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Review article

Pharmacological and non-pharmacological treatments for major depressive disorder in adults: A systematic review and network meta-analysis

Chen Chen, Weiguang Shan*

College of Pharmaceutical Sciences, Zhejiang University of Technology, No. 18 Chaowang Road Xiacheng District, Hangzhou 310014, Zhejiang, China

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ABSTRACT

Depression has brought huge disease burden to the world. This systematic review aimed to compare the efficacy and safety of pharmacological and non-pharmacological treatments for major depressive disorder (MDD). We searched electronic databases with time range from 1990.1.1 to 2018.9.5. Randomized controlled trials (RCTs) including adult patients with MDD were eligible for inclusion. We conducted network meta-analyses using multivariate meta-analyses models under the frequency framework. Primary outcomes were efficacy (response rate) and safety (overall risk of adverse events). We estimated summary odds ratios (ORs) based on group-level data. 20,937 citations were identified, 91 trials comprising 10,991 participants were included in efficacy study, and 32 trials comprising 5245 participants were included in safety study. In terms of efficacy, all treatments studied (acupuncture, mirtazapine, herbal medicine, venlafaxine, physical exercise, cognitive-behavioral therapy (CBT), bupropion, fluoxetine, and vortioxetine) except for probiotics were significantly more effective than placebo. In terms of safety, bupropion, fluoxetine, venlafaxine, and vortioxetine were significantly less safe than placebo. Herbal medicine and mirtazapine had no significant difference in overall risk of adverse events compared with placebo. Acupuncture, CBT, physical exercise and probiotics were lack of eligible safety data.

1. Introduction

Depression is one of the leading causes of disability worldwide. The WHO estimated that depression would account for 13% of the global burden of disease by 2030, and replace cardiovascular disease as the largest disease burden (Levav and Rutz, 2002). Studies have shown that the longer the duration of depression, the lower the response rate and the worse prognosis (Trivedi et al., 2006). Therefore, the best treatment should be taken as early as possible to maximize the therapeutic effect.

Most medication guides recommend second-generation antidepressants (SGAs) as a first-line treatment option (Qaseem et al., 2016), which include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and drugs that modulate other neurotransmitters and/or receptors (Mojtabai and Olfson, 2008). SSRIs and SNRIs account for more than 90% of the global antidepressants market (Artigas, 2013). However, some people with depression may prefer non-pharmacological treatments. Because antidepressants' short-term effects are generally limited and the long-term risks are often not fully studied (Ioannidis, 2008). Multiple non-pharmacological treatments are available, mainly including psychotherapy, complementary and alternative medicine (CAM), physical exercise, etc.

For clinicians, the large quantity and varying quality of scientific publications make evidence-based decisions difficult. A recent review (Gartlehner et al., 2017) of systematic reviews summarized the evidence on more than 140 pharmacological and non-pharmacological treatments for MDD. The authors found that SGAs and CBT present small beneficial treatment effects, while the majority of non-pharmacological treatments for MDD are not evidence based. The primary limitation is that these results rely on results from other investigators but not directly on RCTs. So it may not provide a picture of the totality of the evidence. With similar results, a previous review (Gartlehner et al., 2015) compared the benefits and harms of SGAs with non-pharmacological treatments based on data from clinical trials. SGAs were taken as the same kind of treatment so we could not tell the differences of various drugs compared with non-drug treatments.

This systematic review aimed to compare the efficacy and safety of pharmacological and non-pharmacological treatments for MDD in adults. Primary outcomes were efficacy (response rate, namely the percentage of patients whose scores on a depression scale decreased by 50% or more (Furukawa et al., 2016; Leon, 2001)) and safety (overall risk of adverse events). According to the action mechanism of antidepressants, the universality of their use and the availability of clinical trial data, we focused on bupropion, fluoxetine, mirtazapine,

* Corresponding author.
E-mail address: swg@zjut.edu.cn (W. Shan).

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venlafaxine and vortioxetine in this review. Due to lack of high quality data, among all of the non-pharmacological treatments, our study objects were limited to CBT, CAM (limited to acupuncture, herbal medicine and probiotics) and physical exercise. In this paper, herbal medicine referred to hypericum and traditional Chinese medicine. To sum up, we studied 10 active treatments mentioned above for adult patients with MDD. We did not take combination or augmentation strategies of pharmacological with non-pharmacological treatments into consideration.

2. Methods

2.1. Search strategy

The current systematic review and network meta-analysis was conducted in accordance with the reporting guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) for Network Meta-Analyses (PRISMA-NMA) (Hutton et al., 2015). We searched PubMed, the Cochrane Library, Web of Science and CNKI (China National Knowledge Infrastructure) with time range from 1990.1.1 to 2018.9.5. The search was limited to human studies, written in English or Chinese. Reference lists from identified articles were manually searched for additional relevant studies. All citations were imported into an electronic database (EndNote®X8, Thomson Reuters). All identified articles were screened by two independent reviewers for inclusion. Where there was disagreement on inclusion, consensus was reached through discussion.

2.2. Eligibility criteria

We included studies addressing our predefined eligibility criteria outlined in Table 1.

2.3. Study selection

Two reviewers independently screened the titles and abstracts of the candidate studies, and retrieved full texts of potentially relevant articles. Two reviewers assessed full-text articles independently for inclusion. Disagreements were resolved by consensus.

2.4. Data abstraction

We used a standardized table to abstract the following information: first author(s), publication year, population characteristics, treatments, depression type, duration, measurement tool, sample sizes, outcomes of efficacy and safety, study designs including randomized method, allocation method and blindness.

We recorded intent-to-treat results when reported. For cases in which only per-protocol results were reported, we calculated intent-to-treat results using the number of all randomized patients as the denominator if calculation data were available. Studies without valid data to be calculated were omitted. We did not contact authors of studies for additional information and data.

2.5. Risk of bias assessment

We assessed the risk of bias of trials using the Cochrane risk-of-bias tool (Higgins et al., 2011). The domains of bias include selection bias (including sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias and other bias. Each of above domain was evaluated as 'high risk', 'low risk', or 'unclear risk' according to the tool. Two reviewers independently assessed the risk of bias of each study. Differences were resolved by consensus.

2.6. Statistical analysis

Because of the dearth of studies directly comparing pharmacological and non-pharmacological treatments for MDD, we preplanned to conduct network meta-analyses based on group-level data. The outcome measure for efficacy was the response to treatment on the Hamilton Depression Rating Scale (HAMD) or Montgomery-Åsberg Depression Rating Scale (MADRS) defined as a 50% improvement of scores from baseline. The outcome measure for safety was the overall risk of adverse events defined as the proportion of participants who experienced at least one adverse event during treatment. To synthesize information on dichotomous outcomes, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. We recorded intent-to-treat results and recalculated them with available data if only per-protocol results were reported.

We performed network meta-analyses with Stata SE version 15 (Stata Corp, TX, USA) using the network meta command and Stata routines available at http://www.mtm.uoi.gr. All analyses used random effects restricted maximum likelihood models under the frequency framework in this approach (White, 2011). Heterogeneity was quantified using the I^2 statistic where 25% = small, 50% = moderate, and 75% = high heterogeneity (Higgins et al., 2003). For all analyses, we used the consistency model, which assumes a common estimate for the heterogeneity variance across the different comparisons. To infer whether the inconsistency factor is incompatible with zero, we assessed the 95% confidence interval and a loop-specific z-test. Further, we evaluated the inconsistency between direct and indirect estimates in closed loops using the network sidesplitting which fits the network node-splitting model for multi-arm trials (Dias et al., 2010).

Table 1
Eligibility criteria for relevant studies.

Criteria	Inclusion	Exclusion
Populations	• Adults (18 years or older) who meet a validated diagnostic instruments for MDD	• Under 18 years old • Bipolar depression, psychotic depression, treatment resistant depression, perinatal depression • With severe suicidal tendency
Interventions	• Bupropion, fluoxetine, mirtazapine, venlafaxine and vortioxetine • CBT • CAM (limited to acupuncture, herbal medicine and probiotics) • Physical exercise	• Combination of multiple treatments • Other treatments not covered by the study
Comparators	• Any inactive intervention (e.g., placebo, waiting list, sham treatment, no care), and above active treatments covered by the study	• Other treatments not covered by the study
Outcomes	• Efficacy:treatment response rate • Safety:overall risk of adverse events	• Studies not include outcomes or with incomplete outcomes
Language	• English, Chinese	• Other languages
Timing	• At least 4 weeks	• Less than 4 weeks
Study designs	• RCTs	• Other study designs, secondary analysis

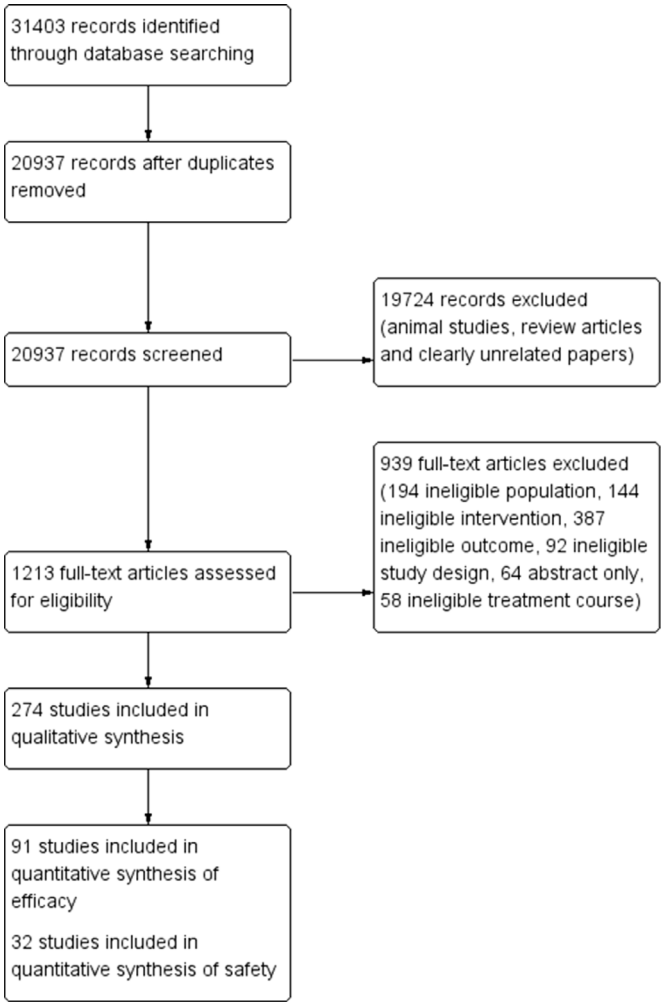

Fig. 1. Study selection flow chart.

3. Results

3.1. Search results and characteristics of included studies

After removal of duplicates, 20,937 citations were identified by the search and 1213 potentially eligible articles were retrieved in full-text. A total of 91 RCTs were identified and included in our network meta-analysis for efficacy, and a total of 32 RCTs were identified and included in our network meta-analysis for safety. Fig. 1 shows the flow of study selection. The characteristics of the included population were comparable at baseline.

3.2. Assessment of bias

The quality of the included RCTs was assessed systematically via Cochrane risk-of-bias tool (Higgins et al., 2011) based on the previously described six domains of bias. Valid evidence shows that if each of the used bias risk domains is 'high risk of bias' or 'unclear risk of bias' then there is a risk of overestimation of benefits and underestimation of harms (Garattini et al., 2016; Hrobjartsson et al., 2014, 2012, 2013; Lundh et al., 2012; Savovic et al., 2012; Schulz et al., 1995; Sutton et al., 2000). For efficacy study, most studies had low risk of randomization, while most studies did not report allocation concealment. About 35% of included studies had high risk of performance bias. The main reason is that our study included many non-pharmacological treatments, such as psychological therapy and physical exercise, which cannot blind the researchers and subjects. A quarter of included studies had high risk of attrition bias because they had more than 15% drop-outs. Most included studies had unclear risk of other biases.

For safety study, all included studies had low risk of selection bias in terms of randomization, while most studies did not report allocation concealment. Most included studies had low risk of performance, detection, attrition and reporting biases. Other bias for most studies was unclear.

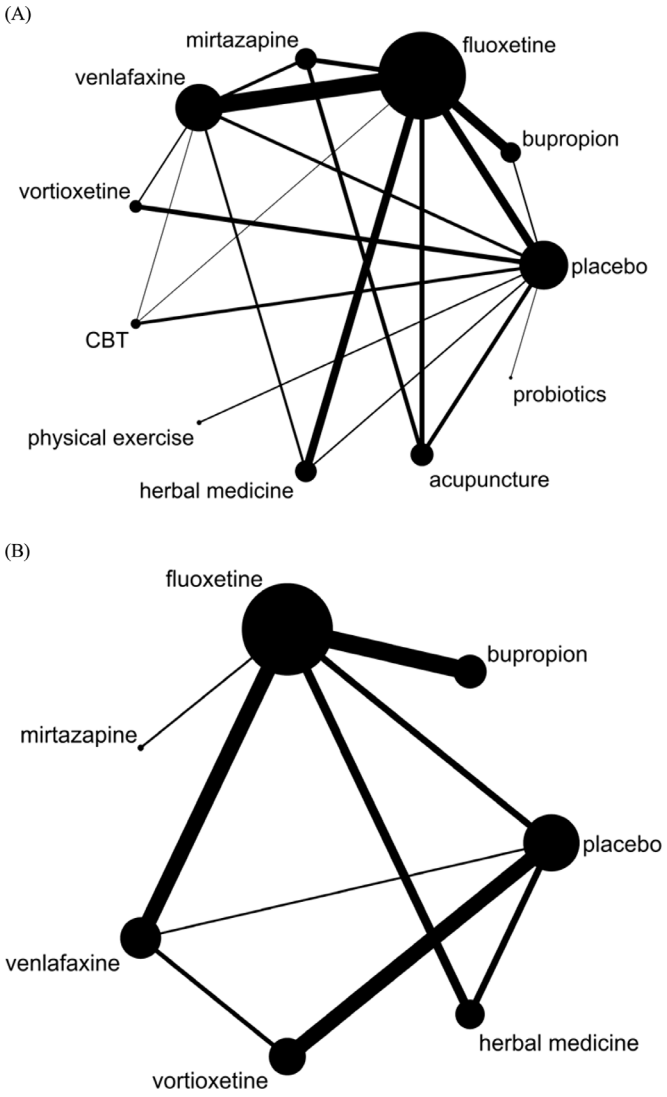

Fig. 2. Display of the network of eligible studies for efficacy (A) and safety (B). Size of every circle is proportional to the number of randomly assigned participants (i.e., sample size). Width of the lines is proportional to the number of trials comparing every pair of treatments.

3.3. Network meta-analysis

A total of 91 studies, 190 arms and 10,991 cases were included in the network meta-analysis for efficacy. A total of 32 studies, 66 arms and 5245 cases were included in the network meta-analysis for safety. Heterogeneity of the pooled sample was found to be moderate for both efficacy (I^2 = 52.7%) and safety (I^2 =60.1%). Fig. 2 presents the network of eligible studies involving 10 treatments and placebo for efficacy (A), and 6 treatments and placebo for safety (B).

In terms of efficacy, network meta-analysis showed all treatments except for probiotics were more effective than placebo measured by response rate. ORs ranged between 3.14 (95% CI, 2.27–4.36) for acupuncture and 1.73 (1.40–2.14) for fluoxetine. 95% CI line of probiotics

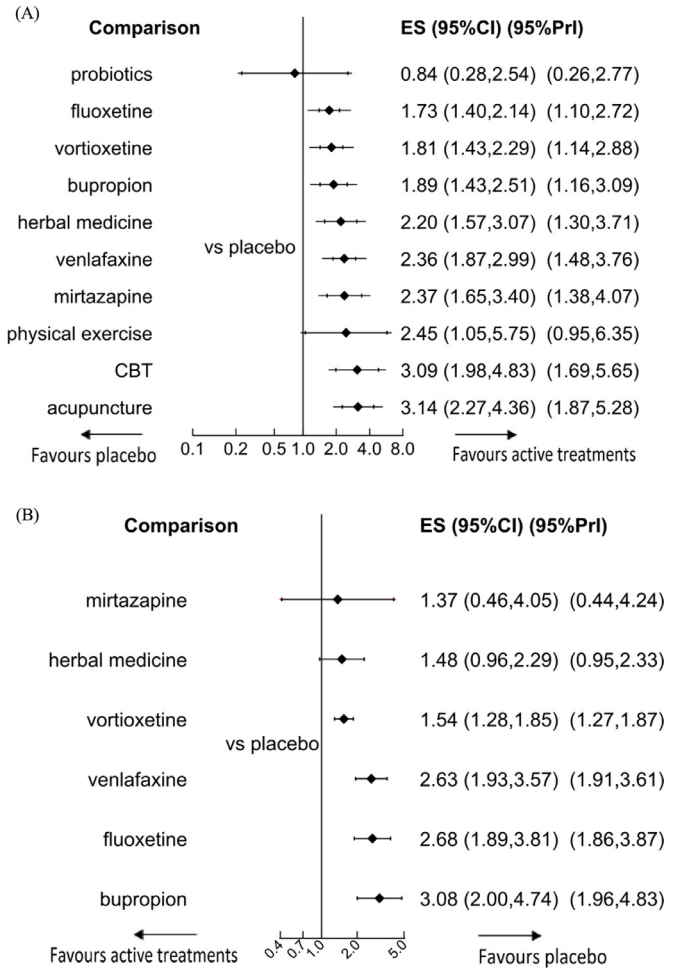

Fig. 3. Results of network meta-analyses for efficacy (A) and safety (B). Placebo was the reference.

(0.84, 0.28–2.54) intersected the invalid line indicating difference was not statistically significant (Fig. 3(A)). In terms of safety, bupropion (3.08, 2.00–4.74), fluoxetine, venlafaxine, and vortioxetine (1.54, 1.28–1.85) were associated with more overall adverse events than placebo. ORs of herbal medicine (1.48, 0.96–2.99) and mirtazapine (1.37, 0.46–4.05) were greater than 1, but showed no significant difference compared with placebo (Fig. 3(B)).

Table 2 shows the relative rank of all treatments studied based on

Table 2
Relative rank of treatments for MDD.

Treatment	Efficacy SUCRA	PrBest	MeanRank	Safety SUCRA	PrBest	MeanRank
placebo	06.5	00.0	10.4	94.7	69.5	01.3
bupropion	40.2	00.0	07.0	06.8	00.0	06.6
fluoxetine	28.1	00.0	08.2	23.4	00.0	05.6
mirtazapine	65.5	01.3	04.5	69.0	27.9	02.9
venlafaxine	66.9	00.5	04.3	24.7	00.0	05.5
vortioxetine	35.0	0.00	07.5	63.9	00.0	03.2
CBT	86.8	37.5	02.3	/	/	/
physical exercise	63.8	22.3	04.6	/	/	/
herbal medicine	57.9	00.7	05.2	67.5	02.6	03.0
acupuncture	90.7	37.2	01.9	/	/	/
probiotics	08.7	00.6	10.1	/	/	/

SUCRA: Surface Under the Cumulative Ranking Curve, the maximum value is 100, the larger the better.
PrBest: the probability that the treatment becomes the best treatment.
MeanRank: the relative mean rank of the treatment among all the treatments.

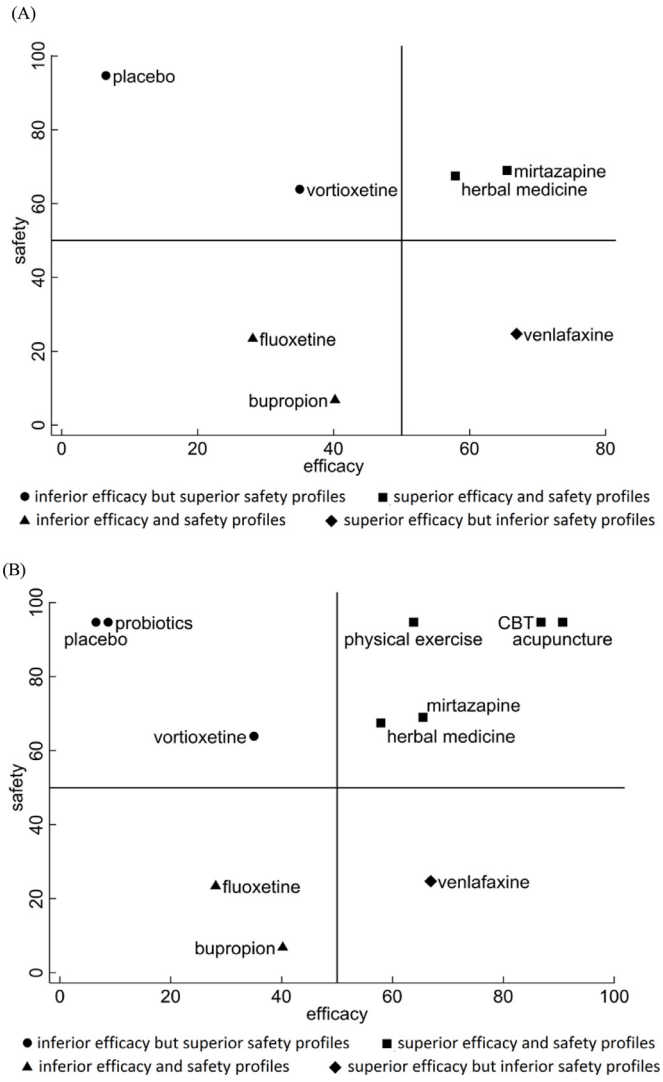

Fig. 4. Two-dimensional graphs for efficacy and safety in available studies (A) and all studies (B).

cumulative probability plots and SUCRAs. Among them, CBT, physical exercise, acupuncture and probiotics were lack of safety data.

Fig. 4 reports the two-dimensional graph of treatments with both available data on efficacy and safety (A), and the two-dimensional graph of all treatments that suppose the treatments without safety data had the same SUCRAs as placebo (B).

4. Discussion

Our systematic review focused on five pharmacological treatments with different mechanisms for MDD, they were bupropion, fluoxetine, mirtazapine, venlafaxine and vortioxetine. In terms of non-pharmacological treatments, we only studied CBT, CAM (limited to acupuncture, herbal medicine and probiotics) and physical exercise due to lack of high quality data. Because of a lack of head-to-head trials, we employed network meta-analyses which enabled us to use a more comprehensive evidence base including placebo-controlled and head-to-head trials.

Results of network meta-analyses indicated that mirtazapine and herbal medicine had a relatively higher response and lower overall adverse events rates than the other included treatments. By contrast, bupropion and fluoxetine had inferior efficacy and safety profiles compared with the other treatments. Vortioxetine had superior safety but inferior efficacy profiles. By contrast, venlafaxine had inferior

safety but superior efficacy profiles. Acupuncture, CBT and physical exercise were associated with superior efficacy profiles but they were lack of eligible safety data. Probiotics were not significantly more effective than placebo and lack of safety data.

To the best of our knowledge, our work is the most comprehensive network meta-analysis to date of the comparative efficacy and safety of pharmacological and non-pharmacological treatments for MDD. An earlier review (Gartlehner et al., 2017) summarized evidence on 28 comparisons covered psychological and behavioral interventions, somatic treatments, CAM therapies, and pharmacological interventions for MDD based on 19 systematic reviews. This review put all the second-generation antidepressants in one category so it neglected differences between drugs. Moreover, secondary data of reviews had significant statistical disadvantage than that of RCTs. For direct comparisons in the absence of inactive intervention, the true effect of treatments cannot be distinguished.

Our current analysis had several notable limitations. First, the scope was limited to adult patients with MDD. We did not include treatments for children and adolescents with MDD, patients with psychotic depression, perinatal depression, treatment resistant depression, or patients with severe suicidal ideas and behaviors. Especially, after the failure of the first step treatment, the information in this paper cannot guide the choice of the next step treatment since qualified trials are rare for treatment resistant depression (Furukawa et al., 2011). Consequently, we cannot gauge the generalizability of our findings to these populations, but it was intended as a methodological strength to assure transitivity in the network. Furthermore, depression has different subtypes that can be parsed in many ways. Some studies define depression as atypical, melancholic, seasonal, agitated subtypes and so on, by identifying clusters of symptoms, neuroendocrine activity, circadian rhythms and other potential biomarkers (Beijers et al., 2019; Gold and Chrousos, 2002; Lewy et al., 1987). While an alternative to subtyping patients is to identify neurophysiological subtypes according to shared signatures of brain dysfunctions (Clementz et al., 2016). Neuroimaging using positron emission tomography (PET) or functional MRI (fMRI) has been used extensively to characterize brain states of depressed patients. Williams (Williams, 2016) focuses on six circuits that have been implicated in abnormal activities expressed in depression and anxiety, and proposes putative biotypes accordingly. By using fMRI in a large multisite sample, Drysdale and colleagues (Drysdale et al., 2017) show that depression can be subdivided into four neurophysiological subtypes defined by distinct patterns of dysfunctional connectivity in limbic and frontostriatal networks. There is evidence that responses of various treatments differ in depression subtypes defined by distinct abnormal brain connectivity (Drysdale et al., 2017; Dunlop et al., 2017; Underwood, 2019).

Second, the heterogeneity of study designs might bias the results. In this paper, it was mainly reflected in the following aspects. (1) The included trials covered patients with different degrees of depression, and no distinction was made according to the severity of the disease. Studies have shown that patients with different initial severity of depression respond differently to treatments, that antidepressants work better for patients with more severe symptoms, and that there is a potential risk of overtreatment for patients with mild symptoms or even those who have not yet met the criteria for clinical depression (Fournier et al., 2010; Khan et al., 2002; Kirsch et al., 2008; Mitchell et al., 2011). In clinical trials of antidepressant registration, it is generally required that the HAMD score of the enrolled patients be above 18–20. According to an estimate by Zimmerman et al. (2002), this limitation would exclude half of the patients who meet the diagnostic criteria for depression in the real world. Evidence for the true efficacy of antidepressants in patients with mild to moderate depression is therefore scarce. (2) Demographic factors such as age and gender might modify the treatment results. Besides, we included some studies aimed at elderly patients, but it has been indicated that elderly depressed patients were significantly different from other adult depressed patients (Fiske et al., 2009). We did not carry out analysis at the individual patient level due to lack of available data. (3) Heterogeneity also existed in the same treatment, e.g. inconsistent doses and durations of antidepressants. Heterogeneity among the non-drug treatments was greater, which was reflected in the differences in the psychotherapists' experience and treatment duration, differences in prescriptions and doses of herbal medicine (though we found no significant differences in response rates ($p = = 0.92 > 0.05$) and overall risk of adverse events ($p = = 0.85 > 0.05$) of different included herbal medicine by using one-sample T test), difference of probiotics species and doses, and differences in physical activities' patterns, intensity, frequency, and duration. Also, the types of inactive interventions could make a difference in the results. In this paper, we did not find eligible studies using waiting list or no-care as inactive interventions. Four studies used sham acupuncture as a comparator of acupuncture, one study used exercise placebo control (lower frequency and intensity) as a comparator of aerobic exercise treatment, and others all used placebo as an inactive intervention, so all inactive interventions included in our analysis had a "placebo effect".

Third, publication bias and selective outcome reporting that may led by commercial interest (Perlis et al., 2005) are potential limitations of all meta-analysis. For a detailed discussion on publication bias in efficacy evaluation of antidepressants, see Turner et al. (2008). In addition, our study limited the publication language to Chinese and English, and methodological studies have found that this might cause language bias, although it has a small impact on the results (Juni et al., 2002).

Forth, HAMD and other depression scales use subjective indicators, which are easy to be affected by outcome evaluators, leading to the improvement of efficacy from the real results. Furthermore, using more than 50% decrease of scores on a depression scale as an indicator of efficacy may not have a good clinical correlation. This dichotomy can be biased, for example by exaggerating the differences between patients who have improved by 50% and those who have improved by 49% (Kirsch and Jakobsen, 2018). Moreover the use of response rates can result discard of data and increases in type 1 and type 2 errors (Altman and Royston, 2006; Cohen, 1983; MacCallum et al., 2002; Maxwell and Delaney, 1993). We did not use standardized mean difference (SMD) of a depression scale as effect size because most studies included did not report standard deviations of mean decreases.

Fifth, we used overall risk of adverse events as the indicator of safety, and therefore we might neglect the harms of rare but serious adverse events. Moreover, we only used response rate as the indictor of efficacy, therefore our review cannot provide a full picture of benefits and harms.

Last but not least, we did not consider the use of antidepressants in combination with non-pharmacological treatments which is a common treatment strategy in routine clinical practice though.

5. Conclusion

Our current analysis provides preliminary evidence for comparative efficacy and safety of pharmacological and non-pharmacological treatments for MDD. We believe that our findings may have important clinical implications, and it also highlights key areas of future research needs. Future trials need to assess outcomes with more standardized measures especially for harms of non-pharmacological treatments and serious adverse events of pharmacological treatments. Additionally, standardized study designs should be made to address heterogeneity and enhance transitivity across studies. To improve the applicability of results, future study should cover important clinical issues that might inform treatment decision making in routine clinical practice (e.g., initial severity of depression, serious adverse events, withdrawal symptoms, drug interactions, combined treatments or multi-step treatments). Particularly, the next wave of treatment trials will really need to subtype depression.

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Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112595.

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