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Complementary therapies for clinical depression: an overview of systematic reviews

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Abstract

Objectives: As clinical practice guidelines vary widely in their search strategies and recommendations of complementary and alternative medicine (CAM) for depression, this overview aimed at systematically summarizing the level-1 evidence on CAM for patients with a clinical diagnosis of depression.

Methods: PubMed, PsycInfo and Central were searched for meta-analyses of randomized controlled trials (RCTs) until June 30, 2018. Outcomes included depression severity, response, remission, relapse, and adverse events. The quality of evidence was assessed according to GRADE considering the methodological quality of the RCTs (ROB) and meta-analyses (AMSTAR), inconsistency, indirectness, imprecision of the evidence, and the potential risk of publication bias.

Results: The literature search revealed 26 meta-analyses conducted between 2002 and 2018 on 1 to 49 RCTs in major, minor, and seasonal depression. In patients with mild to moderate major depression, moderate quality evidence suggested the efficacy of St. John's wort towards placebo and its comparative effectiveness towards standard antidepressants for the treatment for depression severity and response rates, while St. John's wort caused significant less adverse events. In patients with recurrent major depression, moderate quality evidence showed that Mindfulness-based Cognitive Therapy was superior to standard antidepressant drug treatment for the prevention of depression relapse. Other CAM evidence was considered as having low or very low quality.

Conclusions: The effects of all but two CAM treatments found in studies on clinical depressed patients based on low to very low quality of evidence. The evidence has to be downgraded mostly due to avoidable methodological flaws of both the original RCTs and meta-analyses not following the CONSORT and PRISMA guidelines. Further research is needed.

Keywords: Depression, Complementary Therapies, Treatment Outcome, Safety, Systematic Review

Strengths and limitations of this study

- This systematic overview included the comprehensive literature search of important CAM topics defined by the Cochrane Collaboration.
- The inclusion criteria were restricted to meta-analyses of RCTs of patients with a clinical diagnosis of depression.
- The quality of evidence from meta-analyses was assessed according to GRADE.
- There is a possible lack of evidence of newer RCTs that have not been analysed by the included meta-analyses.

Introduction

Depression is one of the most prevalent psychiatric disorders, with about 25% of women and 12% of men suffering from at least one depressive episode during their lifetime.[1-3] According to the criteria for diagnosis recommended by the American Psychiatric Association (APA), depressive disorders can be distinguished by their degree of severity or duration and are also characterized by a high comorbidity and an increase of psychological strain for the affected person.[4] It is evident, that a strong comorbid connection to several chronic conditions like addictions,[5] neurodegenerative diseases,[6 7] or different psychiatric diseases[8-11] exists. This leads depressive disorders as one of the leading causes of disability worldwide.[12]

The most commonly used treatments for depression are antidepressants, psychotherapy, or a combination of drugs and psychotherapy. While both therapies have been shown to be effective,[13-15] more recent meta-analyses also found high dropout and low remission rates[16-21] as well as clinically significant differences between antidepressant drugs and placebos only for patients at the upper end of the very severely depressed category.[22] This may lead patients to search for alternatives. Increasing mainstream use of complementary and alternative medicine (CAM) support this trend, particularly for different physical conditions with comorbid affective disorders.[23-27] While some complementary therapies have become a promising adjunct in the standard treatment of depression,[28 29] others are known for their possible side effects or interactions with standard drugs.[29] Recent clinical practice guidelines, in addition, vary widely in their search strategies and resulting recommendations for CAM treatments. While the ACP,[30] APA,[31] and CANMAT guideline[32] provide a more comprehensive overview and critical appraisal of CAM treatments, the DGPPN,[33] NICE,[34] and WFSBP[35] guidelines mainly focus on St. John's Wort and light therapy. Possible effects and risks of further CAM therapies are not discussed. Thus, the purpose of this overview is to provide a comprehensive search strategy of relevant CAM terms and systematically summarize the existing level-1 evidence for clinical depression as a basis for further guideline recommendations on the efficacy, effectiveness, and safety of CAM therapies.

Methods

This systematic overview of reviews was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[36 37] and the recommendations of the Cochrane Collaboration.[38] The protocol was not prospectively registered in a database.

Inclusion and exclusion criteria

- Types of studies: To be eligible, articles had to be systematic reviews with meta-analyses of randomized controlled clinical trials (RCTs) published in peer-reviewed journals. Conference abstracts or unpublished work were excluded as well as reviews summarizing evidence narratively. In cases of including same or similar original studies, only the review with the most recent, most comprehensive search was included. When systematic reviews reported results of RCTs as well as of designs of lower evidence levels, they were considered only if separate meta-analyses for the included RCTs were performed.
- Types of participants: Only reviews of patients with a diagnosis of major depression or dysthymia were eligible as well as reviews including patients/general population samples with mild depressive symptoms above a clinical cut off or seasonal patterns. In contrast, reviews studying depressive symptoms within specific subpopulations of substance-induced or demented patients, secondary depression due to another medical condition (e.g. post-stroke, cancer, or pain patients), bipolar disorders, or females with premenstrual dysphoric disorder or postpartum depression were excluded. Further restrictions regarding the diagnostic criteria or procedures, regarding age, gender, duration of the condition, or symptom intensity were not applied.
- Types of interventions: Reviews investigating the effectiveness and/or safety of a single, adjunctive or combined CAM treatment were included. For the classification of CAM treatments the definition of the US National Institutes of Health[39] was followed. CAM interventions have to be compared against treatment as usual (TAU)/waiting list, placebo/sham, or standard medical care.

– Types of outcomes: Reviews were eligible if they assessed at least one measure of effectiveness such as severity of depressive symptoms, response rate (generally defined as a 50% decrease in depression scores after a period of up to 12 weeks of treatment),[30] remission rate (generally defined as a period of up to 12 weeks during which a patient is asymptomatic or has only few symptoms to a very mild degree).[40] relapse rates, and/or a measure of safety such as number of adverse events (AE), drug interactions, or numbers needed to harm for study withdrawal due to side effects.

Search strategy

Electronic literature was systematically searched via PubMed, PsycInfo and Central from their inception to January 31, 2018 without restrictions regarding time or language (Table 1). Search terms for CAM treatments were selected in accordance with Cochrane recommendations.[41]. Additional manual search included reference lists of previously published reviews[14 28 29 42] and clinical practice guidelines.[30-35] Using PubMed Informer,[43] the search was updated until June 30, 2018.

Study selection process

To assess eligibility, articles were selected by screening titles and abstracts independently by two authors (HH and DA). Any abstract considered potentially eligible by at least one author was read in full to decide on its eligibility. Disagreements were rechecked with a third author (HC) until consensus was achieved.

Data extraction and quality assessment

Two authors (HH and DA) independently extracted data on the characteristics of the reviews including the type of the intervention, the year of publication, the number and quality of the original RCTs, the total number and age of the participants, and effectiveness and safety outcomes. The quality of the included reviews was assessed using the Assessment of the Methodological Quality of Systematic Reviews (AMSTAR) tool.[44] The AMSTAR tool consists of 11 items asking about important methodological quality criteria of systematic reviews such as: a published apriori design, duplicate study selection and data extraction, a comprehensive literature search including grey literature, a list of included and excluded studies, summarized characteristics and quality assessment of included

studies, assessment of publication bias, appropriate method of data syntheses and deducing conclusions, and a conflict of interests statement. AMSTAR has shown good construct validity and inter-rater reliability. The Intraclass Correlation Coefficient (ICC) of the total AMSTAR score of 11 points was reported as 0.84.[45] For this analysis, the two authors (HH and DA) who independently assessed AMSTAR reached an ICC of 0.96. Disagreements regarding content or quality of the reviews were rechecked with a third author (HC) and resolved by agreement.

Data synthesis

Results were pooled qualitatively by type of the intervention. Outcomes had to be calculated as standard mean differences (SMDs), risk ratios (RRs), hazard ratios (HR), or odds ratios (ORs). If meta-analyses displayed mean differences (MDs), SMDs were calculated using Review Manager Software (RevMan, Version 5.3, The Nordic Cochrane Centre, Copenhagen) for better comparability of the results. RevMan was also used to exclude SMDs/RRs/HRs/ORs of selective RCTs that did not fulfil eligibility criteria of this overview. Effect sizes were classified according to Cohen as SMD = 0.2 – 0.5 = small effect, SMD = 0.5 – 0.8 = medium effect, and SMD > 0.8 = large effect [46] with higher reduction of/improvement in depression scores represented by more negative SMDs or RRs/HRs/ORs less than 1. According to the NICE guideline, a SMD of ≥ 0.5 was considered as a clinically relevant reduction of depression severity.[47] Statistical heterogeneity between studies was assessed by Chi^2 statistics with a p-value of ≤ .10 indicating significant heterogeneity. The magnitude of heterogeneity was categorized by I^2 statistics with I^2 > 25% = moderate heterogeneity, I^2 > 50% = substantial heterogeneity, and I^2 > 75% = considerable heterogeneity.[38]

Quality of evidence

The quality of evidence was assessed according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach[48] individually by two authors (HH and DA). Disagreements were rechecked with a third author (HC) until consensus was achieved. For each outcome, the evidence can be graded as high, moderate, low or very low. Evidence from RCTs is initially assessed as high, but can be downgraded by one level for serious or two levels for very

serious limitations of the study quality (of both RCTs and meta-analyses), inconsistency of the results, indirectness of the evidence, imprecision of the results, and a potential risk of publication bias.[48]

Results

Study selection

A total of 3582 potentially eligible articles were identified by electronic database search. One additional review was retrieved from manual search,[49] one from the updated search until June 2018.[50] After removing duplicates, 2639 articles were excluded by screening of titles and abstracts. The remaining 117 articles were read in full, of which further 91 reviews had to be excluded (Figure 1). Reasons for exclusion comprised 55 reviews where newer and/or more comprehensive reviews on higher quality evidence were available.[49 51-104] Further 15 reviews have to be excluded as they systematically summarized evidence but did not performed a meta-analysis mostly due to clinical heterogeneity or a limited number of available RCTs.[105-119] Eight reviews were excluded as they included mixed depressive samples of bipolar or postpartum cases and did not provide (data for) subgroup analyses for patients with the defined depression criteria.[120-127] Another six reviews contained community samples with non-clinical depression or physically ill patients with comorbid depressive symptoms but displayed no data for patients with a primary diagnosis of depression.[128-133] Four reviews performed meta-analyses on both RCTs and non-RCTs and did not perform subgroup analyses or extracted sufficient data for post hoc analyses.[134-137] Three of the reviews analysed standard instead of complementary therapies and were therefore be excluded. Finally, 26 meta-analyses could be included and reviewed.[50 138-162]

Review characteristics and quality

Characteristics and quality appraisal of the included meta-analyses are summarized in the Supplementary Table 1. Meta-analyses were conducted between 2002 and 2018 and included between 1 to 49 RCTs on 40 to 7104 adult patients. Meta-analyses on children and adolescents were not available or did not meet inclusion criteria. Samples mostly consisted of patients suffering from major depressive disorder[139-142 144-150 153 155 156 158 159] but also included patients with mixed diagnoses

of non-seasonal depression,[50 152 161 162] patients with a diagnosis of seasonal depression,[151] and patients with mild to severe symptoms of depression above a clinical cut-off.[138 140 143 144 150 154 156 157] All but one meta-analysis[140] reported pooled outcomes based on common standardized questionnaires or diagnostic interviews. Effects were analysed mostly up to 12 weeks of treatment (short-term), except for four meta-analyses that included RCTs with effects reported up to 16, 24, or 32 weeks[50 141 142 150 159] and further three meta-analyses with long-term analyses equal to or greater than one year [148 156 162]. The AMSTAR total scores of the included meta-analyses ranged between 4 and 11 points with a median quality of 7 points. The individual AMSTAR-ratings are reported in the Supplementary Table 2.

Synthesis of results

Acupuncture

Manual acupuncture

A high-quality Cochrane review meta-analysed 49 RCTs in major depressed adults as well as those with clinically relevant symptoms of depression for manual acupuncture.[50] For depression severity, significant effect sizes were found in comparisons to TAU and as in adjunction to standard antidepressants, while acupuncture showed similar effects to invasive sham acupuncture and standard antidepressants (Figure 2). The analyses of remission rates did not reveal superiority of acupuncture in the comparisons to TAU, invasive sham, standard antidepressants or in adjunction to standard antidepressants (Figure 4). Adverse events reported in the acupuncture groups were significantly lower than in patients treated with antidepressant drugs. However, most meta-analyses showed significant heterogeneity, a lack of RCTs with low risk of bias and a possibly serious risk of publication bias. Thus, the quality of evidence had to be downgraded to low and very low.

Electroacupuncture

For electroacupuncture, the same Cochrane review[50] revealed very low quality of evidence for the comparisons to TAU and invasive sham for both outcomes, severity (Figure 2) and remission (Figure 4), because of serious limitations of the quality of the RCTs, imprecision, and a high risk of publication

bias. For electroacupuncture monotherapy in comparison to standard antidepressants, low quality evidence homogeneously suggested significant greater effects for severity and similar effects for remission. As an adjunctive treatment to antidepressants, electroacupuncture effectiveness was supported by low quality of evidence showing a significant greater consistent and precise effect for depression severity. Although the mean adjunctive effect can be considered as large, the analysis based on only one RCT with overall low risk of bias and 4 RCTs of lower methodological quality that missed to include adjunctive sham acupuncture. For remission rates, very low quality of evidence suggested no effects in adjunction to antidepressants. In addition, one RCT showed significant less AEs when electroacupuncture was added to standard antidepressants.

Aromatherapy

The literature search revealed no meta-analysis on aromatherapy. A recent systematic review detected no RCTs in patients with a primary diagnosis of depression. However, two out of five of the reviewed studies on inhalation aromatherapy and five out of eight studies on aromatherapy massage have found significant anti-depressive effects in mixed patient samples and healthy adults.[116]

Biofeedback

No meta-analysis on biofeedback was conducted to date. A recent systematic review revealed only one RCT on the defined inclusion criteria for depression showing some effects in contrast to sham psychotherapy.[117]

Herbs

St. John's wort (Hypericum perforatum)

The effectiveness of St. John's wort was meta-analysed by a Cochrane review of 29 RCTs[149] and a more recent, higher quality meta-analysis of 35 RCTs.[141] In comparison to placebo, St. John's wort showed moderate quality evidence of significant greater reductions of depression severity (Figure 2) and response rates (Figure 3). The evidence had to be downgraded due to significant heterogeneity because of higher effects in studies from German-speaking countries than in those from the US or other European countries. In contrast, very low quality of evidence suggested no superiority to

placebo for remission (Figure 4) and response rates (Figure 5). In comparison to standard antidepressants, St. John's wort showed comparable severity reductions, response, remission, and relapse rates. The quality of the evidence of the meta-analyses of severity and relapse rates had to be downgraded to low and very low, respectively. The evidence of the response and remission rates was considered as moderate quality showing the same results in both German and studies from other countries but containing some RCTs with unclear risk of selection bias and detection bias. Moreover, both meta-analyses[141 149] showed similar AEs of St. John's wort to placebo but significant less AEs than standard antidepressants.

Saffron (Crocus sativus)

A moderate-quality meta-analysis examined the effectiveness and safety of saffron on depression severity by including 5 RCTs in adult patients with major depression.[146] It revealed very low quality of evidence for significant greater effects versus placebo and similar effects versus antidepressant medication up to 8 weeks of treatment (Figure 2). No serious adverse events were reported, but patients receiving saffron tend to report more adverse events than those receiving placebo and less adverse events than those receiving antidepressant medication. Reasons for downgrading the evidence included no replication of the results (all included RCTs were conducted by the same research group), the small overall sample size, and the possibly high risk of publication bias.

Curcumin (Curcuma longa)

For the intake of curcumin, a moderate-quality meta-analysis[154] revealed very low quality of evidence suggesting a small but significant short-term effect of low heterogeneity on depression severity by pooling 6 RCTs (Figure 2). No serious adverse events were recorded. Evidence had to be downgraded due to unclear risk of selection, performance, detection, attrition, and reporting bias in over the half of the included RCTs, the imprecision of the pooled effect and the possibly high risk of publication bias.

Traditional Chinese herbs

A comprehensive but low-quality systematic review of 296 RCTs of *Chinese herbal medicine* formulas and single herbs[161] revealed 21 RCTs of mostly unclear to high risk of selection, performance, and detection bias and a serious risk of publication bias. Therefore, the evidence supporting the superiority above placebo and the similarity towards standard antidepressants regarding depression severity (Figure 2) and response rates (Figure 3) was assessed as very low.

Other herbs

For other than the described herbs, no meta-analyses were conducted to date. However, a systematic review[109] found three single RCTs that showed significant improvement in depressive symptoms for *Lavandula angustifolia* as an adjunctive treatment to standard antidepressant drugs versus antidepressant drugs alone and for *Echium amoenum* and *Rhodiola rosea* versus placebo. No serious adverse events were reported.

Homoeopathy

No meta-analysis on *homoeopathic remedies* for depression were conducted yet. A recent systematic review detected no placebo-controlled RCTs in patients with a primary diagnosis of depression.[128]

Hypnosis

No meta-analysis on *hypnosis* or *self-hypnosis* techniques met the inclusion criteria of this overview. The only available review on this topic[126] included 6 RCTs among which only one RCT included adults with mild primary depression. Within the mixed sample of physically ill patients and healthy adults, (self-)hypnosis appeared to be effective in decreasing depressive symptoms.

Light therapy

A high-quality Cochrane review meta-analysed the effects of *bright light therapy* in adjunction to standard antidepressants versus sham light therapy plus antidepressants on severity and response rates in patients suffering from non-seasonal depression.[160] By pooling 18 RCTs of overall unclear risk of bias, it revealed very low quality of evidence for a significant small but inconsistent and imprecise effect on depression severity (Figure 2). A subgroup analysis of two RCTs with low risk of selection

bias and detection bias revealed a significant large effect on depression severity but based on one non-peer-reviewed publication and one RCT that also included bipolar patients. Response rates did not significantly differ between groups (Figure 3). Adverse events were reported non-systematically but appeared to be comparable to sham light therapy except for hypomania that occurred more often under verum light therapy.[160]

For patients with seasonal patterns of depression, a meta-analysis of 8 RCTs[151] revealed very low quality of evidence for a significant medium effect on depression severity of light monotherapy in comparison to sham light therapy (Figure 2). Risk of bias of individual RCTs, heterogeneity, and safety were not analysed leading to an overall low quality of the meta-analysis and downgrading of the evidence.

Massage therapy

The literature search detected no meta-analysis of *massage therapy* in patients with a primary depression. However, massage therapy appeared to be effective in decreasing depressive symptoms in mixed samples of physically ill patients and healthy adult.[132] Future research will show, whether these results may be transferable to primary depressed cases.

Meditative movement therapies

Dance therapy

Short-term effects of improvisatory or structured *dance therapy* as a combination of movement-based work, interactive group components and insight/expressive methods were meta-analysed by a Cochrane review of high methodological quality.[152] It revealed a significant large pooled effect size for depression severity as an adjunctive treatment option to standard medical/psychotherapeutic care based on two RCTs (Figure 2). Although the meta-analyses contained no heterogeneity and no imprecise CI, the evidence had to be downgraded because of mostly unclear/high risk of bias of one of the RCTs as well as the overall small sample size.

Chinese movement therapies

A low-quality meta-analysis on Chinese meditative movement therapies revealed 30 RCTs, of which 2 RCTs on *Qi Gong* and 3 RCTs on *Tai Chi* met inclusion criteria for patients with mild to severe symptoms of primary depression.[150] Very low quality of evidence suggested significant short-term effects for Qi Gong but not for Tai Chi in comparison to TAU. The evidence had to be downgraded due to very serious limitations of the quality of the RCTs and the meta-analysis, significant heterogeneity, imprecision, and a possible high risk of publication bias.

Yoga

A high-quality meta-analysis of complex *yoga* interventions for various depressive disorders found 12 RCTs,[144] of which 5 RCTs of mostly unclear risk of bias met the inclusion criteria of this overview. The pooled short-term effect on depression severity was of large size in comparison to TAU and medium size in comparison to standard exercises (Figure 2). However, the evidence was assessed as very low due to serious limitations of quality of the RCTs, significant heterogeneity, imprecision, and a possible high risk of publication bias.

A further systematic review of yoga in major depressive disorder, revealed 5 newer yoga RCTs but did not perform a meta-analysis because of high clinical heterogeneity. Risk of bias was comparably high and evidence mostly conflicting.[106]

Mindfulness-based interventions

Mindfulness-based Cognitive Therapy (MBCT)

A low-quality meta-analysis of mindfulness-based interventions in patients with major depression found 4 RCTs investigating the effects of MBCT and Cognitive Behavioural Therapy (CBT) on depression severity.[158] It revealed a significant large short-term effect of MBCT in comparison to TAU and similar effects in comparison to CBT (Figure 2). However, the quality of the evidence was considered as very low due to the missing risk of bias assessment, inconsistency, and imprecision.

A further moderate-quality systematic review on MBCT meta-analysed 9 RCTs on an individual patient data level.[148] The sample consisted of patients with recurrent major depression currently in remission. After a period of 60 weeks, MBCT showed a significantly reduced risk of depressive relapse compared

to those receiving antidepressant drugs (Figure 5). No serious adverse events were reported. The evidence was assessed as moderate due to a possibly serious risk of publication bias.

Mindfulness-based stress reduction (MBSR)

RCTs of MBSR and MBSR-like interventions were meta-analysed by a recent review [143] showing a significant large short-term effect on depression severity in comparison to TAU and enhanced TAU (Figure 2). The quality of the evidence was assessed as low because of the overall unclear risk of selection und and performance bias and significant heterogeneity.

Music therapy

Studies on active and receptive *music therapy* in older patients with a diagnosis of depression were summarized by a recent moderate-quality meta-analysis.[162] Out of 19 RCTs, 8 met the inclusion criteria for this overview. Pooled analyses of 5 of them revealed a significant medium effect size on depression severity against TAU up to 52 weeks, however with bigger short-term than long-term effects, considerable heterogeneity and overall unclear risk of selection, performance and detection bias resulting in very low quality of evidence. Further 3 RCTs of the same review revealed low quality evidence for a significant large consistent and precise effect of music therapy as an adjunctive treatment to antidepressants (Figure 2).

A newer Cochrane review[138] found 8 different RCTs showing a significant large pooled effect of music therapy on depression severity against TAU and similar effects as CBT (Figure 2). However, both analyses revealed very low quality of evidence due to mostly unclear selection, performance, detection and reporting bias, significant heterogeneity, and imprecision.

Nutrition therapy

No meta-analyses on specific diets for patients with depression were published to date. A systematic review of 11 RCTs on whole-diet interventions in mostly healthy patients with subthreshold physical conditions revealed conflicting evidence on the effectiveness of those intervention for the reduction of depressive symptoms.[114]

A further systematic review on fasting in patients with chronic pain and inflammatory diseases [110] included 1 RCT and 7 observational studies, which showed promising short-term but questionable longer-term anti-depressive effects.

Religious/spiritual Interventions

Very low to low quality of evidence was found by a moderate-quality systematic review of 9 RCTs on Christian, Muslim, and spiritual CBT adaptions.[140] The analyses showed significant greater medium effects on depression severity against TAU and standard CBT (Figure 2). Safety data were not reported.

Supplements

Inositol

A low quality meta-analysis of 2 RCTs in patients with major depression[153] revealed very low quality evidence for inositol as adjective to standard antidepressants versus placebo in combination to standard antidepressants (Figure 2).

Magnesium

No meta-analysis of magnesium supplementation was found. A recent systematic review detected no RCTs in patients with a primary diagnosis of depression [107].

Omega-3 fatty acids

A high-quality Cochrane review[142] of 26 RCTs found conflicting evidence of the effectiveness of supplementation with omega-3 fatty acids versus placebo in patients with major depression as depression severity significantly improved while response and remission rates did not so (Figure 2-4). One additional RCT with a very low sample size showed similar effects of omega-3 fatty acids on severity and response rates in comparison to antidepressant drug treatment (Figure 2 and 3). However, all meta-analyses were based on very low quality of evidence because of limitations of the study quality, significant heterogeneity, imprecision and a possibly high risk of publication bias.

Probiotics

The effectiveness of the supplementation with probiotics on depression severity was analysed by a moderate-quality meta-analysis of 5 RCTs, of which only one RCT with overall low risk of bias was carried out on patients with major depression.[147] The analysis of the RCT revealed a significant medium but imprecise short-term effect in comparison to placebo (Figure 2). This led to overall very low quality of evidence for probiotics supplementation.

S-adenosyl methionine (SAMe)

A high-quality Cochrane review[145] of the effectiveness and safety of SAMe supplementation on depression severity revealed 2 RCTs of low risk of bias that showed no significant pooled effects for SAMe monotherapy versus placebo. One RCT, also of low risk of bias showed a significant medium short-term effect as adjunctive to standard antidepressant medication, both for depression severity. Further 5 RCTs, which were rated as having overall unclear risk of bias, showed similar pooled effects of SAMe monotherapy on depression severity compared to standard antidepressant medication (Figure 2). Original RCTs reported safety issues insufficiently. For all meta-analyses, the evidence was assessed as low to very low quality because of limitations of the study quality, heterogeneity, imprecision, and a possibly high risk of publication bias.

Tryptophan

A moderate-quality Cochrane review found 2 RCTs investigating the effectiveness and safety of tryptophan supplementation on depression severity.[157] Pooling the effects led to significant greater short-term response rates (Figure 3) as well as significant more adverse events in the tryptophan group than in the placebo group. The evidence was assessed as very low quality because of an unclear risk of detection, attrition and other bias, imprecision, and a possible risk for publication bias.

Vitamins

For Vitamin B6, no meta-analysis was available. A systematic review without meta-analysis revealed 2 RCTs showing no significant effects when compared to placebo.[119]

Two further moderate to high-quality meta-analyses examined the effects of vitamin B9 (Folate) for major depressive patients. While a Cochrane review[159] calculated a significant medium effect size of

folate-intake as an adjunctive intervention to standard drug treatment on depression severity, a more recent review[139] revealed non-significant differences on severity and response rates (Figure 2 and 3). In contrast, a long-term combined intake of Vitamin B6, B9, and B12 was found to be effective for relapse prevention after remission of symptoms as a result of one RCT (Figure 5).[139] However, all comparisons were based on very low quality of evidence mostly due to significant heterogeneity, imprecision, and possible high risk of publication bias.

Another moderate-quality meta-analysis revealed evidence of the effectiveness of vitamin D-intake on depression severity in comparison to placebo.[156] The analysis of the two included RCTs revealed a significant medium short-term effect in favour of vitamin D in major depressed patients up to 8 weeks (Figure 2). The quality of evidence was rated as very low due to limitations of the study quality, missing values of heterogeneity, imprecision, a high risk of publication bias as well as insufficient reporting of adverse events.

Zinc

The effectiveness of zinc for major depression was meta-analysed by a low-quality review of 3 RCTs.[155] It revealed a significant pooled short-term effect of medium size and low heterogeneity when zinc was taken as an adjunctive to standard antidepressant drug treatment (Figure 2). However, the available evidence had to be assessed as very low as the meta-analysis did not perform risk of bias assessments and did not report adverse events.

Discussion

This systematic review provided a comprehensive overview of the evidence of CAM treatments for patients with a diagnosis or clinical symptoms of depression. Moderate quality evidence suggested the efficacy, comparative effectiveness to standard antidepressants, and safety of St. John's wort on depression severity and response rates. For remission and relapse rates, the evidence was conflicting and of lower quality. Moreover, moderate quality evidence showed that MBCT was superior to standard antidepressant drug treatment for the prevention of depression relapse in patients with recurrent major depression. Low quality evidence suggested significant greater effects in favour of

electroacupuncture in comparison to standard antidepressants alone and in adjunction to standard antidepressants for depression severity. For remission rates, low quality evidence revealed comparable effects of electroacupuncture and standard antidepressants. Further significant greater effects, which based on low quality evidence, were found for MBSR versus TAU, music therapy in adjunction to standard antidepressants, faith-adapted CBT versus CBT, and SAMe versus standard antidepressants. Other treatments such as manual acupuncture, aromatherapy, biofeedback, herbs (crocus sativus, curcuma longa, traditional Chinese herbs, lavandula angustifolia, echium amoenum, rhodiola rosea), Homoeopathy, hypnosis, bright light therapy, massage, meditative movement therapies (dance therapy, Qi Gong, Tai Chi, yoga), whole-diet interventions, fasting, and supplementation with inositol, magnesium, omega-3 fatty acids, probiotics, tryptophan, B- and D-vitamins, and zinc were based on very low quality of evidence or no level-1 evidence.

The strengths of the review process included the comprehensive literature search based on a structured list of CAM specific topics, which had been operationalized for the Cochrane Collaboration.[41] It therefore included evidence for more than the previously considered CAM approaches and provided systematic information where further high-quality studies are required. In addition, we only included results of RCTs of patients with a diagnosis of depression or clinical relevant depressive symptoms and excluded RCTs on samples with minor or secondary symptoms of depression by newly calculating effect sizes. Finally, we rated AMSTAR and considered the quality of the meta-analyses as well when grading the quality of the evidence.

The conclusions derived from this overview are limited due to possibly missing evidence from newer RCTs, which have not been summarized by the included systematic reviews and meta-analyses. As it was not within the scope of this overview, we did not separately search for individual RCTs. We also did not include meta-analyses on observational studies of depression risk that may include bigger samples and may provide additional information about further possible treatment approaches. Another reason that limits the quality of evidence consists in the unsatisfactory methodological quality of some of the included meta-analyses. Although the methodological quality of the original RCTs might be acceptable, the bad reporting of some meta-analyses led to downgraded evidence. In

particular, meta-analyses often missed to search for grey literature, cite excluded studies, adequately assess risk of bias of the original studies, and report complete I^2 statistics. As the latter are known to be unstable in meta-analyses with a small numbers of studies,[163] calculating confidence intervals for I^2 should be standard. Moreover, RCTs as well as meta-analyses often missed to systematically report on occurred adverse events, which also limits the significance of the conclusions. In RCTs of non-pharmacological interventions, there is always a high or unclear risk of performance bias and possibly high placebo effects. As such, adding credible sham interventions, controlling for patients' expectances, and performing of ITT analyses is indispensable. However, mete-analyses mostly did not systematically assess these issues. In general, it should be noticed that all evidence is based on short-term pooled effects, except for meta-analyses of St. John's wort, MBCT, music therapy, and B- and D-vitamins that also provided longer-term follow-up data.

Clinical recommendations for patients should follow the country-specific clinical practice guidelines considering the quality of evidence, the accessibility of the treatment, costs, and the preferences of the patients. While the guidelines agree[30 31 33-35 164 165] that clinicians should select between either CBT or second-generation antidepressant drugs for the treatment of major depression, the restricted search strategy of some of the guidelines might limit their recommendations for CAM treatments. For patients who do reject or do not tolerate standard antidepressant drugs, one alternative treatment option may be St. John's wort. It is also recommended by the American Psychiatric Association Task Force report[42] and the CANMAT Depression Work Group[32] as being proven sufficiently for the short-term by placebo-controlled and equivalence trials with standard antidepressants for mild to moderate major depression. Particularly for bridging the gap between diagnosis and getting access to psychotherapy and meanwhile reducing/not-worsening depression severity, St. John's wort may be considered as a possibly better tolerated alternative to standard antidepressant drugs.[166] As St. John's wort is accessible without prescription and currently not regulated by the US Food and Drug Administration, we agree with the ACP guidelines[30] that it remains difficult for patients to obtain quality-controlled remedies. Moreover, St. John's wort is associated with numerous herb-to-drug interactions.[167] Therefore, we would recommend clinicians

to educate their patients about possible effects, side effects and interactions who in turn should not take St. John's wort without professional advise.[33] Despite those limitations, we would not discourage a general therapeutic attempt with St. John's wort, even if we disagree with the NICE guideline in this point.[34] Clinicians may also inform patients with recurrent major depression currently in remission about the superiority of MBCT in comparison to standard antidepressants for relapse prevention.[31-34] Finally, patients should also be informed that many other CAM treatments might show promising effects but cannot be recommended until further higher-quality studies will confirm their effectiveness and safety.

Further research is needed, particularly for interventions that have shown preliminary evidence for reducing secondary symptoms of depression, promising short-term but no longer-term effects, or insufficient evidence due to low methodological quality of the original RCTs and/or the performed meta-analyses. Reporting of clinical trials and meta-analyses should necessarily follow the CONSORT[168] and PRISMA guidelines,[36] respectively, including rigorous documentation and analysis of adverse events. Especially Chinese and Indian trials are still found to be poorly reported and tended to present more positive conclusions than those from western countries.[169 170] Moreover, 7 of the included meta-analyses showed no more than poor methodological quality. All were published in peer-reviewed journals in the past 5 years. One complementary journal is among them, while 6 of the journals are conventional psychiatric journals with impact factors ranging from 2.419 to 4.369. Thus, particularly the review process as well as the editorial work need to be improved. Further clinical practice guidelines should extend their search strategies and include standard search terms for CAM. This is also important for CAM therapies that do not show consistent evidence or that are not yet investigated. This information might be equally interesting for physicians as well as for patients to make an informed decision about the treatment for clinical depression.

Conclusion

This overview of systematic reviews on CAM treatments for clinical depression aimed to provide a systematic search strategy and evidence base, on which further clinical practice guidelines may build their recommendations. To improve quality of trials and meta-analyses, researchers, reviewers as

well as editors are asked to ensure that future articles strictly adhere the CONSORT and PRISMA guidelines.

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Competing interests

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Author contribution statement

HH was responsible for the conception and design of the study, the collection and analysis of the study data and for drafting the manuscript. DA participated in the analysis of the study data and drafting the manuscript. HC participated in the conception and design of the study and the analysis of the study data, and critically revised the manuscript. GD participated in the conception and design of the study, and critically revised the manuscript. All authors approved the final manuscript.

Data Availability

All data analysed within this overview are included in this published article and its supplementary information files.

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Figure legends

Figure 1. Study flow diagram.

Figure 2. Quality of evidence for depression severity. ADM: Antidepressant medication, CBT: Cognitive Behavioural Therapy, CI: Confidence Interval, I^2: Heterogeneity, MBCT: Mindfulness-based Cognitive Therapy, MBSR: Mindfulness-based Stress Reduction, N.c.: Not calculable because of only one included RCT, N.r.: Not reported, SAMe: S-adenosyl methionine, Tau: Treatment as Usual

Figure 3. Quality of evidence for depression response rates. ADM: Antidepressant medication, CI: Confidence Interval, I^2: Heterogeneity, N.c.: Not calculable because of only one included RCT, OR: Odds Ratio, RR: Risk Ratio

Figure 4. Quality of evidence for depression remission rates. ADM: Antidepressant medication, CI: Confidence Interval, I^2: Heterogeneity, N.c.: Not calculable because of only one included RCT, OR: Odds Ratio, RR: Risk Ratio, Tau: Treatment as Usual

Figure 5. Quality of evidence for depression relapse rates. ADM: Antidepressant medication, CI: Confidence Interval, HR: Hazard Ratio, I^2: Heterogeneity, MBCT: Mindfulness-based Cognitive Therapy, N.c.: Not calculable because of only one included RCT, OR: Odds Ratio, RR: Risk Ratio, Tau: Treatment as Usual

Tables

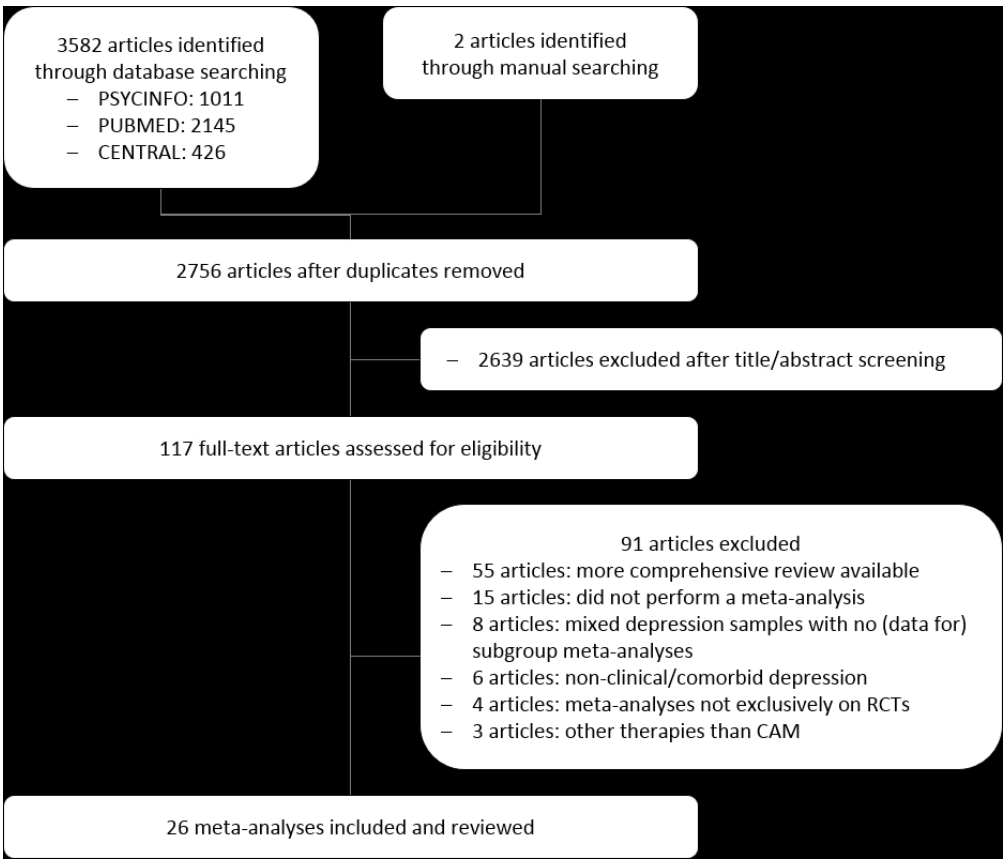
Table 1. Electronic search strategy for PubMed.

#1	(Depression OR Depressive Disorder, Major OR Depressive Disorder, Treatment-Resistant OR Dysthymic Disorder OR Seasonal Affective Disorder)[mh]
#2	(depress* OR dysthym* or "seasonal affective" OR "affective disorder" OR "affective disorders" OR "mood disorder" OR "mood disorders")[tiab]
#3	(Systematic review OR Meta-analysis)[pt] OR (Systematic* OR Meta-analy*)[tiab]
#4	(Acupressure OR Acupuncture OR acid OR Alexander Technique OR alternative OR Aromatherapy OR Aroma Therapy OR Art Therap* OR ayurved* OR Balneotherapy OR Balneo Therapy OR bee OR Biofeedback OR Bio Feedback OR bright light OR Chelation Therapy OR Chinese Traditional Medicine OR Chiropractic OR Chronotherapy OR Color Therapy OR complementary OR craniosacral OR cupping OR Curcumin OR Dance Therapy OR diet OR Distant Healing OR Electroacupuncture OR Feldenkrais OR folic acid OR Folate OR Healing Touch OR herbal OR Herbs OR Homeopath* OR Honey OR Hydrotherapy OR hyperbaric oxygenation OR Hypericum perforatum OR Hyperthermia OR Hypnosis OR Imagery OR Inositol OR Kampo OR Light Therapy OR Magnesium OR Massage OR MBSR OR MBCT OR Meditation OR Mindfulness OR Morita Therapy OR Moxibustion OR Mediterranean OR Music Therap* OR Naturopathy OR Neural Therapy OR Omega-3 OR Osteopath* OR Ozone Therapy OR Phototherapy OR Pollen OR Prayer OR prebiotic* OR probiotic* OR Propolis OR Qi Gong OR Reflexology OR Reiki OR Relaxation OR Rolfing OR Royal Jelly OR S-adenosyl-L-methionine OR Saffron OR Shamanism OR Snoezelen OR Speleotherapy OR Spinal Manipulation OR Spiritual OR St John's Wort OR Supplements OR Tai Chi OR TCM OR Therapeutic Touch OR Traditional Chinese Medicine OR Tryptophan OR Tui na OR Turmeric OR vegan OR vegetarian OR venom OR Vitamin OR Yoga OR zinc)[tiab]
#5	(Acupressure OR Acupuncture OR Acupuncture Therapy OR Acids OR Aromatherapy OR Art Therapy OR Balneology OR Biofeedback, Psychology OR Chelation Therapy OR Chiropractic OR Chronotherapy OR Color Therapy OR Complementary Therapies OR Crocus OR Curcuma OR Dance Therapy OR Diet OR Electroacupuncture OR Fatty Acids, Omega-3 OR Folic Acid OR Homeopathy OR Honey OR Hydrotherapy OR Hypericum OR Hyperthermia, Induced OR Hypnosis OR Imagery OR Inositol OR Magnesium OR Manipulation, Spinal OR Massage OR Medicine, Ayurvedic OR Medicine, Chinese Traditional OR Medicine, Kampo OR Meditation OR Mind-Body Therapies OR Mindfulness OR Moxibustion OR Naturopathy OR Ozone OR Phototherapy OR Plants, Medicinal OR Pollen OR Prebiotics OR Probiotics OR Propolis OR Qigong OR Relaxation OR Shamanism OR Speleotherapy OR Spiritual Therapies OR Supplements, Dietary OR Tai Ji OR Therapeutic Touch OR Tryptophan OR Venoms OR Vitamins OR Yoga OR Zinc)[mh]
#6	(#1 OR #2) AND #3 AND (#4 OR #5)

Supplementary data

Supplementary table 1: Detailed AMSTAR ratings.

Supplementary table 2: Characteristics and outcomes of the included meta-analyses.



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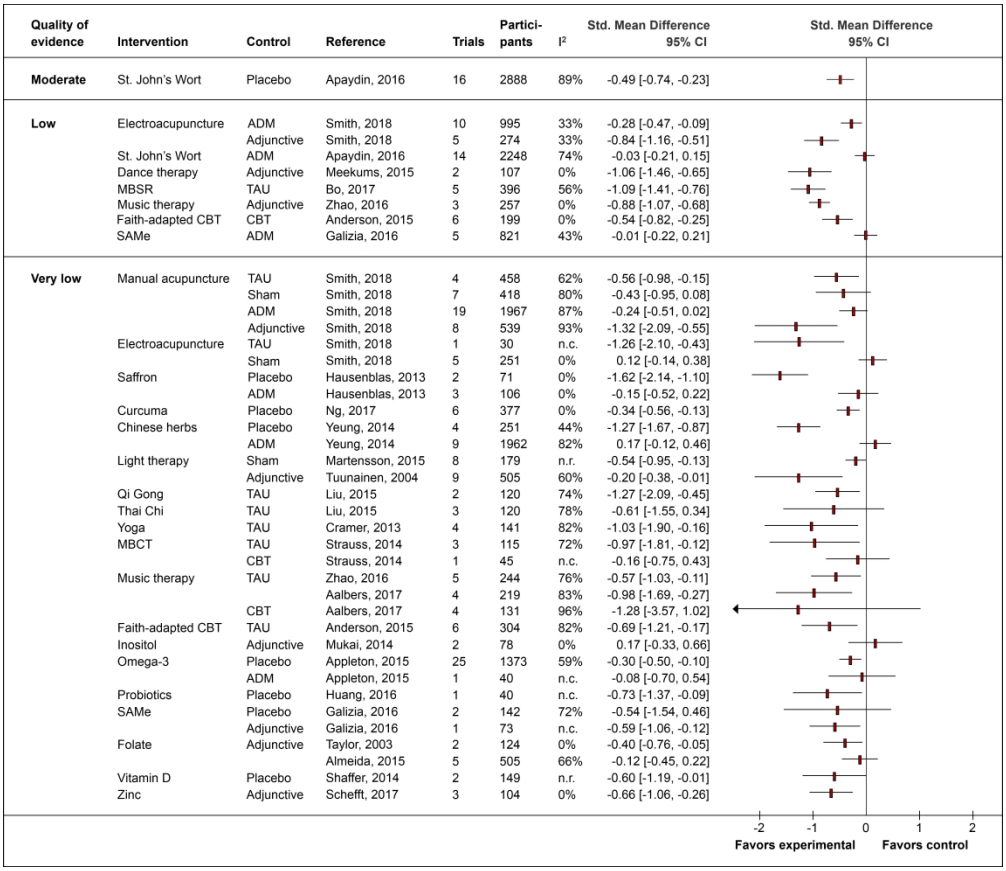

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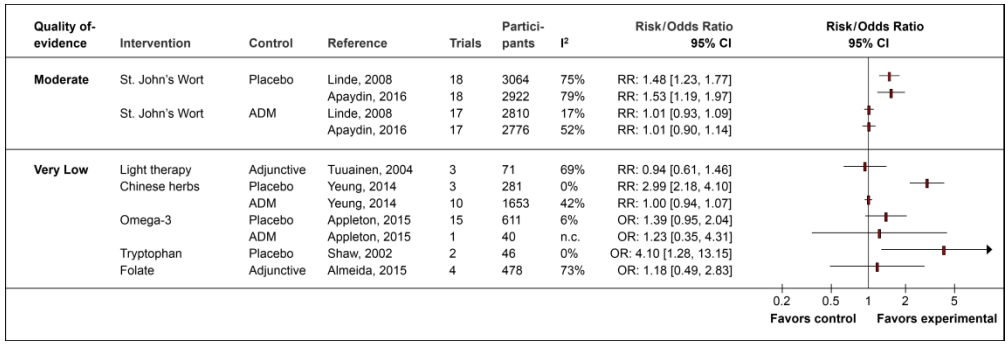

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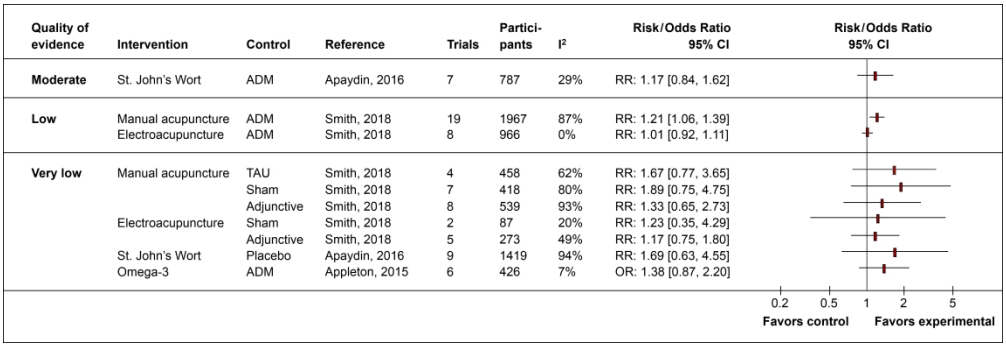

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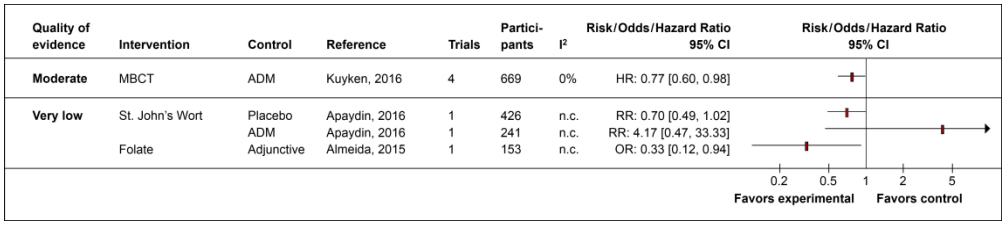

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Supplementary information to "Complementary therapies for clinical depression: an overview of systematic reviews"

by Heidemarie Haller, Dennis Anheyer, Holger Cramer, Gustav Dobos

Supplementary table 1: Characteristics and outcomes of the included meta-analyses.

	Included meta-analysis	Diag-nosis	Num-ber of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Acupuncture									
Manual acupuncture	Smith 2018[50]	MDD, CSD	49 RCTs	SB: 9 PB: 9 DB: 5 AB: 24 RB: 2 OB: 15	AMSTAR: 10	HAMD BDI	1.5-12 weeks	Severity: – Sign. greater effects than TAU (4 RCTs; SMD=-0.56; 95%CI=[-0.98,-0.15]; I^2=62%; p=.03; N=458; ⊕○○○ very low[a,c,d,e]) – No sign. effects versus invasive SHAM (7 RCTs; SMD=-0.43; 95%CI=[-0.95,0.08]; I^2=80%; p<.001; N=418; ⊕○○○ very low[a,c,d,e])[#] – Similar effects as SSRI/TCA (19 RCTs; SMD=-0.24; 95%CI=[-0.51,0.02]; I^2=87%; p<.001; N=1967; ⊕○○○ very low[a,c,e])[§] – Sign. greater effects as adjunctive to SSRI versus SSRI (8 RCTs; SMD=-1.32; 95%CI=[-2.09,-0.55]; I^2=93%; p<.001; N=539; ⊕○○○ very low[a,c,e]) Remission: – No sign. effects versus TAU (2 RCTs; RR=1.67; 95%CI=[0.77,3.65]; I^2=0%; p=.44; N=94; ⊕○○○ very low[a,d,e]) – No sign. effects versus invasive SHAM (5 RCTs; RR=1.89; 95%CI=[0.75,4.75]; I^2=63; p=.03; N=368; ⊕○○○ very low[a,c,d,e])	– Similar AEs as TAU (1 RCT; RR=0.89; 95%CI=[0.35,2.24]; I^2=n.c.; N=320) – Similar AEs as invasive SHAM (1 RCT; RR=2.5; 95%CI=[0.15,40.37]; I^2=n.c.; N=17) – Similar AEs adjunctive to SSRI versus SSRI (2 RCTs; SMD=-0.37; 95%CI=[-1.2,0.47]; I^2=84%; N=150) – Sign. less AEs than SSRI (3 RCTs; SMD=-1.75; 95%CI=[-3.17,-0.32]; I^2=96%; p p<.001; N=481)[#]

								– Sign. smaller effects than SSRI/TCA (18 RCTs; RR=1.21; 95%CI=[1.06,1.39]; I^2=18%; p=.24; N=1952; ⊕⊕○○ low[a,e])[§] – No sign. effects as adjunctive to SSRI versus SSRI (5 RCTs; RR=1.33; 95%CI=[0.65,2.73]; I^2=76%; p=.002; N=299; ⊕○○○ very low[a,c,e])	
Electroacu-puncture	Smith 2018[50]	MDD, CSD	21 RCTs	SB: 6 PB: 3 DB: 5 AB: 16 RB: 1 OB: 12	AMSTAR: 10	HAMD BDI	2-6 weeks	Severity: – Sign. greater effects than TAU (1 RCT; SMD=-1.26; 95%CI=[-2.10,-0.43]; I^2=n.c.; N=30; ⊕○○○ very low[a,c,d,e]) – No sign. effects versus invasive SHAM (5 RCTs; SMD=0.12; 95%CI=[-0.14,0.38]; I^2=0%; p=.82; N=251; ⊕○○○ very low[a,d,e])[#] – Sign. greater effects than SSRI/TCA (10 RCTs; SMD=-0.28; 95%CI=[-0.47,-0.09]; I^2=33%; p=.14; N=995; ⊕⊕○○ low[a,e])[§] – Sign. greater effects as adjunctive to SSRI versus SSRI (5 RCTs; SMD=-0.84; 95%CI=[-1.16,-0.51]; I^2=33%; p=.20; N=274; ⊕⊕○○ low[a,e]) Remission: – No sign. effects versus invasive SHAM (2 RCTs; RR=1.23; 95%CI=[0.35,4.29]; I^2=20; p=.26; N=87; ⊕○○○ very low[a,d,e]) – Similar effects as SSRI/TCA (8 RCTs; RR=1.01; 95%CI=[0.92,1.11]; I^2=0%; p=.43; N=966; ⊕⊕○○ low[a,e])[§] – No sign. effects as adjunctive to SSRI versus SSRI (5 RCTs; RR=1.17; 95%CI=[0.75,1.80]; I^2=49%; p=.10; N=273; ⊕○○○ very low[a,d,e])	– Similar AEs as invasive SHAM (4 RCTs; RR=1.79; 95%CI=[0.99,3.25]; I^2=16%; p=.31; N=244) – Sign. less AEs as adjunctive to SSRI versus SSRI (1 RCT; SMD=-3.39; 95%CI=[-4.27,-2.50]; I^2=n.c.; N=50)
Herbs									

St. John's wort	Linde 2008[149]	MDD	29 RCTs	SB: 18 PB: 29 DB: n.r. AB: 29 RB: n.r. OB: n.r.	AMSTAR: 8	HAMD MADRS	4-12 weeks	Response (50%): – Sign. greater effects than PLACEBO (18 RCTs; RR=1.48; 95%CI=[1.23,1.77]; I^2=75%; p<.001; N=3064; ⊕⊕⊕○ moderate[c]) – Similar effects as SSRI/TCA/TECA (17 RCTs; RR=1.01; 95%CI=[0.93,1.09]; I^2=17%; p=.25; N=2810; ⊕⊕⊕○ moderate[a])	– Similar AEs as PLACEBO (14 RCTs; OR=0.98; 95%CI=[0.78,1.23]; I^2=n.r.; N=2496), – Sign. less than ADMs (14 RCTs; OR=0.56; 95%CI=[0.43,0.74]; I^2=n.r.; N=2663)
	Apaydin 2016[141]	MDD	35 RCTs	SB: 9 PB: 27 DB: 5 AB: 26 RB: 3 OB: 33	AMSTAR: 9	HAMD	4-32 weeks	Severity: – Sign. greater effects than PLACEBO (16 RCTs; SMD=-0.49; 95%CI=[-0.74,-0.23]; I^2=89%; p=n.r.; N=2888; ⊕⊕⊕○ moderate[c]) – Similar effects as ADM (14 RCTs; SMD=-0.03; 95%CI=[-0.21,0.15]; I^2=74%; p=n.r.; N=2248; ⊕⊕○○ low[a,c]) Response (50%): – Sign. greater effects than PLACEBO (18 RCTs; RR=1.53; 95%CI=[1.19,1.97]; I^2=79%; p=n.r.; N=2922; ⊕⊕⊕○ moderate[c]) – Similar effects as ADM (17 RCTs; RR=1.01; 95%CI=[0.90,1.14]; I^2=52%; p=n.r.; N=2776; ⊕⊕⊕○ moderate[a]) Remission: – No sign. effects versus PLACEBO (9 RCTs; RR=1.69; 95%CI=[0.63,4.55]; I^2=94%; p=n.r.; N=1419; ⊕○○○ very low[a,c,d]) – Similar effects as ADM (7 RCTs; RR=1.17; 95%CI=[0.84,1.62]; I^2=29%; p=n.r.; N=787; ⊕⊕⊕○ moderate[a]) Relapse:	– Similar AEs as PLACEBO (13 RCTs; OR=0.83; 95%CI=[0.62,1.13]; I^2=n.r.; N=2600), – Sign. less than ADMs (11 RCTs; OR=0.67; 95%CI=[0.56,0.81]; I^2=n.r.; N=1946)

								– No sign. effects versus PLACEBO (1 RCT; RR=0.70; 95%CI=[0.49,1.02]; I^2=n.c.; N=426; ⊕○○○ very low[a,c,d]) – Similar effects as ADM (1 RCT; RR=4.17; 95%CI=[0.47,33.33]; I^2=n.c.; N=241; ⊕○○○ very low[a,c,d])	
Saffron	Hausenblas 2013[146]	MDD	5 RCTs	SB: 5 PB: 5 DB: 5 AB: 5 RB: n.r. OB: n.r	AMSTAR: 7	HAMD	6-8 weeks	Severity: – Sign. greater effects than PLACEBO (2 RCTs; SMD=-1.62; 95%CI=[-2.14,-1.10]; I^2=0%; p=n.r.; N=71; ⊕○○○ very low[c,d,e]) – Similar effects as SSRI/TCA (3 RCTs; SMD=-0.15; 95%CI=[-0.52,0.22]; I^2=0%; p=n.r.; N=106; ⊕○○○ very low[c,d,e])	– No serious AEs
Curcuma	Ng 2017[154]	MDD, CSD	6 RCTs	SB: 3 PB: 3 DB: 3 AB: 2 RB: 2 OB: 1	AMSTAR: 6	HAMD, BDI	4-8 weeks	Severity: – Sign. greater effects than PLACEBO (6 RCTs; SMD=-0.34; 95%CI=[-0.56,-0.13]; I^2=0%; p=.82; N=377; ⊕○○○ very low[a,d,e])	– No serious AEs
Chinese herbs	Yeung 2014[161]	MND	21 RCTs	SB: 5 PB: 11 DB: 9 AB: 21 RB: 20 OB: 18	AMSTAR: 4	HAMD	6-8,5 weeks	Severity: – Sign. greater effects than PLACEBO (4 RCTs; SMD=-1.27; 95%CI=[-1.67,-0.87]; I^2=44%; p=.14; N=251; ⊕○○○ very low[b,e]# – Similar effects as SSRI/SNRI/TCA/TECA (9 RCTs; SMD=0.17; 95%CI=[-0.12,0.46]; I^2=82%; p<.001; N=1962; ⊕○○○ very low[b,c,e]# Response (30%): – Sign. greater effects than PLACEBO (3 RCTs; RR=2.99; 95%CI=[2.18,4.10]; I^2=0%; p=.53; N=281; ⊕○○○ very low[c,d,e])	– Similar AEs as PLACEBO (3 RCTs; RR=1.29; 95%CI=[0.86,1.95]; I^2=61%; p= n.r.; N=n.r.) – Sign. less AEs than ADMs (29 RCTs; RR=0.23; 95%CI=[0.16,0.33]; I^2=59%; p= n.r.; N=n.r.)

								– Similar effects as SSRI/SNRI/TCA/TECA (10 RCTs; RR=1.00; 95%CI=[0.94,1.07]; I^2=42%; p=.08; N=1635; ⊕○○○ very low[b,c,e])	
Light therapy									
Bright white light	Tuunainen 2004[160]	MND	18	SB: 2 PB: 0 DB: 13 AB: 1 RB: n.r. OB: n.r.	AMSTAR: 9	HAMD, GDS	1 day - 8 weeks	Severity: – Sign. greater effects than adjunctive to ADM than SHAM + ADM (18 RCTs; SMD=-0.20; 95%CI=[-0.38,-0.01]; I^2=60%; p<.001; N=505; ⊕○○○ very low[a,c,d]) Response: – No effects than adjunctive to ADM than SHAM + ADM (3 RCTs; RR=0.94; 95%CI=[0.61,1.46]; I^2=69%; p=.004; N=71; ⊕○○○ very low[a,c,d])	– No serious AEs
	Martensson 2015[151]	SAD	8 RCTs	N.r.	AMSTAR: 5	HAMD, SIGH-SAD	2-6 weeks	Severity: – Sign. greater effects than SHAM (8 RCTs; SMD=-0.54; 95%CI=[-0.95,-0.13]; I^2=n.r.; N=179; ⊕○○○ very low[b,c,d,e])	– N.r.
Meditative movement therapies									
Dance therapy	Meekums 2015[152]	MND	2 RCTs	SB: 1 PB: 0 DB: 1 AB: 2 RB: 2 OB: 1	AMSTAR: 9	HAMD	4-12 weeks	Severity: – Sign. greater effects as adjunctive to ADM versus ADM (2 RCTs; SMD=-1.06; 95%CI=[-1.46,-0.65]; I^2=0%; p=.70; N=107; ⊕⊕○○ low[d,c])#	– No serious AEs
Qi Gong and Tai Chi	Liu 2015[150]	MDD, CSD	5 RCTs	N.r.	AMSTAR: 4	HAMD, GDS, CESD	10-16 weeks	Severity: – Sign. greater effects than TAU for Qi Gong (2 RCTs; SMD=-1.27; 95%CI=[-2.09,-0.45]; I^2=74%; p=.05; N=120; ⊕○○○ very low[b,c,d,e])* but no sign. effects for Tai Chi (3 RCTs; SMD=-0.61; 95%CI=[-1.55,0.34];	– N.r.

								I^2=78%; p=.01; N=120; ⊕○○○ very low[b,c,d,e])*	
Yoga	Cramer 2013[144]	MDD, CSD	5 RCTs	SB: 0 PB: 0 DB: 1 AB: 1 RB: 5 OB: 3	AMSTAR: 8	HAMD, ZGS, GDS, BDI	4-8 weeks	Severity: – Sign. greater effects than TAU (4 RCTs; SMD=-1.03; 95%CI=[-1.90,-0.16]; I^2=82%; p<.001; N=141; ⊕○○○ very low[a,c,d,e])* – Sign. greater effects than EXERCISE (2 RCTs; SMD=-0.59; 95%CI=[-1.90,-0.16]; I^2=68%; p=.08; N=108; ⊕○○○ very low[a,c,d,e])	– N.r.
Mindfulness-based interventions									
MBCT	Strauss 2014[158]	MDD	4 RCTs	N.r.	AMSTAR: 5	HAMD, BDI	8-12 weeks	Severity: – Sign. greater effects than TAU (3 RCTs; SMD=-0.97; 95%CI=[-1.81,-0.12]; I^2=72%; p=.03; N=115; ⊕○○○ very low[b,c,d])[§] – Similar effects as CBT (1 RCT; SMD=-0.16; 95%CI=[-0.75,0.43]; I^2=n.c.; N=45; ⊕○○○ very low[b,c,d])[§]	– N.r.
	Kuyken 2016[148]	MDD	4 RCTs	SB: 4 PB: 0 DB: 3 AB: 4 RB: 4 OB: 4	AMSTAR: 6	SCID, BDI	60 weeks	Relapse: – Sign. greater effects than ADM (4 RCTs; HR=0.77; 95%CI=[0.60,0.98]; I^2=0%; p=.92; N=669; ⊕⊕⊕○ moderate[d])	– No serious AEs
MBSR	Bo 2017[143]	CSD	5 RCTs	SB: 0 PB: 0 DB: 1 AB: 5 RB: 5 OB: n.r.	AMSTAR: 6	HAMD, GDS	8-12 weeks	Severity: – Sign. greater effects than TAU/enhanced TAU (5 RCTs; SMD=-1.09; 95%CI=[-1.41,-0.76]; I^2=56%; p=.06; N=396; ⊕⊕○○ low[a,c])	– N.r.
Music therapy									–

Music therapy	Zhao 2016[162]	MND	8 RCTs	SB: 0 PB: 0 DB: 0 AB: 8 RB: 7 OB: 8	AMSTAR: 7	HAMD, GDS, HADS	4-52 weeks	Severity: – Sign. greater effects than TAU (5 RCTs; SMD=-0.57; 95%CI=[-1.03,-0.11]; I^2=76%; p<.001; N=244; ⊕○○○ very low[a,c,d])* – Sign. greater effects as adjunctive to ADM versus ADM (3 RCTs; SMD=-0.88; 95%CI=[-1.07,-0.68]; I^2=0%; p=.63; N=257; ⊕⊕○○ low[a,e])*	– N.r.
	Aalbers 2017[138]	MDD, CSD	8 RCTs	SB: 2 PB: 1 DB: 1 AB: 7 RB: 2 OB: 3	AMSTAR: 11	HAMD	12 weeks	Severity: – Sign. greater effects than TAU (4 RCTs; SMD=-0.98; 95%CI=[-1.69,-0.27]; I^2=83%; p<.001; N=219; ⊕○○○ very low[a,c,d]) – Similar effects as CBT (4 RCTs; SMD=-1.28; 95%CI=[-3.57,1.02]; I^2=96%; p<.001; N=131; ⊕○○○ very low[a,c,d])	– Similar AEs as TAU (1 RCT; OR=0.45; 95%CI=[0.02,11.46]; I^2=n.c.; N=79)
Religious/spiritual therapies									
Faith-adapted CBT	Anderson 2015[140]	MDD, CSD	9 RCTs	SB: 0 PB: 0 DB: 4 AB: 4 RB: 9 OB: 0	AMSTAR: 7	N.r.	N.r.	Severity: – Sign. greater effects than TAU (6 RCTs; SMD=-0.69; 95%CI=[-1.21,-0.17]; I^2=82%; p=.004; N=304; ⊕○○○ very low[a,c,d])[§] – Sign. greater effects than CBT (6 RCTs; SMD=-0.54; 95%CI=[-0.82,-0.25]; I^2=0%; p=.78; N=199; ⊕⊕○○ low[a,e])[§]	– N.r.
Supplements									–
Inositol	Mukai 2014[153]	MDD	2 RCTs	N.r.	AMSTAR: 4	HAMD	4 weeks	Severity: – No sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (2 RCTs; SMD=0.17; 95%CI=[-0.33,0.66]; I^2=0%; p=.93; N=78; ⊕○○○ very low[b,d,e])	– Similar AEs as adjunctive to ADM (1 RCT; RR=3.21; 95%CI=[0.14,72.55]; I^2=n.c.; N=36)

Omega-3 fatty acids	Appleton 2015[142]	MDD	26 RCTs	SB: 15 PB: 6 DB: 19 AB: 8 RB: 16 OB: 25	AMSTAR: 9	HAMD, MADRS, BDI, GDS, HSCL, IDS	4-16 weeks	Severity: – Sign. greater effects than PLACEBO (25 RCTs; SMD=-0.30; 95%CI=[-0.50,-0.10]; I^2=59%; p<.001; N=1373; ⊕○○○ very low[a,c,d,e]) – Similar effects as SSRI (1 RCT; SMD=-0.08; 95%CI=[-0.70,0.54]; I^2=n.c.; N=40; ⊕○○○ very low[a,c,d,e]) Response (50%): – No sign. effects versus PLACEBO (15 RCTs; OR=1.39; 95%CI=[0.95,2.04]; I^2=6%; p=.38; N=611; ⊕○○○ very low[a,d,e]) – Similar effects as SSRI (1 RCT; OR=1.23; 95%CI=[0.35,4.31]; I^2=n.c.; N=40; ⊕○○○ very low[a,c,d,e]) Remission: – No sign. effects versus PLACEBO (6 RCTs; OR=1.38; 95%CI=[0.87,2.20]; I^2=7%; p=.37; N=426; ⊕○○○ very low[a,d,e])	– Similar AEs as PLACEBO (19 RCT; OR=1.24; 95%CI=[0.95,1.62]; I^2=0%; p=.66; N=1207)
Probiotics	Huang 2016[147]	MDD	1 RCTs	SB: 1 PB: 1 DB: 1 AB: 1 RB: 1 OB: 1	AMSTAR: 7	BDI	8 weeks	Severity: – Sign. greater effects than PLACEBO (1 RCT; SMD=-0.73; 95%CI=[-1.37,-0.09]; I^2=n.c.; N=40; ⊕○○○ very low[c,d,e])	– N.r.
S-adenosyl methionine	Galizia 2016[145]	MDD	8 RCTs	SB: 2 PB: 4 DB: 4 AB: 3 RB: 8 OB: 8	AMSTAR: 9	HAMD	6-12 weeks	Severity: – No sign. effects versus PLACEBO (2 RCTs; SMD=-0.54; 95%CI=[-1.54,0.46]; I^2=72%; p=.06; N=142; ⊕○○○ very low[c,d,e]) – Similar effects as SSRI/TCA (5 RCTs; SMD=-0.01; 95%CI=[-0.22,0.21]; I^2=43%; p=.14; N=821; ⊕⊕○○ low[a,e])[§] – Sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (1 RCT; SMD=-0.59;	– Similar AEs as PLACEBO (2 RCTs; RR=0.70; 95%CI=[0.16,3.01]; I^2=n.r.; N=142) – Similar AEs as adjunctive to ADM (1 RCT, RR=0.58;

								95%CI=[-1.06,-0.12]; I^2=n.c.; N=73; ⊕○○○ very low[c,d,e])[#]	95%CI=[0.10,3.28]; I^2=n.c.; N=73) – Similar AEs as ADM (2 RCTs, RR=0.75; 95%CI=[0.20,2.79]; I^2=n.r.; N=52)
Tryptophan	Shaw 2002[157]	CSD	2 RCTs	SB: 2 PB: 2 DB: n.r. AB: 1 RB: n.r. OB: n.r	AMSTAR: 7	HAMD	3-12 weeks	Response: – Sign. greater effects than PLACEBO (2 RCTs; OR=4.10; 95%CI=[1.28,13.15]; I^2=0%; p=.32; N=46; ⊕○○○ very low[a,d,e])	– Sign. greater AEs than PLACEBO (2 RCTs; OR=7.41; 95%CI=[1.01,54.19]; I^2=0%; p=1.0; N=64)
Vitamin B9 (Folate)	Taylor 2003[159]	MDD	2 RCTs	SB: 0 PB: 2 DB: n.r. AB: 2 RB: n.r. OB: n.r.	AMSTAR: 8	HAMD	10-24 weeks	Severity: – Sign. greater effects as adjunctive to SSRI versus PLACEBO + SSRI (2 RCTs; SMD=-0.40; 95%CI=[-0.76,-0.05]; I^2=0%; p=.96; N=124; ⊕○○○ very low[a,c,d,e])[#]	– Similar AEs as PLACEBO (1 RCT; RR=0.76; 95%CI=[0.55,1.05]; I^2=n.c.; N=127)
	Almeida 2015[139]	MDD	5 RCTs	SB: 4 PB: 5 DB: 4 AB: 3 RB: 4 OB: 1	AMSTAR: 6	HAMD, MADRS	4-52 weeks	Severity: – No sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (5 RCTs; SMD=-0.12; 95%CI=[-0.45,0.22]; I^2=66%; p=.02; N=505; ⊕○○○ very low[c,d,e]) Response (50%): – No sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (4 RCTs; OR=1.18; 95%CI=[0.49,2.83]; I^2=73%; p=.001; N=478; ⊕○○○ very low[c,d,e]) Relapse: – Sign. greater effects as adjunctive to SSRI versus PLACEBO + SSRI (1 RCT, OR=0.33; 95%CI=[0.12,0.94]; I^2=n.c.; N=153; ⊕○○○ very low[c,d,e])	– N.r.

Vitamin D	Shaffer 2014[156]	MDD, CSD	2 RCTs	SB: 0 PB: 0 DB: 1 AB: 0 RB: n.r. OB: n.r.	AMSTAR: 7	HAMD, BDI	8 weeks	Severity: – Sign. greater effects than PLACEBO (2 RCTs; SMD=-0.60; 95%CI=[-1.19,-0.01]; I^2=n.r.; N=149; ⊕○○○ very low[a,c,d,e])	– N.r.
Zinc	Schefft 2017[155]	MDD	3 RCTs	N.r.	AMSTAR: 5	HAMD, BDI	6-12 weeks	Severity: – Sign. greater effects as adjunctive to SSRI/TCA versus SSRI/TCA (3 RCTs; SMD=-0.66; 95%CI=[-1.06,-0.26]; I^2=0%; p=.45; N=104; ⊕○○○ very low[b,d,e])	– N.r.

Abbreviations: AB: Attrition bias; ADM: Antidepressant medication; AE: Adverse events; AMSTAR: Assessment of the Methodological Quality of Systematic Reviews tool; BDI: Beck Depression Inventory; CBT: Cognitive Behavioral Therapy; CESD: Center for Epidemiologic Studies Depression Scale; CSD: Clinical symptoms of depression (questionnaire based diagnosis); DB: Detection bias; GDS: Geriatric Depression Scale; HADS: Hospital Anxiety and Depression Scale; HAMD: Hamilton Rating Scale for Depression; HR: Hazard ratio; HSCL: Hopkins Symptom Checklist Depression Scale; I^2: Heterogeneity; IDS: Inventory of Depressive Symptomology; MADRS: Montgomery-Asberg Depression Rating Scale; MBCT: Mindfulness-based Cognitive Therapy; MBSR: Mindfulness-based Stress Reduction; MDD: Major depressive disorder; MND: Mixed non-seasonal depression; N: Number of patients; N.c.: Not calculable because of only one included RCT; N.r.: Not reported; OB: Other bias; OR: Odds ratio; PB: Performance bias; RCT: Randomized controlled trial; RB: Reporting bias; RR: Risk ratio; SAD: Seasonal Affective Disorder; SB: Selection bias; SCID: Structured Clinical Interview; SIGH-SAD: Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorders; SMD: Standard mean difference; SSRI: Selective serotonin reuptake inhibitors; SNRI: Serotonin-norepinephrine reuptake inhibitor; TAU: Treatment as usual; TCA: Tricyclic antidepressants; TECA: Tetracyclic antidepressants; ZGS: Zung Depression Scale;
*Newly calculated effect measure of selected RCTs meeting eligibility criteria;
#Newly calculated effect measure from mean differences (MDs);
§Newly calculated effect measure from originally separate/combined analyses;
[a]Downgraded one level because of study limitations (overall unclear or high risk of bias);
[b]Downgraded two levels because of study limitations (overall unclear or high risk of bias) and limitations of the meta-analysis (AMSTAR ≤ 5).
[c]Downgraded one level because of inconsistency (significant heterogeneity or no replication of the results);
[d]Downgraded one level because of imprecision (confidence interval includes negligible or no effects or fewer than 250 participants were included in total);
[e]Downgraded one level because of a probably high risk of publication bias.

Supplementary information to "Complementary therapies for clinical depression: an overview of systematic reviews"

by Heidemarie Haller, Dennis Anheyer, Holger Cramer, Gustav Dobos

Supplementary table 2: Detailed AMSTAR ratings.

	Apriori design	Two data extractor and consensus	Compre-hensive literature search	Inclusion of grey literature	List of included & excluded studies	Charac-teristics of studies provided	Adequate risk of bias assessment	Appropriate conclusions	Appropriate data syntheses	Assessment of publica-tion bias	Conflict of interest / funding statement	Sum
Aalbers 2017[138]	1	1	1	1	1	1	1	1	1	1	1	11
Almeida 2015[139]	0	1	1	0	0	1	1	1	1	0	0	6
Anderson 2015[140]	0	0	1	1	0	1	1	1	1	1	0	7
Apaydin 2016 [141]	1	1	1	1	0	1	1	1	1	0	1	9
Appleton 2015[142]	0	1	1	1	1	1	1	1	1	1	0	9
Bo 2017[143]	0	0	1	0	0	1	1	1	1	1	0	6
Cramer 2013[144]	0	1	1	1	1	1	1	1	0	1	0	8
Galizia 2016[145]	0	1	1	1	1	1	1	1	1	1	0	9
Hausenblas 2013[146]	0	1	1	1	0	1	1	1	1	0	0	7
Huang 2013[147]	0	1	1	0	0	1	1	1	1	1	0	7
Kuyken 2016[148]	0	0	1	0	0	1	1	1	1	1	0	6
Linde 2008[149]	0	1	1	1	0	1	1	1	1	1	0	8
Liu 2015[150]	0	0	1	0	0	1	0	1	0	1	0	4
Martensson 2015[151]	0	1	1	0	1	1	0	1	0	0	0	5
Meekums 2015[152]	0	1	1	1	1	1	1	1	1	1	0	9
Mukai 2014[153]	0	1	1	0	0	1	0	1	0	0	0	4
Ng 2017[154]	0	1	1	0	0	1	1	1	1	0	0	6
Schefft 2017[155]	0	1	1	0	0	1	0	1	1	0	0	5
Shaffer 2014[156]	0	1	1	1	1	1	1	1	0	0	0	7
Shaw 2002[157]	0	1	1	1	1	1	0	1	1	0	0	7
Smith 2018[50]	1	1	1	1	1	1	1	1	1	1	0	10
Strauss 2014[158]	0	0	1	1	0	1	0	0	1	1	0	5
Taylor 2003[159]	0	1	1	1	1	1	1	1	1	0	0	8
Tuunainen 2004[160]	0	1	1	1	1	1	1	1	1	1	0	9
Yeung 2014[161]	0	1	1	0	0	0	1	1	0	0	0	4
Zhao 2016[162]	0	1	1	0	0	1	1	1	1	1	0	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N.a.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N.a.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	19-29
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N.a.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N.a.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-50
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Complementary therapies for clinical depression: an overview of systematic reviews

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Keywords:	Depression, Complementary Therapies, Treatment Outcome, Safety, Systematic Review, Meta-analysis

Complementary therapies for clinical depression: an overview of systematic reviews

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Abstract

Objectives: As clinical practice guidelines vary widely in their search strategies and recommendations of complementary and alternative medicine (CAM) for depression, this overview aimed at systematically summarizing the level-1 evidence on CAM for patients with a clinical diagnosis of depression.

Methods: PubMed, PsycInfo and Central were searched for meta-analyses of randomized controlled trials (RCTs) until June 30, 2018. Outcomes included depression severity, response, remission, relapse, and adverse events. The quality of evidence was assessed according to GRADE considering the methodological quality of the RCTs (ROB) and meta-analyses (AMSTAR), inconsistency, indirectness, imprecision of the evidence, and the potential risk of publication bias.

Results: The literature search revealed 26 meta-analyses conducted between 2002 and 2018 on 1 to 49 RCTs in major, minor, and seasonal depression. In patients with mild to moderate major depression, moderate quality evidence suggested the efficacy of St. John's wort towards placebo and its comparative effectiveness towards standard antidepressants for the treatment for depression severity and response rates, while St. John's wort caused significant less adverse events. In patients with recurrent major depression, moderate quality evidence showed that Mindfulness-based Cognitive Therapy was superior to standard antidepressant drug treatment for the prevention of depression relapse. Other CAM evidence was considered as having low or very low quality.

Conclusions: The effects of all but two CAM treatments found in studies on clinical depressed patients based on low to very low quality of evidence. The evidence has to be downgraded mostly due to avoidable methodological flaws of both the original RCTs and meta-analyses not following the CONSORT and PRISMA guidelines. Further research is needed.

Keywords: Depression, Complementary Therapies, Treatment Outcome, Safety, Systematic Review

Strengths and limitations of this study

- This systematic overview included the comprehensive literature search of important CAM topics defined by the Cochrane Collaboration.
- The inclusion criteria were restricted to meta-analyses of RCTs of patients with a clinical diagnosis of depression.
- The quality of evidence from meta-analyses was assessed according to GRADE.
- There is a possible lack of evidence of newer RCTs, which have not been analysed by the included meta-analyses.

Introduction

Depression is one of the most prevalent psychiatric disorders, with about 25% of women and 12% of men suffering from at least one depressive episode during their lifetime.[1-3] According to the criteria for diagnosis recommended by the American Psychiatric Association (APA), depressive disorders can be distinguished by their degree of severity or duration and are also characterized by a high comorbidity and an increase of psychological strain for the affected person.[4] It is evident, that a strong comorbid connection to several chronic conditions like addictions,[5] neurodegenerative diseases,[6 7] or different psychiatric diseases[8-11] exists. This leads depressive disorders as one of the leading causes of disability worldwide.[12]

The most commonly used treatments for depression are antidepressants, psychotherapy, or a combination of drugs and psychotherapy. While both treatment strategies (alone and in combination) have been shown to be effective,[13-15] more recent meta-analyses also found high dropout and low remission rates[16-21] as well as clinically significant differences between antidepressant drugs and placebos only for patients at the upper end of the very severely depressed category.[22] This may lead patients to search for alternatives. Increasing mainstream use of complementary and alternative medicine (CAM) support this trend, particularly for different physical conditions with comorbid affective disorders.[23-27] While some complementary therapies have become a promising adjunct in the standard treatment of depression,[28 29] others are known for their possible side effects or interactions with standard drugs.[29] Recent clinical practice guidelines, in addition, vary widely in their search strategies and resulting recommendations for CAM treatments. While the ACP,[30] APA,[31] and CANMAT guideline[32] provide a more comprehensive overview and critical appraisal of CAM treatments, the DGPPN,[33] NICE,[34] and WFSBP[35] guidelines mainly focus on St. John's Wort and light therapy. Possible effects and risks of further CAM therapies are not discussed. Thus, the purpose of this overview is to provide a comprehensive search strategy of relevant CAM terms and systematically summarize the existing level-1 evidence for clinical depression as a basis for further guideline recommendations on the efficacy, effectiveness, and safety of CAM therapies.

Methods

This systematic overview of reviews was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[36 37] and the recommendations of the Cochrane Collaboration.[38] The protocol was not prospectively registered.

Patient and Public Involvement

For this overview of reviews, patients or public were not involved.

Inclusion and exclusion criteria

- Types of studies: To be eligible, articles had to be systematic reviews with meta-analyses of randomized controlled clinical trials (RCTs) published in peer-reviewed journals. Conference abstracts or unpublished work were excluded as well as reviews summarizing evidence narratively. In cases of including same or similar original studies, only the review with the most recent, most comprehensive search was included. When systematic reviews reported results of RCTs as well as of designs of lower evidence levels, they were considered only if separate meta-analyses for the included RCTs were performed.
- Types of participants: Only reviews of patients with a diagnosis of major depression or dysthymia were eligible as well as reviews including patients/general population samples with mild depressive symptoms above a clinical cut off or seasonal patterns. In contrast, reviews studying depressive symptoms within specific subpopulations of substance-induced or demented patients, secondary depression due to another medical condition (e.g. post-stroke, cancer, or pain patients), bipolar disorders, or females with premenstrual dysphoric disorder or postpartum depression were excluded. Further restrictions regarding the diagnostic criteria or procedures, regarding age, gender, duration of the condition, or symptom intensity were not applied.
- Types of interventions: Reviews investigating the effectiveness and/or safety of a single, adjunctive or combined CAM treatment were included. For the classification of CAM treatments the definition of the US National Institutes of Health[39] was followed. CAM

interventions have to be compared against treatment as usual (TAU)/waiting list, placebo/sham, or standard medical care.

– Types of outcomes: Reviews were eligible if they assessed at least one measure of effectiveness such as severity of depressive symptoms, response rate (generally defined as a 50% decrease in depression scores after a period of up to 12 weeks of treatment),[30] remission rate (generally defined as a period of up to 12 weeks during which a patient is asymptomatic or has only few symptoms to a very mild degree).[40] relapse rates, and/or a measure of safety such as number of adverse events (AE), drug interactions, or numbers needed to harm for study withdrawal due to side effects.

Search strategy

Electronic literature was systematically searched via PubMed, PsycInfo and Central from their inception to January 31, 2018 without restrictions regarding time or language. Search terms for CAM treatments were selected in accordance with Cochrane recommendations (Table 1).[41] Additional manual search included reference lists of previously published reviews[14 28 29 42] and clinical practice guidelines.[30-35] Using PubMed Informer,[43] the search was updated until June 30, 2018.

Study selection process

To assess eligibility, articles were selected by screening titles and abstracts independently by two authors (HH and DA). Any abstract considered potentially eligible by at least one author was read in full to decide on its eligibility. Disagreements were rechecked with a third author (HC) until consensus was achieved.

Data extraction and quality assessment

Two authors (HH and DA) independently extracted data on the characteristics of the reviews including the type of the intervention, the year of publication, the number and quality of the original RCTs, the total number and age of the participants, and effectiveness and safety outcomes. The quality of the included reviews was assessed using the Assessment of the Methodological Quality of Systematic Reviews (AMSTAR) tool.[44] The AMSTAR tool consists of 11 items asking about important methodological quality criteria of systematic reviews such as: a published apriori design, duplicate

study selection and data extraction, a comprehensive literature search including grey literature, a list of included and excluded studies, summarized characteristics and quality assessment of included studies, assessment of publication bias, appropriate method of data syntheses and deducing conclusions, and a conflict of interests statement. AMSTAR has shown good construct validity and inter-rater reliability. The Intraclass Correlation Coefficient (ICC) of the total AMSTAR score of 11 points was reported as 0.84.[45] For this analysis, the two authors (HH and DA) who independently assessed AMSTAR reached an ICC of 0.96. Disagreements regarding content or quality of the reviews were rechecked with a third author (HC) and resolved by agreement.

Data synthesis

Results were pooled qualitatively by type of the intervention. Outcomes had to be calculated as standard mean differences (SMDs), risk ratios (RRs), hazard ratios (HR), or odds ratios (ORs). If meta-analyses displayed mean differences (MDs), SMDs were calculated using Review Manager Software (RevMan, Version 5.3, The Nordic Cochrane Centre, Copenhagen) for better comparability of the results. RevMan was also used to exclude SMDs/RRs/HRs/ORs of selective RCTs that did not fulfil eligibility criteria of this overview. Effect sizes were classified according to Cohen as SMDs of 0.2 to 0.49 = small effect, SMDs of 0.5 – 0.79 = medium effect, and SMDs of > 0.8 = large effect (absolute values)[46] with higher reduction of/improvement in depression scores represented by more negative SMDs or RRs/HRs/ORs less than 1. According to the NICE guideline, a SMD of ≥ 0.5 or ≤ -0.5, respectively was considered as a clinically relevant reduction of depression severity.[47] Statistical heterogeneity between studies was assessed by the chi-squared test with a p-value of ≤ .10 indicating significant heterogeneity. The magnitude of heterogeneity was categorized by the I^2 statistic with I^2 of 0 to 24% = no heterogeneity, I^2 of 25% to 49% = moderate heterogeneity, I^2 of 50% to 74% = substantial heterogeneity, and I^2 of 75% to 100% = considerable heterogeneity.[38]

Quality of evidence

The quality of evidence was assessed according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach[48] individually by two authors (HH and DA). Disagreements were rechecked with a third author (HC) until consensus was achieved. For each

outcome, the evidence can be graded as high, moderate, low or very low. Evidence from RCTs is initially assessed as high, but can be downgraded by one level for serious or two levels for very serious limitations of the study quality (of both RCTs and meta-analyses), inconsistency of the results, indirectness of the evidence, imprecision of the results, and a potential risk of publication bias (as assessed by the included meta-analyses).[48]

Results

Study selection

A total of 3582 potentially eligible articles were identified by electronic database search. One additional review was retrieved from manual search,[49] one from the updated search until June 2018.[50] After removing duplicates, 2639 articles were excluded by screening of titles and abstracts. The remaining 117 articles were read in full, of which further 91 reviews had to be excluded (Figure 1). Reasons for exclusion comprised 55 reviews where newer and/or more comprehensive reviews on higher quality evidence were available.[49 51-104] Further 15 reviews have to be excluded as they systematically summarized evidence but did not performed a meta-analysis mostly due to clinical heterogeneity or a limited number of available RCTs.[105-119] Eight reviews were excluded as they included mixed depressive samples of bipolar or postpartum cases and did not provide (data for) subgroup analyses for patients with the defined depression criteria.[120-127] Another six reviews contained community samples with non-clinical depression or physically ill patients with comorbid depressive symptoms but displayed no data for patients with a primary diagnosis of depression.[128-133] Four reviews performed meta-analyses on both RCTs and non-RCTs and did not perform subgroup analyses or extracted sufficient data for post hoc analyses.[134-137] Three of the reviews analysed standard instead of complementary therapies and were therefore be excluded. Finally, 26 meta-analyses could be included and reviewed.[50 138-162]

Review characteristics and quality

Characteristics and quality appraisal of the included meta-analyses are summarized in the Supplementary Table 1. Meta-analyses were conducted between 2002 and 2018 and included

between 1 to 49 RCTs on 40 to 7104 adult patients. Meta-analyses on children and adolescents were not available or did not meet inclusion criteria. Samples mostly consisted of patients suffering from major depressive disorder[139-142 144-150 153 155 156 158 159] but also included patients with mixed diagnoses of non-seasonal depression,[50 152 161 162] patients with a diagnosis of seasonal depression,[151] and patients with mild to severe symptoms of depression above a clinical cut-off.[138 140 143 144 150 154 156 157] All but one meta-analysis[140] reported pooled outcomes based on common standardized questionnaires or diagnostic interviews. Effects were analysed mostly up to 12 weeks of treatment (short-term), except for four meta-analyses that included RCTs with effects reported up to 16, 24, or 32 weeks[50 141 142 150 159] and further three meta-analyses with long-term analyses equal to or greater than one year [148 156 162]. The AMSTAR total scores of the included meta-analyses ranged between 4 and 11 points with a median quality of 7 points. The individual AMSTAR-ratings are reported in the Supplementary Table 2.

Synthesis of results

Acupuncture

Manual acupuncture

A high-quality Cochrane review meta-analysed 49 RCTs in major depressed adults as well as those with clinically relevant symptoms of depression for manual acupuncture.[50] For depression severity, significant effect sizes were found in comparisons to TAU and as in adjunction to standard antidepressants, while acupuncture showed similar effects to invasive sham acupuncture and standard antidepressants (Figure 2). The analyses of remission rates did not reveal superiority of acupuncture in the comparisons to TAU, invasive sham, standard antidepressants or in adjunction to standard antidepressants (Figure 3). Adverse events reported in the acupuncture groups were significantly lower than in patients treated with antidepressant drugs. However, most meta-analyses showed significant heterogeneity, a lack of RCTs with low risk of bias and a possibly serious risk of publication bias. Thus, the quality of evidence had to be downgraded to low and very low.

Electroacupuncture

For electroacupuncture, the same Cochrane review[50] revealed very low quality of evidence for the comparisons to TAU and invasive sham for both outcomes, severity (Figure 2) and remission (Figure 3), because of serious limitations of the quality of the RCTs, imprecision, and a high risk of publication bias. For electroacupuncture monotherapy in comparison to standard antidepressants, low quality evidence homogeneously suggested significant greater effects for severity and similar effects for remission. As an adjunctive treatment to antidepressants, electroacupuncture effectiveness was supported by low quality of evidence showing a significant greater consistent and precise effect for depression severity. Although the mean adjunctive effect can be considered as large, the analysis based on only one RCT with overall low risk of bias and 4 RCTs of lower methodological quality that missed to include adjunctive sham acupuncture. For remission rates, very low quality of evidence suggested no effects in adjunction to antidepressants. In addition, one RCT showed significant less AEs when electroacupuncture was added to standard antidepressants.

Aromatherapy

The literature search revealed no meta-analysis on aromatherapy. A recent systematic review detected no RCTs in patients with a primary diagnosis of depression. However, two out of five of the reviewed studies on inhalation aromatherapy and five out of eight studies on aromatherapy massage have found significant anti-depressive effects in mixed patient samples and healthy adults.[116]

Biofeedback

No meta-analysis on biofeedback was conducted to date. A recent systematic review revealed only one RCT on the defined inclusion criteria for depression showing some effects in contrast to sham psychotherapy.[117]

Herbs

St. John's wort (Hypericum perforatum)

The effectiveness of St. John's wort was meta-analysed by a Cochrane review of 29 RCTs[149] and a more recent, higher quality meta-analysis of 35 RCTs.[141] In comparison to placebo, St. John's wort showed moderate quality evidence of significant greater reductions of depression severity (Figure 2)

and response rates (Figure 4). The evidence had to be downgraded due to significant heterogeneity because of higher effects in studies from German-speaking countries than in those from the US or other European countries. In contrast, very low quality of evidence suggested no superiority to placebo for remission (Figure 3) and response rates (Figure 5). In comparison to standard antidepressants, St. John's wort showed comparable severity reductions, response, remission, and relapse rates. The quality of the evidence of the meta-analyses of severity and relapse rates had to be downgraded to low and very low, respectively. The evidence of the response and remission rates was considered as moderate quality showing the same results in both German and studies from other countries but containing some RCTs with unclear risk of selection bias and detection bias. Moreover, both meta-analyses[141 149] showed similar AEs of St. John's wort to placebo but significant less AEs than standard antidepressants.

Saffron (Crocus sativus)

A moderate-quality meta-analysis examined the effectiveness and safety of saffron on depression severity by including 5 RCTs in adult patients with major depression.[146] It revealed very low quality of evidence for significant greater effects versus placebo and similar effects versus antidepressant medication up to 8 weeks of treatment (Figure 2). No serious adverse events were reported, but patients receiving saffron tend to report more adverse events than those receiving placebo and less adverse events than those receiving antidepressant medication. Reasons for downgrading the evidence included no replication of the results (all included RCTs were conducted by the same research group), the small overall sample size, and the possibly high risk of publication bias.

Curcumin (Curcuma longa)

For the intake of curcumin, a moderate-quality meta-analysis[154] revealed very low quality of evidence suggesting a small but significant short-term effect of low heterogeneity on depression severity by pooling 6 RCTs (Figure 2). No serious adverse events were recorded. Evidence had to be downgraded due to unclear risk of selection, performance, detection, attrition, and reporting bias in over the half

of the included RCTs, the imprecision of the pooled effect and the possibly high risk of publication bias.

Traditional Chinese herbs

A comprehensive but low-quality systematic review of 296 RCTs of *Chinese herbal medicine* formulas and single herbs[161] revealed 21 RCTs of mostly unclear to high risk of selection, performance, and detection bias and a serious risk of publication bias. Therefore, the evidence supporting the superiority above placebo and the similarity towards standard antidepressants regarding depression severity (Figure 2) and response rates (Figure 4) was assessed as very low.

Other herbs

For other than the described herbs, no meta-analyses were conducted to date. However, a systematic review[109] found three single RCTs that showed significant improvement in depressive symptoms for *Lavandula angustifolia* as an adjunctive treatment to standard antidepressant drugs versus antidepressant drugs alone and for *Echium amoenum* and *Rhodiola rosea* versus placebo. No serious adverse events were reported.

Homoeopathy

No meta-analysis on *homoeopathic remedies* for depression were conducted yet. A recent systematic review detected no placebo-controlled RCTs in patients with a primary diagnosis of depression.[128]

Hypnosis

No meta-analysis on *hypnosis* or *self-hypnosis* techniques met the inclusion criteria of this overview. The only available review on this topic[126] included 6 RCTs among which only one RCT included adults with mild primary depression. Within the mixed sample of physically ill patients and healthy adults, (self-)hypnosis appeared to be effective in decreasing depressive symptoms.

Light therapy

A high-quality Cochrane review meta-analysed the effects of *bright light therapy* in adjunction to standard antidepressants versus sham light therapy plus antidepressants on severity and response

rates in patients suffering from non-seasonal depression.[160] By pooling 18 RCTs of overall unclear risk of bias, it revealed very low quality of evidence for a significant small but inconsistent and imprecise effect on depression severity (Figure 2). A subgroup analysis of two RCTs with low risk of selection bias and detection bias revealed a significant large effect on depression severity but based on one non-peer-reviewed publication and one RCT that also included bipolar patients. Response rates did not significantly differ between groups (Figure 4). Adverse events were reported non-systematically but appeared to be comparable to sham light therapy except for hypomania that occurred more often under verum light therapy.[160]

For patients with seasonal patterns of depression, a meta-analysis of 8 RCTs[151] revealed very low quality of evidence for a significant medium effect on depression severity of light monotherapy in comparison to sham light therapy (Figure 2). Risk of bias of individual RCTs, heterogeneity, and safety were not analysed leading to an overall low quality of the meta-analysis and downgrading of the evidence.

Massage therapy

The literature search detected no meta-analysis of *massage therapy* in patients with a primary depression. However, massage therapy appeared to be effective in decreasing depressive symptoms in mixed samples of physically ill patients and healthy adult.[132] Future research will show, whether these results may be transferable to primary depressed cases.

Meditative movement therapies

Dance therapy

Short-term effects of improvisatory or structured *dance therapy* as a combination of movement-based work, interactive group components and insight/expressive methods were meta-analysed by a Cochrane review of high methodological quality.[152] It revealed a significant large pooled effect size for depression severity as an adjunctive treatment option to standard medical/psychotherapeutic care based on two RCTs (Figure 2). Although the meta-analyses contained no heterogeneity and no

imprecise CI, the evidence had to be downgraded because of mostly unclear/high risk of bias of one of the RCTs as well as the overall small sample size.

Chinese movement therapies

A low-quality meta-analysis on Chinese meditative movement therapies revealed 30 RCTs, of which 2 RCTs on *Qi Gong* and 3 RCTs on *Tai Chi* met inclusion criteria for patients with mild to severe symptoms of primary depression.[150] Very low quality of evidence suggested significant short-term effects for Qi Gong but not for Tai Chi in comparison to TAU. The evidence had to be downgraded due to very serious limitations of the quality of the RCTs and the meta-analysis, significant heterogeneity, imprecision, and a possible high risk of publication bias.

Yoga

A high-quality meta-analysis of complex *yoga* interventions for various depressive disorders found 12 RCTs,[144] of which 5 RCTs of mostly unclear risk of bias met the inclusion criteria of this overview. The pooled short-term effect on depression severity was of large size in comparison to TAU and medium size in comparison to standard exercises (Figure 2). However, the evidence was assessed as very low due to serious limitations of quality of the RCTs, significant heterogeneity, imprecision, and a possible high risk of publication bias.

A further systematic review of yoga in major depressive disorder, revealed 5 newer yoga RCTs but did not perform a meta-analysis because of high clinical heterogeneity. Risk of bias was comparably high and evidence mostly conflicting.[106]

Mindfulness-based interventions

Mindfulness-based Cognitive Therapy (MBCT)

A low-quality meta-analysis of mindfulness-based interventions in patients with major depression found 4 RCTs investigating the effects of MBCT and Cognitive Behavioural Therapy (CBT) on depression severity.[158] It revealed a significant large short-term effect of MBCT in comparison to TAU and similar

effects in comparison to CBT (Figure 2). However, the quality of the evidence was considered as very low due to the missing risk of bias assessment, inconsistency, and imprecision.

A further moderate-quality systematic review on MBCT meta-analysed 9 RCTs on an individual patient data level.[148] The sample consisted of patients with recurrent major depression currently in remission. After a period of 60 weeks, MBCT showed a significantly reduced risk of depressive relapse compared to those receiving antidepressant drugs (Figure 5). No serious adverse events were reported. The evidence was assessed as moderate due to a possibly serious risk of publication bias.

Mindfulness-based stress reduction (MBSR)

RCTs of MBSR and MBSR-like interventions were meta-analysed by a recent review [143] showing a significant large short-term effect on depression severity in comparison to TAU and enhanced TAU (Figure 2). The quality of the evidence was assessed as low because of the overall unclear risk of selection und and performance bias and significant heterogeneity.

Music therapy

Studies on active and receptive *music therapy* in older patients with a diagnosis of depression were summarized by a recent moderate-quality meta-analysis.[162] Out of 19 RCTs, 8 met the inclusion criteria for this overview. Pooled analyses of 5 of them revealed a significant medium effect size on depression severity against TAU up to 52 weeks, however with bigger short-term than long-term effects, considerable heterogeneity and overall unclear risk of selection, performance and detection bias resulting in very low quality of evidence. Further 3 RCTs of the same review revealed low quality evidence for a significant large consistent and precise effect of music therapy as an adjunctive treatment to antidepressants (Figure 2).

A newer Cochrane review[138] found 8 different RCTs showing a significant large pooled effect of music therapy on depression severity against TAU and similar effects as CBT (Figure 2). However, both analyses revealed very low quality of evidence due to mostly unclear selection, performance, detection and reporting bias, significant heterogeneity, and imprecision.

Nutrition therapy

No meta-analyses on specific diets for patients with depression were published to date. A systematic review of 11 RCTs on whole-diet interventions in mostly healthy patients with subthreshold physical conditions revealed conflicting evidence on the effectiveness of those intervention for the reduction of depressive symptoms.[114]

A further systematic review on fasting in patients with chronic pain and inflammatory diseases [110] included 1 RCT and 7 observational studies, which showed promising short-term but questionable longer-term anti-depressive effects.

Religious/spiritual Interventions

Very low to low quality of evidence was found by a moderate-quality systematic review of 9 RCTs on Christian, Muslim, and spiritual CBT adaptions.[140] The analyses showed significant greater medium effects on depression severity against TAU and standard CBT (Figure 2). Safety data were not reported.

Supplements

Inositol

A low quality meta-analysis of 2 RCTs in patients with major depression[153] revealed very low quality evidence for inositol as adjective to standard antidepressants versus placebo in combination to standard antidepressants (Figure 2).

Magnesium

No meta-analysis of magnesium supplementation was found. A recent systematic review detected no RCTs in patients with a primary diagnosis of depression [107].

Omega-3 fatty acids

A high-quality Cochrane review[142] of 26 RCTs found conflicting evidence of the effectiveness of supplementation with omega-3 fatty acids versus placebo in patients with major depression as depression severity significantly improved while response and remission rates did not so (Figure 2-4). One additional RCT with a very low sample size showed similar effects of omega-3 fatty acids on

severity and response rates in comparison to antidepressant drug treatment (Figure 2 and 4). However, all meta-analyses were based on very low quality of evidence because of limitations of the study quality, significant heterogeneity, imprecision and a possibly high risk of publication bias.

Probiotics

The effectiveness of the supplementation with probiotics on depression severity was analysed by a moderate-quality meta-analysis of 5 RCTs, of which only one RCT with overall low risk of bias was carried out on patients with major depression.[147] The analysis of the RCT revealed a significant medium but imprecise short-term effect in comparison to placebo (Figure 2). This led to overall very low quality of evidence for probiotics supplementation.

S-adenosyl methionine (SAMe)

A high-quality Cochrane review[145] of the effectiveness and safety of SAMe supplementation on depression severity revealed 2 RCTs of low risk of bias that showed no significant pooled effects for SAMe monotherapy versus placebo. One RCT, also of low risk of bias showed a significant medium short-term effect as adjunctive to standard antidepressant medication, both for depression severity. Further 5 RCTs, which were rated as having overall unclear risk of bias, showed similar pooled effects of SAMe monotherapy on depression severity compared to standard antidepressant medication (Figure 2). Original RCTs reported safety issues insufficiently. For all meta-analyses, the evidence was assessed as low to very low quality because of limitations of the study quality, heterogeneity, imprecision, and a possibly high risk of publication bias.

Tryptophan

A moderate-quality Cochrane review found 2 RCTs investigating the effectiveness and safety of tryptophan supplementation on depression severity.[157] Pooling the effects led to significant greater short-term response rates (Figure 4) as well as significant more adverse events in the tryptophan group than in the placebo group. The evidence was assessed as very low quality because of an unclear risk of detection, attrition and other bias, imprecision, and a possible risk for publication bias.

Vitamins

For Vitamin B6, no meta-analysis was available. A systematic review without meta-analysis revealed 2 RCTs showing no significant effects when compared to placebo.[119]

Two further moderate to high-quality meta-analyses examined the effects of vitamin B9 (Folate) for major depressive patients. While a Cochrane review[159] calculated a significant medium effect size of folate-intake as an adjunctive intervention to standard drug treatment on depression severity, a more recent review[139] revealed non-significant differences on severity and response rates (Figure 2 and 3). In contrast, a long-term combined intake of Vitamin B6, B9, and B12 was found to be effective for relapse prevention after remission of symptoms as a result of one RCT (Figure 5).[139] However, all comparisons were based on very low quality of evidence mostly due to significant heterogeneity, imprecision, and possible high risk of publication bias.

Another moderate-quality meta-analysis revealed evidence of the effectiveness of vitamin D-intake on depression severity in comparison to placebo.[156] The analysis of the two included RCTs revealed a significant medium short-term effect in favour of vitamin D in major depressed patients up to 8 weeks (Figure 2). The quality of evidence was rated as very low due to limitations of the study quality, missing values of heterogeneity, imprecision, a high risk of publication bias as well as insufficient reporting of adverse events.

Zinc

The effectiveness of zinc for major depression was meta-analysed by a low-quality review of 3 RCTs.[155] It revealed a significant pooled short-term effect of medium size and low heterogeneity when zinc was taken as an adjunctive to standard antidepressant drug treatment (Figure 2). However, the available evidence had to be assessed as very low as the meta-analysis did not perform risk of bias assessments and did not report adverse events.

Discussion

This systematic review provided a comprehensive overview of the evidence of CAM treatments for patients with a diagnosis or clinical symptoms of depression. Moderate quality evidence suggested the efficacy, comparative effectiveness to standard antidepressants, and safety of St. John's wort on

depression severity and response rates. For remission and relapse rates, the evidence was conflicting and of lower quality. Moreover, moderate quality evidence showed that MBCT was superior to standard antidepressant drug treatment for the prevention of depression relapse in patients with recurrent major depression. Low quality evidence suggested significant greater effects in favour of electroacupuncture in comparison to standard antidepressants alone and in adjunction to standard antidepressants for depression severity. For remission rates, low quality evidence revealed comparable effects of electroacupuncture and standard antidepressants. Further significant greater effects, which based on low quality evidence, were found for MBSR versus TAU, music therapy in adjunction to standard antidepressants, faith-adapted CBT versus CBT, and SAMe versus standard antidepressants. Other treatments such as manual acupuncture, aromatherapy, biofeedback, herbs (crocus sativus, curcuma longa, traditional Chinese herbs, lavandula angustifolia, echium amoenum, rhodiola rosea), Homoeopathy, hypnosis, bright light therapy, massage, meditative movement therapies (dance therapy, Qi Gong, Tai Chi, yoga), whole-diet interventions, fasting, and supplementation with inositol, magnesium, omega-3 fatty acids, probiotics, tryptophan, B- and D-vitamins, and zinc were based on very low quality of evidence or no level-1 evidence.

The strengths of the review process included the comprehensive literature search based on a structured list of CAM specific topics, which had been operationalized for the Cochrane Collaboration.[41] It therefore included evidence for more than the previously considered CAM approaches and provided systematic information where further high-quality studies are required. In addition, we only included results of RCTs of patients with a diagnosis of depression or clinical relevant depressive symptoms and excluded RCTs on samples with minor or secondary symptoms of depression by newly calculating effect sizes. Finally, we rated AMSTAR and considered the quality of the meta-analyses as well when grading the quality of the evidence.

The conclusions derived from this overview are limited due to possibly missing evidence from newer RCTs, which have not been summarized by the included systematic reviews and meta-analyses. As it was not within the scope of this overview, we did not separately search for individual RCTs. We also did not include meta-analyses on studies of lower evidence levels, which may include bigger samples

and may provide additional information about further possible treatment approaches. Moreover, we did not search online registries or conference proceedings for unpublished or ongoing meta-analyses, which may limit the conclusions. Another reason that limits the quality of evidence consists in the unsatisfactory methodological quality of some of the included meta-analyses. Although the methodological quality of the original RCTs might be acceptable, the bad reporting of some meta-analyses led to downgraded evidence. In particular, meta-analyses often missed to search for grey literature, cite excluded studies, adequately assess risk of bias of the original studies, and report complete I^2 statistics. As the latter are known to be unstable in meta-analyses with a small numbers of studies,[163] calculating confidence intervals for I^2 should be standard. Moreover, RCTs as well as meta-analyses often missed to systematically report on occurred adverse events, which also limits the significance of the conclusions. In RCTs of non-pharmacological interventions, there is always a high or unclear risk of performance bias and possibly high placebo effects. As such, adding credible sham interventions, controlling for patients' expectances, and performing of ITT analyses is indispensable. However, meta-analyses mostly did not systematically assess these issues. In meta-analyses of pharmacological interventions, the influence of industrial funding sources was often not adequately analysed. Here, subgroup analyses of studies having received no funding/non-industrial funding versus those having received industrial funding are needed. Results of meta-analyses that missed to report funding issues completely should interpreted with caution. In general, it should be noticed that all evidence is based on short-term pooled effects, except for meta-analyses of St. John's wort, MBCT, music therapy, and B- and D-vitamins that also provided longer-term follow-up data.

Clinical recommendations for patients should follow the country-specific clinical practice guidelines considering the quality of evidence, the accessibility of the treatment, costs, and the preferences of the patients. While the guidelines agree[30 31 33-35 164 165] that clinicians should select between either CBT or second-generation antidepressant drugs for the treatment of major depression, the restricted search strategy of some of the guidelines might limit their recommendations for CAM treatments. For patients who do reject or do not tolerate standard antidepressant drugs, one alternative treatment option may be St. John's wort. It is also recommended by the American Psychiatric

Association Task Force report[42] and the CANMAT Depression Work Group[32] as being proven sufficiently for the short-term by placebo-controlled and equivalence trials with standard antidepressants for mild to moderate major depression. Particularly for bridging the gap between diagnosis and getting access to psychotherapy and meanwhile reducing/not-worsening depression severity, St. John's wort may be considered as a possibly better tolerated alternative to standard antidepressant drugs.[166] As St. John's wort is accessible without prescription and currently not regulated by the US Food and Drug Administration, we agree with the ACP guidelines[30] that it remains difficult for patients to obtain quality-controlled remedies. Moreover, St. John's wort is associated with numerous herb-to-drug interactions.[167] Therefore, we would recommend clinicians to educate their patients about possible effects, side effects and interactions who in turn should not take St. John's wort without professional advise.[33] Despite those limitations, we would not discourage a general therapeutic attempt with St. John's wort, even if we disagree with the NICE guideline in this point.[34] Clinicians may also inform patients with recurrent major depression currently in remission about the superiority of MBCT in comparison to standard antidepressants for relapse prevention.[31-34] Finally, patients should also be informed that many other CAM treatments might show promising effects but cannot be recommended until further higher-quality studies will confirm their effectiveness and safety.

Further research is needed, particularly for interventions that have shown preliminary evidence for reducing secondary symptoms of depression, promising short-term but no longer-term effects, or insufficient evidence due to low methodological quality of the original RCTs and/or the performed meta-analyses. Reporting of clinical trials and meta-analyses should necessarily follow the CONSORT[168] and PRISMA guidelines,[36] respectively, including rigorous documentation and analysis of adverse events. Especially Chinese and Indian trials are still found to be poorly reported and tended to present more positive conclusions than those from western countries.[169 170] Moreover, 7 of the included meta-analyses showed no more than poor methodological quality. All were published in peer-reviewed journals in the past 5 years. One complementary journal is among them, while 6 of the journals are conventional psychiatric journals with impact factors ranging from 2.419 to 4.369.

Thus, particularly the review process as well as the editorial work need to be improved. Further clinical practice guidelines should extend their search strategies and include standard search terms for CAM. This is also important for CAM therapies that do not show consistent evidence or that are not yet investigated. This information might be equally interesting for physicians as well as for patients to make an informed decision about the treatment for clinical depression.

Conclusion

This overview of systematic reviews on CAM treatments for clinical depression aimed to provide a systematic search strategy and evidence base, on which further clinical practice guidelines may build their recommendations. To improve quality of trials and meta-analyses, researchers, reviewers as well as editors are asked to ensure that future articles strictly adhere the CONSORT and PRISMA guidelines.

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Author contribution statement

HH was responsible for the conception and design of the study, the collection and analysis of the study data and for drafting the manuscript. DA participated in the analysis of the study data and drafting the manuscript. HC participated in the conception and design of the study and the analysis of the study data, and critically revised the manuscript. GD participated in the conception and design of the study, and critically revised the manuscript. All authors approved the final manuscript.

Data Availability

All data relevant to the study are included in the article or uploaded as supplementary information.

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Figure legends

Figure 1. Study flow diagram.

Figure 2. Quality of evidence for depression severity. ADM: Antidepressant medication, CBT: Cognitive Behavioural Therapy, CI: Confidence Interval, I^2: Heterogeneity, MBCT: Mindfulness-based Cognitive Therapy, MBSR: Mindfulness-based Stress Reduction, N.c.: Not calculable because of only one included RCT, N.r.: Not reported, SAMe: S-adenosyl methionine, Tau: Treatment as Usual

Figure 3. Quality of evidence for depression remission rates. ADM: Antidepressant medication, CI: Confidence Interval, I^2: Heterogeneity, N.c.: Not calculable because of only one included RCT, OR: Odds Ratio, RR: Risk Ratio, Tau: Treatment as Usual

Figure 4. Quality of evidence for depression response rates. ADM: Antidepressant medication, CI: Confidence Interval, I^2: Heterogeneity, N.c.: Not calculable because of only one included RCT, OR: Odds Ratio, RR: Risk Ratio

Figure 5. Quality of evidence for depression relapse rates. ADM: Antidepressant medication, CI: Confidence Interval, HR: Hazard Ratio, I^2: Heterogeneity, MBCT: Mindfulness-based Cognitive Therapy, N.c.: Not calculable because of only one included RCT, OR: Odds Ratio, RR: Risk Ratio, Tau: Treatment as Usual

Tables

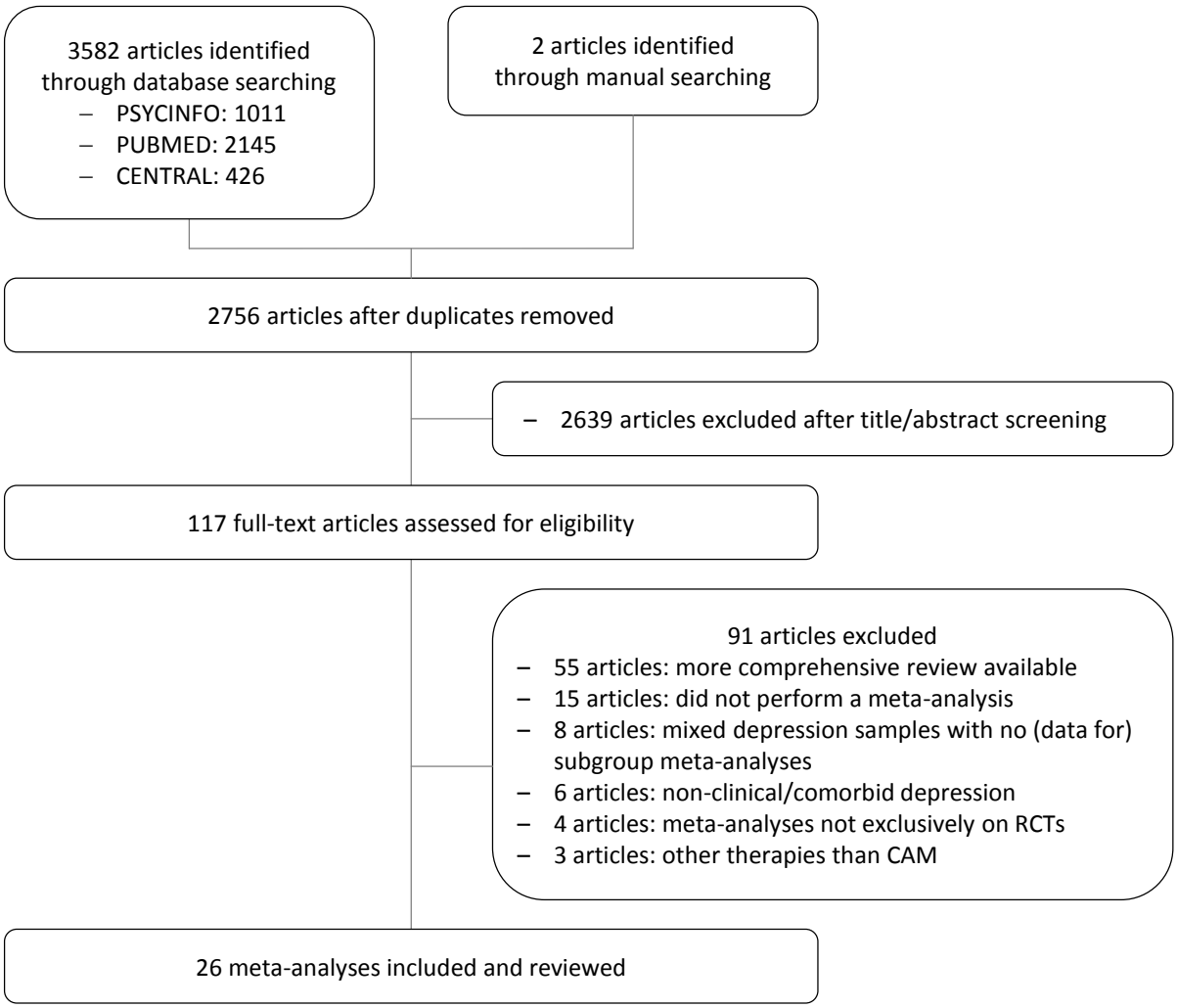
Table 1. Electronic search strategy for PubMed.

#1	(Depression OR Depressive Disorder, Major OR Depressive Disorder, Treatment-Resistant OR Dysthymic Disorder OR Seasonal Affective Disorder)[mh]
#2	(depress* OR dysthym* or "seasonal affective" OR "affective disorder" OR "affective disorders" OR "mood disorder" OR "mood disorders")[tiab]
#3	(Systematic review OR Meta-analysis)[pt] OR (Systematic* OR Meta-analy*)[tiab]
#4	(Acupressure OR Acupuncture OR acid OR Alexander Technique OR alternative OR Aromatherapy OR Aroma Therapy OR Art Therap* OR ayurved* OR Balneotherapy OR Balneo Therapy OR bee OR Biofeedback OR Bio Feedback OR bright light OR Chelation Therapy OR Chinese Traditional Medicine OR Chiropractic OR Chronotherapy OR Color Therapy OR complementary OR craniosacral OR cupping OR Curcumin OR Dance Therapy OR diet OR Distant Healing OR Electroacupuncture OR Feldenkrais OR folic acid OR Folate OR Healing Touch OR herbal OR Herbs OR Homeopath* OR Honey OR Hydrotherapy OR hyperbaric oxygenation OR Hypericum perforatum OR Hyperthermia OR Hypnosis OR Imagery OR Inositol OR Kampo OR Light Therapy OR Magnesium OR Massage OR MBSR OR MBCT OR Meditation OR Mindfulness OR Morita Therapy OR Moxibustion OR Mediterranean OR Music Therap* OR Naturopathy OR Neural Therapy OR Omega-3 OR Osteopath* OR Ozone Therapy OR Phototherapy OR Pollen OR Prayer OR prebiotic* OR probiotic* OR Propolis OR Qi Gong OR Reflexology OR Reiki OR Relaxation OR Rolfing OR Royal Jelly OR S-adenosyl-L-methionine OR Saffron OR Shamanism OR Snoezelen OR Speleotherapy OR Spinal Manipulation OR Spiritual OR St John's Wort OR Supplements OR Tai Chi OR TCM OR Therapeutic Touch OR Traditional Chinese Medicine OR Tryptophan OR Tui na OR Turmeric OR vegan OR vegetarian OR venom OR Vitamin OR Yoga OR zinc)[tiab]
#5	(Acupressure OR Acupuncture OR Acupuncture Therapy OR Acids OR Aromatherapy OR Art Therapy OR Balneology OR Biofeedback, Psychology OR Chelation Therapy OR Chiropractic OR Chronotherapy OR Color Therapy OR Complementary Therapies OR Crocus OR Curcuma OR Dance Therapy OR Diet OR Electroacupuncture OR Fatty Acids, Omega-3 OR Folic Acid OR Homeopathy OR Honey OR Hydrotherapy OR Hypericum OR Hyperthermia, Induced OR Hypnosis OR Imagery OR Inositol OR Magnesium OR Manipulation, Spinal OR Massage OR Medicine, Ayurvedic OR Medicine, Chinese Traditional OR Medicine, Kampo OR Meditation OR Mind-Body Therapies OR Mindfulness OR Moxibustion OR Naturopathy OR Ozone OR Phototherapy OR Plants, Medicinal OR Pollen OR Prebiotics OR Probiotics OR Propolis OR Qigong OR Relaxation OR Shamanism OR Speleotherapy OR Spiritual Therapies OR Supplements, Dietary OR Tai Ji OR Therapeutic Touch OR Tryptophan OR Venoms OR Vitamins OR Yoga OR Zinc)[mh]
#6	(#1 OR #2) AND #3 AND (#4 OR #5)

Supplementary data

Supplementary table 1: Detailed AMSTAR ratings.

Supplementary table 2: Characteristics and outcomes of the included meta-analyses.


3582 articles identified through database searching
– PSYCINFO: 1011
– PUBMED: 2145
– CENTRAL: 426
2 articles identified through manual searching
2756 articles after duplicates removed
– 2639 articles excluded after title/abstract screening
117 full-text articles assessed for eligibility
91 articles excluded
– 55 articles: more comprehensive review available
– 15 articles: did not perform a meta-analysis
– 8 articles: mixed depression samples with no (data for) subgroup meta-analyses
– 6 articles: non-clinical/comorbid depression
– 4 articles: meta-analyses not exclusively on RCTs
– 3 articles: other therapies than CAM
26 meta-analyses included and reviewed

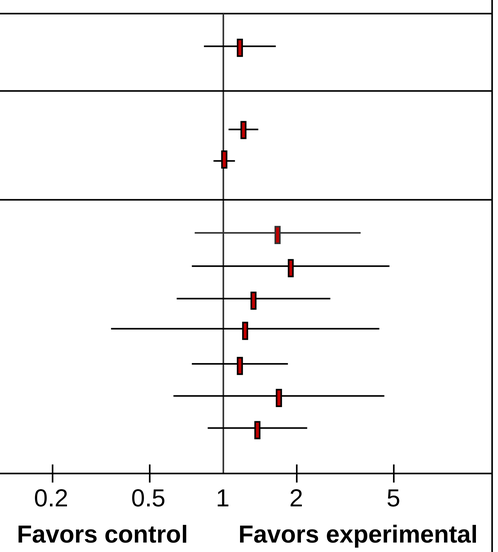
Quality of evidence	Intervention	Control	Reference	Trials	Partici-pants	I^2	Std. Mean Difference 95% CI
Moderate	St. John's Wort	Placebo	Apaydin, 2016	16	2888	89%	-0.49 [-0.74, -0.23]
Low	Electroacupuncture	ADM	Smith, 2018	10	995	33%	-0.28 [-0.47, -0.09]
		Adjunctive	Smith, 2018	5	274	33%	-0.84 [-1.16, -0.51]
	St. John's Wort	ADM	Apaydin, 2016	14	2248	74%	-0.03 [-0.21, 0.15]
	Dance therapy	Adjunctive	Meekums, 2015	2	107	0%	-1.06 [-1.46, -0.65]
	MBSR	TAU	Bo, 2017	5	396	56%	-1.09 [-1.41, -0.76]
	Music therapy	Adjunctive	Zhao, 2016	3	257	0%	-0.88 [-1.07, -0.68]
	Faith-adapted CBT	CBT	Anderson, 2015	6	199	0%	-0.54 [-0.82, -0.25]
	SAMe	ADM	Galizia, 2016	5	821	43%	-0.01 [-0.22, 0.21]
Very low	Manual acupuncture	TAU	Smith, 2018	4	458	62%	-0.56 [-0.98, -0.15]
		Sham	Smith, 2018	7	418	80%	-0.43 [-0.95, 0.08]
		ADM	Smith, 2018	19	1967	87%	-0.24 [-0.51, 0.02]
		Adjunctive	Smith, 2018	8	539	93%	-1.32 [-2.09, -0.55]
	Electroacupuncture	TAU	Smith, 2018	1	30	n.c.	-1.26 [-2.10, -0.43]
		Sham	Smith, 2018	5	251	0%	0.12 [-0.14, 0.38]
	Saffron	Placebo	Hausenblas, 2013	2	71	0%	-1.62 [-2.14, -1.10]
		ADM	Hausenblas, 2013	3	106	0%	-0.15 [-0.52, 0.22]
	Curcuma	Placebo	Ng, 2017	6	377	0%	-0.34 [-0.56, -0.13]
	Chinese herbs	Placebo	Yeung, 2014	4	251	44%	-1.27 [-1.67, -0.87]
		ADM	Yeung, 2014	9	1962	82%	0.17 [-0.12, 0.46]
	Light therapy	Sham	Martensson, 2015	8	179	n.r.	-0.54 [-0.95, -0.13]
		Adjunctive	Tuunainen, 2004	9	505	60%	-0.20 [-0.38, -0.01]
	Qi Gong	TAU	Liu, 2015	2	120	74%	-1.27 [-2.09, -0.45]
	Thai Chi	TAU	Liu, 2015	3	120	78%	-0.61 [-1.55, 0.34]
	Yoga	TAU	Cramer, 2013	4	141	82%	-1.03 [-1.90, -0.16]
	MBCT	TAU	Strauss, 2014	3	115	72%	-0.97 [-1.81, -0.12]
		CBT	Strauss, 2014	1	45	n.c.	-0.16 [-0.75, 0.43]
	Music therapy	TAU	Zhao, 2016	5	244	76%	-0.57 [-1.03, -0.11]
			Aalbers, 2017	4	219	83%	-0.98 [-1.69, -0.27]
		CBT	Aalbers, 2017	4	131	96%	-1.28 [-3.57, 1.02]
	Faith-adapted CBT	TAU	Anderson, 2015	6	304	82%	-0.69 [-1.21, -0.17]
	Inositol	Adjunctive	Mukai, 2014	2	78	0%	0.17 [-0.33, 0.66]
	Omega-3	Placebo	Appleton, 2015	25	1373	59%	-0.30 [-0.50, -0.10]
		ADM	Appleton, 2015	1	40	n.c.	-0.08 [-0.70, 0.54]
	Probiotics	Placebo	Huang, 2016	1	40	n.c.	-0.73 [-1.37, -0.09]
	SAMe	Placebo	Galizia, 2016	2	142	72%	-0.54 [-1.54, 0.46]
		Adjunctive	Galizia, 2016	1	73	n.c.	-0.59 [-1.06, -0.12]
	Folate	Adjunctive	Taylor, 2003	2	124	0%	-0.40 [-0.76, -0.05]
			Almeida, 2015	5	505	66%	-0.12 [-0.45, 0.22]
	Vitamin D	Placebo	Shaffer, 2014	2	149	n.r.	-0.60 [-1.19, -0.01]
	Zinc	Adjunctive	Schefft, 2017	3	104	0%	-0.66 [-1.06, -0.26]

Std. Mean Difference 95% CI

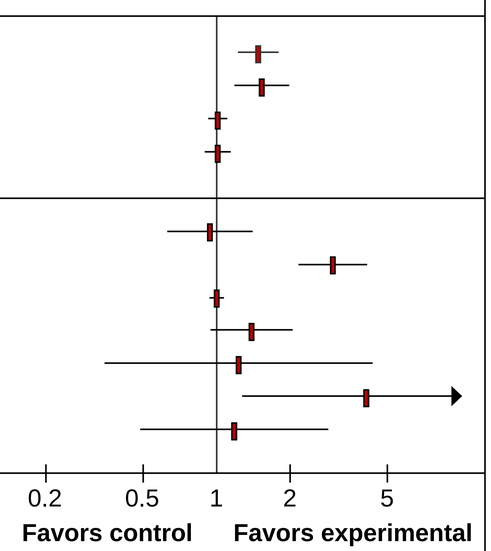
-2 -1 0 1 2

Favors experimental Favors control

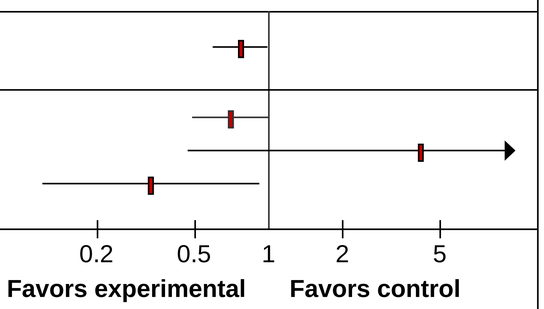
Quality of evidence	Intervention	Control	Reference	Trials	Partici-pants	I^2	Risk/Odds Ratio 95% CI
Moderate	St. John's Wort	ADM	Apaydin, 2016	7	787	29%	RR: 1.17 [0.84, 1.62]
Low	Manual acupuncture	ADM	Smith, 2018	19	1967	87%	RR: 1.21 [1.06, 1.39]
	Electroacupuncture	ADM	Smith, 2018	8	966	0%	RR: 1.01 [0.92, 1.11]
Very low	Manual acupuncture	TAU	Smith, 2018	4	458	62%	RR: 1.67 [0.77, 3.65]
		Sham	Smith, 2018	7	418	80%	RR: 1.89 [0.75, 4.75]
		Adjunctive	Smith, 2018	8	539	93%	RR: 1.33 [0.65, 2.73]
	Electroacupuncture	Sham	Smith, 2018	2	87	20%	RR: 1.23 [0.35, 4.29]
		Adjunctive	Smith, 2018	5	273	49%	RR: 1.17 [0.75, 1.80]
	St. John's Wort	Placebo	Apaydin, 2016	9	1419	94%	RR: 1.69 [0.63, 4.55]
	Omega-3	ADM	Appleton, 2015	6	426	7%	OR: 1.38 [0.87, 2.20]



Quality of-evidence	Intervention	Control	Reference	Trials	Partici-pants	I^2	Risk/Odds Ratio 95% CI
Moderate	St. John's Wort	Placebo	Linde, 2008	18	3064	75%	RR: 1.48 [1.23, 1.77]
			Apaydin, 2016	18	2922	79%	RR: 1.53 [1.19, 1.97]
	St. John's Wort	ADM	Linde, 2008	17	2810	17%	RR: 1.01 [0.93, 1.09]
			Apaydin, 2016	17	2776	52%	RR: 1.01 [0.90, 1.14]
Very Low	Light therapy	Adjunctive	Tuuainen, 2004	3	71	69%	RR: 0.94 [0.61, 1.46]
	Chinese herbs	Placebo	Yeung, 2014	3	281	0%	RR: 2.99 [2.18, 4.10]
		ADM	Yeung, 2014	10	1653	42%	RR: 1.00 [0.94, 1.07]
	Omega-3	Placebo	Appleton, 2015	15	611	6%	OR: 1.39 [0.95, 2.04]
		ADM	Appleton, 2015	1	40	n.c.	OR: 1.23 [0.35, 4.31]
	Tryptophan	Placebo	Shaw, 2002	2	46	0%	OR: 4.10 [1.28, 13.15]
	Folate	Adjunctive	Almeida, 2015	4	478	73%	OR: 1.18 [0.49, 2.83]



Quality of evidence	Intervention	Control	Reference	Trials	Partici-pants	I^2	Risk/Odds/Hazard Ratio 95% CI
Moderate	MBCT	ADM	Kuyken, 2016	4	669	0%	HR: 0.77 [0.60, 0.98]
Very low	St. John's Wort	Placebo	Apaydin, 2016	1	426	n.c.	RR: 0.70 [0.49, 1.02]
		ADM	Apaydin, 2016	1	241	n.c.	RR: 4.17 [0.47, 33.33]
	Folate	Adjunctive	Almeida, 2015	1	153	n.c.	OR: 0.33 [0.12, 0.94]



Supplementary information to "Complementary therapies for clinical depression: an overview of systematic reviews"
by Heidemarie Haller, Dennis Anheyer, Holger Cramer, Gustav Dobos

Supplementary table 1: Characteristics and outcomes of the included meta-analyses.

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Acupuncture									
Manual acupuncture	Smith 2018[50]	MDD, CSD	49 RCTs	SB: 9 PB: 9 DB: 5 AB: 24 RB: 2 OB: 15	AMSTAR: 10	HAMD BDI	1.5-12 weeks	Severity: – Sign. greater effects than TAU (4 RCTs; SMD=-0.56; 95%CI=[-0.98,-0.15]; I^2=62%; p=.03; N=458; ⊕○○○ very low[a,c,d,e]) – No sign. effects versus invasive SHAM (7 RCTs; SMD=-0.43; 95%CI=[-0.95,0.08]; I^2=80%; p<.001; N=418; ⊕○○○ very low[a,c,d,e])[#] – Similar effects as SSRI/TCA (19 RCTs; SMD=-0.24; 95%CI=[-0.51,0.02]; I^2=87%; p<.001; N=1967; ⊕○○○ very low[a,c,e])[§] – Sign. greater effects as adjunctive to SSRI versus SSRI (8 RCTs; SMD=-1.32; 95%CI=[-2.09,-0.55]; I^2=93%; p<.001; N=539; ⊕○○○ very low[a,c,e]) Remission: – No sign. effects versus TAU (2 RCTs; RR=1.67; 95%CI=[0.77,3.65]; I^2=0%; p=.44; N=94; ⊕○○○ very low[a,d,e]) – No sign. effects versus invasive SHAM (5 RCTs; RR=1.89; 95%CI=[0.75,4.75]; I^2=63; p=.03; N=368; ⊕○○○ very low[a,c,d,e]) – Sign. smaller effects than SSRI/TCA (18 RCTs; RR=1.21; 95%CI=[1.06,1.39]; I^2=18%; p=.24; N=1952; ⊕⊕○○ low[a,e])[§] – No sign. effects as adjunctive to SSRI versus SSRI (5 RCTs; RR=1.33; 95%CI=[0.65,2.73]; I^2=76%; p=.002; N=299; ⊕○○○ very low[a,c,e])	– Similar AEs as TAU (1 RCT; RR=0.89; 95%CI=[0.35,2.24]; I^2=n.c.; N=320) – Similar AEs as invasive SHAM (1 RCT; RR=2.5; 95%CI=[0.15,40.37]; I^2=n.c.; N=17) – Similar AEs adjunctive to SSRI versus SSRI (2 RCTs; SMD=-0.37; 95%CI=[-1.2,0.47]; I^2=84%; N=150) – Sign. less AEs than SSRI (3 RCTs; SMD=-1.75; 95%CI=[-3.17,-0.32]; I^2=96%; p p<.001; N=481)[#]

Supplementary table 1: continued

2

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Electroacu-puncture	Smith 2018[50]	MDD, CSD	21 RCTs	SB: 6 PB: 3 DB: 5 AB: 16 RB: 1 OB: 12	AMSTAR: 10	HAMD BDI	2-6 weeks	Severity: – Sign. greater effects than TAU (1 RCT; SMD=-1.26; 95%CI=[-2.10,-0.43]; I^2=n.c.; N=30; ⊕○○○ very low[a,c,d,e]) – No sign. effects versus invasive SHAM (5 RCTs; SMD=0.12; 95%CI=[-0.14,0.38]; I^2=0%; p=.82; N=251; ⊕○○○ very low[a,d,e])[#] – Sign. greater effects than SSRI/TCA (10 RCTs; SMD=-0.28; 95%CI=[-0.47,-0.09]; I^2=33%; p=.14; N=995; ⊕⊕○○ low[a,e])[§] – Sign. greater effects as adjunctive to SSRI versus SSRI (5 RCTs; SMD=-0.84; 95%CI=[-1.16,-0.51]; I^2=33%; p=.20; N=274; ⊕⊕○○ low[a,e]) Remission: – No sign. effects versus invasive SHAM (2 RCTs; RR=1.23; 95%CI=[0.35,4.29]; I^2=20; p=.26; N=87; ⊕○○○ very low[a,d,e]) – Similar effects as SSRI/TCA (8 RCTs; RR=1.01; 95%CI=[0.92,1.11]; I^2=0%; p=.43; N=966; ⊕⊕○○ low[a,e])[§] – No sign. effects as adjunctive to SSRI versus SSRI (5 RCTs; RR=1.17; 95%CI=[0.75,1.80]; I^2=49%; p=.10; N=273; ⊕○○○ very low[a,d,e])	– Similar AEs as invasive SHAM (4 RCTs; RR=1.79; 95%CI=[0.99,3.25]; I^2=16%; p=.31; N=244) – Sign. less AEs as adjunctive to SSRI versus SSRI (1 RCT; SMD=-3.39; 95%CI=[-4.27,-2.50]; I^2=n.c.; N=50)
Herbs									
St. John's wort	Linde 2008[149]	MDD	29 RCTs	SB: 18 PB: 29 DB: n.r. AB: 29 RB: n.r. OB: n.r.	AMSTAR: 8	HAMD MADRS	4-12 weeks	Response (50%): – Sign. greater effects than PLACEBO (18 RCTs; RR=1.48; 95%CI=[1.23,1.77]; I^2=75%; p<.001; N=3064; ⊕⊕⊕○ moderate[c]) – Similar effects as SSRI/TCA/TECA (17 RCTs; RR=1.01; 95%CI=[0.93,1.09]; I^2=17%; p=.25; N=2810; ⊕⊕⊕○ moderate[a])	– Similar AEs as PLACEBO (14 RCTs; OR=0.98; 95%CI=[0.78,1.23]; I^2=n.r.; N=2496), – Sign. less than ADMs (14 RCTs; OR=0.56; 95%CI=[0.43,0.74]; I^2=n.r.; N=2663)

Supplementary table 1: continued 3

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
St. John's wort (continued)	Apaydin 2016[141]	MDD	35 RCTs	SB: 9 PB: 27 DB: 5 AB: 26 RB: 3 OB: 33	AMSTAR: 9	HAMD	4-32 weeks	Severity: – Sign. greater effects than PLACEBO (16 RCTs; SMD=-0.49; 95%CI=[-0.74,-0.23]; I^2=89%; p=n.r.; N=2888; ⊕⊕⊕○ moderate[c]) – Similar effects as ADM (14 RCTs; SMD=-0.03; 95%CI=[-0.21,0.15]; I^2=74%; p=n.r.; N=2248; ⊕⊕○○ low[a,c]) Response (50%): – Sign. greater effects than PLACEBO (18 RCTs; RR=1.53; 95%CI=[1.19,1.97]; I^2=79%; p=n.r.; N=2922; ⊕⊕⊕○ moderate[c]) – Similar effects as ADM (17 RCTs; RR=1.01; 95%CI=[0.90,1.14]; I^2=52%; p=n.r.; N=2776; ⊕⊕⊕○ moderate[a]) Remission: – No sign. effects versus PLACEBO (9 RCTs; RR=1.69; 95%CI=[0.63,4.55]; I^2=94%; p=n.r.; N=1419; ⊕○○○ very low[a,c,d]) – Similar effects as ADM (7 RCTs; RR=1.17; 95%CI=[0.84,1.62]; I^2=29%; p=n.r.; N=787; ⊕⊕⊕○ moderate[a]) Relapse: – No sign. effects versus PLACEBO (1 RCT; RR=0.70; 95%CI=[0.49,1.02]; I^2=n.c.; N=426; ⊕○○○ very low[a,c,d]) – Similar effects as ADM (1 RCT; RR=4.17; 95%CI=[0.47,33.33]; I^2=n.c.; N=241; ⊕○○○ very low[a,c,d])	– Similar AEs as PLACEBO (13 RCTs; OR=0.83; 95%CI=[0.62,1.13]; I^2=n.r.; N=2600), – Sign. less than ADMs (11 RCTs; OR=0.67; 95%CI=[0.56,0.81]; I^2=n.r.; N=1946)
Saffron	Hausenblas 2013[146]	MDD	5 RCTs	SB: 5 PB: 5 DB: 5 AB: 5 RB: n.r. OB: n.r	AMSTAR: 7	HAMD	6-8 weeks	Severity: – Sign. greater effects than PLACEBO (2 RCTs; SMD=-1.62; 95%CI=[-2.14,-1.10]; I^2=0%; p=n.r.; N=71; ⊕○○○ very low[c,d,e]) – Similar effects as SSRI/TCA (3 RCTs; SMD=-0.15; 95%CI=[-0.52,0.22]; I^2=0%; p=n.r.; N=106; ⊕○○○ very low[c,d,e])	– No serious AEs

Supplementary table 1: continued

4

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Curcuma	Ng 2017[154]	MDD, CSD	6 RCTs	SB: 3 PB: 3 DB: 3 AB: 2 RB: 2 OB: 1	AMSTAR: 6	HAMD, BDI	4-8 weeks	Severity: – Sign. greater effects than PLACEBO (6 RCTs; SMD=-0.34; 95%CI=[-0.56,-0.13]; I^2=0%; p=.82; N=377; ⊕○○○ very low[a,d,e])	– No serious AEs
Chinese herbs	Yeung 2014[161]	MND	21 RCTs	SB: 5 PB: 11 DB: 9 AB: 21 RB: 20 OB: 18	AMSTAR: 4	HAMD	6-8,5 weeks	Severity: – Sign. greater effects than PLACEBO (4 RCTs; SMD=-1.27; 95%CI=[-1.67,-0.87]; I^2=44%; p=.14; N=251; ⊕○○○ very low[b,e])[#] – Similar effects as SSRI/SNRI/TCA/TECA (9 RCTs; SMD=0.17; 95%CI=[-0.12,0.46]; I^2=82%; p<.001; N=1962; ⊕○○○ very low[b,c,e])[#] Response (30%): – Sign. greater effects than PLACEBO (3 RCTs; RR=2.99; 95%CI=[2.18,4.10]; I^2=0%; p=.53; N=281; ⊕○○○ very low[c,d,e]) – Similar effects as SSRI/SNRI/TCA/TECA (10 RCTs; RR=1.00; 95%CI=[0.94,1.07]; I^2=42%; p=.08; N=1635; ⊕○○○ very low[b,c,e])	– Similar AEs as PLACEBO (3 RCTs; RR=1.29; 95%CI=[0.86,1.95]; I^2=61%; p= n.r.; N=n.r.) – Sign. less AEs than ADMs (29 RCTs; RR=0.23; 95%CI=[0.16,0.33]; I^2=59%; p= n.r.; N=n.r.)
Light therapy									
Bright white light	Tuunainen 2004[160]	MND	18	SB: 2 PB: 0 DB: 13 AB: 1 RB: n.r. OB: n.r.	AMSTAR: 9	HAMD, GDS	1 day - 8 weeks	Severity: – Sign. greater effects than adjunctive to ADM than SHAM + ADM (18 RCTs; SMD=-0.20; 95%CI=[-0.38,-0.01]; I^2=60%; p<.001; N=505; ⊕○○○ very low[a,c,d]) Response: – No effects than adjunctive to ADM than SHAM + ADM (3 RCTs; RR=0.94; 95%CI=[0.61,1.46]; I^2=69%; p=.004; N=71; ⊕○○○ very low[a,c,d])	– No serious AEs
	Martensson 2015[151]	SAD	8 RCTs	N.r.	AMSTAR: 5	HAMD, SIGH-SAD	2-6 weeks	Severity: – Sign. greater effects than SHAM (8 RCTs; SMD=-0.54; 95%CI=[-0.95,-0.13]; I^2=n.r.; N=179; ⊕○○○ very low[b,c,d,e])	N.r.

Supplementary table 1: continued 5

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Meditative movement therapies									
Dance therapy	Meekums 2015[152]	MND	2 RCTs	SB: 1 PB: 0 DB: 1 AB: 2 RB: 2 OB: 1	AMSTAR: 9	HAMD	4-12 weeks	Severity: – Sign. greater effects as adjunctive to ADM versus ADM (2 RCTs; SMD=-1.06; 95%CI=[-1.46,-0.65]; I^2=0%; p=.70; N=107; ⊕⊕○○ low[d,c])[#]	– No serious AEs
Qi Gong and Tai Chi	Liu 2015[150]	MDD, CSD	5 RCTs	N.r.	AMSTAR: 4	HAMD, GDS, CESD	10-16 weeks	Severity: – Sign. greater effects than TAU for Qi Gong (2 RCTs; SMD=-1.27; 95%CI=[-2.09,-0.45]; I^2=74%; p=.05; N=120; ⊕○○○ very low[b,c,d,e])* but no sign. effects for Tai Chi (3 RCTs; SMD=-0.61; 95%CI=[-1.55,0.34]; I^2=78%; p=.01; N=120; ⊕○○○ very low[b,c,d,e])*	N.r.
Yoga	Cramer 2013[144]	MDD, CSD	5 RCTs	SB: 0 PB: 0 DB: 1 AB: 1 RB: 5 OB: 3	AMSTAR: 8	HAMD, ZGS, GDS, BDI	4-8 weeks	Severity: – Sign. greater effects than TAU (4 RCTs; SMD=-1.03; 95%CI=[-1.90,-0.16]; I^2=82%; p<.001; N=141; ⊕○○○ very low[a,c,d,e])* – Sign. greater effects than EXERCISE (2 RCTs; SMD=-0.59; 95%CI=[-1.90,-0.16]; I^2=68%; p=.08; N=108; ⊕○○○ very low[a,c,d,e])	N.r.
Mindfulness-based interventions									
MBCT	Strauss 2014[158]	MDD	4 RCTs	N.r.	AMSTAR: 5	HAMD, BDI	8-12 weeks	Severity: – Sign. greater effects than TAU (3 RCTs; SMD=-0.97; 95%CI=[-1.81,-0.12]; I^2=72%; p=.03; N=115; ⊕○○○ very low[b,c,d])[§] – Similar effects as CBT (1 RCT; SMD=-0.16; 95%CI=[-0.75,0.43]; I^2=n.c.; N=45; ⊕○○○ very low[b,c,d])[§]	N.r.

Supplementary table 1: continued

6

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
MBCT (continued)	Kuyken 2016[148]	MDD	4 RCTs	SB: 4 PB: 0 DB: 3 AB: 4 RB: 4 OB: 4	AMSTAR: 6	SCID, BDI	60 weeks	Relapse: – Sign. greater effects than ADM (4 RCTs; HR=0.77; 95%CI=[0.60,0.98]; I^2=0%; p=.92; N=669; ⊕⊕⊕○ moderate[d])	– No serious AEs
MBSR	Bo 2017[143]	CSD	5 RCTs	SB: 0 PB: 0 DB: 1 AB: 5 RB: 5 OB: n.r.	AMSTAR: 6	HAMD, GDS	8-12 weeks	Severity: – Sign. greater effects than TAU/enhanced TAU (5 RCTs; SMD=-1.09; 95%CI=[-1.41,-0.76]; I^2=56%; p=.06; N=396; ⊕⊕○○ low[a,c])	N.r.
Music therapy									
Music therapy	Zhao 2016[162]	MND	8 RCTs	SB: 0 PB: 0 DB: 0 AB: 8 RB: 7 OB: 8	AMSTAR: 7	HAMD, GDS, HADS	4-52 weeks	Severity: – Sign. greater effects than TAU (5 RCTs; SMD=-0.57; 95%CI=[-1.03,-0.11]; I^2=76%; p<.001; N=244; ⊕○○○ very low[a,c,d])* – Sign. greater effects as adjunctive to ADM versus ADM (3 RCTs; SMD=-0.88; 95%CI=[-1.07,-0.68]; I^2=0%; p=.63; N=257; ⊕⊕○○ low[a,e])*	N.r.
	Aalbers 2017[138]	MDD, CSD	8 RCTs	SB: 2 PB: 1 DB: 1 AB: 7 RB: 2 OB: 3	AMSTAR: 11	HAMD	12 weeks	Severity: – Sign. greater effects than TAU (4 RCTs; SMD=-0.98; 95%CI=[-1.69,-0.27]; I^2=83%; p<.001; N=219; ⊕○○○ very low[a,c,d]) – Similar effects as CBT (4 RCTs; SMD=-1.28; 95%CI=[-3.57,1.02]; I^2=96%; p<.001; N=131; ⊕○○○ very low[a,c,d])	– Similar AEs as TAU (1 RCT; OR=0.45; 95%CI=[0.02,11.46]; I^2=n.c.; N=79)

Supplementary table 1: continued 7

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Religious/spiritual therapies									
Faith-adapted CBT	Anderson 2015[140]	MDD, CSD	9 RCTs	SB: 0 PB: 0 DB: 4 AB: 4 RB: 9 OB: 0	AMSTAR: 7	N.r.	N.r.	Severity: – Sign. greater effects than TAU (6 RCTs; SMD=-0.69; 95%CI=[-1.21,-0.17]; I^2=82%; p=.004; N=304; ⊕○○○ very ow[a,c,d])[§] – Sign. greater effects than CBT (6 RCTs; SMD=-0.54; 95%CI=[-0.82,-0.25]; I^2=0%; p=.78; N=199; ⊕⊕○○ low[a,e])[§]	N.r.
Supplements									
Inositol	Mukai 2014[153]	MDD	2 RCTs	N.r.	AMSTAR: 4	HAMD	4 weeks	Severity: – No sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (2 RCTs; SMD=0.17; 95%CI=[-0.33,0.66]; I^2=0%; p=.93; N=78; ⊕○○○ very low[b,d,e])	– Similar AEs as adjunctive to ADM (1 RCT; RR=3.21; 95%CI=[0.14,72.55]; I^2=n.c.; N=36)
Omega-3 fatty acids	Appleton 2015[142]	MDD	26 RCTs	SB: 15 PB: 6 DB: 19 AB: 8 RB: 16 OB: 25	AMSTAR: 9	HAMD, MADRS, BDI, GDS, HSCL, IDS	4-16 weeks	Severity: – Sign. greater effects than PLACEBO (25 RCTs; SMD=-0.30; 95%CI=[-0.50,-0.10]; I^2=59%; p<.001; N=1373; ⊕○○○ very low[a,c,d,e]) – Similar effects as SSRI (1 RCT; SMD=-0.08; 95%CI=[-0.70,0.54]; I^2=n.c.; N=40; ⊕○○○ very low[a,c,d,e]) Response (50%): – No sign. effects versus PLACEBO (15 RCTs; OR=1.39; 95%CI=[0.95,2.04]; I^2=6%; p=.38; N=611; ⊕○○○ very low[a,d,e]) – Similar effects as SSRI (1 RCT; OR=1.23; 95%CI=[0.35,4.31]; I^2=n.c.; N=40; ⊕○○○ very low[a,c,d,e]) Remission: – No sign. effects versus PLACEBO (6 RCTs; OR=1.38; 95%CI=[0.87,2.20]; I^2=7%; p=.37; N=426; ⊕○○○ very low[a,d,e])	– Similar AEs as PLACEBO (19 RCT; OR=1.24; 95%CI=[0.95,1.62]; I^2=0%; p=.66; N=1207)

Supplementary table 1: continued

8

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Probiotics	Huang 2016[147]	MDD	1 RCTs	SB: 1 PB: 1 DB: 1 AB: 1 RB: 1 OB: 1	AMSTAR: 7	BDI	8 weeks	Severity: – Sign. greater effects than PLACEBO (1 RCT; SMD=-0.73; 95%CI=[-1.37,-0.09]; I^2=n.c.; N=40; ⊕○○○ very low[c,d,e])	N.r.
S-adenosyl methionine	Galizia 2016[145]	MDD	8 RCTs	SB: 2 PB: 4 DB: 4 AB: 3 RB: 8 OB: 8	AMSTAR: 9	HAMD	6-12 weeks	Severity: – No sign. effects versus PLACEBO (2 RCTs; SMD=-0.54; 95%CI=[-1.54,0.46]; I^2=72%; p=.06; N=142; ⊕○○○ very low[c,d,e]) – Similar effects as SSRI/TCA (5 RCTs; SMD=-0.01; 95%CI=[-0.22,0.21]; I^2=43%; p=.14; N=821; ⊕⊕○○ low[a,e])[§] – Sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (1 RCT; SMD=-0.59; 95%CI=[-1.06,-0.12]; I^2=n.c.; N=73; ⊕○○○ very low[c,d,e])[#]	– Similar AEs as PLACEBO (2 RCTs; RR=0.70; 95%CI=[0.16,3.01]; I^2=n.r.; N=142) – Similar AEs as adjunctive to ADM (1 RCT, RR=0.58; 95%CI=[0.10,3.28]; I^2=n.c.; N=73) – Similar AEs as ADM (2 RCTs, RR=0.75; 95%CI=[0.20,2.79]; I^2=n.r.; N=52)
Tryptophan	Shaw 2002[157]	CSD	2 RCTs	SB: 2 PB: 2 DB: n.r. AB: 1 RB: n.r. OB: n.r	AMSTAR: 7	HAMD	3-12 weeks	Response: – Sign. greater effects than PLACEBO (2 RCTs; OR=4.10; 95%CI=[1.28,13.15]; I^2=0%; p=.32; N=46; ⊕○○○ very low[a,d,e])	– Sign. greater AEs than PLACEBO (2 RCTs; OR=7.41; 95%CI=[1.01,54.19]; I^2=0%; p=1.0; N=64)
Vitamin B9 (Folate)	Taylor 2003[159]	MDD	2 RCTs	SB: 0 PB: 2 DB: n.r. AB: 2 RB: n.r. OB: n.r.	AMSTAR: 8	HAMD	10-24 weeks	Severity: – Sign. greater effects as adjunctive to SSRI versus PLACEBO + SSRI (2 RCTs; SMD=-0.40; 95%CI=[-0.76,-0.05]; I^2=0%; p=.96; N=124; ⊕○○○ very low[a,c,d,e])[#]	– Similar AEs as PLACEBO (1 RCT; RR=0.76; 95%CI=[0.55,1.05]; I^2=n.c.; N=127)

Supplementary table 1: continued

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Vitamin B9 (Folate) (continued)	Almeida 2015[139]	MDD	5 RCTs	SB: 4 PB: 5 DB: 4 AB: 3 RB: 4 OB: 1	AMSTAR: 6	HAMD, MADRS	4-52 weeks	Severity: – No sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (5 RCTs; SMD=-0.12; 95%CI=[-0.45,0.22]; I^2=66%; p=.02; N=505; ⊕○○○ very low[c,d,e]) Response (50%): – No sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (4 RCTs; OR=1.18; 95%CI=[0.49,2.83]; I^2=73%; p=.001; N=478; ⊕○○○ very low[c,d,e]) Relapse: – Sign. greater effects as adjunctive to SSRI versus PLACEBO + SSRI (1 RCT, OR=0.33; 95%CI=[0.12, 0.94]; I^2=n.c.; N=153; ⊕○○○ very low[c,d,e])	N.r.
Vitamin D	Shaffer 2014[156]	MDD, CSD	2 RCTs	SB: 0 PB: 0 DB: 1 AB: 0 RB: n.r. OB: n.r.	AMSTAR: 7	HAMD, BDI	8 weeks	Severity: – Sign. greater effects than PLACEBO (2 RCTs; SMD=-0.60; 95%CI=[-1.19,-0.01]; I^2=n.r.; N=149; ⊕○○○ very low[a,c,d,e])	N.r.
Zinc	Schefft 2017[155]	MDD	3 RCTs	N.r.	AMSTAR: 5	HAMD, BDI	6-12 weeks	Severity: – Sign. greater effects as adjunctive to SSRI/TCA versus SSRI/TCA (3 RCTs; SMD=-0.66; 95%CI=[-1.06,-0.26]; I^2=0%; p=.45; N=104; ⊕○○○ very low[b,d,e])	N.r.

Abbreviations: AB: Attrition bias; ADM: Antidepressant medication; AE: Adverse events; AMSTAR: Assessment of the Methodological Quality of Systematic Reviews tool; BDI: Beck Depression Inventory; CBT: Cognitive Behavioral Therapy; CESD: Center for Epidemiologic Studies Depression Scale; CSD: Clinical symptoms of depression (questionnaire based diagnosis); DB: Detection bias; GDS: Geriatric Depression Scale; HADS: Hospital Anxiety and Depression Scale; HAMD: Hamilton Rating Scale for Depression; HR: Hazard ratio; HSCL: Hopkins Symptom Checklist Depression Scale; I^2: Heterogeneity; IDS: Inventory of Depressive Symptomology; MADRS: Montgomery-Asberg Depression Rating Scale; MBCT: Mindfulness-based Cognitive Therapy; MBSR: Mindfulness-based Stress Reduction; MDD: Major depressive disorder; MND: Mixed non-seasonal depression; N: Number of patients; N.c.: Not calculable because of only one included RCT; N.r.: Not reported; OB: Other bias; OR: Odds ratio; PB: Performance bias; RCT: Randomized controlled trial; RB: Reporting bias; RR: Risk ratio; SAD: Seasonal Affective Disorder; SB: Selection bias; SCID: Structured Clinical Interview; SIGH-SAD: Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorders; SMD: Standard mean difference; SSRI: Selective serotonin reuptake inhibitors; SNRI: Serotonin-norepinephrine reuptake inhibitor; TAU: Treatment as usual; TCA: Tricyclic antidepressants; TECA: Tetracyclic antidepressants; ZGS: Zung Depression Scale.

Supplementary table 1: continued

Notes:
*Newly calculated effect measure of selected RCTs meeting eligibility criteria;
[#]Newly calculated effect measure from mean differences (MDs);
[§]Newly calculated effect measure from originally separate/combined analyses.
[a]Downgraded one level because of study limitations (overall unclear or high risk of bias);
[b]Downgraded two levels because of study limitations (overall unclear or high risk of bias) and limitations of the meta-analysis (AMSTAR ≤ 5);
[c]Downgraded one level because of inconsistency (significant heterogeneity or no replication of the results);
[d]Downgraded one level because of imprecision (confidence interval includes negligible or no effects or fewer than 250 participants were included in total);
[e]Downgraded one level because of a probably high risk of publication bias.

Supplementary information to "Complementary therapies for clinical depression: an overview of systematic reviews"
by Heidemarie Haller, Dennis Anheyer, Holger Cramer, Gustav Dobos

Supplementary table 2: Detailed AMSTAR ratings.

	Apriori design	Two data extractor and con-sensus	Compre-hensive literature search	Inclusion of grey literature	List of included and excluded studies	Charac-teristics of studies provided	Adequate risk of bias assessment	Appropriate conclusions	Appropriate data syntheses	Assess-ment of publica-tion bias	Conflict of interest / funding statement	Sum
Aalbers 2017[138]	1	1	1	1	1	1	1	1	1	1	1	11
Almeida 2015[139]	0	1	1	0	0	1	1	1	1	0	0	6
Anderson 2015[140]	0	0	1	1	0	1	1	1	1	1	0	7
Apaydin 2016 [141]	1	1	1	1	0	1	1	1	1	0	1	9
Appleton 2015[142]	0	1	1	1	1	1	1	1	1	1	0	9
Bo 2017[143]	0	0	1	0	0	1	1	1	1	1	0	6
Cramer 2013[144]	0	1	1	1	1	1	1	1	0	1	0	8
Galizia 2016[145]	0	1	1	1	1	1	1	1	1	1	0	9
Hausenblas 2013[146]	0	1	1	1	0	1	1	1	1	0	0	7
Huang 2013[147]	0	1	1	0	0	1	1	1	1	1	0	7
Kuyken 2016[148]	0	0	1	0	0	1	1	1	1	1	0	6
Linde 2008[149]	0	1	1	1	0	1	1	1	1	1	0	8
Liu 2015[150]	0	0	1	0	0	1	0	1	0	1	0	4
Martensson 2015[151]	0	1	1	0	1	1	0	1	0	0	0	5
Meekums 2015[152]	0	1	1	1	1	1	1	1	1	1	0	9
Mukai 2014[153]	0	1	1	0	0	1	0	1	0	0	0	4
Ng 2017[154]	0	1	1	0	0	1	1	1	1	0	0	6
Schefft 2017[155]	0	1	1	0	0	1	0	1	1	0	0	5
Shaffer 2014[156]	0	1	1	1	1	1	1	1	0	0	0	7
Shaw 2002[157]	0	1	1	1	1	1	0	1	1	0	0	7
Smith 2018[50]	1	1	1	1	1	1	1	1	1	1	0	10
Strauss 2014[158]	0	0	1	1	0	1	0	0	1	1	0	5
Taylor 2003[159]	0	1	1	1	1	1	1	1	1	0	0	8
Tuunainen 2004[160]	0	1	1	1	1	1	1	1	1	1	0	9
Yeung 2014[161]	0	1	1	0	0	0	1	1	0	0	0	4
Zhao 2016[162]	0	1	1	0	0	1	1	1	1	1	0	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N.a.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N.a.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	19-29
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N.a.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N.a.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-50
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Keywords:	Depression, Complementary Therapies, Treatment Outcome, Safety, Systematic Review, Meta-analysis

Complementary therapies for clinical depression: an overview of systematic reviews

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Abstract

Objectives: As clinical practice guidelines vary widely in their search strategies and recommendations of complementary and alternative medicine (CAM) for depression, this overview aimed at systematically summarizing the level-1 evidence on CAM for patients with a clinical diagnosis of depression.

Methods: PubMed, PsycInfo and Central were searched for meta-analyses of randomized controlled trials (RCTs) until June 30, 2018. Outcomes included depression severity, response, remission, relapse, and adverse events. The quality of evidence was assessed according to GRADE considering the methodological quality of the RCTs (ROB) and meta-analyses (AMSTAR), inconsistency, indirectness, imprecision of the evidence, and the potential risk of publication bias.

Results: The literature search revealed 26 meta-analyses conducted between 2002 and 2018 on 1 to 49 RCTs in major, minor, and seasonal depression. In patients with mild to moderate major depression, moderate quality evidence suggested the efficacy of St. John's wort towards placebo and its comparative effectiveness towards standard antidepressants for the treatment for depression severity and response rates, while St. John's wort caused significant less adverse events. In patients with recurrent major depression, moderate quality evidence showed that Mindfulness-based Cognitive Therapy was superior to standard antidepressant drug treatment for the prevention of depression relapse. Other CAM evidence was considered as having low or very low quality.

Conclusions: The effects of all but two CAM treatments found in studies on clinical depressed patients based on low to very low quality of evidence. The evidence has to be downgraded mostly due to avoidable methodological flaws of both the original RCTs and meta-analyses not following the CONSORT and PRISMA guidelines. Further research is needed.

Keywords: Depression, Complementary Therapies, Treatment Outcome, Safety, Systematic Review

Strengths and limitations of this study

- This systematic overview included the comprehensive literature search of important CAM topics defined by the Cochrane Collaboration.
- The inclusion criteria were restricted to meta-analyses of RCTs of patients with a clinical diagnosis of depression.
- The quality of evidence from meta-analyses was assessed according to GRADE.
- There is a possible lack of evidence of newer RCTs, which have not been analysed by the included meta-analyses.

Introduction

Depression is one of the most prevalent psychiatric disorders, with about 25% of women and 12% of men suffering from at least one depressive episode during their lifetime.[1-3] According to the criteria for diagnosis recommended by the American Psychiatric Association (APA), depressive disorders can be distinguished by their degree of severity or duration and are also characterized by a high comorbidity and an increase of psychological strain for the affected person.[4] It is evident, that a strong comorbid connection to several chronic conditions like addictions,[5] neurodegenerative diseases,[6 7] or different psychiatric diseases[8-11] exists. This leads depressive disorders as one of the leading causes of disability worldwide.[12]

The most commonly used treatments for depression are antidepressants, psychotherapy, or a combination of drugs and psychotherapy. While both treatment strategies (alone and in combination) have been shown to be effective,[13-15] more recent meta-analyses also found high dropout and low remission rates[16-21] as well as clinically significant differences between antidepressant drugs and placebos only for patients at the upper end of the very severely depressed category.[22] This may lead patients to search for alternatives. Increasing mainstream use of complementary and alternative medicine (CAM) support this trend, particularly for different physical conditions with comorbid affective disorders.[23-27] The NIH defines CAM as therapeutic approaches that are usually not included in conventional Western medicine systems.[28] CAM therapies used in combination with conventional care are considered as complementary, those used instead of conventional care as alternative practices. Types of CAM approaches include natural products, such as herbs and dietary supplements (vitamins, minerals, and probiotics) and mind and body practices, such as yoga, chiropractic and osteopathic manipulation, meditation, relaxation, acupuncture, tai chi, qi gong, and hypnotherapy. Practices of traditional healers from Europe (naturopathy, homeopathy), Asia (Ayurveda, traditional Chinese medicine), and other continents are also classified as CAM.[28] While some complementary therapies have become a promising adjunct in the standard treatment of depression,[29 30] others are known for their possible side effects or interactions with standard drugs.[30] Recent clinical practice guidelines, in addition, vary widely in their search strategies and

resulting recommendations for CAM treatments. While the ACP,[31] APA,[32] and CANMAT guideline[33] provide a more comprehensive overview and critical appraisal of CAM treatments, the DGPPN,[34] NICE,[35] and WFSBP[36] guidelines mainly focus on St. John's Wort and light therapy. Possible effects and risks of further CAM therapies are not discussed. Thus, the purpose of this overview is to provide a comprehensive search strategy of relevant CAM terms and systematically summarize the existing level-1 evidence for clinical depression as a basis for further guideline recommendations on the efficacy, effectiveness, and safety of CAM therapies.

Methods

This systematic overview of reviews was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[37 38] and the recommendations of the Cochrane Collaboration.[39] The protocol was not prospectively registered.

Patient and Public Involvement

For this overview of reviews, patients or public were not involved.

Inclusion and exclusion criteria

- Types of studies: To be eligible, articles had to be systematic reviews with meta-analyses of randomized controlled clinical trials (RCTs) published in peer-reviewed journals. Conference abstracts or unpublished work were excluded as well as reviews summarizing evidence narratively. In cases of including same or similar original studies, only the review with the most recent, most comprehensive search was included. When systematic reviews reported results of RCTs as well as of designs of lower evidence levels, they were considered only if separate meta-analyses for the included RCTs were performed.
- Types of participants: Only reviews of patients with a diagnosis of major depression or dysthymia were eligible as well as reviews including patients/general population samples with mild depressive symptoms above a clinical cut off or seasonal patterns. In contrast, reviews studying depressive symptoms within specific subpopulations of substance-induced or demented patients, secondary depression due to another medical condition (e.g. post-stroke, cancer, or pain patients), bipolar disorders, or females with premenstrual dysphoric

disorder or postpartum depression were excluded. Further restrictions regarding the diagnostic criteria or procedures, regarding age, gender, duration of the condition, or symptom intensity were not applied.

- Types of interventions: Reviews investigating the effectiveness and/or safety of a single, adjunctive or combined CAM treatment were included. For the classification of CAM treatments the definition of the US National Institutes of Health[40] was followed. CAM interventions have to be compared against treatment as usual (TAU)/waiting list, placebo/sham, or standard medical care.
- Types of outcomes: Reviews were eligible if they assessed at least one measure of effectiveness such as severity of depressive symptoms, response rate (generally defined as a 50% decrease in depression scores after a period of up to 12 weeks of treatment),[31] remission rate (generally defined as a period of up to 12 weeks during which a patient is asymptomatic or has only few symptoms to a very mild degree).[41] relapse rates, and/or a measure of safety such as number of adverse events (AE), drug interactions, or numbers needed to harm for study withdrawal due to side effects.

Search strategy

Electronic literature was systematically searched via PubMed, PsycInfo and Central from their inception to January 31, 2018 without restrictions regarding time or language. Search terms for CAM treatments were selected in accordance with Cochrane recommendations (Table 1).[42] Additional manual search included reference lists of previously published reviews[14 29 30 43] and clinical practice guidelines.[31-36] Using PubMed Informer,[44] the search was updated until June 30, 2018.

Study selection process

To assess eligibility, articles were selected by screening titles and abstracts independently by two authors (HH and DA). Any abstract considered potentially eligible by at least one author was read in full to decide on its eligibility. Disagreements were rechecked with a third author (HC) until consensus was achieved.

Data extraction and quality assessment

Two authors (HH and DA) independently extracted data on the characteristics of the reviews including the type of the intervention, the year of publication, the number and quality of the original RCTs, the total number and age of the participants, and effectiveness and safety outcomes. The quality of the included reviews was assessed using the Assessment of the Methodological Quality of Systematic Reviews (AMSTAR) tool.[45] The AMSTAR tool consists of 11 items asking about important methodological quality criteria of systematic reviews such as: a published apriori design, duplicate study selection and data extraction, a comprehensive literature search including grey literature, a list of included and excluded studies, summarized characteristics and quality assessment of included studies, assessment of publication bias, appropriate method of data syntheses and deducing conclusions, and a conflict of interests statement. AMSTAR has shown good construct validity and inter-rater reliability. The Intraclass Correlation Coefficient (ICC) of the total AMSTAR score of 11 points was reported as 0.84.[46] For this analysis, the two authors (HH and DA) who independently assessed AMSTAR reached an ICC of 0.96. Disagreements regarding content or quality of the reviews were rechecked with a third author (HC) and resolved by agreement.

Data synthesis

Results were pooled qualitatively by type of the intervention. Outcomes had to be calculated as standard mean differences (SMDs), risk ratios (RRs), hazard ratios (HR), or odds ratios (ORs). If meta-analyses displayed mean differences (MDs), SMDs were calculated using Review Manager Software (RevMan, Version 5.3, The Nordic Cochrane Centre, Copenhagen) for better comparability of the results. RevMan was also used to exclude SMDs/RRs/HRs/ORs of selective RCTs that did not fulfil eligibility criteria of this overview. Effect sizes were classified according to Cohen as SMDs of 0.2 to 0.49 = small effect, SMDs of 0.5 – 0.79 = medium effect, and SMDs of > 0.8 = large effect (absolute values)[47] with higher reduction of/improvement in depression scores represented by more negative SMDs or RRs/HRs/ORs less than 1. According to the NICE guideline, a SMD of ≥ 0.5 or ≤ -0.5, respectively was considered as a clinically relevant reduction of depression severity.[48] Statistical heterogeneity between studies was assessed by the chi-squared test with a p-value of ≤ .10 indicating significant heterogeneity. The magnitude of heterogeneity was categorized by the I^2

statistic with I^2 of 0 to 24% = no heterogeneity, I^2 of 25% to 49% = moderate heterogeneity, I^2 of 50% to 74% = substantial heterogeneity, and I^2 of 75% to 100% = considerable heterogeneity.[39]

Quality of evidence

The quality of evidence was assessed according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach[49] individually by two authors (HH and DA). Disagreements were rechecked with a third author (HC) until consensus was achieved. For each outcome, the evidence can be graded as high, moderate, low or very low. Evidence from RCTs is initially assessed as high, but can be downgraded by one level for serious or two levels for very serious limitations of the study quality (of both RCTs and meta-analyses), inconsistency of the results, indirectness of the evidence, imprecision of the results, and a potential risk of publication bias (as assessed by the included meta-analyses).[49]

Results

Study selection

A total of 3582 potentially eligible articles were identified by electronic database search. One additional review was retrieved from manual search,[50] one from the updated search until June 2018.[51] After removing duplicates, 2639 articles were excluded by screening of titles and abstracts. The remaining 117 articles were read in full, of which further 91 reviews had to be excluded (Figure 1). Reasons for exclusion comprised 55 reviews where newer and/or more comprehensive reviews on higher quality evidence were available.[50 52-105] Further 15 reviews have to be excluded as they systematically summarized evidence but did not performed a meta-analysis mostly due to clinical heterogeneity or a limited number of available RCTs.[106-120] Eight reviews were excluded as they included mixed depressive samples of bipolar or postpartum cases and did not provide (data for) subgroup analyses for patients with the defined depression criteria.[121-128] Another six reviews contained community samples with non-clinical depression or physically ill patients with comorbid depressive symptoms but displayed no data for patients with a primary diagnosis of depression.[129-134] Four reviews performed meta-analyses on both RCTs and non-RCTs and did not perform subgroup

analyses or extracted sufficient data for post hoc analyses.[135-138] Three of the reviews analysed standard instead of complementary therapies and were therefore be excluded. Finally, 26 meta-analyses could be included and reviewed.[51 139-163]

Review characteristics and quality

Characteristics and quality appraisal of the included meta-analyses are summarized in the Supplementary Table 1. Meta-analyses were conducted between 2002 and 2018 and included between 1 to 49 RCTs on 40 to 7104 adult patients. Meta-analyses on children and adolescents were not available or did not meet inclusion criteria. Samples mostly consisted of patients suffering from major depressive disorder[140-143 145-151 154 156 157 159 160] but also included patients with mixed diagnoses of non-seasonal depression,[51 153 162 163] patients with a diagnosis of seasonal depression,[152] and patients with mild to severe symptoms of depression above a clinical cut-off.[139 141 144 145 151 155 157 158] All but one meta-analysis[141] reported pooled outcomes based on common standardized questionnaires or diagnostic interviews. Effects were analysed mostly up to 12 weeks of treatment (short-term), except for four meta-analyses that included RCTs with effects reported up to 16, 24, or 32 weeks[51 142 143 151 160] and further three meta-analyses with long-term analyses equal to or greater than one year [149 157 163]. The AMSTAR total scores of the included meta-analyses ranged between 4 and 11 points with a median quality of 7 points. The individual AMSTAR-ratings are reported in the Supplementary Table 2.

Synthesis of results

Acupuncture

Manual acupuncture

A high-quality Cochrane review meta-analysed 49 RCTs in major depressed adults as well as those with clinically relevant symptoms of depression for manual acupuncture.[51] For depression severity, significant effect sizes were found in comparisons to TAU and as in adjunction to standard antidepressants, while acupuncture showed similar effects to invasive sham acupuncture and standard antidepressants (Figure 2). The analyses of remission rates did not reveal superiority of

acupuncture in the comparisons to TAU, invasive sham, standard antidepressants or in adjunction to standard antidepressants (Figure 3). Adverse events reported in the acupuncture groups were significantly lower than in patients treated with antidepressant drugs. However, most meta-analyses showed significant heterogeneity, a lack of RCTs with low risk of bias and a possibly serious risk of publication bias. Thus, the quality of evidence had to be downgraded to low and very low.

Electroacupuncture

For electroacupuncture, the same Cochrane review[51] revealed very low quality of evidence for the comparisons to TAU and invasive sham for both outcomes, severity (Figure 2) and remission (Figure 3), because of serious limitations of the quality of the RCTs, imprecision, and a high risk of publication bias. For electroacupuncture monotherapy in comparison to standard antidepressants, low quality evidence homogeneously suggested significant greater effects for severity and similar effects for remission. As an adjunctive treatment to antidepressants, electroacupuncture effectiveness was supported by low quality of evidence showing a significant greater consistent and precise effect for depression severity. Although the mean adjunctive effect can be considered as large, the analysis based on only one RCT with overall low risk of bias and 4 RCTs of lower methodological quality that missed to include adjunctive sham acupuncture. For remission rates, very low quality of evidence suggested no effects in adjunction to antidepressants. In addition, one RCT showed significant less AEs when electroacupuncture was added to standard antidepressants.

Aromatherapy

The literature search revealed no meta-analysis on aromatherapy. A recent systematic review detected no RCTs in patients with a primary diagnosis of depression. However, two out of five of the reviewed studies on inhalation aromatherapy and five out of eight studies on aromatherapy massage have found significant anti-depressive effects in mixed patient samples and healthy adults.[117]

Biofeedback

No meta-analysis on biofeedback was conducted to date. A recent systematic review revealed only one RCT on the defined inclusion criteria for depression showing some effects in contrast to sham psychotherapy.[118]

Herbs

St. John's wort (Hypericum perforatum)

The effectiveness of St. John's wort was meta-analysed by a Cochrane review of 29 RCTs[150] and a more recent, higher quality meta-analysis of 35 RCTs.[142] In comparison to placebo, St. John's wort showed moderate quality evidence of significant greater reductions of depression severity (Figure 2) and response rates (Figure 4). The evidence had to be downgraded due to significant heterogeneity because of higher effects in studies from German-speaking countries than in those from the US or other European countries. In contrast, very low quality of evidence suggested no superiority to placebo for remission (Figure 3) and response rates (Figure 5). In comparison to standard antidepressants, St. John's wort showed comparable severity reductions, response, remission, and relapse rates. The quality of the evidence of the meta-analyses of severity and relapse rates had to be downgraded to low and very low, respectively. The evidence of the response and remission rates was considered as moderate quality showing the same results in both German and studies from other countries but containing some RCTs with unclear risk of selection bias and detection bias. Moreover, both meta-analyses[142 150] showed similar AEs of St. John's wort to placebo but significant less AEs than standard antidepressants.

Saffron (Crocus sativus)

A moderate-quality meta-analysis examined the effectiveness and safety of saffron on depression severity by including 5 RCTs in adult patients with major depression.[147] It revealed very low quality of evidence for significant greater effects versus placebo and similar effects versus antidepressant medication up to 8 weeks of treatment (Figure 2). No serious adverse events were reported, but patients receiving saffron tend to report more adverse events than those receiving placebo and less adverse events than those receiving antidepressant medication. Reasons for downgrading the

evidence included no replication of the results (all included RCTs were conducted by the same research group), the small overall sample size, and the possibly high risk of publication bias.

Curcumin (Curcuma longa)

For the intake of curcumin, a moderate-quality meta-analysis[155] revealed very low quality of evidence suggesting a small but significant short-term effect of low heterogeneity on depression severity by pooling 6 RCTs (Figure 2). No serious adverse events were recorded. Evidence had to be downgraded due to unclear risk of selection, performance, detection, attrition, and reporting bias in over the half of the included RCTs, the imprecision of the pooled effect and the possibly high risk of publication bias.

Traditional Chinese herbs

A comprehensive but low-quality systematic review of 296 RCTs of *Chinese herbal medicine* formulas and single herbs[162] revealed 21 RCTs of mostly unclear to high risk of selection, performance, and detection bias and a serious risk of publication bias. Therefore, the evidence supporting the superiority above placebo and the similarity towards standard antidepressants regarding depression severity (Figure 2) and response rates (Figure 4) was assessed as very low.

Other herbs

For other than the described herbs, no meta-analyses were conducted to date. However, a systematic review[110] found three single RCTs that showed significant improvement in depressive symptoms for *Lavandula angustifolia* as an adjunctive treatment to standard antidepressant drugs versus antidepressant drugs alone and for *Echium amoenum* and *Rhodiola rosea* versus placebo. No serious adverse events were reported.

Homoeopathy

No meta-analysis on *homoeopathic remedies* for depression were conducted yet. A recent systematic review detected no placebo-controlled RCTs in patients with a primary diagnosis of depression.[129]

Hypnosis

No meta-analysis on *hypnosis* or *self-hypnosis* techniques met the inclusion criteria of this overview. The only available review on this topic[127] included 6 RCTs among which only one RCT included adults with mild primary depression. Within the mixed sample of physically ill patients and healthy adults, (self-)hypnosis appeared to be effective in decreasing depressive symptoms.

Light therapy

A high-quality Cochrane review meta-analysed the effects of *bright light therapy* in adjunction to standard antidepressants versus sham light therapy plus antidepressants on severity and response rates in patients suffering from non-seasonal depression.[161] By pooling 18 RCTs of overall unclear risk of bias, it revealed very low quality of evidence for a significant small but inconsistent and imprecise effect on depression severity (Figure 2). A subgroup analysis of two RCTs with low risk of selection bias and detection bias revealed a significant large effect on depression severity but based on one non-peer-reviewed publication and one RCT that also included bipolar patients. Response rates did not significantly differ between groups (Figure 4). Adverse events were reported non-systematically but appeared to be comparable to sham light therapy except for hypomania that occurred more often under verum light therapy.[161]

For patients with seasonal patterns of depression, a meta-analysis of 8 RCTs[152] revealed very low quality of evidence for a significant medium effect on depression severity of light monotherapy in comparison to sham light therapy (Figure 2). Risk of bias of individual RCTs, heterogeneity, and safety were not analysed leading to an overall low quality of the meta-analysis and downgrading of the evidence.

Massage therapy

The literature search detected no meta-analysis of *massage therapy* in patients with a primary depression. However, massage therapy appeared to be effective in decreasing depressive symptoms in mixed samples of physically ill patients and healthy adult.[133] Future research will show, whether these results may be transferable to primary depressed cases.

Meditative movement therapies

Dance therapy

Short-term effects of improvisatory or structured *dance therapy* as a combination of movement-based work, interactive group components and insight/expressive methods were meta-analysed by a Cochrane review of high methodological quality.[153] It revealed a significant large pooled effect size for depression severity as an adjunctive treatment option to standard medical/psychotherapeutic care based on two RCTs (Figure 2). Although the meta-analyses contained no heterogeneity and no imprecise CI, the evidence had to be downgraded because of mostly unclear/high risk of bias of one of the RCTs as well as the overall small sample size.

Chinese movement therapies

A low-quality meta-analysis on Chinese meditative movement therapies revealed 30 RCTs, of which 2 RCTs on *Qi Gong* and 3 RCTs on *Tai Chi* met inclusion criteria for patients with mild to severe symptoms of primary depression.[151] Very low quality of evidence suggested significant short-term effects for Qi Gong but not for Tai Chi in comparison to TAU. The evidence had to be downgraded due to very serious limitations of the quality of the RCTs and the meta-analysis, significant heterogeneity, imprecision, and a possible high risk of publication bias.

Yoga

A high-quality meta-analysis of complex *yoga* interventions for various depressive disorders found 12 RCTs,[145] of which 5 RCTs of mostly unclear risk of bias met the inclusion criteria of this overview. The pooled short-term effect on depression severity was of large size in comparison to TAU and medium size in comparison to standard exercises (Figure 2). However, the evidence was assessed as very low due to serious limitations of quality of the RCTs, significant heterogeneity, imprecision, and a possible high risk of publication bias.

A further systematic review of yoga in major depressive disorder, revealed 5 newer yoga RCTs but did not perform a meta-analysis because of high clinical heterogeneity. Risk of bias was comparably high and evidence mostly conflicting.[107]

Mindfulness-based interventions

Mindfulness-based Cognitive Therapy (MBCT)

A low-quality meta-analysis of mindfulness-based interventions in patients with major depression found 4 RCTs investigating the effects of MBCT and Cognitive Behavioural Therapy (CBT) on depression severity.[159] It revealed a significant large short-term effect of MBCT in comparison to TAU and similar effects in comparison to CBT (Figure 2). However, the quality of the evidence was considered as very low due to the missing risk of bias assessment, inconsistency, and imprecision.

A further moderate-quality systematic review on MBCT meta-analysed 9 RCTs on an individual patient data level.[149] The sample consisted of patients with recurrent major depression currently in remission. After a period of 60 weeks, MBCT showed a significantly reduced risk of depressive relapse compared to those receiving antidepressant drugs (Figure 5). No serious adverse events were reported. The evidence was assessed as moderate due to a possibly serious risk of publication bias.

Mindfulness-based stress reduction (MBSR)

RCTs of MBSR and MBSR-like interventions were meta-analysed by a recent review [144] showing a significant large short-term effect on depression severity in comparison to TAU and enhanced TAU (Figure 2). The quality of the evidence was assessed as low because of the overall unclear risk of selection und and performance bias and significant heterogeneity.

Music therapy

Studies on active and receptive *music therapy* in older patients with a diagnosis of depression were summarized by a recent moderate-quality meta-analysis.[163] Out of 19 RCTs, 8 met the inclusion criteria for this overview. Pooled analyses of 5 of them revealed a significant medium effect size on depression severity against TAU up to 52 weeks, however with bigger short-term than long-term effects, considerable heterogeneity and overall unclear risk of selection, performance and detection bias resulting in very low quality of evidence. Further 3 RCTs of the same review revealed low quality evidence for a significant large consistent and precise effect of music therapy as an adjunctive treatment to antidepressants (Figure 2).

A newer Cochrane review[139] found 8 different RCTs showing a significant large pooled effect of music therapy on depression severity against TAU and similar effects as CBT (Figure 2). However, both analyses revealed very low quality of evidence due to mostly unclear selection, performance, detection and reporting bias, significant heterogeneity, and imprecision.

Nutrition therapy

No meta-analyses on specific diets for patients with depression were published to date. A systematic review of 11 RCTs on whole-diet interventions in mostly healthy patients with subthreshold physical conditions revealed conflicting evidence on the effectiveness of those intervention for the reduction of depressive symptoms.[115]

A further systematic review on fasting in patients with chronic pain and inflammatory diseases [111] included 1 RCT and 7 observational studies, which showed promising short-term but questionable longer-term anti-depressive effects.

Religious/spiritual Interventions

Very low to low quality of evidence was found by a moderate-quality systematic review of 9 RCTs on Christian, Muslim, and spiritual CBT adaptions.[141] The analyses showed significant greater medium effects on depression severity against TAU and standard CBT (Figure 2). Safety data were not reported.

Supplements

Inositol

A low quality meta-analysis of 2 RCTs in patients with major depression[154] revealed very low quality evidence for inositol as adjective to standard antidepressants versus placebo in combination to standard antidepressants (Figure 2).

Magnesium

No meta-analysis of magnesium supplementation was found. A recent systematic review detected no RCTs in patients with a primary diagnosis of depression [108].

Omega-3 fatty acids

A high-quality Cochrane review[143] of 26 RCTs found conflicting evidence of the effectiveness of supplementation with omega-3 fatty acids versus placebo in patients with major depression as depression severity significantly improved while response and remission rates did not so (Figure 2-4). One additional RCT with a very low sample size showed similar effects of omega-3 fatty acids on severity and response rates in comparison to antidepressant drug treatment (Figure 2 and 4). However, all meta-analyses were based on very low quality of evidence because of limitations of the study quality, significant heterogeneity, imprecision and a possibly high risk of publication bias.

Probiotics

The effectiveness of the supplementation with probiotics on depression severity was analysed by a moderate-quality meta-analysis of 5 RCTs, of which only one RCT with overall low risk of bias was carried out on patients with major depression.[148] The analysis of the RCT revealed a significant medium but imprecise short-term effect in comparison to placebo (Figure 2). This led to overall very low quality of evidence for probiotics supplementation.

S-adenosyl methionine (SAMe)

A high-quality Cochrane review[146] of the effectiveness and safety of SAMe supplementation on depression severity revealed 2 RCTs of low risk of bias that showed no significant pooled effects for SAMe monotherapy versus placebo. One RCT, also of low risk of bias showed a significant medium short-term effect as adjunctive to standard antidepressant medication, both for depression severity. Further 5 RCTs, which were rated as having overall unclear risk of bias, showed similar pooled effects of SAMe monotherapy on depression severity compared to standard antidepressant medication (Figure 2). Original RCTs reported safety issues insufficiently. For all meta-analyses, the evidence was assessed as low to very low quality because of limitations of the study quality, heterogeneity, imprecision, and a possibly high risk of publication bias.

Tryptophan

A moderate-quality Cochrane review found 2 RCTs investigating the effectiveness and safety of tryptophan supplementation on depression severity.[158] Pooling the effects led to significant greater short-term response rates (Figure 4) as well as significant more adverse events in the tryptophan group than in the placebo group. The evidence was assessed as very low quality because of an unclear risk of detection, attrition and other bias, imprecision, and a possible risk for publication bias.

Vitamins

For Vitamin B6, no meta-analysis was available. A systematic review without meta-analysis revealed 2 RCTs showing no significant effects when compared to placebo.[120]

Two further moderate to high-quality meta-analyses examined the effects of vitamin B9 (Folate) for major depressive patients. While a Cochrane review[160] calculated a significant medium effect size of folate-intake as an adjunctive intervention to standard drug treatment on depression severity, a more recent review[140] revealed non-significant differences on severity and response rates (Figure 2 and 3). In contrast, a long-term combined intake of Vitamin B6, B9, and B12 was found to be effective for relapse prevention after remission of symptoms as a result of one RCT (Figure 5).[140] However, all comparisons were based on very low quality of evidence mostly due to significant heterogeneity, imprecision, and possible high risk of publication bias.

Another moderate-quality meta-analysis revealed evidence of the effectiveness of vitamin D-intake on depression severity in comparison to placebo.[157] The analysis of the two included RCTs revealed a significant medium short-term effect in favour of vitamin D in major depressed patients up to 8 weeks (Figure 2). The quality of evidence was rated as very low due to limitations of the study quality, missing values of heterogeneity, imprecision, a high risk of publication bias as well as insufficient reporting of adverse events.

Zinc

The effectiveness of zinc for major depression was meta-analysed by a low-quality review of 3 RCTs.[156] It revealed a significant pooled short-term effect of medium size and low heterogeneity when zinc was taken as an adjunctive to standard antidepressant drug treatment (Figure 2).

However, the available evidence had to be assessed as very low as the meta-analysis did not perform risk of bias assessments and did not report adverse events.

Discussion

This systematic review provided a comprehensive overview of the evidence of CAM treatments for patients with a diagnosis or clinical symptoms of depression. Moderate quality evidence suggested the efficacy, comparative effectiveness to standard antidepressants, and safety of St. John's wort on depression severity and response rates. For remission and relapse rates, the evidence was conflicting and of lower quality. Moreover, moderate quality evidence showed that MBCT was superior to standard antidepressant drug treatment for the prevention of depression relapse in patients with recurrent major depression. Low quality evidence suggested significant greater effects in favour of electroacupuncture in comparison to standard antidepressants alone and in adjunction to standard antidepressants for depression severity. For remission rates, low quality evidence revealed comparable effects of electroacupuncture and standard antidepressants. Further significant greater effects, which based on low quality evidence, were found for MBSR versus TAU, music therapy in adjunction to standard antidepressants, faith-adapted CBT versus CBT, and SAMe versus standard antidepressants. Other treatments such as manual acupuncture, aromatherapy, biofeedback, herbs (crocus sativus, curcuma longa, traditional Chinese herbs, lavandula angustifolia, echium amoenum, rhodiola rosea), Homoeopathy, hypnosis, bright light therapy, massage, meditative movement therapies (dance therapy, Qi Gong, Tai Chi, yoga), whole-diet interventions, fasting, and supplementation with inositol, magnesium, omega-3 fatty acids, probiotics, tryptophan, B- and D-vitamins, and zinc were based on very low quality of evidence or no level-1 evidence.

The strengths of the review process included the comprehensive literature search based on a structured list of CAM specific topics, which had been operationalized for the Cochrane Collaboration.[42] It therefore included evidence for more than the previously considered CAM approaches and provided systematic information where further high-quality studies are required. In addition, we only included results of RCTs of patients with a diagnosis of depression or clinical relevant depressive symptoms and excluded RCTs on samples with minor or secondary symptoms of

depression by newly calculating effect sizes. Finally, we rated AMSTAR and considered the quality of the meta-analyses as well when grading the quality of the evidence.

The conclusions derived from this overview are limited due to possibly missing evidence from newer RCTs, which have not been summarized by the included systematic reviews and meta-analyses. As it was not within the scope of this overview, we did not separately search for individual RCTs. We also did not include meta-analyses on studies of lower evidence levels, which may include bigger samples and may provide additional information about further possible treatment approaches. Moreover, we did not search online registries or conference proceedings for unpublished or ongoing meta-analyses, which may limit the conclusions. Another reason that limits the quality of evidence consists in the unsatisfactory methodological quality of some of the included meta-analyses. Although the methodological quality of the original RCTs might be acceptable, the bad reporting of some meta-analyses led to downgraded evidence. In particular, meta-analyses often missed to search for grey literature, cite excluded studies, adequately assess risk of bias of the original studies, and report complete I^2 statistics. As the latter are known to be unstable in meta-analyses with a small numbers of studies,[164] calculating confidence intervals for I^2 should be standard. Moreover, RCTs as well as meta-analyses often missed to systematically report on occurred adverse events, which also limits the significance of the conclusions. In RCTs of non-pharmacological interventions, there is always a high or unclear risk of performance bias and possibly high placebo effects. As such, adding credible sham interventions, controlling for patients' expectances, and performing of ITT analyses is indispensable. However, meta-analyses mostly did not systematically assess these issues. In meta-analyses of pharmacological interventions, the influence of industrial funding sources was often not adequately analysed. Here, subgroup analyses of studies having received no funding/non-industrial funding versus those having received industrial funding are needed. Results of meta-analyses that missed to report funding issues completely should interpreted with caution. In general, it should be noticed that all evidence is based on short-term pooled effects, except for meta-analyses of St. John's wort, MBCT, music therapy, and B- and D-vitamins that also provided longer-term follow-up data.

Clinical recommendations for patients should follow the country-specific clinical practice guidelines considering the quality of evidence, the accessibility of the treatment, costs, and the preferences of the patients. While the guidelines agree[31 32 34-36 165 166] that clinicians should select between either CBT or second-generation antidepressant drugs for the treatment of major depression, the restricted search strategy of some of the guidelines might limit their recommendations for CAM treatments. For patients who do reject or do not tolerate standard antidepressant drugs, one alternative treatment option may be St. John's wort. It is also recommended by the American Psychiatric Association Task Force report[43] and the CANMAT Depression Work Group[33] as being proven sufficiently for the short-term by placebo-controlled and equivalence trials with standard antidepressants for mild to moderate major depression. Particularly for bridging the gap between diagnosis and getting access to psychotherapy and meanwhile reducing/not-worsening depression severity, St. John's wort may be considered as a possibly better tolerated alternative to standard antidepressant drugs.[167] As St. John's wort is accessible without prescription and currently not regulated by the US Food and Drug Administration, we agree with the ACP guidelines[31] that it remains difficult for patients to obtain quality-controlled remedies. Moreover, St. John's wort is associated with numerous herb-to-drug interactions.[168] Therefore, we would recommend clinicians to educate their patients about possible effects, side effects and interactions who in turn should not take St. John's wort without professional advise.[34] Despite those limitations, we would not discourage a general therapeutic attempt with St. John's wort, even if we disagree with the NICE guideline in this point.[35] Clinicians may also inform patients with recurrent major depression currently in remission about the superiority of MBCT in comparison to standard antidepressants for relapse prevention.[32-35] Finally, patients should also be informed that many other CAM treatments might show promising effects but cannot be recommended until further higher-quality studies will confirm their effectiveness and safety.

Further research is needed, particularly for interventions that have shown preliminary evidence for reducing secondary symptoms of depression, promising short-term but no longer-term effects, or insufficient evidence due to low methodological quality of the original RCTs and/or the performed

meta-analyses. Reporting of clinical trials and meta-analyses should necessarily follow the CONSORT[169] and PRISMA guidelines,[37] respectively, including rigorous documentation and analysis of adverse events. Especially Chinese and Indian trials are still found to be poorly reported and tended to present more positive conclusions than those from western countries.[170 171] Moreover, 7 of the included meta-analyses showed no more than poor methodological quality. All were published in peer-reviewed journals in the past 5 years. One complementary journal is among them, while 6 of the journals are conventional psychiatric journals with impact factors ranging from 2.419 to 4.369. Thus, particularly the review process as well as the editorial work need to be improved. Further clinical practice guidelines should extend their search strategies and include standard search terms for CAM. This is also important for CAM therapies that do not show consistent evidence or that are not yet investigated. This information might be equally interesting for physicians as well as for patients to make an informed decision about the treatment for clinical depression.

Conclusion

This overview of systematic reviews on CAM treatments for clinical depression aimed to provide a systematic search strategy and evidence base, on which further clinical practice guidelines may build their recommendations. To improve quality of trials and meta-analyses, researchers, reviewers as well as editors are asked to ensure that future articles strictly adhere the CONSORT and PRISMA guidelines.

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Author contribution statement

HH was responsible for the conception and design of the study, the collection and analysis of the study data and for drafting the manuscript. DA participated in the analysis of the study data and drafting the manuscript. HC participated in the conception and design of the study and the analysis of the study data, and critically revised the manuscript. GD participated in the conception and design of the study, and critically revised the manuscript. All authors approved the final manuscript.

Data Availability

All data relevant to the study are included in the article or uploaded as supplementary information.

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Figure legends

Figure 1. Study flow diagram.

Figure 2. Quality of evidence for depression severity. ADM: Antidepressant medication, CBT: Cognitive Behavioural Therapy, CI: Confidence Interval, I^2: Heterogeneity, MBCT: Mindfulness-based Cognitive Therapy, MBSR: Mindfulness-based Stress Reduction, N.c.: Not calculable because of only one included RCT, N.r.: Not reported, SAMe: S-adenosyl methionine, Tau: Treatment as Usual

Figure 3. Quality of evidence for depression remission rates. ADM: Antidepressant medication, CI: Confidence Interval, I^2: Heterogeneity, N.c.: Not calculable because of only one included RCT, OR: Odds Ratio, RR: Risk Ratio, Tau: Treatment as Usual

Figure 4. Quality of evidence for depression response rates. ADM: Antidepressant medication, CI: Confidence Interval, I^2: Heterogeneity, N.c.: Not calculable because of only one included RCT, OR: Odds Ratio, RR: Risk Ratio

Figure 5. Quality of evidence for depression relapse rates. ADM: Antidepressant medication, CI: Confidence Interval, HR: Hazard Ratio, I^2: Heterogeneity, MBCT: Mindfulness-based Cognitive Therapy, N.c.: Not calculable because of only one included RCT, OR: Odds Ratio, RR: Risk Ratio, Tau: Treatment as Usual

Tables

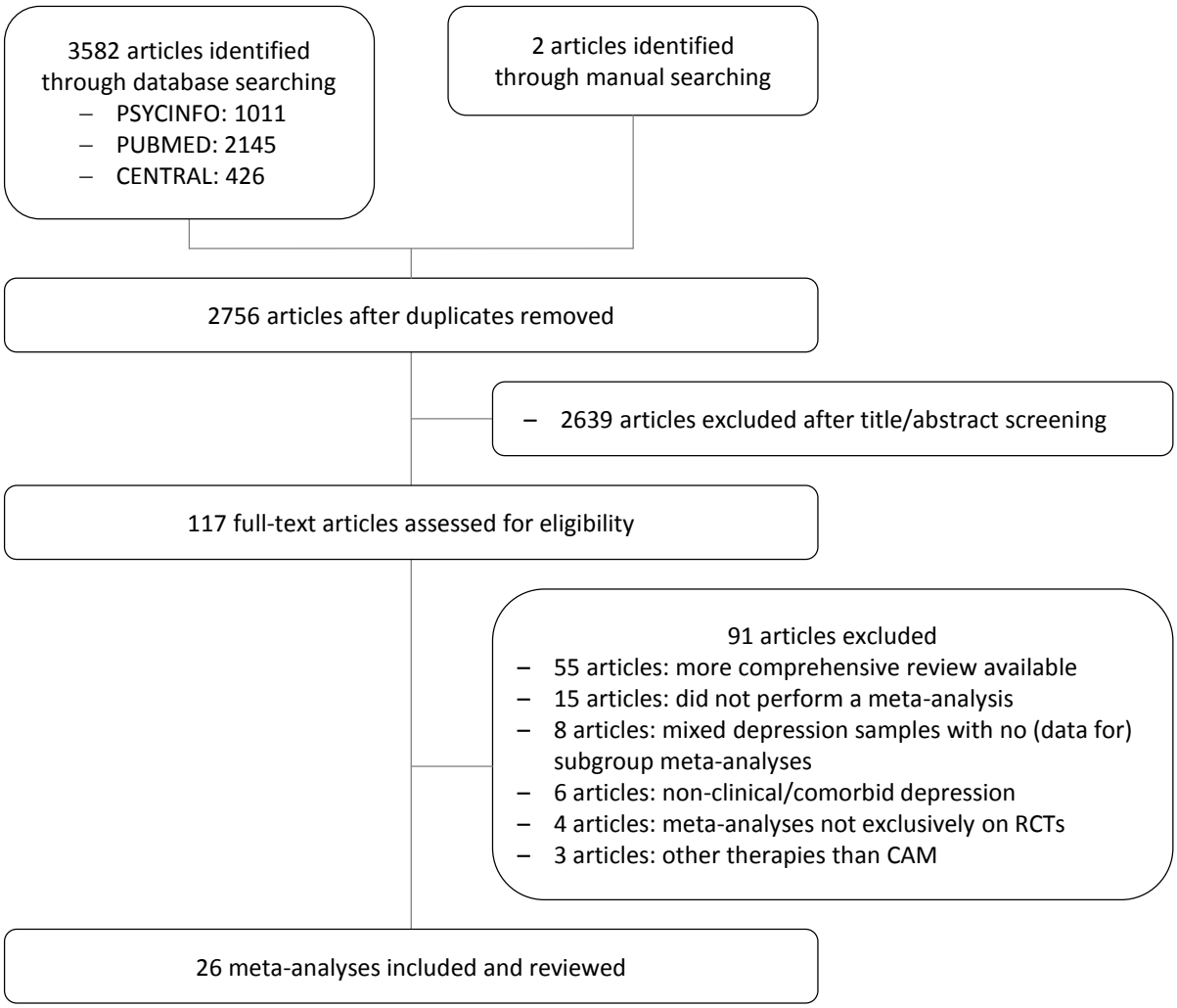
Table 1. Electronic search strategy for PubMed.

#1	(Depression OR Depressive Disorder, Major OR Depressive Disorder, Treatment-Resistant OR Dysthymic Disorder OR Seasonal Affective Disorder)[mh]
#2	(depress* OR dysthym* or "seasonal affective" OR "affective disorder" OR "affective disorders" OR "mood disorder" OR "mood disorders")[tiab]
#3	(Systematic review OR Meta-analysis)[pt] OR (Systematic* OR Meta-analy*)[tiab]
#4	(Acupressure OR Acupuncture OR acid OR Alexander Technique OR alternative OR Aromatherapy OR Aroma Therapy OR Art Therap* OR ayurved* OR Balneotherapy OR Balneo Therapy OR bee OR Biofeedback OR Bio Feedback OR bright light OR Chelation Therapy OR Chinese Traditional Medicine OR Chiropractic OR Chronotherapy OR Color Therapy OR complementary OR craniosacral OR cupping OR Curcumin OR Dance Therapy OR diet OR Distant Healing OR Electroacupuncture OR Feldenkrais OR folic acid OR Folate OR Healing Touch OR herbal OR Herbs OR Homeopath* OR Honey OR Hydrotherapy OR hyperbaric oxygenation OR Hypericum perforatum OR Hyperthermia OR Hypnosis OR Imagery OR Inositol OR Kampo OR Light Therapy OR Magnesium OR Massage OR MBSR OR MBCT OR Meditation OR Mindfulness OR Morita Therapy OR Moxibustion OR Mediterranean OR Music Therap* OR Naturopathy OR Neural Therapy OR Omega-3 OR Osteopath* OR Ozone Therapy OR Phototherapy OR Pollen OR Prayer OR prebiotic* OR probiotic* OR Propolis OR Qi Gong OR Reflexology OR Reiki OR Relaxation OR Rolfing OR Royal Jelly OR S-adenosyl-L-methionine OR Saffron OR Shamanism OR Snoezelen OR Speleotherapy OR Spinal Manipulation OR Spiritual OR St John's Wort OR Supplements OR Tai Chi OR TCM OR Therapeutic Touch OR Traditional Chinese Medicine OR Tryptophan OR Tui na OR Turmeric OR vegan OR vegetarian OR venom OR Vitamin OR Yoga OR zinc)[tiab]
#5	(Acupressure OR Acupuncture OR Acupuncture Therapy OR Acids OR Aromatherapy OR Art Therapy OR Balneology OR Biofeedback, Psychology OR Chelation Therapy OR Chiropractic OR Chronotherapy OR Color Therapy OR Complementary Therapies OR Crocus OR Curcuma OR Dance Therapy OR Diet OR Electroacupuncture OR Fatty Acids, Omega-3 OR Folic Acid OR Homeopathy OR Honey OR Hydrotherapy OR Hypericum OR Hyperthermia, Induced OR Hypnosis OR Imagery OR Inositol OR Magnesium OR Manipulation, Spinal OR Massage OR Medicine, Ayurvedic OR Medicine, Chinese Traditional OR Medicine, Kampo OR Meditation OR Mind-Body Therapies OR Mindfulness OR Moxibustion OR Naturopathy OR Ozone OR Phototherapy OR Plants, Medicinal OR Pollen OR Prebiotics OR Probiotics OR Propolis OR Qigong OR Relaxation OR Shamanism OR Speleotherapy OR Spiritual Therapies OR Supplements, Dietary OR Tai Ji OR Therapeutic Touch OR Tryptophan OR Venoms OR Vitamins OR Yoga OR Zinc)[mh]
#6	(#1 OR #2) AND #3 AND (#4 OR #5)

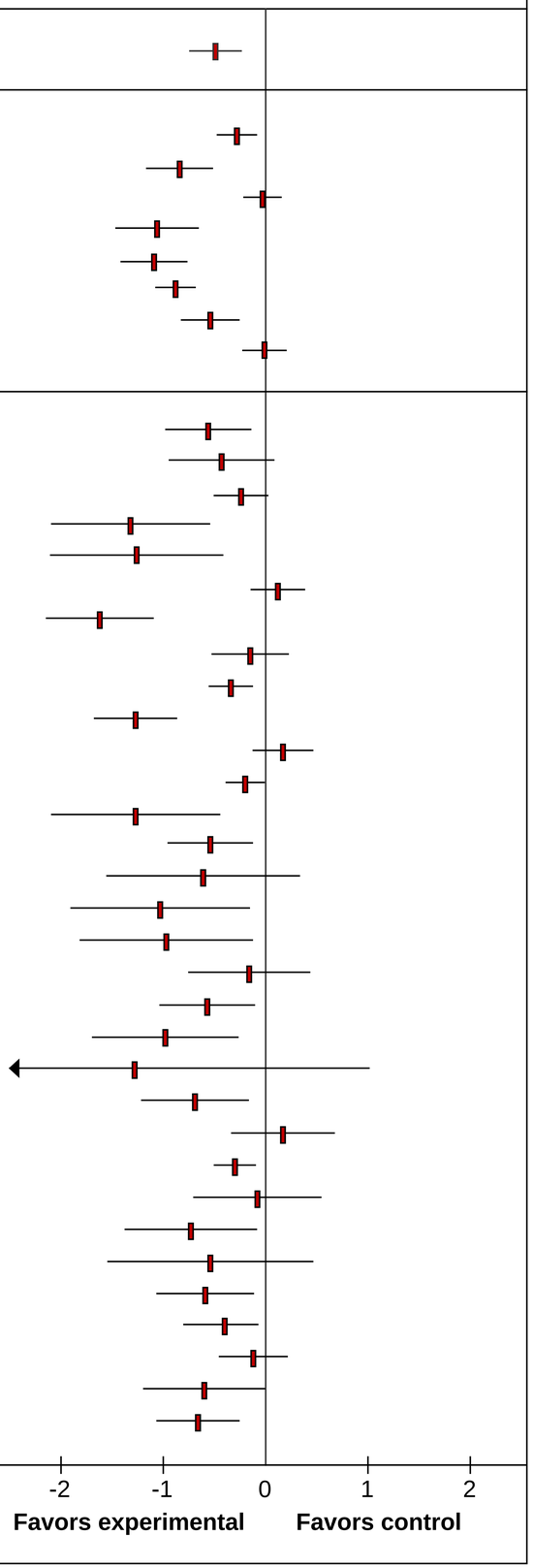
Supplementary data

Supplementary table 1: Detailed AMSTAR ratings.

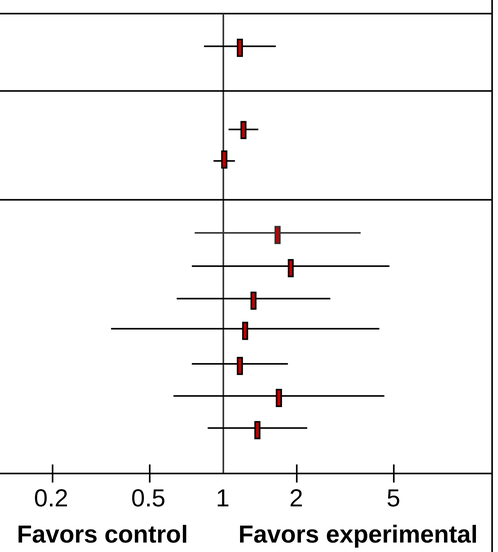
Supplementary table 2: Characteristics and outcomes of the included meta-analyses.


3582 articles identified through database searching
– PSYCINFO: 1011
– PUBMED: 2145
– CENTRAL: 426
2 articles identified through manual searching
2756 articles after duplicates removed
– 2639 articles excluded after title/abstract screening
117 full-text articles assessed for eligibility
91 articles excluded
– 55 articles: more comprehensive review available
– 15 articles: did not perform a meta-analysis
– 8 articles: mixed depression samples with no (data for) subgroup meta-analyses
– 6 articles: non-clinical/comorbid depression
– 4 articles: meta-analyses not exclusively on RCTs
– 3 articles: other therapies than CAM
26 meta-analyses included and reviewed

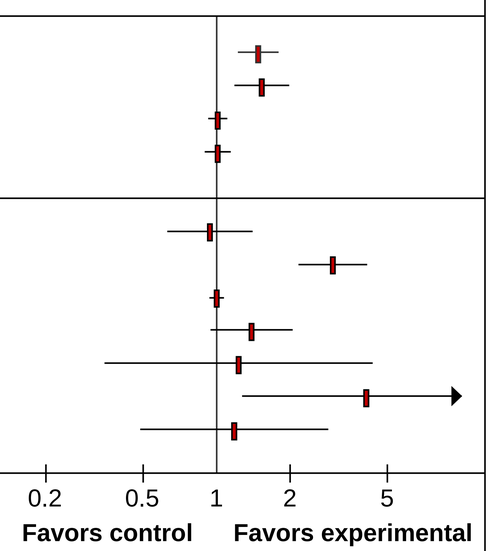
Quality of evidence	Intervention	Control	Reference	Trials	Partici-pants	I^2	Std. Mean Difference 95% CI
Moderate	St. John's Wort	Placebo	Apaydin, 2016[142]	16	2888	89%	-0.49 [-0.74, -0.23]
Low	Electroacupuncture	ADM	Smith, 2018[51]	10	995	33%	-0.28 [-0.47, -0.09]
		Adjunctive	Smith, 2018[51]	5	274	33%	-0.84 [-1.16, -0.51]
	St. John's Wort	ADM	Apaydin, 2016[142]	14	2248	74%	-0.03 [-0.21, 0.15]
	Dance therapy	Adjunctive	Meekums, 2015[153]	2	107	0%	-1.06 [-1.46, -0.65]
	MBSR	TAU	Bo, 2017[144]	5	396	56%	-1.09 [-1.41, -0.76]
	Music therapy	Adjunctive	Zhao, 2016[163]	3	257	0%	-0.88 [-1.07, -0.68]
	Faith-adapted CBT	CBT	Anderson, 2015[141]	6	199	0%	-0.54 [-0.82, -0.25]
	SAMe	ADM	Galizia, 2016[146]	5	821	43%	-0.01 [-0.22, 0.21]
Very low	Manual acupuncture	TAU	Smith, 2018[51]	4	458	62%	-0.56 [-0.98, -0.15]
		Sham	Smith, 2018[51]	7	418	80%	-0.43 [-0.95, 0.08]
		ADM	Smith, 2018[51]	19	1967	87%	-0.24 [-0.51, 0.02]
		Adjunctive	Smith, 2018[51]	8	539	93%	-1.32 [-2.09, -0.55]
	Electroacupuncture	TAU	Smith, 2018[51]	1	30	n.c.	-1.26 [-2.10, -0.43]
		Sham	Smith, 2018[51]	5	251	0%	0.12 [-0.14, 0.38]
	Saffron	Placebo	Hausenblas, 2013[147]	2	71	0%	-1.62 [-2.14, -1.10]
		ADM	Hausenblas, 2013[147]	3	106	0%	-0.15 [-0.52, 0.22]
	Curcuma	Placebo	Ng, 2017[155]	6	377	0%	-0.34 [-0.56, -0.13]
	Chinese herbs	Placebo	Yeung, 2014[162]	4	251	44%	-1.27 [-1.67, -0.87]
		ADM	Yeung, 2014[162]	9	1962	82%	0.17 [-0.12, 0.46]
	Light therapy	Sham	Martensson, 2015[152]	8	179	n.r.	-0.54 [-0.95, -0.13]
		Adjunctive	Tuunainen, 2004[161]	9	505	60%	-0.20 [-0.38, -0.01]
	Qi Gong	TAU	Liu, 2015[151]	2	120	74%	-1.27 [-2.09, -0.45]
	Thai Chi	TAU	Liu, 2015[151]	3	120	78%	-0.61 [-1.55, 0.34]
	Yoga	TAU	Cramer, 2013[145]	4	141	82%	-1.03 [-1.90, -0.16]
	MBCT	TAU	Strauss, 2014[159]	3	115	72%	-0.97 [-1.81, -0.12]
		CBT	Strauss, 2014[159]	1	45	n.c.	-0.16 [-0.75, 0.43]
	Music therapy	TAU	Zhao, 2016[163]	5	244	76%	-0.57 [-1.03, -0.11]
			Aalbers, 2017[139]	4	219	83%	-0.98 [-1.69, -0.27]
		CBT	Aalbers, 2017[139]	4	131	96%	-1.28 [-3.57, 1.02]
	Faith-adapted CBT	TAU	Anderson, 2015[141]	6	304	82%	-0.69 [-1.21, -0.17]
	Inositol	Adjunctive	Mukai, 2014[154]	2	78	0%	0.17 [-0.33, 0.66]
	Omega-3	Placebo	Appleton, 2015[143]	25	1373	59%	-0.30 [-0.50, -0.10]
		ADM	Appleton, 2015[143]	1	40	n.c.	-0.08 [-0.70, 0.54]
	Probiotics	Placebo	Huang, 2016[148]	1	40	n.c.	-0.73 [-1.37, -0.09]
	SAMe	Placebo	Galizia, 2016[146]	2	142	72%	-0.54 [-1.54, 0.46]
		Adjunctive	Galizia, 2016[146]	1	73	n.c.	-0.59 [-1.06, -0.12]
	Folate	Adjunctive	Taylor, 2003[160]	2	124	0%	-0.40 [-0.76, -0.05]
			Almeida, 2015[140]	5	505	66%	-0.12 [-0.45, 0.22]
	Vitamin D	Placebo	Shaffer, 2014[157]	2	149	n.r.	-0.60 [-1.19, -0.01]
	Zinc	Adjunctive	Schefft, 2017[157]	3	104	0%	-0.66 [-1.06, -0.26]



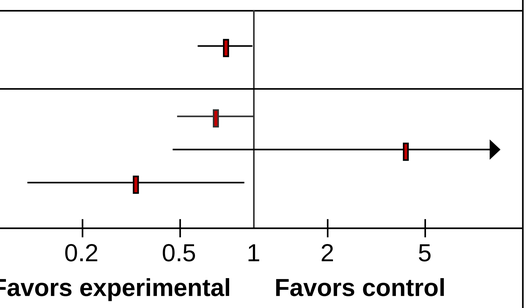
Quality of evidence	Intervention	Control	Reference	Trials	Partici-pants	I^2	Risk/Odds Ratio 95% CI
Moderate	St. John's Wort	ADM	Apaydin, 2016[142]	7	787	29%	RR: 1.17 [0.84, 1.62]
Low	Manual acupuncture	ADM	Smith, 2018[51]	19	1967	87%	RR: 1.21 [1.06, 1.39]
	Electroacupuncture	ADM	Smith, 2018[51]	8	966	0%	RR: 1.01 [0.92, 1.11]
Very low	Manual acupuncture	TAU	Smith, 2018[51]	4	458	62%	RR: 1.67 [0.77, 3.65]
		Sham	Smith, 2018[51]	7	418	80%	RR: 1.89 [0.75, 4.75]
		Adjunctive	Smith, 2018[51]	8	539	93%	RR: 1.33 [0.65, 2.73]
	Electroacupuncture	Sham	Smith, 2018[51]	2	87	20%	RR: 1.23 [0.35, 4.29]
		Adjunctive	Smith, 2018[51]	5	273	49%	RR: 1.17 [0.75, 1.80]
	St. John's Wort	Placebo	Apaydin, 2016[142]	9	1419	94%	RR: 1.69 [0.63, 4.55]
	Omega-3	ADM	Appleton, 2015[143]	6	426	7%	OR: 1.38 [0.87, 2.20]



Quality of-evidence	Intervention	Control	Reference	Trials	Partici-pants	I^2	Risk/Odds Ratio 95% CI
Moderate	St. John's Wort	Placebo	Linde, 2008[150]	18	3064	75%	RR: 1.48 [1.23, 1.77]
			Apaydin, 2016[142]	18	2922	79%	RR: 1.53 [1.19, 1.97]
	St. John's Wort	ADM	Linde, 2008[150]	17	2810	17%	RR: 1.01 [0.93, 1.09]
			Apaydin, 2016[142]	17	2776	52%	RR: 1.01 [0.90, 1.14]
Very Low	Light therapy	Adjunctive	Tuuainen, 2004[161]	3	71	69%	RR: 0.94 [0.61, 1.46]
	Chinese herbs	Placebo	Yeung, 2014[162]	3	281	0%	RR: 2.99 [2.18, 4.10]
		ADM	Yeung, 2014[162]	10	1653	42%	RR: 1.00 [0.94, 1.07]
	Omega-3	Placebo	Appleton, 2015[143]	15	611	6%	OR: 1.39 [0.95, 2.04]
		ADM	Appleton, 2015[143]	1	40	n.c.	OR: 1.23 [0.35, 4.31]
	Tryptophan	Placebo	Shaw, 2002[158]	2	46	0%	OR: 4.10 [1.28, 13.15]
	Folate	Adjunctive	Almeida, 2015[158]	4	478	73%	OR: 1.18 [0.49, 2.83]



Quality of evidence	Intervention	Control	Reference	Trials	Partici-pants	I^2	Risk/Odds/Hazard Ratio 95% CI
Moderate	MBCT	ADM	Kuyken, 2016[149]	4	669	0%	HR: 0.77 [0.60, 0.98]
Very low	St. John's Wort	Placebo	Apaydin, 2016[142]	1	426	n.c.	RR: 0.70 [0.49, 1.02]
		ADM	Apaydin, 2016[142]	1	241	n.c.	RR: 4.17 [0.47, 33.33]
	Folate	Adjunctive	Almeida, 2015[140]	1	153	n.c.	OR: 0.33 [0.12, 0.94]



Supplementary information to "Complementary therapies for clinical depression: an overview of systematic reviews"
by Heidemarie Haller, Dennis Anheyer, Holger Cramer, Gustav Dobos

Supplementary table 1: Characteristics and outcomes of the included meta-analyses.

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Acupuncture									
Manual acupuncture	Smith 2018[51]	MDD, CSD	49 RCTs	SB: 9 PB: 9 DB: 5 AB: 24 RB: 2 OB: 15	AMSTAR: 10	HAMD BDI	1.5-12 weeks	Severity: – Sign. greater effects than TAU (4 RCTs; SMD=-0.56; 95%CI=[-0.98,-0.15]; I^2=62%; p=.03; N=458; ⊕○○○ very low[a,c,d,e]) – No sign. effects versus invasive SHAM (7 RCTs; SMD=-0.43; 95%CI=[-0.95,0.08]; I^2=80%; p<.001; N=418; ⊕○○○ very low[a,c,d,e])[#] – Similar effects as SSRI/TCA (19 RCTs; SMD=-0.24; 95%CI=[-0.51,0.02]; I^2=87%; p<.001; N=1967; ⊕○○○ very low[a,c,e])[§] – Sign. greater effects as adjunctive to SSRI versus SSRI (8 RCTs; SMD=-1.32; 95%CI=[-2.09,-0.55]; I^2=93%; p<.001; N=539; ⊕○○○ very low[a,c,e]) Remission: – No sign. effects versus TAU (2 RCTs; RR=1.67; 95%CI=[0.77,3.65]; I^2=0%; p=.44; N=94; ⊕○○○ very low[a,d,e]) – No sign. effects versus invasive SHAM (5 RCTs; RR=1.89; 95%CI=[0.75,4.75]; I^2=63; p=.03; N=368; ⊕○○○ very low[a,c,d,e]) – Sign. smaller effects than SSRI/TCA (18 RCTs; RR=1.21; 95%CI=[1.06,1.39]; I^2=18%; p=.24; N=1952; ⊕⊕○○ low[a,e])[§] – No sign. effects as adjunctive to SSRI versus SSRI (5 RCTs; RR=1.33; 95%CI=[0.65,2.73]; I^2=76%; p=.002; N=299; ⊕○○○ very low[a,c,e])	– Similar AEs as TAU (1 RCT; RR=0.89; 95%CI=[0.35,2.24]; I^2=n.c.; N=320) – Similar AEs as invasive SHAM (1 RCT; RR=2.5; 95%CI=[0.15,40.37]; I^2=n.c.; N=17) – Similar AEs adjunctive to SSRI versus SSRI (2 RCTs; SMD=-0.37; 95%CI=[-1.2,0.47]; I^2=84%; N=150) – Sign. less AEs than SSRI (3 RCTs; SMD=-1.75; 95%CI=[-3.17,-0.32]; I^2=96%; p p<.001; N=481)[#]

Supplementary table 1: continued

2

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Electroacu-puncture	Smith 2018[51]	MDD, CSD	21 RCTs	SB: 6 PB: 3 DB: 5 AB: 16 RB: 1 OB: 12	AMSTAR: 10	HAMD BDI	2-6 weeks	Severity: – Sign. greater effects than TAU (1 RCT; SMD=-1.26; 95%CI=[-2.10,-0.43]; I^2=n.c.; N=30; ⊕○○○ very low[a,c,d,e]) – No sign. effects versus invasive SHAM (5 RCTs; SMD=0.12; 95%CI=[-0.14,0.38]; I^2=0%; p=.82; N=251; ⊕○○○ very low[a,d,e])[#] – Sign. greater effects than SSRI/TCA (10 RCTs; SMD=-0.28; 95%CI=[-0.47,-0.09]; I^2=33%; p=.14; N=995; ⊕⊕○○ low[a,e])[§] – Sign. greater effects as adjunctive to SSRI versus SSRI (5 RCTs; SMD=-0.84; 95%CI=[-1.16,-0.51]; I^2=33%; p=.20; N=274; ⊕⊕○○ low[a,e]) Remission: – No sign. effects versus invasive SHAM (2 RCTs; RR=1.23; 95%CI=[0.35,4.29]; I^2=20; p=.26; N=87; ⊕○○○ very low[a,d,e]) – Similar effects as SSRI/TCA (8 RCTs; RR=1.01; 95%CI=[0.92,1.11]; I^2=0%; p=.43; N=966; ⊕⊕○○ low[a,e])[§] – No sign. effects as adjunctive to SSRI versus SSRI (5 RCTs; RR=1.17; 95%CI=[0.75,1.80]; I^2=49%; p=.10; N=273; ⊕○○○ very low[a,d,e])	– Similar AEs as invasive SHAM (4 RCTs; RR=1.79; 95%CI=[0.99,3.25]; I^2=16%; p=.31; N=244) – Sign. less AEs as adjunctive to SSRI versus SSRI (1 RCT; SMD=-3.39; 95%CI=[-4.27,-2.50]; I^2=n.c.; N=50)
Herbs									
St. John's wort	Linde 2008[150]	MDD	29 RCTs	SB: 18 PB: 29 DB: n.r. AB: 29 RB: n.r. OB: n.r.	AMSTAR: 8	HAMD MADRS	4-12 weeks	Response (50%): – Sign. greater effects than PLACEBO (18 RCTs; RR=1.48; 95%CI=[1.23,1.77]; I^2=75%; p<.001; N=3064; ⊕⊕⊕○ moderate[c]) – Similar effects as SSRI/TCA/TECA (17 RCTs; RR=1.01; 95%CI=[0.93,1.09]; I^2=17%; p=.25; N=2810; ⊕⊕⊕○ moderate[a])	– Similar AEs as PLACEBO (14 RCTs; OR=0.98; 95%CI=[0.78,1.23]; I^2=n.r.; N=2496), – Sign. less than ADMs (14 RCTs; OR=0.56; 95%CI=[0.43,0.74]; I^2=n.r.; N=2663)

Supplementary table 1: continued 3

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
St. John's wort (continued)	Apaydin 2016[142]	MDD	35 RCTs	SB: 9 PB: 27 DB: 5 AB: 26 RB: 3 OB: 33	AMSTAR: 9	HAMD	4-32 weeks	Severity: – Sign. greater effects than PLACEBO (16 RCTs; SMD=-0.49; 95%CI=[-0.74,-0.23]; I^2=89%; p=n.r.; N=2888; ⊕⊕⊕○ moderate[c]) – Similar effects as ADM (14 RCTs; SMD=-0.03; 95%CI=[-0.21,0.15]; I^2=74%; p=n.r.; N=2248; ⊕⊕○○ low[a,c]) Response (50%): – Sign. greater effects than PLACEBO (18 RCTs; RR=1.53; 95%CI=[1.19,1.97]; I^2=79%; p=n.r.; N=2922; ⊕⊕⊕○ moderate[c]) – Similar effects as ADM (17 RCTs; RR=1.01; 95%CI=[0.90,1.14]; I^2=52%; p=n.r.; N=2776; ⊕⊕⊕○ moderate[a]) Remission: – No sign. effects versus PLACEBO (9 RCTs; RR=1.69; 95%CI=[0.63,4.55]; I^2=94%; p=n.r.; N=1419; ⊕○○○ very low[a,c,d]) – Similar effects as ADM (7 RCTs; RR=1.17; 95%CI=[0.84,1.62]; I^2=29%; p=n.r.; N=787; ⊕⊕⊕○ moderate[a]) Relapse: – No sign. effects versus PLACEBO (1 RCT; RR=0.70; 95%CI=[0.49,1.02]; I^2=n.c.; N=426; ⊕○○○ very low[a,c,d]) – Similar effects as ADM (1 RCT; RR=4.17; 95%CI=[0.47,33.33]; I^2=n.c.; N=241; ⊕○○○ very low[a,c,d])	– Similar AEs as PLACEBO (13 RCTs; OR=0.83; 95%CI=[0.62,1.13]; I^2=n.r.; N=2600), – Sign. less than ADMs (11 RCTs; OR=0.67; 95%CI=[0.56,0.81]; I^2=n.r.; N=1946)
Saffron	Hausenblas 2013[147]	MDD	5 RCTs	SB: 5 PB: 5 DB: 5 AB: 5 RB: n.r. OB: n.r	AMSTAR: 7	HAMD	6-8 weeks	Severity: – Sign. greater effects than PLACEBO (2 RCTs; SMD=-1.62; 95%CI=[-2.14,-1.10]; I^2=0%; p=n.r.; N=71; ⊕○○○ very low[c,d,e]) – Similar effects as SSRI/TCA (3 RCTs; SMD=-0.15; 95%CI=[-0.52,0.22]; I^2=0%; p=n.r.; N=106; ⊕○○○ very low[c,d,e])	– No serious AEs

Supplementary table 1: continued

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	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Curcuma	Ng 2017[155]	MDD, CSD	6 RCTs	SB: 3 PB: 3 DB: 3 AB: 2 RB: 2 OB: 1	AMSTAR: 6	HAMD, BDI	4-8 weeks	Severity: – Sign. greater effects than PLACEBO (6 RCTs; SMD=-0.34; 95%CI=[-0.56,-0.13]; I^2=0%; p=.82; N=377; ⊕○○○ very low[a,d,e])	– No serious AEs
Chinese herbs	Yeung 2014[162]	MND	21 RCTs	SB: 5 PB: 11 DB: 9 AB: 21 RB: 20 OB: 18	AMSTAR: 4	HAMD	6-8,5 weeks	Severity: – Sign. greater effects than PLACEBO (4 RCTs; SMD=-1.27; 95%CI=[-1.67,-0.87]; I^2=44%; p=.14; N=251; ⊕○○○ very low[b,e])[#] – Similar effects as SSRI/SNRI/TCA/TECA (9 RCTs; SMD=0.17; 95%CI=[-0.12,0.46]; I^2=82%; p<.001; N=1962; ⊕○○○ very low[b,c,e])[#] Response (30%): – Sign. greater effects than PLACEBO (3 RCTs; RR=2.99; 95%CI=[2.18,4.10]; I^2=0%; p=.53; N=281; ⊕○○○ very low[c,d,e]) – Similar effects as SSRI/SNRI/TCA/TECA (10 RCTs; RR=1.00; 95%CI=[0.94,1.07]; I^2=42%; p=.08; N=1635; ⊕○○○ very low[b,c,e])	– Similar AEs as PLACEBO (3 RCTs; RR=1.29; 95%CI=[0.86,1.95]; I^2=61%; p= n.r.; N=n.r.) – Sign. less AEs than ADMs (29 RCTs; RR=0.23; 95%CI=[0.16,0.33]; I^2=59%; p= n.r.; N=n.r.)
Light therapy									
Bright white light	Tuunainen 2004[161]	MND	18	SB: 2 PB: 0 DB: 13 AB: 1 RB: n.r. OB: n.r.	AMSTAR: 9	HAMD, GDS	1 day - 8 weeks	Severity: – Sign. greater effects than adjunctive to ADM than SHAM + ADM (18 RCTs; SMD=-0.20; 95%CI=[-0.38,-0.01]; I^2=60%; p<.001; N=505; ⊕○○○ very low[a,c,d]) Response: – No effects than adjunctive to ADM than SHAM + ADM (3 RCTs; RR=0.94; 95%CI=[0.61,1.46]; I^2=69%; p=.004; N=71; ⊕○○○ very low[a,c,d])	– No serious AEs
	Martensson 2015[152]	SAD	8 RCTs	N.r.	AMSTAR: 5	HAMD, SIGH-SAD	2-6 weeks	Severity: – Sign. greater effects than SHAM (8 RCTs; SMD=-0.54; 95%CI=[-0.95,-0.13]; I^2=n.r.; N=179; ⊕○○○ very low[b,c,d,e])	– N.r.

Supplementary table 1: continued 5

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Meditative movement therapies									
Dance therapy	Meekums 2015[153]	MND	2 RCTs	SB: 1 PB: 0 DB: 1 AB: 2 RB: 2 OB: 1	AMSTAR: 9	HAMD	4-12 weeks	Severity: – Sign. greater effects as adjunctive to ADM versus ADM (2 RCTs; SMD=-1.06; 95%CI=[-1.46,-0.65]; I^2=0%; p=.70; N=107; ⊕⊕○○ low[d,c])[#]	– No serious AEs
Qi Gong and Tai Chi	Liu 2015[151]	MDD, CSD	5 RCTs	N.r.	AMSTAR: 4	HAMD, GDS, CESD	10-16 weeks	Severity: – Sign. greater effects than TAU for Qi Gong (2 RCTs; SMD=-1.27; 95%CI=[-2.09,-0.45]; I^2=74%; p=.05; N=120; ⊕○○○ very low[b,c,d,e])* but no sign. effects for Tai Chi (3 RCTs; SMD=-0.61; 95%CI=[-1.55,0.34]; I^2=78%; p=.01; N=120; ⊕○○○ very low[b,c,d,e])*	– N.r.
Yoga	Cramer 2013[145]	MDD, CSD	5 RCTs	SB: 0 PB: 0 DB: 1 AB: 1 RB: 5 OB: 3	AMSTAR: 8	HAMD, ZGS, GDS, BDI	4-8 weeks	Severity: – Sign. greater effects than TAU (4 RCTs; SMD=-1.03; 95%CI=[-1.90,-0.16]; I^2=82%; p<.001; N=141; ⊕○○○ very low[a,c,d,e])* – Sign. greater effects than EXERCISE (2 RCTs; SMD=-0.59; 95%CI=[-1.90,-0.16]; I^2=68%; p=.08; N=108; ⊕○○○ very low[a,c,d,e])	– N.r.
Mindfulness-based interventions									
MBCT	Strauss 2014[159]	MDD	4 RCTs	N.r.	AMSTAR: 5	HAMD, BDI	8-12 weeks	Severity: – Sign. greater effects than TAU (3 RCTs; SMD=-0.97; 95%CI=[-1.81,-0.12]; I^2=72%; p=.03; N=115; ⊕○○○ very low[b,c,d])[§] – Similar effects as CBT (1 RCT; SMD=-0.16; 95%CI=[-0.75,0.43]; I^2=n.c.; N=45; ⊕○○○ very low[b,c,d])[§]	– N.r.

Supplementary table 1: continued

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	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
MBCT (continued)	Kuyken 2016[149]	MDD	4 RCTs	SB: 4 PB: 0 DB: 3 AB: 4 RB: 4 OB: 4	AMSTAR: 6	SCID, BDI	60 weeks	Relapse: – Sign. greater effects than ADM (4 RCTs; HR=0.77; 95%CI=[0.60,0.98]; I^2=0%; p=.92; N=669; ⊕⊕⊕○ moderate[d])	– No serious AEs
MBSR	Bo 2017[144]	CSD	5 RCTs	SB: 0 PB: 0 DB: 1 AB: 5 RB: 5 OB: n.r.	AMSTAR: 6	HAMD, GDS	8-12 weeks	Severity: – Sign. greater effects than TAU/enhanced TAU (5 RCTs; SMD=-1.09; 95%CI=[-1.41,-0.76]; I^2=56%; p=.06; N=396; ⊕⊕○○ low[a,c])	– N.r.
Music therapy									
Music therapy	Zhao 2016[163]	MND	8 RCTs	SB: 0 PB: 0 DB: 0 AB: 8 RB: 7 OB: 8	AMSTAR: 7	HAMD, GDS, HADS	4-52 weeks	Severity: – Sign. greater effects than TAU (5 RCTs; SMD=-0.57; 95%CI=[-1.03,-0.11]; I^2=76%; p<.001; N=244; ⊕○○○ very low[a,c,d])* – Sign. greater effects as adjunctive to ADM versus ADM (3 RCTs; SMD=-0.88; 95%CI=[-1.07,-0.68]; I^2=0%; p=.63; N=257; ⊕⊕○○ low[a,e])*	– N.r.
	Aalbers 2017[139]	MDD, CSD	8 RCTs	SB: 2 PB: 1 DB: 1 AB: 7 RB: 2 OB: 3	AMSTAR: 11	HAMD	12 weeks	Severity: – Sign. greater effects than TAU (4 RCTs; SMD=-0.98; 95%CI=[-1.69,-0.27]; I^2=83%; p<.001; N=219; ⊕○○○ very low[a,c,d]) – Similar effects as CBT (4 RCTs; SMD=-1.28; 95%CI=[-3.57,1.02]; I^2=96%; p<.001; N=131; ⊕○○○ very low[a,c,d])	– Similar AEs as TAU (1 RCT; OR=0.45; 95%CI=[0.02,11.46]; I^2=n.c.; N=79)

Supplementary table 1: continued 7

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Religious/spiritual therapies									
Faith-adapted CBT	Anderson 2015[141]	MDD, CSD	9 RCTs	SB: 0 PB: 0 DB: 4 AB: 4 RB: 9 OB: 0	AMSTAR: 7	N.r.	N.r.	Severity: – Sign. greater effects than TAU (6 RCTs; SMD=-0.69; 95%CI=[-1.21,-0.17]; I^2=82%; p=.004; N=304; ⊕○○○ very ow[a,c,d])[§] – Sign. greater effects than CBT (6 RCTs; SMD=-0.54; 95%CI=[-0.82,-0.25]; I^2=0%; p=.78; N=199; ⊕⊕○○ low[a,e])[§]	– N.r.
Supplements									
Inositol	Mukai 2014[155]	MDD	2 RCTs	N.r.	AMSTAR: 4	HAMD	4 weeks	Severity: – No sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (2 RCTs; SMD=0.17; 95%CI=[-0.33,0.66]; I^2=0%; p=.93; N=78; ⊕○○○ very low[b,d,e])	– Similar AEs as adjunctive to ADM (1 RCT; RR=3.21; 95%CI=[0.14,72.55]; I^2=n.c.; N=36)
Omega-3 fatty acids	Appleton 2015[143]	MDD	26 RCTs	SB: 15 PB: 6 DB: 19 AB: 8 RB: 16 OB: 25	AMSTAR: 9	HAMD, MADRS, BDI, GDS, HSCL, IDS	4-16 weeks	Severity: – Sign. greater effects than PLACEBO (25 RCTs; SMD=-0.30; 95%CI=[-0.50,-0.10]; I^2=59%; p<.001; N=1373; ⊕○○○ very low[a,c,d,e]) – Similar effects as SSRI (1 RCT; SMD=-0.08; 95%CI=[-0.70,0.54]; I^2=n.c.; N=40; ⊕○○○ very low[a,c,d,e]) Response (50%): – No sign. effects versus PLACEBO (15 RCTs; OR=1.39; 95%CI=[0.95,2.04]; I^2=6%; p=.38; N=611; ⊕○○○ very low[a,d,e]) – Similar effects as SSRI (1 RCT; OR=1.23; 95%CI=[0.35,4.31]; I^2=n.c.; N=40; ⊕○○○ very low[a,c,d,e]) Remission: – No sign. effects versus PLACEBO (6 RCTs; OR=1.38; 95%CI=[0.87,2.20]; I^2=7%; p=.37; N=426; ⊕○○○ very low[a,d,e])	– Similar AEs as PLACEBO (19 RCT; OR=1.24; 95%CI=[0.95,1.62]; I^2=0%; p=.66; N=1207)

Supplementary table 1: continued

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	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Probiotics	Huang 2016[148]	MDD	1 RCTs	SB: 1 PB: 1 DB: 1 AB: 1 RB: 1 OB: 1	AMSTAR: 7	BDI	8 weeks	Severity: – Sign. greater effects than PLACEBO (1 RCT; SMD=-0.73; 95%CI=[-1.37,-0.09]; I^2=n.c.; N=40; ⊕○○○ very low[c,d,e])	– N.r.
S-adenosyl methionine	Galizia 2016[146]	MDD	8 RCTs	SB: 2 PB: 4 DB: 4 AB: 3 RB: 8 OB: 8	AMSTAR: 9	HAMD	6-12 weeks	Severity: – No sign. effects versus PLACEBO (2 RCTs; SMD=-0.54; 95%CI=[-1.54,0.46]; I^2=72%; p=.06; N=142; ⊕○○○ very low[c,d,e]) – Similar effects as SSRI/TCA (5 RCTs; SMD=-0.01; 95%CI=[-0.22,0.21]; I^2=43%; p=.14; N=821; ⊕⊕○○ low[a,e])[§] – Sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (1 RCT; SMD=-0.59; 95%CI=[-1.06,-0.12]; I^2=n.c.; N=73; ⊕○○○ very low[c,d,e])[#]	– Similar AEs as PLACEBO (2 RCTs; RR=0.70; 95%CI=[0.16,3.01]; I^2=n.r.; N=142) – Similar AEs as adjunctive to ADM (1 RCT, RR=0.58; 95%CI=[0.10,3.28]; I^2=n.c.; N=73) – Similar AEs as ADM (2 RCTs, RR=0.75; 95%CI=[0.20,2.79]; I^2=n.r.; N=52)
Tryptophan	Shaw 2002[158]	CSD	2 RCTs	SB: 2 PB: 2 DB: n.r. AB: 1 RB: n.r. OB: n.r	AMSTAR: 7	HAMD	3-12 weeks	Response: – Sign. greater effects than PLACEBO (2 RCTs; OR=4.10; 95%CI=[1.28,13.15]; I^2=0%; p=.32; N=46; ⊕○○○ very low[a,d,e])	– Sign. greater AEs than PLACEBO (2 RCTs; OR=7.41; 95%CI=[1.01,54.19]; I^2=0%; p=1.0; N=64)
Vitamin B9 (Folate)	Taylor 2003[160]	MDD	2 RCTs	SB: 0 PB: 2 DB: n.r. AB: 2 RB: n.r. OB: n.r.	AMSTAR: 8	HAMD	10-24 weeks	Severity: – Sign. greater effects as adjunctive to SSRI versus PLACEBO + SSRI (2 RCTs; SMD=-0.40; 95%CI=[-0.76,-0.05]; I^2=0%; p=.96; N=124; ⊕○○○ very low[a,c,d,e])[#]	– Similar AEs as PLACEBO (1 RCT; RR=0.76; 95%CI=[0.55,1.05]; I^2=n.c.; N=127)

Supplementary table 1: continued 9

	Included meta-analysis	Diag-nosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instru-ments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Vitamin B9 (Folate) (continued)	Almeida 2015[140]	MDD	5 RCTs	SB: 4 PB: 5 DB: 4 AB: 3 RB: 4 OB: 1	AMSTAR: 6	HAMD, MADRS	4-52 weeks	Severity: – No sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (5 RCTs; SMD=-0.12; 95%CI=[-0.45,0.22]; I^2=66%; p=.02; N=505; ⊕○○○ very low[c,d,e]) Response (50%): – No sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (4 RCTs; OR=1.18; 95%CI=[0.49,2.83]; I^2=73%; p=.001; N=478; ⊕○○○ very low[c,d,e]) Relapse: – Sign. greater effects as adjunctive to SSRI versus PLACEBO + SSRI (1 RCT, OR=0.33; 95%CI=[0.12, 0.94]; I^2=n.c.; N=153; ⊕○○○ very low[c,d,e])	– N.r.
Vitamin D	Shaffer 2014[157]	MDD, CSD	2 RCTs	SB: 0 PB: 0 DB: 1 AB: 0 RB: n.r. OB: n.r.	AMSTAR: 7	HAMD, BDI	8 weeks	Severity: – Sign. greater effects than PLACEBO (2 RCTs; SMD=-0.60; 95%CI=[-1.19,-0.01]; I^2=n.r.; N=149; ⊕○○○ very low[a,c,d,e])	– N.r.
Zinc	Schefft 2017[156]	MDD	3 RCTs	N.r.	AMSTAR: 5	HAMD, BDI	6-12 weeks	Severity: – Sign. greater effects as adjunctive to SSRI/TCA versus SSRI/TCA (3 RCTs; SMD=-0.66; 95%CI=[-1.06,-0.26]; I^2=0%; p=.45; N=104; ⊕○○○ very low[b,d,e])	– N.r.

Abbreviations: AB: Attrition bias; ADM: Antidepressant medication; AE: Adverse events; AMSTAR: Assessment of the Methodological Quality of Systematic Reviews tool; BDI: Beck Depression Inventory; CBT: Cognitive Behavioral Therapy; CESD: Center for Epidemiologic Studies Depression Scale; CSD: Clinical symptoms of depression (questionnaire based diagnosis); DB: Detection bias; GDS: Geriatric Depression Scale; HADS: Hospital Anxiety and Depression Scale; HAMD: Hamilton Rating Scale for Depression; HR: Hazard ratio; HSCL: Hopkins Symptom Checklist Depression Scale; I^2: Heterogeneity; IDS: Inventory of Depressive Symptomology; MADRS: Montgomery-Asberg Depression Rating Scale; MBCT: Mindfulness-based Cognitive Therapy; MBSR: Mindfulness-based Stress Reduction; MDD: Major depressive disorder; MND: Mixed non-seasonal depression; N: Number of patients; N.c.: Not calculable because of only one included RCT; N.r.: Not reported; OB: Other bias; OR: Odds ratio; PB: Performance bias; RCT: Randomized controlled trial; RB: Reporting bias; RR: Risk ratio; SAD: Seasonal Affective Disorder; SB: Selection bias; SCID: Structured Clinical Interview; SIGH-SAD: Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorders; SMD: Standard mean difference; SSRI: Selective serotonin reuptake inhibitors; SNRI: Serotonin-norepinephrine reuptake inhibitor; TAU: Treatment as usual; TCA: Tricyclic antidepressants; TECA: Tetracyclic antidepressants; ZGS: Zung Depression Scale.

Supplementary table 1: continued

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Notes:
*Newly calculated effect measure of selected RCTs meeting eligibility criteria;
[#]Newly calculated effect measure from mean differences (MDs);
[§]Newly calculated effect measure from originally separate/combined analyses.
[a]Downgraded one level because of study limitations (overall unclear or high risk of bias);
[b]Downgraded two levels because of study limitations (overall unclear or high risk of bias) and limitations of the meta-analysis (AMSTAR ≤ 5);
[c]Downgraded one level because of inconsistency (significant heterogeneity or no replication of the results);
[d]Downgraded one level because of imprecision (confidence interval includes negligible or no effects or fewer than 250 participants were included in total);
[e]Downgraded one level because of a probably high risk of publication bias.

Supplementary information to "Complementary therapies for clinical depression: an overview of systematic reviews"
by Heidemarie Haller, Dennis Anheyer, Holger Cramer, Gustav Dobos

Supplementary table 2: Detailed AMSTAR ratings.

	Apriori design	Two data extractor and consensus	Comprehensive literature search	Inclusion of grey literature	List of included and excluded studies	Characteristics of studies provided	Adequate risk of bias assessment	Appropriate conclusions	Appropriate data syntheses	Assessment of publication bias	Conflict of interest / funding statement	Sum
Aalbers 2017[139]	1	1	1	1	1	1	1	1	1	1	1	11
Almeida 2015[140]	0	1	1	0	0	1	1	1	1	0	0	6
Anderson 2015[141]	0	0	1	1	0	1	1	1	1	1	0	7
Apaydin 2016[142]	1	1	1	1	0	1	1	1	1	0	1	9
Appleton 2015[143]	0	1	1	1	1	1	1	1	1	1	0	9
Bo 2017[144]	0	0	1	0	0	1	1	1	1	1	0	6
Cramer 2013[145]	0	1	1	1	1	1	1	1	0	1	0	8
Galizia 2016[146]	0	1	1	1	1	1	1	1	1	1	0	9
Hausenblas 2013[147]	0	1	1	1	0	1	1	1	1	0	0	7
Huang 2013[148]	0	1	1	0	0	1	1	1	1	1	0	7
Kuyken 2016[149]	0	0	1	0	0	1	1	1	1	1	0	6
Linde 2008[150]	0	1	1	1	0	1	1	1	1	1	0	8
Liu 2015[151]	0	0	1	0	0	1	0	1	0	1	0	4
Martensson 2015[152]	0	1	1	0	1	1	0	1	0	0	0	5
Meekums 2015[153]	0	1	1	1	1	1	1	1	1	1	0	9
Mukai 2014[154]	0	1	1	0	0	1	0	1	0	0	0	4
Ng 2017[155]	0	1	1	0	0	1	1	1	1	0	0	6
Schefft 2017[156]	0	1	1	0	0	1	0	1	1	0	0	5
Shaffer 2014[157]	0	1	1	1	1	1	1	1	0	0	0	7
Shaw 2002[158]	0	1	1	1	1	1	0	1	1	0	0	7
Smith 2018[51]	1	1	1	1	1	1	1	1	1	1	0	10
Strauss 2014[159]	0	0	1	1	0	1	0	0	1	1	0	5
Taylor 2003[160]	0	1	1	1	1	1	1	1	1	0	0	8
Tuunainen 2004[161]	0	1	1	1	1	1	1	1	1	1	0	9
Yeung 2014[162]	0	1	1	0	0	0	1	1	0	0	0	4
Zhao 2016[163]	0	1	1	0	0	1	1	1	1	1	0	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N.a.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N.a.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	19-29
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N.a.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N.a.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-50
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

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