
				ADM	Flexible dosage	17	-	-		19.1 (4.2)		
Mohr, 2001	Design I; OL; SC; North America	No	Individuals with multiple sclerosis and HAMD17 ≥16 and BDI ≥16 Moderate MDD Outpatients; 3ry care	SCBT	16 sessions (each session 50 mins); face to face	20	43.9 (10)**	73%*	HAMD17	21 (3.4)	16	-
				SRT	25-200 mg, flexible dosing	21	-	-		20.5 (3.5)		
Oakes, 2012a	Design I; DB; MC; North America	Yes	18-65 years with MDD (DSM-IV), MADRS score ≥22 and CGI score ≥4 Moderate to severe MDD Outpatients; Unclear	DLX	60-60 mg, fixed dosing	257	42.2 (12.2)	60%	HAMD17	22.9 (4.3)	36	-
				PLC	0-0 mg	127	43.7 (12.5)	61%		22.8 (3.7)		
Oakes, 2012b	Design I; DB; MC; North America	Yes	18-65 years with MDD (DSM-IV), MADRS score ≥22 and CGI score ≥4 Moderate to severe MDD Outpatients; Unclear	DLX	60-60 mg, fixed dosing	261	44.7 (12.2)	65%	HAMD17	22.8 (4.5)	36	-
				PLC	0-0 mg	131	43.9 (11.9)	66%		22.9 (4.9)		
Quera-Salva, 2010	Design III; DB; MC; Cross-continental	Yes	18-60 year olds with MDD (DSM-IV) Moderate to severe MDD Outpatients; 1ry care	AGM	25-50 mg, flexible dosing	71	41.3 (12.4)	NA	HAMD17	26.1 (2.3)	24	18
				ESC	10-20 mg, flexible dosing	67	41.4 (10.7)	NA		26.1 (2.9)		
Quigley, 2019	Design I; OL; SC; North America	No	18-65 year olds with MDD (DSM-IV) All MDD severities Outpatients; 1ry and 2ry care and community	SCBT	16 sessions; face to face	54	NA	NA	HAMD17	16.79 (5.0)	16	-
				ADM	No specific treatment	50	NA	NA		16.42 (5.3)		
Rief, 2018	Design I; OL; SC; Europe	No	Adults with MDD (DSM-IV), BDI score >14, and able to practice physical exercise All MDD severities Outpatients; 2ry care	CBASP	16 sessions (each session 50 mins); face to face	43	40.4 (13.0)	67%	BDI-II	28.12(8.14)	16	-
				CBT-E	16 sessions (each session 50 mins); face to face	45	35.9 (11.1)	53%		30.54 (8.6)		
				CBT-M	16 sessions (each session 50 mins); face to face	43	36.3 (12.7)	54%		29.2 (8.3)		
				WL	No treatment	42	38.8 (13.7)	48%		28.3 (10.1)		
Robinson, 2014	Design I; DB; MC; Cross-continental	Yes	≥ 65 years with recurrent MDD (DSM-IV), MMSE ≥20 and MDRS ≥20 Moderate to severe MDD Unclear; Unclear	DLX	60-60 mg, fixed dosing	249	73.01 (6.26)	66%	HAMD17	19.4 (5.6)	24	12
				PLC	0-0 mg	121	73.1 (5.64)	59%		19.3 (5.8)		
Rush, 2001	Design I; DB; MC; North America	Yes	Recurrent MDD with ≥18 on HAMD 21 Moderate to severe MDD Outpatients; Unclear	BUP	100-300 mg, flexible dosing	122	39 (*)	48%	HAMD21	24.8 (4.6)	16	-
				SRT	50-200 mg, flexible dosing	126	40 (*)	48%		24.8 (4.6)		
Study 043, 2002	Design I; DB; MC; Europe	Yes	18-70 year olds with MDD (DSM-IV) and HAMD ≥22 at baseline Severe MDD	CIT	20-40 mg, flexible dosing	176	41.5 (12)	60%	HAMD21	27.4 (3.9)	24	-

			Outpatients	reboxetine	8-10 mg, flexible dosing	183	42.8 (13.3)	69%		27.4 (3.5)		
Thase, 2018	Design I; RB; MC; North America	No	Adult patients with MDD (DSM-IV) All MDD severities Outpatients; 2ry care	SCBT	20 sessions (50 mins each), face to face	77	46 (13.7)	67%	HAMD17	19.6 (3.8)	16	-
				CCBT	12 sessions (50 mins first session then 25 minutes) and 9 internet modules (25 mins each), computer	77	46.5 (15.1)	65%		19.8 (3.5)		
Zu, 2014	Design I; RB; MC; Asia	No	17-60 year olds with MDD (DSM-IV) for <1 year and HAMD17 ≥17 Moderate to severe MDD	ADM	No specific ADM, flexible dosage	60	41.3 (11.5)	48%	HAMD17	23.2 (5.3)	24	-
				SCBT	20 sessions (1 hour each), face to face	30	32.7 (7.4)	50%		19.6 (3.8)		
				ADM plus SCBT	20 sessions (1 hour each), face to face	60	36.6 (10.6)	49%		25.1 (6.0)		
			Outpatients; 1ry and 2ry care and community	TAU	-	30	43.8 (9.1)	62%		21.6 (5.1)		

11.1.5 Detailed GRADE Assessment of the primary outcomes

Outcome	Certainty assessment						№ of patients (event/total)		Effect		Certainty
Comparator	№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Relapse											
ADM vs CBT	1	serious	not serious	not serious	serious	Only one study contributing to results	5/57 (8.8%)	4/113 (3.5%)	**RR 2.48** (0.69 to 8.87)	**52 more per 1,000** (from 11 fewer to 279 more)	⊕⊕◯◯ LOW[a,b]
ADM vs ADM plus CBT	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs ADM plus CBT	0	-	-		-	-	-	-	not estimable	-	-
ADM vs placebo	2	serious	not serious	not serious	not serious	Different study designs	56/301 (18.6%)	95/235 (40.4%)	not estimable	-	⊕⊕⊕◯ MODERATE[a]
ADM vs TAU	0	-	-	-	-	-	-	-	not estimable	-	-
ADM vs WL	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs placebo	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs WL	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs TAU	0	-	-	-	-	-	-	-	not estimable	-	-

Recurrence											
ADM vs CBT	0	-	-	-	-	-	-	-	not estimable	-	-
ADM vs ADM plus CBT	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs ADM plus CBT	0	-	-	-	-	-	-	-	not estimable	-	-
ADM vs placebo	0	-	-	-	-	-	-	-	not estimable	-	-
ADM vs TAU	0	-	-	-	-	-	-	-	not estimable	-	-
ADM vs WL	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs placebo	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs WL	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs TAU	0	-	-	-	-	-	-	-	not estimable	-	-
Quality of life											
ADM vs CBT	1	serious	not serious	serious	serious	only one study contributing to results [b]	72	68	3.10 [-2.89; 9.09]	-	⊕◯◯◯ VERY LOW[a,b,c]
ADM vs ADM plus CBT	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs ADM plus CBT	0	-	-	-	-	-	-	-	not estimable	-	-
ADM vs placebo	0	-	-	-	-	-	-	-	not estimable	-	-
ADM vs TAU	1	serious	not serious	serious	serious	only one study contributing to results [b]	80	80	24.0 [23.88; 24.12]	-	⊕◯◯◯ VERY LOW[a,b,c]
ADM vs WL	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs placebo	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs WL	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs TAU	0	-	-	-	-	-	-	-	not estimable	-	-
Social functioning											
ADM vs CBT	1	serious	not serious	serious	serious	only one study contributing to results	60	30	0.14 [-0.30; 0.58]	-	⊕◯◯◯ VERY LOW[a,b,c]

ADM vs ADM plus CBT	1	serious	not serious	serious	serious	only one study contributing to results	60	60	-0.28 [-0.64; 0.08]	-	⊕◯◯◯ VERY LOW[a,b,c]
CBT vs ADM plus CBT	1	serious	not serious	serious	serious	only one study contributing to results	30	60	-0.60 [-1.05; -0.16]	-	⊕⊕◯◯ LOW[a,b,c]
ADM vs placebo	1	not serious	not serious	not serious	serious	only one study contributing to results	137	141	-0.76 [-1.01; -0.52]	-	⊕⊕⊕◯ MODERATE[b]
ADM vs TAU	0	-	-	-	-	-	-	-	-	-	-
ADM vs WL	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs placebo	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs WL	0	-	-	-	-	-	-	-	not estimable	-	-
CBT vs TAU	1	serious	not serious	serious	serious	only one study contributing to results	30	30	-0.18 [-0.68; 0.33]	-	⊕◯◯◯ VERY LOW[a,b,c]
Worsening of depression symptoms											
ADM vs CBT	1	not serious	not serious	serious	serious	only one study contributing to results, epilepsy population	6/72	5/68	**RR 1.13** (0.36 to 3.54)	**10 more per 1,000** (from 47 fewer to 187 more)	⊕⊕◯◯ LOW[a,c]
ADM vs ADM plus CBT	0	-	-	-	-	-	-	-	-	-	-
CBT vs ADM plus CBT	0	-	-	-	-	-	-	-	-	-	-
ADM vs placebo	0	-	-	-	-	-	-	-	-	-	-
ADM vs TAU	0	-	-	-	-	-	-	-	-	-	-
ADM vs WL	0	-	-	-	-	-	-	-	-	-	-
CBT vs placebo	0	-	-	-	-	-	-	-	-	-	-

CBT vs WL	1	not serious	not serious	not serious	serious	only one study contributing to results	10/131	4/43	**RR 0.86** (0.27 to 2.76)	**10 more per 1,000** (from 68 fewer to 164 more)	⊕⊕⊕◯ MODERATE[b]
CBT vs TAU	0	-	-	-	-	-	-	-	-	-	-
All-cause mortality											
ADM vs CBT	1	not serious	not serious	serious	serious	only one study contributing to results, epilepsy population	0/72	1/68	not estimable	**-**	⊕⊕◯◯ LOW[b,c]
ADM vs ADM plus CBT	0	-	-	-	-	-	-	-	-	-	-
CBT vs ADM plus CBT	0	-	-	-	-	-	-	-	-	-	-
ADM vs placebo	3	not serious	not serious	very serious	not serious	different populations and study designs	1/303	0/227	not estimable	-	⊕⊕◯◯ LOW[d]
ADM vs TAU	0	-	-	-	-	-	-	-	-	-	-
ADM vs WL	0	-	-	-	-	-	-	-	-	-	-
CBT vs placebo	0	-	-	-	-	-	-	-	-	-	-
CBT vs WL	0	-	-	-	-	-	-	-	-	-	-
CBT vs TAU	0	-	-	-	-	-	-	-	-	-	-

a. Downgraded one point as majority of studies judged as of overall poor quality regarding risk of bias.

b. Downgraded one point due to imprecision (defined as wide confidence intervals including no effect or low overall sample size (defined as <400 participants for continuous outcomes or below optimal information size for dichotomous outcomes)).

c. Downgraded one point due to indirectness related to the population of interest.

d. Downgraded two points due to indirectness related to the population of interest and the different designs of the RCTs.

11.1.6 Additional Estimates

11.1.6.1 Additional relapse estimates

Continuation phase

Individual drug and class level pairwise comparisons – Design I

Comparison	RR (95% CI)
Individual level	
CT vs FXT	0.61 (0.17; 2.16)
CT vs REBT	3.05 (0.57; 16.28)
FXT vs REBT	5.00 (0.96; 25.97)
Class level	
Standard CBT vs SSRI	0.44 (0.14; 1.39)

Individual drug and class level pairwise comparisons – Design III

Comparison	RR (95% CI)
Individual level	
AGM vs FXT	0.80 (0.44; 1.46)
AGM vs PLC	0.44 (0.25; 0.77)
FXT vs PLC	0.54 (0.32; 0.92)
Class level	
Atypical vs PLC	0.44 (0.25; 0.77)
Atypical vs SSRI	0.80 (0.44; 1.46)
SSRI vs PLC	0.54 (0.32; 0.92)

Maintenance phase

Individual drug level network meta-analysis (upper triangle refers to direct estimates) – Design II

AGM	.	.	1.10 (0.77; 1.58)
1.66 (0.88; 3.16)	**CT**	1.17 (0.57; 2.37)	0.66 (0.35; 1.24)
1.94 (1.01; 3.74)	1.17 (0.66; 2.05)	**FXT**	0.57 (0.29; 1.10)
1.10 (0.77; 1.58)	0.66 (0.39; 1.12)	0.57 (0.33; 0.98)	**PLC**

Class level network meta-analysis (upper triangle refers to direct estimates) – Design II

Atypical	.	1.10 (0.77; 1.58)	.
1.66 (0.88; 3.45)	**Standard CBT**	0.66 (0.35; 1.24)	1.17 (0.57; 2.37)
1.10 (0.77; 1.58)	0.66 (0.35; 1.24)	**PLC**	1.77 (0.91; 3.44)
1.94 (0.91; 4.15)	1.17 (0.57; 2.37)	1.77 (0.91; 3.44)	**SSRI**

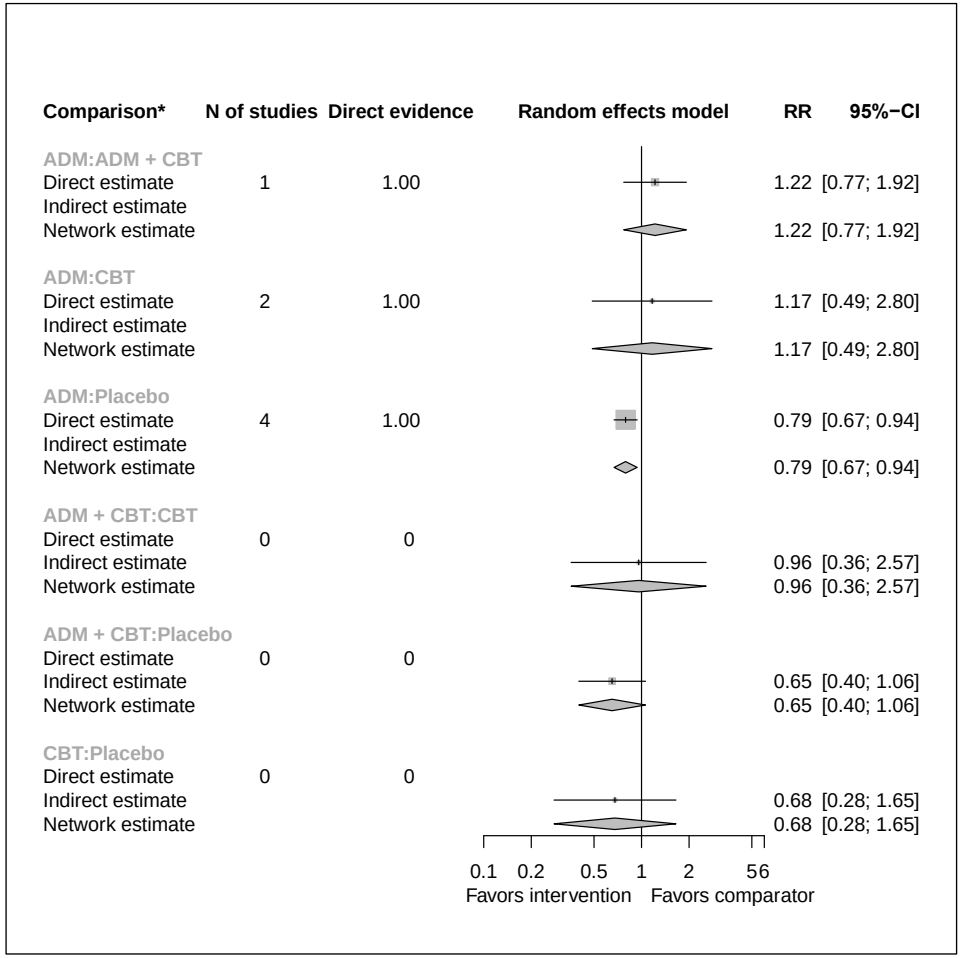
11.1.6.2 Extracted quality of life estimates from studies

Study Name	Treatment	Follow-up timepoint (weeks)	Scale	Measure (mean)	Measure (SD)
A-Tjak	**ACT**	**Baseline**	EUROHIS	20.16	0.93
		30		24.95	0.85
	CBT	**Baseline**	EUROHIS	20.79	1
		30		26.1	0.94
CL3-20098-062	**AGM**	**Baseline**	VAS		
		24		+21.6	28.6
	DLX	**Baseline**			
		24		+27.9	26.3
Corruble	**AGM**	**Baseline**	VAS feeling good	21.5	15.9
		12		35.5 (change)	31.1
		24		40.7	31.9
	ESC	**Baseline**		19.4	13.9
		12		37.2	30.1
		24		38	34
Gilliam	**SRT**	**Baseline**	QOLIE-89	51.5	14.9
		8			
		16		66.1	17.7
	CBT	**Baseline**		50.1	13.6
		8			
		16		63	18.4
Kumar	**SRT**	**Baseline**	WHO5	43.5	0.54
		12 weeks		64	0.22
		24 weeks		88	0.26
	Control 'only diabetes medication'	**Baseline**	WHO5	43.8	0.58
		12 weeks		56	0.39
		24 weeks		64	0.48
Kooistra	**BCBT**	**Baseline**	EQ5D3L	0	
		10		0.09	0.05
		20		0.2	0.1
		30		0.31	0.16
	SCBT	**Baseline**		0	
		10		0.1	0.05
		20		0.24	0.09
		30		0.39	0.13

11.1.6.3 Additional acceptability estimates

Acute phase

Network meta-analysis estimates



*intervention on the left side and comparator on the right side of the comparison

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; RR: risk ratio; CI: confidence interval

Individual drug level network meta-analysis (upper triangle refers to direct estimates)

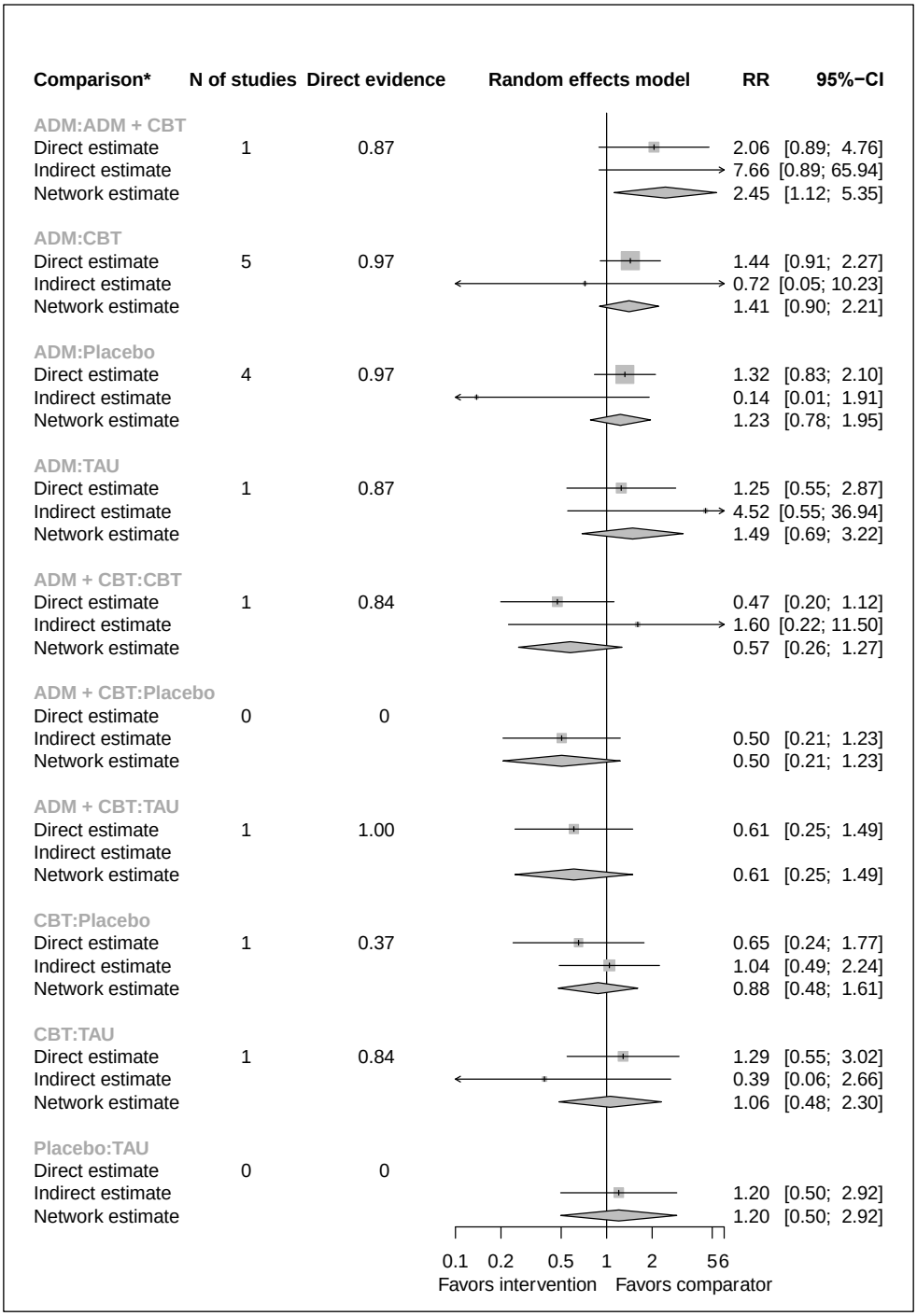
AGM	.	1.13 (0.74; 1.72)	0.81 (0.50; 1.32)	0.97 (0.69; 1.36)	0.58 (0.35; 0.96)
0.61 (0.28; 1.33)	**BUP**	.	.	1.58 (0.79; 3.18)	.
0.94 (0.68; 1.31)	1.54 (0.66; 3.57)	**DLX**	.	.	0.82 (0.69; 0.99)
0.81 (0.50; 1.32)	1.32 (0.53; 3.31)	0.86 (0.48; 1.55)	**ESC**	.	.
0.97 (0.69; 1.36)	1.58 (0.79; 3.18)	1.03 (0.64; 1.65)	1.20 (0.66; 2.16)	**PAR**	.
0.75 (0.54; 1.05)	1.23 (0.53; 2.85)	0.80 (0.67; 0.95)	0.93 (0.51; 1.68)	0.77 (0.48; 1.25)	**PLC**

Class level network meta-analysis (upper triangle refers to direct estimates)

Atypical	.	0.58 (0.35; 0.96)	1.13 (0.74; 1.72)	0.99 (0.76; 1.28)
1.22 (0.41; 3.68)	**Standard CBT**	.	.	0.81 (0.33; 1.97)
0.75 (0.54; 1.05)	0.61 (0.19; 1.95)	**PLC**	1.21 (1.01; 1.45)	.
0.94 (0.68; 1.31)	0.77 (0.24; 2.43)	1.25 (1.05; 1.49)	**SNRI**	.
0.99 (0.76; 1.28)	0.81 (0.28; 2.36)	1.31 (0.86; 2.01)	1.05 (0.69; 1.59)	**SSRI**

Continuation phase

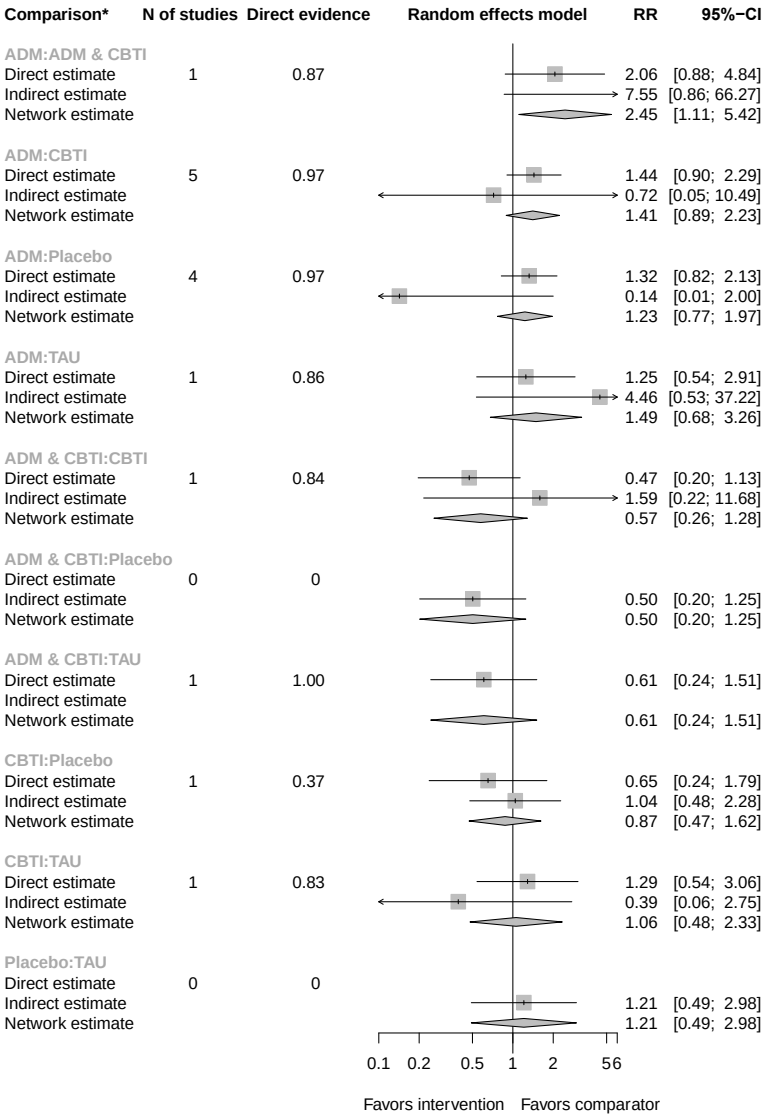
Network meta-analysis estimates



*intervention on the left side and comparator on the right side of the comparison

Legend: ADM: antidepressant medication; CBT: cognitive behavioural therapy; RR: risk ratio; CI: confidence interval

Sensitivity analysis (excluding 1st («older») generation antidepressants



Individual drug level network meta-analysis (upper triangle refers to direct estimates) – Design I

AGM	.	.	.	1.27 (0.97; 1.68)	.	.	.	.	1.18 (0.87; 1.59)	.	.	.	.
2.42 (1.41; 4.16)	**BA**	.	1.22 (0.45; 3.34)	.	.	.	.	.	0.37 (0.18; 0.75)	0.72 (0.31; 1.67)	.	.	.
1.53 (0.88; 2.66)	0.63 (0.32; 1.27)	**BUP**	.	.	.	.	.	.	.	.	.	0.84 (0.65; 1.09)	.
2.71 (1.77; 4.16)	1.12 (0.64; 1.94)	1.77 (0.97; 3.23)	**CT**	.	.	0.76 (0.28; 2.06)	.	.	0.38 (0.26; 0.57)	0.59 (0.24; 1.44)	0.68 (0.26; 1.78)	.	.
1.42 (1.11; 1.82)	0.59 (0.34; 1.01)	0.93 (0.52; 1.65)	0.52 (0.33; 0.82)	**DLX**	.	.	.	.	.	0.96 (0.73; 1.27)	.	.	.
1.41 (0.99; 2.02)	0.58 (0.33; 1.01)	0.92 (0.53; 1.59)	0.52 (0.34; 0.80)	1.00 (0.67; 1.48)	**ESC**	.	.	.	0.73 (0.57; 0.93)	.	.	.	.
2.07 (0.84; 5.08)	0.85 (0.33; 2.24)	1.35 (0.50; 3.65)	0.76 (0.35; 1.68)	1.46 (0.59; 3.61)	1.47 (0.60; 3.60)	**FXT**	.	.	.	.	0.89 (0.37; 2.14)	.	.
1.24 (0.74; 2.09)	0.51 (0.26; 1.00)	0.81 (0.40; 1.65)	0.46 (0.25; 0.84)	0.87 (0.54; 1.42)	0.88 (0.49; 1.57)	0.60 (0.22; 1.62)	**IMI**	.	.	1.23 (0.73; 2.06)	.	.	1.04 (0.64; 1.69)
1.11 (0.68; 1.81)	0.46 (0.24; 0.87)	0.73 (0.45; 1.18)	0.41 (0.24; 0.70)	0.78 (0.47; 1.31)	0.79 (0.49; 1.27)	0.54 (0.21; 1.40)	0.90 (0.46; 1.74)	**MIR**	0.91 (0.55; 1.50)	.	.	1.19 (0.72; 1.95)	.
1.03 (0.79; 1.35)	0.43 (0.26; 0.70)	0.67 (0.41; 1.10)	0.38 (0.27; 0.54)	0.73 (0.53; 1.00)	0.73 (0.57; 0.93)	0.50 (0.21; 1.19)	0.83 (0.49; 1.41)	0.93 (0.62; 1.40)	**PAR**	1.94 (1.13; 3.35)	.	1.30 (0.77; 2.20)	.
1.52 (1.11; 2.08)	0.63 (0.37; 1.06)	0.99 (0.56; 1.77)	0.56 (0.36; 0.87)	1.07 (0.84; 1.38)	1.08 (0.72; 1.61)	0.74 (0.30; 1.81)	1.23 (0.81; 1.86)	1.37 (0.82; 2.30)	1.47 (1.07; 2.03)	**PLC**	.	0.27 (0.03; 2.26)	0.85 (0.50; 1.42)
1.84 (0.76; 4.48)	0.76 (0.29; 1.97)	1.20 (0.45; 3.22)	0.68 (0.31; 1.48)	1.30 (0.53; 3.19)	1.30 (0.53; 3.17)	0.89 (0.42; 1.87)	1.48 (0.55; 3.98)	1.65 (0.64; 4.28)	1.78 (0.76; 4.20)	1.21 (0.49; 2.95)	**REBT**	.	.
1.29 (0.79; 2.10)	0.53 (0.28; 1.01)	0.84 (0.65; 1.09)	0.48 (0.28; 0.82)	0.91 (0.54; 1.52)	0.91 (0.57; 1.47)	0.62 (0.24; 1.62)	1.04 (0.53; 2.02)	1.16 (0.77; 1.74)	1.25 (0.83; 1.88)	0.85 (0.51; 1.42)	0.70 (0.27; 1.81)	**SRT**	.
1.29 (0.77; 2.17)	0.53 (0.27; 1.04)	0.84 (0.41; 1.72)	0.48 (0.26; 0.87)	0.91 (0.56; 1.48)	0.91 (0.51; 1.63)	0.62 (0.23; 1.69)	1.04 (0.69; 1.56)	1.16 (0.60; 2.26)	1.25 (0.74; 2.12)	0.85 (0.56; 1.29)	0.70 (0.26; 1.88)	1.00 (0.52; 1.95)	**VEN**

Individual drug level network meta-analysis after excluding 1st generation antidepressants (upper triangle refers to direct estimates) – Design I

AGM	.	.	.	1.27 (0.97; 1.68)	.	.	.	1.18 (0.87; 1.59)	.	.	.	.
2.49 (1.44; 4.30)	**BA**	.	1.22 (0.45; 3.34)	.	.	.	.	0.37 (0.18; 0.75)	0.72 (0.31; 1.67)	.	.	.
1.52 (0.88; 2.65)	0.61 (0.30; 1.24)	**BUP**	.	.	.	.	.	.	.	.	0.84 (0.65; 1.09)	.
3.03 (1.71; 5.38)	1.22 (0.65; 2.28)	1.99 (0.96; 4.12)	**CT**	.	.	0.76 (0.28; 2.06)	.	0.38 (0.26; 0.57)	0.59 (0.24; 1.44)	0.68 (0.26; 1.78)	.	.
1.43 (1.11; 1.83)	0.57 (0.33; 0.99)	0.94 (0.53; 1.67)	0.47 (0.26; 0.84)	**DLX**	.	.	.	.	0.96 (0.73; 1.27)	.	.	.
1.40 (0.98; 2.01)	0.56 (0.32; 0.99)	0.92 (0.53; 1.59)	0.46 (0.26; 0.84)	0.98 (0.66; 1.47)	**ESC**	.	.	0.73 (0.57; 0.93)	.	.	.	.
2.31 (0.87; 6.15)	0.93 (0.34; 2.55)	1.52 (0.52; 4.44)	0.76 (0.35; 1.68)	1.62 (0.61; 4.31)	1.65 (0.61; 4.43)	**FXT**	.	.	.	0.89 (0.37; 2.14)	.	.
1.10 (0.68; 1.80)	0.44 (0.23; 0.85)	0.73 (0.45; 1.18)	0.36 (0.19; 0.72)	0.77 (0.46; 1.30)	0.79 (0.49; 1.27)	0.48 (0.17; 1.35)	**MIR**	0.91 (0.55; 1.50)	.	.	1.19 (0.72; 1.95)	.
1.03 (0.79; 1.34)	0.41 (0.25; 0.69)	0.67 (0.41; 1.10)	0.34 (0.20; 0.58)	0.72 (0.52; 0.99)	0.73 (0.57; 0.93)	0.44 (0.17; 1.15)	0.93 (0.62; 1.40)	**PAR**	1.94 (1.13; 3.35)	.	1.30 (0.77; 2.20)	.
1.54 (1.12; 2.11)	0.62 (0.36; 1.05)	1.01 (0.57; 1.81)	0.51 (0.29; 0.88)	1.08 (0.84; 1.39)	1.10 (0.73; 1.65)	0.67 (0.25; 1.75)	1.39 (0.83; 2.35)	1.50 (1.08; 2.08)	**PLC**	.	0.27 (0.03; 2.26)	0.85 (0.50; 1.42)
2.06 (0.78; 5.42)	0.83 (0.30; 2.25)	1.35 (0.47; 3.92)	0.68 (0.31; 1.48)	1.44 (0.55; 3.80)	1.47 (0.55; 3.91)	0.89 (0.42; 1.87)	1.86 (0.66; 5.23)	2.01 (0.78; 5.18)	1.34 (0.51; 3.48)	**REBT**	.	.
1.28 (0.79; 2.08)	0.51 (0.27; 0.99)	0.84 (0.65; 1.09)	0.42 (0.21; 0.83)	0.90 (0.54; 1.50)	0.91 (0.57; 1.47)	0.55 (0.20; 1.57)	1.16 (0.77; 1.75)	1.25 (0.83; 1.88)	0.83 (0.49; 1.40)	0.62 (0.22; 1.75)	**SRT**	.
1.31 (0.71; 2.40)	0.52 (0.25; 1.10)	0.86 (0.39; 1.87)	0.43 (0.20; 0.92)	0.91 (0.51; 1.63)	0.93 (0.48; 1.80)	0.56 (0.19; 1.69)	1.18 (0.57; 2.47)	1.27 (0.69; 2.35)	0.85 (0.50; 1.42)	0.63 (0.21; 1.89)	1.02 (0.49; 2.12)	**VEN**

Class level network meta-analysis (upper triangle refers to direct estimates) – Design I

Atypical	.	.	.	.	1.27 (0.88; 1.83)	0.98 (0.79; 1.22)	.
1.77 (0.96; 3.27)	**Standard CBT**	0.82 (0.29; 2.31)	.	0.59 (0.23; 1.49)	.	0.53 (0.30; 0.95)	.
2.34 (1.09; 5.03)	1.32 (0.53; 3.26)	**CBT-3**	.	0.72 (0.30; 1.72)	.	0.37 (0.17; 0.79)	.
0.59 (0.39; 0.89)	0.33 (0.17; 0.66)	0.25 (0.11; 0.57)	**NARI**	.	.	1.62 (1.13; 2.32)	.
1.49 (1.03; 2.18)	0.84 (0.43; 1.65)	0.64 (0.29; 1.42)	2.54 (1.50; 4.30)	**Placebo**	0.98 (0.72; 1.33)	0.49 (0.28; 0.87)	0.82 (0.49; 1.37)
1.38 (1.00; 1.91)	0.78 (0.40; 1.51)	0.59 (0.27; 1.31)	2.35 (1.42; 3.89)	0.92(0.70; 1.23)	**SNRI**	.	0.96 (0.59; 1.56)
0.95 (0.77; 1.17)	0.54 (0.30; 0.96)	0.41 (0.19; 0.86)	1.62 (1.13; 2.32)	0.64 (0.43; 0.94)	0.69 (0.48; 0.98)	**SSRI**	.
1.28 (0.72; 2.26)	0.72 (0.32; 1.62)	0.55 (0.22; 1.37)	2.17 (1.09; 4.32)	0.86 (0.52; 1.41)	0.92 (0.57; 1.51)	1.31 (0.84; 2.03)	**TCA**

Class level network meta-analysis after excluding 1st generation antidepressants (upper triangle refers to direct estimates) – Design I

Atypical	.	.	.	.	1.27 (0.88; 1.83)	0.98 (0.79; 1.22)
2.13 (1.43; 3.18)	**Standard CBT**	0.82 (0.29; 2.31)	.	0.59 (0.23; 1.49)	.	0.49 (0.30; 0.95)
2.19 (1.30; 3.69)	1.03 (0.59; 1.81)	**CBT-3**	.	0.72 (0.30; 1.72)	.	0.37 (0.17; 0.79)
0.59 (0.42; 0.83)	0.28 (0.17; 0.44)	0.27 (0.15; 0.48)	**NARI**	.	.	1.62 (1.13; 2.32)
1.47 (1.09; 1.99)	0.69 (0.44; 1.07)	0.67 (0.40; 1.14)	2.49 (1.63; 3.80)	**Placebo**	0.98 (0.72; 1.33)	0.49 (0.28; 0.87)
1.37 (1.06; 1.78)	0.65 (0.41; 1.00)	0.63 (0.37; 1.08)	2.32 (1.54; 3.50)	0.93 (0.74; 1.18)	**SNRI**	.
0.96 (0.81; 1.14)	0.45 (0.31; 0.65)	0.44 (0.26; 0.72)	1.62 (1.21; 2.17)	0.65 (0.48; 0.89)	0.70 (0.52; 0.93)	**SSRI**

Individual drug level network meta-analysis (upper triangle refers to direct estimates) – Design III

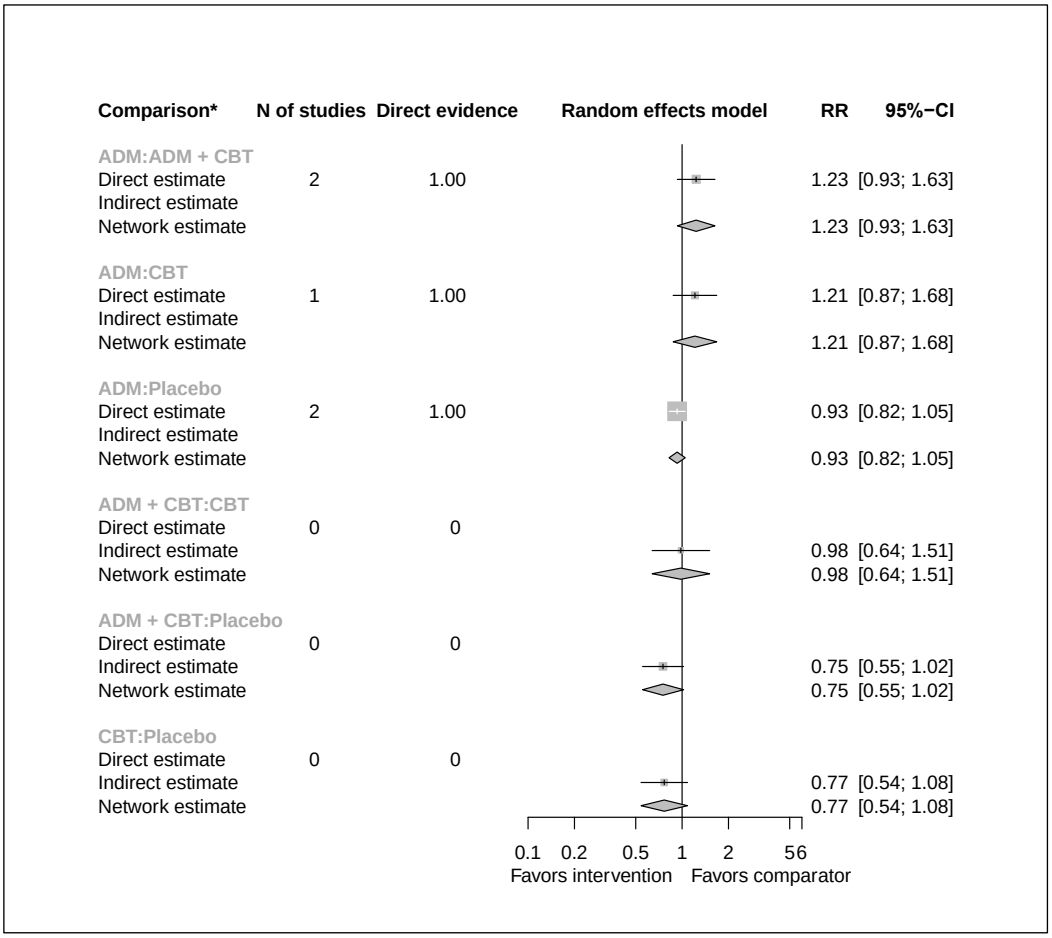
AGM	0.77 (0.56; 1.07)	0.57 (0.36; 0.90)	0.71 (0.57; 0.89)
0.77 (0.56; 1.07)	**ESC**	.	.
0.57 (0.36; 0.90)	0.73 (0.42; 1.29)	**FXT**	.
0.71 (0.57; 0.89)	0.92 (0.62; 1.37)	1.25 (0.75; 2.09)	**PLC**

Class level network meta-analysis (upper triangle refers to direct estimates) – Design III

Atypical	0.72 (0.50; 1.02)	0.82 (0.62; 1.08)
0.72 (0.50; 1.02)	**PLC**	.
0.82 (0.62; 1.08)	1.14 (0.73; 1.79)	**SSRI**

Maintenance phase

Network meta-analysis estimates (study design I)



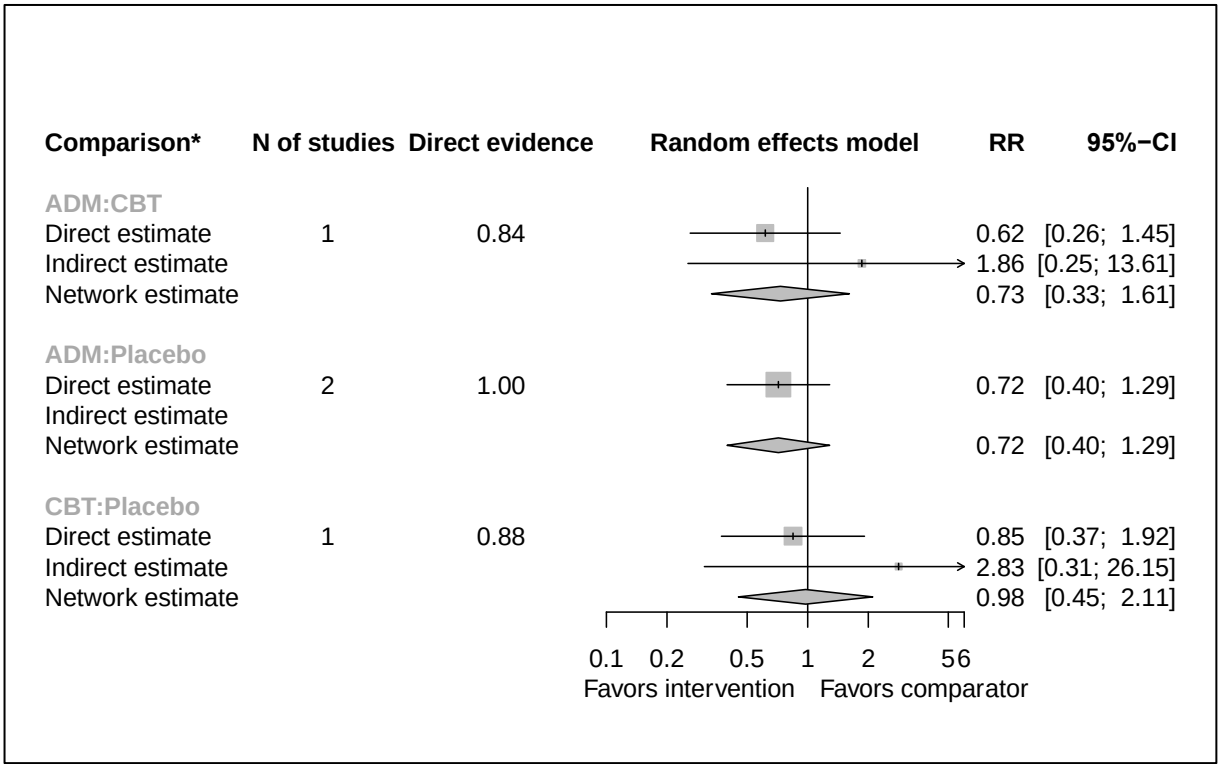
Individual drug level network meta-analysis (upper triangle refers to direct estimates)

AGM	1.27 (0.97; 1.66)	.
1.27 (0.97; 1.66)	**DLX**	0.93 (0.82; 1.05)
1.18 (0.88; 1.58)	0.93 (0.82; 1.05)	**PLC**

Class level network meta-analysis (upper triangle refers to direct estimates)

Atypical	.	1.27 (0.97; 1.66)
1.18 (0.94; 1.58)	**PLC**	1.08 (0.95; 1.22)
1.27 (0.97; 1.66)	1.08 (0.95; 1.22)	**SNRI**

Network meta-analysis estimates (study design II)



Individual drug level network meta-analysis (upper triangle refers to direct estimates)

AGM	.	0.95 (0.72; 1.26)	.
1.12 (0.73; 1.71)	**CT**	0.85 (0.61; 1.16)	1.62 (1.08; 2.45)
0.95 (0.72; 1.26)	0.85 (0.61; 1.16)	**PLC**	1.92 (1.28; 2.88)
1.82 (1.11; 2.98)	1.62 (1.08; 2.45)	1.92 (1.28; 2.88)	**FLX**

Class level network meta-analysis (upper triangle refers to direct estimates)

Atypical	.	0.95 (0.72; 1.26)	.
1.12 (0.73; 1.71)	**Standard CBT**	0.85 (0.61; 1.16)	1.62 (1.08; 2.45)
0.95 (0.72; 1.26)	0.85 (0.61; 1.16)	**PLC**	1.92 (1.28; 2.88)
1.82 (1.11; 2.98)	1.62 (1.08; 2.45)	1.92 (1.28; 2.88)	**SSRI**

Treatment ranking

Rank	**P-Score (Acute phase)**	
1	ADM plus CBT	0.76
2	CBT	0.64
3	ADM	0.52
4	Placebo	0.08
Rank	**P-Score (continuation phase, design I)**	
1	ADM plus CBT	0.93
2	TAU	0.55
3	CBT	0.53
4	Placebo	0.39
5	ADM	0.11
Rank	**P-Score (maintenance phase, design I)**	
1	ADM plus CBT	0.81
2	CBT	0.76
3	ADM	0.36
4	Placebo	0.07
Rank	**P-Score (maintenance phase, design II)**	
1	ADM	0.83
2	CBT	0.37
3	Placebo	0.30

11.1.6.4 Estimates on worsening of depression as an adverse effect of treatment from studies

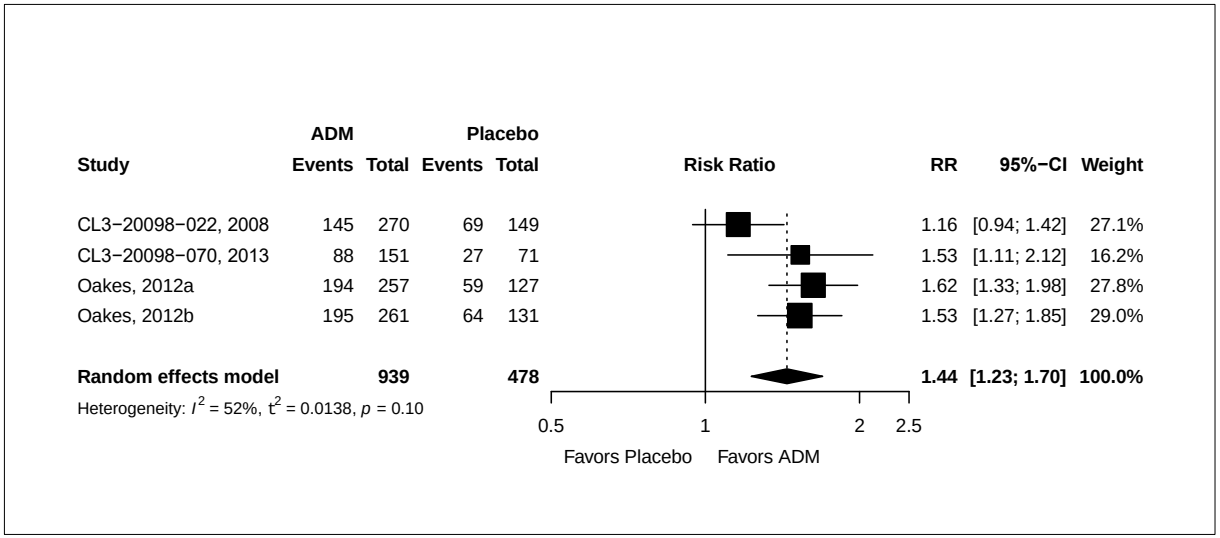
Comparison	**Number of studies**	**Estimate**
Individual level analysis		
SRT vs SCBT	1	1.13 [0.36; 3.54]
CBASP vs WL	1	0.65 [0.20; 2.14]
CBASP vs CBTm	1	1.33 [0.32; 5.61]

CBASP vs CBTe	1	1.05 [0.28; 3.92]
CBTe vs CBTm	1	1.27 [0.30; 5.36]
CBTm vs WL	1	0.49 [0.13; 1.82]
CBTe vs WL	1	0.62 [0.19; 2.05]
Class level analysis		
SSRI vs CBT	1	1.13 [0.36; 3.54]
3-CBT vs CBT	1	0.88 [0.24; 3.23]
CBT vs WL	1	0.86 [0.27; 2.76]
3-CBT vs WL	1	0.65 [0.20; 2.14]

11.1.6.5 Additional estimates for response outcome

Acute phase

Sensitivity analysis of response in the acute phase after removing Barber et al and Lecrubier et al



Individual drug level network meta-analysis (upper triangle refers to direct estimates)

AGM	.	0.92 (0.70; 1.21)	1.07 (0.86; 1.33)	0.91 (0.66; 1.26)	.	.	1.01 (0.75; 1.34)	1.26 (0.97; 1.64)	.	.
1.24 (0.82; 1.88)	**BUP**	.	.	.	.	.	0.89 (0.47; 1.66)	.	1.05 (0.76; 1.44)	.
0.86 (0.68; 1.07)	0.69 (0.44; 1.08)	**DLX**	.	.	.	.	.	1.53 (1.13; 2.08)	.	.
1.07 (0.86; 1.33)	0.86 (0.54; 1.37)	1.25 (0.92; 1.70)	**ESC**	.	.	.	.	.	.	.
1.06 (0.84; 1.34)	0.86 (0.55; 1.34)	1.24 (0.93; 1.66)	1.00 (0.72; 1.37)	**FXT**	.	.	.	1.21 (0.87; 1.69)	.	1.01 (0.78; 1.30)
1.06 (0.76; 1.47)	0.85 (0.52; 1.38)	1.24 (0.86; 1.77)	0.99 (0.67; 1.46)	0.99 (0.72; 1.36)	**IMI**	.	.	1.04 (0.73; 1.48)	.	1.29 (0.88; 1.89)
1.09 (0.69; 1.73)	0.88 (0.59; 1.32)	1.28 (0.79; 2.07)	1.02 (0.62; 1.70)	1.03 (0.64; 1.65)	1.04 (0.62; 1.73)	**MIR**	.	.	1.21 (0.92; 1.59)	.

1.02 (0.78; 1.34)	0.82 (0.53; 1.27)	1.20 (0.85; 1.69)	0.96 (0.68; 1.35)	0.96 (0.68; 1.36)	0.97 (0.64; 1.47)	0.93 (0.57; 1.53)	**PAR**	.	.	.
1.20 (0.99; 1.45)	0.97 (0.65; 1.45)	1.41 (1.12; 1.77)	1.12 (0.84; 1.50)	1.13 (0.91; 1.40)	1.14 (0.86; 1.51)	1.10 (0.71; 1.69)	1.18 (0.85; 1.62)	**PLC**	1.13 (0.78; 1.63)	1.25 (0.85; 1.83)
1.33 (0.92; 1.91)	1.07 (0.79; 1.43)	1.55 (1.05; 2.30)	1.24 (0.81; 1.90)	1.25 (0.85; 1.84)	1.26 (0.81; 1.94)	1.21 (0.92; 1.59)	1.30 (0.86; 1.96)	1.10 (0.79; 1.54)	**SRT**	.
1.23 (0.93; 1.61)	0.99 (0.62; 1.56)	1.43 (1.05; 1.96)	1.15 (0.81; 1.62)	1.15 (0.93; 1.43)	1.16 (0.87; 1.55)	1.12 (0.69; 1.82)	1.20 (0.82; 1.75)	1.02 (0.81; 1.29)	0.92 (0.62; 1.38)	**VEN**

Class level network meta-analysis (upper triangle refers to direct estimates)

Atypical	.	1.27 (0.97; 1.66)	0.92 (0.69; 1.22)	1.05 (0.92; 1.19)	.
1.32 (0.97; 1.80)	**NARI**	.	.	0.80 (0.59; 1.08)	.
1.15 (098; 1.36)	0.88 (0.63; 1.22)	**PLC**	0.84 (0.66; 1.07)	0.95 (0.74; 1.23)	0.95 (0.66; 1.37)
1.01 (0.86; 1.19)	0.77 (0.55; 1.07)	0.88 (0.74; 1.03)	**SNRI**	0.99 (0.76; 1.30)	0.76 (0.52; 1.13)
1.03 (0.94; 1.17)	0.80 (0.60; 1.06)	0.91 (0.78; 1.07)	1.04 (0.88; 1.22)	**SSRI**	.
0.95 (0.70; 1.27)	0.72 (0.47; 1.08)	0.82 (0.63; 1.07)	0.94 (0.71; 1.23)	0.90 (0.63; 1.28)	**TCA**

Continuation phase

Individual drug level network meta-analysis (upper triangle refers to direct estimates) – Design I

BA	.	0.96 (0.78; 1.18)	.	.	.	1.32 (1.06; 1.65)	3.49 (2.07; 5.88)	.	.	.
3.01 (1.46; 6.23)	**BUP**	.	.	.	.	.	.	.	0.90 (0.76; 1.06)	.
0.96 (0.81; 1.14)	0.32 (0.15; 0.66)	**CT**	.	1.05 (0.76; 1.44)	.	1.37 (1.11; 1.69)	3.63 (2.17; 6.08)	0.93 (0.69; 1.25)	.	.
1.23 (1.01; 1.50)	0.41 (0.20; 0.85)	1.28 (1.05; 1.56)	**ESC**	.	.	1.07 (0.97; 1.18)	.	.	.	.
1.01 (0.75; 1.37)	0.33 (0.16; 0.72)	1.05 (0.81; 1.35)	0.82 (0.60; 1.13)	**FXT**	.	.	.	0.89 (0.66; 1.20)	.	.
3.45 (2.17; 5.46)	1.14 (0.55; 2.38)	3.58 (2.26; 5.68)	2.80 (1.75; 4.48)	3.41 (2.02; 5.77)	**IMI**	.	1.01 (0.66; 1.55)	.	.	0.76 (0.52; 1.11)
1.32 (1.11; 1.57)	0.44 (0.21; 0.90)	1.37 (1.16; 1.62)	1.07 (0.97; 1.18)	1.31 (0.96; 1.77)	0.38 (0.24; 0.61)	**PAR**	2.65 (1.57; 4.47)	.	.	.

3.49 (2.55; 4.79)	1.16 (0.60; 2.23)	3.63 (2.65; 4.97)	2.84 (2.04; 3.95)	3.46 (2.31; 5.18)	1.01 (0.72; 1.42)	2.65 (1.93; 3.64)	**PLC**	.	0.78 (0.41; 1.46)	0.75 (0.51; 1.10)
0.90 (0.67; 1.21)	0.30 (0.14; 0.64)	0.93 (0.73; 1.19)	0.73 (0.53; 1.00)	0.89 (0.69; 1.14)	0.26 (0.15; 0.44)	0.68 (0.51; 0.92)	0.26 (0.17; 0.38)	**REBT**	.	.
2.71 (1.34; 5.50)	0.90 (0.76; 1.06)	2.82 (1.39; 5.71)	2.20 (1.08; 4.49)	2.69 (1.27; 5.69)	0.79 (0.38; 1.61)	2.06 (1.02; 4.17)	0.78 (0.41; 1.46)	3.02 (1.43; 6.38)	**SRT**	.
2.62 (1.67; 4.09)	0.87 (0.42; 1.79)	2.72 (1.74; 4.25)	2.12 (1.34; 3.36)	2.59 (1.55; 4.33)	0.76 (0.55; 1.04)	1.98 (1.27; 3.11)	0.75 (0.54; 1.03)	2.91 (1.75; 4.85)	0.96 (0.48; 1.96)	**VEN**

Class level network meta-analysis (upper triangle refers to direct estimates) – Design I

Atypical	.	.	.	.	0.89 [0.57; 1.38]	0.90 [0.57; 1.42]	.	.
0.59 [0.36; 0.99]	**CBT**	1.22 [0.84; 1.77]	.	3.63 [1.86; 7.09]	.	1.23 [0.87; 1.74]	.	23.39 [3.19; 171.37]
0.68 [0.39; 1.18]	1.14 [0.80; 1.64]	**CBT-3**	.	3.49 [1.78; 6.85]	.	1.32 [0.81; 2.13]	.	14.65 [1.93; 110.95]
1.01 [0.55; 1.85]	1.70 [0.97; 2.97]	1.49 [0.82; 2.72]	**NARI**	.	.	0.81 [0.52; 1.27]	.	.
1.50 [0.92; 2.46]	2.53 [1.55; 4.11]	2.21 [1.31; 3.73]	1.49 [0.80; 2.77]	**Placebo**	0.75 [0.42; 1.33]	0.52 [0.31; 0.86]	0.99 [0.54; 1.81]	.
0.97 [0.65; 1.44]	1.63 [0.93; 2.87]	1.43 [0.79; 2.60]	0.96 [0.50; 1.86]	0.65 [0.41; 1.03]	**SNRI**	.	1.32 [0.74; 2.34]	.
0.82 [0.55; 1.23]	1.38 [0.99; 1.92]	1.21 [0.81; 1.80]	0.81 [0.52; 1.27]	0.55 [0.36; 0.84]	0.84 [0.52; 1.37]	**SSRI**	.	.
1.36 [0.72; 2.58]	2.30 [1.14; 4.63]	2.01 [0.97; 4.17]	1.35 [0.61; 2.98]	0.91 [0.51; 1.62]	1.41 [0.81; 2.44]	1.66 [0.87; 3.19]	**TCA**	.
12.44 [1.61; 95.82]	20.96 [2.88; 152.51]	18.35 [2.49; 135.06]	12.32 [1.58; 96.23]	8.29 [1.08; 63.51]	12.82 [1.64; 100.13]	15.18 [2.04; 112.75]	9.11 [1.12; 74.25]	**WL**

Individual drug level network meta-analysis (upper triangle refers to direct estimates) – Design III

AGM	1.02 (0.91; 1.14)	1.68 (1.40; 2.02)
1.02 (0.91; 1.14)	**ESC**	.
1.68 (1.40; 2.02)	1.65 (1.33; 2.04)	**PLC**

Class level network meta-analysis (upper triangle refers to direct estimates) – Design III

Atypical	1.68 (1.40; 2.02)	.	1.02 (0.91; 1.14)
1.68 (1.40; 2.02)	**PLC**	.	.
1.19 (0.74; 1.92)	0.71 (0.42; 1.18)	**SARI**	0.86 (0.54; 1.36)
1.02 (0.91; 1.14)	0.61 (0.49; 0.75)	0.86 (0.54; 1.36)	**SSRI**

Treatment ranking

Rank	P-Score (continuation phase, design I)	
1	CBT	0.98
2	ADM	0.68
3	Placebo	0.33
4	WL	0.009
Rank	**P-Score (maintenance phase, design I)**	
1	ADM plus CBT	0.90
2	ADM	0.39
3	CBT	0.21

11.1.6.6 Additional estimates for remission outcome

Acute phase

Individual drug level network meta-analysis (upper triangle refers to direct estimates)

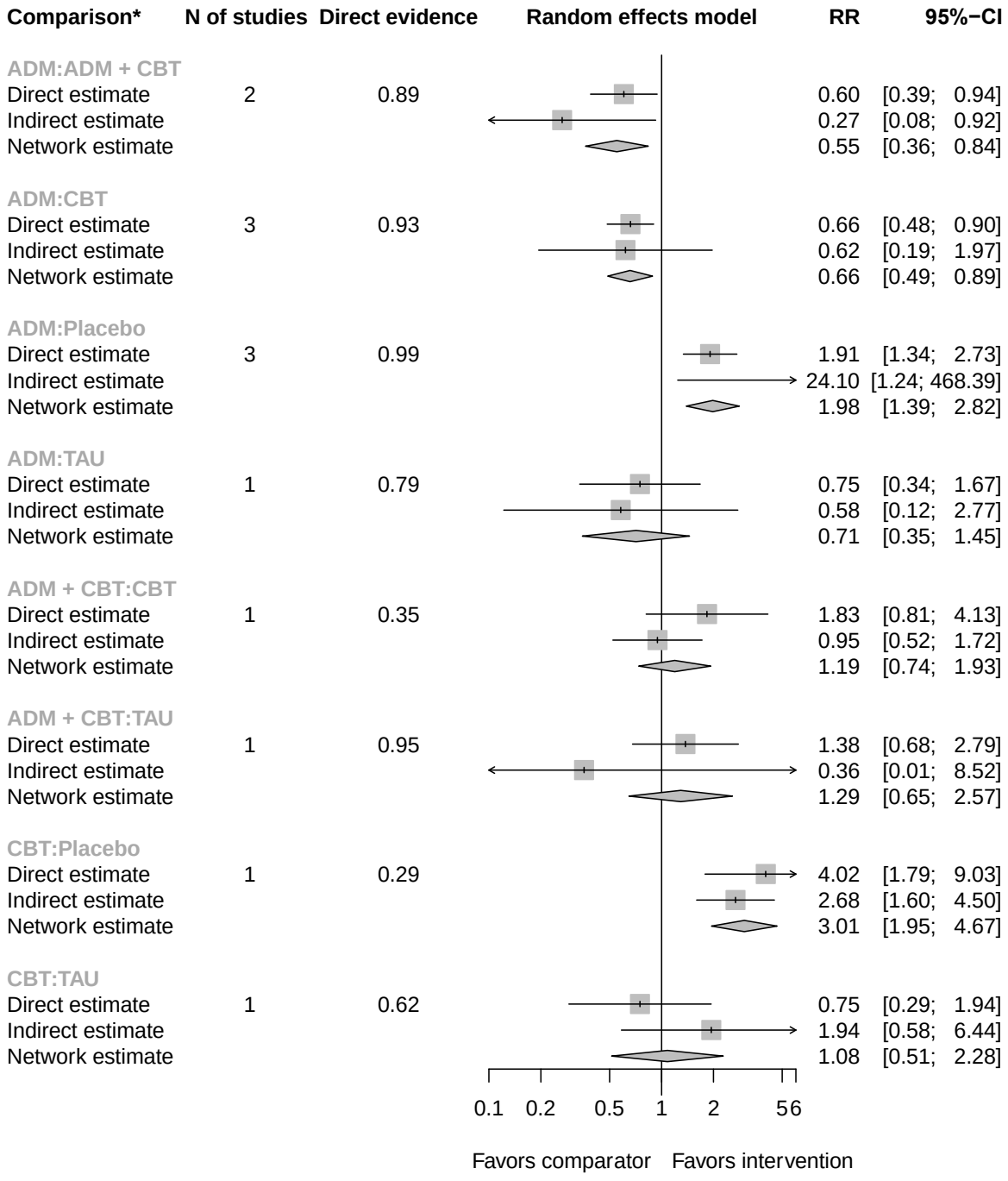
AGM	.	0.63 (0.45; 0.88)	1.10 (0.91; 1.33)	0.74 (0.42; 1.29)	1.00 (0.74; 1.34)	1.06 (0.67; 1.68)	.	.
1.05 (0.47; 2.31)	**BUP**	.	.	.	.	.	1.06 (0.75; 1.48)	.
0.63 (0.49; 0.81)	0.60 (0.28; 1.28)	**DLX**	.	.	.	1.60 (1.41; 1.83)	.	.
1.02 (0.87; 1.21)	0.98 (0.43; 2.19)	1.63 (1.20; 2.21)	**ESC**	.	1.23 (1.04; 1.45)	.	.	.
0.82 (0.55; 1.22)	0.78 (0.34; 1.82)	1.30 (0.87; 1.95)	0.80 (0.52; 1.24)	**FXT**	.	1.13 (0.68; 1.89)	.	1.26 (1.12; 1.42)
1.19 (0.98; 1.44)	1.13 (0.50; 2.56)	1.89 (1.37; 2.61)	1.16 (1.00; 1.35)	1.45 (0.93; 2.27)	**PAR**	.	.	.
1.01 (0.77; 1.31)	0.96 (0.45; 2.03)	1.60 (1.41; 1.82)	0.99 (0.72; 1.34)	1.23 (0.83; 1.83)	0.85 (0.61; 1.17)	**PLC**	1.10 (0.56; 2.14)	.
1.11 (0.54; 2.27)	1.06 (0.75; 1.48)	1.76 (0.89; 3.47)	1.08 (0.52; 2.26)	1.35 (0.62; 2.94)	0.93 (0.44; 1.96)	1.10 (0.56; 2.14)	**SRT**	.
1.03 (0.68; 1.57)	0.98 (0.42; 2.31)	1.64 (1.08; 2.50)	1.01 (0.64; 1.58)	1.26 (1.12; 1.42)	0.87 (0.55; 1.38)	1.02 (0.68; 1.55)	0.93 (0.42; 2.04)	**VEN**

Class level network meta-analysis (upper triangle refers to direct estimates)

Atypical	.	1.10 [0.63; 1.91]	0.63 [0.37; 1.09]	1.00 [0.76; 1.31]
1.01 [0.59; 1.72]	**NARI**	.	.	0.93 [0.58; 1.50]
1.25 [0.89; 1.75]	1.24 [0.70; 2.20]	**Placebo**	0.60 [0.45; 0.81]	0.97 [0.58; 1.61]
0.82 [0.59; 1.13]	0.81 [0.46; 1.42]	0.66 [0.50; 0.85]	**SNRI**	0.79 [0.51; 1.24]
0.94 [0.73; 1.20]	0.93 [0.58; 1.50]	0.75 [0.54; 1.04]	1.15 [0.85; 1.56]	**SSRI**

Continuation phase

Network meta-analysis estimates (study design I)



Individual drug level network meta-analysis (upper triangle refers to direct estimates) – Design I

BA	.	1.57 (0.98; 2.52)	.	.	.	2.43 (1.55; 3.79)	4.93 (2.22; 10.96)	.	.
4.42 (1.78; 10.96)	**BUP**	.	.	.	.	.	.	.	0.88 (0.71; 1.08)
1.57 (1.08; 2.28)	0.35 (0.14; 0.89)	**CT**	.	.	1.29 (0.80; 2.07)	1.55 (0.91; 2.63)	3.14 (1.34; 7.35)	0.98 (0.64; 1.49)	.
2.24 (1.15; 4.37)	0.51 (0.22; 1.19)	1.43 (0.73; 2.81)	**DLX**	.	.	.	2.20 (1.44; 3.34)	.	.
2.16 (1.48; 3.16)	0.49 (0.19; 1.23)	1.38 (0.92; 2.07)	0.96 (0.49; 1.91)	**ESC**	.	1.12 (0.99; 1.27)	.	.	.
2.02 (1.19; 3.43)	0.46 (0.17; 1.23)	1.29 (0.88; 1.88)	0.90 (0.41; 1.95)	0.93 (0.53; 1.63)	**FXT**	.	.	0.76 (0.47; 1.22)	.
2.43 (1.69; 3.48)	0.55 (0.22; 1.37)	1.55 (1.05; 2.28)	1.08 (0.55; 2.12)	1.12 (0.99; 1.27)	1.20 (0.70; 2.07)	**PAR**	2.03 (0.88; 4.68)	.	.
4.93 (2.94; 8.27)	1.11 (0.53; 2.35)	3.14 (1.85; 5.33)	2.20 (1.44; 3.34)	2.28 (1.33; 3.91)	2.44 (1.27; 4.69)	2.03 (1.20; 3.43)	**PLC**	.	0.79 (0.38; 1.61)
1.53 (0.92; 2.57)	0.35 (0.13; 0.93)	0.98 (0.68; 1.40)	0.68 (0.32; 1.47)	0.71 (0.41; 1.22)	0.76 (0.52; 1.11)	0.63 (0.37; 1.07)	0.31 (0.16; 0.59)	**REBT**	.
3.87 (1.60; 9.37)	0.88 (0.71; 1.08)	2.47 (1.01; 6.01)	1.73 (0.75; 3.96)	1.79 (0.73; 4.39)	1.92 (0.73; 5.05)	1.60 (0.66; 3.88)	0.79 (0.38; 1.61)	2.53 (0.97; 6.59)	**SRT**

Class level network meta-analysis (upper triangle refers to direct estimates) – Design I

Atypical	.	.	.	.	.	0.88 [0.71; 1.08]
0.61 [0.44; 0.85]	**CBT**	0.64 [0.40; 1.02]	.	3.14 [1.34; 7.35]	.	1.37 [1.03; 1.81]
0.37 [0.25; 0.54]	0.60 [0.43; 0.84]	**CBT-3**	.	4.93 [2.22; 10.96]	.	2.43 [1.55; 3.79]
1.16 [0.89; 1.52]	1.90 [1.41; 2.57]	3.18 [2.20; 4.59]	**NARI**	.	.	0.75 [0.64; 0.89]
1.57 [0.99; 2.50]	2.57 [1.66; 3.98]	4.30 [2.71; 6.81]	1.35 [0.87; 2.11]	**Placebo**	0.45 [0.30; 0.69]	0.64 [0.37; 1.11]
0.72 [0.38; 1.34]	1.17 [0.64; 2.14]	1.95 [1.05; 3.64]	0.61 [0.33; 1.13]	0.45 [0.30; 0.69]	**SNRI**	.
0.88 [0.71; 1.08]	1.43 [1.11; 1.84]	2.39 [1.73; 3.32]	0.75 [0.64; 0.89]	0.56 [0.37; 0.84]	1.22 [0.68; 2.21]	**SSRI**

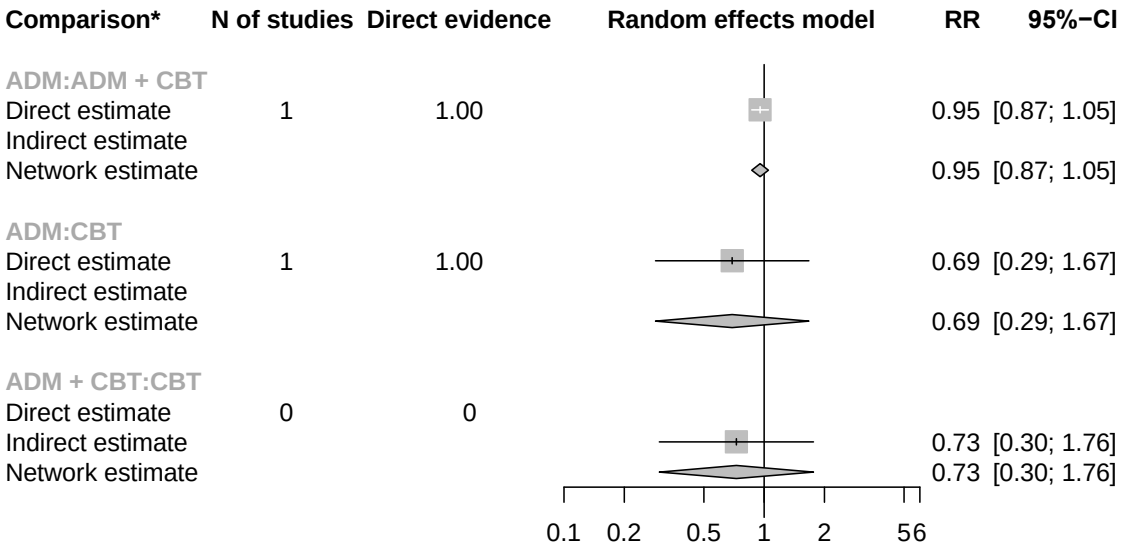
Individual drug level network meta-analysis (upper triangle refers to direct estimates) – Design III

AGM	1.11 (0.96; 1.29)	2.61 (1.85; 3.68)
1.11 (0.96; 1.29)	**ESC**	.
2.61 (1.85; 3.68)	2.35 (1.62; 3.42)	**PLC**

Class level network meta-analysis (upper triangle refers to direct estimates) – Design III

Atypical	2.61 (1.85; 3.68)	1.11 (0.96; 1.29)
2.61 (1.85; 3.68)	**PLC**	.
1.11 (0.96; 1.29)	0.43 (0.29; 0.62)	**SSRI**

Maintenance phase



Treatment ranking

Rank	P-Score (continuation-Design I)	
1	ADM plus CBT	0.88
2	CBT	0..70
3	TAU	0.62
4	ADM	0.30
5	Placebo	0.001
Rank	**P-Score (maintenance-Design I)**	
1	ADM plus CBT	0.67
2	CBT	0.59
3	ADM	0.24

11.1.6.7 Additional estimates for tolerability (drop-out due to side effects) outcome

Acute phase

Individual drug level network meta-analysis (upper triangle refers to direct estimates)

AGM	.	0.94 (0.47; 1.87)	0.32 (0.13; 0.80)	0.77 (0.18; 3.39)	0.68 (0.37; 1.26)	1.13 (0.48; 2.63)
0.36 (0.03; 4.09)	**BUP**	.	.	.	1.90 (0.18; 20.10)	.
0.90 (0.52; 1.55)	2.51 (0.21; 30.53)	**DLX**	.	.	.	1.35 (0.86; 2.12)
0.32 (0.13; 0.80)	0.90 (0.07; 12.17)	0.36 (0.12; 1.04)	**ESC**	.	.	.
0.80 (0.27; 2.35)	2.22 (0.15; 32.05)	0.89 (0.29; 2.71)	2.46 (0.60; 10.12)	**FXT**	.	1.45 (0.33; 6.36)
0.68 (0.37; 1.26)	1.90 (0.18; 20.10)	0.76 (0.33; 1.73)	2.10 (0.70; 6.29)	0.85 (0.25; 2.97)	**PAR**	.
1.19 (0.67; 2.10)	3.32 (0.27; 40.61)	1.32 (0.87; 2.01)	3.68 (1.26; 10.74)	1.49 (0.51; 4.41)	1.75 (0.76; 4.04)	**PLC**

Class level network meta-analysis (upper triangle refers to direct estimates)

Atypical	1.13 (0.48; 2.63)	0.94 (0.47; 1.87)	0.59 (0.37; 0.94)
1.14 (0.66; 1.99)	**PLC**	0.74 (0.47; 1.17)	0.69 (0.16; 3.03)
0.87 (0.51; 1.50)	0.76 (0.50; 1.16)	**SNRI**	.
0.60 (0.38; 0.95)	0.53 (0.27; 1.03)	0.69 (0.35; 1.36)	**SSRI**

Continuation phase

Network meta-analysis estimates (study design I)

Comparison	N studies	Direct estimate: RR (95% CI)	Network estimate: RR (95% CI)
ADM: CBT	1	16.7 (0.99; 283.36)	16.51 (0.98; 277.71)
ADM: Placebo	5	3.04 (1.44; 6.39)	3.04 (1.44; 6.39)
CBT: Placebo	1	0.20 (0.01; 4.86)	0.18 (0.01; 3.33)

Individual drug level network meta-analysis (upper triangle refers to direct estimates) – Design I

AGM	.	.	.	1.34 (0.77; 2.33)	.	.	.	0.81 (0.45; 1.44)	.	.	.
9.54 (1.02; 88.93)	**BA**	.	.	.	.	.	.	0.12 (0.01; 2.04)	0.41 (0.02; 9.81)	.	.
18.42 (3.16; 107.51)	1.93 (0.13; 27.93)	**BUP**	.	.	.	.	.	.	.	0.24 (0.08; 0.70)	.
9.98 (1.07; 93.07)	1.05 (0.05; 20.66)	0.54 (0.04; 7.84)	**CT**	.	.	.	.	0.12 (0.01; 1.95)	0.39 (0.02; 9.39)	.	.
1.30 (0.75; 2.25)	0.14 (0.01; 1.34)	0.07 (0.01; 0.44)	0.13 (0.01; 1.28)	**DXT**	.	.	.	.	9.25 (0.54; 157.66)	.	.
1.49 (0.72; 3.07)	0.16 (0.02; 1.41)	0.08 (0.01; 0.45)	0.15 (0.02; 1.35)	1.15 (0.47; 2.80)	**ESC**	.	.	0.57 (0.36; 0.89)	2.02 (0.19; 21.93)	.	.
2.36 (0.53; 10.57)	0.25 (0.02; 2.63)	0.13 (0.02; 0.94)	0.24 (0.02; 2.51)	1.81 (0.38; 8.64)	1.58 (0.37; 6.81)	**IMI**	.	.	2.53 (0.83; 7.72)	.	0.95 (0.43; 2.09)
0.81 (0.28; 2.38)	0.08 (0.01; 0.88)	0.04 (0.01; 0.25)	0.08 (0.01; 0.84)	0.62 (0.19; 2.06)	0.54 (0.20; 1.50)	0.34 (0.07; 1.78)	**MIR**	0.93 (0.35; 2.49)	.	8.30 (1.09; 63.28)	.
0.83 (0.47; 1.47)	0.09 (0.01; 0.76)	0.05 (0.01; 0.24)	0.08 (0.01; 0.73)	0.64 (0.29; 1.39)	0.56 (0.36; 0.87)	0.35 (0.08; 1.46)	1.03 (0.41; 2.57)	**PAR**	4.77 (0.62; 36.65)	8.89 (1.12; 70.30)	.
5.97 (1.75; 20.41)	0.63 (0.07; 5.66)	0.32 (0.05; 1.96)	0.60 (0.07; 5.41)	4.59 (1.25; 16.89)	4.01 (1.23; 13.03)	2.53 (1.07; 6.00)	7.37 (1.82; 29.90)	7.18 (2.31; 22.30)	**PLC**	0.27 (0.03; 2.38)	0.37 (0.12; 1.12)
4.48 (1.09; 18.33)	0.47 (0.04; 5.45)	0.24 (0.08; 0.70)	0.45 (0.04; 5.21)	3.44 (0.77; 15.35)	3.00 (0.77; 11.74)	1.90 (0.35; 10.32)	5.53 (1.40; 21.88)	5.39 (1.47; 19.78)	0.75 (0.17; 3.22)	**SRT**	.
2.23 (0.50; 9.97)	0.23 (0.02; 2.48)	0.12 (0.02; 0.89)	0.22 (0.02; 2.37)	1.71 (0.36; 8.15)	1.50 (0.35; 6.43)	0.95 (0.47; 1.92)	2.75 (0.53; 14.21)	2.68 (0.65; 11.10)	0.37 (0.16; 0.88)	0.50 (0.09; 2.70)	**VEN**

Class level network meta-analysis (upper triangle refers to direct estimates) – Design I

Atypical	.	.	.	.	1.34 (0.44; 4.07)	0.78 (0.37; 1.64)	.
6.48 (0.31; 135.53)	**Standard CBT**	0.96 (0.02; 52.96)	.	0.59 (0.02; 19.63)	.	0.12 (0.01; 2.44)	.
6.20 (0.30; 129.42)	0.96 (0.02; 52.96)	**CBT-3**	.	0.62 (0.02; 20.53)	.	0.13 (0.01; 2.56)	.

0.21 (0.05; 0.85)	0.03 (0.00; 0.81)	0.03 (0.00; 0.84)	**NARI**	.	.	3.85 (1.17; 12.67)	.
3.36 (1.06; 10.71)	0.52 (0.02; 11.54)	0.54 (0.02; 12.07)	15.75 (3.09; 80.29)	**Placebo**	0.31 (0.10; 0.94)	0.29 (0.07; 1.17)	0.39 (0.09; 1.72)
1.18 (0.45; 3.15)	0.18 (0.01; 4.18)	0.19 (0.01; 4.37)	5.55 (1.10; 27.98)	0.35 (0.12; 1.04)	**SNRI**	.	1.06 (0.30; 3.69)
0.82 (0.41; 1.66)	0.13 (0.01; 2.46)	0.13 (0.01; 2.58)	3.85 (1.17; 12.67)	0.24 (0.08; 0.74)	0.64 (0.30; 1.37)	**SSRI**	.
1.28 (0.30; 5.47)	0.20 (0.01; 5.24)	0.21 (0.01; 5.4)	5.99 (0.89; 40.47)	0.38 (0.10; 1.44)	1.08 (0.33; 3.58)	1.56 (0.35; 6.93)	**TCA**

Maintenance phase

Individual drug level network meta-analysis (upper triangle refers to direct estimates) – Design I

AGM	1.32 (0.77; 2.28)	**.**
1.32 (0.77; 2.28)	**DLX**	**1.03 (0.68; 1.56)**
1.36 (0.69; 2.70)	1.03 (0.68; 1.56)	**PLC**

Class level network meta-analysis (upper triangle refers to direct estimates) – Design I

Atypical	.	1.32 (0.77; 2.28)
1.36 (0.69; 2.70)	**Placebo**	0.97 (0.64; 1.48)
1.32 (0.77; 2.28)	0.97 (0.64; 1.48)	**SNRI**

Treatment ranking

Rank	P-Score (continuation phase, design I)	
1	CBT	0.92
2	Placebo	0.56
3	ADM	0.01

11.1.6.8 Additional estimates for adverse effects

RR estimates (95% confidence intervals) of adverse effects across different comparisons

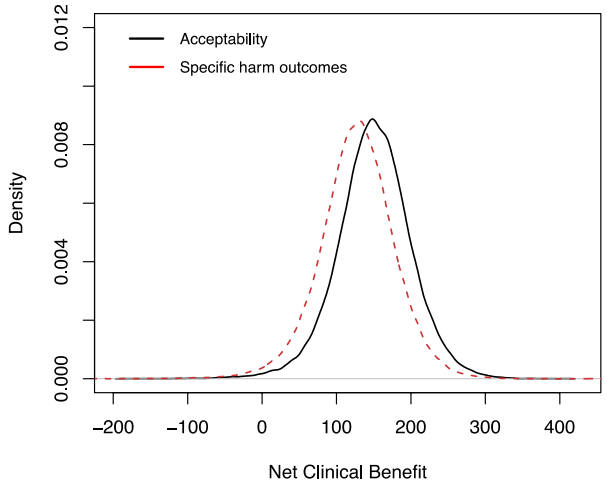
Adverse effect	Comparison	Acute phase			Continuation phase						Maintenance phase								
					Design I			Design III			Design I			Design II			Design III		
		N	RR (95% CI)	I^2	N	RR (95% CI)	I^2	N	RR (95% CI)	I^2	N	RR (95% CI)	I^2	N	RR (95% CI)	I^2	N	RR (95% CI)	I^2
Any side effect	ADM vs CBT	-	-	-	1	17.84 [2.32; 137.40]	-	-	-	-	-	-	-	-	-	-	-	-	-
	ADM vs ADM plus CBT	-	-	-	-	-	-	-	-	-	1	1.28 [0.89; 1.84]	-	-	-	-			-
	ADM vs Placebo	1	1.43 [1.02; 2.01]	-	2	1.54 [0.71; 3.35]	80%	1	1.44 [1.08; 1.92]	-	2	1.22 [0.74; 1.99]	85%	-	-	-	-	-	-
Serious side effects	ADM vs CBT	-	-	-	1	0.79 [0.36; 1.70]	-	-	-	-	-	-		1	1.00 [0.06; 15.73]	-	-	-	-
	ADM vs ADM plus CBT	-	-	-	-	-	-	-	-	-	1	1.12 [0.63; 1.98]	-	-	-	-	-	-	-
	ADM vs Placebo	-	-	-	4	0.92 [0.57; 1.51]	0%	1	1.03 [0.07; 16.29]	-	-	-	-	1	0.80 [0.05; 12.60]	-	-	-	-
	CBT vs placebo	-	-	-	-	-	-	-	-	-	-	-	-	1	0.80 [0.05; 12.60]		-	-	-
Blood and lymphatic system	ADM vs Placebo										1	1.28[0.52; 3.16]	-						
Cardiac	ADM vs Placebo	2	1.00 [0.09; 10.93]	0%	1	2.02 [0.07; 59.54]	-	1	0.94 [0.55; 1.60]	-	3	1.24 [0.24; 6.44]	0%	-	-	-	-	-	-
Gastrointestinal	ADM vs CBT	-	-	-	1	4.72 [1.92; 11.63]	-	-	-	-	-	-	-	-	-	-	-	-	-
	ADM vs Placebo	3	1.64 [1.36; 1.98]	0%	3	1.90 [1.25; 2.90]	10%	2	1.76 [1.04; 2.98]	0%	2	1.62 [0.81; 3.26]	32%	-	-	-	-	-	-
General	ADM vs Placebo	2	1.81 [0.76; 4.29]	61%	3	2.37 [0.78; 7.21]	14%	-	-	-	1	0.92 [0.51; 1.66]	-	-	-	-	-	-	-
Hepato-biliary	ADM vs Placebo							1	1.88 [0.09; 41.17]	-									
Metabolic and nutrition	ADM vs Placebo	2	0.78 [0.08; 7.61]	0%	-	-	-	-	-	-	2	4.64 [0.86; 24.95]	0%	-	-	-	-	-	-
Musculoskeletal and connective tissue	ADM vs CBT				1	1.21 [0.48; 3.08]	-	-	-	-	-	-	-	-	-	-	-	-	-
	ADM vs Placebo	-	-	-	1	0.51 [0.05; 5.48]	-	-	-	-	-	-	-	-	-	-	-	-	-
Nervous system	ADM vs CBT				2	1.91 [1.11; 3.28]	9%	-	-	-	-	-	-	-	-	-	-	-	
	ADM vs Placebo	4	1.12 [0.88; 1.41]	17%	3	2.05 [1.33; 3.18]	17%	2	1.31 [0.81; 2.12]	0%	1	2.19 [1.05; 4.58]	-						
Psychiatric	ADM vs CBT	-	-	-	2	4.20 [0.54; 32.59]	52%	-	-	-	-	-	-	-	-	-	-	-	-

	ADM vs Placebo	1	4.23 [0.55; 32.76]	-	-	-	-	1	1.54 [0.26; 9.10]	-	1	1.70 [0.87; 3.38]	-	-	-	-	-	-	-
	CBT vs WL	-	-	-	1	0.59 [0.23; 1.49]	-	-	-	-	-	-	-	-	-	-	-	-	-
Reproductive system and breast	**ADM vs Placebo**	-	-	-	2	8.07 [0.96; 68.26]	49%	-	-	-									
Respiratory, thoracic and mediastinal	**ADM vs CBT**				1	0.63 [0.19; 2.14]	-												
	ADM vs Placebo				1	4.86 [0.27; 88.23]	-	1	1.37 [0.31; 6.02]	-	2	1.69 [0.78; 3.68]	0%						
Suicidal behaivor	**ADM vs CBT**				1	0.16 [0.01; 3.09]	-												
	ADM vs ADM plus CBT										1	1.01 [0.06; 16.03]	-						
	ADM vs Placebo	2	0.66 [0.08; 5.60]	0%	1	1.94 [0.09; 42.78]	-												
Vascular	**ADM vs Placebo**	-	-	-	1	0.67 [0.20; 2.32]	-	-	-	-	-	-	-	-	-	-	-	-	-

N: number of trials; RR: risk ratio; CI: confidence interval; ADM: antidepressant medication; CBT: cognitive behavioral therapy intervention; WL: waiting list

11.2 Benefit-Harm Assessment Appendix

Distribution of net clinical benefit of CT/REBT vs. SSRIs over 12 months



Net clinical benefit and expected events of benefit and harm outcomes over 12 months for CT/REBT compared to SSRI.

			Expected events per 1000 patients in 12 months			
Treatment contrasts	**Pr. net clinical benefit in 12 months, %**	**Net clinical benefit per 1000 patients in 12 months (2.5th, 97.5th centiles)**	**Relapse with CBT/ADM**	**Acceptability with CBT/ADM**	**Neurological AE with CBT/ADM**	**Psychiatric AEs with CBT/ADM**
CT/REBT vs. SSRI (Specific harms)	918.8	127 (27 to 255)	133/242	–	296/487	129/301
CT/REBT vs. SSRI (Acceptability or dropout)	99.4%	150 (48 to 248)	133/242	455/711		

11.3 Economic Review Appendix

11.3.1 Economics search strategies

EMBASE search
Database(s): **Embase** 1974 to 2020 June 30
Search Strategy:

#	Searches	Results
1	exp depressive disorder, major/ or exp depressive disorder/ or exp depression/	471020
2	depress*.ti.	185064
3	1 or 2	506607
4	(antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or serotonin modulator*).mp.	269426
5	exp Antidepressive Agents/	437918
6	exp Neurotransmitter Uptake Inhibitors/	167
7	exp Monoamine Oxidase Inhibitors/	44301
8	(Agomelatine or Amitriptylin*or Buproprion or Amfebutamone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Desvenlafaxine or Duloxetine or Doxepin or Escitalopram or Fluoxetine or Fluvoxamine or Imipramin or (Lu AA21004 or Vortioxetine) or Mianserin or Mirtazapine or Moclobemide or Paroxetine or Reboxetine or Sertraline or Trazodone or Trimipramine or Vortioxetine or Venlafaxine).mp.	138745
9	4 or 5 or 6 or 7 or 8	520250
10	CBT.mp.	16699
11	exp Cognitive Therapy/	45346
12	(cognitive adj2 behavio?ral adj3 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	34746
13	mindfulness.mp.	11810
14	(acceptance and commitment).mp.	2452
15	((problem-solving or problem solving) adj2 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	3042
16	((meta-cognitive or metacognitive) adj2 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	727

17	((rational-emotive or rational emotive) adj2 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	399
18	((third-wave or third wave) adj2 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	145
19	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	80671
20	3 and (9 or 19)	137742
21	cost effectiveness*.ti,ab,kw.	88453
22	cost utility.ti,ab,kw.	7876
23	cost benefit.ti,ab,kw.	15901
24	health economic*.ti,ab,kw.	13927
25	economic evaluation*.ti,ab,kw.	17927
26	21 or 22 or 23 or 24 or 25	120389
27	20 and 26	1290
28	limit 27 to yr="1995 -Current"	1261

MEDLINE search

Database(s): **Ovid MEDLINE(R) ALL** 1946 to June 30, 2020
Search Strategy:

#	Searches	Results
1	exp depressive disorder, major/ or exp depressive disorder/ or exp depression/	215220
2	depress*.ti.	149316
3	1 or 2	255100
4	(antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or serotonin modulator*).mp.	178052
5	exp Antidepressive Agents/	148353
6	exp Neurotransmitter Uptake Inhibitors/	146260
7	exp Monoamine Oxidase Inhibitors/	21656
8	(Agomelatine or Amitriptylin*or Buproprion or Amfebutamone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Desvenlafaxine or Duloxetine or Doxepin or Escitalopram or Fluoxetine or Fluvoxamine or Imipramin or (Lu AA21004 or Vortioxetine) or Mianserin or Mirtazapine or Moclobemide or Paroxetine or Reboxetine or Sertraline or Trazodone or Trimipramine or Vortioxetine or Venlafaxine).mp.	45386
9	4 or 5 or 6 or 7 or 8	327094
10	CBT.mp.	11000
11	exp Cognitive Therapy/	28367
12	(cognitive adj2 behavio?ral adj3 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	34294
13	mindfulness.mp.	7990
14	(acceptance and commitment).mp.	1817
15	((problem-solving or problem solving) adj2 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	2240
16	((meta-cognitive or metacognitive) adj2 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	514
17	((rational-emotive or rational emotive) adj2 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	297
18	((third-wave or third wave) adj2 (therap* or theor* or intervention* or train* or treatment* or psychotherap* or program* or method* or approach*)).mp.	93

19	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	47375
20	3 and (9 or 19)	62066
21	cost effectiveness*.ti,ab,kw.	60299
22	cost utility.ti,ab,kw.	4699
23	cost benefit.ti,ab,kw.	10178
24	health economic*.ti,ab,kw.	9087
25	economic evaluation*.ti,ab,kw.	12378
26	21 or 22 or 23 or 24 or 25	81860
27	20 and 26	679
28	limit 27 to yr="1995 -Current"	662

York CRD search

		Hits
1	((((cost benefit) OR (cost effectiveness) OR (cost utility) OR (economic evaluation) IN DARE, NHSEED, HTA) FROM 1995 TO 2020))	21634
2	((MeSH DESCRIPTOR Depression EXPLODE ALL TREES))	639
3	((MeSH DESCRIPTOR Depressive Disorder EXPLODE ALL TREES))	1030
4	((depress*) FROM 1995 TO 2020)	3063
5	((#2 OR #3 OR #4))	3090
6	((#1 AND #5))	776

11.3.2 List of excluded studies from full text screening of cost-effectiveness analyses of antidepressants or cognitive behavioural therapy for depression

First author	Year	Title
ANOTHER REASON (e.g. Mencacci et al. studies were sub-national and overlapped with included Mencacci et al. national study		
Driessen	2007	Cognitive behavioral therapy versus short psychodynamic supportive psychotherapy in the outpatient treatment of depression: A randomized controlled trial
Lanati	2014	Economic Evaluation of Agomelatine for Major Depressive Disorders Relative to other Antidepressants in the Italian Setting
Pahlevan	2020	Cost-Utility Analysis of Mindfulness-Based Cognitive Therapy Versus Antidepressant Pharmacotherapy for Prevention of Depressive Relapse in a Canadian Context
Mencacci	2013	C-QUALITY: Cost and quality-of-life pharmacoeconomic analysis of antidepressants used in major depressive disorder in the regional Italian settings of Veneto and Sardinia
Mencacci	2013	Cost-effectiveness evaluation of escitalopram in major depressive disorder in Italy
PUBLISHED BEFORE 2006		
Ahrens	1995	Depression and quality of life. Cost benefit analysis and therapy. [German]
Antonuccio	1997	A cost-effectiveness analysis of cognitive behavior therapy and fluoxetine (Prozac) in the treatment of depression
Ausejo	1997	A clinical and economic evaluation of selective serotonin reuptake inhibitors in major depression; Randomised controlled trial of non-directive counselling, cognitive-behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care
Baladi	1997	Selective serotonin reuptake inhibitors (SSRIs) for major depression. Part 2. The cost-effectiveness of SSRIs in treatment of depression
Bentkover	1995	Cost analysis of paroxetine versus imipramine in major depression
Borghi	2000	Economic impact of using mirtazapine compared to amitriptyline and fluoxetine in the treatment of moderate and severe depression in the UK
Bower	2000	Randomised controlled trial of non-directive counselling, cognitive-behaviour therapy, and usual general practitioner care for patients with depression. II: cost effectiveness
Brown	1999	Cost-effectiveness of mirtazapine relative to amitriptyline in the treatment of moderate and severe depression in France
Brown	1999	Cost-effectiveness of mirtazapine compared to amitriptyline and fluoxetine in the treatment of moderate and severe depression in austria
Brown	2000	Cost-effectiveness of mirtazapine relative to fluoxetine in the treatment of moderate and severe depression in France
Casciano	1999	A pharmacoeconomic evaluation of major depressive disorder (Italy)
Casciano	2001	The health economic impact of antidepressant usage from a payer's perspective: a multinational study
Chisholm	2004	Reducing the global burden of depression: population-level analysis of intervention cost-effectiveness in 14 world regions
Cohen	1995	Pharmacoeconomic issues in the treatment of depression
Dardennes	1999	Comparison of the cost-effectiveness of milnacipran (a SNRI) with TCAs and SSRIs: a modeling approach
Dardennes	1999	Milnacipran, tricyclic antidepressants or selective serotonin reuptake inhibitors. A comparative cost-effectiveness study of treatment of depressive episodes. [French]
Dardennes	2000	Economic assessment of a maintenance treatment strategy in prevention of recurrent depressive disorder
Dickinson	2005	RCT of a care manager intervention for major depression in primary care: 2-year costs for patients with physical vs psychological complaints
Doyle	2001	A multinational pharmacoeconomic evaluation of acute Major Depressive Disorder (MDD): A comparison of cost-effectiveness between venlafaxine, SSRIs and TCAs
Einarson	1995	A model to evaluate the cost-effectiveness of oral therapies in the management of patients with major depressive disorders
Einarson	1997	Pharmacoeconomic analysis of venlafaxine in the treatment of major depressive disorder
Fernandez	2005	Evaluation of the cost effectiveness of escitalopram versus venlafaxine XR in major depressive disorder
Forder	1996	A comparison of the cost-effectiveness of sertraline versus tricyclic antidepressants in primary care

Francois	2002	Introduction of escitalopram, a new SSRI in Finland: Comparison of cost-effectiveness between the other SSRIS and SNRI for the treatment of depression and estimation of the budgetary impact
Francois	2003	A pharmacoeconomic evaluation of escitalopram, a new selective serotonin reuptake inhibitor. Comparison of cost-effectiveness between escitalopram, citalopram, fluoxetine, and venlafaxine for the treatment of depression in Norway
Frank	1999	The value of mental health care at the system level: the case of treating depression
Freeman	2000	Pharmacoeconomic analysis of antidepressants for major depressive disorder in the United Kingdom
Haby	2004	Cost-effectiveness of cognitive behavioural therapy and selective serotonin reuptake inhibitors for major depression in children and adolescents
Hemels	2004	Cost-effectiveness analysis of escitalopram: a new SSRI in the first-line treatment of major depressive disorder in Austria
Howard	2004	A clinical- and cost-effectiveness comparison of venlafaxine and selective serotonin reuptake inhibitors (SSRIs) in the management of patients with major depressive disorder from the perspective of an Austrian sickness fund
Kaltenthaler	2002	A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety
Kamlet	1995	Cost utility analysis of maintenance treatment for recurrent depression
Katon	2005	Cost-effectiveness of improving primary care treatment of late-life depression
Kim	2003	Burdens and benefits of placebos in antidepressant clinical trials: a decision and cost-effectiveness analysis
Kind	1995	Modelling the cost-effectiveness of the prophylactic use of SSRIs in the treatment of depression
King	2000	Randomised controlled trial of non-directive counselling, cognitive-behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care
Kulp	2005	Cost-effectiveness of outpatient treatment in depressive patients with escitalopram in Germany
Lafuma	1999	[Clinico-economic assessment of milnacipran in the prevention of depressive episodes]
Lapierre	1995	Direct cost of depression: Analysis of treatment costs of paroxetine versus impramine in Canada
Lave	1998	Cost-effectiveness of treatments for major depression in primary care practice
Lenox-Smith	2004	Cost effectiveness of representatives of three classes of antidepressants used in major depression in the UK
Lothgren	2004	A cost-effectiveness analysis of escitalopram as first line treatment of depression in Sweden
Lynch	2005	Cost-effectiveness of an intervention to prevent depression in at-risk teens
McCrone	2004	Cost-effectiveness of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial
Melton	1997	Economic evaluation of paroxetine and imipramine in depressed outpatients
Miller	2003	Counseling versus antidepressant therapy for the treatment of mild to moderate depression in primary care: economic analysis
Montgomery	1996	Economic analysis of treating depression with nefazodone v imipramine
Nuijten	1998	Cost effectiveness of fluvoxamine in the treatment of recurrent depression in France
Nuijten	1995	A Markov process analysis comparing the cost effectiveness of maintenance therapy with citalopram versus standard therapy in major depression
Obenchain	1997	Bootstrap analyses of cost effectiveness in antidepressant pharmacotherapy
O'Connor	2005	Pharmacoeconomic analysis of sertraline treatment of depression in patients with unstable angina or a recent myocardial infarction
Patel	2003	Efficacy and cost-effectiveness of drug and psychological treatments for common mental disorders in general health care in Goa, India: A randomised, controlled trial
Peveler	2005	A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibators and lofepramine
Razali	1999	Cost-effectiveness of cyclic antidepressants in a developing country
Regan	2003	An economic analysis of SSRI length of therapy
Revicki	1995	Modelling the cost effectiveness of antidepressant treatment in primary care

Revicki	1997	Cost-effectiveness of newer antidepressants compared with tricyclic antidepressants in managed care settings
Revicki	1997	Acute medical costs of fluoxetine versus tricyclic antidepressants
Revicki	1998	Depression, health-related quality of life, and medical cost outcomes of receiving recommended levels of antidepressant treatment
Revicki	2005	Cost-effectiveness of evidence-based pharmacotherapy or cognitive behavior therapy compared with community referral for major depression in predominantly low-income minority women
Romeo	2004	The cost-effectiveness of mirtazapine versus paroxetine in treating people with depression in primary care
Sacristan	2000	Cost-effectiveness of fluoxetine plus pindolol in patients with major depressive disorder: Results from a randomized, double-blind clinical trial
Schoenbaum	2005	Gender patterns in cost effectiveness of quality improvement for depression: results of a randomized, controlled trial
Schoenbaum	2001	Cost-effectiveness of practice-initiated quality improvement for depression
Sclar	1995	Antidepressant pharmacotherapy: economic evaluation of fluoxetine, paroxetine and sertraline in a health maintenance organization
Scott	2003	Use of cognitive therapy for relapse prevention in chronic depression: cost-effectiveness study
Simon	1999	Long-term outcomes of initial antidepressant drug choice in a "real world" randomized trial
Simon	2001	Cost-effectiveness of systematic depression treatment for high utilizers of general medical care
Simpson	2001	A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression
Simpson	2003	A randomized controlled trial to evaluate the effectiveness and cost-effectiveness of psychodynamic counselling for general practice patients with chronic depression
Sorensen	1995	Modelling cost-effectiveness issues in the treatment of clinical depression
Sullivan	2004	A comparison of the direct costs and cost effectiveness of serotonin reuptake inhibitors and associated adverse drug reactions
Tome	1997	Cost-benefit and cost-effectiveness analysis of the rapid onset of selective serotonin reuptake inhibitors by augmentation
Tome	1998	Cost effectiveness study of a year follow-up of selective serotonin reuptake inhibitor(SSRI) and augmentor combination compared with SSRI and placebo
Trivedi	2004	Cost and effectiveness of venlafaxine extended-release and selective serotonin reuptake inhibitors in the acute phase of outpatient treatment for major depressive disorder
Van Baardewijk	2005	Cost effectiveness of duloxetine compared with venlafaxine-XR in the treatment of major depressive disorder
Vos	2005	Cost-effectiveness of cognitive-behavioural therapy and drug interventions for major depression
Wade	2005	A probabilistic cost-effectiveness analysis of escitalopram, generic citalopram and venlafaxine as a first-line treatment of major depressive disorder in the UK
Wells	1999	The design of Partners in Care: Evaluating the cost-effectiveness of improving care for depression in primary care
White	2003	Economic impact of patient adherence with antidepressant therapy within a managed care organization
Woods	1997	Cost effectiveness of antidepressant treatment reassessed
Zimmer	1999	Direct and indirect costs of venlafaxine treatment of depression in the elderly with comorbid medical disorders
INCORRECT COMPARATOR		
Baumann	2020	Cost-Utility of Internet-Based Cognitive Behavioral Therapy in Unipolar Depression: A Markov Model Simulation
Brabyn	2016	The second randomised evaluation of the effectiveness, cost-effectiveness and acceptability of computerised therapy (REEACT-2) trial: Does the provision of telephone support enhance the effectiveness of computer-delivered cognitive behaviour therapy? a randomised controlled trial
Kooistra	2019	Cost and Effectiveness of Blended Versus Standard Cognitive Behavioral Therapy for Outpatients With Depression in Routine Specialized Mental Health Care: Pilot Randomized Controlled Trial
INCORRECT STUDY DESIGN		

Fansi	2015	[Notice on equal access to physiotherapy services. Part I - Review of the evidence on the effectiveness and cost of psychotherapy compared to treatment of adults with anxiety and depressive disorders]
Holman	2011	Cost-effectiveness of cognitive behaviour therapy versus talking and usual care for depressed older people in primary care
Kafali	2014	Cost-effectiveness of a randomized trial to treat depression among Latinos
Kaplan	2012	Assessing the comparative-effectiveness of antidepressants commonly prescribed for depression in the US Medicare population
Kuyken	2008	Mindfulness-based cognitive therapy to prevent relapse in recurrent depression
Lagerveld	2012	Work-focused treatment of common mental disorders and return to work: a comparative outcome study
Marynchenko	2011	Economic outcomes of switching treatment in major depressive disorder patients
McHugh	2016	An evaluation of access to psychological services Ireland: Year one outcomes
Mihalopoulos	2005	Exploratory economic analyses of two primary care mental health projects: implications for sustainability
Moscarelli	2014	The cost-effectiveness of cognitive behavioural therapy for the depression in Latinos
Norquist	2008	Cost-effectiveness of depression treatment for adolescents
Rice	2014	Online and social networking interventions for the treatment of depression in young people: a systematic review
Rodgers	2012	The clinical effectiveness and cost-effectiveness of low-intensity psychological interventions for the secondary prevention of relapse after depression: a systematic review
Sanglier	2012	Increasing escitalopram dose is associated with fewer discontinuations than switch or combination approaches in patients initially on escitalopram 10mg
Sicras-Mainar	2010	Comparison of escitalopram vs. citalopram and venlafaxine in the treatment of major depression in Spain: clinical and economic consequences
Toney	2007	Identifying and managing depression in women
Wade	2005	A pharmacoeconomic evaluation of escitalopram versus citalopram in the treatment of severe depression in the United Kingdom
Wang	2007	Telephone screening, outreach, and care management for depressed workers and impact on clinical and work productivity outcomes: A randomized controlled trial
Weisz	2009	Cognitive-behavioral therapy versus usual clinical care for youth depression: an initial test of transportability to community clinics and clinicians
Wu	2008	Comparison of escitalopram versus citalopram for the treatment of major depressive disorder in a geriatric population
Wu	2012	Treatment persistence and health care costs of adult MDD patients treated with escitalopram vs. citalopram in a Medicaid population
Wu	2011	Comparing treatment persistence, healthcare resource utilization, and costs in adult patients with major depressive disorder treated with escitalopram or citalopram
Wu	2011	Economic impact of therapeutic substitution of a brand selective serotonin reuptake inhibitor with an alternative generic selective serotonin reuptake inhibitor in patients with major depressive disorder
Xie	2009	Cost effectiveness analysis of escitalopram compared to venlafaxine and fluvoxamine in treatment of major depressive disorder
Yu	2011	Impact of initiation timing of SSRI or SNRI on depressed adolescent healthcare utilization and costs
IQWIG	2013	Health economic evaluation of venlafaxine, duloxetine, bupropion, and mirtazapine compared to further prescribable pharmaceutical treatments
DUPLICATE OF ANOTHER STUDY		
Anonymous	2019	Ontario health technology assessment series: Internet-delivered cognitive behavioural therapy for major depression and anxiety disorders: A health technology assessment
Domino	2008	Cost-effectiveness of treatments for adolescent depression: results from TADS
Health Quality	2017	Psychotherapy for Major Depressive Disorder and Generalized Anxiety Disorder: A Health Technology Assessment
Littlewood	2015	A randomised controlled trial of computerised cognitive behaviour therapy for the treatment of depression in primary care: The Randomised Evaluation of the Effectiveness and Acceptability of Computerised Therapy (REEACT) trial
Penarrubia	2006	Cost-utility of selective serotonin reuptake inhibitors for depression in primary care in Catalonia

Richards	2017	Cost and Outcome of BehaviouRal Activation (COBRA): a randomised controlled trial of behavioural activation versus cognitive behavioural therapy for depression
Soini	2014	Cost-Utility of Vortioxetine in the Treatment of Major Depressive Disorder: Comparison with Agomelatine, Bupropion, Sertraline and Venlafaxine in the Finnish Setting
Titov	2014	Clinical and cost-effectiveness of therapist-guided internet-delivered cognitive behavior therapy for older adults with symptoms of depression: a randomized controlled trial; The effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse/recurrence: results of a randomised controlled trial (the PREVENT study)
van Roijen	2006	Cost-utility of brief psychological treatment for depression and anxiety
Watkins	2013	The cost-effectiveness of depression treatment for co-occurring disorders: a clinical trial
INCORRECT INTERVENTION		
Beil	2013	Cost-effectiveness of alternative treatments for depression in low-income women
Berghout	2010	A cost-utility analysis of psychoanalysis versus psychoanalytic psychotherapy
Biesheuvel-Leliefeld	2018	A supported self-help for recurrent depression in primary care; An economic evaluation alongside a multi-center randomised controlled trial
Bosmans	2006	Cost-effectiveness of a disease management program for major depression in elderly primary care patients
Dijkstra-Kersten	2019	Supported self-help to prevent relapse or recurrence of depression: Who benefits most?
Ekers	2011	Cost utility of behavioural activation delivered by the non-specialist
Fortney	2014	Population-level cost-effectiveness of implementing evidence-based practices into routine care
Gensichen	2013	Cost-effectiveness of depression case management in small practices
Green	2014	Cost-effectiveness of collaborative care for depression in UK primary care: economic evaluation of a randomised controlled trial (CADET)
Horrell	2014	One-day cognitive-behavioural therapy self-confidence workshops for people with depression: randomised controlled trial
Jahoda	2018	Behavioural activation versus guided self-help for depression in adults with learning disabilities: The beatit RCT
Johnson	2019	Randomized cost-effectiveness trial of group interpersonal psychotherapy (IPT) for prisoners with major depression
Klein	2018	Economic Evaluation of an Internet-Based Preventive Cognitive Therapy With Minimal Therapist Support for Recurrent Depression: Randomized Controlled Trial
Klug	2010	Effectiveness of home treatment for elderly people with depression: randomised controlled trial
Koeser	2013	Economic evaluation of audio based resilience training for depression in primary care
Kresimon	2012	Medical care of patients with moderate depression under hypericum extract STW3-VI compared to SSRI in routine outpatient treatment. [German]
Naversnik	2013	Cost-effectiveness of a novel e-health depression service
Naversnik	2014	Routine real-time cost-effectiveness monitoring of a web-based depression intervention: a risk-sharing proposal
Pizzi	2014	Cost-effectiveness of a community-integrated home-based depression intervention in older African Americans
Rubio-Valera	2013	Cost-effectiveness of a community pharmacist intervention in patients with depression: a randomized controlled trial (PRODEFAR Study)
Schene	2007	Adjuvant occupational therapy for work-related major depression works: randomized trial including economic evaluation
Shimodera	2012	Cost-effectiveness of family psychoeducation to prevent relapse in major depression: results from a randomized controlled trial
Sobocki	2006	Model to assess the cost-effectiveness of new treatments for depression
Sussman	2017	Cost-effectiveness of brexpiprazole adjunctive treatment for major depressive disorder
Tournier	2009	Economic impact of non-persistence to antidepressant therapy in the Quebec community-dwelling elderly population
Vataire	2014	Core discrete event simulation model for the evaluation of health care technologies in major depressive disorder

Yan	2019	Cost-effectiveness analysis of a randomized study of depression treatment options in primary care suggests stepped-care treatment may have economic benefits
Yoon	2018	Comparing Cost-Effectiveness of Aripiprazole Augmentation With Other "Next-Step" Depression Treatment Strategies: A Randomized Clinical Trial
INCORRECT LANGUAGE		
Rejas Gutierrez	2016	[Economic evaluation of desvenlafaxine in the treatment of major depressive disorder in Spain]
Rey	2016	[Cost-effectiveness of a brief intervention to support indigenous women in Hidalgo (Mexico) who live with alcohol abusers]
INCORRECT OUTCOME		
Alaoui	2016	Combining time-driven activity-based costing with clinical outcome in cost-effectiveness analysis to measure value in treatment of depression
Brown	2011	Outcome, costs and patient engagement for group and individual CBT for depression: a naturalistic clinical study
Christensen	2018	Cost per successfully treated patient for vortioxetine versus duloxetine in adults with major depressive disorder: an analysis of the complete symptoms of depression and functional outcome
Demyttenaere	2005	A cost-effectiveness model of escitalopram, citalopram, and venlafaxine as first-line treatment for major depressive disorder in Belgium
Fantino	2007	Cost-effectiveness of escitalopram vs. citalopram in major depressive disorder
Gabarron	2006	Effectiveness and cost-effectiveness of antidepressant treatment in primary health care: A six-month randomised study comparing fluoxetine to imipramine
Serrano-Blanco	2006	Effectiveness and cost-effectiveness of antidepressant treatment in primary health care: a six-month randomised study comparing fluoxetine to imipramine
Simon	2009	Incremental benefit and cost of telephone care management and telephone psychotherapy for depression in primary care
Sorensen	2007	A Danish cost-effectiveness model of escitalopram in comparison with citalopram and venlafaxine as first-line treatments for major depressive disorder in primary care
Volkl	2007	Treatment of depression in Germany: An analysis of cost-effectiveness with remission. [German]
Wade	2008	Escitalopram and duloxetine in major depressive disorder: a pharmacoeconomic comparison using UK cost data
Watkins	2009	The health value and cost of care for major depression
INCORRECT POPULATION		
Anonymous	2017	Psychotherapy for major depressive disorder and generalized anxiety disorder: A health technology assessment
Ammerman	2017	Cost-effectiveness of In-Home Cognitive Behavioral Therapy for low-income depressed mothers participating in early childhood prevention programs
Anderson	2014	Cost-effectiveness of classroom-based cognitive behaviour therapy in reducing symptoms of depression in adolescents: a trial-based analysis
Aziz	2005	Cost-utility of 2 maintenance treatments for older adults with depression who responded to a course of electroconvulsive therapy: results from a decision analytic model
Banerjee	2013	Study of the use of antidepressants for depression in dementia: the HTA-SADD trial – a multicentre, randomised, double-blind, placebo-controlled trial of the clinical effectiveness and cost-effectiveness of sertraline and mirtazapine
Bosmans	2013	Cost-effectiveness of a stepped care programme to prevent depression and anxiety in residents in homes for the older people: a randomised controlled trial
Bosmans	2008	Cost-effectiveness of usual general practitioner care with or without antidepressant medication for patients with minor or mild-major depression
Bosmans	2012	Cost-effectiveness of problem-solving treatment in comparison with usual care for primary care patients with mental health problems: a randomized trial
Byford	2007	Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive behavioural therapy in adolescents with major depression
Calear	2009	Systematic review of school-based prevention and early intervention programs for depression
Dickerson	2018	Cost-effectiveness of cognitive behavioral therapy for depressed youth declining antidepressants
Domino	2009	Relative cost-effectiveness of treatments for adolescent depression: 36-week results from the tads randomized trial
Garmy	2019	Evaluation of a school-based cognitive-behavioral depression prevention program

Gilmer	2008	Improving treatment of depression among Latinos with diabetes using project Dulce and IMPACT
Goodyer	2017	Cognitive-behavioural therapy and short-term psychoanalytic psychotherapy versus brief psychosocial intervention in adolescents with unipolar major depression (IMPACT): A multicentre, pragmatic, observer-blind, randomised controlled trial
Hakkaart-van Roijen	2006	Cost-utility of brief psychological treatment for depression and anxiety
Hay	2018	Cost-Effectiveness of a Technology-Facilitated Depression Care Management Adoption Model in Safety-Net Primary Care Patients with Type 2 Diabetes
Kamagata	2018	Improvements in Quality-Adjusted Life Years and Cost-Utility After Pharmacotherapy for Premenstrual Dysphoric Disorder: A Retrospective Study
Katon	2006	Cost-effectiveness and net benefit of enhanced treatment of depression for older adults with diabetes and depression
Kendrick	2006	Cost-effectiveness of referral for generic care or problem-solving treatment from community mental health nurses, compared with usual general practitioner care for common mental disorders
Kolovos	2018	Cost effectiveness of guided Internet-based interventions for depression in comparison with control conditions: An individual-participant data meta-analysis
Ladapo	2012	Cost-effectiveness of enhanced depression care after acute coronary syndrome: Results from the coronary psychosocial evaluation studies randomized controlled trial
Lee	2017	The cost-effectiveness of the online mindspot clinic for the treatment of depression and anxiety in Australia
Maljanen	2012	The cost-effectiveness of short-term psychodynamic psychotherapy and solution-focused therapy in the treatment of depressive and anxiety disorders during a one-year follow-up
Malone	2007	A budget-impact and cost-effectiveness model for second-line treatment of major depression
Meuldijk	2015	Economic evaluation of concise cognitive behavioural therapy or pharmacotherapy for depressive and anxiety disorders
Morriss	2016	Efficacy and cost-effectiveness of a specialist depression service versus usual specialist mental health care to manage persistent depression: a randomised controlled trial
Mukuria	2013	Cost-effectiveness of an Improving Access to Psychological Therapies service
Nordstrom	2010	Cost effectiveness of escitalopram versus SNRIs in second-step treatment of major depressive disorder in Sweden
Pan	2014	Cost-effectiveness and cost-utility of selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and tricyclic antidepressants in depression with comorbid cardiovascular disease
Parvathy	2016	Fluoxetine vs Venlafaxine: Economic evaluation in post stroke depression
Richards	2020	A pragmatic randomized waitlist-controlled effectiveness and cost-effectiveness trial of digital interventions for depression and anxiety
Roijen	2006	Cost-utility of brief psychological treatment for depression and anxiety
Romeo	2011	Treatment and prevention of depression after surgery for hip fracture in older people: cost-effectiveness analysis
Saha	2020	Economic evaluation of mindfulness group therapy for patients with depression, anxiety, stress and adjustment disorders compared with treatment as usual
Schotanus-Dijkstra	2018	Towards sustainable mental health promotion: trial-based health-economic evaluation of a positive psychology intervention versus usual care
Scuffham	2008	Are n-of-1 trials an economically viable option to improve access to selected high cost medications? The Australian experience
Serfaty	2019	Manualised cognitive-behavioural therapy in treating depression in advanced cancer: The CanTalk RCT
Serrano-Blanco	2006	Cost-utility of selective serotonin reuptake inhibitors for depression in primary care in Catalonia
Serrano-Blanco	2009	Fluoxetine and imipramine: are there differences in cost-utility for depression in primary care?
Shearer	2019	Refractory depression-cost-effectiveness of radically open dialectical behaviour therapy: Findings of economic evaluation of RefraMED trial
Simon	2007	Cost-effectiveness of systematic depression treatment among people with diabetes mellitus
Singh	2017	Cost-effective drug switch options after unsuccessful treatment with an ssri for depression
Smit	2006	Cost-effectiveness of preventing depression in primary care patients: randomised trial

Soini	2017	Cost-utility analysis of vortioxetine versus agomelatine, bupropion SR, sertraline and venlafaxine XR after treatment switch in major depressive disorder in Finland
Stallard	2013	A cluster randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of classroom-based cognitive-behavioural therapy (CBT) in reducing symptoms of depression in high-risk adolescents
Stant	2008	Cost-effectiveness of cognitive self-therapy in patients with depression and anxiety disorders
Titov	2015	Clinical and Cost-Effectiveness of Therapist-Guided Internet-Delivered Cognitive Behavior Therapy for Older Adults With Symptoms of Depression: A Randomized Controlled Trial
van der Weele	2012	Effects of a stepped-care intervention programme among older subjects who screened positive for depressive symptoms in general practice: the PROMODE randomised controlled trial
van Eeden	2015	An economic evaluation of an augmented cognitive behavioural intervention vs. computerized cognitive training for post-stroke depressive symptoms
Voigt	2017	Cost effectiveness analysis comparing repetitive transcranial magnetic stimulation to antidepressant medications after a first treatment failure for major depressive disorder in newly diagnosed patients - A lifetime analysis
Watanabe	2015	Cost-effectiveness of cognitive behavioral therapy for insomnia comorbid with depression: Analysis of a randomized controlled trial
Watkins	2014	The cost-effectiveness of depression treatment for co-occurring disorders: A clinical trial
Young	2017	Cost-utility evaluation of vortioxetine in patients with Major Depressive Disorder experiencing inadequate response to alternative antidepressants in the United Kingdom
Zhong	2020	Health outcomes and cost-effectiveness of treating depression in people with HIV in Sub-Saharan Africa: a model-based analysis
INCORRECT SETTING		
Araya	2006	Cost-effectiveness of a primary care treatment program for depression in low-income women in Santiago, Chile
Chisholm	2012	Cost effectiveness of strategies to combat neuropsychiatric conditions in sub-Saharan Africa and South East Asia: mathematical modelling study
Choi	2016	Cost-effectiveness of vortioxetine versus venlafaxine (extended release) in the treatment of major depressive disorder in South Korea
Dimitrova	2012	New therapeutic alternative for the treatment of depression: therapeutic and cost-effective profiles
Gureje	2007	Cost-effectiveness of an essential mental health intervention package in Nigeria
Khoo	2015	Network meta-analysis and cost-effectiveness analysis of new generation antidepressants
Kongsakon	2008	The treatment of major depressive disorders (MDD) in Thailand using escitalopram compared to fluoxetine and venlafaxine: a pharmacoeconomic evaluation
Leelahanaj	2010	The cost-effectiveness of aripiprazole as adjunctive therapy in major depressive disorder: Thai economic model
Leelahanaj	2012	Switching to sertraline or venlafaxine after failure of SSRIs treatment in major depressive disorder: an economic evaluation of the STAR*D trial
Machado	2007	The economic impact of introducing serotonin-noradrenaline reuptake inhibitors into the Brazilian national drug formulary: cost-effectiveness and budget-impact analyses
Machado	2008	Pharmacoeconomics of antidepressants in moderate-to-severe depressive disorder in Colombia
Nakimuli-Mpungu	2020	Effectiveness and cost-effectiveness of group support psychotherapy delivered by trained lay health workers for depression treatment among people with HIV in Uganda: a cluster-randomised trial
Pan	2015	Pharmacological treatment of depression with and without headache disorders: An appraisal of cost effectiveness and cost utility of antidepressants
Pan	2015	Depression and pain: An appraisal of cost effectiveness and cost utility of antidepressants
Prukkanone	2012	Cost-effectiveness analysis for antidepressants and cognitive behavioral therapy for major depression in Thailand
Sado	2009	Cost-effectiveness of combination therapy versus antidepressant therapy for management of depression in Japan
Sado	2019	Does the rapid response of an antidepressant contribute to better cost-effectiveness? Comparison between mirtazapine and SSRIs for first-line treatment of depression in Japan

Salomon	2012	Intervention strategies to reduce the burden of non-communicable diseases in Mexico: cost effectiveness analysis
Sathyanarayana Rao	2017	The prospective, 24-week assessment of cost-efficacy of and compliance to antidepressant medications in a rural setting (PACECAR) study
Sava	2009	Cost-effectiveness and cost-utility of cognitive therapy, rational emotive behavioral therapy, and fluoxetine (Prozac) in treating depression: A randomized clinical trial
Saylan	2013	Cost-effectiveness analysis of aripiprazole augmentation treatment of patients with major depressive disorder compared to olanzapine and quetiapine augmentation in Turkey: a microsimulation approach
Siskind	2010	Cost-effectiveness of improved primary care treatment of depression in women in Chile
Siskind	2008	Cost-effectiveness of group psychotherapy for depression in Uganda
Wang	2020	Successfully treated patients with vortioxetine versus venlafaxine: a simplified cost-effectiveness analysis based on a head-to-head study in Asian patients with major depressive disorder

11.3.3 Characteristics of cost-effectiveness analyses of antidepressants or cognitive behavioural therapy for depression

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
ANTIDEPRESSANTS										
Annemans et al. (158)	2014	Cost-effectiveness analysis of pharmaceutical treatment options in the first-line management of major depressive disorder in Belgium	Belgium	Escitalopram	Comparators were citalopram, fluoxetine, paroxetine, sertraline, duloxetine, venlafaxine, and mirtazapine	Decision tree	1 year	First-line treatment of major depressive disorder	Pharmaceutical (Lundbeck SAS)	A1
Armstrong et al. (159)	2007	Cost-utility comparison of escitalopram and sertraline in the treatment of major depressive disorder	USA	10–20 mg/day of escitalopram	50–200 mg/day of sertraline	Decision analytic model	6 months	Major depressive disorder	Pharmaceutical (Forest Laboratories)	A2
Benedict et al. (170)	2010	Economic evaluation of duloxetine versus serotonin selective reuptake inhibitors and venlafaxine XR in treating major depressive disorder in Scotland	Scotland	Duloxetine	Various comparators, which comprised of: venlafaxine XR, mirtazapine, and SSRIs (as a group).	Markov model	48 weeks	Moderate to severe MDD in primary care (>= 19 on the Hamilton Depression Scale (HAMD-17))	Pharmaceutical (Eli Lilly and Boehringer Ingelheim)	A3

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Hollingworth et al. (190)	2019	Cost-Effectiveness of Sertraline in Primary Care According to Initial Severity and Duration of Depressive Symptoms: Findings from the PANDA RCT.	United Kingdom	Sertraline, starting at 50 mg daily for 1 week, increasing to 100 mg daily for up to 11 weeks (with the option of increasing to 150 mg if required).	Placebo	Within-trial analysis	12 weeks	Eligible participants aged between 18 and 74 were identified in primary care with depression or low mood during the past 2 years and had not received antidepressant or anti-anxiety medication in the previous 8 weeks	Government	A4

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Kendrick et al. (163)	2009	Randomised controlled trial to determine the clinical and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care. The THREAD (THREshold for AntiDepressant response) study	United Kingdom (England)	Selective serotonin reuptake inhibitor (SSRI) treatment plus supportive care. The SSRI initially prescribed was either fluvoxamine, sertraline, paroxetine, citalopram or escitalopram.	Supportive care alone	Within-trial analysis	26 weeks	Patients diagnosed with new episodes of depression, were potentially in need of treatment, and had at least one somatic symptom on the Bradford Somatic Inventory	Government	A5
Kendrick et al. (162)	2006	Cost-effectiveness and cost-utility of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine: Randomised controlled trial	United Kingdom (England)	Fluoxetine, paroxetine or sertraline (SSRIs)	Amitriptyline, dothiepin or imipramine (tricyclic antidepressants)	Within-trial analysis	12 months	Adults diagnosed with depression by their GP and accepting antidepressant treatment.	Government	A6

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Lenox-Smith et al. (167)	2009	Cost effectiveness of venlafaxine compared with generic fluoxetine or generic amitriptyline in major depressive disorder in the UK	United Kingdom	First line venlafaxine; second line fluoxetine	Various combinations of venlafaxine, fluoxetine and amitriptyline; administered in different orders (first-line/second-line)	Decision tree	6 months	Acute major depressive disorder	Pharmaceutical (Wyeth)	A7
Maniadakis et al. (168)	2013	Economic evaluation of agomelatine relative toother antidepressants for treatment of majordepressive disorders in Greece	Greece	Agomelatine	Branded and generic venlafaxine, escitalopram, fluoxetine and sertraline.	Markov model	2 years	MDD	Pharmaceutical (Servier Hellas)	A8
Mencacci et al. (169)	2013	C-QUALITY: Cost and Quality-of-Life Pharmacoeconomic Analysis of Antidepressants in Major Depressive Disorder in Italy	Italy	Escitalopram	Various (citalopram, sertraline, paroxetine, fluoxetine, fluvoxamine, duloxetine, or venlafaxine)	Decision tree model	12 months	Patients with a first diagnosis of MDD receiving an antidepressant for the first time	Pharmaceutical (Lundbeck SAS)	A9

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Nordstrom et al. (171)	2012	Cost-Effectiveness Evaluation in Sweden of Escitalopram Comparedwith Venlafaxine Extended-Release as First-Line Treatment in MajorDepressive Disorder	Sweden	Escitalopram	Generic venlafaxine extended-release (XR)	Decision tree	6 months	Adult patients (18-65 years) with moderate to severe MDD seeking treatment in a primary care setting	Pharmaceutical (Lundbeck SAS)	A10
Nuijten et al. (172)	2012	Cost-Effectiveness of Escitalopram in Major Depressive Disorder in the Dutch Health Care Setting	Netherlands	Escitalopram	Two comparators: venlafaxine XR; citalopram.	Decision tree	26 weeks	Major depressive disorder	Pharmaceutical (Lundbeck SAS)	A11
Ramsberg et al. (174)	2012	Effectiveness and Cost-Effectiveness of Antidepressants in Primary Care: A Multiple Treatment Comparison Meta-Analysis and Cost-Effectiveness Model	Sweden	Escitalopram	Various (citalopram, duloxetine, fluoxetine, fluvoxamine mirtazapine, paroxetine, reboxetine, sertraline and venlafaxine)	Decision tree	One year	MDD in primary care which is not yet treated	None	A12

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Rubio-Valera et al. (178)	2019	Cost-effectiveness of antidepressants versus active monitoring for mild-to-moderate major depressive disorder: a multisite non-randomized-controlled trial in primary care (INFAP study)	Barcelona (Spain)	Antidepressants (SSRIs)	Active monitoring (monitoring the patient over 10-12 weeks through a recommended 6-8 follow-up visits)	Within-trial analysis	12 months	Adult patients with a new episode of major depression.	Government	A13
Sobocki et al. (180)	2008	The cost-utility of maintenance treatment with venlafaxine in patients with recurrent major depressive disorder	Sweden	Maintenance treatment with venlafaxine for two years	Placebo	Markov simulation model	2 years	Recurrent major depressive disorder. At least 2 MDD episodes in past 5 years. Received venlafaxine XR for 6 months prior to randomisation, and responded to this.	Pharmaceutical (Wyeth)	A14
COGNITIVE BEHAVIOURAL THERAPY										

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Duarte et al. (181)	2017	Cost-effectiveness of computerized cognitive-behavioural therapy for the treatment of depression in primary care: findings from the Randomised Evaluation of the Effectiveness and Acceptability of Computerised Therapy (REEACT) trial	England	Computerized cognitive–behavioural therapy (cCBT); MoodGYM	Usual GP care alone	Within-trial analysis	24 months	Presenting with depression according to a self-report questionnaire [score of ⩾10 on the Patient Health Questionnaire (PHQ-9) depression severity instrument	Government	C1
Evans-Lacko et al. (185)	2016	Evaluating the economic impactof screening and treatment for depressionin the workplace	Germany	Psychotherapy (CBT)	Pharmacotherapy (citalopram)	Decision tree	27 months	The target population is employed adults with mild (F32.0, F33.0), moderate (F32.1, F33.1) or severe major depressive disorder (F32.2/F32.3, F33.2/F33.3) based on ICD-10 diagnoses	Expert Platform on Mental Health - focus on depression	C2

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Geraedts et al. (186)	2015	Economic Evaluation of a Web-Based Guided Self-Help Intervention for Employees With Depressive Symptoms	Netherlands	Happy@Work internet intervention partly comprising of problem-solving treatment cognitive therapy. 6 weekly lessons and optional 1-week extra time	CAU group only received an e-mail with the randomization outcome and were advised to consult their (occupational) physician or a psychologist if they wanted treatment for their depressive symptoms.	Within-trial analysis	12 months	Employees with elevated depressive symptoms (ie, scoring 16 or higher on the Center for Epidemiologic Studies Depression Scale [CES-D]), average CES-D score of sample was between 25.7 and 26.1 .	Government	C3
Gerhards et al. (187)	2010	Economic evaluation of online computerised cognitive–behavioural therapy without support for depression in primary care: randomised trial	Netherlands	Unsupported, online CCBT (i.e. Colour Your Life)	Treatment as usual (TAU) by a GP	Within-trial analysis	12 months	At least mild to moderate depressive complaints (diagnosed by BDI-II score >=16) for at least 3 months	Government	C4

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Health Quality Ontario (188)	2019	Internet-Delivered Cognitive Behavioural Therapy for Major Depression and Anxiety Disorders: A Health Technology Assessment	Canada	Guided internet-delivered CBT (iCBT)	Usual care	Decision-tree model	12 months	Adults with mild to moderate major depression	Government	C5
Hollinghurst et al. (189)	2010	Cost-effectiveness of therapist-delivered online cognitive–behavioural therapy for depression: randomised controlled trial	United Kingdom	Online CBT up to 10 sessions of 55 minutes each	Usual care	Within-trial analysis	8 months	Patients aged 18-75 with a new ICD-10 diagnosis of depression	Non-for-profit (BUPA foundation)	C6

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Holst et al. (160)	2018	Cost-effectiveness analysis of internet-mediated cognitive behavioural therapy for depression in the primary care setting: results based on a controlled trial Authors	Sweden	Internet-mediated CBT (ICBT), consisting of 7 modules accessible for 12 weeks	Treatment as usual (treatment typically provided at primary care center)	Within-trial	12 months	All patients aged ≥18 years with a probable diagnosis of mild to moderate depression. Mild and moderate depression was based on Diagnostic and Statistical Manual of Mental Disorders IV criteria and the Montgomery Åsberg Depression Rating Scale—self rating version (MADRS-S). Patients had to have a MADRS-S score <35	Government	C7

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Kaltenthaler et al. (161)	2006	Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation	United Kingdom	Computerised CBT (CCBT) for 2 months (Beating the blues (BtB) consisting of eight 1-hour interactive computer sessions)	Treatment as usual (TAU) for 2 months	decision tree	18 months	patients with depression in a primary care setting	Government	C8
Koeser et al.(164)	2015	Modelling the cost-effectiveness of pharmacotherapy compared with cognitive-behavioural therapy and combination therapy for the treatment of moderate to severe depression in the UK	United Kingdom	CBT consisting of 16 sessions and two additional `booster` sessions	Pharmacotherapy (assumed to be 20 mg daily dose of citalopram over 15 months)	Decision tree	27 months	Adults with moderate or severe MDD	None	C9
Kraepelien et al. (165)	2018	Cost-effectiveness of internet-based cognitive–behavioural therapy and physical exercise for depression	Sweden	Internet-based CBT (ICBT) for 12 weeks	Treatment as usual (TAU) in which participants were allowed to use primary care	Within-trial analysis	3 months	Aged 18–67 years; and present with ≥10 on the Patient Health Questionnaire (PHQ-9)	Public sector (government primarily)	C10

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Kuyken et al. (166)	2015	Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial	United Kingdom	Mindfulness-based cognitive therapy (MBCT) in which participants learn mindfulness practices and cognitive-behavioural skills. The programme consists of eight 2·25 h group sessions, normally over consecutive weeks, and four refresher sessions	Patients in a maintenance antidepressant group, who received support from their GPs to maintain a therapeutic level of antidepressant medication for the 2-year follow-up period	Within-trial analysis	2 years	Recurrent MDD, currently on anti-depressants, and had 3 or more previous MDD episodes	Government	C11

Phillips et al. (173)	2014	Randomized controlled trial of computerized cognitive behavioural therapy for depressive symptoms: effectiveness and costs of a workplace intervention	United Kingdom	Interactive computerized CBT (cCBT) programme (MoodGYM); five, 1 h-long modules, usually taken weekly	Website links sent weekly to participants in the control arm	Within-trial analysis	6 weeks	Employees aged over 18 years and met the following criterion: on the Patient Health Questionnaire -9 (PHQ-9), the employee scored 2 or more on five of the nine items, including 2 or more on item 1 (little interest in doing things) or item 2 (feeling hopeless). To be eligible the employee also had to confirm that at least one of the items identified as a problem for them made it difficult to work, take care of things at home, or get along with other people.	Non-for-profit	C12

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Richards et al. (175)	2016	Cost and Outcome of Behavioural Activation versus Cognitive Behavioural Therapy for Depression (COBRA): a randomised, controlled, non-inferiority trial	United Kingdom	Behavioral activation (BA) (could also be considered comparator)	Maximum of 20 face-to-face sessions of CBT (could also be considered intervention)	Within-trial analysis	18 months	MDD adults	Government	C13
Romero-Sanchiz et al. (176)	2017	Economic evaluation of a guided and unguided internet-based CBT intervention for major depression: Results from a multi-center, three-armed randomized controlled trial conducted in primary care	Spain	Internet-delivered, CBT-based self-help program called "Smiling is fun"; low-intensity and therapist guided. CBT consisted of 10 modules.	Usual care (treatment as usual)	Within-trial	12 months	18-65 years, BDI-II score of 14-28 (indicating mild/moderate symptoms); symptoms lasting longer than 2 weeks	Government	C14

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Ross et al. (177)	2019	The Cost-Effectiveness of Cognitive Behavioral Therapy Versus Second-Generation Antidepressants for Initial Treatment of Major Depressive Disorder in the United States; A Decision Analytic Model	USA	CBT	second-generation antidepressant (SGA)	Deterministic, state-transition model	1 to 5 years	Adults with newly diagnosed major depressive disorder in the United States.	Government	C15
Simon et al. (179)	2006	Treatment options in moderate and severe depression: decision analysis supporting a clinical guideline	United Kingdom	Combination therapy (pharmacotherapy plus 3 months of CBT (16 sessions)	Pharmacotherapy (3 months of daily 40 mg fluoxetine)	Decision model	15 months	Moderate and severe depression in secondary care.	Government	C16

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Solomon et al. (182)	2015	e-CBT (myCompass), Antidepressant Medication, and Face-to-Face Psychological Treatment for Depression in Australia: A Cost-Effectiveness Comparison	Australia	CBT-based public health intervention combining mobile phone and Web technology, myCompass	TAU, in this case drug treatment with a prescribed antidepressant for an acute depressive episode, plus a 21-week maintenance phase of drug therapy after remission of symptoms	Decision tree	28 weeks	Mild to moderate depression	Government	C17

Authors	Year	Title	Country	Intervention	Comparator	Modelling approach	Time horizon	Population	Funder	Analysis code
Stant et al. (183)	2009	Cost-Effectiveness of a Psychoeducational Relapse Prevention Program for Depression in Primary Care	Netherlands	Brief Cognitive Behavioral Therapy Followed by Psychoeducational Prevention Program (PEP) (CBT-Enhanced PEP). Brief Cognitive Behavioral Therapy component comprised of patients attending 10 to 12 individual 45 minute sessions of cognitive behavioral therapy.	Usual care	Within-trial analysis	36 months	Patients diagnosed with a current, or only very recently in partial remission, DSM-IV major depression	Government	C18
Warmerdam et al. (184)	2010	Cost-Utility and Cost-Effectiveness of Internet-Based Treatment for Adults With Depressive Symptoms: Randomized Trial	Netherlands	Cognitive behavioral therapy, which consisted of 8 lessons, 1 lesson a week followed by a booster session after 12 weeks.	Waiting list control group with unrestricted access to usual care	Within-trial analysis	12 weeks	Center of Epidemiologic Studies Depression scale (CES-D) >= 16 (mean score of participants at baseline = 31.7)	University	C19

KEY: CBT= cognitive behavioural therapy; MDD= major depressive disorder; SSRI= selective serotonin reuptake inhibitor; TAU= treatment as usual

11.3.4 Results of cost-effectiveness analyses of antidepressants or cognitive behavioural therapy for depression

Analysis code	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
ANTIDEPRESSANTS													
A1	Annemans et al. (158)	2014	1,129	1,113 for venlafaxine; ranged from 1,134 to 1,257 for all other comparators	0.701	0.698 for venlafaxine; ranged from 0.685 to 0.697 for all other comparators	6,352 euros when comparator was venlafaxine; escitalopram was dominant for all other comparators	Euros	Not required	Not required	€30,000	At a threshold of €30,000 per QALY, the PSA showed that the probability of escitalopram being identified as the optimal strategy ranged from 61% (vs. venlafaxine) to 100% (vs. fluoxetine).	Favourable

Analysis code	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
A2	Armstrong et al. (159)	2007	$919	$1351	0.40296	0.39268	Escitalopram is dominant (effectively)	United States Dollars (assumed)	Not stated/required	Not stated/required	Not stated	In a Monte Carlo simulation of 10,000 patients, it was indicated there was an 88.5% probability that escitalopram was the dominant therapy, suggesting both lower costs and greater QALYs	Favourable

Analysis	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
A3	Benedict et al. (170)	2010	£543	Ranged from £486 to £585, depending on comparator	0.665	Ranged from 0.656 to 0.663, depending on comparator	Across all comparators, duloxetine was either dominant, or ICER was less than £6,304.	Great British Pounds	Not stated/required	Not stated/required	£20,000	In CEAC, duloxetine was more cost effective than venlafaxine XR or mirtazapine, for any WTP threshold	Favourable
A4	Hollingworth et al. (190)	2019	£154.01	£176.50	0.182	0.177	Sertraline dominant (effectively)	Great British Pounds	Not required	Not required	£20,000	Sertraline had a high probability (> 95%) of being cost-effective if the health system was willing to pay at least £20,000 per QALY gained.	Favourable

Analysis	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
A5	Kendrick et al. (163)	2009	759	629	0.3305	0.3176	£14,854	Great British Pounds	Not stated/required	Not stated/required	£20,000–£30,000	The cost-effectiveness acceptability curve for utility suggested that adding an SSRI to supportive care was cost-effective at the values of £20,000–£30,000 per quality-adjusted life-year.	Favourable
A6	Kendrick et al. (162)	2006	817	712	0.59	0.55	2'692	Great British Pounds	Not required	Not required	£20,000 to £30,000	Cost-effectiveness acceptability curves suggested SSRIs were most cost-effective.	Favourable

Analysis code	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
A7	Lenox-Smith et al. (167)	2009	1533	Depending on comparator, ranging from 1,525 to 1576	0.0981	Depending on comparator, ranging from 0.0840 to 0.0971	Depending on comparator, ICER was 7,215 or better	Great British Pounds	Not stated/required	Not stated/required	Not stated	Sensitivity analysis showed that even if fluoxetine or amitriptyline were given away free, a scenario starting with venlafaxine would still be the least costly treatment over a 6-month period.	Favourable

Analysis code	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
A8	Maniadakis et al. (168)	2013	5'434	Depending on comparator, ranging from 5,386 to 5,650	1.461	Depending on comparator, ranging from 1.427 to 1.447	Depending on comparator, ICER was 3,303 or better.	Euros	3.50%	3.50%	40,000 to 60,000	In the probabilistic sensitivity analysis agomelatine was dominant in 44.5%, 89.6%, 70.6% and 84.6% of simulated samples against branded venlafaxine, escitalopram, fluoxetine and sertraline, respectively.	Favourable
A9	Mencacci et al. (169)	2013	1'562	Depending on comparator, ranging from 1579 to 1868	0.732	Depending on comparator, ranging from 0.697 to 0.729	Dominant	Euros	Not required	Not required	25'000	Sensitivity analyses support the robustness of the model.	Favourable

Analysis code	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
A 10	Nordstrom et al. (171)	2012	7377	7547	0.3151	0.3065	Dominant	Euros	Not required	Not required	22,080; and 28,800	Sensitivity analyses found that the decision analytic model was most sensitive to the escitalopram remission probability.	Favourable
A 11	Nuijten et al. (172)	2012	17'321	Venlafaxine was 17,584; Citalopram was 19,313	0.3237	Venlafaxine was 0.3175; Citalopram was 0.3070	Dominant	Euros	Not required	Not required	Suggested between 10,000 to 80,000 per QALY gained	The model was sensitive to the efficacy of escitalopram (with efficacy reduced by 5%, escitalopram was dominant over citalopram but not venlafaxine XR).	Favourable

Analysis code	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
A 12	Ramsberg et al (174)	2012	5'088	Ranging from 5,074 to 5,267, depending on comparator	0.6978	Ranging from 0.6847 to 0.6942, depending on comparator	Dominant for all comparators, except for venlafaxine for which ICER of 3723 was produced	Euros	Not required	Not required	Not stated	Probability that escitalopram is cost-effective is approximately 65 to 70% at willingness-to-pay thresholds ranging from 0 euros to 100,000 euros per QALY gained	Favourable

Analysis code	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
A 13	Rubio-Valera et al. (178)	2019	Not stated	Not stated	Not stated	Not stated	6’142	Euros	Not stated/required	Not stated/required	25’000	At 6 months, for a willingness to pay (WTP) of 25,000 €/QALY, antidepressants had a probability of 0.89 (healthcare perspective) and 0.81 (government perspective) of being more cost-effective than AM. At 12 months, this probability was 0.86 (healthcare perspective) and 0.73 (government perspective)	Favourable

Analysis code	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
A 14	Sobocki et al. (180)	2008	Not reported	Not reported	Not reported	Not reported	$18,548	United States Dollars	3%	3%	Unable to define for Sweden	In a probabilistic sensitivity analysis, it was found that maintenance treatment with venlafaxine is cost-effective with 90% probability at a willingness to pay per QALY of $67,000 or less.	Favourable
COGNITIVE BEHAVIOURAL THERAPY													

Analysis	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
C1	Duarte et al. (181)	2017	1098	1020	1.356	1.388	Dominated	Great British Pounds	3.50%	3.50%	£20,000	At a £20 000 per QALY threshold, usual GP care alone had the highest probability of being cost-effective (0.55) followed by MoodGYM (0.42) and Beating the Blues (0.04).	Unfavourable

Analysis code	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
C2	Evans-Lacko et al. (185)	2016	31’397	30’508	1.3	1.26	22’225	Euros	3.40%	3.40%	€ 50’000	Sensitivity analysis which estimated results using varying time frames for the length of intervention found the incremental cost-effectiveness ratio (ICER) did not change significantly	Favourable

Analysis	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
C3	Geraedts et al. (186)	2015	22,974	23,482	0.79	0.78	Intervention is (effectively) dominant	Euros	Not required	Not required	Not stated	At a willingness to pay of 0 (€/unit of effect), the intervention's probabilities of cost-effectiveness were 0.62 (societal perspective) and 0.55 (employer's perspective).	Neutral
C4	Gerhards et al. (187)	2010	9092	9765	0.71	0.72	Not stated	Euros	Not stated/required	Not stated/required	Range from 0 to 80,000 euros	In PSA, computerised CBT tends to be the most optimal treatment compared with both TAU and CCBT plus TAU	Favourable

Analysis	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
C5	Health Quality Ontario (188)	2019	1,666.26	409.4	0.826	0.787	31,575	Canadian dollars	Not required	Not required	100,000	The probability of cost-effectiveness of guided iCBT for major depression was 67% at willingness-to-pay of $100,000 per QALY gained	Favourable
C6	Hollinghurst et al. (189)	2010	764	295	0.522	0.495	17,173	Great British Pounds	Not required	Not required	20,000	In PSA, there was a 94% chance that the CBT intervention is cost-effective at £20,000 per QALY gained	Favourable

Analysis code	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
C7	Holst et al. (160)	2018	47,679	50,343	0.74	0.79	5371 per QALY lost	Swedish kronor	Not required	Not required	Not stated	The uncertainty of the study estimates when assessed by bootstrapping indicated that no firm conclusion could be drawn as to whether ICBT treatment compared with TaU was the most cost-effective use of resources.	Neutral
C8	Kaltenthaler et al. (161)	2006	584	437	1.1	1.02	1801	Great British Pounds	3.50%	3.50%	£30,000 (implied)	The probability of accepting BtB over TAU at £30,000 is 86.8%	Uncertain

Analysis code	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
C9	Koeser et al.(164)	2015	4,418	3,645	1.274	1.236	20,039	Great British Pounds	3.50%	3.50%	£25,000	In PSA, CBT has 43% probability of being most cost-effective treatment assuming willingness-to-pay of £25,000 per QALY gained	Neutral/uncertain
C10	Kraepelien et al. (165)	2018	810.77	513.25	Not stated	Not stated	8,817	Euros	Not required	Not required	€21 536	At the established willingness-to-pay threshold of €21 536 (£20 000) per QALY, the probability of ICBT being cost-effective is 90%, compared with TAU	Favourable

Analysis code	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
C 11	Kuyken et al. (166)	2015	2484	2360	1.49	1.53	MBCT dominated	Great British Pounds	3.50%	3.50%	Not stated	In cost-effectiveness acceptability curve, the probability of MBCT-TS being more cost effective than maintenance antidepressants does not rise above 52%.	Unfavourable
C 12	Phillips et al. (173)	2014	125	149	0.082	0.083	Not calculated	Great British Pounds	Not stated/required	Not stated/required	Not stated	Not explicitly performed	Unfavourable
C 13	Richards et al. (175)	2016	For BA, £2596	For CBT, £3250	For BA, 0.985	For CBT, 0.935	BA is dominant	Great British Pounds	3.50%	3.50%	£20,000 to £30,000 per QALY gained	BA has approximately 80% probability of being cost effective assuming threshold of £20,000 to £30,000 per QALY gained	For CBT, unfavourable

Analysis code	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
C 14	Romero-Sanchiz et al. (176)	2017	1757	1716	0.788	0.705	496.72	Euros	Not required	Not required	£20,000 or 21,000 - 25,000 euros	In majority of PSA simulations, CBT interventions exhibited more utility than the control intervention	Favourable

Analysis	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
C 15	Ross et al. (177)	2019	1 year, 9,000; 5 years, 55,400	1 year, 8,100; 5 years, 57,200	1 year, 0.715; 5 years, 3.293	1 year, 0.708; 5 years, 3.238	1 year, 119,000; 5 years, dominant	United States Dollars	3%	3%	100,000	In probabilistic sensitivity analyses, SGA had a 64% to 77% likelihood of having an incremental cost-effectiveness ratio of $100 000 or less per QALY at 1 year; CBT had a 73% to 77% likelihood at 5 years.	Neutral

Analysis	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
C 16	Simon et al. (179)	2006	1297	660	0.89 (moderate), 0.63 (severe)	0.84 (moderate), 0.52 (severe)	ICER 14 540 for moderate depression; 5777 for severe depression	Great British Pounds	Not required	Not required	£30,000	There is 97% probability that combination therapy is more cost-effective than antidepressant therapy alone for severe depression and 88% probability for moderate depression, assuming £30 000 threshold	Uncertain (for moderate depression)

Analysis	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
C 17	Solomon et al. (182)	2015	334.96	524.91	0.26	0.24	Dominant (effectively)	Australian Dollars	Not required	Not required	50'000	The probability that myCompass is cost-effective, compared with TAU, or conventional CBT, at a WTP threshold of AUD 50,000 is 75.5%.	Favourable
C 18	Stant et al. (183)	2009	9254	8200	2.27	2.31	Dominated	Euros	0% in base-case	0% in base-case	Not stated	No PSA for the cost-effectiveness analysis component	Unfavourable

Analysis code	Authors	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention QALYs	Mean comparator QALYs	ICER	Currency	Discount rate costs	Discount rate QALYs	Threshold	Sensitivity analysis	Intervention cost-effectiveness
C19	Warmerdam et al. (184)	2010	2814	2558	0.16	0.15	22,609	Euros	Not stated/required	Not stated/required	30,000	Cost-utility analysis showed that cognitive behavioral therapy and problem-solving therapy had a 52% and 61% probability respectively of being more acceptable than waiting when the willingness to pay is € 30,000 for one quality-adjusted life-year	Favourable

KEY: CBT= cognitive behavioural therapy; GP= general practitioner; ICER= incremental cost effectiveness ratios; MBCT= Mindfulness-based cognitive therapy; PSA= probabilistic sensitivity analysis; QALYs= quality adjusted life years; SGA= second generation antidepressants

11.3.5 Reporting of the CHEERS checklist for the cost utility analyses (CUAs) of antidepressants or cognitive behavioural therapy for depression

Authors	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q23	Q24
ANTIDEPRESSANT CUAS																									
Annemans et al. (158)	2014	1	1	1	0.5	1	1	1	0.5	1	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	0.5
Armstrong et al. (159)	2007	1	1	1	0.5	1	0.5	1	1	0.5	1	0.5	1	0.5	0	0.5	1	0.5	1	1	1	1	0.5	1	0
Benedict et al. (170)	2010	1	1	1	1	1	1	1	1	0.5	1	0.5	1	1	0	0.5	1	1	1	1	1	1	1	1	1
Hollingworth et al. (190)	2019	1	1	1	1	1	1	0.5	1	1	0.5	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1
Kendrick et al. (163)	2009	1	1	1	1	0.5	0.5	1	0.5	1	1	1	1	1	0.5	0.5	0.5	1	1	1	1	1	0.5	1	1
Kendrick et al. (162)	2006	1	1	1	1	0.5	1	1	0.5	1	0.5	0.5	1	1	1	0.5	1	1	1	1	1	1	1	1	1
Lenox-Smith et al. (167)	2009	1	1	0.5	0.5	0.5	0	1	0.5	0.5	0.5	1	1	0.5	1	1	0	1	0.5	1	0.5	1	0.5	1	1
Maniadakis et al. (168)	2013	1	1	1	0.5	1	1	1	0.5	1	1	0.5	0.5	1	1	0.5	1	1	1	1	1	1	0.5	1	1
Mencacci et al. (169)	2013	1	1	1	0.5	1	1	0.5	0.5	1	0.5	0.5	0.5	1	0.5	0.5	1	1	0.5	1	0.5	1	1	1	1
Nordstrom et al. (171)	2012	1	0.5	1	1	1	1	1	1	1	0.5	0.5	1	1	1	1	1	1	1	1	1	1	1	1	0.5
Nuijten et al. (172)	2012	0.5	0.5	1	0.5	1	0.5	1	1	1	0.5	0.5	0.5	1	0.5	0.5	1	0.5	1	1	1	1	1	0.5	1
Ramsberg et al. (174)	2012	1	0.5	1	0.5	0.5	1	1	1	1	0.5	1	0.5	0.5	0.5	0.5	1	1	1	1	1	1	0.5	1	1
Rubio-Valera et al. (178)	2019	1	1	1	1	1	1	1	0.5	0	0.5	0.5	1	1	1	0.5	0.5	1	0.5	0	1	1	1	1	1
Sobocki et al. (180)	2008	0.5	1	1	1	0.5	1	1	1	1	1	0.5	1	0.5	1	1	1	1	1	0.5	1	1	1	1	1
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Duarte et al. (181)	2017	0.5	1	1	1	1	1	1	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Evans-Lacko et al. (185)	2016	0.5	0.5	1	1	1	0.5	0.5	1	1	1	1	1	1	1	0.5	1	0.5	0.5	1	0.5	1	1	1	1
Geraedts et al. (186)	2015	1	1	1	1	1	1	0.5	0.5	1	1	0.5	1	1	1	0.5	1	1	1	1	1	1	1	1	1

Authors	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q23	Q24
Gerhards et al. (187)	2010	1	0.5	1	1	1	1	1	0.5	1	0.5	1	1	1	1	0.5	1	1	0.5	0.5	1	1	1	1	1
Health Quality Ontario (188)	2019	0.5	1	1	1	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.5	0.5	0.5
Hollinghurst et al. (189)	2010	1	1	1	1	0.5	1	1	0.5	1	1	0.5	1	1	1	0.5	1	1	1	1	1	1	1	0	1
Holst et al. (160)	2018	1	1	1	1	1	1	1	0.5	1	0.5	0.5	1	1	1	0	1	1	1	1	1	1	1	1	1
Kaltenthaler et al. (161)	2006	0.5	1	1	0.5	1	1	1	1	1	0.5	1	1	1	0	0.5	1	0.5	1	1	1	1	1	1	1
Koeser et al. (164)	2015	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1	0	1
Kraepelien et al. (165)	2018	0.5	1	1	1	1	1	0.5	0.5	1	0.5	0.5	1	1	1	0.5	1	1	0.5	0.5	1	1	1	1	1
Kuyken et al. (166)	2015	1	0	1	1	1	1	1	0.5	1	0.5	1	1	1	1	1	0.5	0	1	1	0.5	1	1	1	1
Phillips et al. (173)	2014	1	0	0.5	1	1	0	1	0.5	0	0.5	1	1	1	0	1	1	1	1	1	0	0	0	1	0
Richards et al. (175)	2016	1	0	1	1	1	1	1	0.5	1	1	1	1	1	0.5	1	1	1	1	1	1	1	1	1	1
Romero-Sanchiz et al. (176)	2017	1	0.5	1	1	1	1	1	0.5	1	1	1	1	1	1	0.5	1	1	1	1	1	1	1	1	1
Ross et al. (177)	2019	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	0.5	1	1	1	1	1	1	1	1	1
Simon et al. (179)	2006	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Solomon et al. (182)	2015	1	0.5	1	0.5	1	1	1	0.5	1	1	0.5	0.5	1	1	1	1	1	1	1	0.5	1	1	1	1
Stant et al. (183)	2009	1	1	1	1	1	1	1	1	0.5	1	0.5	1	1	1	0.5	1	1	1	1	1	1	1	1	0
Warmerdam et al. (184)	2010	1	1	1	1	0.5	1	1	0.5	0	1	0.5	1	1	1	0.5	1	1	1	1	1	1	1	1	1

KEY: CHEERS= Consolidated Health Economic Evaluation Reporting Standards; Q= question.

* For CHEERS checklist item, score of 0 indicates the item was not completed by the study authors, score of 0.5 indicates partial completion, and score of 1 indicates full completion.

11.3.6 Methods for estimating costs in the cost utility analyses of antidepressants or cognitive behavioural therapy for depression

Study	Year	Cost year	Perspective	Outpatient/community	Inpatient	Medication	CBT intervention	Out of pocket	Productivity (patient/carer)	Measurement of resource use
ANTIDEPRESSANTS										
Annemans et al. (158)(158)	2014	2011	National Institute for Health and Disability Insurance	✓	Specialist care	✓				Number of health care visits were based on a published Belgian study (Demyttenaere et al).
Armstrong et al. (159)	2007	Not stated	Managed care organisation	✓		✓				Resource use in terms of discontinuation and adverse event probability were taken from the published literature
Benedict et al. (170)	2010	2007	Health service	✓	✓	✓				Resource use (for outpatient visits and hospitalisations) was based on the answers of a Scottish panel consisting of 3 clinicians.

Study	Year	Cost year	Perspective	Outpatient/community	Inpatient	Medication	CBT intervention	Out of pocket	Productivity (patient/carer)	Measurement of resource use
Hollingworth et al. (190)	2019	2017/2018	Health and social service	✓	✓	✓				Health service resource use for items including medication, outpatient visits, and hospital admission, were collected either via electronic GP records or via a patient-reported questionnaire which was administered over the course of the trial.
Kendrick et al. (163)	2009	2006-2007	Health service	✓	✓	✓				Resource use data was collected via an adapted version of the Client Services Receipt Inventory (CSRI), and also obtained from general practice computerised medical records. These sources were used to estimate resource use for outpatient visits, inpatient stays, and medication use.

Study	Year	Cost year	Perspective	Outpatient/community	Inpatient	Medication	CBT intervention	Out of pocket	Productivity (patient/carer)	Measurement of resource use
Kendrick et al. (162)	2006	2001/2002	Health service	✓	✓	✓				Resource use for health and social services and medications used during the trial, was recorded and obtained either via patient's self-reports or on practice records.
Lenox-Smith et al. (167)	2009	2006	Health service (inferred)	✓	Rehabilitation	✓				Resource use based on a previously published analysis UK model from Lenox-Smith et al. (2004)
Maniadakis et al. (168)	2013	2012	Societal	✓	✓	✓			✓	Resource use during a depressive episode or remission was based on expert opinion and reflect local practice.
Mencacci et al. (169)	2013	2013	Health service	✓	✓	✓				Resource use for GP and specialist visits was obtained from an expert panel to reflect Italian normal clinical practice.

Study	Year	Cost year	Perspective	Outpatient/community	Inpatient	Medication	CBT intervention	Out of pocket	Productivity (patient/carer)	Measurement of resource use
Nordstrom et al. (171)	2012	2009	Societal	✓	✓	✓			✓	Resource use for outpatient visits and inpatient stays associated with different health states, was estimated from a Swedish study (HEADIS).
Nuijten et al. (172)	2012	2010	Societal	✓	✓	✓			✓	A Dutch Delphi Panel was used to estimate resource utilisation for consultations and hospitalisations for depression for each treatment strategy, and also used to estimate treatment discontinuation rates.
Ramsberg et al. (174)	2012	2009	Health care	✓	Specialist care	✓				Costs of specialist care were based on resource use from a previous study which utilised a Swedish expert panel. Costs of primary care were based on a previous Swedish study.

Study	Year	Cost year	Perspective	Outpatient/community	Inpatient	Medication	CBT intervention	Out of pocket	Productivity (patient/carer)	Measurement of resource use
Rubio-Valera et al. (178)	2019	2015	Health care	✓	✓	✓				Resource use was recorded using the Client Service Receipt Inventory, for different items including medical tests, hospital stays, outpatient visits. Resource use of psychotropic medications was collected from medical records.
Sobocki et al. (180)	2008	2005	Societal	✓	Unclear	✓			✓	Costs associated with the different health states of the Markov model, appeared to be derived from resource use data obtained from the Swedish HEADIS study on primary care visits, hospital visits and visits to other health professionals (e.g. psychologists and counsellors).
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Duarte et al. (181)	2017	2011 to 2012	Health service	✓	✓	✓	✓			Healthcare resource use (inpatient stays, outpatient consultations, medication) was obtained via data collection.

Study	Year	Cost year	Perspective	Outpatient/community	Inpatient	Medication	CBT intervention	Out of pocket	Productivity (patient/carer)	Measurement of resource use
Evans-Lacko et al. (185)	2016	2013	Unclear	✓	✓	✓	Unclear		✓	Treatment visits related to depression severity were based on a combination of assumptions and German guidelines (German Society for Psychiatry, Psychotherapy and Neurology (DGPPN) 2015). Other health service resource use (outpatient consultations and inpatient stays) according to depression severity was based on a German study (Kleine-Budde et al. (2013)).

Study	Year	Cost year	Perspective	Outpatient/community	Inpatient	Medication	CBT intervention	Out of pocket	Productivity (patient/carer)	Measurement of resource use
Geraedts et al. (186)	2015	2012	Employer	Only occupational health			✓		✓	CBT intervention resource use was based on average time investment of the coaches. Trimbos and iMTA Questionnaire on Costs Associated with Psychiatric Illness (TIC-P) was used to estimate health service resource use. Questions were used to record number of visits to occupational health.
Gerhards et al. (187)	2010	2007	Societal	✓	Hospital care	✓	✓	✓	✓	Health care resource use was based on a monthly questionnaire for medical and psychological services. Login data was used to estimate usage of the computerised CBT.
Health Quality Ontario (188)	2019	2018	Local government (Ontario)	✓		✓	✓			Usage of guided iCBT was based on expert consultation and literature findings. Usage of usual care was based on a mix of assumptions and literature findings.

Study	Year	Cost year	Perspective	Outpatient/community	Inpatient	Medication	CBT intervention	Out of pocket	Productivity (patient/carer)	Measurement of resource use
Hollinghurst et al. (189)	2010	2007	Health service	✓		✓	✓			Resource use was recorded by participants in a diary for outpatient visits, mental heath related secondary care and prescribed medication.
Holst et al. (160)	2018	2013	Societal	✓		✓	✓	✓	✓	Resource use for clinician visits as well as phone counselling appointments, were obtained from electronic patient records.
Kaltenthaler et al. (161)	2006	Not stated	Not stated	Implied	Implied	✓	✓		Unclear	Usage of computerised cognitive behavioural therapy (CCBT) was based on a mix of assumptions and literature findings. Health service costs for depression stratified by severity levels, were derived from a previous UK study which collected data on resource use (McCrone et al, 2004).

Study	Year	Cost year	Perspective	Outpatient/community	Inpatient	Medication	CBT intervention	Out of pocket	Productivity (patient/carer)	Measurement of resource use
Koeser et al.(164)	2015	2012	Health service	✓	Implied	✓	✓			Pharmacotherapy resource use (citalopram) consistent with the RCTs informing the model. Consultations resource use based on UK guidelines (National Institute of Health and Care Excellence). CBT resource use (16 sessions plus 2 booster sessions) based on an assumption. Other health care resource use by depression severity based on a previous study (Kukyen et al. (2008)).

Study	Year	Cost year	Perspective	Outpatient/community	Inpatient	Medication	CBT intervention	Out of pocket	Productivity (patient/carer)	Measurement of resource use
Kraepelien et al. (165)	2018	2012	Health care provider	✓			✓			The Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness, was used to collect data on healthcare resource use (e.g. seeing a general practitioner or social worker). For the CBT intervention, it was unclear from the study how the time spent treating patients was recorded.
Kuyken et al. (166)	2015	2011/2012	Health and social service	✓	✓	✓	✓			GP records, Adult Service Use Schedule (AD-SUS), and trial therapist records were used to estimate resource use (e.g. for therapist time, drugs, heath services).
Phillips et al. (173)	2014	Not stated	Societal (implied)	✓	✓	✓	Unclear		✓	Resource use used for the cost-effectiveness analysis was collected using Client Service Receipt Inventory (CSRI).

Study	Year	Cost year	Perspective	Outpatient/community	Inpatient	Medication	CBT intervention	Out of pocket	Productivity (patient/carer)	Measurement of resource use
Richards et al. (175)	2016	2013 to 2014	Health and social service	✓	✓	✓	✓			CBT resource use was collected from clinical records, and additional resource use information obtained from therapists and trainers. The Adult Service Use Schedule was used to measure other health and social care services used, including psychotropic medications.
Romero-Sanchiz et al. (176)	2017	2014	Societal	✓	✓	✓	No, as no further costs involved		✓	Resource use for health services was based on the Spanish version of the Client Service Receipt Inventory (CSRI).

Study	Year	Cost year	Perspective	Outpatient/community	Inpatient	Medication	CBT intervention	Out of pocket	Productivity (patient/carer)	Measurement of resource use
Ross et al. (177)	2019	2014	Health care	✓	Implied	✓	✓			Comparator (antidepressants) cost resource use were based on national guidelines and published literature. National guidelines and trial protocols were used to estimate number of CBT sessions and physician visits. Other health care costs were based on insurance claims data.
Simon et al. (179)	2006	2002/2003	Health service	✓	✓	✓	✓			Resource use relating to CBT sessions, outpatient visits, and specialist visits, were obtained from a range of published studies. Resource use relating to medication use was based primarily on published antidepressant therapy protocol.

Study	Year	Cost year	Perspective	Outpatient/community	Inpatient	Medication	CBT intervention	Out of pocket	Productivity (patient/carer)	Measurement of resource use
Solomon et al. (182)	2015	2013/2014	Health provider	✓		✓	✓			Resource use were obtained from the literature and administrative data. Number of CBT sessions attended was based on an administrative dataset. Rate of psychiatric consultations was based on a published study.
Stant et al. (183)	2009	2003	Societal	✓	✓	✓	✓	✓	✓	Resource usage related to CBT sessions (e.g. staff time), was registered during the trial via a bespoke questionnaire.
Warmerdam et al. (184)	2010	2007	Societal	✓		✓	✓	✓	✓	Participants' health service resource use was recorded using the Trimbos and Institute of Medical Technology Assessment Cost Questionnaire for Psychiatry.

KEY: CBT= cognitive behavioural therapy; GP= general practitioner; RCT= randomized controlled trial. *✓ indicates cost item was included in the study; blank space indicates cost item was not included in the study.

11.3.7 Clinical and utility inputs used in the cost utility analyses of antidepressants or cognitive behavioural therapy for depression

Authors	Year	Description of main clinical inputs	Description of main utility inputs
ANTIDEPRESSANTS			
Annemans et al. (158)	2014	Rates of remission: estimated from meta-analysis conducted by the tandvards-och lakemedelsformansverket (TLV) in Sweden. Rate of remission for escitalopram: 47.56% Rate of remission for the seven comparators: ranged from 40.21% (fluoxetine) to 45.68% (venlafaxine) Rates of relapse: 14.2% for all treatments	Obtained from Sobocki et al. (2006), which was a naturalistic longitudinal observational study in Sweden (n=447) The study used the EQ-5D to estimate the following utility estimates, which were used for the model: 0.81 (achieved remission); 0.57 (not achieved remission); 0.69 (mid-point estimate used for during assessment period)
Armstrong et al. (159)	2007	Probability of clinical response based on two clinical trials, by Burke et al. (2002) and Ventura et al. (2007) respectively. The health states obtained at the end of the clinical studies were assumed to persist for 6 months. Efficacy in terms of depression response was assumed to be the same in both arms for the 6 months' duration of the model. Based on Burke et al. (2002), probability of clinical response estimated at 0.593 for escitalopram 20 mg. Based on Ventura et al. (2007), probability of clinical response estimated at 0.750 for escitalopram 10 mg, 0.585 for sertraline 50 mg, 0.627 for sertraline 100 mg, 0.570 for sertraline 150 mg, and 0.589 for sertraline 200 mg.	QALY estimates based on Sullivan et al. (2004) Estimated QALYs: resolution of depression (0.424). Estimated QALY decrements: diarrhea (-0.011); ejaculation disorder (-0.01225), headache (-0.02875); insomnia (-0.03225); nausea (-0.0162)
Benedict et al. (170)	2010	For duloxentine, clinical probabilities obtained from various Eli Lilly trials For venlafaxine, clinical probabilities obtained from various Eli Lilly trials For SSRIs, clinical probabilities obtained primarily from meta-analysis by Thase et al. (2007) For mirtazapine, clinical probabilities obtained from meta-analysis by Stahl et al. (1997). Clinical probabilities at 8 weeks used for the model were similar between duloxetine and venlafaxine for response (approximately 60%) and remission (approximately 40%). In contrast to duloxetine and venlafaxine, clinical probabilities at 8 weeks used for the model were lower for SSRIs and mirtazapine for response (approximately 50%) and remission (approximately 30%).	Following utilities for the model were derived from EQ-5D scores of the almost 300 European patients in the trials (Eli Lilly), using the UK tariffs: 0.79 for remitters, 0.68 for responders, 0.55 for non-responders and 0.53 for those dropping out. Following utility was taken from Revicki and Wood (1998): utility of patients achieving remission and staying in remission without treatment (0.86).

Authors	Year	Description of main clinical inputs	Description of main utility inputs
Hollingworth et al. (190)	2019	Not applicable	EQ-5D-5L administered in the PANDA trial (n=655)
Kendrick et al. (163)	2009	Not applicable	SF-36 administered in the ISRCTN84854789 trial (n=220)
Kendrick et al. (162)	2006	Not applicable	EQ-5D administered in the AHEAD trial (n=327)
Lenox-Smith et al. (167)	2009	Based on a search of head-to-head trials of venlafaxine and fluoxetine which identified 13 trials which were then pooled, the following inputs were estimated: Venlafaxine remission probability (520/1294), response probability (783/1294), adverse drug reaction probability (210/1419). Fluoxetine remission probability (442/1339), response probability (721/1339), adverse drug reaction probability (133/1411). Probabilities for amitriptyline did not appear to the specified, and were based on a literature search which identified 1 study which provided the relevant data.	Utility was assumed to be 1.0 for non-depressed subject. Utility was assumed to be 0.59 for a subject with major depression.
Maniadakis et al. (168)	2013	For remission rates, taken from various clinical trials. For agomelatine, it was estimated as the pooled estimate from 3 clinical trials. It was then assumed that venlafaxine and escitalopram have the same remission rate as for agomelatine. For discontinuation rates, for agomelatine it was derived from several clinical trials. For the other comparators, it was derived from a single clinical trial for each of the comparators. For relapse rates, for agomelatine this was based on a Weibull survival function fitted to data from an agomelatine study. The relapse rate for venlafaxine was assumed to be equivalent to that for agomelatine. The relapse rate for the other comparators was based on estimates for the comparator versus placebo, from meta-analysis.	For health state healthy, 0.86; for health state remission 0.81; for health state depressive episode 0.57. These were taken from a study by Sobocki et al. (2006). Utility decrements for adverse drug reactions were primarily taken from a study by Sullivan et al. (2004).
Mencacci et al. (169)	2013	First line drug remission probabilities were adapted from a study by Wessling et al. and estimated as follows: 0.4756 for escitalopram; ranging from 0.2677 (fluvoxamine) to 0.4568 (venlafaxine XR) for the other comparators.	Utility inputs were quantified by an expert panel as follows: patient in remission (0.847); patient not in remission (0.49); patient in relapse (0.55); patient who attempts suicide (0.267).

Authors	Year	Description of main clinical inputs	Description of main utility inputs
Nordstrom et al. (171)	2012	Remission probabilities were sourced from a study by Montgomery et al. (2006), and were 62.1% for escitalopram and 57.9% for venlafaxine. Relapse probabilities were assumed to be the same irrespective of treatment (11.7%). This assumption was based on other studies which observed similar relapse probabilities between treatments.	Utility inputs were 0.800 for remission health state, 0480 for switch health state, and 0.520 for stop health state; taken from Swedish HEADIS data which used the EQ-5D, published by Marteu et al. (2009). Utility decrements for adverse events were derived from a study by Sullivan et al.
Nuijten et al. (172)	2012	Clinical probabilities at 8 weeks were obtained from a systematic review by Cipriani et al. (2009) for remission, and were estimated at 49.59% for escitalopram, 47.23% for venlafaxine, and 35.92% for citalopram. Clinical probabilities were obtained from a Delphi panel for relapse between 8 and 26 weeks, and were estimated at 16.25% for all three treatments. Adverse event probabilities at 8 weeks were primarily obtained from a systematic review by Cipriani et al. (2009).	Utility inputs The following utilities associated with health states taken from Nordstrom et al. (2009): baseline (0.47), remission (0.80), switch (0.52), discontinuation (0.48), relapse (0.47). Utility decrements for adverse events were taken from Sullivan et al. (2004)
Ramsberg et al. (174)	2012	Probabilities of remission were estimated through a systematic review and meta-analysis of RCTs with duration of 8-12 weeks and in the outpatient setting, which was undertaken by the study authors. These were estimated at 0.487 for escitalopram, and ranged from 0.399 (imipramine) to 0.458 (mirtazapine) for the other study comparators.	These were obtained from a Swedish observational study by Sobocki et al. (2006), and were estimated at 0.81 for remission health state, and the utility decrement for depression estimated at 0.24.
Rubio-Valera et al. (178)	2019	Not applicable	EQ-5D-3L administered in the INFAP trial (n=263)
Sobocki et al. (180)	2008	Risk of relapse was estimated using a Weibull survival function comparing venlafaxine to placebo, from a clinical trial by Keller et al. Increased risk of recurrence with previous episodes was estimated at 1.15, from a study by Kessing et al. Increased risk of death with depressive episode was estimated at 20.4, from a study by Harris et al.	These were sourced from the HEADIS study which used the EQ-5D measure. For episode health state: 0.57 For remission health state: 0.81 For death health state: 0.00 (by definition)
COGNITIVE BEHAVIOURAL THERAPY			
Duarte et al. (181)	2017	Not applicable	EQ-5D-3L administered in the REEACT trial (n=691)

Authors	Year	Description of main clinical inputs	Description of main utility inputs
Evans-Lacko et al. (185)	2016	Three potential clinical outcomes were modelled: full remission, partial response and non-response. Model parameters related to treatment outcomes were obtained from Koeser et al. (2015) Probability of completed treatment estimated at 0.8223 for CBT strategy and 0.706 for anti-depressant strategy. Probability of depression relapse estimated to be higher for anti-depressant strategy relative to CBT strategy.	Utilities were based on UK study from Koeser et al. (2008) which estimated mean EQ-5D utilities for remitters, responders and non-responders based on previously collected trial data.
Geraedts et al. (186)	2015	Not applicable	EQ-5D-3L administered in the NTR2993 trial (n=231)
Gerhards et al. (187)	2010	Not applicable	EQ-5D administered in the Colour Your Life CBT trial (n=303)
Health Quality Ontario (188)	2019	Probability of response (improvement) estimated at 0.73 for guided iCBT based on Arnberg et al. (2014), and estimated at 0.70 for medication (part of usual care) based on Koeser et al. (2015). Probability of recovery estimated at 0.48 for guided iCBT based on Andrews et al. (2018), and estimated at 0.62 for medication (part of usual care) based on Cipriani et al. (2014).	For normal health, `well` state, estimated at 0.94, sourced from Lenert et al. (2000). For mild major depressive episode, estimated at 0.79 and for moderate major depressive episode estimated at 0.67; sourced from Schaffer et al. (2002) For guided iCBT, major depression, at 12 months, estimated at 0.84, sourced from Duarte et al. (2017) and Littlewood et al. (2015).
Hollinghurst et al. (189)	2010	Not applicable	EQ-5D administered in the Therapist delivered internet psychotherapy trial (n=297)
Holst et al. (160)	2018	Not applicable	EQ-5D-3L administered in the PRIM-NET trial (n=90)

Authors	Year	Description of main clinical inputs	Description of main utility inputs
Kaltenthaler et al. (161)	2006	The main source of clinical inputs, including all transition probabilities, was the BtB CBT trial reported by Proudfoot et al. Patients in the model are assumed to spend 6 months in their new severity state following treatment. At the end of this 6-month period, patients who improved may stay the same or relapse. The rate of non-compliance was assumed to be 30%, which the authors state was similar to in the Proudfoot trial and other similar trials. The probability of staying in the minimal depression health state was higher for patients treated with BtB CBT (1) than for TAU patients (0.75). The probability of staying in the severe depression health state was lower for patients treated with BtB CBT (0.25) than for TAU patients (0.458). However, the probability of moving from mild depression health state to moderate or severe depression health state was higher for BtB CBT patients (0.500+0.25=0.75) than for TAU patients (0.268+0.083=0.351).	Utility inputs were obtained for minimal depression at 0.88 based on values from the general population (people with minimal depression were assumed to have the same utility score as people from the general population). Utility inputs were obtained for mild depression at 0.78, moderate to severe depression at 0.58, and for severe depression at 0.38, based on a study by Richards et al, which used EQ-5D data from 62 patients.
Koeser et al.(164)	2015	The January 2013 update of a database by Cuijpers et al. (2008), was used as a basis for identifying RCTs in order to undertake a random-effects meta-analysis. From this, it was estimated that the probability of relapse among remitters was lower for CBT than for pharmacotherapy, at 12 months and also at 24 months (see Figure 2 of the study).	Mean EQ-5D utilities were calculated at 0.80 for remitters, 0.62 for responders, and 0.48 for non-responders, using data from a trial by Kuyken et al. (2008) on patients with recurrent depression.
Kraepelien et al. (165)	2018	Not applicable	EQ-5D-3L administered in the Regassa trial (n=945)
Kuyken et al. (166)	2015	Not applicable	EQ-5D administered in the PREVENT trial (n=424)
Phillips et al. (173)	2014	Not applicable	EQ-5D-3L administered in the MOODGYM CBT trial (n=637)
Richards et al. (175)	2016	Not applicable	EQ-5D-3L administered in the COBRA trial (n=221)
Romero-Sanchiz et al. (176)	2017	Not applicable	EQ-5D-3L administered in the Smiling is fun trial (n=296)

Authors	Year	Description of main clinical inputs	Description of main utility inputs
Ross et al. (177)	2019	Relative risks of CBT versus antidepressants were primarily taken from a study by Gartlehner et al. (2016), and estimated at 1.02 for initial remission probability, 1.11 for initial response probability, 0.73 for annual relapse probability, and 0.40 for annual discontinuation due to adverse event probability.	Utility inputs derived from a prospective study of patients treated for MDD by Sapin et al. (2004) and were estimated at: 0.85 for patients in remission, 0.72 for patients with response, and 0.58 for patients without response.
Simon et al. (179)	2006	For pharmacotherapy treatment strategy, absolute risk of treatment non-completion was 0.30, absolute risk of no remission during treatment was 0.70, and absolute risk of relapse at 12-month follow-up was 0.55. For CBT plus pharmacotherapy treatment strategy, risk difference in treatment non-completion was -0.06, risk difference in no remission during treatment was -0.18, and risk difference in relapse at 12-month follow-up was -0.17. Risk/risk difference parameters related to treatment non-completion and no remission during treatment, were sourced from a National Collaborating Centre for Mental Health (NCCMH) study from 2005. Risk/risk difference parameters related to relapse at 12-month follow-up, were sourced from from studies by Blackburn et al. (1986) and Simons et al. (1986).	Quality of weights were sourced from Revicki and Wood (1998), and were 0.30 for severe depression, 0.63 for moderate depression; 0.80 for remission, treatment; and 0.86 for remission, no treatment.
Solomon et al. (182)	2015	Effect sizes for myCompass were sourced from the myCompass RCT trial data published by Proudfoot et al. (2013). Effect sizes for initial were 0.462 for TAU (sourced from a review of clinical trials by Casacalenda et al. (2002)), 0.449 for myCompass CBT. Effect sizes for maintenance were 0.374 for TAU (sourced from clinical trial data from Warden et al. (2007)), 0.349 for myCompass CBT.	Utilities were sourced from a study by Kaltenthaler et al. (2006): mild depression (0.78); moderate depression (0.58); maintenance state (0.88).
Stant et al. (183)	2009	Not applicable	EQ-5D administered in the PEP and CBT trial (n=267)
Warmerdam et al. (184)	2010	Not applicable	EQ-5D administered in the ISRCTN16823487 trial (n=263)

11.3.8 Adaptation tables to adjust international cost-effectiveness results for Switzerland.

Correction for different resource utilisation

Current expenditure on health, per capita, US$ purchasing power parities.

Country	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Australia	2,154	2,289	2,481	2,577	2,817	2,872	2,995	3,198	3,350	3,422	3,595	3,809	3,854	4,093	4,190	4,381	4,606	4,711	4,965	5,187
Belgium	2,297	2,403	2,644	2,916	3,099	3,117	3,204	3,317	3,559	3,733	3,919	4,065	4,244	4,436	4,522	4,654	4,777	5,014	5,103	5,428
Canada	2,451	2,623	2,758	2,913	3,121	3,292	3,476	3,695	3,836	3,937	4,141	4,191	4,301	4,397	4,533	4,610	5,021	5,155	5,287	5,418
Germany	2,894	3,008	3,240	3,329	3,391	3,430	3,564	3,749	3,955	4,168	4,422	4,566	4,743	4,949	5,149	5,295	5,668	6,011	6,224	6,646
Greece	1,418	1,700	1,951	2,048	2,101	2,194	2,301	2,425	2,665	2,742	2,605	2,290	2,146	2,067	2,017	2,081	2,221	2,239	2,266	2,384
Italy	2,030	2,151	2,293	2,289	2,451	2,504	2,661	2,695	2,932	2,945	3,103	3,098	3,072	3,043	3,037	3,090	3,274	3,399	3,485	3,649
Netherlands	2,646	2,882	3,297	3,309	3,495	3,583	3,827	4,075	4,378	4,444	4,473	4,567	4,782	4,924	4,935	4,928	5,075	5,264	5,436	5,765
Spain	1,523	1,635	1,804	2,015	2,123	2,212	2,392	2,484	2,672	2,750	2,736	2,734	2,729	2,764	2,858	3,020	3,149	3,322	3,430	3,616
Sweden	2,195	2,398	2,636	2,675	2,772	2,809	3,006	3,222	3,414	3,460	3,433	4,462	4,680	4,731	4,866	5,002	5,122	5,318	5,434	5,782
Switzerland	3,325	3,552	3,887	3,915	4,108	4,106	4,231	4,596	4,905	5,071	5,087	5,260	5,565	5,924	6,159	6,468	6,808	7,037	7,280	7,732
United Kingdom	1,916	2,135	2,384	2,506	2,769	2,773	2,970	3,110	3,242	3,315	3,431	3,497	3,639	3,694	3,780	3,828	3,990	4,126	4,290	4,653
USA	4,557	4,909	5,326	5,736	6,094	6,443	6,807	7,157	7,396	7,670	7,922	8,131	8,405	8,611	9,034	9,498	9,880	10,213	10,637	11,072

Ratio Switzerland/Country - Current expenditure on health, per capita.

Country	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Australia	1.544	1.552	1.567	1.519	1.458	1.429	1.413	1.437	1.464	1.482	1.415	1.381	1.444	1.447	1.470	1.476	1.478	1.494	1.466	1.491
Belgium	1.447	1.478	1.470	1.342	1.326	1.317	1.321	1.385	1.378	1.359	1.298	1.294	1.311	1.335	1.362	1.390	1.425	1.403	1.427	1.425
Canada	1.356	1.354	1.409	1.344	1.316	1.247	1.217	1.244	1.279	1.288	1.229	1.255	1.294	1.347	1.359	1.403	1.356	1.365	1.377	1.427
Germany	1.149	1.181	1.200	1.176	1.211	1.197	1.187	1.226	1.240	1.217	1.151	1.152	1.173	1.197	1.196	1.222	1.201	1.171	1.170	1.164
Greece	2.345	2.090	1.992	1.911	1.955	1.872	1.839	1.895	1.840	1.849	1.952	2.297	2.594	2.866	3.054	3.107	3.065	3.144	3.213	3.244
Italy	1.638	1.652	1.695	1.710	1.676	1.640	1.590	1.705	1.673	1.722	1.639	1.698	1.812	1.947	2.028	2.093	2.079	2.070	2.089	2.119
Netherlands	1.256	1.233	1.179	1.183	1.175	1.146	1.106	1.128	1.120	1.141	1.137	1.152	1.164	1.203	1.248	1.312	1.341	1.337	1.339	1.341
Spain	2.183	2.173	2.155	1.943	1.935	1.856	1.769	1.850	1.836	1.844	1.859	1.924	2.039	2.143	2.155	2.141	2.162	2.118	2.123	2.138
Sweden	1.515	1.482	1.474	1.464	1.482	1.462	1.408	1.426	1.437	1.466	1.482	1.179	1.189	1.252	1.266	1.293	1.329	1.323	1.340	1.337
Switzerland	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
United Kingdom	1.736	1.664	1.631	1.562	1.484	1.481	1.425	1.478	1.513	1.530	1.483	1.504	1.529	1.603	1.629	1.689	1.706	1.705	1.697	1.662
USA	0.730	0.724	0.730	0.683	0.674	0.637	0.622	0.642	0.663	0.661	0.642	0.647	0.662	0.688	0.682	0.681	0.689	0.689	0.684	0.698

Correction for different prices of healthcare services

Purchasing Power Parities for GDP, National currency per US$

Country	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Australia	1.310	1.330	1.340	1.350	1.370	1.390	1.400	1.430	1.480	1.440	1.500	1.510	1.540	1.450	1.450	1.470	1.450	1.470	1.450	1.440
Belgium	0.900	0.892	0.873	0.877	0.889	0.892	0.875	0.880	0.867	0.849	0.836	0.832	0.822	0.806	0.800	0.800	0.781	0.773	0.770	0.755
Canada	1.230	1.220	1.230	1.230	1.230	1.210	1.210	1.210	1.230	1.200	1.220	1.240	1.240	1.220	1.230	1.250	1.210	1.200	1.200	1.190
Germany	0.943	0.930	0.913	0.897	0.876	0.873	0.849	0.838	0.820	0.810	0.805	0.789	0.787	0.775	0.769	0.778	0.753	0.741	0.741	0.737
Greece	0.670	0.668	0.663	0.686	0.695	0.709	0.693	0.719	0.708	0.704	0.721	0.713	0.685	0.631	0.611	0.609	0.589	0.576	0.567	0.557
Italy	0.805	0.816	0.823	0.834	0.853	0.855	0.824	0.810	0.784	0.771	0.773	0.759	0.748	0.737	0.740	0.738	0.701	0.687	0.683	0.671
Netherlands	0.890	0.905	0.901	0.927	0.909	0.897	0.873	0.861	0.848	0.848	0.853	0.836	0.824	0.798	0.809	0.810	0.796	0.778	0.780	0.785
Spain	0.740	0.747	0.742	0.760	0.767	0.770	0.737	0.733	0.726	0.718	0.726	0.714	0.695	0.675	0.662	0.665	0.643	0.630	0.635	0.627
Sweden	9.160	9.400	9.410	9.500	9.300	9.480	9.120	8.880	8.780	8.910	9.020	8.840	8.650	8.600	8.730	8.850	8.820	8.720	8.830	8.750
Switzerland	1.790	1.770	1.710	1.720	1.690	1.690	1.600	1.530	1.490	1.470	1.470	1.400	1.350	1.310	1.280	1.240	1.200	1.180	1.170	1.150
United Kingdom	0.704	0.694	0.690	0.697	0.688	0.708	0.697	0.710	0.702	0.709	0.702	0.706	0.702	0.695	0.698	0.692	0.689	0.682	0.687	0.680
USA	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Ratio Switzerland/Country - Purchasing Power Parities for GDP.

Country	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Australia	1.366	1.331	1.276	1.274	1.234	1.216	1.143	1.070	1.007	1.021	0.980	0.927	0.877	0.903	0.883	0.844	0.828	0.803	0.807	0.799
Belgium	1.989	1.984	1.959	1.961	1.901	1.895	1.829	1.739	1.719	1.731	1.758	1.683	1.642	1.625	1.600	1.550	1.536	1.527	1.519	1.523
Canada	1.455	1.451	1.390	1.398	1.374	1.397	1.322	1.264	1.211	1.225	1.205	1.129	1.089	1.074	1.041	0.992	0.992	0.983	0.975	0.966
Germany	1.898	1.903	1.873	1.918	1.929	1.936	1.885	1.826	1.817	1.815	1.826	1.774	1.715	1.690	1.664	1.594	1.594	1.592	1.579	1.560
Greece	2.672	2.650	2.579	2.507	2.432	2.384	2.309	2.128	2.105	2.088	2.039	1.964	1.971	2.076	2.095	2.036	2.037	2.049	2.063	2.065
Italy	2.224	2.169	2.078	2.062	1.981	1.977	1.942	1.889	1.901	1.907	1.902	1.845	1.805	1.777	1.730	1.680	1.712	1.718	1.713	1.714
Netherlands	2.011	1.956	1.898	1.855	1.859	1.884	1.833	1.777	1.757	1.733	1.723	1.675	1.638	1.642	1.582	1.531	1.508	1.517	1.500	1.465
Spain	2.419	2.369	2.305	2.263	2.203	2.195	2.171	2.087	2.052	2.047	2.025	1.961	1.942	1.941	1.934	1.865	1.866	1.873	1.843	1.834
Sweden	0.195	0.188	0.182	0.181	0.182	0.178	0.175	0.172	0.170	0.165	0.163	0.158	0.156	0.152	0.147	0.140	0.136	0.135	0.133	0.131
Switzerland	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
United Kingdom	2.543	2.550	2.478	2.468	2.456	2.387	2.296	2.155	2.123	2.073	2.094	1.983	1.923	1.885	1.834	1.792	1.742	1.730	1.703	1.691
USA	1.790	1.770	1.710	1.720	1.690	1.690	1.600	1.530	1.490	1.470	1.470	1.400	1.350	1.310	1.280	1.240	1.200	1.180	1.170	1.150

Correction for costs changes over time

Healthcare cost growth rate in Switzerland, %

Year	Growth rate
2000	3.608%
2001	5.119%
2002	3.276%
2003	2.910%
2004	3.226%
2005	1.360%
2006	0.496%
2007	3.736%
2008	4.309%
2009	3.225%
2010	1.302%
2011	2.241%
2012	2.431%
2013	2.736%
2014	2.082%
2015	2.969%
2016	2.995%
2017	1.864%
2018	0.018%

Overall healthcare cost increase depending on reference year.

Reference year	Overall growth rate until 2018
2000	57.74%
2001	50.06%
2002	45.30%
2003	41.19%
2004	36.78%
2005	34.94%
2006	34.28%
2007	29.44%
2008	24.10%
2009	20.22%
2010	18.67%
2011	16.07%
2012	13.32%
2013	10.30%
2014	8.05%
2015	4.93%
2016	1.88%
2017	0.02%
2018	-