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Efficacy and tolerability of MAOIs for the treatment of depressive episodes in mood disorders: a systematic review and network meta-analysis

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Abstract

Background: Monoamine oxidase inhibitors (MAOIs) are considered third-line treatments for treatment resistant depression; however, they are underused in clinical practice.

Aims: This study aimed to assess the efficacy, tolerability and acceptability of MAOIs for the treatment of depression in comparison with other antidepressant treatments.

Methods: A systematic review and network meta-analysis of randomized clinical trials was performed to compare the efficacy, tolerability and acceptability between MAOIs and other antidepressant treatments for the treatment of depressive episodes.

Results: A total of 83 double-blinded, randomized controlled trials were included in the analysis, with 7765 participants assigned to an active treatment and 1844 assigned to placebo. Several MAOIs, including isocarboxazid, phenelzine, tranylcypromine and moclobemide, showed significantly higher efficacy compared with placebo. The tolerability and acceptability of MAOIs was comparable to other antidepressants.

Limitations: A disproportionate number of studies investigating the most commonly used MAOIs, such as moclobemide and phenelzine, and a lack of specific studies focusing on treatment-resistant and atypical depression.

Conclusions: MAOIs are similar in efficacy to other antidepressants for the treatment of depression. However, more studies are needed comparing MAOI treatment in people with treatment-resistant, atypical and bipolar depression.

Keywords: Monoamine oxidase inhibitors, antidepressants, treatment, depression, mood disorders, psychiatry, mental health, neuroscience.

Summation	This review demonstrates the substantive efficacy of MAOIs in treatment of depressive disorders.
	Results suggest comparable tolerability to other antidepressants if used within dietary and other safety constraints.
	Findings highlight the need for contemporary studies investigating MAOI effects in treatment-resistant and atypical depression populations.
Limitations	Most studies included in the review were published before 2000, varied in quality and lacked consistent reporting of data.
	There were a disproportionate number of studies for each MAOI, favouring moclobemide and phenelzine.

	Conclusions could not be drawn for treatment of bipolar depression, treatment-resistant depression or atypical depression due to lack of studies focusing on these populations.

1. INTRODUCTION

Depressive episodes experienced by people with major depressive disorder (MDD) or bipolar disorders (BD) can be challenging to treat effectively and are associated with poor quality of life and functional outcomes (1). They are also associated with higher rates of health care utilisation, worse overall health outcomes and are a substantial risk factor for completed suicide (1,2). However, clinical response to first-line psychological or pharmacological therapies occurs in only 40-60% of people with MDD or bipolar depression and only 30-45% of people with MDD or bipolar depression experience clinical remission after receiving pharmacological treatment (3,4). Evidence based therapeutic options for this large unmet need are required.

Current guidelines for the treatment of depressive episodes in MDD or BD aim to systematise the use of agents with antidepressant properties in clinical practice (5). For MDD, these state that when an antidepressant is initially prescribed, it should typically be a selective serotonin reuptake inhibitor (SSRI) due to their similar efficacy to other antidepressants, accompanied by a favourable benefit/risk ratio (6,7). Next step pharmacological treatment strategies include an antidepressant dose increase, a switch to an alternative antidepressant such as a serotonin and noradrenaline reuptake inhibitor (SNRI), or augmenting with an additional agent (8). For bipolar depression, other strategies are recommended, such as the use of a mood stabilizer (i.e., lamotrigine) or the introduction of atypical antipsychotics, such as quetiapine or lurasidone (9). Monoamine-oxidase inhibitors (MAOIs) are currently suggested as possible third-line treatments for depressive episodes in MDD and BD (7,9–11).

MAOIs produce antidepressant effects by inhibiting monoamine-oxidase (MAO) enzyme activity, which in turn inhibits the breakdown of monoamines neurotransmitters such as serotonin, dopamine and norepinephrine. There are two isoforms of MAO (MAO-A and MAO-B), encoded by two different genes located on the X chromosome (Xp11.23). These differ in substrate specificities, inhibitor affinity, inhibitor sensitivities, and tissue localization. MAO-A has higher affinity for serotonin and norepinephrine than MAO-B (12). MAOIs are typically classified into reversible and irreversible – referring to the bond the drugs form with the MAO enzyme. Phenelzine, tranylcypromine, selegiline (commonly administered via transdermal patches) and isocarboxazid are examples of irreversible MAOIs used in clinical practice, whereas moclobemide is the main reversible MAOI used (11,13,14).

The use of MAOIs has declined substantially in clinical practice (15). This may be due to concerns about MAOI tolerability, inexperience in the clinical use of MAOIs, and marketing of or preference for the use of SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs). It may also reflect the dietary restrictions and safety concerns about the use of MAOIs. In people treated with MAOIs, a potentially fatal hypertensive crisis can be caused by consumption of foods and beverages with a high content of tyramine. The use of a tyramine restricted diet is necessary to mitigate these risks (16–18). MAOIs are also associated with increased risks of serotonin syndrome and orthostatic hypotension, the latter of which is particularly seen with use of high doses of irreversible MAOIs (19). Whilst these safety concerns are significant, MAOIs (ensuring they are prescribed and used within these safety constraints) remain a potentially important treatment option for those experiencing mood disorders, particularly for those experiencing treatment-resistant depression or atypical depression in MDD or BD.

Recently, a network meta-analysis examining the efficacy of MAOIs has been published (20–23). However, this study included a limited number of MAOIs, with relative paucity of studies due to narrow inclusion criteria, and exclusion of studies not reporting binary outcomes. In this present systematic review and network meta-analysis of double-blind, randomised controlled trials, we compared the efficacy, tolerability and acceptability of MAOIs with other antidepressant treatments in people experiencing a MDD or BD depressive episode. The aim of this study was to investigate the efficacy and safety of MAOI use compared to other antidepressant classes, and to examine whether there was any difference in efficacy between individual MAOI medications particularly comparing reversible versus irreversible MAOIs.

2. METHODS

2.1. Search strategy

The following electronic databases were systematically searched with no data limits or language restrictions: PubMed, Cochrane Library, EMBASE, PsycINFO and the National Institute of Health website ClinicalTrials.gov. All potentially relevant publications not available from electronic databases were retrieved manually from the bibliography of selected articles to identify additional studies. The search was conducted by two review authors (AGP, AC) using terms for MAOI ("monoamine oxidase inhibitor*", “MAOI”, "MAO inhibitor*", combined with a list of all the antidepressants included in our study) and for depression (“depression”, “depressed”, “depressive”, “bipolar”, “affective”, “mood disorder*”, “schizoaffective”) to be present in the title or the abstract. Data extraction from identified studies was conducted by the study authors. The study protocol was registered with the UK National Institute for Health Research PROSPERO International prospective register of systematic reviews (ID: CRD42020164681).

2.2. Types of studies

This systematic review and meta-analysis included only studies which were double-blind, randomised controlled trials, cross-over trials or cluster randomised trials. All studies compared the efficacy and acceptability of a MAOI against a comparator. Comparators were limited to placebo, antidepressant treatment, combination of treatment (e.g. a MAOI with another antidepressant), or other interventions for treatment of depression (e.g. cognitive behavioural therapy). Single-blind and quasi-randomized studies were excluded. Studies in both inpatient and outpatient settings were included. The search included articles from inception to November 9th 2019. An updated search with the same string was conducted on November 15th 2021 and did not identify additional articles. No language restriction was applied. Systematic reviews, meta-analyses, editorials, opinion papers, case reports or series, studies which were not double-blind or did not use validated scales for outcome were also excluded. Trials not including a MAOI arm, studies involving post-hoc analyses on data already published in other papers, and studies where the protocol involved treatment with a MAOI for less than 4 weeks were excluded.

2.3. Types of participants

Participants included were those aged 18 years or older, of both sexes, with a diagnosis of any subtypes of major depressive disorder (mild, moderate, severe, with/without psychotic features) or bipolar disorder depressive episodes (rapid cycling, type I, type II), or intermittent, minor, chronic and seasonal depression, defined by any standardized criteria, such as DSM-III, DSM-III-R, DSM-IV, DSM-5, ICD-9, ICD-10, Research Diagnostic Criteria or Feighner criteria. Participants with treatment-resistant depression were also included. Co-morbid psychiatric disorders were not considered as exclusion criteria, however studies in which depression was not the primary diagnosis were excluded. Studies allowing the use of rescue medications were not excluded if they could be used equally in all groups.

2.4. Types of interventions

Studies comparing MAOIs, both reversible and irreversible (tranylcypromine, isocarboxazid, phenelzine, moclobemide, selegiline, nialamide, bifemelane, mebanazine, brofaromine, pirlindole and toloxatone), or combinations of MAOI with any antidepressant classes, or drugs with antidepressant effects or placebo were included. Studies that used psychotherapy as non-pharmacological interventions were also included. Any dose range of drug interventions were considered for inclusion and both fixed-dose and flexible-dose designs were allowed.

2.5. Outcome measures

As the main aim of this study was to assess the efficacy of MAOIs in the treatment of depressive symptoms, the primary outcome was the endpoint score on a validated depressive symptom rating scale, such as Hamilton Depression Rating Scale (HDRS), Clinical Global Impression (CGI), Montgomery-Asberg Depression Rating Scale (MADRS), Inventory for Depressive Symptomatology (IDS), or the difference between baseline and endpoint scores. Where endpoint scores were not reported, change in scores were used instead. Where mean scores were not reported, percentage of participants with treatment response was used. Since the HDRS has historically been the gold standard for measuring depression severity (24), HDRS was used for assessing therapeutic response whenever possible.

Additional outcomes measures included tolerability (treatment-associated adverse effects, measured as the proportion of participants experiencing adverse events) and acceptability (treatment discontinuation, measured as the proportion of participants who discontinued the study for any reason).

2.6. Study selection

Two authors (AGP and AC) independently reviewed references and abstracts obtained by the search to assess their eligibility. The full text of the remaining articles was obtained to determine their eligibility according to our inclusion and exclusion criteria. In cases of articles not displaying an abstract, the full text was obtained to decide on eligibility. Any discrepancies were resolved in consensus with the rest of the authors.

2.7. Data extraction

Four researchers (AGP, AC, NG, KA) independently assessed the eligibility of the identified studies by a systematic screening of titles and abstracts to decide their inclusion or exclusion, and subsequently, the full texts were assessed for eligibility. In case of disagreement, the decision about their inclusion was made by the study team through consensus. A data extraction spreadsheet was used to register the relevant data for each article. Data extraction was initiated on September 6th 2020. The information extracted included study details (study name, author, year of publication, design, setting), participant characteristics (mean age, number of men and women, sample size, diagnosis, diagnostic criteria for depression), intervention aspects (duration, drugs compared, mean doses), outcomes measured, effect size for the different outcomes and statistical significance, and risk of bias measured with the Cochrane Risk of Bias (RoB2) tool. For each study, end of trial data was chosen for the subsequent analysis. In studies which provided data for multiple time points, the last follow up point was chosen for data collection and further analyses.

2.8. Study quality assessment

The quality of included studies, including risk of bias, was assessed using the tool described in the Cochrane Collaboration Handbook (25) by two researchers (AGP and TJ). Discrepancies were resolved by these two authors after discussion. This tool was used to assess quality on the

following domains of bias: random sequence generation, allocation concealment, selective reporting, blinding of participants and personnel, blinding of outcome assessment, and incomplete outcome data. If all domains were rated as "low risk" then the overall risk of bias was considered low. If at least one domain was rated to have "some concerns" then the overall risk of bias was considered moderate. Studies were assessed as high overall risk of bias if at least one domain was rated as "high risk" or multiple domains rated to have "some concerns". We also used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of the body of evidence. The GRADE methodology involves rating the initial quality of evidence for an association as high (with interventional data), followed by downgrading based on five criteria (risk of bias, inconsistency, imprecision, indirectness and publication bias), and upgrading based on three criteria (large effect size, dose-response gradient, and plausible confounding) (26).

Publication bias for commonly used MAOIs including isocarboxazid, moclobemide, phenelzine and tranylcypromine was assessed using a funnel plot and calculating Eggers' test.

2.9. Data analysis

Different effect estimates (e.g., odds ratios, expected difference in change of depressive score between groups, frequency table of response in each arm) were derived from the included studies. The analysis was based on intention-to-treat study data. Where this data was not available, overall number of participants were used instead. Studies with zero-cell counts in all groups were excluded as they did not provide any information. However, in studies with zero-cell counts in one group, a small number (i.e., 0.5) was added to group counts to make calculation of Cohen's d possible. Due to diverse methods for reporting effect sizes among studies, all effect sizes were converted to Cohen's d effect size and its standard error (SE). For multi-arm studies, Cohen's d (SE) was calculated for each pairwise comparison (27,28). To account for the multi-arm nature of some studies, we separately analysed multi-arm studies and calculated their effect sizes accounting for their dependence; the method is described previously (29,30). Then, effect sizes from multi-arm studies and two-arm studies were merged to calculate the pooled estimates.

A random-effect network meta-analysis was performed using the 'netmeta' package (28) in R (version 4.0.2) to compare different treatments. We used methods based on graph theory, which was described in detail previously (30). To account for complex treatments (a treatment that is combination of other treatments) in the network analysis, an additive component network meta-analysis model was used to evaluate the influence of individual components, reported above (28,31). We excluded studies that could not be connected to the network as no other studies used the same treatments.

The performance of the network analysis was assessed by tests of heterogeneity and inconsistency. We also calculated the total inconsistency based on the full design-by-treatment interaction random-effects model as suggested before (32). Moreover, a net-heat method was used to identify potential inconsistencies (33). The impact of individual studies on the network meta-analysis was measured by the reduction of the precision if the study was removed or ignored from the network. We also ran sensitivity analyses to determine whether removing high-impact studies from network analysis changed the interpretation of results.

The findings of the network analysis were summarized through 1) a network graph where the nodes in the graph layout correspond to the treatments and edges display the observed treatment comparisons; 2) a forest plot for comparison of treatments with placebo being the reference group and different treatments being ranked by the strength of the evidence (standard error of estimate); and 3) a league table showing all pairwise comparisons in a network meta-analysis and their confidence intervals. Similar methods were used for analysis and reporting of secondary outcomes (i.e., tolerance and adverse effects). All figures/tables report a combined direct and indirect effect.

3. RESULTS

3.1. Characteristics of Studies Included in the Meta-Analysis

The initial search screen identified 2091 studies. The results of the search, numbers of studies excluded and reasons for exclusion are shown in in **Figure 1**. From the 153 records retrieved in full-text, 78 articles were finally included in our study, containing a total of 83 double-blind, parallel, RCTs conducted between 1965 and 2013. Five of these studies reported on two

separate RCTs, hence the number of RCTs was greater than the number of articles included. The included studies reported quantitative information about efficacy, and some on tolerability and/or acceptability, of MAOIs compared to placebo or other drugs, and were suitable for meta-analysis.

Figure 1 about here

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The 83 studies included in the meta-analysis were all double-blind RCTs with a total of 9609 participants (**Supplementary Table 2**), of whom 7765 participants were randomly assigned to an active treatment and 1844 were randomly assigned to placebo. Sample sizes for each study ranged from 16 to 492 participants, with mean of 180.2 participants (SD 103.6). Study durations varied from 4 to 52 weeks, with mean of 7.7 weeks (SD 7.8). From studies in which data about the number of male and female participants included was provided (8993 individuals), 62.3% were women. Most participants were reported to experience a moderate-to-severe major depressive episode, with a mean reported baseline severity score on the Hamilton Depression Rating Scale 17-item of 24.9 (SD 6.4). Whereas most studies included participants with MDD, eight studies included participants with bipolar disorders, and only one focused specifically on bipolar depression (34). Only two studies investigated populations with treatment-resistant depression exclusively (35,36); two studies included people with atypical depression, but also included people with other types of depression and these studies did not report outcomes separately.

3.2. MAOI treatment efficacy

A total of 24 antidepressant agents, as well as placebo, lithium, lamotrigine, L-5-hydroxytryptophan (L-5HTP), Cognitive Behaviour Therapy (CBT), and combinations of antidepressants or mood stabilisers were included in the meta-analysis. When testing for inconsistency, a random-effect model accounted for the heterogeneity found in our network (Q statistic: 22.6, p-value for test: 0.191). All non-MAOI antidepressants included, as well as lithium, lamotrigine, L-5HTP and CBT, were compared with at least one MAOI: tranylcypromine, isocarboxazid, phenelzine, moclobemide, selegiline (patch), selegiline (oral), nialamide, bifemelane, mebanazine, brofaromine, pirlindole, toloxatone, tranylcypromine plus amitriptyline, moclobemide plus amitriptyline, or moclobemide plus thioridazine.

Studies comparing the efficacy of different treatments are represented in the network plot (**Figure 2**). The most frequently studied MAOI was moclobemide, which was included in 41 studies, followed by phenelzine, assessed by 22 studies. Most studies assessing moclobemide included comparisons with imipramine, clomipramine, fluoxetine and placebo, whereas most studies assessing the efficacy of phenelzine used imipramine or placebo as a comparator.

Figure 2 about here

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Figure 3 shows the network meta-analysis' results for the efficacy of the different treatments compared with placebo (83 RCTs, comprising 9609 patients) for treatment response in depressive episodes. MAOIs, or treatments containing MAOIs, that showed significantly greater efficacy effect sizes than placebo were: phenelzine (*d* -1.07, 95% confidence interval (CI) -1.30, -0.84), moclobemide (*d* -0.88, 95% CI -1.12, -0.63), tranylcypromine (*d* -1.00, 95% CI -1.37, -0.62), isocarboxazid (*d* -0.92, 95% CI -1.44, -0.40), brofaromine (*d* -0.69, 95% CI -1.19, -0.19), pirlindole (*d* -1.06, 95% CI -1.69, -0.43), toloxatone (*d* -1.42, 95% CI -2.13, -0.71), mebanazine (*d* -1.52, 95% CI -2.71, -0.33), and the combinations of amitriptyline with moclobemide (*d* -1.28, 95% CI -2.19, -0.37), amitriptyline with tranylcypromine (*d* -1.40, 95% CI -2.31, -0.48), and moclobemide with thioridazine (*d* -1.27, 95% CI -2.39, -0.15). Selegiline did not show significantly greater efficacy than placebo in our analysis (oral: *d* -0.46, 95% CI -1.36, 0.44; patch: *d* 0.13, 95% CI -0.25, 0.50).

Figure 3 about here

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Comparisons were also conducted with moclobemide as a reference which found significantly greater efficacy compared with placebo (*d* 0.88, 95% CI 0.63, 1.12) and with selegiline (patch) (*d* 1.00, 95% CI 0.55, 1.45). Otherwise, there were no significant differences in efficacy with other comparators (**Supplementary Figure 1**).

The treatment efficacy league table showing the comparison effect sizes among the different treatments included in the meta-analysis is shown in the lower triangle of **Table 1**. Phenelzine showed superiority over imipramine when total effect sizes were compared *(d* 0.35, 95% CI 0.14, 0.57).

Table 1 about here

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An efficacy meta-regression analysis was performed for all clinical trials which involved isocarboxazid, moclobemide, phenelzine or tranylcypromine. This was conducted according to participant gender in each study and found statistically significant differences in efficacy in those studies with higher proportion of women (**Supplementary Figure 2**).

Treatment-resistant depression study results

Two studies of MAOI effects in participants with treatment-resistant depression were eligible to be included. The first study investigated MAOI effects in 78 participants with treatment-resistant depression and revealed that a moclobemide plus thioridazine treatment group experienced similar response rates compared to moclobemide plus placebo (74% and 77% respectively) after four weeks of treatment (35). A second study in people with treatment-resistant depression (36) found that 5/11 participants (45%) experienced a clinical response to tranylcypromine and 1/10 participants (10%) to nomifensine and, in a cross-over study with

non-responders, 5/8 participants (62%) responded to tranylcypromine and 0/5 participants to nomifensine (36).

3.2. MAOI tolerability and acceptability

Studies comparing the tolerability of different treatments are represented in the network plot (**Figure 4**). The MAOIs most included in tolerability analyses were moclobemide, phenelzine and selegiline (patch) but no studies assessing tolerability or acceptability for isocarboxazid were found.

Figure 4 about here

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In the analysis of tolerability (28 RCTs, comprising 3844 patients), the MAOI medications that showed higher statistically significant adverse effect rates compared to placebo were selegiline (patch) (*d* 0.33, 95% CI 0.03, 0.63) and tranylcypromine (*d* 0.83, 95% CI 0.08, 1.59) (**Figure 5).** However, moclobemide and phenelzine were not found to have any significant differences compared to placebo.

Figure 5 about here

The tolerability league table demonstrates the total effect sizes amongst the different treatments in which this was assessed (**Table 2**).

As illustrated by the network meta-analysis, moclobemide, phenelzine and selegiline (patch) were the MAOIs most included in acceptability analyses, whereas clomipramine and imipramine were the most included non-MAOI drugs (**Figure 6**).

Figure 6 about here

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Regarding acceptability (58 RCTs, comprising 7281 patients), the following MAOIs were included in the meta-analysis: moclobemide, phenelzine, selegiline (patch), tranylcypromine, pirlindole, brofaromine, selegiline (oral), toloxatone **(Figure 7).** When compared to placebo, MAOIs had no significant differences in dropout rates compared to placebo. The only significant result was seen with CBT *(d* -1.22, 95% CI -2.25, -0.20) which demonstrated superior acceptability to all other comparators.

Figure 7 about here

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The acceptability league table shows the total effect sizes amongst the different treatments in which dropouts were reported (upper triangle of **Table 1**). Placebo and the MAOIs moclobemide, phenelzine, transdermal selegiline and tranylcypromine were all found to have higher dropout rates than CBT.

Table 2 about here

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3.3 Consistency of results, quality of studies and assessment of publication bias

Net-heat plots based on the random-effect network meta-analysis for efficacy, tolerability and acceptability show minor to moderate inconsistency in the network (**Supplementary Figures 3-5**). Our impact sensitivity analyses showed that removing high-impact studies does not change interpretations of our findings.

Following the GRADE methodology, we graded the quality of evidence for all three outcomes of efficacy, acceptability and tolerability as low because risk of bias of inconsistency, publication bias and imprecision may exist. The quality of studies assessed according to the Cochrane Collaboration Risk of Bias tool 2.0 (RoB), found that 75.0% of studies were rated as showing a low risk of bias, 15.5% moderate risk and 9.5% high risk (**Supplementary Table**

3). Our sensitivity analyses showed that removing studies with moderate-to-high risk of bias does not change interpretations of our findings.

Publication bias was assessed for eligible trials of isocarboxazid, moclobemide, phenelzine or tranylcypromine for efficacy (**Supplementary Figure 6**). When compared with placebo, Eggers' test did not indicate the presence of funnel plot asymmetry (p=0.298).

4. DISCUSSION

4.1. Main findings

This network meta-analysis evaluated whether MAOIs are associated with significant differences in efficacy, tolerability and acceptability, compared to other antidepressant treatments and to placebo. Our study was a comprehensive review of 11 different MAOIs which included 83 double-blind studies, with a total of 9609 participants. Our results are in line with another recent MAOI network meta-analysis (23). However, this previous analysis only included 52 studies which focused on a narrower range of MAOIs, excluding some medications which remain relevant in clinical practice such as isocarboxazid, with a paucity of studies involving other MAOI antidepressants. As a consequence, there were fewer analyses assessing comparisons with other antidepressants. Finally, this previous meta-analysis assessed efficacy and acceptability of MAOIs, but not tolerability, which is key due to the association of these medications with clinically-relevant adverse effects.

In our meta-analysis, we found that moclobemide, isocarboxazid, tranylcypromine and phenelzine, but not selegiline, were significantly more effective than placebo in improving depressive symptoms in adults with mood disorders. Efficacy related effect sizes were similar for these MAOIs; 0.88 for moclobemide, 0.92 for isocarboxazid, 1.0 for tranylcypromine and 1.07 for phenelzine. We note that our MAOI efficacy effect size estimates are higher than those reported for other antidepressant drug classes (37). This may be a consequence of many of the MAOI studies included in our analysis being older, using relatively smaller participant sample sizes, and being conducted in non-treatment resistant populations. Whilst efficacy was demonstrated in both men and women, we found from our meta-regression higher efficacy effects in studies with a higher proportion of women. This is an interesting finding, and we would suggest that future studies explore whether women benefit greater from treatment with

MAOIs than men, or if this is a reflection of the severity of depression of participants included in these studies.

Experiences from clinical settings and a previous meta-analysis suggest that irreversible MAOIs might be more effective than reversible MAOIs such as moclobemide (38). However, in our study we did not find significant differences in efficacy between reversible and irreversible MAOIs, except for the selegiline patch. This may reflect irreversible MAOI studies using lower maximum doses than are suggested in some expert guidelines (39). It may also be attributable to the variation in case mix of participants. For example, irreversible MAOIs might be utilised more for individuals with refractory depression, whilst the potentially more tolerable reversible MAOIs might be used for less refractory depression, although this data was not specified in the included studies. Regarding selegiline, it is unclear whether the lack of efficacy found in our analysis results from pharmacokinetic differences (as selegiline is administered through oral or transdermal route), dosage, or a true lack of efficacy. When combined direct and indirect effect sizes were compared across antidepressants, phenelzine showed superiority over imipramine, with no significant differences in effect sizes in other comparisons between MAOIs and TCAs. This suggests that, with an exception, overall efficacy of MAOIs and TCAs may be comparable.

Unfortunately, the available MAOI studies did not focus on efficacy in three populations of people with depression with particular unmet clinical need: bipolar depression, atypical depression and treatment-resistant depression. Our study does not allow us to make conclusions about the comparable efficacy of MAOIs in patients with bipolar depression, as most studies including people with bipolar depression did not report results separately from unipolar populations. Only one study specifically focused on bipolar depression; this found significant differences in CGI scale score at the end of follow-up, with 81% of participants treated with tranylcypromine and 48% of participants treated with imipramine showing a response to treatment (34). We note that a previous systematic review also provides evidence of the efficacy of tranylcypromine for the treatment of bipolar depression (40). No studies reported treatment results in exclusively atypical depression, and only two studies in treatment-resistant depression populations (35,36). The studies in treatment-resistant depression participants indicated a lack of benefit with the addition of thioridazine to treatment with moclobemide (35) and, in a study with a small number of participants, the superiority of tranylcypromine compared to nomifensine in treatment response (36). However, the evidence base for the effect of MAOIs in treatment-resistant depression populations is extremely limited and no studies to

our knowledge have compared the efficacy of other commonly used MAOIs, such as moclobemide and phenelzine, with other antidepressants in treatment-resistant depression populations. Given that MAOIs are currently mainly used to treat people with treatment-resistant depression and/or atypical depression, our study highlights a significant gap in the evidence base which we suggest should be addressed.

Our analysis found that MAOIs were generally similar to other antidepressants in their tolerability profile, and that moclobemide and also pirlindole showed a significant tolerability superiority over fluvoxamine and clomipramine. In addition, our analysis found that MAOI's generally had comparable tolerability to placebo, with the exception of tranylcypromine and selegiline patch which showed inferior tolerability. We found no statistically significant acceptability differences for MAOIs compared with other antidepressants, which supports that acceptability concerns should not necessarily be a limiting factor for the prescription of an MAOI.

4.2. Clinical implications

Our network meta-analysis results provide a comprehensive assessment of the efficacy, tolerability and acceptability of MAOIs compared with other antidepressant treatments and to placebo. The data presented in this review supports our initial hypothesis that MAOIs (with the exception of the selegiline patch in our analysis) have a broadly similar efficacy, tolerability and acceptability profile to other commonly used antidepressants, such as TCAs and SSRIs, if used with appropriate dietary and other safeguards. It is well established that patients taking MAOIs must adhere to strict dietary restrictions to mitigate risks associated with tyramine consumption - particularly hypertensive crises. Careful consideration should also be given to reduce the risk of orthostatic hypotension with MAOI use, especially with irreversible MAOIs used in the higher dose range (41). Our findings suggest that if patients are willing to adhere to these restrictions, then overall tolerability concerns may be an insufficient reason for withholding MAOI treatment compared to other antidepressant classes.

The findings from our study also show a generally similar efficacy profile between MAOIs and other antidepressants, with the exception of the selegiline patch, but this finding may be influenced by the inclusion of non-treatment-resistant populations. MAOIs have been highlighted to have potentially life-saving efficacy in treatment-resistant depression (39). It is disappointing that the available MAOI studies do not allow us to empirically assess this. Further MAOI clinical trials, with a focus on treatment-resistant depression, bipolar depression

and atypical depression, might allow for the identification of specific clinical profiles associated with better therapeutic responses to MAOIs which would be particularly important to inform the treatment pathways of people with depression who have not responded to other options.

4.3. Strengths and limitations

Our study has several strengths. It is the first meta-analysis, to our knowledge, of the efficacy of MAOIs in depression that also assesses tolerability and includes studies with a minimum duration of at least four weeks. Moreover, only double-blind randomized clinical trials were included. This data significantly extends previous evidence with a greater number of studies than previous meta-analyses.

This study has some limitations from the field. MAOIs that are less used in clinical practice, such as toloxatone, pirlindole or brofaromine, are represented by a small number of studies, not allowing thorough network comparisons. Moreover, some of the MAOIs included in our study are not currently available or licensed for the treatment of depression. Phenelzine and moclobemide are the MAOIs with the greatest evidence in our results, reflecting that their use in clinical practice is more common compared to other MAOIs. In addition, most studies included in this meta-analysis are old - the latest article was published in 2013, and the oldest in 1965. Another limitation concerns the variation in participant characteristics with heterogeneity in the types of depression reported in studies. Unfortunately, very few studies focused on bipolar depression – this population remains a priority for a contemporary study of MAOI therapy. As discussed above, studies investigating MAOI effects exclusively in treatment-resistant or atypical depression populations are also needed.

Limitations of our review include that we could not examine the effect of MAOI dosage on treatment effect size due to the varying quality of included studies and lack of consistent reporting. Moreover, the variability in effect sizes among the studies included was high, and there was also a risk of bias in some of the included studies. Additionally, we tried wherever possible to use HAM-D initial and final scores for treatment effect comparisons but not all studies reported these. For studies that did not include this, analyses were performed from MAOI response rates, typically percentage reduction in either HAM-D or CGI scores. Finally, the number of studies for some comparisons were low, which reflects the MAOI research field, as illustrated by isocarboxazid where only two studies were identified. Despite these limitations, we found a low to mid level of inconsistency in most analyses. When observations

responsible for these inconsistencies were removed, the general findings and interpretations remained the same.

5. CONCLUSIONS

This network meta-analysis provides the most comprehensive available evidence to our knowledge to guide clinicians about use of MAOIs. Our network meta-analysis results suggest that MAOI antidepressants have considerable efficacy and generally comparable tolerability and acceptability to alternative antidepressants, if they are used within the dietary and other restrictions associated with MAOI use. Although MAOIs are often used for treatment-resistant or atypical depression, the lack of studies exclusively in these groups means that we were not able to assess whether MAOI treatments are superior in treatment response to other antidepressants these populations. To advance the field, we would suggest that future studies particularly focus on MAOI treatment effects in treatment-resistant, atypical and bipolar depression populations.

Declaration of interest

AGP has received CME-related honoraria, or consulting fees from Angelini, Janssen-Cilag, Rovi, Casen Recordati, LCN and Lundbeck. EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Adamed, Angelini, Biogen, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Janssen, Lundbeck, Medincell, Merck, Novartis, Orion Corporation, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work. SD has received grant support from the NHMRC Australia. IP has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck, Lundbeck/Otsuka, CASEN Recordati and Angelini, with no financial or other relationship relevant to the subject of this article. MB is supported by a NHMRC Leadership 3 Investigator grant (GNT2017131). MB: Grant/Research Support: MRFF, NHMRC, Congressionally Directed Medical Research Programs (CDMRP) USA, AEDRTC Australian Eating Disorders Research and Translation Centre, Patient-Centered Outcomes Research Institute (PCORI), Baszucki Brain Research Fund, Danmarks Frie Forskningsfond. Psykiatrisk Center Kobenhavn, Stanley Medical Research Institute, Victorian

Government Department of Jobs, Precincts and Regions, Wellcome Trust, Victorian Medical Research Acceleration Fund, Controversias Psiquiatria Barcelona, CRE, Victorian COVID-19 Research Fund, Consultancies: Lundbeck, Sandoz, Servier, Medisquire, HealthEd, ANZJP, EPA, Janssen, Medplan, RANZCP, Abbott India, ASCP, International Society of Bipolar Disorder, Precision Psychiatry, Penn State College of Medicine, Shanghai Mental Health Centre (last 3 years) – all unrelated to this work. PRAS reports non-financial support from Janssen Research and Development LLC, personal fees and non-financial support from Frontiers in Psychiatry, personal fees from Allergan, funding from National Institute for Health and Care Research (NIHR) UK, and grant funding from the Medical Research Council UK, NIHR, King's Health Partners and H Lundbeck A/S, outside the submitted work.

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Author contribution

AGP, AC, SD, MB and PRAS contributed to the development of the research question, the study design and protocol. AGP and AC led the data extraction and the manuscript writing. NG, TJ, EMB, KA and NB collaborated in data extraction. ML contributed to data extraction and the data analyses including leading the network meta-analysis. IP and EV have collaborated in the article writing. SD, PRA and MB contributed to developing and finalising the manuscript.

Data availability

The data that support the findings of this study are available from the corresponding author, AH, upon reasonable request.

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		0.75 (-0.21; 1.71)		**1.71 (0.48; 2.95)**	0.61 (-0.18; 1.41)	0.32 (-1.52; 2.15)	0.70 (-0.29; 1.69)	0.64 (-0.20; 1.49)	0.41 (-0.60; 1.42)	0.62 (-0.10; 1.34)		0.50 (-0.89; 1.89)			0.61 (-0.09; 1.31)	0.85 (-0.29; 1.99)		0.48 (-0.36; 1.32)	0.53 (-0.17; 1.23)	0.43 (-0.45; 1.32)	0.49 (-0.22; 1.21)	0.87 (-0.16; 1.90)	0.55 (-0.25; 1.36)	0.66 (-0.2 1.58
ATL+MB																								
0.12 (-0.27; 0.51)	ATL+TR																							
-0.59 (-1.63; 0.45)	-0.71 (-1.72; 0.31)	BRF		0.96 (-0.25; 2.17)	-0.14 (-0.93; 0.65)	-0.44 (-2.27; 1.40)	-0.05 (-1.03; 0.94)	-0.11 (-0.94; 0.73)	-0.34 (-1.34; 0.66)	-0.13 (-0.83; 0.56)		-0.25 (-1.26; 0.76)			-0.14 (-0.83; 0.55)	0.10 (-1.04; 1.24)		-0.27 (-1.06; 0.53)	-0.22 (-0.93; 0.48)	-0.32 (-1.17; 0.54)	-0.26 (-0.90; 0.39)	0.12 (-0.86; 1.11)	-0.20 (-0.94; 0.55)	-0.1 (-1.0 0.82
-0.57 (-6.60; 5.45)	-0.70 (-6.72; 5.33)	0.01 (-5.96; 5.99)	BPR																					
-0.69 (-1.98; 0.59)	-0.81 (-2.10; 0.47)	-0.11 (-1.15; 0.94)	-0.12 (-6.14; 5.90)	CBT	-1.10 (-2.22; 0.02)	-1.40 (-3.39; 0.59)	-1.01 (-2.28; 0.25)	-1.07 (-2.22; 0.08)	**-1.31 (-2.59; -0.02)**	**-1.10 (-2.15; -0.05)**		-1.21 (-2.79; 0.36)			**-1.10 (-2.16; -0.05)**	-0.86 (-2.25; 0.52)		**-1.23 (-2.36; -0.10)**	**-1.19 (-2.23; -0.15)**	**-1.28 (-2.45; -0.11)**	**-1.22 (-2.25; -0.20)**	-0.84 (-2.11; 0.42)	**-1.16 (-2.25; -0.07)**	-1.0 (-2.2 0.16
-0.49 (-1.42; 0.44)	-0.61 (-1.58; 0.36)	0.10 (-0.52; 0.72)	0.09 (-5.88; 6.05)	0.21 (-0.79; 1.20)	CMP	-0.30 (-2.07; 1.47)	0.09 (-0.70; 0.88)	0.03 (-0.57; 0.63)	-0.21 (-1.02; 0.61)	0.00 (-0.47; 0.48)		-0.11 (-1.39; 1.16)			-0.00 (-0.38; 0.37)	0.24 (-0.74; 1.21)		-0.13 (-0.77; 0.51)	-0.09 (-0.60; 0.43)	-0.18 (-0.86; 0.50)	-0.12 (-0.59; 0.34)	0.26 (-0.62; 1.14)	-0.06 (-0.66; 0.54)	0.0 (-0.6 0.75
0.03 (-1.83; 1.89)	-0.09 (-1.94; 1.77)	0.62 (-1.08; 2.33)	0.61 (-5.56; 6.78)	0.73 (-1.13; 2.59)	0.52 (-1.15; 2.19)	DPR	0.39 (-1.48; 2.25)	0.33 (-1.46; 2.12)	0.09 (-1.78; 1.97)	0.30 (-1.42; 2.02)		0.19 (-1.91; 2.28)			0.29 (-1.44; 2.03)	0.54 (-1.42; 2.49)		0.17 (-1.61; 1.95)	0.21 (-1.49; 1.91)	0.12 (-1.69; 1.93)	0.18 (-1.54; 1.90)	0.56 (-1.32; 2.43)	0.24 (-1.52; 2.00)	0.3 (-1.4 2.17
0.01 (-1.16; 1.18)	-0.11 (-1.31; 1.09)	0.60 (-0.35; 1.54)	0.59 (-5.42; 6.59)	0.71 (-0.51; 1.92)	0.50 (-0.33; 1.33)	-0.02 (-1.84; 1.79)	DTP	-0.06 (-0.90; 0.78)	-0.29 (-1.30; 0.71)	-0.09 (-0.84; 0.67)		-0.20 (-1.61; 1.20)			-0.09 (-0.79; 0.61)	0.15 (-0.99; 1.29)		-0.22 (-1.09; 0.65)	-0.18 (-0.96; 0.60)	-0.27 (-1.17; 0.63)	-0.21 (-0.96; 0.54)	0.17 (-0.89; 1.23)	-0.15 (-0.99; 0.69)	-0.0 (-0.9 0.87
-0.56 (-1.54; 0.43)	-0.68 (-1.70; 0.35)	0.03 (-0.68; 0.74)	0.02 (-5.96; 5.99)	0.14 (-0.91; 1.18)	-0.07 (-0.61; 0.48)	-0.59 (-2.29; 1.11)	-0.57 (-1.46; 0.32)	FXT	-0.24 (-1.10; 0.63)	-0.03 (-0.58; 0.52)		-0.14 (-1.45; 1.16)			-0.04 (-0.50; 0.43)	0.21 (-0.81; 1.22)		-0.16 (-0.86; 0.54)	-0.12 (-0.70; 0.46)	-0.21 (-0.94; 0.52)	-0.15 (-0.69; 0.39)	0.23 (-0.69; 1.15)	-0.09 (-0.75; 0.57)	0.0 (-0.7 0.77
-0.82 (-2.12; 0.49)	-0.94 (-2.27; 0.40)	-0.23 (-1.34; 0.89)	-0.24 (-6.27; 5.79)	-0.12 (-1.48; 1.23)	-0.33 (-1.34; 0.69)	-0.85 (-2.76; 1.06)	-0.83 (-2.06; 0.41)	-0.26 (-1.33; 0.81)	FVX	0.21 (-0.57; 0.99)		0.09 (-1.33; 1.51)			0.20 (-0.52; 0.93)	0.44 (-0.71; 1.60)		0.08 (-0.82; 0.97)	0.12 (-0.69; 0.92)	0.03 (-0.89; 0.94)	0.08 (-0.69; 0.86)	0.46 (-0.61; 1.54)	0.14 (-0.72; 1.00)	0.2 (-0.6 1.19
-0.56 (-1.47; 0.36)	-0.68 (-1.59; 0.24)	0.03 (-0.50; 0.57)	0.02 (-5.94; 5.97)	0.14 (-0.80; 1.07)	-0.07 (-0.46; 0.32)	-0.59 (-2.22; 1.04)	-0.57 (-1.37; 0.24)	0.00 (-0.51; 0.51)	0.26 (-0.74; 1.26)	IMP		-0.12 (-1.34; 1.11)			-0.01 (-0.29; 0.28)	0.23 (-0.71; 1.18)		-0.13 (-0.66; 0.40)	-0.09 (-0.39; 0.21)	-0.18 (-0.78; 0.42)	-0.12 (-0.40; 0.15)	0.25 (-0.54; 1.05)	-0.06 (-0.53; 0.40)	0.0 (-0.6 0.70
-0.36 (-1.37; 0.66)	-0.48 (-1.52; 0.56)	0.23 (-0.49; 0.95)	0.22 (-5.76; 6.20)	0.34 (-0.72; 1.40)	0.13 (-0.40; 0.67)	-0.39 (-2.10; 1.32)	-0.37 (-1.29; 0.56)	0.20 (-0.48; 0.88)	0.46 (-0.64; 1.56)	0.20 (-0.34; 0.74)	ISO													
-1.44 (-3.18; 0.29)	-1.56 (-3.23; 0.10)	-0.86 (-2.38; 0.67)	-0.87 (-7.00; 5.26)	-0.75 (-2.47; 0.98)	-0.95 (-2.46; 0.55)	-1.48 (-3.66; 0.71)	-1.45 (-3.11; 0.21)	-0.89 (-2.42; 0.65)	-0.63 (-2.39; 1.13)	-0.89 (-2.35; 0.58)	-1.09 (-2.63; 0.46)	L-5HTP												
-0.60 (-2.11; 0.92)	-0.72 (-2.22; 0.79)	-0.01 (-1.11; 1.10)	-0.02 (-6.10; 6.06)	0.10 (-1.42; 1.62)	-0.11 (-1.37; 1.16)	-0.63 (-2.66; 1.40)	-0.61 (-2.06; 0.85)	-0.04 (-1.35; 1.27)	0.22 (-1.35; 1.79)	-0.04 (-1.27; 1.19)	-0.24 (-1.56; 1.08)	0.85 (-1.04; 2.73)	LI+MPT		0.11 (-1.11; 1.33)	0.35 (-1.17; 1.87)		-0.02 (-1.30; 1.27)	0.03 (-1.20; 1.25)	-0.07 (-1.39; 1.25)	-0.01 (-1.20; 1.19)	0.37 (-1.04; 1.78)	0.05 (-1.20; 1.31)	0.1 (-1.2 1.52
-0.59 (-1.91; 0.72)	-0.71 (-2.06; 0.63)	-0.01 (-1.13; 1.12)	-0.02 (-6.06; 6.02)	0.10 (-1.26; 1.46)	-0.10 (-1.13; 0.92)	-0.63 (-2.54; 1.28)	-0.60 (-1.85; 0.64)	-0.04 (-1.12; 1.04)	0.22 (-1.16; 1.60)	-0.04 (-1.05; 0.97)	-0.24 (-1.34; 0.87)	0.85 (-0.92; 2.62)	0.00 (-1.57; 1.58)	MPT									
0.24 (-1.24; 1.73)	0.12 (-1.36; 1.61)	0.83 (-0.46; 2.12)	0.82 (-5.25; 6.89)	0.94 (-0.55; 2.43)	0.73 (-0.51; 1.97)	0.21 (-1.79; 2.20)	0.23 (-1.20; 1.66)	0.80 (-0.48; 2.09)	1.06 (-0.49; 2.60)	0.80 (-0.39; 1.99)	0.60 (-0.69; 1.89)	1.69 (-0.19; 3.56)	0.84 (-0.86; 2.54)	0.84 (-0.72; 2.39)	MZ								
-0.35 (-2.00; 1.29)	-0.47 (-2.14; 1.19)	0.23 (-1.26; 1.73)	0.22 (-5.89; 6.34)	0.34 (-1.34; 2.02)	0.14 (-1.29; 1.56)	-0.39 (-2.54; 1.76)	-0.36 (-1.95; 1.22)	0.20 (-1.26; 1.67)	0.46 (-1.23; 2.16)	0.20 (-1.21; 1.62)	0.00 (-1.48; 1.48)	1.09 (-0.93; 3.11)	0.24 (-1.62; 2.10)	0.24 (-1.46; 1.94)	-0.60 (-2.44; 1.24)	MSR							
-0.40 (-1.28; 0.48)	-0.52 (-1.44; 0.40)	0.19 (-0.36; 0.73)	0.18 (-5.78; 6.13)	0.29 (-0.65; 1.24)	0.09 (-0.22; 0.40)	-0.43 (-2.08; 1.21)	-0.41 (-1.18; 0.36)	0.16 (-0.29; 0.61)	0.42 (-0.55; 1.39)	0.16 (-0.09; 0.40)	-0.04 (-0.55; 0.47)	1.04 (-0.43; 2.51)	0.20 (-1.04; 1.43)	0.19 (-0.79; 1.18)	-0.64 (-1.85; 0.56)	-0.05 (-1.44; 1.34)	MB	0.24 (-0.66; 1.14)		-0.12 (-0.65; 0.40)	-0.08 (-0.43; 0.27)	-0.18 (-0.74; 0.39)	-0.12 (-0.39; 0.16)	0.26 (-0.53; 1.06)	-0.06 (-0.52; 0.41)	0.0 (-0.5 0.64
-0.01 (-1.41; 1.40)	-0.13 (-1.56; 1.30)	0.58 (-0.64; 1.80)	0.57 (-5.49; 6.62)	0.69 (-0.76; 2.13)	0.48 (-0.65; 1.62)	-0.04 (-2.01; 1.93)	-0.02 (-1.35; 1.32)	0.55 (-0.63; 1.73)	0.81 (-0.65; 2.27)	0.55 (-0.57; 1.67)	0.35 (-0.86; 1.56)	1.44 (-0.40; 3.27)	0.59 (-1.06; 2.24)	0.59 (-0.88; 2.06)	-0.25 (-1.88; 1.38)	0.35 (-1.42; 2.11)	0.39 (-0.70; 1.49)	MB+TRZ		-0.37 (-1.41; 0.67)	-0.32 (-1.29; 0.64)	-0.42 (-1.48; 0.65)	-0.36 (-1.30; 0.58)	0.02 (-1.18; 1.22)	-0.30 (-1.31; 0.72)	-0.2 (-1.2 0.89
-1.18 (-2.96; 0.59)	-1.30 (-3.01; 0.41)	-0.59 (-2.17; 0.98)	-0.61 (-6.75; 5.53)	-0.49 (-2.25; 1.28)	-0.69 (-2.24; 0.86)	-1.22 (-3.43; 1.00)	-1.19 (-2.89; 0.51)	-0.62 (-2.21; 0.96)	-0.37 (-2.17; 1.43)	-0.63 (-2.14; 0.89)	-0.83 (-2.42; 0.77)	0.26 (-1.78; 2.30)	-0.59 (-2.51; 1.33)	-0.59 (-2.40; 1.22)	-1.43 (-3.34; 0.49)	-0.83 (-2.89; 1.23)	-0.78 (-2.30; 0.74)	-1.18 (-3.05; 0.70)	NFS						
-0.71 (-1.73; 0.32)	-0.83 (-1.84; 0.19)	-0.12 (-0.81; 0.58)	-0.13 (-6.10; 5.84)	-0.01 (-1.05; 1.03)	-0.22 (-0.82; 0.39)	-0.74 (-2.44; 0.96)	-0.72 (-1.64; 0.21)	-0.15 (-0.84; 0.54)	0.11 (-0.99; 1.21)	-0.15 (-0.66; 0.37)	-0.35 (-1.06; 0.36)	0.74 (-0.79; 2.27)	-0.11 (-1.41; 1.19)	-0.11 (-1.22; 1.00)	-0.95 (-2.23; 0.33)	-0.35 (-1.84; 1.13)	-0.31 (-0.83; 0.22)	-0.70 (-1.91; 0.51)	0.48 (-1.10; 2.05)	NTL	0.04 (-0.49; 0.57)	-0.05 (-0.78; 0.68)	0.01 (-0.48; 0.50)	0.39 (-0.50; 1.28)	0.07 (-0.55; 0.68)	0.1 (-0.6 0.96
-0.20 (-1.12; 0.72)	-0.32 (-1.24; 0.59)	0.38 (-0.16; 0.92)	0.37 (-5.58; 6.33)	0.49 (-0.43; 1.41)	0.29 (-0.13; 0.70)	-0.24 (-1.86; 1.38)	-0.21 (-1.03; 0.61)	0.35 (-0.18; 0.89)	0.61 (-0.40; 1.62)	**0.35 (0.14; 0.57)**	0.15 (-0.40; 0.71)	1.24 (-0.23; 2.71)	0.39 (-0.84; 1.62)	0.39 (-0.63; 1.41)	-0.45 (-1.62; 0.72)	0.15 (-1.27; 1.57)	0.20 (-0.09; 0.48)	-0.20 (-1.33; 0.93)	0.98 (-0.54; 2.49)	0.50 (-0.01; 1.01)	PNZ	-0.09 (-0.71; 0.53)	-0.03 (-0.33; 0.26)	0.34 (-0.46; 1.15)	0.03 (-0.45; 0.50)	0.1 (-0.5 0.82
-0.21 (-1.28; 0.86)	-0.33 (-1.43; 0.76)	0.37 (-0.42; 1.17)	0.36 (-5.62; 6.35)	0.48 (-0.63; 1.59)	0.28 (-0.41; 0.96)	-0.25 (-1.99; 1.50)	-0.22 (-1.21; 0.76)	0.34 (-0.42; 1.11)	0.60 (-0.55; 1.75)	0.34 (-0.30; 0.99)	0.14 (-0.65; 0.93)	1.23 (-0.36; 2.82)	0.38 (-0.98; 1.75)	0.38 (-0.78; 1.54)	-0.46 (-1.80; 0.88)	0.14 (-1.38; 1.66)	0.19 (-0.43; 0.80)	-0.21 (-1.46; 1.05)	0.97 (-0.66; 2.60)	0.49 (-0.30; 1.28)	-0.01 (-0.66; 0.64)	PLD	0.06 (-0.51; 0.62)	0.44 (-0.50; 1.37)	0.12 (-0.56; 0.80)	0.2 (-0.6 1.04
-1.28 (-2.19; -0.37)	**-1.40 (-2.31; -0.48)**	**-0.69 (-1.19; -0.19)**	-0.70 (-6.66; 5.25)	-0.58 (-1.51; 0.34)	**-0.79 (-1.17; -0.40)**	-1.31 (-2.94; 0.32)	**-1.29 (-2.09; -0.48)**	**-0.72 (-1.23; -0.21)**	-0.46 (-1.46; 0.54)	**-0.72 (-0.94; -0.50)**	**-0.92 (-1.44; -0.40)**	0.17 (-1.30; 1.63)	-0.68 (-1.89; 0.53)	-0.68 (-1.69; 0.33)	**-1.52 (-2.71; -0.33)**	-0.92 (-2.33; 0.49)	**-0.88 (-1.12; -0.63)**	**-1.27 (-2.39; -0.15)**	-0.09 (-1.61; 1.42)	**-0.57 (-1.07; -0.07)**	**-1.07 (-1.30; -0.84)**	**-1.06 (-1.69; -0.43)**	PBO	0.38 (-0.36; 1.12)	0.06 (-0.31; 0.44)	0.1 (-0.4 0.82
-0.82 (-2.10; 0.46)	-0.94 (-2.22; 0.34)	-0.23 (-1.26; 0.80)	-0.24 (-6.27; 5.78)	-0.12 (-1.42; 1.17)	-0.33 (-1.31; 0.65)	-0.85 (-2.72; 1.01)	-0.83 (-2.04; 0.38)	-0.26 (-1.30; 0.77)	-0.00 (-1.35; 1.34)	-0.26 (-1.19; 0.66)	-0.46 (-1.50; 0.58)	0.62 (-1.10; 2.34)	-0.22 (-1.73; 1.29)	-0.23 (-1.58; 1.13)	-1.06 (-2.56; 0.43)	-0.47 (-2.14; 1.21)	-0.42 (-1.35; 0.51)	-0.81 (-2.25; 0.63)	0.36 (-1.40; 2.12)	-0.11 (-1.14; 0.91)	-0.62 (-1.55; 0.31)	-0.61 (-1.70; 0.49)	0.46 (-0.44; 1.36)	SLG-O	-0.32 (-1.15; 0.52)	-0.2 (-1.2 0.78
-1.40 (-2.39; -0.42)	**-1.52 (-2.51; -0.53)**	**-0.81 (-1.44; -0.19)**	-0.83 (-6.80; 5.14)	-0.71 (-1.71; 0.29)	**-0.91 (-1.45; -0.37)**	-1.44 (-3.11; 0.24)	**-1.41 (-2.30; -0.52)**	**-0.85 (-1.48; -0.21)**	-0.59 (-1.66; 0.48)	**-0.85 (-1.28; -0.41)**	**-1.05 (-1.69; -0.40)**	0.04 (-1.47; 1.55)	-0.81 (-2.08; 0.46)	-0.81 (-1.89; 0.27)	**-1.65 (-2.90; -0.40)**	-1.05 (-2.51; 0.41)	**-1.00 (-1.45; -0.55)**	**-1.40 (-2.58; -0.21)**	-0.22 (-1.78; 1.34)	**-0.70 (-1.32; -0.07)**	**-1.20 (-1.64; -0.76)**	**-1.19 (-1.92; -0.46)**	-0.13 (-0.50; 0.25)	-0.58 (-1.56; 0.39)	SLG-P	0.1 (-0.6 0.86
-0.01 (-1.23; 1.20)	-0.13 (-1.38; 1.12)	0.57 (-0.43; 1.58)	0.56 (-5.42; 6.54)	0.68 (-0.59; 1.95)	0.48 (-0.42; 1.38)	-0.05 (-1.89; 1.80)	-0.02 (-1.17; 1.12)	0.54 (-0.41; 1.50)	0.80 (-0.49; 2.09)	0.54 (-0.34; 1.42)	0.34 (-0.65; 1.33)	1.43 (-0.27; 3.12)	0.58 (-0.91; 2.08)	0.58 (-0.72; 1.88)	-0.26 (-1.73; 1.21)	0.34 (-1.29; 1.97)	-0.26 (-0.46; 1.23)	-0.39 (-1.39; 1.38)	-0.57 (-2.91)	-0.30 (-0.30; 1.68)	-0.70 (-0.70; 1.08)	-0.85 (-0.85; 1.24)	**(0.38; 2.14)**	-0.45 (-0.45; 2.06)	**(0.43; 2.35)**	STL
0.15 (-0.97; 1.26)	0.03 (-1.12; 1.17)	0.73 (-0.13; 1.59)	0.72 (-5.27; 6.71)	0.84 (-0.32; 2.00)	0.63 (-0.12; 1.39)	0.11 (-1.66; 1.88)	0.13 (-0.90; 1.17)	0.70 (-0.12; 1.52)	0.96 (-0.23; 2.15)	0.70 (-0.01; 1.42)	0.50 (-0.35; 1.35)	1.59 (-0.03; 3.21)	0.74 (-0.66; 2.14)	0.74 (-0.46; 1.94)	-0.10 (-1.48; 1.28)	0.50 (-1.05; 2.05)	0.54 (-0.14; 1.23)	0.15 (-1.14; 1.44)	1.33 (-0.33; 2.99)	0.85 (0.00; 1.70)	0.35 (-0.38; 1.08)	0.36 (-0.56; 1.27)	**1.42 (0.71; 2.13)**	0.96 (-0.18; 2.11)	1.55 (0.75; 2.35)	0.1 (-0.9 1.25
-0.28 (-1.28; 0.72)	-0.40 (-1.28; 0.48)	0.31 (-0.26; 0.87)	0.30 (-5.67; 6.26)	0.42 (-0.57; 1.40)	0.21 (-0.29; 0.70)	-0.31 (-1.98; 1.35)	-0.29 (-1.15; 0.57)	0.28 (-0.32; 0.87)	0.54 (-0.51; 1.58)	0.28 (-0.09; 0.65)	0.08 (-0.54; 0.70)	1.16 (-0.25; 2.58)	0.32 (-0.93; 1.56)	0.31 (-0.74; 1.37)	-0.52 (-1.75; 0.71)	0.07 (-1.37; 1.52)	0.12 (-0.27; 0.51)	-0.27 (-1.43; 0.89)	-0.56; 2.37)	0.43 (-0.14; 0.99)	-0.08 (-0.46; 0.31)	-0.07 (-0.78; 0.65)	**1.00 (0.62; 1.37)**	0.54 (-0.44; 1.52)	**1.12 (0.59; 1.66)**	-0.2 (-1.2 0.66
-0.27 (-1.81; 1.28)	-0.39 (-1.96; 1.18)	0.32 (-1.07; 1.70)	0.31 (-5.78; 6.40)	0.43 (-1.16; 2.01)	0.22 (-1.09; 1.53)	-0.30 (-2.38; 1.77)	-0.28 (-1.77; 1.21)	0.29 (-1.06; 1.64)	0.55 (-1.05; 2.15)	0.29 (-1.01; 1.58)	0.09 (-1.28; 1.46)	1.17 (-0.77; 3.12)	0.33 (-1.45; 2.10)	0.32 (-0.97; 1.62)	-0.51 (-2.26; 1.24)	0.08 (-1.80; 1.97)	0.13 (-1.14; 1.40)	-0.26 (-1.94; 1.42)	0.91 (-1.07; 2.89)	0.44 (-0.94; 1.81)	-0.07 (-1.37; 1.24)	-0.06 (-1.47; 1.36)	1.01 (-0.29; 2.30)	0.55 (-1.03; 2.13)	1.13 (-0.22; 2.48)	-0.2 (-1.7 1.27

Table 1. League table of all included treatments compared for efficacy (blue cells; lower triangle) and acceptability (red cells; upper triangle). The numbers show the Cohen's D effect size (95% CI). Significant differences are marked in bold. ATL:

amitriptyline; MB: moclobemide; TR: tranylcypromine; BRF: brofaromine; BPR: buproprion; CBT: cognitive behavioral therapy; CMP: clomipramine; DPR: desipramine; DTP: dothiepin; FXT: fluoxetine; FVX: fluvoxamine; IMP: imipramine; ISO: isocarboxazide; L-5HTP: L-5-hydroxytryptophan; LI: lithium; MPT: maprotiline; MZ: mebanazine; MSR: mianserin; TRZ: thioridazine; NFS: nomifensine; NTL: nortriptyline; PNZ: phenelzine; PLD: pirlindole; PBO: placebo; SLG-O: selegiline (oral); SLG-P: selegiline (patch); STL: sertraline; TOL: toloxatone; VLX: viloxazine.

ATL														
-0.92 (-1.85; 0.00)	CMP													
-1.15 (-2.78; 0.48)	-0.22 (-1.70; 1.25)	DPR												
-0.70 (-1.65; 0.25)	0.22 (-0.42; 0.86)	0.45 (-1.04; 1.93)	DTP											
-0.46 (-1.39; 0.47)	0.46 (-0.14; 1.07)	0.69 (-0.79; 2.16)	0.24 (-0.40; 0.89)	FXT										
-0.94 (-1.89; 0.01)	-0.02 (-0.64; 0.61)	0.21 (-1.28; 1.69)	-0.24 (-0.91; 0.43)	-0.48 (-1.12; 0.16)	FVX									
-0.56 (-1.41; 0.30)	0.37 (-0.12; 0.85)	0.59 (-0.83; 2.01)	0.14 (-0.39; 0.68)	-0.10 (-0.59; 0.40)	0.38 (-0.14; 0.91)	IMP								
-0.40 (-1.51; 0.71)	0.52 (-0.33; 1.37)	0.75 (-0.78; 2.28)	0.30 (-0.58; 1.18)	0.06 (-0.80; 0.92)	0.54 (-0.34; 1.42)	0.16 (-0.60; 0.91)	MZ							
-0.44 (-1.27; 0.38)	**0.48 (0.06; 0.90)**	0.70 (-0.71; 2.11)	0.26 (-0.22; 0.74)	0.02 (-0.42; 0.45)	**0.50 (0.03; 0.96)**	0.11 (-0.12; 0.35)	-0.04 (-0.78; 0.70)	MB						
-0.67 (-1.79; 0.45)	0.25 (-0.62; 1.12)	0.48 (-1.13; 2.08)	0.03 (-0.87; 0.93)	-0.21 (-1.09; 0.67)	0.27 (-0.63; 1.17)	-0.11 (-0.92; 0.69)	-0.27 (-1.34; 0.79)	-0.23 (-0.99; 0.54)	MB+TRZ					
-0.45 (-1.43; 0.53)	0.47 (-0.20; 1.15)	0.70 (-0.70; 2.09)	0.25 (-0.46; 0.96)	0.01 (-0.68; 0.69)	0.49 (-0.22; 1.19)	0.11 (-0.44; 0.66)	-0.05 (-0.85; 0.75)	-0.01 (-0.54; 0.52)	0.22 (-0.71; 1.15)	NTL				
-0.51 (-1.46; 0.43)	0.41 (-0.22; 1.04)	0.63 (-0.70; 1.97)	0.19 (-0.48; 0.86)	-0.05 (-0.69; 0.58)	0.43 (-0.23; 1.09)	0.04 (-0.45; 0.53)	-0.11 (-0.87; 0.64)	-0.07 (-0.54; 0.40)	0.16 (-0.74; 1.05)	-0.06 (-0.47; 0.35)	PNZ			
-0.25 (-1.18; 0.68)	**0.67 (0.06; 1.29)**	0.90 (-0.55; 2.35)	0.45 (-0.20; 1.11)	0.21 (-0.41; 0.83)	**0.69 (0.04; 1.34)**	0.31 (-0.18; 0.80)	0.15 (-0.66; 0.96)	0.19 (-0.25; 0.64)	0.42 (-0.46; 1.31)	0.20 (-0.42; 0.83)	0.27 (-0.31; 0.84)	PLD		
-0.16 (-1.04; 0.71)	**0.76 (0.24; 1.28)**	0.99 (-0.39; 2.36)	0.54 (-0.03; 1.11)	0.30 (-0.23; 0.83)	**0.78 (0.22; 1.34)**	**0.40 (0.05; 0.74)**	0.24 (-0.44; 0.91)	0.28 (-0.03; 0.59)	0.51 (-0.32; 1.33)	0.29 (-0.14; 0.72)	0.35 (0.00; 0.70)	0.09 (-0.36; 0.54)	PBO	
-0.49 (-1.42; 0.44)	0.43 (-0.17; 1.03)	0.66 (-0.75; 2.07)	0.21 (-0.43; 0.86)	-0.03 (-0.64; 0.58)	0.45 (-0.19; 1.09)	0.07 (-0.39; 0.52)	-0.09 (-0.83; 0.65)	-0.05 (-0.48; 0.38)	0.18 (-0.70; 1.06)	-0.04 (-0.56; 0.49)	0.02 (-0.44; 0.49)	-0.24 (-0.78; 0.30)	**-0.33 (-0.63; -0.03)**	SLG-P
-1.00 (-2.07; 0.08)	-0.07 (-0.88; 0.74)	0.15 (-1.42; 1.72)	-0.29 (-1.14; 0.55)	-0.54 (-1.35; 0.28)	-0.06 (-0.89; 0.78)	-0.44 (-1.17; 0.29)	-0.60 (-1.61; 0.42)	-0.55 (-1.25; 0.14)	-0.33 (-1.36; 0.71)	-0.55 (-1.42; 0.33)	-0.48 (-1.32; 0.35)	-0.75 (-1.57; 0.08)	**-0.83 (-1.59; -0.08)**	-0.51 (-1.32; 0.31)

Table 2. League table of all included treatments compared for tolerability. Significant differences are marked in bold. ATL: amitriptyline; CMP: clomipramine; DPR: desipramine; DTP: dothiepin; FXT: fluoxetine; FVX: fluvoxamine; IMP: imipramine; MZ: mebanazine; MB: moclobemide; TRZ: thioridazine; NTL: nortriptyline; PNZ: phenelzine; PLD: pirlindole; PBO: placebo; SLG-P: selegiline (patch); TR: tranylcypromine.

PRISMA 2009 Flow Diagram; Search carried out on November 15th, 2021.

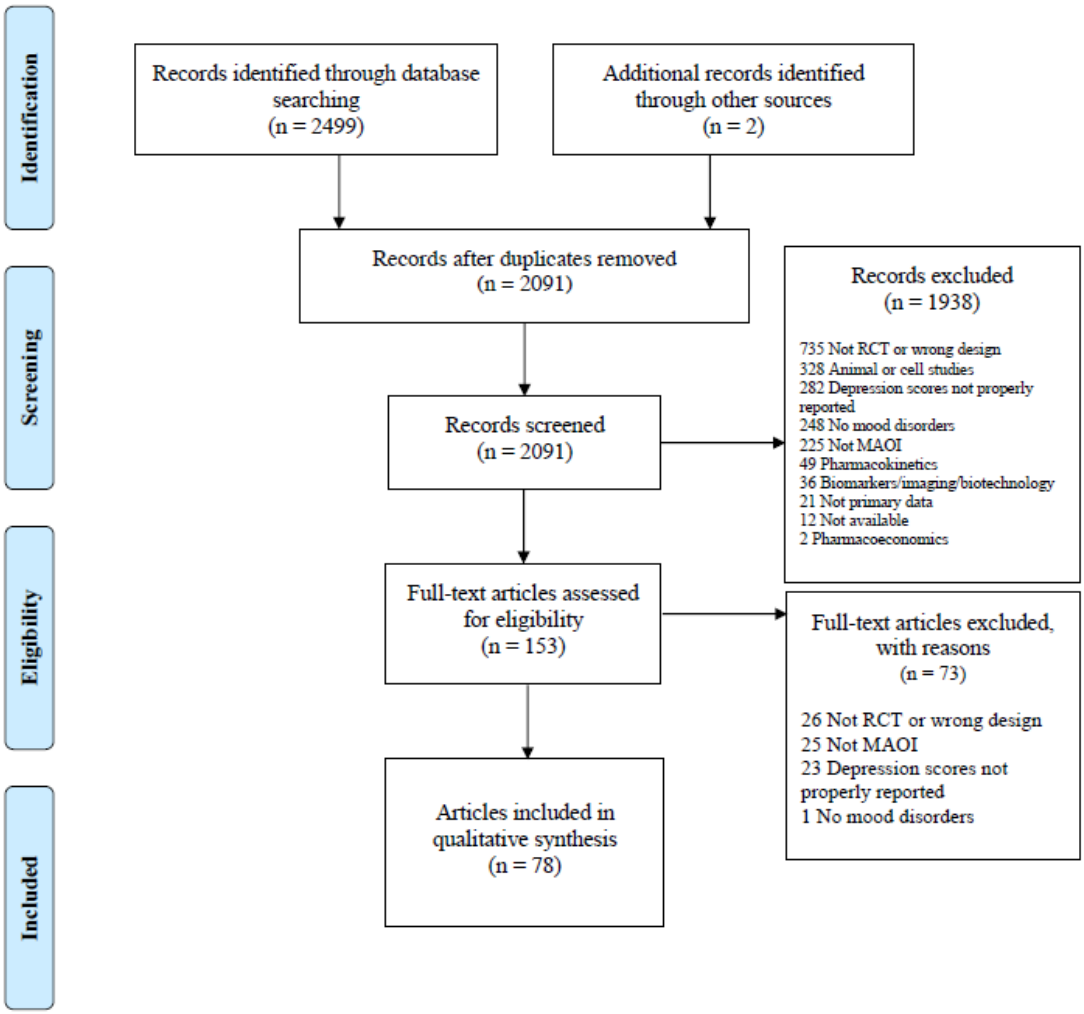

Figure 1. PRISMA Flow diagram of the included studies.

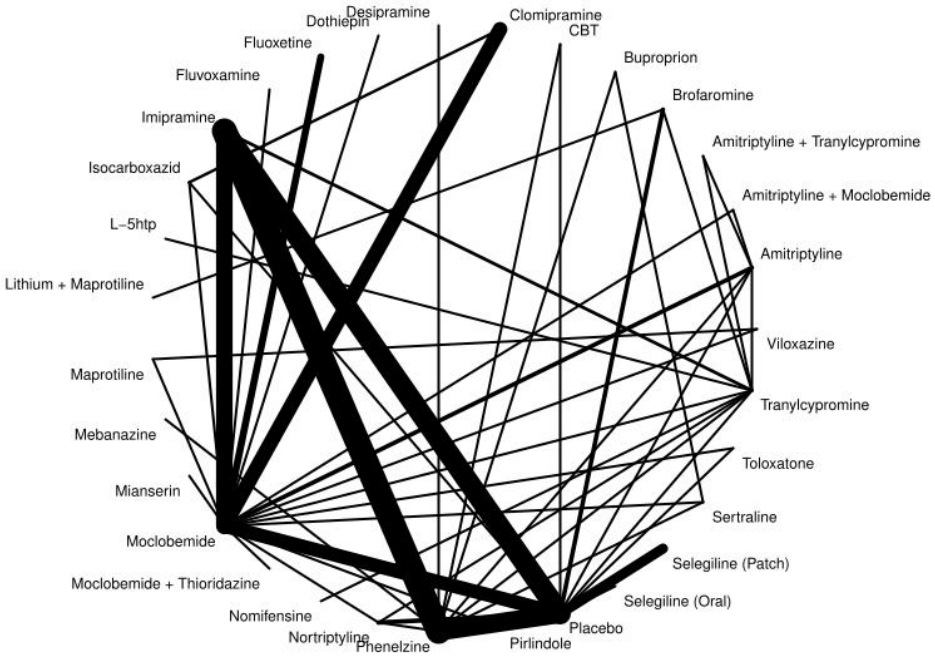

Figure 2. Network meta-analysis of all eligible trials compared for efficacy. Width of the lines is proportional to the number of trials comparing every pair of treatments. CBT: cognitive behavioral therapy; L-5htp: L-5-hydroxytryptophan.

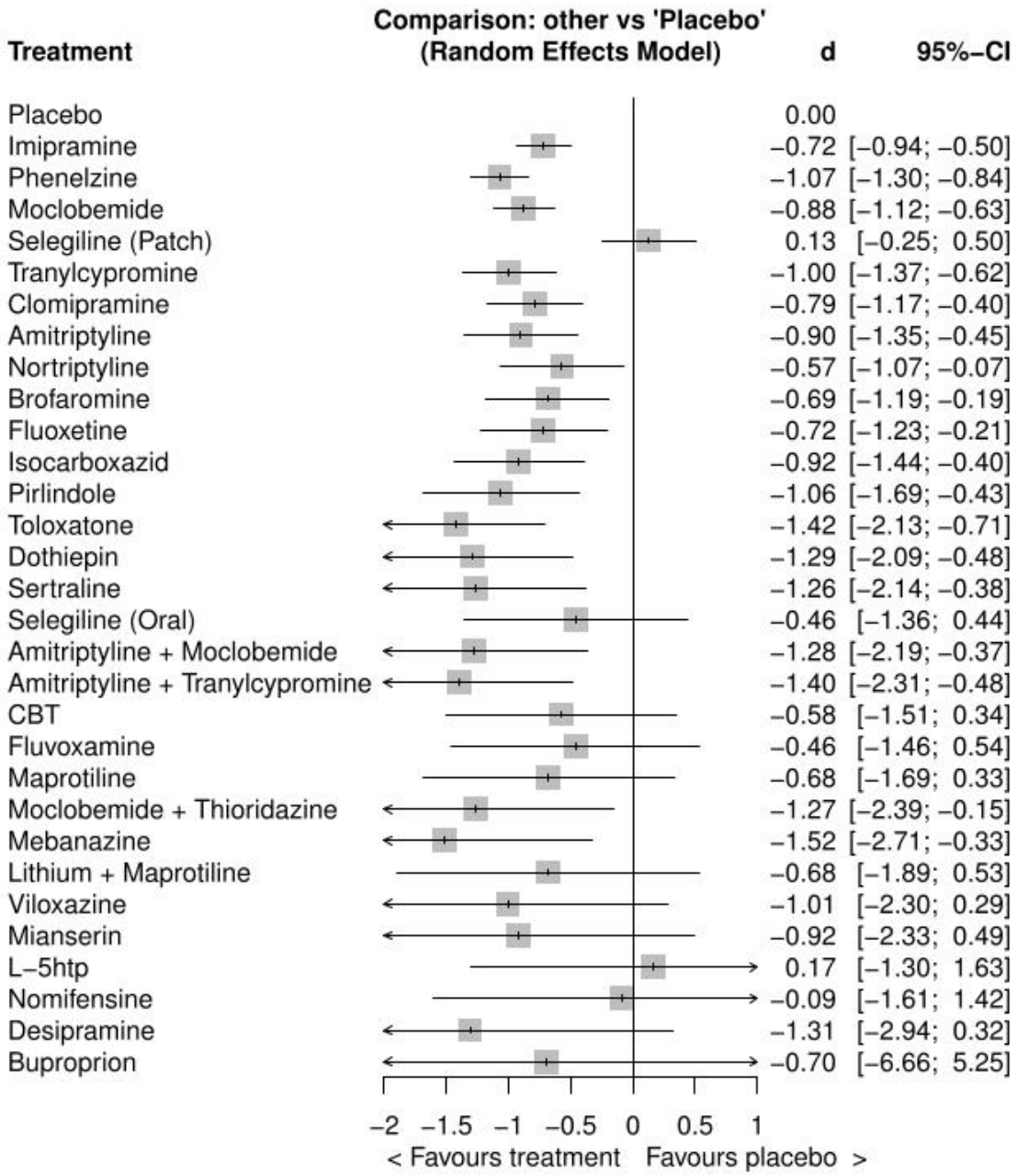
Comparison: other vs 'Placebo'
Treatment
(Random Effects Model)
d
95%−CI
Placebo 0.00
Imipramine −0.72 [−0.94; −0.50]
Phenelzine −1.07 [−1.30; −0.84]
Moclobemide −0.88 [−1.12; −0.63]
Selegiline (Patch) 0.13 [−0.25; 0.50]
Tranylcypromine −1.00 [−1.37; −0.62]
Clomipramine −0.79 [−1.17; −0.40]
Amitriptyline −0.90 [−1.35; −0.45]
Nortriptyline −0.57 [−1.07; −0.07]
Brofaromine −0.69 [−1.19; −0.19]
Fluoxetine −0.72 [−1.23; −0.21]
Isocarboxazid −0.92 [−1.44; −0.40]
Pirlindole −1.06 [−1.69; −0.43]
Toloxatone −1.42 [−2.13; −0.71]
Dothiepin −1.29 [−2.09; −0.48]
Sertraline −1.26 [−2.14; −0.38]
Selegiline (Oral) −0.46 [−1.36; 0.44]
Amitriptyline + Moclobemide −1.28 [−2.19; −0.37]
Amitriptyline + Tranylcypromine −1.40 [−2.31; −0.48]
CBT −0.58 [−1.51; 0.34]
Fluvoxamine −0.46 [−1.46; 0.54]
Maprotiline −0.68 [−1.69; 0.33]
Moclobemide + Thioridazine −1.27 [−2.39; −0.15]
Mebanazine −1.52 [−2.71; −0.33]
Lithium + Maprotiline −0.68 [−1.89; 0.53]
Viloxazine −1.01 [−2.30; 0.29]
Mianserin −0.92 [−2.33; 0.49]
L−5htp 0.17 [−1.30; 1.63]
Nomifensine −0.09 [−1.61; 1.42]
Desipramine −1.31 [−2.94; 0.32]
Buproprion −0.70 [−6.66; 5.25]
−2 −1.5 −1 −0.5 0 0.5 1
< Favours treatment Favours placebo >

Figure 3. Forest plot of network meta-analysis of all eligible trials for efficacy. Thirty different treatments were compared with placebo. d=Cohen's D effect size. CI=confidence interval. CBT: cognitive behavioral therapy; L-5htp: L-5-hydroxytryptophan.

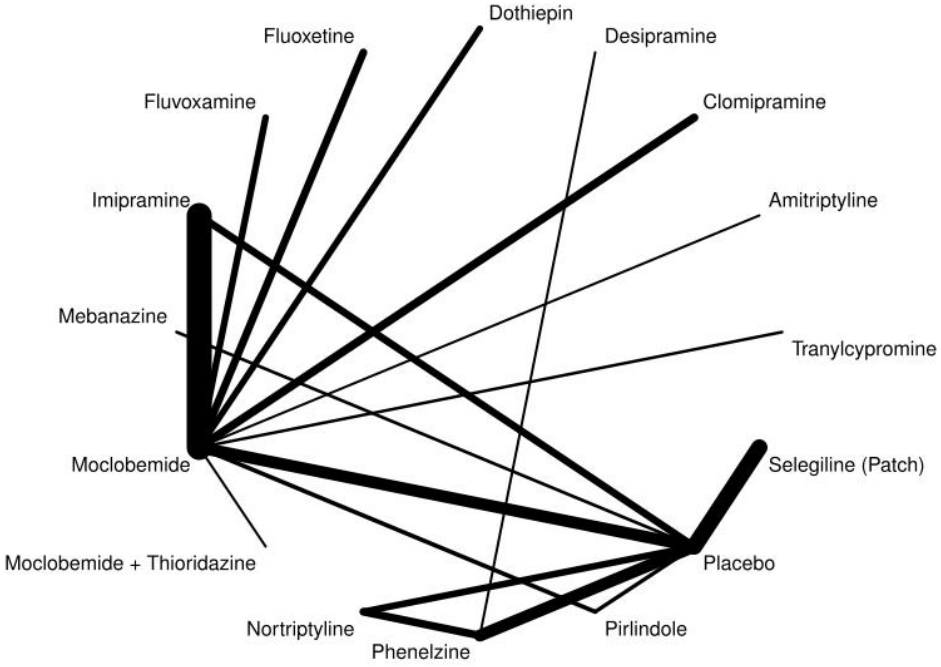

Figure 4. Network meta-analysis of all eligible trials compared for tolerability. Width of the lines is proportional to the number of trials comparing every pair of treatments.

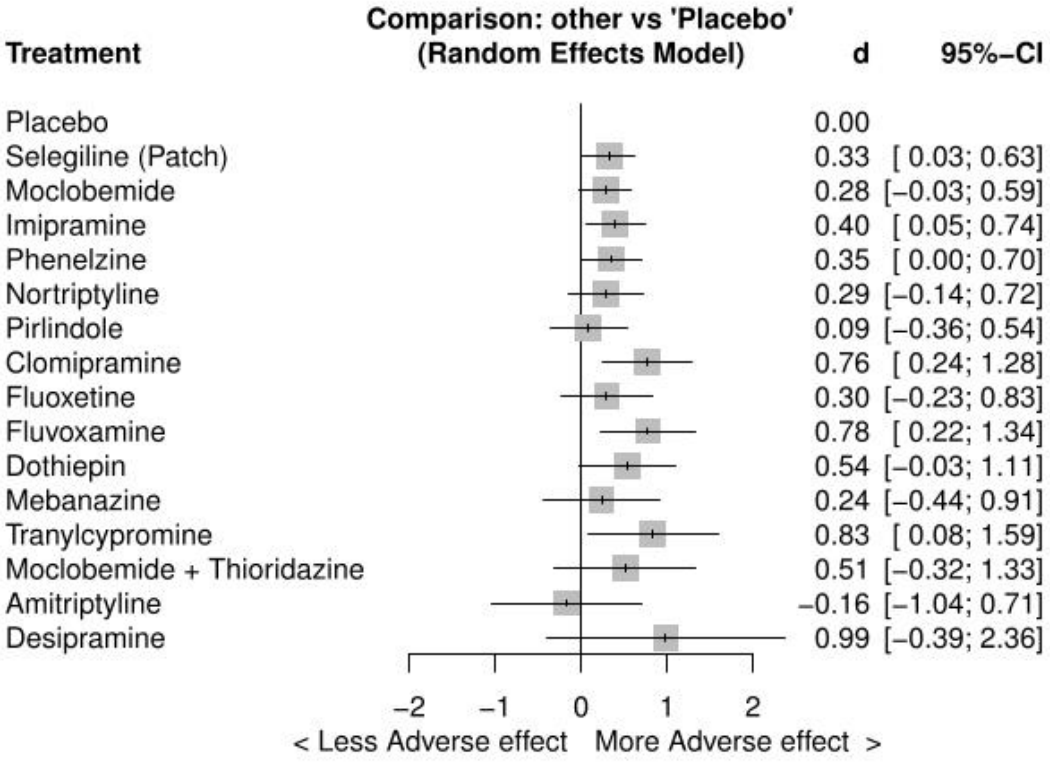

Figure 5. Forest plot of network meta-analysis of all eligible trials for tolerability. Fifteen different treatments were compared with placebo. d=Cohen's D effect size. CI=confidence interval.

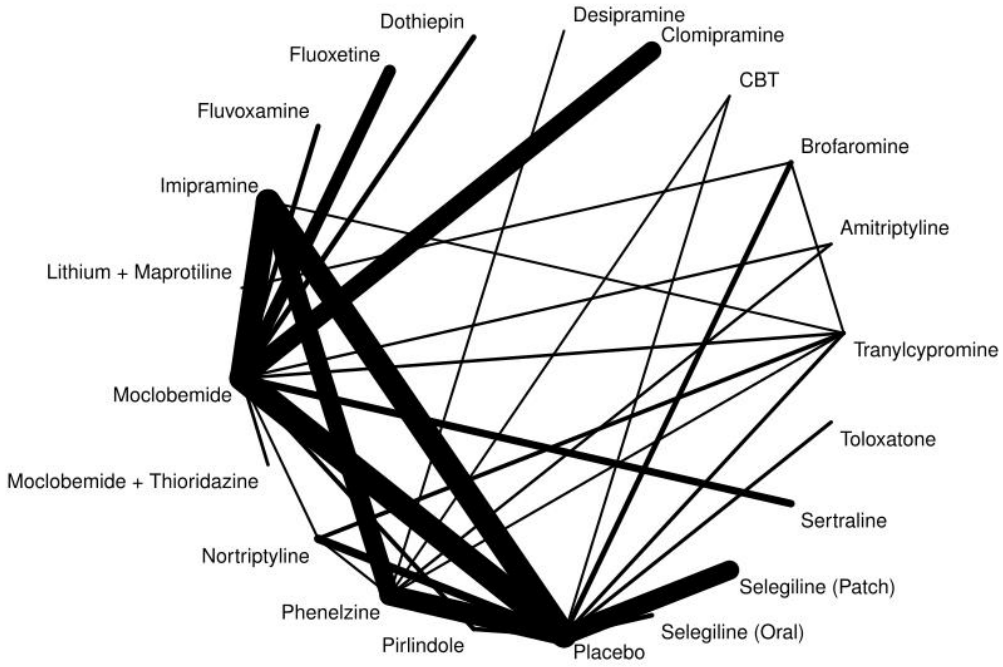

Figure 6. Network meta-analysis of all eligible trials compared for acceptability. Width of the lines is proportional to the number of trials comparing every pair of treatments. CBT: cognitive behavioral therapy.

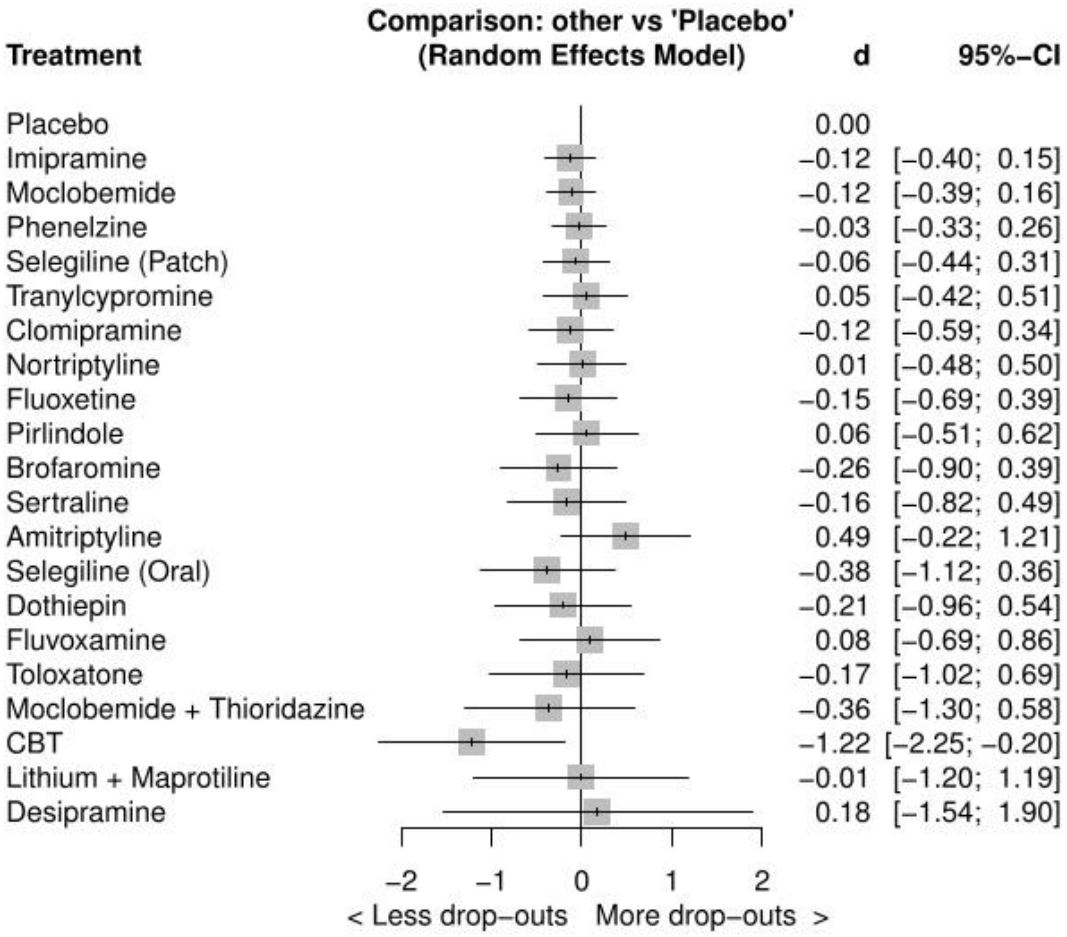

Figure 7. Forest plot of network meta-analysis of all eligible trials for acceptability. Twenty different treatments were compared with placebo. d=Cohen's D effect size; CI=confidence interval. CBT: cognitive behavioral therapy.