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Title page

Homeopathy in the treatment of depression: a systematic review

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ABSTRACT

Introduction: Depression is a common reason for patients to consult homeopaths. This review aims to assess the efficacy, effectiveness and safety of homeopathy in depression.

Methods: Thirty databases/sources used to identify studies reporting on homeopathy in depression, published between 1982 and 2016. Studies were assessed for their risk of bias, model validity, aspect of homeopathy and comparator.

Results: Eighteen studies assessing homeopathy in depression were identified. Two double-blind placebo-controlled trials of homeopathic medicinal products (HMPs) for depression were identified. The first trial (N=91) with high risk of bias found HMPs were non-inferior to fluoxetine at 4 (p=0.654) and 8 weeks (p=0.965); whereas the second trial (N=133), with low risk of bias, found HMPs was comparable to fluoxetine (p=0.082) and superior to placebo (p<0.005) at 6 weeks. The remaining research had unclear/high risk of bias. A non-placebo-controlled RCT found standardised treatment by homeopaths comparable to fluvoxamine; a cohort study of patients receiving treatment provided by GPs practising homeopathy reported significantly lower consumption of psychotropic drugs and improved depression; and patient-reported outcomes showed at least moderate improvement in 10 of 12 uncontrolled studies. Fourteen titles provided safety data. All adverse events were mild or moderate, and transient. No evidence suggested treatment was unsafe.

Conclusions: Limited evidence from two placebo-controlled double-blinded trials suggests HMPs might be comparable to antidepressants and superior to placebo in depression, and patients treated by homeopaths report improvement in depression. Overall, the evidence gives a potentially promising risk benefit ratio. There is a need for additional high quality studies.

KEY WORDS: mental health; depression; complementary medicine; homeopathy; systematic review

INTRODUCTION

Depression is the third most common burden of disease worldwide and is expected to become the leading burden of disease by 2030 [1]. The National Institute for Health and Clinical Excellence primarily recommends non-medical interventions such as cognitive behavioural therapy in sub-threshold, mild and moderate depression as the first line treatment [2]. If these interventions are ineffective or the depression is severe, antidepressant drugs are recommended. These treatment options help some but not all patients, there is concern about the overuse of psychotropic drugs, and insufficient alternatives. Some patients seek complementary and alternative medicine (CAM) treatment options, and depression and other mental health problems are among the most common reasons why patients seek homeopathy [3,4]. Homeopathy is controversial in some quarters, but despite this there is widespread use. A recent systematic review of 12-month prevalence of homeopathy use in eleven countries (USA, UK, Australia, Israel, Canada, Switzerland, Norway, Germany, South Korea, Japan and Singapore) found that a small but significant percentage of these general populations consulted homeopaths and/or purchased over-the-counter homeopathic medicines [5].

According to the MeSH term (E02.190.388) homeopathy is "*a system of therapeutics founded by Samuel Hahnemann (1755-1843), based on the Law of Similars where 'like cures like'. Diseases are treated by highly diluted substances that cause, in healthy persons, symptoms like those of the disease to be treated*." These substances, which are referred to as Homeopathic Medicinal Products (HMPs), are regulated through European Directives for medicinal products [6]. Treatment by homeopaths involves consultations and subsequent prescription of individually tailored HMPs based on information obtained during consultations. Standardised medicines for clinical complaints also exist.

There is a need to assess the existing research evidence for homeopathy in depression due to the prevalence of depression in all countries worldwide, the limited effect of existing recommended interventions, and the fact that patients use homeopathy as an alternative or a complement to

conventional treatment. One systematic review assessing research evidence for homeopathy in depression concluded that there was limited evidence due to a lack of high quality trials [7]. Another review on homeopathy in psychiatric conditions, which included only randomised placebo-controlled trials found none reporting on depression [8]. The aim of this review is to update these previous reviews and to assess the evidence for the efficacy, effectiveness and safety of homeopathy in patients with depression. The first draft of this updated review was published in the first author's (PV) PhD Thesis [9]. This article presents the results of our updated review.

METHODS

Search strategy

A systematic search of 30 databases and other sources was carried out, including e.g. CINAHL, Cochrane Library, EMBASE, PubMed/MEDLINE, and PsycINFO (supplementary material, appendix A). Literature searches were carried out by one researcher (PV) from 9 to 12.08.2012, with update searches on 15.11.2013 and 05.07.2016. A second researcher (PF) checked all searches and found them to be appropriate. Screening of all articles (at titles/abstract and full-text level) was carried out by both researchers. Reference lists were checked and 44 researchers in 19 countries were contacted to identify additional titles.

Inclusion criteria were studies reporting on homeopathic treatment of patients with diagnosed or self-reported depression between 1982 and July 2016. In a previous extensive literature search, the authors found that most homeopathy trials were published after 1982, and none published prior to 1982 reported on mental health problems [10]. We therefore limited our search to studies published after 1982. This date also coincides with the time when selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed antidepressants to date, came onto the market. No language limitations were set. Exclusion criteria were studies not reporting outcomes in patients suffering from depression as the primary focus; bipolar disorder; HMPs used in anthroposophical medicine, administered as injections or concentrations higher than 1:10,000 or one 100^{th} of the smallest dose used in conventional drugs (and therefore not available without a prescription in EU/EEA countries); animal studies; studies with less than 10 participants; conference abstracts; and reports presented in books.

Search strategies were adapted to each database, using variations of the words "homeopathy," "homeopathic drugs," "potentised," "depression," "depressive disorder," "dysthymia" and "dysthymic disorder", using wildcard symbols, and Boolean operators to combine terms.

The PICO may be describes as follows: Participants were patients with diagnosed or self-reported depression. The intervention was treatment provided by homeopaths or use of homeopathic medicinal products (HMPs). The comparator could be placebo, other depression medication or other depression treatment, waiting list, or no comparator. Outcomes were primary outcomes focusing on depression.

Data extraction and analysis

Articles were translated where necessary (Farsi n=1, Portuguese n=1, Spanish n=1). Data were extracted, appraised and analysed by one author (PV) and checked by a second (PF). Consensus of understanding was reached for all studies.

Data extracted from identified articles were input according to the Cochrane Consumers and Communication Review Group's data extraction template. Risk of bias was assessed according to the Cochrane Collaboration's guidelines, focusing on the main outcome measure for each trial [11]. Within-study publication bias, also referred to as outcome reporting bias or selective reporting bias, was reported for each included study. We also considered the potential risk of between-study publication bias. Controlled and uncontrolled studies were reported according to the STROBE statement [12]. We planned to carry out a meta-analysis in the event that the results of at least two trials could be presented at an aggregated level. This was however not carried out as we only found analysable data from two trials of which one was a non-inferiority trial and the other a superiority trial.

An important question when assessing research evidence is whether individual studies provide the "best possible" outcome that could be expected with the tested intervention in the particular field of research. An assessment of the model validity of studies, the degree to which the design and setting corresponds to "best practice" [13], was therefore determined using recommendations put forward by Mathie et al. [14].

Type of studies

The identified studies were categorised into three groups and described separately: those assessing the efficacy of HMPs; those assessing the effectiveness of treatment by homeopaths; and those describing the outcomes of patients treated by homeopaths.

Randomised double-blinded placebo-controlled trials were used to assess the efficacy of HMPs. To assess the effectiveness of treatment provided by homeopaths (consultations and HMPs), non-blinded randomised controlled trials (RCTs) and observational studies (cohort and case control studies) were

used. Uncontrolled studies (UCs) (including surveys) were used to assess outcomes during and after treatment, but not as evidence of causal links. Where possible, results were reported in an aggregated form, summarising outcomes for more than one study. Where p-values were reported, ≤ 0.05 was considered statistically significant. To assess the safety of homeopathy, adverse event reporting from all three groups was considered.

RESULTS

Search results

Thirty databases and other sources identified 3,692 titles. After addition of 31 titles identified through reference lists (n=24), contact with other researchers (n=7), and removal of duplicates, 2,649 titles were screened. Results of the literature search are presented in figure 1, reported according to PRISMA [15]. Eighteen original studies were identified, including three placebo-controlled double-blind trials [16-18], a non-placebo controlled randomised trial [19], a non-randomised trial [20], an observational cohort [21], and 12 uncontrolled studies and surveys [22-33].

The efficacy of homeopathic medicinal products

The efficacy of homeopathic medicinal products prescribed for patients suffering from diagnosed depression was assessed in three RCTs (table 1) [16-18].

In the most recently published placebo-controlled double-blinded double-dummy trial, the efficacy of individualised HMPs was compared to fluoxetine and placebo in 133 menopausal women suffering from moderate to severe diagnosed depression [18]. All women underwent a full consultation with a homeopath who prescribed an individually adapted HMP, with follow-up consultations at 4 and 6 weeks. Patients received either an HMP plus a placebo for fluoxetine (n=44); fluoxetine and placebo for an HMP (n=46); or placebo for both (n=43). HMPs were prescribed daily in liquid C30 or C200 potency. Fluoxetine-hydrochlorine 20 mg was increased to 40 mg after 4 weeks in case of non-response. The intention-to-treat analysis showed a 5.0 point difference in favour of HMPs compared to placebo, measured on the 17-item Hamilton Rating Scale for Depression (HRSD) at 6 weeks ($p<0.001$). Fluoxetine was better than placebo by 3.2 points ($p<0.001$). Results were clinically significant (minimum 3.0 points). Differences between homeopathy and fluoxetine were non-significant ($p=0.082$). Response rates (min. 50% HRSD decrease) at 6 weeks were better for homeopathy (54.4%) and fluoxetine (41.3%), compared to placebo (11.6%) ($p<0.001$), whereas differences in remission rates (min. 7 point HRSD reduction) were not statistically significant

(homeopathy 15.9%, fluoxetine 15.2%, placebo 4.7%, p=0.194). Secondary outcomes included the Beck Depression Inventory (BDI), with non-significant differences (p=0.130); and the Greene Climacteric Scale (GS), measuring vasomotor, somatic and psychological symptoms including anxiety and depression, with significant differences (p=0.002), where HMPs were superior to placebo, but not significantly superior to fluoxetine. Fluoxetine was not significantly better than placebo. There were no serious adverse events due to homeopathy. The prevalence of non-serious adverse events was similar in the three groups and included insomnia (n=6, 13.6%), dyspepsia (n=6, 13.6%), nausea (n=5, 11.4%), fatigue (n=5, 11.4%), anxiety (n=4, 9.1%), dizziness (n=4, 9.1%), diarrhoea (n=3, 6.8%), headache (n=3, 6.8%), and constipation (n=2, 4.5%). The study was well described, it included a sample size calculation and multiple imputation was used for missing data. The risk of bias was low (figure 2) and the trial had acceptable model validity (figure 3).

A non-inferiority placebo-controlled double-dummy trial included 91 participants diagnosed with acute moderate to severe depression receiving either individually prescribed HMPs (Q-potencies daily) together with a placebo for fluoxetine; or fluoxetine (20 mg daily, increased to 40 mg after 4 weeks if no response) together with a placebo for HMPs [16]. All patients underwent the same medical and homeopathic assessment. Both groups (homeopathy n=48, fluoxetine n=43) improved over time (p<0.001) on the Montgomery Åsberg Depression Rating Scale (MADRS), with no significant between group differences at 4 weeks (95% CI -6.95, 0.86, p=0.65) and 8 weeks (95% CI -6.05, 0.77, p=0.97). The pre-fixed margin of non-inferiority was (Δ) 1.45, which was 1/3-1/2 of the advantage of fluoxetine over placebo, and the minimum considered of clinical relevance. Secondary outcomes were also similar in the two groups, including response rates (min. 50% MADRS reduction) at 4 weeks (fluoxetine 63.9%, homeopathy 65.8%) and 8 weeks (fluoxetine 84.6%, homeopathy 82.8%); and remission rates (MADRS < 11) at 4 weeks (fluoxetine 47.2%, homeopathy 55.3%, p=0.42) and 8 weeks (fluoxetine 76.9%, homeopathy 72.4%, p=0.72). The sample size was sufficient to establish non-inferiority of homeopathy compared to fluoxetine. The trial was well described, although only percentages (and not numbers) were provided for secondary outcomes (response & remission rates). The trial had high risk of bias due to high attrition rates (40% in both trial arms), and acceptable model validity.

The third randomised placebo-controlled trial had low risk of bias, but recruited only 44 out of 228 participants and was therefore underpowered and statistical tests were not carried out [17].

The effectiveness of treatment provided by homeopaths

The effectiveness of treatment provided by homeopaths was assessed in a non-placebo randomised controlled trial [19], a non-randomised trial [20], and an observational cohort [21] (table 2).

In a non-placebo controlled randomised trial including 211 menopausal women with self-reported depression, the effectiveness of a standardised homeopathic medicinal product (Ignatia Homaccord [Ignatia amara & Moschus moschiferus], Heel GmbH) (n=110) prescribed daily for all patients was compared to fluvoxamine (n=101) [19]. Reduction in scores in the two groups at 6 weeks were comparable when measured on the Hamilton Depression Rating Scale (HDRS) (homeopathy 61%, fluoxetine 58%), as well as the Beck Depression Inventory (BDI) (homeopathy 66%, fluoxetine 65%). Response rates (min. 50% improvement) were also comparable (homeopathy 68%, fluoxetine 65%). All between group differences were not statistically significant ($p>0.05$). Results must be interpreted with caution, due to methodological weaknesses resulting in high risk of bias. The trial had inadequate model validity as the intervention was not based on the 'like treats like' principle so a substantial number of homeopaths would not support the choice of intervention for this group of patients.

In an observational cohort study, 710 depressed patients' use of psychotropic drugs was assessed over a time period of 12 months (table 2) [21]. Compared to patients treated by general practitioners solely practising conventional medicine (GP-CM n=161), patients treated by GPs mainly practising homeopathy (GP-Ho n=289) or partially practising homeopathy (GP-Mx n=260), used significantly less psychotropic drugs (OR 0.29, 95% CI 0.19-0.44, $p<0.001$; OR 0.62, 95% CI, 0.41-0.94, $p=0.02$). Results controlled for potential confounding factors and baseline characteristics, and were not affected by depression severity. Similarly, the rate of clinical improvement (HADS score < 9) was better in the GP-Ho group compared to the GP-CM group (OR 1.70, 95% CI 1.10-2.87, $p=0.05$), but not when comparing GP-Mx patients to GP-CM patients (OR 1.49, 95% CI 0.89-2.50, $p=0.13$). There was potential selection bias due to low participation rates (45%), although this was similar across all three groups and differences between participants and non-participants were comparable. Baseline between group differences in anxiety and depression severity and history of suicide attempt could explain some, but not all between group differences in outcomes. Model validity was uncertain.

A trial that was considered by the reviewers to be non-randomised, suggested the combination of cognitive behavioural therapy (CBT) and homeopathy, was more effective than placebo or either treatment alone [20]. Results should be interpreted with caution due to high risk of bias (figure 4) and model validity was uncertain as it could not be assessed (figure 5).

Outcomes during and after treatment provided by homeopaths

Eleven uncontrolled studies (table 3) reported outcomes in a total of 595 patients (median 33, range 22-201) during or after treatment provided by homeopaths, including eight prospective uncontrolled

studies [23,26-29,31-33], three surveys [24,25,30], and a retrospective case series [22]. Studies were highly heterogeneous and could only to a limited extent be presented in an aggregated form.

Six uncontrolled studies and surveys included 391 depressed patients (median 43, range 28-201) who were subsets of larger patient groups with various diagnoses [24,28,30-33]. Patient-reported numerical rating scales showed at least moderate improvement (+2, +3 or +4 on seven- and nine-point numerical rating scales) in 50% to 86% of patients (median 67%), and slight or no improvement in 7% to 50% of patients (median 22%) following individualised treatment provided by homeopaths. The time point for outcome assessment varied considerably (e.g. from 6 months to 7 years after treatment start), thereby reducing the generalisability of results.

A study including 83 patients diagnosed with depression receiving individualised treatment provided by homeopaths showed significant improvements at 3, 6, 9 and 12 months on the 17-point Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), the Clinical Global Impression (CGI-1) and Clinical Global Improvement (CGI-2) (all at p=0.001) [29]. At 12 months, 75% to 100% improvement in HDRS scores was seen in 57.8% (n=48); 50% to < 75% improvement in 20.5% (n=17); 25% to < 50% improvement in 2.4% (n=2); and 19.3% (n=16) did not experience a significant change. Results were better for moderately and severely depressed patients, compared to those suffering from mild depression.

A retrospective case series of 15 patients diagnosed with depression found statistically significant improvements on the Montgomery Åsberg Depression Rating Scale (MADRS) at the 2nd (mean 7 weeks) and 3rd (14.5 weeks) consultation (p<0.001) [22]. A minimum improvement of 50% was found in 14 out of 15 patients by the 3rd consultation.

The remaining four titles included two small prospective studies, one with marked improvement in more than half the patients using the SF-36 wellbeing questionnaire at 12 months [23], a second with improvement in depression in almost three quarters of patients after at least 2 months [26], and a third with 10% to 100% improvement in depression severity after at least 2 months [25]. Results of the last study are presented in the safety section [27].

All uncontrolled studies have a high risk of selection, performance and detection bias, as there are no control groups and there is no blinding of patients, practitioners and assessors (figure 6). Risk of reporting bias was considered to be low for most studies [22-26,28,30-33]. Only two studies had low risk of attrition bias and other forms of bias [22,29]. The remaining studies only provided limited information about depression and used outcome measures not validated for depression, therefore leading to uncertain risk of attrition bias and other forms of bias. A single study was considered to

have acceptable model validity [22] and one had inadequate model validity [27] (figure 7). The remaining had overall uncertain model validity as each of these had at least one unclear key domain (rationale, principles, appropriate and sensitive outcome measure).

Safety of homeopathic medicines and treatment by homeopaths in depression

Four controlled trials [16-19], a cohort study [21], and nine uncontrolled studies provided data relating to the safety of homeopathy [22-24,27,29-33]. No serious adverse events were reported according to NIH/NCI criteria (2010).

Adverse events in the homeopathy and fluoxetine groups were comparable in three placebo-controlled double-blinded trials [16-18]. No patient needed to interrupt treatment due to adverse events [18], or adverse events were more common in the fluoxetine (21.4%) than the homeopathy (10.7%) group [16]; more patients discontinued treatment due to adverse events in the fluoxetine (n=8) than the homeopathy (n=3) group; and a greater number of patients randomised to homeopathy (n=5) than fluoxetine (n=1) were excluded from the trial as a result of an intensification of depressive symptoms. However, these trials were not powered to assess adverse effects and differences were not statistically significant. The cohort study did not detect statistically significant differences in the prevalence of self-reported injuries (GP-Ho 9.5%, GP-Mx 7.1%, GP-CM 14.8%) or suicide attempts (GP-Ho 1.5%, GP-Mx 1.9%, GP-CM 5.0%) [21]. In the non-placebo RCT, the standardised HMP was better tolerated than fluvoxamine, but no significance tests were presented [19].

One uncontrolled study identified mild to moderate adverse events in 26% (n=9) of patients [27]. Four studies did not identify any adverse events [29], or any deterioration of health [30-32], whereas others reported one [22,24], or two patients with slight deterioration [33], or three that were not better or worse [23].

In summary, few adverse events or cases of deteriorated state of health were reported and there was no evidence to suggest that treatment provided by homeopaths for patients suffering from diagnosed or self-reported depression was unsafe.

DISCUSSION

This systematic review adds 17 original research studies to a previous systematic review [7], and includes only one title identified in the previous review. This updated review adds to the evidence of the efficacy of HMPs and changes in patient-reported outcomes following treatment provided by homeopaths. We cannot exclude the possibility that some studies have been overlooked particularly as

we excluded conference abstracts from our search strategy. However, we reduced the risk of between-studies publication bias through the use of several large generic databases and smaller homeopathy- and CAM-specific databases, by not setting any language limitations, and by contacting experts in the field in 19 countries. We consider it less likely that results of unidentified studies would significantly affect the overall results, as the results for non-English studies and studies published in non-peer-reviewed journals suggested comparable results.

The review used a novel approach to the assimilation of evidence by considering three different types of evidence: those assessing the efficacy of HMPs; those assessing the effectiveness of treatment by homeopaths; and those describing the outcomes of patients treated by homeopaths.

A weakness of the overall evidence is the limited extent to which aggregated results can be presented due to the heterogeneity of studies. Placebo-controlled RCTs can help answer the question of whether a specific part of an intervention, in this case HMPs, are effective to treat depression. Pragmatic RCTs and cohort studies can be used to test the effectiveness of the "whole treatment package", in this case treatment provided by homeopaths for depressed patients. The evidence from two placebo-controlled double-blinded trials, one with high and another with low risk of bias, suggests that homeopathic medicines may be non-inferior to fluoxetine. These findings are supported by two studies assessing the effectiveness of treatment by homeopaths; an observational study of GPs which found less use of psychotropic drugs and improved results for patients consulting with GPs prescribing HMPs, and a non-placebo RCT suggesting that the effectiveness of a standardised homeopathic medicine is comparable to the effectiveness of an antidepressant. The results of these non-blinded studies must be interpreted with caution as they were associated with high risk of bias. However, a single placebo-controlled trial with low risk of bias found homeopathic medicines were superior to placebo and the results were clinically significant.

The lack of controls and randomisation in uncontrolled studies precludes any conclusions about the effectiveness of interventions, but provides evidence of patient-reported outcomes following treatment by homeopaths. Most uncontrolled studies were small and had limitations reducing the reliability of results: high or unclear risk of detection, reporting and attrition bias due to no use of blinded assessors, insufficient information on drop-out and non-responders, and with the exception of two studies, outcome measures had not been validated for depressed patients. Strengths of uncontrolled studies were that all except one referred to patients with a diagnosis of depression, and described their reported changes in depression symptoms in "real world" practice [35]. Results showed at least moderate improvement in most patients in 10 out of 12 studies, whereas one only reported changes in symptoms and the other only adverse events. Model validity was uncertain or inadequate for all

except one uncontrolled study. It is therefore not possible to say if the treatments are representative of "best practice".

Overall, the results should be interpreted with caution due to high and unclear risk of bias for most dimensions in most trials and studies. The highest quality evidence from a single randomised placebo-controlled trial found HMPs were non-inferior to antidepressants and superior to placebo. The remaining research evidence suggested that HMPs were non-inferior to antidepressants or patients improved over the duration of a treatment course provided by homeopaths. There was no evidence to suggest treatment was harmful.

Comparison with other interventions and recommendations for future research

"Talking therapies" and antidepressants remain the interventions most commonly recommended for depressed patients by health services. The research evidence presented in this systematic review suggested HMPs might be at least as effective as some commonly used antidepressants. Systematic reviews assessing antidepressants have been associated with small effect sizes [e.g. 36], with only clinically significant effects for patients suffering from very severe depression [34]. Does this mean that the effect of HMPs in the reported homeopathy trials, were placebo effects? Such an assumption was negated in one of the trials identifying a statistically and clinically significant effect of HMPs compared to placebo. Further research is needed in order to confirm whether HMPs are superior to placebo and comparable or superior to commonly used antidepressants, and whether they are safe. Such results would also need to be carried out in different groups of patients, including different depression severity groups (mild, moderate and severe depression), different age groups (e.g. adolescents, elderly), and patients with various comorbidities (e.g. pain, cancer), if results are to be generalised to different populations of depressed patients. Moreover, pragmatic RCTs are needed in order to test the effectiveness and cost-effectiveness of the "whole treatment package" provided by homeopaths, including consultations and medication, compared to commonly used interventions such as consultations with psychologists or with GPs who prescribe antidepressants.

Although some authors report up to moderate effect sizes of psychological interventions compared to waitlist or usual care controls for patients with depression [e.g. 37], the "true" effect is commonly overestimated [e.g. 38], and some authors found no significant differences when comparing "talking therapies" such as psychotherapy to antidepressants, or when comparing combinations of psychotherapy and antidepressants to antidepressants alone [34]. No RCTs comparing the effectiveness of the "whole treatment package" including consultations and individually adapted medication provided by homeopaths to usual care were identified in the review. This research is

required in order to assess the effectiveness of homeopathy in "real world practice" as an alternative or an adjunctive intervention to "talking therapy" interventions and antidepressant treatment.

The risk benefit ratio should also be considered for clinical decision making. Transient mild to moderate adverse events were identified. Although the studies included in our depression review were not powered to assess adverse events, there was no evidence to suggest the intervention was unsafe. Further sufficiently powered research should look into the safety of homeopathic treatment.

CONCLUSIONS

The existing limited research evidence suggests that the effectiveness of homeopathic medicinal products for depressed patients is comparable to some antidepressants and superior to placebo, with clinically significant effects. A significant proportion of patients report improvements in depression following treatment provided by homeopaths in uncontrolled studies and surveys. No evidence suggested treatment was unsafe. However, further research is still needed to test the efficacy of homeopathic medicinal products, the effectiveness of treatment provided by homeopaths, and the safety of the intervention.

CONTRIBUTORSHIP STATEMENT

All three authors (PV, PF, CR) contributed significantly to this article, including the design of this systematic review, the analysis and interpretation of data, and the drafting and revision of the article. All three authors approved the final version.

CONFLICT OF INTEREST

None

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Figure 1. Flow of information in the systematic review

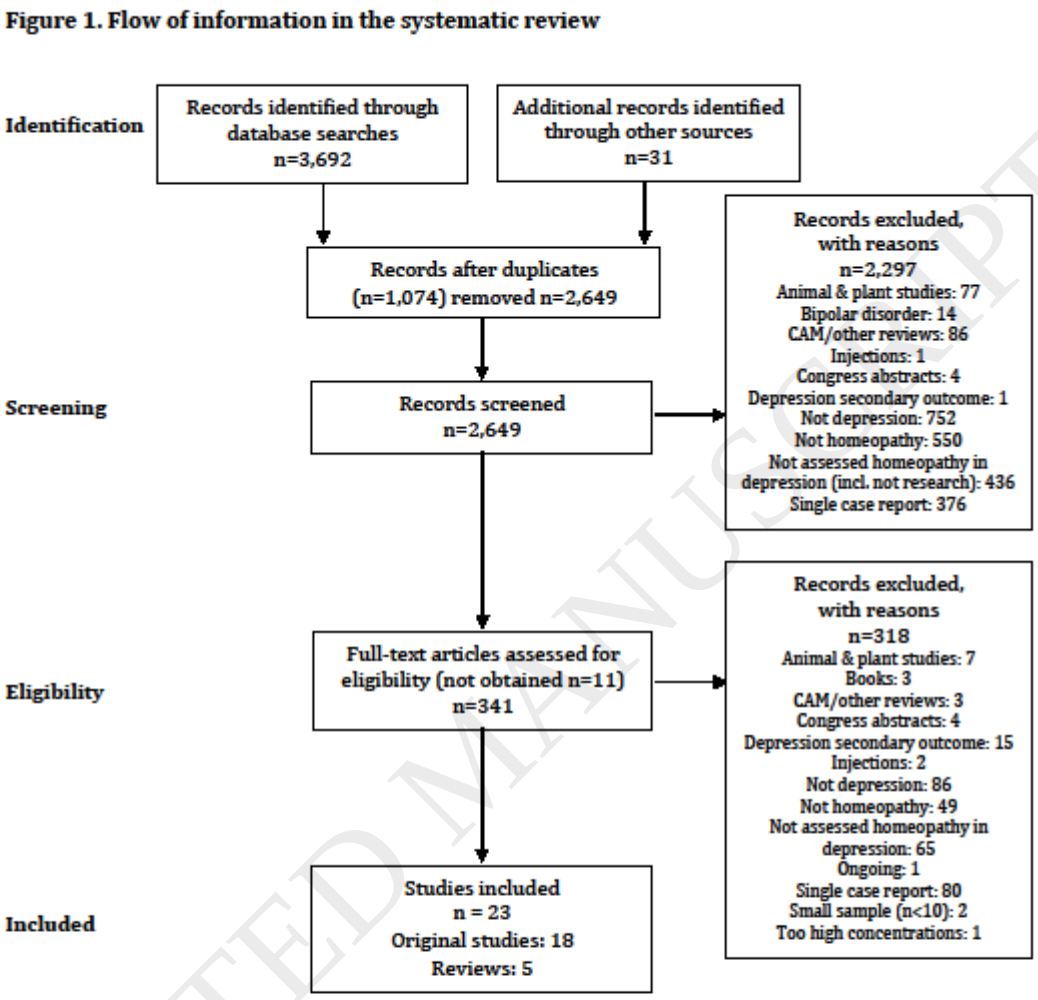
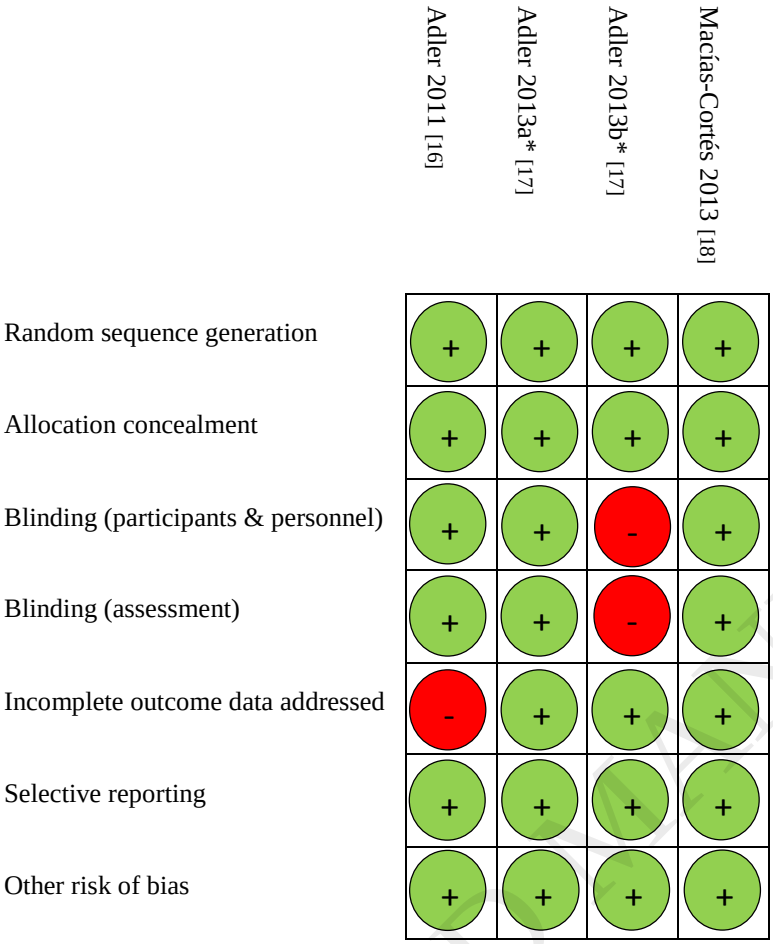


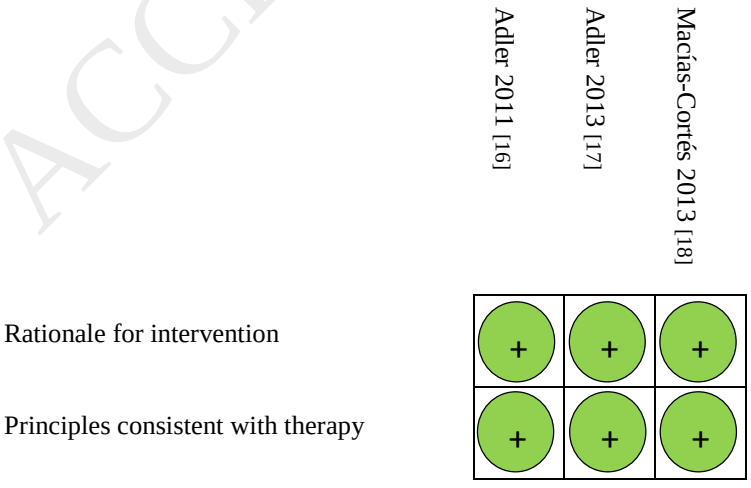
Figure 2. Risk of bias assessment for RCTs comparing homeopathic medicines to placebo for depression



Risk of bias indications: Plus (+) = Low risk of bias. Question mark (?) = Uncertain risk of bias. Minus (-) = High risk of bias.

* Adler et al. 2013a compared HMPs to placebo, Adler et al. 2013b compared shorter to longer consultations.

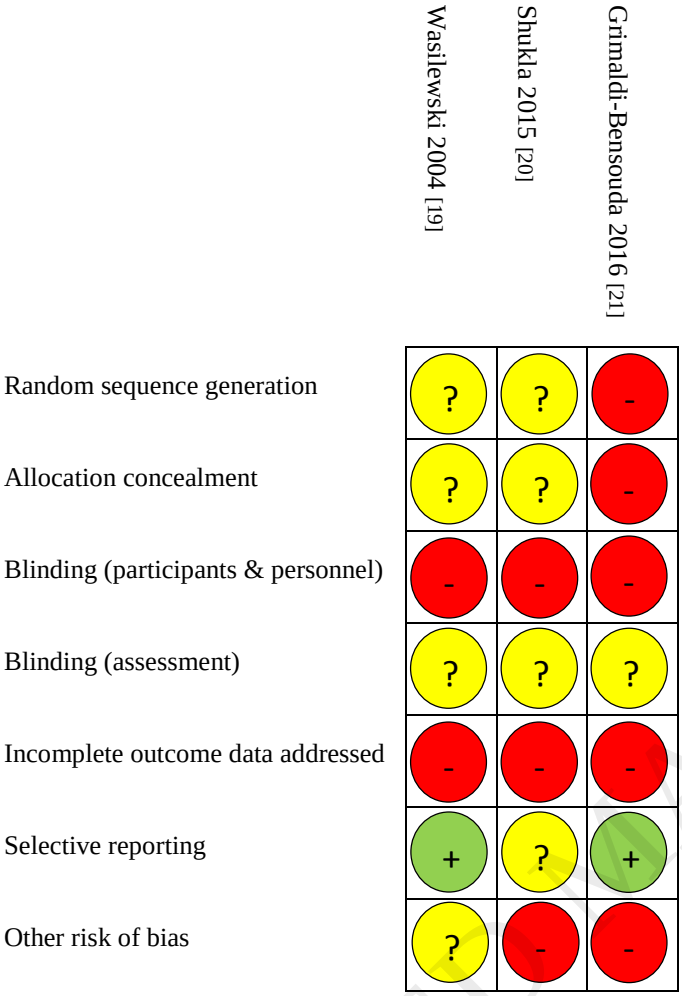
Figure 3. Model validity for RCTs comparing homeopathic medicines to placebo for depression



Practitioner qualified & experienced	+	+	+
Outcome measure reflects expected effect	+	+	+
Outcome measure sufficiently sensitive	+	+	+
Follow-up length appropriate	+	+	+

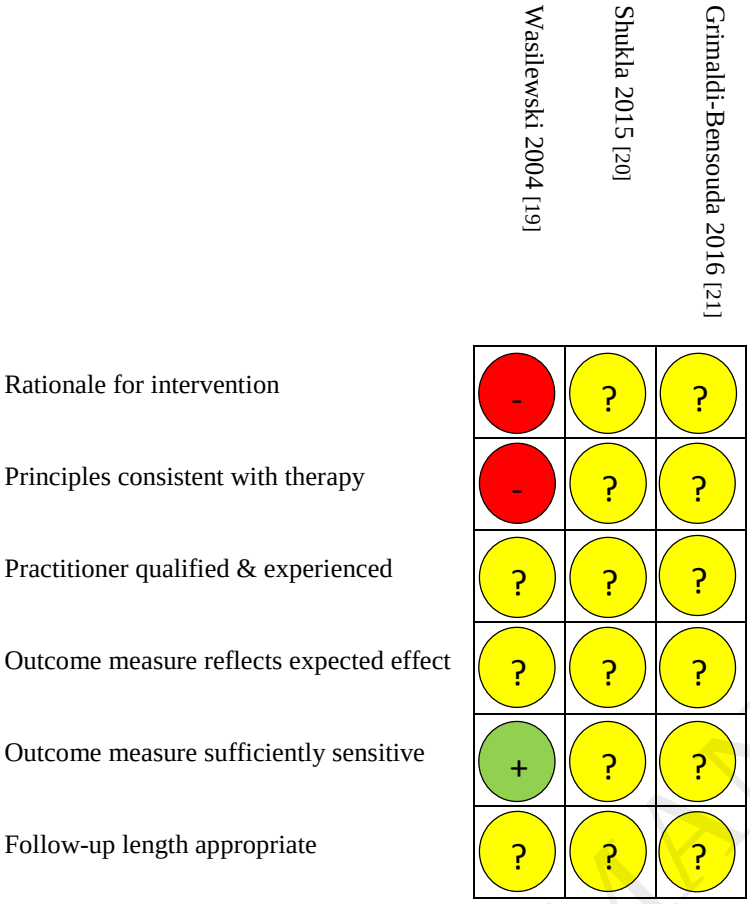
Model validity indications: Plus (+) = Acceptable model validity. Question mark (?) = Uncertain model validity. Minus (-) = Inadequate model validity.

Figure 4. Risk of bias assessment for observational studies and non-placebo trials assessing the effectiveness of treatment by homeopaths



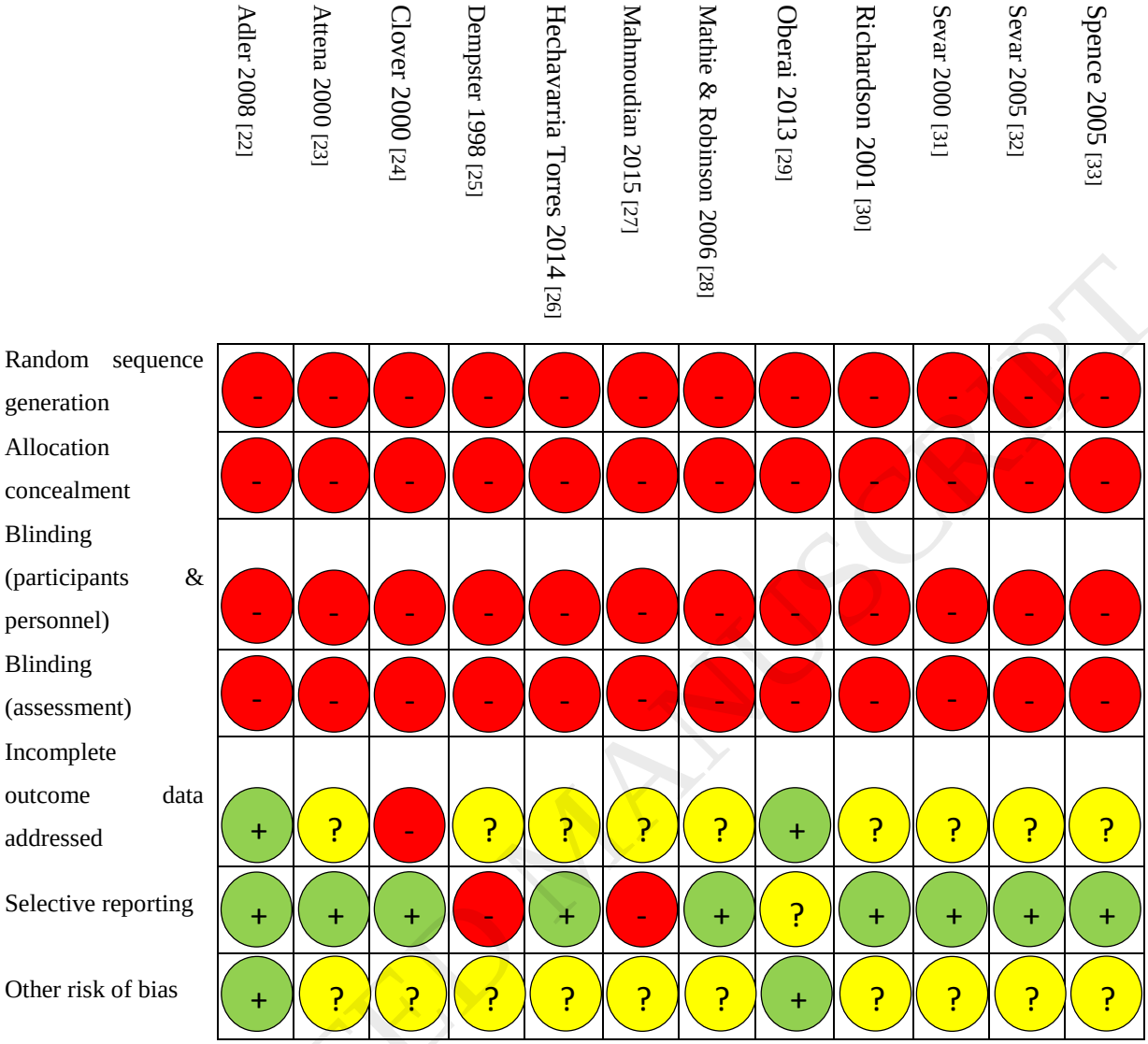
Risk of bias indications: Plus (+) = Low risk of bias. Question mark (?) = Uncertain risk of bias. Minus (-) = High risk of bias.

Figure 5. Model validity for RCTs comparing homeopathic medicines to placebo for depression



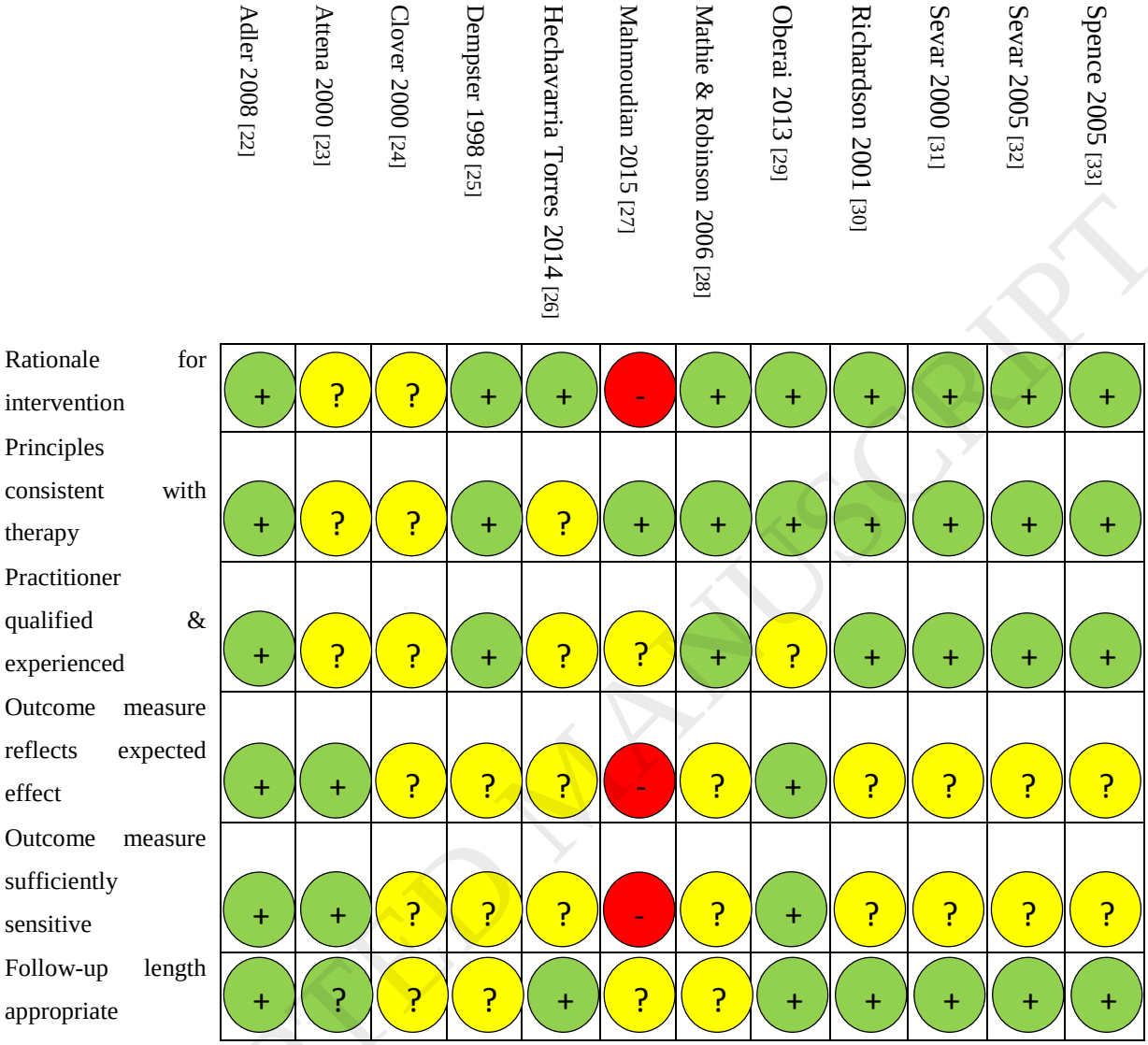
Model validity indications: Plus (+) = Acceptable model validity. Question mark (?) = Uncertain model validity. Minus (-) = Inadequate model validity.

Figure 6. Risk of bias assessment for uncontrolled studies



Risk of bias indications: Plus (+) = Low risk of bias. Question mark (?) = Uncertain risk of bias. Minus (-) = High risk of bias.

Figure 7. Model validity for uncontrolled studies



Model validity indications: Plus (+) = Acceptable model validity. Question mark (?) = Uncertain model validity. Minus (-) = Inadequate model validity.

Table 1. Randomised controlled trials comparing homeopathic medicines to placebo for depression (main outcome)

Author, year, country	RCT Design	Sample, recruitment, setting	Intervention	Control	Outcome measures	Results
Adler et al. 2011 [16] Brazil	Non-inferiority trial 2 arms double-blinded, double-dummy, placebo-controlled,	Moderate to severe depression (DSM-IV according to SCID + MADRS score min.15) N=91 Homeopathic medicine + placebo for fluoxetine (H) n=48 Fluoxetine + placebo homeopathic medicine (F) n=43 **Recruitment**: MD referral within public health system **Setting**: Depression outpatient clinic	Homeopathic medicine (H) + placebo for fluoxetine-hydrochlorine, for 8 weeks, plus consultations with a homeopath Homeopath: 1	Fluoxetine-hydrochlorine (F) 20 mg daily, for 8 weeks, increased to 40 mg after 4 weeks if no response + placebo homeopathic medicine for, plus consultations with a homeopath	**Primary**: MADRS at 4 & 8 weeks **Secondary**: Response & remission rates at 4 & 8 weeks Tolerability at 4 & 8 weeks	Homeopathy non-inferior to fluoxetine at 4 and 8 weeks **Between group difference** for mean MADRS score non-significant at 4 weeks (95% CI -6.95, 0.86, p=0.65) and 8 weeks (95% CI -6.05, 0.77, p=0.97) **Time effect** for both groups p<0.001 **Response rates** for H / F were comparable at: 4 weeks: 63.9% / 65.8% 8 weeks: 84.6% / 82.8% **Remission rates** H / F were comparable at: 4 weeks: 47.1% / 55.3%, p=0.42 8 weeks: 76.9% / 72.4%, p=0.72 **Tolerability comparable** Adverse events (AE): H: 10.7%, F: 21.4% (p=0.28) Discontinued due to AE: H: n=3. F: n=8 (p=0.07) Excluded due to worsening: H: n=5. F: n=1 (p=0.21)
Adler et al. 2013, Germany [17]	Four-armed placebo-controlled trial*	Acute major depression (moderate episode) (psychiatrist diagnosis, depression degree HAM-D score 17-24) N=44 **Recruitment**: outpatient practices, radio & TV interviews, advertisement in newspapers and underground trains **Setting**: Integrative Medicine outpatient clinic of the Charité – Universitäts-medizin Berlin	Consultation with homeopath + homeopathic medicine (H) daily Homeopath: 1	Consultation with homeopath + Placebo homeopathic medicine daily	**Primary**: HAM-D 6 weeks **Secondary**: HAM-D 2 & 4 weeks SF-12 & BDI 2, 4 & 6 weeks Adverse events Treatment expectations	Only 44 out of 223 recruited Data only analysed descriptively **At 6 weeks**: No relevant differences between homeopathic medicines and placebo on HAM-D and BDI **Adverse events**: H: n=19 (of 30), 63.3%. P: n=9 (of 14), 64.3% No serious adverse events & no suicide ideation
Macías-Cortés et al. 2013, Mexico [18]	Placebo-controlled trial double-blinded, double-dummy	Moderate to severe depression (diagnosed according to DSM-IV, degree of depression HRSD score 14-24) in peri- and post-menopausal women N=133 **Recruitment**: Internet advertisements, community groups, liaison with health	Intervention (H): Homeopathic medicine + placebo for fluoxetine, plus consultations with a homeopath n=44 Homeopath: 1	Control 1 (F): Fluoxetine + placebo for homeopathic medicine, plus consultations with a homeopath n=46 Control 2 (P):	**Primary**: HRSD (17-item) 4 & 6 weeks Clinically significant: min. 3 points **Secondary**: Response: min.50% decrease Remission: 7 points or less	**At 6 weeks**:** **HRSD**: Homeopathy better than placebo by 5.0 points (p<0.001) Fluoxetine better than placebo by 3.2 points (p<0.001) **BDI**: No statistically significant difference **GS**: Statistically significant differences (p=0.002). Homeopathy better than placebo, not better than fluoxetine. Fluoxetine not better than placebo.

		professionals, posters at study site, brochures for hospital population **Setting**: Hospital Juárez de México, Ministry of Health		Placebo for Fluoxetine + placebo for homeopathic medicine, plus consultations with a homeopath n=43	BDI at 4 & 6 weeks GS at 4 & 6 weeks Adverse events 4 & 6 weeks	**Response** 6 weeks (min.50% decrease on HRSD): H: 54.4%, F: 41.3%, P: 11.6% ($p<0.001$) **Remission** at 6 weeks (min. 7 point reduction on HRSD): H: 15.9%, F: 15.2%, P: 4.7% ($p=0.194$) **Adverse events** (AE): No serious AE. All AE mild and tolerable with no interruption of medication, except 1 fluoxetine patient (increased anxiety & insomnia) Prevalence H similar to F ($p=0.062$) and P ($p=0.999$)

* Four armed trial: Intervention and verum, each in treatment arms with shorter (30 minutes) and more extensive (60 minutes) consultations.
** Results were also statistically significant at 4 weeks, but only 6-week results are presented in the table.
SCID: Structured Clinical Interview. MADRS: Montgomery & Åsberg Depression Rating Scale. Homeopathic remedies potentised (diluted & succussed) at following concentrations Q2=$2x10^{-16}$, Q3=$8x10^{-21}$, Q4=$1.6x10^{-25}$ (Q4 surpasses Avogadro's number). Tolerability measured using the side effect rating scale of the Scandinavian Society of Psychopharmacology.
HRSD/HAM-D: Hamilton Rating Scale for Depression (17-item) Homeopathic remedies potentised (diluted & succussed) at following concentrations C30=$1x10^{-60}$, C200=$1x10^{-400}$ (both surpass Avogadro's number).
BDI: Beck Depression Inventory. GS: Green Climacteric Scale (vasomotor, somatic and psychological symptoms, and sexual function). SF-12: Short Form-12 Health Survey.

Table 2. Observational studies and non-placebo trials assessing the effectiveness of treatment by homeopaths

Author, year, country	Design	Sample, treatment groups, recruitment, setting	Intervention	Control	Outcome measures	Results
Wasilewski 2004, Poland [19]	Randomised controlled trial comparing homeopathic complex to anti-depressant (no placebo control)	Depression in menopausal women, N=211 (First depressive episode n=135, Recurrence n=76) **Recruitment**: unknown **Setting**: Neuro-psychiatric clinic, Łódź,	Standardised homeopathic medicine (H) 2x daily n=110	Fluvoxamine (F) 50mg 3x daily n=101	HDRS & BDI at 6 weeks	No significant between group differences in HDRS and BDI scores at 6 weeks Completion rates: H 91% (100 of 110), F 81% (82 of 101) **Reduction in depression scores** at 6 weeks: HDRS BDI Min. 50% better H: 61% 66% 68% (n=68) F: 58% 65% 65% (n=53) All between group differences n.s. (p>0.05) **Tolerability**: Homeopathy significantly better tolerated than Fluvoxamine (p-value not reported). Side-effects of Fluvoxamine were especially nausea/gastric symptoms (common side-effects for F). Drop-out due to side effects: Homeopathy n=2. Fluvoxamine n=12
Shukla et al. 2015, India [20]	Unclear, most likely a non-randomised trial with 4 groups	Depression (questionnaire, details unknown) N=208 **Recruitment**: Colleges, clinics and Hospitals in Allahabad	Group 1 Individualised homeopathic medicine alone n=52 Group 2 CBT + individualised homeopathic medicine n=52	Group 3 CBT alone (frequency unknown) n=52 Group 4 Placebo + practitioner consultations (type and frequency unknown) n=52	Not specified Time of assessment possibly at 6 months	No outcome measures reported Authors state that combined CBT + individualised homeopathic medicine was better compared to CBT alone, homeopathy alone or placebo (p=0.05)
Grimaldi-Bensouda et al. 2016, France [21]	Observational cohort study	Depression (ICD-9 + min. score of 9 on HADS) N=710 **Recruitment/ setting**: GPs randomly selected from the French National Directory of Physicians in primary care	Treatment by GP mainly practising homeopathy (GP-Ho) n=289	Treatment by GP partially practising homeopathy (GP-Mx) n=260 Treatment by GP not practising homeopathy (GP-CM) n=161	**Primary**: Consumption of psychotropic drugs over 12 months **Secondary**: HADS at 12 months Self-reported injuries & suicide attempts	GP-Ho group reported lower use of psychotropic drugs over 12 months: GP-Ho 50.0%, GP-Mx 63.5%, GP-CM 68.0% **Drug use compared to GP-CM:** GP-Ho: OR 0.29 (95% CI 0.19, 0.44, p<0.001) GP-Mx: OR 0.62 (95% CI 0.41, 0.94, p=0.02) (results not affected by ADD severity) **Clinical improvement (HADS < 9) at 12 months, compared to GP-CM:** GP-Ho: OR 1.70 (95% CI 1.10, 2.87, p=0.05) GP-Mx: OR 1.49 (95% CI 0.89, 2.50, p=0.13) (controlled for confounders and baseline characteristics) **Self-reported injuries/suicide attempts:** GP-Ho 9.5% / 1.5% (p>0.05), GP-Mx 7.1% / 1.9% (p>0.05), GP-CM 14.8% / 5.0% (p>0.05)

ADD: Anxiety and depression disorders. HADS: Hospital Anxiety and Depression Scale. OR: Odds ratio. CBT: Cognitive behavioural therapy. SF-36: Short Form (36) Health Survey.
Mulimen: consists of Ambra grisea, Calcium carbonicum, Cimicifuga racemosa, Gelsemium sempervirens, Hypericum perforatum, Kalium carbonicum, Sepia officinalis, Urtica dioica.

HDRS: Hamilton Depression Rating Scale. BDI: Beck Depression Inventory

Table 3. Uncontrolled studies and surveys reporting on patient outcomes during or after treatment provided by homeopaths

Depression primary outcome measure

Author, year, country	Design	Sample, recruitment, setting	Intervention	Control	Outcome measures	Results
Adler et al. 2008, Brazil [22]	Case series, retrospective	All new patients diagnosed with depression (DSM-IV according to SCID) over a 10 month period N=15 Onset of depression: median 3 years (IQR 1-15, range 0-22) Last episode lasting: median 7 months (IQR 5-18, range 1-60) **Recruitment/setting**: Homeopathy clinic for depressive disorders, Jundiaí, Brazil	Individualised homeopathy for up to 4 consultations: 10 different homeopathic remedies were prescribed No other concurrent treatment Homeopath: 1	Before to after assessment	MADRS score at first three follow-up consultations Remission rates Patient-completed outcome measure	**At 2nd & 3rd consultation**: Statistically significant reduction in MADRS scores At 4th consultation: Insufficient data to assess scores **At 3rd consultation** (mean 14-15 weeks): > 50% decrease in MADRS scores in 14 of 15 patients (93%) One patient referred for antidepressant drug therapy
Attena et al. 2000, Italy [23]	Prospective, uncontrolled study	Diagnosed depression (out of 648 consecutive patients diagnosed with sub-acute and chronic conditions) n=24 **Recruitment/setting**: Private clinic with three doctors practicing unconventional medicine	Pluralist homeopathy (more than one remedy at the time) Follow-up at 3 and 6 months Homeopaths: 3	Before to after assessment	SF-36, question 2: How do you evaluate your health 1 year after you started treatment? Questionnaire completed over the telephone, called by researcher (not practitioner)	**1 year after started treatment**: Marked improvement: n=13 (54.2%) Moderate improvement: n=8 (33.3%) No improvement/worse: n=3 (12.5%)
Clover 2000, UK [24]	Survey	Diagnosed depression in patients with carcinoma of the breast (from 1000 consecutive patients with various complaints) n=14 **Recruitment**: from GPs and hospital doctors **Setting**: Homeopathic hospital outpatient clinic, Tunbridge Wells	Individualised homeopathic treatment: Details of treatment unknown (study period 12 months) Homeopaths: Unknown (>1)	Before to after assessment	7-point numerical self-reported rating scale at follow-up consultations Completed by patient with a clinic clerk after follow-up consultation in the absence of a doctor or nurse	**7-point NRS at follow-up consultation**: +3 n=9 64.3% +2: n=3 21.4% +1: n=1 7.1% 0: n=0 0.0% -1: n=1 7.1% -2/-3/-4: n=0 0.0% + improvement, - deterioration (see footnote) Response rate at follow-up consultations (n=2500): 55% (n=1372), no response 45% (n=822) Response rate for depressed patients not reported.
Dempster 1998, UK [25]	Survey of random selection of patients, retrospective	Diagnosed depression N=12 Depression n=8 Mild depression n=2 Post-natal depression n=2 **Recruitment**: from GPs	Individualised homeopathic treatment in a single practice, treatment for min.1 month Homeopath: 1	Before to after assessment	Self-reported improvement in depression given in percent, assessment 2-36 months after treatment Postal questionnaire	**Improvement in depression**: Median 85%, mode 90% (n=4). Interquartile range 55-90%. Range 10%-100% **Improvement long-standing depression (min.4 yrs) (n=5)**: 30%, 80%, 80%, 90%, 100%

		Setting: NHS GP practice, West Yorkshire			completed by patient	**Improvement recently developed depression (max.4 months) (n=4):** 60%, 90%, 90%, 100% 8 of 11 patients stopped their medication (for depression n=6, uncertain n=2) (one was not taking any medication)
Hechavarria Torres et al. 2014, Cuba [26]	Uncontrolled study, most probably prospective	Diagnosed depression (ICD-10) (suicidal patients excluded) n=35 **Recruitment**: unclear **Setting**: Center for Development of Natural and Traditional Medicine Teaching Hospital General of Santiago de Cuba	Individualised homeopathic treatment, no concurrent conventional treatment, but behavioural support (unspecified), treatment for min.2 months Number of homeopaths not specified	Before to after assessment	Assessment by a specialist from before to after therapy, with response categories: A) Improved: symptoms disappear/decline in number B) Unchanged C) Worse: symptoms increased in number or intensity	**Improvement in depression**: **No depression**: 74.3% (26 of 35 patients) **Improved symptoms**: 73.4% (163 of 222) including: depression, inability to feel/enjoy, thoughts of death/suicide, hopelessness, feelings of worthlessness, self-reproach/guilt, hypochondria and/or anxiety, sleep disturbances, tiredness/fatigue
Mahmoudian 2015, Iran [27]	Reported as "qualitative", but corresponds better to an uncontrolled study	Chronic depression in war veterans n=35 **Recruitment**: not reported **Setting**: not reported	Standardised Natrium muriaticum 30C to all participants, followed by individualised homeopathic treatment Homeopaths: not reported	Before to after assessment	Aggravations: increase in previous symptoms or appearance of new symptoms No effectiveness outcomes	No effectiveness outcomes **Aggravations**: Mild to moderate: n=9 (26%) including: Headache (n=3). desquamation skin lesions (n=2), anger (n=2), anxiety (n=1), "obstinacy" with family (n=1) Missing data: n=7 (20.0%) due to "inadequate information"
Mathie & Robinson 2006, UK [28]	Uncontrolled study, prospective	Diagnosed depression (of 961 consecutive patients with various complaints) n=55 **Recruitment**: For NHS GPs (n=10) patients attended their doctor in the normal way; self-referral for private practitioners (n=2) **Setting**: 10 NHS and 2 private homeopathy GP practices, in England and Scotland	Individualised homeopathic treatment Homeopaths: 14	Before to after assessment	7-point numerical self-reported rating scale at last follow-up consultation, max. 6 months Patient-completed outcome at consultation with homeopath	**7-point NRS at latest follow-up consultation** (n=55): Major or moderate improvement (+2 or +3): n=35, 63.6% Data not given for mild improvement (+1), no change/unsure (0) and deterioration (-1/-2/-3) Participants: With follow-up n=55. Drop-out n=2
Oberai et al. 2013, India [29]	Uncontrolled study, prospective	Diagnosed depression (ICD-10 criteria, min. 2 typical symptoms + 2 common symptoms, excluded if min. 25% improvement in HDRS after 1 week of placebo) n=83 Onset of depression episode: mean 1.92 years (SD 1.02) **Recruitment**: Patients admitted to the institute indoor patient	Individualised homeopathic treatment, 6 months Number of homeopaths not specified	Before, during & after assessment	**Primary**: HDRS at 0, 3, 6 & 12 months **Secondary**: BDI, CGI-1, CGI-2 at 0, 3, 6 & 12 months Adverse events Outcome measures completed by patients and collected by investigators and	**Primary**: HDRS baseline (mean, SD): Baseline: 17.98 (4.9). 12 months: 5.8 (5.9) HDRS 0, 3, 6 & 12 months (repeated Measure ANOVA): p=0.001. Effect size=0.74 **Secondary**: BDI (mean SD): Baseline: 23.4 (6.9) 12 months: 7.1 (8.7) BDI 0, 3, 6 & 12 months (repeated Measure ANOVA): p=0.001. Effect size = 0.72 CGI-1 (median, IQR): Baseline: 4 (3.2-5), 12 months: 1 (1-2)

		department **Setting**: Central Research Institute, Kottayam, Kerala			consultant psychiatrist	CGI-1 0, 3, 6 & 12 months (Friedman's tests): p=0.001. Effect size: 0.82 CGI-2 (median, IQR): 3 months: 2 (2-3). 12 months: 1 (1-1) CGI-2 3, 6 & 12 months (Friedman's tests): p=0.001. Effect size: 0.79 Adverse events: None
Richardson 2001, UK [30]	Survey	Diagnosed depression (out of 1100 consecutive medically diagnosed patients with various complaints) n=30 **Recruitment**: from GPs **Setting**: Department of homeopathic medicine, Liverpool	Individualised homeopathic treatment, mean 3.7 consultations (min.3), study period 1 year Homeopaths: 4?	Before to after assessment	GHHOS (self-reported) after treatment, after mean 3.7 consultations (min. 3) (study period 1 year) Patient-completed outcome handed to receptionist, clinic doctor completed a separate form recording the outcome score (unclear procedure)	**GHOOS after treatment (min. 3 consultations, mean 3.7):** +2/+3/+4: n=15 50.0% +3/+4: n=8 26.7% +2: n=7 23.3% +1/0: n=15 50.0% -1/-2/-3/-4: n=0 0.0% + improvement, - deterioration (see footnote) **Participants**: Response rate for depressed patients not reported. Only patients with follow-up consultations included. Number of patients with no follow-up consultation not reported.
Sevar 2000, UK [31]	Uncontrolled study, prospective	Diagnosed depression (out of 829 consecutive medically diagnosed patients with various complaints) n=64 **Recruitment**: uncertain **Setting**: Private MD homeopathy clinic, Cumbria	Individualised homeopathic treatment: First consultation 75 minutes, follow-up 30 minutes Homeopaths: 1	Before to after assessment	GHHOS (self-reported) after treatment, assessment period 6 months – 7 years Patient-reported outcome, data collected by homeopath	**GHOOS after treatment (range 6 months – 7 years):** +3/+4: n=40 62.5% +2: n=5 7.8% +1/0: n=10 15.6% -1/-2/-3/-4: n=0 0.0% Unknown: n=9 14.1% + improvement, - deterioration (see footnote) The 40 patients who experienced considerable improvement, were able to discontinue antidepressants **Participants:** Response rate 86% (n=55), No response 14% (n=9)
Sevar 2005, UK [32]	Uncontrolled study, prospective	Diagnosed depression (out of 455 consecutive medically diagnosed patients with various complaints) n=27 **Recruitment**: uncertain **Setting**: Private MD homeopathy clinic, Cumbria	Individualised homeopathic treatment: First consultation 75 minutes, follow-up 45 minutes (1st) or 30 minutes (other), mean 11 months (min. 6), mean 2.4 consultations (all 455 patients) Homeopaths: 1	Before to after assessment	GHHOS after treatment, mean 11 months (min. 6) Combined patient- and clinician-reported outcome	**GHOOS after treatment (mean 11 months, min. 6):** +4: n=1 3.7% +3: n=16 59.3% +2: n=4 14.8% +1: n=1 3.7% 0: n=5 18.5% -1/-2/-3/-4: n=0 0.0% Unknown: n=0 0.0% + indicates improvement, - indicates deterioration (see footnote) 14 patients (52%) were able to significantly reduce or discontinue antidepressants **Participants:** Response rate 100% (n=27)
Spence et al.	Uncontrolled	Diagnosed depression (ICD-10,	Individualised	Before to after	7-point numerical self-	**7-point NRS after mean 3.6 consultations:**

2005, UK [33]	study, prospective	from 6,888 consecutive diagnosed patients in a university-hospital outpatient clinic) N=201 **Recruitment**: from GPs and hospital specialist consultants **Setting**: NHS university homeopathic hospital outpatient clinic, Bristol	homeopathic treatment: First consultation 45 minutes, follow-up 15 minutes, mean total 3.6 consultations (for all patients), study period 6 years Homeopaths: 12	assessment	reported rating scale at follow-up consultations, length not given (study period 6 years) Patient-reported outcome, data collected by homeopath	+3 n=38 18.9% +2: n=69 34.3% +1: n=36 17.9% 0: n=46 22.9% -1: n=2 1.0% -2/-3/-4: n=0 0.0% + improvement, - deterioration (see footnote) **Participants:** 5% were unable to score (n=8) or the results were influenced by other factors (e.g. other treatment) (n=2)

Adler et al. (2008): SCID: Structured Clinical Interview. IQR: Interquartile range. MADRS: Montgomery & Åsberg Depression Rating Scale.
Clover (2000): 7-point NRS: 7-point Numerical Rating: +3 Much better, +2 Better/Moderately better, +1 Slightly better, 0 No change, -1 Slightly worse, -2 Worse/Moderately worse, -3 Much worse.
Mathie & Robinson (2005): 7-point NRS: 7-point Numerical Rating Scale: +3 Much better, +2 Better/Moderately better, +1 Slightly better, 0 No change, -1 Slightly worse, -2 Worse/Moderately worse, -3 Much worse.
Oberai et al. (2013): IQR: Interquartile range. NHS: National Health Service. HDRS: Hamilton Depression Rating Scale (17-point). BDI: Beck Depression Inventory (21-point). CGI-1: Clinical Global Impression (scale 1-7). CGI-2: Clinical Global Improvement (scale 1-7).
Richardson (2001), Sevar (2000): GHHOS: Glasgow Hospital Homeopathic Outcomes Scale, 9-point numerical rating scale including +4 Cured/Back to normal, +3 Major Improvement, +2 Moderate improvement, affecting daily living, +1 Slight improvement, no effect on daily living, 0 No change/Unsure, -1 Slight deterioration, no effect on daily living, -2 Moderate deterioration, affecting daily living, -3 Major deterioration, -4 Disastrous deterioration.
Sevar (2005): NHS: National Health Service. GHHOS: Glasgow Hospital Homeopathic Outcomes Scale, 9-point numerical rating scale including +4 Cured/Back to normal, +3 Major Improvement, +2 Moderate improvement, affecting daily living, +1 Slight improvement, no effect on daily living, 0 No change/Unsure, -1 Slight deterioration, no effect on daily living, -2 Moderate deterioration, affecting daily living, -3 Major deterioration,-4 Disastrous deterioration.
Spence et al. (2006): NHS: National Health Service. 7-point NRS: 7-point Numerical Rating Scale: +3 Major improvement, +2 Moderate improvement, +1 Mild improvement, 0 No change or unsure, -1 Mild deterioration, -2 Moderate deterioration, -3 Major deterioration