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Complementary therapies for clinical depression: an overview of systematic reviews

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Manuscripts

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2 1 **Complementary therapies for clinical depression: an overview of systematic reviews**
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1
2 **18 Abstract**
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5 **19 Objectives:** As clinical practice guidelines vary widely in their search strategies and recommendations
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7 **20** of complementary and alternative medicine (CAM) for depression, this overview aimed at
8
9 **21** systematically summarizing the level-1 evidence on CAM for patients with a clinical diagnosis of
10
11 **22** depression.
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14 **23 Methods:** PubMed, PsycInfo and Central were searched for meta-analyses of randomized controlled
15
16 **24** trials (RCTs) until June 30, 2018. Outcomes included depression severity, response, remission,
17
18 **25** relapse, and adverse events. The quality of evidence was assessed according to GRADE considering
19
20 **26** the methodological quality of the RCTs (ROB) and meta-analyses (AMSTAR), inconsistency,
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22 **27** indirectness, imprecision of the evidence, and the potential risk of publication bias.
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26 **28 Results:** The literature search revealed 26 meta-analyses conducted between 2002 and 2018 on 1 to
27
28 **29** 49 RCTs in major, minor, and seasonal depression. In patients with mild to moderate major
29
30 **30** depression, moderate quality evidence suggested the efficacy of St. John's wort towards placebo and
31
32 **31** its comparative effectiveness towards standard antidepressants for the treatment for depression
33
34 **32** severity and response rates, while St. John's wort caused significant less adverse events. In patients
35
36 **33** with recurrent major depression, moderate quality evidence showed that Mindfulness-based
37
38 **34** Cognitive Therapy was superior to standard antidepressant drug treatment for the prevention of
39
40 **35** depression relapse. Other CAM evidence was considered as having low or very low quality.
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45 **36 Conclusions:** The effects of all but two CAM treatments found in studies on clinical depressed
46
47 **37** patients based on low to very low quality of evidence. The evidence has to be downgraded mostly
48
49 **38** due to avoidable methodological flaws of both the original RCTs and meta-analyses not following the
50
51 **39** CONSORT and PRISMA guidelines. Further research is needed.
52
53

54 **40 Keywords:** Depression, Complementary Therapies, Treatment Outcome, Safety, Systematic Review
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1
2 41 **Strengths and limitations of this study**
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- 4 42 ▪ This systematic overview included the comprehensive literature search of important CAM
5
6 43 topics defined by the Cochrane Collaboration.
7
8 44 ▪ The inclusion criteria were restricted to meta-analyses of RCTs of patients with a clinical
9
10 45 diagnosis of depression.
11
12
13 46 ▪ The quality of evidence from meta-analyses was assessed according to GRADE.
14
15 47 ▪ There is a possible lack of evidence of newer RCTs that have not been analysed by the
16
17 48 included meta-analyses.
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49 Introduction

50 Depression is one of the most prevalent psychiatric disorders, with about 25% of women and 12% of
51 men suffering from at least one depressive episode during their lifetime.¹⁻³ According to the criteria
52 for diagnosis recommended by the American Psychiatric Association (APA), depressive disorders can
53 be distinguished by their degree of severity or duration and are also characterized by a high
54 comorbidity and an increase of psychological strain for the affected person.⁴ It is evident, that a
55 strong comorbid connection to several chronic conditions like addictions,⁵ neurodegenerative
56 diseases,^{6,7} or different psychiatric diseases⁸⁻¹¹ exists. This leads depressive disorders as one of the
57 leading causes of disability worldwide.¹²

58 The most commonly used treatments for depression are antidepressants, psychotherapy, or a
59 combination of drugs and psychotherapy. While both therapies have been shown to be effective,¹³⁻¹⁵
60 more recent meta-analyses also found high dropout and low remission rates¹⁶⁻²¹ as well as clinically
61 significant differences between antidepressant drugs and placebos only for patients at the upper end
62 of the very severely depressed category.²² This may lead patients to search for alternatives.

63 Increasing mainstream use of complementary and alternative medicine (CAM) support this trend,
64 particularly for different physical conditions with comorbid affective disorders.²³⁻²⁷ While some
65 complementary therapies have become a promising adjunct in the standard treatment of
66 depression,^{28,29} others are known for their possible side effects or interactions with standard drugs.²⁹

67 Recent clinical practice guidelines, in addition, vary widely in their search strategies and resulting
68 recommendations for CAM treatments. While the ACP,³⁰ APA,³¹ and CANMAT guideline³² provide a
69 more comprehensive overview and critical appraisal of CAM treatments, the DGPPN,³³ NICE,³⁴ and
70 WFSBP³⁵ guidelines mainly focus on St. John's Wort and light therapy. Possible effects and risks of
71 further CAM therapies are not discussed. Thus, the purpose of this overview is to provide a
72 comprehensive search strategy of relevant CAM terms and systematically summarize the existing
73 level-1 evidence for clinical depression as a basis for further guideline recommendations on the
74 efficacy, effectiveness, and safety of CAM therapies.

75 **Methods**

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

79 **Inclusion and exclusion criteria**

- 80 – Types of studies: To be eligible, articles had to be systematic reviews with meta-analyses of
81 randomized controlled clinical trials (RCTs) published in peer-reviewed journals. Conference
82 abstracts or unpublished work were excluded as well as reviews summarizing evidence
83 narratively. In cases of including same or similar original studies, only the review with the
84 most recent, most comprehensive search was included. When systematic reviews reported
85 results of RCTs as well as of designs of lower evidence levels, they were considered only if
86 separate meta-analyses for the included RCTs were performed.
- 87 – Types of participants: Only reviews of patients with a diagnosis of major depression or
88 dysthymia were eligible as well as reviews including patients/general population samples
89 with mild depressive symptoms above a clinical cut off or seasonal patterns. In contrast,
90 reviews studying depressive symptoms within specific subpopulations of substance-induced
91 or demented patients, secondary depression due to another medical condition (e.g. post-
92 stroke, cancer, or pain patients), bipolar disorders, or females with premenstrual dysphoric
93 disorder or postpartum depression were excluded. Further restrictions regarding the
94 diagnostic criteria or procedures, regarding age, gender, duration of the condition, or
95 symptom intensity were not applied.
- 96 – Types of interventions: Reviews investigating the effectiveness and/or safety of a single,
97 adjunctive or combined CAM treatment were included. For the classification of CAM
98 treatments the definition of the US National Institutes of Health³⁹ was followed. CAM
99 interventions have to be compared against treatment as usual (TAU)/waiting list,
100 placebo/sham, or standard medical care.

1
2 101 – Types of outcomes: Reviews were eligible if they assessed at least one measure of
3
4 102 effectiveness such as severity of depressive symptoms, response rate (generally defined as a
5
6 103 50% decrease in depression scores after a period of up to 12 weeks of treatment),³⁰
7
8 104 remission rate (generally defined as a period of up to 12 weeks during which a patient is
9
10 105 asymptomatic or has only few symptoms to a very mild degree).⁴⁰ relapse rates, and/or a
11
12 106 measure of safety such as number of adverse events (AE), drug interactions, or numbers
13
14 107 needed to harm for study withdrawal due to side effects.
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16
17

18 108 **Search strategy**

19
20 109 Electronic literature was systematically searched via PubMed, PsycInfo and Central from their
21
22 110 inception to January 31, 2018 without restrictions regarding time or language (Table 1). Search terms
23
24 111 for CAM treatments were selected in accordance with Cochrane recommendations.⁴¹ Additional
25
26 112 manual search included reference lists of previously published reviews^{14 28 29 42} and clinical practice
27
28 113 guidelines.³⁰⁻³⁵ Using PubMed Informer,⁴³ the search was updated until June 30, 2018.
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32 114 **Study selection process**

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34 115 To assess eligibility, articles were selected by screening titles and abstracts independently by two
35
36 116 authors (HH and DA). Any abstract considered potentially eligible by at least one author was read in
37
38 117 full to decide on its eligibility. Disagreements were rechecked with a third author (HC) until
39
40 118 consensus was achieved.
41
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44 119 **Data extraction and quality assessment**

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46 120 Two authors (HH and DA) independently extracted data on the characteristics of the reviews
47
48 121 including the type of the intervention, the year of publication, the number and quality of the original
49
50 122 RCTs, the total number and age of the participants, and effectiveness and safety outcomes. The
51
52 123 quality of the included reviews was assessed using the Assessment of the Methodological Quality of
53
54 124 Systematic Reviews (AMSTAR) tool.⁴⁴ The AMSTAR tool consists of 11 items asking about important
55
56 125 methodological quality criteria of systematic reviews such as: a published apriori design, duplicate
57
58 126 study selection and data extraction, a comprehensive literature search including grey literature, a list
59
60 127 of included and excluded studies, summarized characteristics and quality assessment of included

1
2 128 studies, assessment of publication bias, appropriate method of data syntheses and deducing
3
4 129 conclusions, and a conflict of interests statement. AMSTAR has shown good construct validity and
5
6 130 inter-rater reliability. The Intraclass Correlation Coefficient (ICC) of the total AMSTAR score of 11
7
8 131 points was reported as 0.84.⁴⁵ For this analysis, the two authors (HH and DA) who independently
9
10 132 assessed AMSTAR reached an ICC of 0.96. Disagreements regarding content or quality of the reviews
11
12
13 133 were rechecked with a third author (HC) and resolved by agreement.

16 134 **Data synthesis**

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18
19 135 Results were pooled qualitatively by type of the intervention. Outcomes had to be calculated as
20
21 136 standard mean differences (SMDs), risk ratios (RRs), hazard ratios (HR), or odds ratios (ORs). If meta-
22
23 137 analyses displayed mean differences (MDs), SMDs were calculated using Review Manager Software
24
25 138 (RevMan, Version 5.3, The Nordic Cochrane Centre, Copenhagen) for better comparability of the
26
27
28 139 results. RevMan was also used to exclude SMDs/RRs/HRs/ORs of selective RCTs that did not fulfil
29
30 140 eligibility criteria of this overview. Effect sizes were classified according to Cohen as SMD = 0.2 – 0.5 =
31
32 141 small effect, SMD = 0.5 – 0.8 = medium effect, and SMD > 0.8 = large effect ⁴⁶ with higher reduction
33
34 142 of/improvement in depression scores represented by more negative SMDs or RRs/HRs/ORs less than
35
36
37 143 1. According to the NICE guideline, a SMD of ≥ 0.5 was considered as a clinically relevant reduction of
38
39 144 depression severity.⁴⁷ Statistical heterogeneity between studies was assessed by Chi² statistics with a
40
41 145 p-value of $\leq .10$ indicating significant heterogeneity. The magnitude of heterogeneity was categorized
42
43 146 by I² statistics with I² > 25% = moderate heterogeneity, I² > 50% = substantial heterogeneity, and I² >
44
45 147 75% = considerable heterogeneity.³⁸

48 148 **Quality of evidence**

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51 149 The quality of evidence was assessed according to the Grades of Recommendation, Assessment,
52
53 150 Development, and Evaluation (GRADE) approach⁴⁸ individually by two authors (HH and DA).
54
55
56 151 Disagreements were rechecked with a third author (HC) until consensus was achieved. For each
57
58 152 outcome, the evidence can be graded as high, moderate, low or very low. Evidence from RCTs is
59
60 153 initially assessed as high, but can be downgraded by one level for serious or two levels for very

1
2 154 serious limitations of the study quality (of both RCTs and meta-analyses), inconsistency of the results,
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4 155 indirectness of the evidence, imprecision of the results, and a potential risk of publication bias.⁴⁸
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8 156 **Results**

9 10 157 **Study selection**

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12 158 A total of 3582 potentially eligible articles were identified by electronic database search. One
13
14 159 additional review was retrieved from manual search,⁴⁹ one from the updated search until June
15
16 160 2018.⁵⁰ After removing duplicates, 2639 articles were excluded by screening of titles and abstracts.
17
18 161 The remaining 117 articles were read in full, of which further 91 reviews had to be excluded (Figure
19
20 162 1). Reasons for exclusion comprised 55 reviews where newer and/or more comprehensive reviews
21
22 163 on higher quality evidence were available.^{49 51-104} Further 15 reviews have to be excluded as they
23
24 164 systematically summarized evidence but did not performed a meta-analysis mostly due to clinical
25
26 165 heterogeneity or a limited number of available RCTs.¹⁰⁵⁻¹¹⁹ Eight reviews were excluded as they
27
28 166 included mixed depressive samples of bipolar or postpartum cases and did not provide (data for)
29
30 167 subgroup analyses for patients with the defined depression criteria.¹²⁰⁻¹²⁷ Another six reviews
31
32 168 contained community samples with non-clinical depression or physically ill patients with comorbid
33
34 169 depressive symptoms but displayed no data for patients with a primary diagnosis of depression.¹²⁸⁻¹³³
35
36 170 Four reviews performed meta-analyses on both RCTs and non-RCTs and did not perform subgroup
37
38 171 analyses or extracted sufficient data for post hoc analyses.¹³⁴⁻¹³⁷ Three of the reviews analysed
39
40 172 standard instead of complementary therapies and were therefore be excluded. Finally, 26 meta-
41
42 173 analyses could be included and reviewed.^{50 138-162}
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49 174 **Review characteristics and quality**

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51 175 Characteristics and quality appraisal of the included meta-analyses are summarized in the
52
53 176 Supplementary Table 1. Meta-analyses were conducted between 2002 and 2018 and included
54
55 177 between 1 to 49 RCTs on 40 to 7104 adult patients. Meta-analyses on children and adolescents were
56
57 178 not available or did not meet inclusion criteria. Samples mostly consisted of patients suffering from
58
59 179 major depressive disorder^{139-142 144-150 153 155 156 158 159} but also included patients with mixed diagnoses
60

1
2 180 of non-seasonal depression,^{50 152 161 162} patients with a diagnosis of seasonal depression,¹⁵¹ and
3
4 181 patients with mild to severe symptoms of depression above a clinical cut-off.^{138 140 143 144 150 154 156 157} All
5
6 182 but one meta-analysis¹⁴⁰ reported pooled outcomes based on common standardized questionnaires
7
8 183 or diagnostic interviews. Effects were analysed mostly up to 12 weeks of treatment (short-term),
9
10 184 except for four meta-analyses that included RCTs with effects reported up to 16, 24, or 32 weeks^{50 141}
11
12
13 185 ^{142 150 159} and further three meta-analyses with long-term analyses equal to or greater than one year
14
15 186 ^{148 156 162}. The AMSTAR total scores of the included meta-analyses ranged between 4 and 11 points
16
17 187 with a median quality of 7 points. The individual AMSTAR-ratings are reported in the Supplementary
18
19
20 188 Table 2.

189 **Synthesis of results**

190 ***Acupuncture***

191 *Manual acupuncture*

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

202 *Electroacupuncture*

203 For electroacupuncture, the same Cochrane review⁵⁰ revealed very low quality of evidence for the
204 comparisons to TAU and invasive sham for both outcomes, severity (Figure 2) and remission (Figure
205 4), because of serious limitations of the quality of the RCTs, imprecision, and a high risk of publication

1
2 206 bias. For electroacupuncture monotherapy in comparison to standard antidepressants, low quality
3
4 207 evidence homogeneously suggested significant greater effects for severity and similar effects for
5
6 208 remission. As an adjunctive treatment to antidepressants, electroacupuncture effectiveness was
7
8 209 supported by low quality of evidence showing a significant greater consistent and precise effect for
9
10 210 depression severity. Although the mean adjunctive effect can be considered as large, the analysis
11
12 211 based on only one RCT with overall low risk of bias and 4 RCTs of lower methodological quality that
13
14 212 missed to include adjunctive sham acupuncture. For remission rates, very low quality of evidence
15
16 213 suggested no effects in adjunction to antidepressants. In addition, one RCT showed significant less
17
18 214 AEs when electroacupuncture was added to standard antidepressants.
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22 215 **Aromatherapy**

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24
25 216 The literature search revealed no meta-analysis on aromatherapy. A recent systematic review
26
27 217 detected no RCTs in patients with a primary diagnosis of depression. However, two out of five of the
28
29 218 reviewed studies on inhalation aromatherapy and five out of eight studies on aromatherapy massage
30
31 219 have found significant anti-depressive effects in mixed patient samples and healthy adults.¹¹⁶
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35 220 **Biofeedback**

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38 221 No meta-analysis on biofeedback was conducted to date. A recent systematic review revealed only
39
40 222 one RCT on the defined inclusion criteria for depression showing some effects in contrast to sham
41
42 223 psychotherapy.¹¹⁷
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45 224 **Herbs**

46 225 *St. John's wort (Hypericum perforatum)*

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51 226 The effectiveness of St. John's wort was meta-analysed by a Cochrane review of 29 RCTs¹⁴⁹ and a
52
53 227 more recent, higher quality meta-analysis of 35 RCTs.¹⁴¹ In comparison to placebo, St. John's wort
54
55 228 showed moderate quality evidence of significant greater reductions of depression severity (Figure 2)
56
57 229 and response rates (Figure 3). The evidence had to be downgraded due to significant heterogeneity
58
59 230 because of higher effects in studies from German-speaking countries than in those from the US or
60
231 other European countries. In contrast, very low quality of evidence suggested no superiority to

1
2 232 placebo for remission (Figure 4) and response rates (Figure 5). In comparison to standard
3
4 233 antidepressants, St. John's wort showed comparable severity reductions, response, remission, and
5
6 234 relapse rates. The quality of the evidence of the meta-analyses of severity and relapse rates had to
7
8 235 be downgraded to low and very low, respectively. The evidence of the response and remission rates
9
10 236 was considered as moderate quality showing the same results in both German and studies from
11
12 237 other countries but containing some RCTs with unclear risk of selection bias and detection bias.
13
14 238 Moreover, both meta-analyses^{141 149} showed similar AEs of St. John's wort to placebo but significant
15
16 239 less AEs than standard antidepressants.

20 240 *Saffron (Crocus sativus)*

23 241 A moderate-quality meta-analysis examined the effectiveness and safety of saffron on depression
24
25 242 severity by including 5 RCTs in adult patients with major depression.¹⁴⁶ It revealed very low quality of
26
27 243 evidence for significant greater effects versus placebo and similar effects versus antidepressant
28
29 244 medication up to 8 weeks of treatment (Figure 2). No serious adverse events were reported, but
30
31 245 patients receiving saffron tend to report more adverse events than those receiving placebo and less
32
33 246 adverse events than those receiving antidepressant medication. Reasons for downgrading the
34
35 247 evidence included no replication of the results (all included RCTs were conducted by the same
36
37 248 research group), the small overall sample size, and the possibly high risk of publication bias.

42 249 *Curcumin (Curcuma longa)*

45 250 For the intake of curcumin, a moderate-quality meta-analysis¹⁵⁴ revealed very low quality of evidence
46
47 251 suggesting a small but significant short-term effect of low heterogeneity on depression severity by
48
49 252 pooling 6 RCTs (Figure 2). No serious adverse events were recorded. Evidence had to be downgraded
50
51 253 due to unclear risk of selection, performance, detection, attrition, and reporting bias in over the half
52
53 254 of the included RCTs, the imprecision of the pooled effect and the possibly high risk of publication
54
55 255 bias.

59 256 *Traditional Chinese herbs*

1
2 257 A comprehensive but low-quality systematic review of 296 RCTs of *Chinese herbal medicine* formulas
3
4 258 and single herbs¹⁶¹ revealed 21 RCTs of mostly unclear to high risk of selection, performance, and
5
6 259 detection bias and a serious risk of publication bias. Therefore, the evidence supporting the superiority
7
8 260 above placebo and the similarity towards standard antidepressants regarding depression severity
9
10
11 261 (Figure 2) and response rates (Figure 3) was assessed as very low.
12

13 14 262 *Other herbs*

15
16 263 For other than the described herbs, no meta-analyses were conducted to date. However, a
17
18 264 systematic review¹⁰⁹ found three single RCTs that showed significant improvement in depressive
19
20 265 symptoms for *Lavandula angustifolia* as an adjunctive treatment to standard antidepressant drugs
21
22 266 versus antidepressant drugs alone and for *Echium amoenum* and *Rhodiola rosea* versus placebo. No
23
24 267 serious adverse events were reported.
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28 268 *Homoeopathy*

29
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31 269 No meta-analysis on *homoeopathic remedies* for depression were conducted yet. A recent systematic
32
33 270 review detected no placebo-controlled RCTs in patients with a primary diagnosis of depression.¹²⁸
34
35

36 271 *Hypnosis*

37
38
39 272 No meta-analysis on *hypnosis* or *self-hypnosis* techniques met the inclusion criteria of this overview.
40
41 273 The only available review on this topic¹²⁶ included 6 RCTs among which only one RCT included adults
42
43 274 with mild primary depression. Within the mixed sample of physically ill patients and healthy adults,
44
45 275 (self-)hypnosis appeared to be effective in decreasing depressive symptoms.
46
47
48

49 276 *Light therapy*

50
51
52 277 A high-quality Cochrane review meta-analysed the effects of *bright light therapy* in adjunction to
53
54 278 standard antidepressants versus sham light therapy plus antidepressants on severity and response
55
56 279 rates in patients suffering from non-seasonal depression.¹⁶⁰ By pooling 18 RCTs of overall unclear risk
57
58 280 of bias, it revealed very low quality of evidence for a significant small but inconsistent and imprecise
59
60 281 effect on depression severity (Figure 2). A subgroup analysis of two RCTs with low risk of selection

1
2 282 bias and detection bias revealed a significant large effect on depression severity but based on one
3
4 283 non-peer-reviewed publication and one RCT that also included bipolar patients. Response rates did
5
6 284 not significantly differ between groups (Figure 3). Adverse events were reported non-systematically
7
8 285 but appeared to be comparable to sham light therapy except for hypomania that occurred more
9
10
11 286 often under verum light therapy.¹⁶⁰

12
13
14 287 For patients with seasonal patterns of depression, a meta-analysis of 8 RCTs¹⁵¹ revealed very low
15
16 288 quality of evidence for a significant medium effect on depression severity of light monotherapy in
17
18 289 comparison to sham light therapy (Figure 2). Risk of bias of individual RCTs, heterogeneity, and safety
19
20 290 were not analysed leading to an overall low quality of the meta-analysis and downgrading of the
21
22 291 evidence.

25 292 **Massage therapy**

26
27
28 293 The literature search detected no meta-analysis of *massage therapy* in patients with a primary
29
30 294 depression. However, massage therapy appeared to be effective in decreasing depressive symptoms
31
32 295 in mixed samples of physically ill patients and healthy adult.¹³² Future research will show, whether
33
34 296 these results may be transferable to primary depressed cases.

37 297 **Meditative movement therapies**

40 298 *Dance therapy*

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43
44 299 Short-term effects of improvisatory or structured *dance therapy* as a combination of movement-
45
46 300 based work, interactive group components and insight/expressive methods were meta-analysed by a
47
48 301 Cochrane review of high methodological quality.¹⁵² It revealed a significant large pooled effect size
49
50 302 for depression severity as an adjunctive treatment option to standard medical/psychotherapeutic
51
52 303 care based on two RCTs (Figure 2). Although the meta-analyses contained no heterogeneity and no
53
54 304 imprecise CI, the evidence had to be downgraded because of mostly unclear/high risk of bias of one
55
56 305 of the RCTs as well as the overall small sample size.

57 306 *Chinese movement therapies*

1
2 307 A low-quality meta-analysis on Chinese meditative movement therapies revealed 30 RCTs, of which 2
3
4 308 RCTs on *Qi Gong* and 3 RCTs on *Tai Chi* met inclusion criteria for patients with mild to severe
5
6 309 symptoms of primary depression.¹⁵⁰ Very low quality of evidence suggested significant short-term
7
8 310 effects for Qi Gong but not for Tai Chi in comparison to TAU. The evidence had to be downgraded
9
10
11 311 due to very serious limitations of the quality of the RCTs and the meta-analysis, significant
12
13 312 heterogeneity, imprecision, and a possible high risk of publication bias.

16 313 *Yoga*

17
18
19 314 A high-quality meta-analysis of complex *yoga* interventions for various depressive disorders found 12
20
21 315 RCTs,¹⁴⁴ of which 5 RCTs of mostly unclear risk of bias met the inclusion criteria of this overview. The
22
23 316 pooled short-term effect on depression severity was of large size in comparison to TAU and medium
24
25 317 size in comparison to standard exercises (Figure 2). However, the evidence was assessed as very low
26
27 318 due to serious limitations of quality of the RCTs, significant heterogeneity, imprecision, and a possible
28
29 319 high risk of publication bias.

30
31
32
33 320 A further systematic review of yoga in major depressive disorder, revealed 5 newer yoga RCTs but did
34
35 321 not perform a meta-analysis because of high clinical heterogeneity. Risk of bias was comparably high
36
37 322 and evidence mostly conflicting.¹⁰⁶

40 323 ***Mindfulness-based interventions***

43 324 *Mindfulness-based Cognitive Therapy (MBCT)*

44
45
46 325 A low-quality meta-analysis of mindfulness-based interventions in patients with major depression
47
48 326 found 4 RCTs investigating the effects of MBCT and Cognitive Behavioural Therapy (CBT) on depression
49
50 327 severity.¹⁵⁸ It revealed a significant large short-term effect of MBCT in comparison to TAU and similar
51
52 328 effects in comparison to CBT (Figure 2). However, the quality of the evidence was considered as very
53
54 329 low due to the missing risk of bias assessment, inconsistency, and imprecision.

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56
57
58 330 A further moderate-quality systematic review on MBCT meta-analysed 9 RCTs on an individual patient
59
60 331 data level.¹⁴⁸ The sample consisted of patients with recurrent major depression currently in remission.
332 After a period of 60 weeks, MBCT showed a significantly reduced risk of depressive relapse compared

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

335 *Mindfulness-based stress reduction (MBSR)*

336 RCTs of MBSR and MBSR-like interventions were meta-analysed by a recent review¹⁴³ showing a
337 significant large short-term effect on depression severity in comparison to TAU and enhanced TAU
338 (Figure 2). The quality of the evidence was assessed as low because of the overall unclear risk of
339 selection and performance bias and significant heterogeneity.

340 *Music therapy*

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

349 A newer Cochrane review¹³⁸ found 8 different RCTs showing a significant large pooled effect of music
350 therapy on depression severity against TAU and similar effects as CBT (Figure 2). However, both
351 analyses revealed very low quality of evidence due to mostly unclear selection, performance,
352 detection and reporting bias, significant heterogeneity, and imprecision.

353 *Nutrition therapy*

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

1
2 358 A further systematic review on fasting in patients with chronic pain and inflammatory diseases¹¹⁰
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4 359 included 1 RCT and 7 observational studies, which showed promising short-term but questionable
5
6 360 longer-term anti-depressive effects.
7

8 9 361 ***Religious/spiritual Interventions***

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11
12 362 Very low to low quality of evidence was found by a moderate-quality systematic review of 9 RCTs on
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14 363 Christian, Muslim, and spiritual CBT adaptations.¹⁴⁰ The analyses showed significant greater medium
15
16 364 effects on depression severity against TAU and standard CBT (Figure 2). Safety data were not
17
18 365 reported.
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20 21 22 366 ***Supplements***

23 24 25 367 *Inositol*

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28 368 A low quality meta-analysis of 2 RCTs in patients with major depression¹⁵³ revealed very low quality
29
30 369 evidence for inositol as adjunctive to standard antidepressants versus placebo in combination to standard
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32 370 antidepressants (Figure 2).
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34 35 371 *Magnesium*

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38 372 No meta-analysis of magnesium supplementation was found. A recent systematic review detected no
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40 373 RCTs in patients with a primary diagnosis of depression¹⁰⁷.
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42 43 374 *Omega-3 fatty acids*

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46 375 A high-quality Cochrane review¹⁴² of 26 RCTs found conflicting evidence of the effectiveness of
47
48 376 supplementation with omega-3 fatty acids versus placebo in patients with major depression as
49
50 377 depression severity significantly improved while response and remission rates did not so (Figure 2-4).
51

52
53 378 One additional RCT with a very low sample size showed similar effects of omega-3 fatty acids on
54
55 379 severity and response rates in comparison to antidepressant drug treatment (Figure 2 and 3).
56

57 380 However, all meta-analyses were based on very low quality of evidence because of limitations of the
58
59 381 study quality, significant heterogeneity, imprecision and a possibly high risk of publication bias.
60

382 *Probiotics*

1
2 383 The effectiveness of the supplementation with probiotics on depression severity was analysed by a
3
4 384 moderate-quality meta-analysis of 5 RCTs, of which only one RCT with overall low risk of bias was
5
6 385 carried out on patients with major depression.¹⁴⁷ The analysis of the RCT revealed a significant
7
8 386 medium but imprecise short-term effect in comparison to placebo (Figure 2). This led to overall very
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11 387 low quality of evidence for probiotics supplementation.

12 13 14 388 *S-adenosyl methionine (SAME)*

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16
17 389 A high-quality Cochrane review¹⁴⁵ of the effectiveness and safety of SAME supplementation on
18
19 390 depression severity revealed 2 RCTs of low risk of bias that showed no significant pooled effects for
20
21 391 SAME monotherapy versus placebo. One RCT, also of low risk of bias showed a significant medium
22
23 392 short-term effect as adjunctive to standard antidepressant medication, both for depression severity.
24
25 393 Further 5 RCTs, which were rated as having overall unclear risk of bias, showed similar pooled effects
26
27 394 of SAME monotherapy on depression severity compared to standard antidepressant medication
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29 395 (Figure 2). Original RCTs reported safety issues insufficiently. For all meta-analyses, the evidence was
30
31 396 assessed as low to very low quality because of limitations of the study quality, heterogeneity,
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33 397 imprecision, and a possibly high risk of publication bias.

34 35 36 37 398 *Tryptophan*

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40 399 A moderate-quality Cochrane review found 2 RCTs investigating the effectiveness and safety of
41
42 400 tryptophan supplementation on depression severity.¹⁵⁷ Pooling the effects led to significant greater
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44 401 short-term response rates (Figure 3) as well as significant more adverse events in the tryptophan
45
46 402 group than in the placebo group. The evidence was assessed as very low quality because of an
47
48 403 unclear risk of detection, attrition and other bias, imprecision, and a possible risk for publication bias.

49 50 51 52 404 *Vitamins*

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54
55 405 For Vitamin B6, no meta-analysis was available. A systematic review without meta-analysis revealed
56
57 406 2 RCTs showing no significant effects when compared to placebo.¹¹⁹

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60 407 Two further moderate to high-quality meta-analyses examined the effects of vitamin B9 (Folate) for
408 major depressive patients. While a Cochrane review¹⁵⁹ calculated a significant medium effect size of

1
2 409 folate-intake as an adjunctive intervention to standard drug treatment on depression severity, a
3
4 410 more recent review¹³⁹ revealed non-significant differences on severity and response rates (Figure 2
5
6 411 and 3). In contrast, a long-term combined intake of Vitamin B6, B9, and B12 was found to be
7
8 412 effective for relapse prevention after remission of symptoms as a result of one RCT (Figure 5).¹³⁹
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10 413 However, all comparisons were based on very low quality of evidence mostly due to significant
11
12 414 heterogeneity, imprecision, and possible high risk of publication bias.

15
16 415 Another moderate-quality meta-analysis revealed evidence of the effectiveness of vitamin D-intake
17
18 416 on depression severity in comparison to placebo.¹⁵⁶ The analysis of the two included RCTs revealed a
19
20 417 significant medium short-term effect in favour of vitamin D in major depressed patients up to 8
21
22 418 weeks (Figure 2). The quality of evidence was rated as very low due to limitations of the study
23
24 419 quality, missing values of heterogeneity, imprecision, a high risk of publication bias as well as
25
26 420 insufficient reporting of adverse events.

30 421 *Zinc*

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33 422 The effectiveness of zinc for major depression was meta-analysed by a low-quality review of 3
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35 423 RCTs.¹⁵⁵ It revealed a significant pooled short-term effect of medium size and low heterogeneity
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37 424 when zinc was taken as an adjunctive to standard antidepressant drug treatment (Figure 2).
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39 425 However, the available evidence had to be assessed as very low as the meta-analysis did not perform
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41 426 risk of bias assessments and did not report adverse events.

45 427 **Discussion**

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48 428 This systematic review provided a comprehensive overview of the evidence of CAM treatments for
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50 429 patients with a diagnosis or clinical symptoms of depression. Moderate quality evidence suggested
51
52 430 the efficacy, comparative effectiveness to standard antidepressants, and safety of St. John's wort on
53
54 431 depression severity and response rates. For remission and relapse rates, the evidence was conflicting
55
56 432 and of lower quality. Moreover, moderate quality evidence showed that MBCT was superior to
57
58 433 standard antidepressant drug treatment for the prevention of depression relapse in patients with
59
60 434 recurrent major depression. Low quality evidence suggested significant greater effects in favour of

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2 435 electroacupuncture in comparison to standard antidepressants alone and in adjunction to standard
3
4 436 antidepressants for depression severity. For remission rates, low quality evidence revealed
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6 437 comparable effects of electroacupuncture and standard antidepressants. Further significant greater
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8 438 effects, which based on low quality evidence, were found for MBSR versus TAU, music therapy in
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10 439 adjunction to standard antidepressants, faith-adapted CBT versus CBT, and SAME versus standard
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12 440 antidepressants. Other treatments such as manual acupuncture, aromatherapy, biofeedback, herbs
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14 441 (crocus sativus, curcuma longa, traditional Chinese herbs, lavandula angustifolia, echium amoenum,
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16 442 rhodiola rosea), Homoeopathy, hypnosis, bright light therapy, massage, meditative movement
17
18 443 therapies (dance therapy, Qi Gong, Tai Chi, yoga), whole-diet interventions, fasting, and
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20 444 supplementation with inositol, magnesium, omega-3 fatty acids, probiotics, tryptophan, B- and D-
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22 445 vitamins, and zinc were based on very low quality of evidence or no level-1 evidence.
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27 446 The strengths of the review process included the comprehensive literature search based on a
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29 447 structured list of CAM specific topics, which had been operationalized for the Cochrane
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31 448 Collaboration.⁴¹ It therefore included evidence for more than the previously considered CAM
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33 449 approaches and provided systematic information where further high-quality studies are required. In
34
35 450 addition, we only included results of RCTs of patients with a diagnosis of depression or clinical
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37 451 relevant depressive symptoms and excluded RCTs on samples with minor or secondary symptoms of
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39 452 depression by newly calculating effect sizes. Finally, we rated AMSTAR and considered the quality of
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41 453 the meta-analyses as well when grading the quality of the evidence.
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46 454 The conclusions derived from this overview are limited due to possibly missing evidence from newer
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48 455 RCTs, which have not been summarized by the included systematic reviews and meta-analyses. As it
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50 456 was not within the scope of this overview, we did not separately search for individual RCTs. We also
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52 457 did not include meta-analyses on observational studies of depression risk that may include bigger
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54 458 samples and may provide additional information about further possible treatment approaches.

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57 459 Another reason that limits the quality of evidence consists in the unsatisfactory methodological
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59 460 quality of some of the included meta-analyses. Although the methodological quality of the original
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461 RCTs might be acceptable, the bad reporting of some meta-analyses led to downgraded evidence. In

1
2 462 particular, meta-analyses often missed to search for grey literature, cite excluded studies, adequately
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4 463 assess risk of bias of the original studies, and report complete I^2 statistics. As the latter are known to
5
6 464 be unstable in meta-analyses with a small numbers of studies,¹⁶³ calculating confidence intervals for
7
8 465 I^2 should be standard. Moreover, RCTs as well as meta-analyses often missed to systematically report
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10 466 on occurred adverse events, which also limits the significance of the conclusions. In RCTs of non-
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12 467 pharmacological interventions, there is always a high or unclear risk of performance bias and possibly
13
14 468 high placebo effects. As such, adding credible sham interventions, controlling for patients'
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16 469 expectancies, and performing of ITT analyses is indispensable. However, meta-analyses mostly did not
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18 470 systematically assess these issues. In general, it should be noticed that all evidence is based on short-
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20 471 term pooled effects, except for meta-analyses of St. John's wort, MBCT, music therapy, and B- and D-
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22 472 vitamins that also provided longer-term follow-up data.

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27 473 Clinical recommendations for patients should follow the country-specific clinical practice guidelines
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29 474 considering the quality of evidence, the accessibility of the treatment, costs, and the preferences of
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31 475 the patients. While the guidelines agree^{30 31 33-35 164 165} that clinicians should select between either CBT
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33 476 or second-generation antidepressant drugs for the treatment of major depression, the restricted
34
35 477 search strategy of some of the guidelines might limit their recommendations for CAM treatments.
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37 478 For patients who do reject or do not tolerate standard antidepressant drugs, one alternative
38
39 479 treatment option may be St. John's wort. It is also recommended by the American Psychiatric
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41 480 Association Task Force report⁴² and the CANMAT Depression Work Group³² as being proven
42
43 481 sufficiently for the short-term by placebo-controlled and equivalence trials with standard
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45 482 antidepressants for mild to moderate major depression. Particularly for bridging the gap between
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47 483 diagnosis and getting access to psychotherapy and meanwhile reducing/not-worsening depression
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49 484 severity, St. John's wort may be considered as a possibly better tolerated alternative to standard
50
51 485 antidepressant drugs.¹⁶⁶ As St. John's wort is accessible without prescription and currently not
52
53 486 regulated by the US Food and Drug Administration, we agree with the ACP guidelines³⁰ that it
54
55 487 remains difficult for patients to obtain quality-controlled remedies. Moreover, St. John's wort is
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57 488 associated with numerous herb-to-drug interactions.¹⁶⁷ Therefore, we would recommend clinicians

1
2 489 to educate their patients about possible effects, side effects and interactions who in turn should not
3
4 490 take St. John's wort without professional advise.³³ Despite those limitations, we would not
5
6 491 discourage a general therapeutic attempt with St. John's wort, even if we disagree with the NICE
7
8 492 guideline in this point.³⁴ Clinicians may also inform patients with recurrent major depression
9
10 493 currently in remission about the superiority of MBCT in comparison to standard antidepressants for
11
12 494 relapse prevention.³¹⁻³⁴ Finally, patients should also be informed that many other CAM treatments
13
14 495 might show promising effects but cannot be recommended until further higher-quality studies will
15
16 496 confirm their effectiveness and safety.
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20 497 Further research is needed, particularly for interventions that have shown preliminary evidence for
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22 498 reducing secondary symptoms of depression, promising short-term but no longer-term effects, or
23
24 499 insufficient evidence due to low methodological quality of the original RCTs and/or the performed
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26 500 meta-analyses. Reporting of clinical trials and meta-analyses should necessarily follow the
27
28 501 CONSORT¹⁶⁸ and PRISMA guidelines,³⁶ respectively, including rigorous documentation and analysis of
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30 502 adverse events. Especially Chinese and Indian trials are still found to be poorly reported and tended
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32 503 to present more positive conclusions than those from western countries.^{169 170} Moreover, 7 of the
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34 504 included meta-analyses showed no more than poor methodological quality. All were published in
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36 505 peer-reviewed journals in the past 5 years. One complementary journal is among them, while 6 of
37
38 506 the journals are conventional psychiatric journals with impact factors ranging from 2.419 to 4.369.
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41 507 Thus, particularly the review process as well as the editorial work need to be improved. Further
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43 508 clinical practice guidelines should extend their search strategies and include standard search terms
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45 509 for CAM. This is also important for CAM therapies that do not show consistent evidence or that are
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47 510 not yet investigated. This information might be equally interesting for physicians as well as for
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49 511 patients to make an informed decision about the treatment for clinical depression.
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512 **Conclusion**

513 This overview of systematic reviews on CAM treatments for clinical depression aimed to provide a
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55 514 systematic search strategy and evidence base, on which further clinical practice guidelines may build
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57 515 their recommendations. To improve quality of trials and meta-analyses, researchers, reviewers as
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1
2 516 well as editors are asked to ensure that future articles strictly adhere the CONSORT and PRISMA
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4 517 guidelines.
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15
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17
18 525 association that might create a conflict of interest regarding the submitted manuscript.

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21
22 526 **Author contribution statement**

23
24 527 HH was responsible for the conception and design of the study, the collection and analysis of the
25
26 528 study data and for drafting the manuscript. DA participated in the analysis of the study data and
27
28 529 drafting the manuscript. HC participated in the conception and design of the study and the analysis
29
30 530 of the study data, and critically revised the manuscript. GD participated in the conception and design
31
32 531 of the study, and critically revised the manuscript. All authors approved the final manuscript.

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35
36 532 **Data Availability**

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39 533 All data analysed within this overview are included in this published article and its supplementary
40
41 534 information files.

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2 **Figure legends**
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5 **Figure 1. Study flow diagram.**
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8 **Figure 2. Quality of evidence for depression severity.** ADM: Antidepressant medication, CBT:
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10 Cognitive Behavioural Therapy, CI: Confidence Interval, I²: Heterogeneity, MBCT: Mindfulness-based
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12 Cognitive Therapy, MBSR: Mindfulness-based Stress Reduction, N.c.: Not calculable because of only
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14 one included RCT, N.r.: Not reported, S-adenosyl methionine, Tau: Treatment as Usual
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18 **Figure 3. Quality of evidence for depression response rates.** ADM: Antidepressant medication, CI:
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20 Confidence Interval, I²: Heterogeneity, N.c.: Not calculable because of only one included RCT, OR:
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22 Odds Ratio, RR: Risk Ratio
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26 **Figure 4. Quality of evidence for depression remission rates.** ADM: Antidepressant medication, CI:
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28 Confidence Interval, I²: Heterogeneity, N.c.: Not calculable because of only one included RCT, OR:
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30 Odds Ratio, RR: Risk Ratio, Tau: Treatment as Usual
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34 **Figure 5. Quality of evidence for depression relapse rates.** ADM: Antidepressant medication, CI:
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36 Confidence Interval, HR: Hazard Ratio, I²: Heterogeneity, MBCT: Mindfulness-based Cognitive
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38 Therapy, N.c.: Not calculable because of only one included RCT, OR: Odds Ratio, RR: Risk Ratio, Tau:
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40 Treatment as Usual
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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)

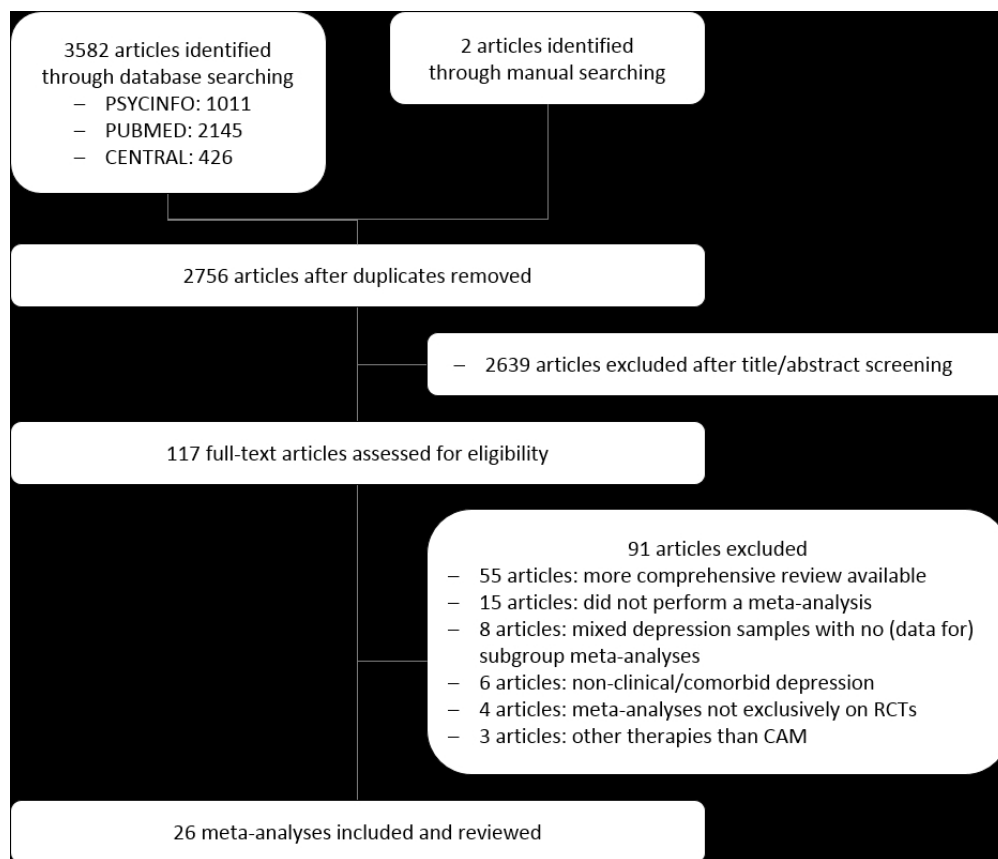
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Supplementary data

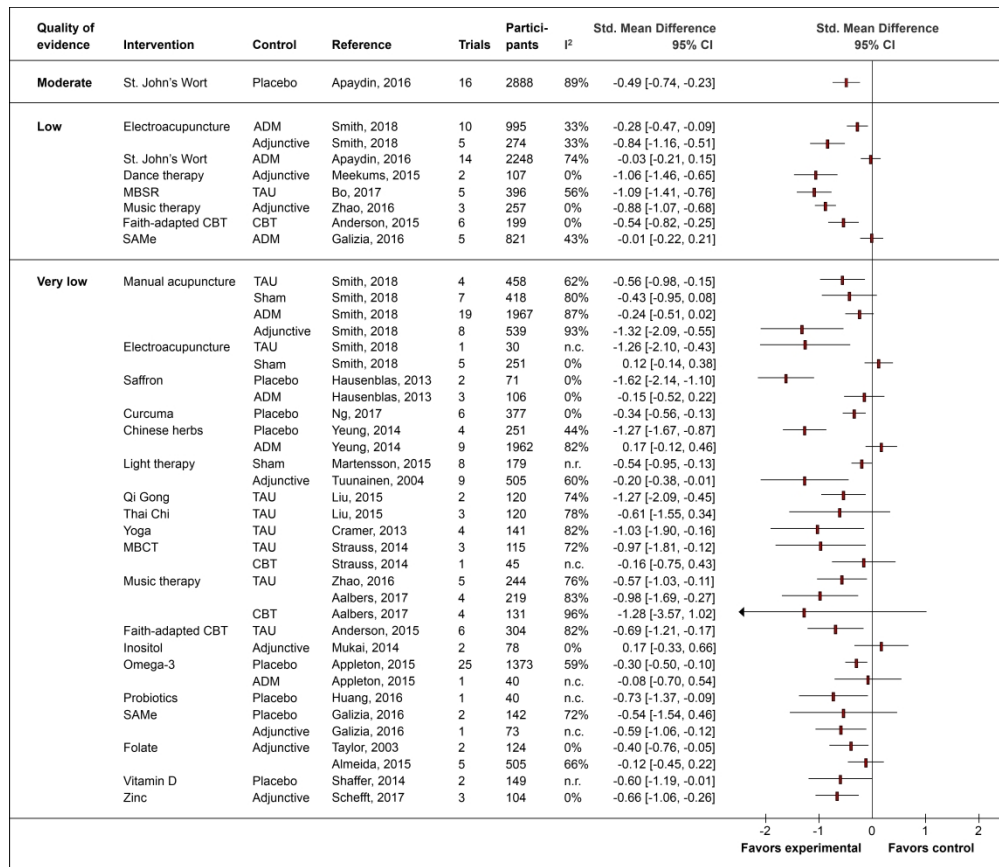
Supplementary table 1: Detailed AMSTAR ratings.

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

For peer review only

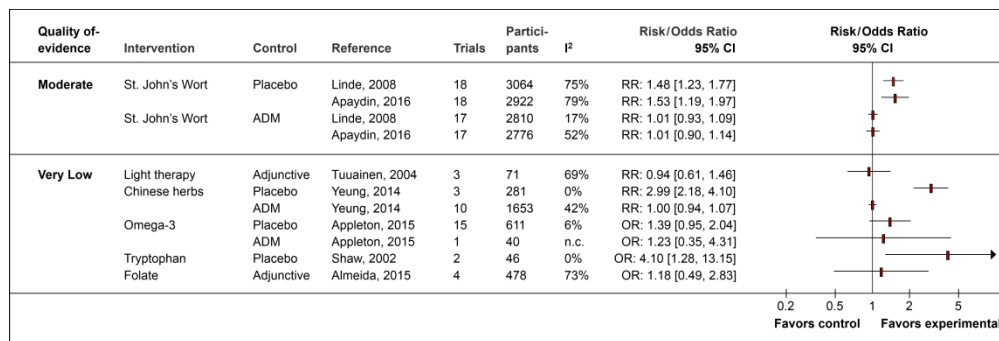


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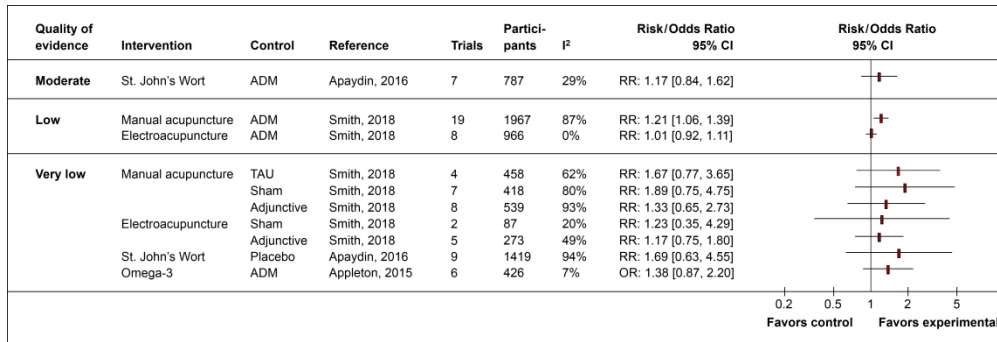
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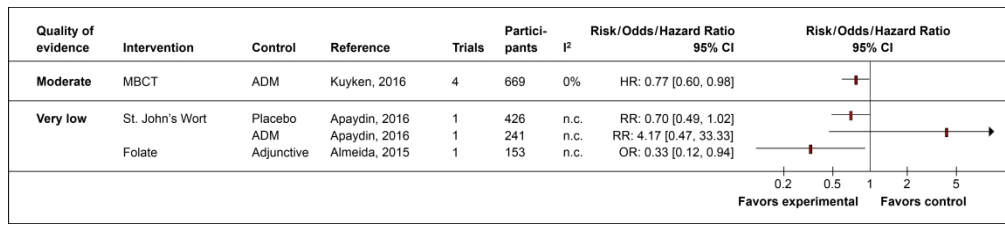
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Supplementary information to “Complementary therapies for clinical depression: an overview of systematic reviews”

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

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

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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<.001; N=481) [#]

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									– 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})	
Electroacupuncture	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})	– 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)	
								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})		

Herbs

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2	St. John's wort	Linde 2008 ¹⁴⁹	MDD 29 RCTs	SB: 18	AMSTAR: 8	HAMD 4-12	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 AEs as PLACEBO (14 RCTs; OR=0.98; 95%CI=[0.78,1.23]; I ² =n.r.; N=2496),	
3				PB: 29		MADRS weeks				– Sign. less than ADMs (14 RCTs; OR=0.56; 95%CI=[0.43,0.74]; I ² =n.r.; N=2663)
4				DB: n.r.						
5				AB: 29						
6				RB: n.r.						
7				OB: n.r.						
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13	Apaydin 2016 ¹⁴¹	MDD 35 RCTs	SB: 9 PB: 27 DB: 5 AB: 26 RB: 3 OB: 33	AMSTAR: 9	HAMD 4-32	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 AEs as PLACEBO (13 RCTs; OR=0.83; 95%CI=[0.62,1.13]; I ² =n.r.; N=2600),		
14									weeks	– Sign. less than ADMs (11 RCTs; OR=0.67; 95%CI=[0.56,0.81]; I ² =n.r.; N=1946)
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								– 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]; I²=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									
									–

1										
2	Music therapy	Zhao	MND	8 RCTs	SB: 0	AMSTAR:	HAMD,	4-52	Severity:	– N.r.
3		2016 ¹⁶²			PB: 0	7	GDS,	weeks	– Sign. greater effects than TAU (5 RCTs;	
4					DB: 0		HADS		SMD=-0.57; 95%CI=[-1.03,-0.11]; I ² =76%;	
5					AB: 8				p<.001; N=244; ⊕○○○ very low ^{a,c,d} *	
6					RB: 7				– Sign. greater effects as adjunctive to ADM	
7					OB: 8				versus ADM (3 RCTs; SMD=-0.88; 95%CI=[-	
8									1.07,-0.68]; I ² =0%; p=.63; N=257; ⊕⊕○○	
9									low ^{a,e} *)	
10										
11										
12		Aalbers	MDD,	8 RCTs	SB: 2	AMSTAR:	HAMD	12 weeks	Severity:	– Similar AEs as TAU (1
13		2017 ¹³⁸	CSD		PB: 1	11			– Sign. greater effects than TAU (4 RCTs;	RCT; OR=0.45;
14					DB: 1			SMD=-0.98; 95%CI=[-1.69,-0.27]; I ² =83%;	95%CI=[0.02,11.46];	
15					AB: 7			p<.001; N=219; ⊕○○○ very low ^{a,c,d})	I ² =n.c.; N=79)	
16					RB: 2			– Similar effects as CBT (4 RCTs; SMD=-		
17					OB: 3			1.28; 95%CI=[-3.57,1.02]; I ² =96%;		
18								p<.001; N=131; ⊕○○○ very low ^{a,c,d})		
19										
20										
21	Religious/spiritual therapies									
22	Faith-adapted CBT	Anderson	MDD,	9 RCTs	SB: 0	AMSTAR:	N.r.	N.r.	Severity:	– N.r.
23		2015 ¹⁴⁰	CSD		PB: 0	7			– Sign. greater effects than TAU (6	
24					DB: 4				RCTs; SMD=-0.69; 95%CI=[-1.21,-	
25					AB: 4				0.17]; I ² =82%; p=.004; N=304;	
26					RB: 9				⊕○○○ very low ^{a,c,d}) [§]	
27					OB: 0				– Sign. greater effects than CBT (6 RCTs;	
28								SMD=-0.54; 95%CI=[-0.82,-0.25];		
29								I ² =0%; p=.78; N=199; ⊕⊕○○ low ^{a,e}) [§]		
30										
31										
32	Supplements									
33	Inositol	Mukai	MDD	2 RCTs	N.r.	AMSTAR:	HAMD	4 weeks	Severity:	– Similar AEs as
34		2014 ¹⁵³				4			– No sign. effects as adjunctive to SSRI versus	adjunctive to ADM (1
35									PLACEBO + SSRI (2 RCTs; SMD=0.17;	RCT; RR=3.21;
36									95%CI=[-0.33,0.66]; I ² =0%; p=.93; N=78;	95%CI=[0.14,72.55];
37								⊕○○○ very low ^{b,d,e})	I ² =n.c.; N=36)	
38										
39										
40										
41										
42										
43										
44										
45										
46										

1										
2	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)
24	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.
32	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, 2 RCTs CSD	SB: 0 PB: 0 DB: 1 AB: 0 RB: n.r. OB: n.r.	AMSTAR: 7	HAMD, 8 weeks BDI	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, 6-12 weeks BDI	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; I²: 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;

^aDowngraded one level because of study limitations (overall unclear or high risk of bias);

^bDowngraded two levels because of study limitations (overall unclear or high risk of bias) and limitations of the meta-analysis (AMSTAR ≤ 5).

^cDowngraded one level because of inconsistency (significant heterogeneity or no replication of the results);

^dDowngraded one level because of imprecision (confidence interval includes negligible or no effects or fewer than 250 participants were included in total);

^eDowngraded 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 & 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 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

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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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BMJ Open

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

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Manuscripts

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2 1 **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

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2 41 **Strengths and limitations of this study**
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- 4 42 ▪ This systematic overview included the comprehensive literature search of important CAM
5
6 43 topics defined by the Cochrane Collaboration.
7
8 44 ▪ The inclusion criteria were restricted to meta-analyses of RCTs of patients with a clinical
9
10 45 diagnosis of depression.
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13 46 ▪ The quality of evidence from meta-analyses was assessed according to GRADE.
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15 47 ▪ There is a possible lack of evidence of newer RCTs, which have not been analysed by the
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17 48 included meta-analyses.
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49 Introduction

50 Depression is one of the most prevalent psychiatric disorders, with about 25% of women and 12% of
51 men suffering from at least one depressive episode during their lifetime.¹⁻³ According to the criteria
52 for diagnosis recommended by the American Psychiatric Association (APA), depressive disorders can
53 be distinguished by their degree of severity or duration and are also characterized by a high
54 comorbidity and an increase of psychological strain for the affected person.⁴ It is evident, that a
55 strong comorbid connection to several chronic conditions like addictions,⁵ neurodegenerative
56 diseases,^{6,7} or different psychiatric diseases⁸⁻¹¹ exists. This leads depressive disorders as one of the
57 leading causes of disability worldwide.¹²

58 The most commonly used treatments for depression are antidepressants, psychotherapy, or a
59 combination of drugs and psychotherapy. While both treatment strategies (alone and in
60 combination) have been shown to be effective,¹³⁻¹⁵ more recent meta-analyses also found high
61 dropout and low remission rates¹⁶⁻²¹ as well as clinically significant differences between
62 antidepressant drugs and placebos only for patients at the upper end of the very severely depressed
63 category.²² This may lead patients to search for alternatives. Increasing mainstream use of
64 complementary and alternative medicine (CAM) support this trend, particularly for different physical
65 conditions with comorbid affective disorders.²³⁻²⁷ While some complementary therapies have
66 become a promising adjunct in the standard treatment of depression,^{28,29} others are known for their
67 possible side effects or interactions with standard drugs.²⁹ Recent clinical practice guidelines, in
68 addition, vary widely in their search strategies and resulting recommendations for CAM treatments.
69 While the ACP,³⁰ APA,³¹ and CANMAT guideline³² provide a more comprehensive overview and
70 critical appraisal of CAM treatments, the DGPPN,³³ NICE,³⁴ and WFSBP³⁵ guidelines mainly focus on
71 St. John's Wort and light therapy. Possible effects and risks of further CAM therapies are not
72 discussed. Thus, the purpose of this overview is to provide a comprehensive search strategy of
73 relevant CAM terms and systematically summarize the existing level-1 evidence for clinical
74 depression as a basis for further guideline recommendations on the efficacy, effectiveness, and
75 safety of CAM therapies.

76 **Methods**

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

80 **Patient and Public Involvement**

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

82 **Inclusion and exclusion criteria**

- 83 – Types of studies: To be eligible, articles had to be systematic reviews with meta-analyses of
84 randomized controlled clinical trials (RCTs) published in peer-reviewed journals. Conference
85 abstracts or unpublished work were excluded as well as reviews summarizing evidence
86 narratively. In cases of including same or similar original studies, only the review with the
87 most recent, most comprehensive search was included. When systematic reviews reported
88 results of RCTs as well as of designs of lower evidence levels, they were considered only if
89 separate meta-analyses for the included RCTs were performed.
- 90 – Types of participants: Only reviews of patients with a diagnosis of major depression or
91 dysthymia were eligible as well as reviews including patients/general population samples
92 with mild depressive symptoms above a clinical cut off or seasonal patterns. In contrast,
93 reviews studying depressive symptoms within specific subpopulations of substance-induced
94 or demented patients, secondary depression due to another medical condition (e.g. post-
95 stroke, cancer, or pain patients), bipolar disorders, or females with premenstrual dysphoric
96 disorder or postpartum depression were excluded. Further restrictions regarding the
97 diagnostic criteria or procedures, regarding age, gender, duration of the condition, or
98 symptom intensity were not applied.
- 99 – Types of interventions: Reviews investigating the effectiveness and/or safety of a single,
100 adjunctive or combined CAM treatment were included. For the classification of CAM
101 treatments the definition of the US National Institutes of Health³⁹ was followed. CAM

1
2 102 interventions have to be compared against treatment as usual (TAU)/waiting list,
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4 103 placebo/sham, or standard medical care.
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6 104 – Types of outcomes: Reviews were eligible if they assessed at least one measure of
7
8 105 effectiveness such as severity of depressive symptoms, response rate (generally defined as a
9
10 106 50% decrease in depression scores after a period of up to 12 weeks of treatment),³⁰
11
12 107 remission rate (generally defined as a period of up to 12 weeks during which a patient is
13
14 108 asymptomatic or has only few symptoms to a very mild degree).⁴⁰ relapse rates, and/or a
15
16 109 measure of safety such as number of adverse events (AE), drug interactions, or numbers
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18 110 needed to harm for study withdrawal due to side effects.
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23 111 **Search strategy**

24
25 112 Electronic literature was systematically searched via PubMed, PsycInfo and Central from their
26
27 113 inception to January 31, 2018 without restrictions regarding time or language. Search terms for CAM
28
29 114 treatments were selected in accordance with Cochrane recommendations (Table 1).⁴¹ Additional
30
31 115 manual search included reference lists of previously published reviews^{14 28 29 42} and clinical practice
32
33 116 guidelines.³⁰⁻³⁵ Using PubMed Informer,⁴³ the search was updated until June 30, 2018.
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37 117 **Study selection process**

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39 118 To assess eligibility, articles were selected by screening titles and abstracts independently by two
40
41 119 authors (HH and DA). Any abstract considered potentially eligible by at least one author was read in
42
43 120 full to decide on its eligibility. Disagreements were rechecked with a third author (HC) until
44
45 121 consensus was achieved.
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49 122 **Data extraction and quality assessment**

50
51 123 Two authors (HH and DA) independently extracted data on the characteristics of the reviews
52
53 124 including the type of the intervention, the year of publication, the number and quality of the original
54
55 125 RCTs, the total number and age of the participants, and effectiveness and safety outcomes. The
56
57 126 quality of the included reviews was assessed using the Assessment of the Methodological Quality of
58
59 127 Systematic Reviews (AMSTAR) tool.⁴⁴ The AMSTAR tool consists of 11 items asking about important
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128 methodological quality criteria of systematic reviews such as: a published apriori design, duplicate

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2 129 study selection and data extraction, a comprehensive literature search including grey literature, a list
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4 130 of included and excluded studies, summarized characteristics and quality assessment of included
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6 131 studies, assessment of publication bias, appropriate method of data syntheses and deducing
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8 132 conclusions, and a conflict of interests statement. AMSTAR has shown good construct validity and
9
10 133 inter-rater reliability. The Intraclass Correlation Coefficient (ICC) of the total AMSTAR score of 11
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12 134 points was reported as 0.84.⁴⁵ For this analysis, the two authors (HH and DA) who independently
13
14 135 assessed AMSTAR reached an ICC of 0.96. Disagreements regarding content or quality of the reviews
15
16 136 were rechecked with a third author (HC) and resolved by agreement.
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20 137 **Data synthesis**

21
22 138 Results were pooled qualitatively by type of the intervention. Outcomes had to be calculated as
23
24 139 standard mean differences (SMDs), risk ratios (RRs), hazard ratios (HR), or odds ratios (ORs). If meta-
25
26 140 analyses displayed mean differences (MDs), SMDs were calculated using Review Manager Software
27
28 141 (RevMan, Version 5.3, The Nordic Cochrane Centre, Copenhagen) for better comparability of the
29
30 142 results. RevMan was also used to exclude SMDs/RRs/HRs/ORs of selective RCTs that did not fulfil
31
32 143 eligibility criteria of this overview. Effect sizes were classified according to Cohen as SMDs of 0.2 to
33
34 144 0.49 = small effect, SMDs of 0.5 – 0.79 = medium effect, and SMDs of > 0.8 = large effect (absolute
35
36 145 values)⁴⁶ with higher reduction of/improvement in depression scores represented by more negative
37
38 146 SMDs or RRs/HRs/ORs less than 1. According to the NICE guideline, a SMD of ≥ 0.5 or ≤ -0.5 ,
39
40 147 respectively was considered as a clinically relevant reduction of depression severity.⁴⁷ Statistical
41
42 148 heterogeneity between studies was assessed by the chi-squared test with a p-value of $\leq .10$
43
44 149 indicating significant heterogeneity. The magnitude of heterogeneity was categorized by the I^2
45
46 150 statistic with I^2 of 0 to 24% = no heterogeneity, I^2 of 25% to 49% = moderate heterogeneity, I^2 of 50%
47
48 151 to 74% = substantial heterogeneity, and I^2 of 75% to 100% = considerable heterogeneity.³⁸
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54 152 **Quality of evidence**

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56
57 153 The quality of evidence was assessed according to the Grades of Recommendation, Assessment,
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59 154 Development, and Evaluation (GRADE) approach⁴⁸ individually by two authors (HH and DA).
60
155 Disagreements were rechecked with a third author (HC) until consensus was achieved. For each

1
2 156 outcome, the evidence can be graded as high, moderate, low or very low. Evidence from RCTs is
3
4 157 initially assessed as high, but can be downgraded by one level for serious or two levels for very
5
6 158 serious limitations of the study quality (of both RCTs and meta-analyses), inconsistency of the results,
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8 159 indirectness of the evidence, imprecision of the results, and a potential risk of publication bias (as
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10 160 assessed by the included meta-analyses).⁴⁸
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15 161 **Results**

16 162 **Study selection**

17 163 A total of 3582 potentially eligible articles were identified by electronic database search. One
18
19 164 additional review was retrieved from manual search,⁴⁹ one from the updated search until June
20
21 165 2018.⁵⁰ After removing duplicates, 2639 articles were excluded by screening of titles and abstracts.
22
23 166 The remaining 117 articles were read in full, of which further 91 reviews had to be excluded (Figure
24
25 167 1). Reasons for exclusion comprised 55 reviews where newer and/or more comprehensive reviews
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27 168 on higher quality evidence were available.^{49 51-104} Further 15 reviews have to be excluded as they
28
29 169 systematically summarized evidence but did not performed a meta-analysis mostly due to clinical
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31 170 heterogeneity or a limited number of available RCTs.¹⁰⁵⁻¹¹⁹ Eight reviews were excluded as they
32
33 171 included mixed depressive samples of bipolar or postpartum cases and did not provide (data for)
34
35 172 subgroup analyses for patients with the defined depression criteria.¹²⁰⁻¹²⁷ Another six reviews
36
37 173 contained community samples with non-clinical depression or physically ill patients with comorbid
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39 174 depressive symptoms but displayed no data for patients with a primary diagnosis of depression.¹²⁸⁻¹³³
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41 175 Four reviews performed meta-analyses on both RCTs and non-RCTs and did not perform subgroup
42
43 176 analyses or extracted sufficient data for post hoc analyses.¹³⁴⁻¹³⁷ Three of the reviews analysed
44
45 177 standard instead of complementary therapies and were therefore be excluded. Finally, 26 meta-
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47 178 analyses could be included and reviewed.^{50 138-162}
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55 179 **Review characteristics and quality**

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58 180 Characteristics and quality appraisal of the included meta-analyses are summarized in the
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60 181 Supplementary Table 1. Meta-analyses were conducted between 2002 and 2018 and included

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2 182 between 1 to 49 RCTs on 40 to 7104 adult patients. Meta-analyses on children and adolescents were
3
4 183 not available or did not meet inclusion criteria. Samples mostly consisted of patients suffering from
5
6 184 major depressive disorder^{139-142 144-150 153 155 156 158 159} but also included patients with mixed diagnoses
7
8 185 of non-seasonal depression,^{50 152 161 162} patients with a diagnosis of seasonal depression,¹⁵¹ and
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10 186 patients with mild to severe symptoms of depression above a clinical cut-off.^{138 140 143 144 150 154 156 157} All
11
12 187 but one meta-analysis¹⁴⁰ reported pooled outcomes based on common standardized questionnaires
13
14 188 or diagnostic interviews. Effects were analysed mostly up to 12 weeks of treatment (short-term),
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16 189 except for four meta-analyses that included RCTs with effects reported up to 16, 24, or 32 weeks^{50 141}
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18 190 ^{142 150 159} and further three meta-analyses with long-term analyses equal to or greater than one year
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20 191 ^{148 156 162}. The AMSTAR total scores of the included meta-analyses ranged between 4 and 11 points
21
22 192 with a median quality of 7 points. The individual AMSTAR-ratings are reported in the Supplementary
23
24 193 Table 2.

194 **Synthesis of results**

195 ***Acupuncture***

196 *Manual acupuncture*

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

207 *Electroacupuncture*

1
2 208 For electroacupuncture, the same Cochrane review⁵⁰ revealed very low quality of evidence for the
3
4 209 comparisons to TAU and invasive sham for both outcomes, severity (Figure 2) and remission (Figure
5
6 210 3), because of serious limitations of the quality of the RCTs, imprecision, and a high risk of publication
7
8 211 bias. For electroacupuncture monotherapy in comparison to standard antidepressants, low quality
9
10 212 evidence homogeneously suggested significant greater effects for severity and similar effects for
11
12 213 remission. As an adjunctive treatment to antidepressants, electroacupuncture effectiveness was
13
14 214 supported by low quality of evidence showing a significant greater consistent and precise effect for
15
16 215 depression severity. Although the mean adjunctive effect can be considered as large, the analysis
17
18 216 based on only one RCT with overall low risk of bias and 4 RCTs of lower methodological quality that
19
20 217 missed to include adjunctive sham acupuncture. For remission rates, very low quality of evidence
21
22 218 suggested no effects in adjunction to antidepressants. In addition, one RCT showed significant less
23
24 219 AEs when electroacupuncture was added to standard antidepressants.
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29 220 **Aromatherapy**

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32 221 The literature search revealed no meta-analysis on aromatherapy. A recent systematic review
33
34 222 detected no RCTs in patients with a primary diagnosis of depression. However, two out of five of the
35
36 223 reviewed studies on inhalation aromatherapy and five out of eight studies on aromatherapy massage
37
38 224 have found significant anti-depressive effects in mixed patient samples and healthy adults.¹¹⁶
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42 225 **Biofeedback**

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45 226 No meta-analysis on biofeedback was conducted to date. A recent systematic review revealed only
46
47 227 one RCT on the defined inclusion criteria for depression showing some effects in contrast to sham
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49 228 psychotherapy.¹¹⁷
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52 229 **Herbs**

53 54 55 230 *St. John's wort (Hypericum perforatum)*

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58 231 The effectiveness of St. John's wort was meta-analysed by a Cochrane review of 29 RCTs¹⁴⁹ and a
59
60 232 more recent, higher quality meta-analysis of 35 RCTs.¹⁴¹ In comparison to placebo, St. John's wort
233 showed moderate quality evidence of significant greater reductions of depression severity (Figure 2)

1
2 234 and response rates (Figure 4). The evidence had to be downgraded due to significant heterogeneity
3
4 235 because of higher effects in studies from German-speaking countries than in those from the US or
5
6 236 other European countries. In contrast, very low quality of evidence suggested no superiority to
7
8 237 placebo for remission (Figure 3) and response rates (Figure 5). In comparison to standard
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10 238 antidepressants, St. John's wort showed comparable severity reductions, response, remission, and
11
12 239 relapse rates. The quality of the evidence of the meta-analyses of severity and relapse rates had to
13
14 240 be downgraded to low and very low, respectively. The evidence of the response and remission rates
15
16 241 was considered as moderate quality showing the same results in both German and studies from
17
18 242 other countries but containing some RCTs with unclear risk of selection bias and detection bias.
19
20 243 Moreover, both meta-analyses^{141 149} showed similar AEs of St. John's wort to placebo but significant
21
22 244 less AEs than standard antidepressants.
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25 245 *Saffron (Crocus sativus)*

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27 246 A moderate-quality meta-analysis examined the effectiveness and safety of saffron on depression
28
29 247 severity by including 5 RCTs in adult patients with major depression.¹⁴⁶ It revealed very low quality of
30
31 248 evidence for significant greater effects versus placebo and similar effects versus antidepressant
32
33 249 medication up to 8 weeks of treatment (Figure 2). No serious adverse events were reported, but
34
35 250 patients receiving saffron tend to report more adverse events than those receiving placebo and less
36
37 251 adverse events than those receiving antidepressant medication. Reasons for downgrading the
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39 252 evidence included no replication of the results (all included RCTs were conducted by the same
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41 253 research group), the small overall sample size, and the possibly high risk of publication bias.
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48 254 *Curcumin (Curcuma longa)*

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51 255 For the intake of curcumin, a moderate-quality meta-analysis¹⁵⁴ revealed very low quality of evidence
52
53 256 suggesting a small but significant short-term effect of low heterogeneity on depression severity by
54
55 257 pooling 6 RCTs (Figure 2). No serious adverse events were recorded. Evidence had to be downgraded
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57 258 due to unclear risk of selection, performance, detection, attrition, and reporting bias in over the half
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2 259 of the included RCTs, the imprecision of the pooled effect and the possibly high risk of publication
3
4 260 bias.

7 261 *Traditional Chinese herbs*

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10 262 A comprehensive but low-quality systematic review of 296 RCTs of *Chinese herbal medicine* formulas
11
12 263 and single herbs¹⁶¹ revealed 21 RCTs of mostly unclear to high risk of selection, performance, and
13
14 264 detection bias and a serious risk of publication bias. Therefore, the evidence supporting the superiority
15
16 265 above placebo and the similarity towards standard antidepressants regarding depression severity
17
18 266 (Figure 2) and response rates (Figure 4) was assessed as very low.

21 267 *Other herbs*

22
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24 268 For other than the described herbs, no meta-analyses were conducted to date. However, a
25
26 269 systematic review¹⁰⁹ found three single RCTs that showed significant improvement in depressive
27
28 270 symptoms for *Lavandula angustifolia* as an adjunctive treatment to standard antidepressant drugs
29
30 271 versus antidepressant drugs alone and for *Echium amoenum* and *Rhodiola rosea* versus placebo. No
31
32 272 serious adverse events were reported.

35 273 *Homoeopathy*

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38
39 274 No meta-analysis on *homoeopathic remedies* for depression were conducted yet. A recent systematic
40
41 275 review detected no placebo-controlled RCTs in patients with a primary diagnosis of depression.¹²⁸

43 276 *Hypnosis*

44
45
46
47 277 No meta-analysis on *hypnosis* or *self-hypnosis* techniques met the inclusion criteria of this overview.
48
49 278 The only available review on this topic¹²⁶ included 6 RCTs among which only one RCT included adults
50
51 279 with mild primary depression. Within the mixed sample of physically ill patients and healthy adults,
52
53 280 (self-)hypnosis appeared to be effective in decreasing depressive symptoms.

54 281 *Light therapy*

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57
58 282 A high-quality Cochrane review meta-analysed the effects of *bright light therapy* in adjunction to
59
60 283 standard antidepressants versus sham light therapy plus antidepressants on severity and response

1
2 284 rates in patients suffering from non-seasonal depression.¹⁶⁰ By pooling 18 RCTs of overall unclear risk
3
4 285 of bias, it revealed very low quality of evidence for a significant small but inconsistent and imprecise
5
6 286 effect on depression severity (Figure 2). A subgroup analysis of two RCTs with low risk of selection
7
8 287 bias and detection bias revealed a significant large effect on depression severity but based on one
9
10 288 non-peer-reviewed publication and one RCT that also included bipolar patients. Response rates did
11
12 289 not significantly differ between groups (Figure 4). Adverse events were reported non-systematically
13
14 290 but appeared to be comparable to sham light therapy except for hypomania that occurred more
15
16 291 often under verum light therapy.¹⁶⁰

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18
19
20 292 For patients with seasonal patterns of depression, a meta-analysis of 8 RCTs¹⁵¹ revealed very low
21
22 293 quality of evidence for a significant medium effect on depression severity of light monotherapy in
23
24 294 comparison to sham light therapy (Figure 2). Risk of bias of individual RCTs, heterogeneity, and safety
25
26 295 were not analysed leading to an overall low quality of the meta-analysis and downgrading of the
27
28 296 evidence.

297 **Massage therapy**

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

302 **Meditative movement therapies**

303 *Dance therapy*

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

1
2 309 imprecise CI, the evidence had to be downgraded because of mostly unclear/high risk of bias of one
3
4 310 of the RCTs as well as the overall small sample size.
5

6 7 311 *Chinese movement therapies* 8

9
10 312 A low-quality meta-analysis on Chinese meditative movement therapies revealed 30 RCTs, of which 2
11
12 313 RCTs on *Qi Gong* and 3 RCTs on *Tai Chi* met inclusion criteria for patients with mild to severe
13
14 314 symptoms of primary depression.¹⁵⁰ Very low quality of evidence suggested significant short-term
15
16 315 effects for Qi Gong but not for Tai Chi in comparison to TAU. The evidence had to be downgraded
17
18 316 due to very serious limitations of the quality of the RCTs and the meta-analysis, significant
19
20 317 heterogeneity, imprecision, and a possible high risk of publication bias.
21
22

23 24 318 *Yoga* 25

26
27 319 A high-quality meta-analysis of complex *yoga* interventions for various depressive disorders found 12
28
29 320 RCTs,¹⁴⁴ of which 5 RCTs of mostly unclear risk of bias met the inclusion criteria of this overview. The
30
31 321 pooled short-term effect on depression severity was of large size in comparison to TAU and medium
32
33 322 size in comparison to standard exercises (Figure 2). However, the evidence was assessed as very low
34
35 323 due to serious limitations of quality of the RCTs, significant heterogeneity, imprecision, and a possible
36
37 324 high risk of publication bias.
38
39

40
41 325 A further systematic review of yoga in major depressive disorder, revealed 5 newer yoga RCTs but did
42
43 326 not perform a meta-analysis because of high clinical heterogeneity. Risk of bias was comparably high
44
45 327 and evidence mostly conflicting.¹⁰⁶
46
47

48 328 ***Mindfulness-based interventions*** 49

50 51 329 *Mindfulness-based Cognitive Therapy (MBCT)* 52

53
54 330 A low-quality meta-analysis of mindfulness-based interventions in patients with major depression
55
56 331 found 4 RCTs investigating the effects of MBCT and Cognitive Behavioural Therapy (CBT) on depression
57
58 332 severity.¹⁵⁸ It revealed a significant large short-term effect of MBCT in comparison to TAU and similar
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1
2 333 effects in comparison to CBT (Figure 2). However, the quality of the evidence was considered as very
3
4 334 low due to the missing risk of bias assessment, inconsistency, and imprecision.

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6
7 335 A further moderate-quality systematic review on MBCT meta-analysed 9 RCTs on an individual patient
8
9 336 data level.¹⁴⁸ The sample consisted of patients with recurrent major depression currently in remission.
10
11 337 After a period of 60 weeks, MBCT showed a significantly reduced risk of depressive relapse compared
12
13 338 to those receiving antidepressant drugs (Figure 5). No serious adverse events were reported. The
14
15 339 evidence was assessed as moderate due to a possibly serious risk of publication bias.

16 340 *Mindfulness-based stress reduction (MBSR)*

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18
19 341 RCTs of MBSR and MBSR-like interventions were meta-analysed by a recent review ¹⁴³ showing a
20
21 342 significant large short-term effect on depression severity in comparison to TAU and enhanced TAU
22
23 343 (Figure 2). The quality of the evidence was assessed as low because of the overall unclear risk of
24
25 344 selection and performance bias and significant heterogeneity.

26 345 *Music therapy*

27
28
29 346 Studies on active and receptive *music therapy* in older patients with a diagnosis of depression were
30
31 347 summarized by a recent moderate-quality meta-analysis.¹⁶² Out of 19 RCTs, 8 met the inclusion
32
33 348 criteria for this overview. Pooled analyses of 5 of them revealed a significant medium effect size on
34
35 349 depression severity against TAU up to 52 weeks, however with bigger short-term than long-term
36
37 350 effects, considerable heterogeneity and overall unclear risk of selection, performance and detection
38
39 351 bias resulting in very low quality of evidence. Further 3 RCTs of the same review revealed low quality
40
41 352 evidence for a significant large consistent and precise effect of music therapy as an adjunctive
42
43 353 treatment to antidepressants (Figure 2).

44
45
46 354 A newer Cochrane review¹³⁸ found 8 different RCTs showing a significant large pooled effect of music
47
48 355 therapy on depression severity against TAU and similar effects as CBT (Figure 2). However, both
49
50 356 analyses revealed very low quality of evidence due to mostly unclear selection, performance,
51
52 357 detection and reporting bias, significant heterogeneity, and imprecision.

53 358 *Nutrition therapy*

1
2 359 No meta-analyses on specific diets for patients with depression were published to date. A systematic
3
4 360 review of 11 RCTs on whole-diet interventions in mostly healthy patients with subthreshold physical
5
6 361 conditions revealed conflicting evidence on the effectiveness of those intervention for the reduction
7
8 362 of depressive symptoms.¹¹⁴

10
11 363 A further systematic review on fasting in patients with chronic pain and inflammatory diseases¹¹⁰
12
13 364 included 1 RCT and 7 observational studies, which showed promising short-term but questionable
14
15 365 longer-term anti-depressive effects.

18 366 ***Religious/spiritual Interventions***

20
21 367 Very low to low quality of evidence was found by a moderate-quality systematic review of 9 RCTs on
22
23 368 Christian, Muslim, and spiritual CBT adaptations.¹⁴⁰ The analyses showed significant greater medium
24
25 369 effects on depression severity against TAU and standard CBT (Figure 2). Safety data were not
26
27 370 reported.

30 371 ***Supplements***

32 372 *Inositol*

33
34 373 A low quality meta-analysis of 2 RCTs in patients with major depression¹⁵³ revealed very low quality
35
36 374 evidence for inositol as adjective to standard antidepressants versus placebo in combination to standard
37
38 375 antidepressants (Figure 2).

40 376 *Magnesium*

41
42 377 No meta-analysis of magnesium supplementation was found. A recent systematic review detected no
43
44 378 RCTs in patients with a primary diagnosis of depression¹⁰⁷.

46 379 *Omega-3 fatty acids*

47
48 380 A high-quality Cochrane review¹⁴² of 26 RCTs found conflicting evidence of the effectiveness of
49
50 381 supplementation with omega-3 fatty acids versus placebo in patients with major depression as
51
52 382 depression severity significantly improved while response and remission rates did not so (Figure 2-4).

53
54 383 One additional RCT with a very low sample size showed similar effects of omega-3 fatty acids on

1
2 384 severity and response rates in comparison to antidepressant drug treatment (Figure 2 and 4).

3
4 385 However, all meta-analyses were based on very low quality of evidence because of limitations of the
5
6 386 study quality, significant heterogeneity, imprecision and a possibly high risk of publication bias.

7
8
9 387 *Probiotics*

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11
12 388 The effectiveness of the supplementation with probiotics on depression severity was analysed by a
13
14 389 moderate-quality meta-analysis of 5 RCTs, of which only one RCT with overall low risk of bias was
15
16 390 carried out on patients with major depression.¹⁴⁷ The analysis of the RCT revealed a significant
17
18 391 medium but imprecise short-term effect in comparison to placebo (Figure 2). This led to overall very
19
20 392 low quality of evidence for probiotics supplementation.

21
22
23
24 393 *S-adenosyl methionine (SAME)*

25
26
27 394 A high-quality Cochrane review¹⁴⁵ of the effectiveness and safety of SAME supplementation on
28
29 395 depression severity revealed 2 RCTs of low risk of bias that showed no significant pooled effects for
30
31 396 SAME monotherapy versus placebo. One RCT, also of low risk of bias showed a significant medium
32
33 397 short-term effect as adjunctive to standard antidepressant medication, both for depression severity.
34
35 398 Further 5 RCTs, which were rated as having overall unclear risk of bias, showed similar pooled effects
36
37 399 of SAME monotherapy on depression severity compared to standard antidepressant medication
38
39 400 (Figure 2). Original RCTs reported safety issues insufficiently. For all meta-analyses, the evidence was
40
41 401 assessed as low to very low quality because of limitations of the study quality, heterogeneity,
42
43 402 imprecision, and a possibly high risk of publication bias.

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47 403 *Tryptophan*

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49
50 404 A moderate-quality Cochrane review found 2 RCTs investigating the effectiveness and safety of
51
52 405 tryptophan supplementation on depression severity.¹⁵⁷ Pooling the effects led to significant greater
53
54 406 short-term response rates (Figure 4) as well as significant more adverse events in the tryptophan
55
56 407 group than in the placebo group. The evidence was assessed as very low quality because of an
57
58 408 unclear risk of detection, attrition and other bias, imprecision, and a possible risk for publication bias.

59
60
409 *Vitamins*

1
2 410 For Vitamin B6, no meta-analysis was available. A systematic review without meta-analysis revealed
3
4 411 2 RCTs showing no significant effects when compared to placebo.¹¹⁹
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6

7 412 Two further moderate to high-quality meta-analyses examined the effects of vitamin B9 (Folate) for
8
9 413 major depressive patients. While a Cochrane review¹⁵⁹ calculated a significant medium effect size of
10
11 414 folate-intake as an adjunctive intervention to standard drug treatment on depression severity, a
12
13 415 more recent review¹³⁹ revealed non-significant differences on severity and response rates (Figure 2
14
15 and 3). In contrast, a long-term combined intake of Vitamin B6, B9, and B12 was found to be
16
17 416 effective for relapse prevention after remission of symptoms as a result of one RCT (Figure 5).¹³⁹
18
19 417 However, all comparisons were based on very low quality of evidence mostly due to significant
20
21 418 heterogeneity, imprecision, and possible high risk of publication bias.
22
23 419

24
25 420 Another moderate-quality meta-analysis revealed evidence of the effectiveness of vitamin D-intake
26
27 421 on depression severity in comparison to placebo.¹⁵⁶ The analysis of the two included RCTs revealed a
28
29 422 significant medium short-term effect in favour of vitamin D in major depressed patients up to 8
30
31 423 weeks (Figure 2). The quality of evidence was rated as very low due to limitations of the study
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33 424 quality, missing values of heterogeneity, imprecision, a high risk of publication bias as well as
34
35 425 insufficient reporting of adverse events.
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39 426 *Zinc*

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42 427 The effectiveness of zinc for major depression was meta-analysed by a low-quality review of 3
43
44 428 RCTs.¹⁵⁵ It revealed a significant pooled short-term effect of medium size and low heterogeneity
45
46 429 when zinc was taken as an adjunctive to standard antidepressant drug treatment (Figure 2).
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49 430 However, the available evidence had to be assessed as very low as the meta-analysis did not perform
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51 431 risk of bias assessments and did not report adverse events.
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54 55 432 **Discussion**

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57 433 This systematic review provided a comprehensive overview of the evidence of CAM treatments for
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59 434 patients with a diagnosis or clinical symptoms of depression. Moderate quality evidence suggested
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435 the efficacy, comparative effectiveness to standard antidepressants, and safety of St. John's wort on

1
2 436 depression severity and response rates. For remission and relapse rates, the evidence was conflicting
3
4 437 and of lower quality. Moreover, moderate quality evidence showed that MBCT was superior to
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6 438 standard antidepressant drug treatment for the prevention of depression relapse in patients with
7
8 439 recurrent major depression. Low quality evidence suggested significant greater effects in favour of
9
10 440 electroacupuncture in comparison to standard antidepressants alone and in adjunction to standard
11
12 441 antidepressants for depression severity. For remission rates, low quality evidence revealed
13
14 442 comparable effects of electroacupuncture and standard antidepressants. Further significant greater
15
16 443 effects, which based on low quality evidence, were found for MBSR versus TAU, music therapy in
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18 444 adjunction to standard antidepressants, faith-adapted CBT versus CBT, and SAME versus standard
19
20 445 antidepressants. Other treatments such as manual acupuncture, aromatherapy, biofeedback, herbs
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22 446 (crocus sativus, curcuma longa, traditional Chinese herbs, lavandula angustifolia, echium amoenum,
23
24 447 rhodiola rosea), Homoeopathy, hypnosis, bright light therapy, massage, meditative movement
25
26 448 therapies (dance therapy, Qi Gong, Tai Chi, yoga), whole-diet interventions, fasting, and
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28 449 supplementation with inositol, magnesium, omega-3 fatty acids, probiotics, tryptophan, B- and D-
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30 450 vitamins, and zinc were based on very low quality of evidence or no level-1 evidence.
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36 451 The strengths of the review process included the comprehensive literature search based on a
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38 452 structured list of CAM specific topics, which had been operationalized for the Cochrane
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40 453 Collaboration.⁴¹ It therefore included evidence for more than the previously considered CAM
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42 454 approaches and provided systematic information where further high-quality studies are required. In
43
44 455 addition, we only included results of RCTs of patients with a diagnosis of depression or clinical
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46 456 relevant depressive symptoms and excluded RCTs on samples with minor or secondary symptoms of
47
48 457 depression by newly calculating effect sizes. Finally, we rated AMSTAR and considered the quality of
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50 458 the meta-analyses as well when grading the quality of the evidence.
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55 459 The conclusions derived from this overview are limited due to possibly missing evidence from newer
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57 460 RCTs, which have not been summarized by the included systematic reviews and meta-analyses. As it
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59 461 was not within the scope of this overview, we did not separately search for individual RCTs. We also
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462 did not include meta-analyses on studies of lower evidence levels, which may include bigger samples

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2 463 and may provide additional information about further possible treatment approaches. Moreover, we
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4 464 did not search online registries or conference proceedings for unpublished or ongoing meta-analyses,
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6 465 which may limit the conclusions. Another reason that limits the quality of evidence consists in the
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8 466 unsatisfactory methodological quality of some of the included meta-analyses. Although the
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10 467 methodological quality of the original RCTs might be acceptable, the bad reporting of some meta-
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12 468 analyses led to downgraded evidence. In particular, meta-analyses often missed to search for grey
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14 469 literature, cite excluded studies, adequately assess risk of bias of the original studies, and report
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16 470 complete I^2 statistics. As the latter are known to be unstable in meta-analyses with a small numbers
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18 471 of studies,¹⁶³ calculating confidence intervals for I^2 should be standard. Moreover, RCTs as well as
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20 472 meta-analyses often missed to systematically report on occurred adverse events, which also limits
21
22 473 the significance of the conclusions. In RCTs of non-pharmacological interventions, there is always a
23
24 474 high or unclear risk of performance bias and possibly high placebo effects. As such, adding credible
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26 475 sham interventions, controlling for patients' expectancies, and performing of ITT analyses is
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28 476 indispensable. However, meta-analyses mostly did not systematically assess these issues. In meta-
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30 477 analyses of pharmacological interventions, the influence of industrial funding sources was often not
31
32 478 adequately analysed. Here, subgroup analyses of studies having received no funding/non-industrial
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34 479 funding versus those having received industrial funding are needed. Results of meta-analyses that
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36 480 missed to report funding issues completely should be interpreted with caution. In general, it should be
37
38 481 noticed that all evidence is based on short-term pooled effects, except for meta-analyses of St. John's
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40 482 wort, MBCT, music therapy, and B- and D-vitamins that also provided longer-term follow-up data.
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42 483 Clinical recommendations for patients should follow the country-specific clinical practice guidelines
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44 484 considering the quality of evidence, the accessibility of the treatment, costs, and the preferences of
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46 485 the patients. While the guidelines agree^{30 31 33-35 164 165} that clinicians should select between either CBT
47
48 486 or second-generation antidepressant drugs for the treatment of major depression, the restricted
49
50 487 search strategy of some of the guidelines might limit their recommendations for CAM treatments.
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52 488 For patients who do reject or do not tolerate standard antidepressant drugs, one alternative
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54 489 treatment option may be St. John's wort. It is also recommended by the American Psychiatric
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2 490 Association Task Force report⁴² and the CANMAT Depression Work Group³² as being proven
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4 491 sufficiently for the short-term by placebo-controlled and equivalence trials with standard
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6 492 antidepressants for mild to moderate major depression. Particularly for bridging the gap between
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8 493 diagnosis and getting access to psychotherapy and meanwhile reducing/not-worsening depression
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10 494 severity, St. John's wort may be considered as a possibly better tolerated alternative to standard
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12 495 antidepressant drugs.¹⁶⁶ As St. John's wort is accessible without prescription and currently not
13
14 496 regulated by the US Food and Drug Administration, we agree with the ACP guidelines³⁰ that it
15
16 497 remains difficult for patients to obtain quality-controlled remedies. Moreover, St. John's wort is
17
18 498 associated with numerous herb-to-drug interactions.¹⁶⁷ Therefore, we would recommend clinicians
19
20 499 to educate their patients about possible effects, side effects and interactions who in turn should not
21
22 500 take St. John's wort without professional advise.³³ Despite those limitations, we would not
23
24 501 discourage a general therapeutic attempt with St. John's wort, even if we disagree with the NICE
25
26 502 guideline in this point.³⁴ Clinicians may also inform patients with recurrent major depression
27
28 503 currently in remission about the superiority of MBCT in comparison to standard antidepressants for
29
30 504 relapse prevention.³¹⁻³⁴ Finally, patients should also be informed that many other CAM treatments
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32 505 might show promising effects but cannot be recommended until further higher-quality studies will
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34 506 confirm their effectiveness and safety.
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40 507 Further research is needed, particularly for interventions that have shown preliminary evidence for
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42 508 reducing secondary symptoms of depression, promising short-term but no longer-term effects, or
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44 509 insufficient evidence due to low methodological quality of the original RCTs and/or the performed
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46 510 meta-analyses. Reporting of clinical trials and meta-analyses should necessarily follow the
47
48 511 CONSORT¹⁶⁸ and PRISMA guidelines,³⁶ respectively, including rigorous documentation and analysis of
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50 512 adverse events. Especially Chinese and Indian trials are still found to be poorly reported and tended
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52 513 to present more positive conclusions than those from western countries.^{169 170} Moreover, 7 of the
53
54 514 included meta-analyses showed no more than poor methodological quality. All were published in
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56 515 peer-reviewed journals in the past 5 years. One complementary journal is among them, while 6 of
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58 516 the journals are conventional psychiatric journals with impact factors ranging from 2.419 to 4.369.

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2 517 Thus, particularly the review process as well as the editorial work need to be improved. Further
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4 518 clinical practice guidelines should extend their search strategies and include standard search terms
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6 519 for CAM. This is also important for CAM therapies that do not show consistent evidence or that are
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8 520 not yet investigated. This information might be equally interesting for physicians as well as for
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11 521 patients to make an informed decision about the treatment for clinical depression.
12

13 14 522 **Conclusion**

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16 523 This overview of systematic reviews on CAM treatments for clinical depression aimed to provide a
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18 524 systematic search strategy and evidence base, on which further clinical practice guidelines may build
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20 525 their recommendations. To improve quality of trials and meta-analyses, researchers, reviewers as
21
22 526 well as editors are asked to ensure that future articles strictly adhere the CONSORT and PRISMA
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25 527 guidelines.
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15

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17
18 535 association that might create a conflict of interest regarding the submitted manuscript.
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21
22 536 **Author contribution statement**
23

24 537 HH was responsible for the conception and design of the study, the collection and analysis of the
25
26 538 study data and for drafting the manuscript. DA participated in the analysis of the study data and
27
28 539 drafting the manuscript. HC participated in the conception and design of the study and the analysis
29
30 540 of the study data, and critically revised the manuscript. GD participated in the conception and design
31
32 541 of the study, and critically revised the manuscript. All authors approved the final manuscript.
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36 542 **Data Availability**
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39 543 All data relevant to the study are included in the article or uploaded as supplementary information.
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2 **Figure legends**
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5 **Figure 1. Study flow diagram.**
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8 **Figure 2. Quality of evidence for depression severity.** ADM: Antidepressant medication, CBT:
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10 Cognitive Behavioural Therapy, CI: Confidence Interval, I²: Heterogeneity, MBCT: Mindfulness-based
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12 Cognitive Therapy, MBSR: Mindfulness-based Stress Reduction, N.c.: Not calculable because of only
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14 one included RCT, N.r.: Not reported, S-adenosyl methionine, Tau: Treatment as Usual
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18 **Figure 3. Quality of evidence for depression remission rates.** ADM: Antidepressant medication, CI:
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20 Confidence Interval, I²: Heterogeneity, N.c.: Not calculable because of only one included RCT, OR:
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22 Odds Ratio, RR: Risk Ratio, Tau: Treatment as Usual
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26 **Figure 4. Quality of evidence for depression response rates.** ADM: Antidepressant medication, CI:
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28 Confidence Interval, I²: Heterogeneity, N.c.: Not calculable because of only one included RCT, OR:
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30 Odds Ratio, RR: Risk Ratio
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33 **Figure 5. Quality of evidence for depression relapse rates.** ADM: Antidepressant medication, CI:
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35 Confidence Interval, HR: Hazard Ratio, I²: Heterogeneity, MBCT: Mindfulness-based Cognitive
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37 Therapy, N.c.: Not calculable because of only one included RCT, OR: Odds Ratio, RR: Risk Ratio, Tau:
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39 Treatment as Usual
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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)

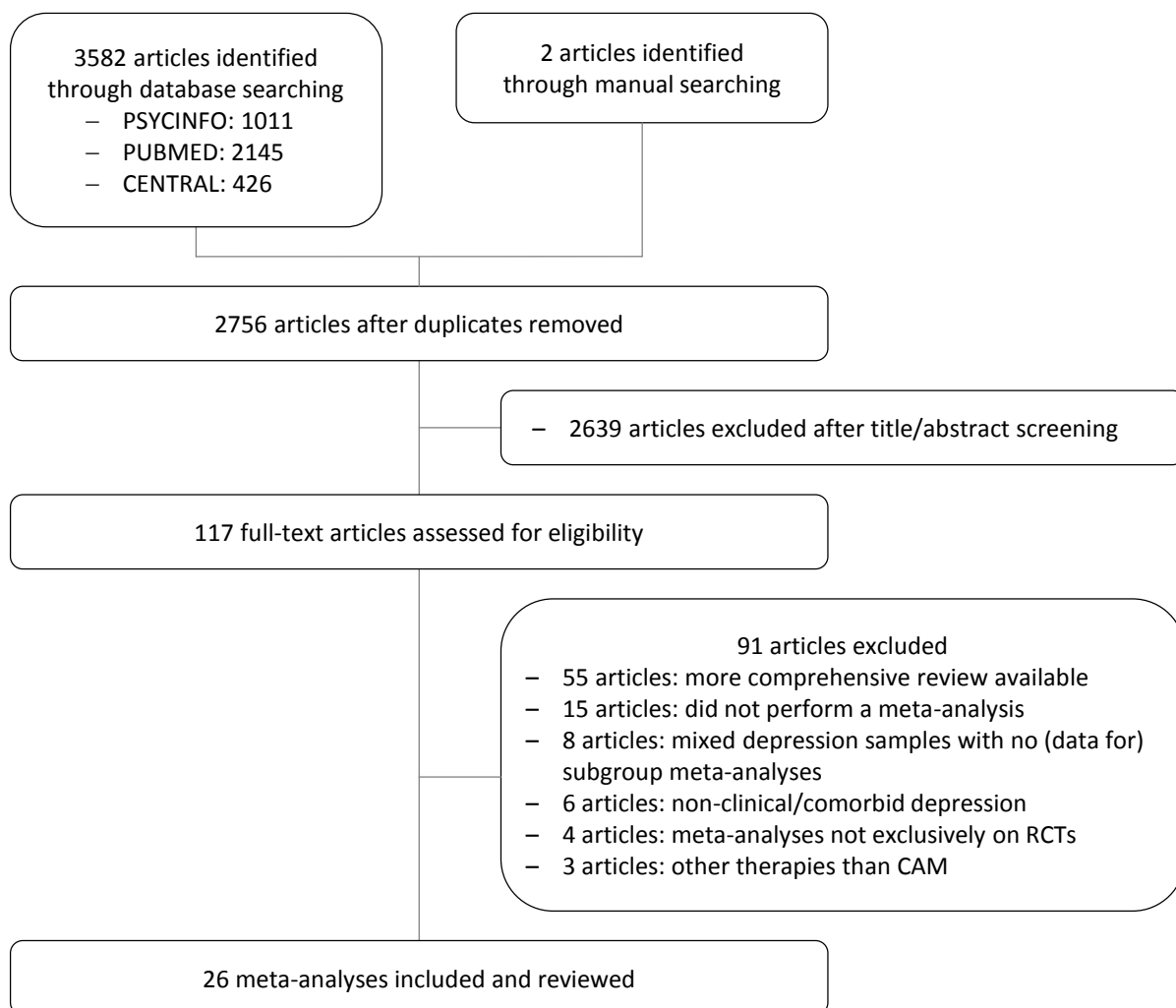
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Supplementary data

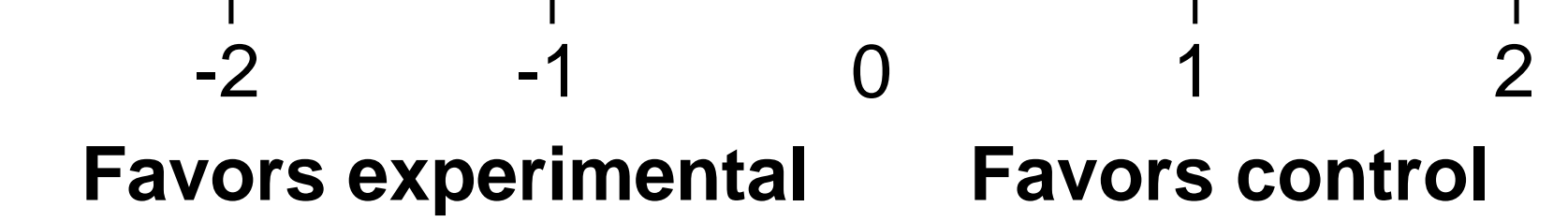
Supplementary table 1: Detailed AMSTAR ratings.

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

For peer review only



Quality of evidence	Intervention	Control	Reference	Trials	Parti- pants	I ²	Std. Mean Difference 95% CI	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]	
	Electroacupuncture	Adjunctive	Smith, 2018	8	539	93%	-1.32 [-2.09, -0.55]	
		TAU	Smith, 2018	1	30	n.c.	-1.26 [-2.10, -0.43]	
	Saffron	Sham	Smith, 2018	5	251	0%	0.12 [-0.14, 0.38]	
		Placebo	Hausenblas, 2013	2	71	0%	-1.62 [-2.14, -1.10]	
	Curcuma	ADM	Hausenblas, 2013	3	106	0%	-0.15 [-0.52, 0.22]	
		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	Strauss, 2014	3	115	72%	-0.97 [-1.81, -0.12]	
	Music therapy	CBT	Strauss, 2014	1	45	n.c.	-0.16 [-0.75, 0.43]	
		TAU	Zhao, 2016	5	244	76%	-0.57 [-1.03, -0.11]	
		TAU	Aalbers, 2017	4	219	83%	-0.98 [-1.69, -0.27]	
	Faith-adapted CBT	CBT	Aalbers, 2017	4	131	96%	-1.28 [-3.57, 1.02]	
		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]		
Vitamin D	Placebo	Almeida, 2015	5	505	66%	-0.12 [-0.45, 0.22]		
	Adjunctive	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]		



Quality of evidence	Intervention	Control	Reference	Trials	Partici- pants	I ²	Risk/Odds Ratio 95% CI	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	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%
	Omega-3	ADM	Yeung, 2014		10	1653	42%	RR: 1.00 [0.94, 1.07]
			Tryptophan	Placebo	Appleton, 2015	15	611	6%
	Folate	Adjunctive			Appleton, 2015	1	40	n.c.
			Shaw, 2002	2	46	0%	OR: 4.10 [1.28, 13.15]	
	Almeida, 2015	4	478	73%	OR: 1.18 [0.49, 2.83]			

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Favors control Favors experimental

Quality of evidence	Intervention	Control	Reference	Trials	Parti- pants	I ²	Risk/Odds/Hazard Ratio 95% CI	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]	

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Favors experimental Favors control

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	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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

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	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Electroacupuncture	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	<p>Severity:</p> <ul style="list-style-type: none"> – Sign. greater effects than TAU (1 RCT; SMD=-1.26; 95%CI=[-2.10,-0.43]; I²=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]; I²=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]; I²=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]; I²=33%; p=.20; N=274; ⊕⊕○○ low^{a,e}) <p>Remission:</p> <ul style="list-style-type: none"> – No sign. effects versus invasive SHAM (2 RCTs; RR=1.23; 95%CI=[0.35,4.29]; I²=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]; I²=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]; I²=49%; p=.10; N=273; ⊕○○○ very low^{a,d,e}) 	<ul style="list-style-type: none"> – Similar AEs as invasive SHAM (4 RCTs; RR=1.79; 95%CI=[0.99,3.25]; I²=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]; I²=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	<p>Response (50%):</p> <ul style="list-style-type: none"> – Sign. greater effects than PLACEBO (18 RCTs; RR=1.48; 95%CI=[1.23,1.77]; I²=75%; p<.001; N=3064; ⊕⊕⊕○ moderate^c) – Similar effects as SSRI/TCA/TECA (17 RCTs; RR=1.01; 95%CI=[0.93,1.09]; I²=17%; p=.25; N=2810; ⊕⊕⊕○ moderate^a) 	<ul style="list-style-type: none"> – Similar AEs as PLACEBO (14 RCTs; OR=0.98; 95%CI=[0.78,1.23]; I²=n.r.; N=2496), – Sign. less than ADMs (14 RCTs; OR=0.56; 95%CI=[0.43,0.74]; I²=n.r.; N=2663)

Supplementary table 1: continued

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	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)
37 38 39 40 41 42 43 44 45 46	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

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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,cj} #	– 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

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	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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 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)

Supplementary table 1: continued

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	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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

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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.

^aDowngraded one level because of study limitations (overall unclear or high risk of bias);

^bDowngraded two levels because of study limitations (overall unclear or high risk of bias) and limitations of the meta-analysis (AMSTAR ≤ 5);

^cDowngraded one level because of inconsistency (significant heterogeneity or no replication of the results);

^dDowngraded one level because of imprecision (confidence interval includes negligible or no effects or fewer than 250 participants were included in total);

^eDowngraded one level because of a probably high risk of publication bias.

For peer review only

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 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

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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

Page 1 of 2

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

For more information, visit: www.prisma-statement.org.

Page 2 of 2

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

BMJ Open

Complementary therapies for clinical depression: an overview of systematic reviews

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-028527.R2
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Date Submitted by the Author:	18-Jun-2019
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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Mental health, Patient-centred medicine
Keywords:	Depression, Complementary Therapies, Treatment Outcome, Safety, Systematic Review, Meta-analysis

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Manuscripts

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2 1 **Complementary therapies for clinical depression: an overview of systematic reviews**
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8 4 Heidemarie Haller^{1*}, Dennis Anheyer¹, Holger Cramer¹, Gustav Dobos¹
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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

1
2 41 **Strengths and limitations of this study**
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- 4 42 ▪ This systematic overview included the comprehensive literature search of important CAM
5
6 43 topics defined by the Cochrane Collaboration.
7
8 44 ▪ The inclusion criteria were restricted to meta-analyses of RCTs of patients with a clinical
9
10 45 diagnosis of depression.
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12
13 46 ▪ The quality of evidence from meta-analyses was assessed according to GRADE.
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15 47 ▪ There is a possible lack of evidence of newer RCTs, which have not been analysed by the
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17 48 included meta-analyses.
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49 Introduction

50 Depression is one of the most prevalent psychiatric disorders, with about 25% of women and 12% of
51 men suffering from at least one depressive episode during their lifetime.¹⁻³ According to the criteria
52 for diagnosis recommended by the American Psychiatric Association (APA), depressive disorders can
53 be distinguished by their degree of severity or duration and are also characterized by a high
54 comorbidity and an increase of psychological strain for the affected person.⁴ It is evident, that a
55 strong comorbid connection to several chronic conditions like addictions,⁵ neurodegenerative
56 diseases,^{6,7} or different psychiatric diseases⁸⁻¹¹ exists. This leads depressive disorders as one of the
57 leading causes of disability worldwide.¹²

58 The most commonly used treatments for depression are antidepressants, psychotherapy, or a
59 combination of drugs and psychotherapy. While both treatment strategies (alone and in
60 combination) have been shown to be effective,¹³⁻¹⁵ more recent meta-analyses also found high
61 dropout and low remission rates¹⁶⁻²¹ as well as clinically significant differences between
62 antidepressant drugs and placebos only for patients at the upper end of the very severely depressed
63 category.²² This may lead patients to search for alternatives. Increasing mainstream use of
64 complementary and alternative medicine (CAM) support this trend, particularly for different physical
65 conditions with comorbid affective disorders.²³⁻²⁷ The NIH defines CAM as therapeutic approaches
66 that are usually not included in conventional Western medicine systems.²⁸ CAM therapies used in
67 combination with conventional care are considered as complementary, those used instead of
68 conventional care as alternative practices. Types of CAM approaches include natural products, such
69 as herbs and dietary supplements (vitamins, minerals, and probiotics) and mind and body practices,
70 such as yoga, chiropractic and osteopathic manipulation, meditation, relaxation, acupuncture, tai chi,
71 qi gong, and hypnotherapy. Practices of traditional healers from Europe (naturopathy, homeopathy),
72 Asia (Ayurveda, traditional Chinese medicine), and other continents are also classified as CAM.²⁸
73 While some complementary therapies have become a promising adjunct in the standard treatment
74 of depression,^{29,30} others are known for their possible side effects or interactions with standard
75 drugs.³⁰ Recent clinical practice guidelines, in addition, vary widely in their search strategies and

1
2 76 resulting recommendations for CAM treatments. While the ACP,³¹ APA,³² and CANMAT guideline³³
3
4 77 provide a more comprehensive overview and critical appraisal of CAM treatments, the DGPPN,³⁴
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6 78 NICE,³⁵ and WFSBP³⁶ guidelines mainly focus on St. John's Wort and light therapy. Possible effects
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8 79 and risks of further CAM therapies are not discussed. Thus, the purpose of this overview is to provide
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10 a comprehensive search strategy of relevant CAM terms and systematically summarize the existing
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12 level-1 evidence for clinical depression as a basis for further guideline recommendations on the
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14 efficacy, effectiveness, and safety of CAM therapies.
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18 83 **Methods**

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20 84 This systematic overview of reviews was conducted in accordance with the Preferred Reporting Items
21
22 for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^{37 38} and the recommendations of the
23
24 Cochrane Collaboration.³⁹ The protocol was not prospectively registered.
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28 87 **Patient and Public Involvement**

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30 88 For this overview of reviews, patients or public were not involved.
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32

33 89 **Inclusion and exclusion criteria**

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35 90 – Types of studies: To be eligible, articles had to be systematic reviews with meta-analyses of
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37 91 randomized controlled clinical trials (RCTs) published in peer-reviewed journals. Conference
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39 92 abstracts or unpublished work were excluded as well as reviews summarizing evidence
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41 93 narratively. In cases of including same or similar original studies, only the review with the
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43 94 most recent, most comprehensive search was included. When systematic reviews reported
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45 95 results of RCTs as well as of designs of lower evidence levels, they were considered only if
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47 96 separate meta-analyses for the included RCTs were performed.
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51 97 – Types of participants: Only reviews of patients with a diagnosis of major depression or
52
53 98 dysthymia were eligible as well as reviews including patients/general population samples
54
55 99 with mild depressive symptoms above a clinical cut off or seasonal patterns. In contrast,
56
57 100 reviews studying depressive symptoms within specific subpopulations of substance-induced
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59 101 or demented patients, secondary depression due to another medical condition (e.g. post-
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102 stroke, cancer, or pain patients), bipolar disorders, or females with premenstrual dysphoric

1
2 103 disorder or postpartum depression were excluded. Further restrictions regarding the
3
4 104 diagnostic criteria or procedures, regarding age, gender, duration of the condition, or
5
6 105 symptom intensity were not applied.
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8
9 106 – Types of interventions: Reviews investigating the effectiveness and/or safety of a single,
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11 107 adjunctive or combined CAM treatment were included. For the classification of CAM
12
13 108 treatments the definition of the US National Institutes of Health⁴⁰ was followed. CAM
14
15 109 interventions have to be compared against treatment as usual (TAU)/waiting list,
16
17 110 placebo/sham, or standard medical care.
18
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20 111 – Types of outcomes: Reviews were eligible if they assessed at least one measure of
21
22 112 effectiveness such as severity of depressive symptoms, response rate (generally defined as a
23
24 113 50% decrease in depression scores after a period of up to 12 weeks of treatment),³¹
25
26 114 remission rate (generally defined as a period of up to 12 weeks during which a patient is
27
28 115 asymptomatic or has only few symptoms to a very mild degree).⁴¹ relapse rates, and/or a
29
30 116 measure of safety such as number of adverse events (AE), drug interactions, or numbers
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32 117 needed to harm for study withdrawal due to side effects.
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36 118 **Search strategy**

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38 119 Electronic literature was systematically searched via PubMed, PsycInfo and Central from their
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41 120 inception to January 31, 2018 without restrictions regarding time or language. Search terms for CAM
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43 121 treatments were selected in accordance with Cochrane recommendations (Table 1).⁴² Additional
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45 122 manual search included reference lists of previously published reviews^{14 29 30 43} and clinical practice
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47 123 guidelines.³¹⁻³⁶ Using PubMed Informer,⁴⁴ the search was updated until June 30, 2018.
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50 124 **Study selection process**

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52 125 To assess eligibility, articles were selected by screening titles and abstracts independently by two
53
54 126 authors (HH and DA). Any abstract considered potentially eligible by at least one author was read in
55
56 127 full to decide on its eligibility. Disagreements were rechecked with a third author (HC) until
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58 128 consensus was achieved.
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129 **Data extraction and quality assessment**

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2 130 Two authors (HH and DA) independently extracted data on the characteristics of the reviews
3
4 131 including the type of the intervention, the year of publication, the number and quality of the original
5
6 132 RCTs, the total number and age of the participants, and effectiveness and safety outcomes. The
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8 133 quality of the included reviews was assessed using the Assessment of the Methodological Quality of
9
10 134 Systematic Reviews (AMSTAR) tool.⁴⁵ The AMSTAR tool consists of 11 items asking about important
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12 135 methodological quality criteria of systematic reviews such as: a published apriori design, duplicate
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14 136 study selection and data extraction, a comprehensive literature search including grey literature, a list
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16 137 of included and excluded studies, summarized characteristics and quality assessment of included
17
18 138 studies, assessment of publication bias, appropriate method of data syntheses and deducing
19
20 139 conclusions, and a conflict of interests statement. AMSTAR has shown good construct validity and
21
22 140 inter-rater reliability. The Intraclass Correlation Coefficient (ICC) of the total AMSTAR score of 11
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24 141 points was reported as 0.84.⁴⁶ For this analysis, the two authors (HH and DA) who independently
25
26 142 assessed AMSTAR reached an ICC of 0.96. Disagreements regarding content or quality of the reviews
27
28 143 were rechecked with a third author (HC) and resolved by agreement.
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34 144 **Data synthesis**

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36 145 Results were pooled qualitatively by type of the intervention. Outcomes had to be calculated as
37
38 146 standard mean differences (SMDs), risk ratios (RRs), hazard ratios (HR), or odds ratios (ORs). If meta-
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40 147 analyses displayed mean differences (MDs), SMDs were calculated using Review Manager Software
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42 148 (RevMan, Version 5.3, The Nordic Cochrane Centre, Copenhagen) for better comparability of the
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44 149 results. RevMan was also used to exclude SMDs/RRs/HRs/ORs of selective RCTs that did not fulfil
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46 150 eligibility criteria of this overview. Effect sizes were classified according to Cohen as SMDs of 0.2 to
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48 151 0.49 = small effect, SMDs of 0.5 – 0.79 = medium effect, and SMDs of > 0.8 = large effect (absolute
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50 152 values)⁴⁷ with higher reduction of/improvement in depression scores represented by more negative
51
52 153 SMDs or RR/HR/ORs less than 1. According to the NICE guideline, a SMD of ≥ 0.5 or ≤ -0.5 ,
53
54 154 respectively was considered as a clinically relevant reduction of depression severity.⁴⁸ Statistical
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56 155 heterogeneity between studies was assessed by the chi-squared test with a p-value of $\leq .10$
57
58 156 indicating significant heterogeneity. The magnitude of heterogeneity was categorized by the I^2
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1
2 157 statistic with I^2 of 0 to 24% = no heterogeneity, I^2 of 25% to 49% = moderate heterogeneity, I^2 of 50%
3
4 158 to 74% = substantial heterogeneity, and I^2 of 75% to 100% = considerable heterogeneity.³⁹

159 **Quality of evidence**

160 The quality of evidence was assessed according to the Grades of Recommendation, Assessment,
161 Development, and Evaluation (GRADE) approach⁴⁹ individually by two authors (HH and DA).
162 Disagreements were rechecked with a third author (HC) until consensus was achieved. For each
163 outcome, the evidence can be graded as high, moderate, low or very low. Evidence from RCTs is
164 initially assessed as high, but can be downgraded by one level for serious or two levels for very
165 serious limitations of the study quality (of both RCTs and meta-analyses), inconsistency of the results,
166 indirectness of the evidence, imprecision of the results, and a potential risk of publication bias (as
167 assessed by the included meta-analyses).⁴⁹

168 **Results**

169 **Study selection**

170 A total of 3582 potentially eligible articles were identified by electronic database search. One
171 additional review was retrieved from manual search,⁵⁰ one from the updated search until June
172 2018.⁵¹ After removing duplicates, 2639 articles were excluded by screening of titles and abstracts.
173 The remaining 117 articles were read in full, of which further 91 reviews had to be excluded (Figure
174 1). Reasons for exclusion comprised 55 reviews where newer and/or more comprehensive reviews
175 on higher quality evidence were available.⁵⁰⁻⁵²⁻¹⁰⁵ Further 15 reviews have to be excluded as they
176 systematically summarized evidence but did not performed a meta-analysis mostly due to clinical
177 heterogeneity or a limited number of available RCTs.¹⁰⁶⁻¹²⁰ Eight reviews were excluded as they
178 included mixed depressive samples of bipolar or postpartum cases and did not provide (data for)
179 subgroup analyses for patients with the defined depression criteria.¹²¹⁻¹²⁸ Another six reviews
180 contained community samples with non-clinical depression or physically ill patients with comorbid
181 depressive symptoms but displayed no data for patients with a primary diagnosis of depression.¹²⁹⁻¹³⁴
182 Four reviews performed meta-analyses on both RCTs and non-RCTs and did not perform subgroup

1
2 183 analyses or extracted sufficient data for post hoc analyses.¹³⁵⁻¹³⁸ Three of the reviews analysed
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4 184 standard instead of complementary therapies and were therefore be excluded. Finally, 26 meta-
5
6 185 analyses could be included and reviewed.^{51 139-163}
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9 186 **Review characteristics and quality**

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12 187 Characteristics and quality appraisal of the included meta-analyses are summarized in the
13
14 188 Supplementary Table 1. Meta-analyses were conducted between 2002 and 2018 and included
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16 189 between 1 to 49 RCTs on 40 to 7104 adult patients. Meta-analyses on children and adolescents were
17
18 190 not available or did not meet inclusion criteria. Samples mostly consisted of patients suffering from
19
20 191 major depressive disorder^{140-143 145-151 154 156 157 159 160} but also included patients with mixed diagnoses
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22 192 of non-seasonal depression,^{51 153 162 163} patients with a diagnosis of seasonal depression,¹⁵² and
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24 193 patients with mild to severe symptoms of depression above a clinical cut-off.^{139 141 144 145 151 155 157 158} All
25
26 194 but one meta-analysis¹⁴¹ reported pooled outcomes based on common standardized questionnaires
27
28 195 or diagnostic interviews. Effects were analysed mostly up to 12 weeks of treatment (short-term),
29
30 196 except for four meta-analyses that included RCTs with effects reported up to 16, 24, or 32 weeks^{51 142}
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32 197 ^{143 151 160} and further three meta-analyses with long-term analyses equal to or greater than one year
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34 198 ^{149 157 163}. The AMSTAR total scores of the included meta-analyses ranged between 4 and 11 points
35
36 199 with a median quality of 7 points. The individual AMSTAR-ratings are reported in the Supplementary
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41 200 Table 2.
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44 201 **Synthesis of results**

46 202 ***Acupuncture***

48 203 *Manual acupuncture*

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53 204 A high-quality Cochrane review meta-analysed 49 RCTs in major depressed adults as well as those
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55 205 with clinically relevant symptoms of depression for manual acupuncture.⁵¹ For depression severity,
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57 206 significant effect sizes were found in comparisons to TAU and as in adjunction to standard
58
59 207 antidepressants, while acupuncture showed similar effects to invasive sham acupuncture and
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208 standard antidepressants (Figure 2). The analyses of remission rates did not reveal superiority of

1
2 209 acupuncture in the comparisons to TAU, invasive sham, standard antidepressants or in adjunction to
3
4 210 standard antidepressants (Figure 3). Adverse events reported in the acupuncture groups were
5
6 211 significantly lower than in patients treated with antidepressant drugs. However, most meta-analyses
7
8 212 showed significant heterogeneity, a lack of RCTs with low risk of bias and a possibly serious risk of
9
10 213 publication bias. Thus, the quality of evidence had to be downgraded to low and very low.

214 *Electroacupuncture*

215 For electroacupuncture, the same Cochrane review⁵¹ revealed very low quality of evidence for the
216 comparisons to TAU and invasive sham for both outcomes, severity (Figure 2) and remission (Figure
217 3), because of serious limitations of the quality of the RCTs, imprecision, and a high risk of publication
218 bias. For electroacupuncture monotherapy in comparison to standard antidepressants, low quality
219 evidence homogeneously suggested significant greater effects for severity and similar effects for
220 remission. As an adjunctive treatment to antidepressants, electroacupuncture effectiveness was
221 supported by low quality of evidence showing a significant greater consistent and precise effect for
222 depression severity. Although the mean adjunctive effect can be considered as large, the analysis
223 based on only one RCT with overall low risk of bias and 4 RCTs of lower methodological quality that
224 missed to include adjunctive sham acupuncture. For remission rates, very low quality of evidence
225 suggested no effects in adjunction to antidepressants. In addition, one RCT showed significant less
226 AEs when electroacupuncture was added to standard antidepressants.

227 *Aromatherapy*

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

232 *Biofeedback*

1
2 233 No meta-analysis on biofeedback was conducted to date. A recent systematic review revealed only
3
4 234 one RCT on the defined inclusion criteria for depression showing some effects in contrast to sham
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6 235 psychotherapy.¹¹⁸
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9 236 **Herbs**

12 237 *St. John's wort (Hypericum perforatum)*

15 238 The effectiveness of St. John's wort was meta-analysed by a Cochrane review of 29 RCTs¹⁵⁰ and a
16
17 239 more recent, higher quality meta-analysis of 35 RCTs.¹⁴² In comparison to placebo, St. John's wort
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19 240 showed moderate quality evidence of significant greater reductions of depression severity (Figure 2)
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21 241 and response rates (Figure 4). The evidence had to be downgraded due to significant heterogeneity
22
23 242 because of higher effects in studies from German-speaking countries than in those from the US or
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25 243 other European countries. In contrast, very low quality of evidence suggested no superiority to
26
27 244 placebo for remission (Figure 3) and response rates (Figure 5). In comparison to standard
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29 245 antidepressants, St. John's wort showed comparable severity reductions, response, remission, and
30
31 246 relapse rates. The quality of the evidence of the meta-analyses of severity and relapse rates had to
32
33 247 be downgraded to low and very low, respectively. The evidence of the response and remission rates
34
35 248 was considered as moderate quality showing the same results in both German and studies from
36
37 249 other countries but containing some RCTs with unclear risk of selection bias and detection bias.
38
39 250 Moreover, both meta-analyses^{142 150} showed similar AEs of St. John's wort to placebo but significant
40
41 251 less AEs than standard antidepressants.
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47 252 *Saffron (Crocus sativus)*

50 253 A moderate-quality meta-analysis examined the effectiveness and safety of saffron on depression
51
52 254 severity by including 5 RCTs in adult patients with major depression.¹⁴⁷ It revealed very low quality of
53
54 255 evidence for significant greater effects versus placebo and similar effects versus antidepressant
55
56 256 medication up to 8 weeks of treatment (Figure 2). No serious adverse events were reported, but
57
58 257 patients receiving saffron tend to report more adverse events than those receiving placebo and less
59
60 258 adverse events than those receiving antidepressant medication. Reasons for downgrading the

1
2 259 evidence included no replication of the results (all included RCTs were conducted by the same
3
4 260 research group), the small overall sample size, and the possibly high risk of publication bias.

7 261 *Curcumin (Curcuma longa)*

8
9
10 262 For the intake of curcumin, a moderate-quality meta-analysis¹⁵⁵ revealed very low quality of evidence
11
12 263 suggesting a small but significant short-term effect of low heterogeneity on depression severity by
13
14 264 pooling 6 RCTs (Figure 2). No serious adverse events were recorded. Evidence had to be downgraded
15
16 265 due to unclear risk of selection, performance, detection, attrition, and reporting bias in over the half
17
18 266 of the included RCTs, the imprecision of the pooled effect and the possibly high risk of publication
19
20
21 267 bias.

24 268 *Traditional Chinese herbs*

25
26
27 269 A comprehensive but low-quality systematic review of 296 RCTs of *Chinese herbal medicine* formulas
28
29 270 and single herbs¹⁶² revealed 21 RCTs of mostly unclear to high risk of selection, performance, and
30
31 271 detection bias and a serious risk of publication bias. Therefore, the evidence supporting the superiority
32
33 272 above placebo and the similarity towards standard antidepressants regarding depression severity
34
35 273 (Figure 2) and response rates (Figure 4) was assessed as very low.

39 274 *Other herbs*

40
41
42 275 For other than the described herbs, no meta-analyses were conducted to date. However, a
43
44 276 systematic review¹¹⁰ found three single RCTs that showed significant improvement in depressive
45
46 277 symptoms for *Lavandula angustifolia* as an adjunctive treatment to standard antidepressant drugs
47
48 278 versus antidepressant drugs alone and for *Echium amoenum* and *Rhodiola rosea* versus placebo. No
49
50
51 279 serious adverse events were reported.

53 280 *Homoeopathy*

54
55
56 281 No meta-analysis on *homoeopathic remedies* for depression were conducted yet. A recent systematic
57
58 282 review detected no placebo-controlled RCTs in patients with a primary diagnosis of depression.¹²⁹

59 283 *Hypnosis*

1
2 284 No meta-analysis on *hypnosis* or *self-hypnosis* techniques met the inclusion criteria of this overview.
3
4 285 The only available review on this topic¹²⁷ included 6 RCTs among which only one RCT included adults
5
6 286 with mild primary depression. Within the mixed sample of physically ill patients and healthy adults,
7
8 287 (self-)hypnosis appeared to be effective in decreasing depressive symptoms.

11 288 **Light therapy**

14 289 A high-quality Cochrane review meta-analysed the effects of *bright light therapy* in adjunction to
15
16 290 standard antidepressants versus sham light therapy plus antidepressants on severity and response
17
18 291 rates in patients suffering from non-seasonal depression.¹⁶¹ By pooling 18 RCTs of overall unclear risk
19
20 292 of bias, it revealed very low quality of evidence for a significant small but inconsistent and imprecise
21
22 293 effect on depression severity (Figure 2). A subgroup analysis of two RCTs with low risk of selection
23
24 294 bias and detection bias revealed a significant large effect on depression severity but based on one
25
26 295 non-peer-reviewed publication and one RCT that also included bipolar patients. Response rates did
27
28 296 not significantly differ between groups (Figure 4). Adverse events were reported non-systematically
29
30 297 but appeared to be comparable to sham light therapy except for hypomania that occurred more
31
32 298 often under verum light therapy.¹⁶¹

34
35
36
37 299 For patients with seasonal patterns of depression, a meta-analysis of 8 RCTs¹⁵² revealed very low
38
39 300 quality of evidence for a significant medium effect on depression severity of light monotherapy in
40
41 301 comparison to sham light therapy (Figure 2). Risk of bias of individual RCTs, heterogeneity, and safety
42
43 302 were not analysed leading to an overall low quality of the meta-analysis and downgrading of the
44
45 303 evidence.

48 49 304 **Massage therapy**

51
52 305 The literature search detected no meta-analysis of *massage therapy* in patients with a primary
53
54 306 depression. However, massage therapy appeared to be effective in decreasing depressive symptoms
55
56 307 in mixed samples of physically ill patients and healthy adult.¹³³ Future research will show, whether
57
58 308 these results may be transferable to primary depressed cases.

59 309 **Meditative movement therapies**

1
2 310 *Dance therapy*
3

4
5 311 Short-term effects of improvisatory or structured *dance therapy* as a combination of movement-
6
7 312 based work, interactive group components and insight/expressive methods were meta-analysed by a
8
9 313 Cochrane review of high methodological quality.¹⁵³ It revealed a significant large pooled effect size
10
11 314 for depression severity as an adjunctive treatment option to standard medical/psychotherapeutic
12
13 315 care based on two RCTs (Figure 2). Although the meta-analyses contained no heterogeneity and no
14
15 316 imprecise CI, the evidence had to be downgraded because of mostly unclear/high risk of bias of one
16
17 317 of the RCTs as well as the overall small sample size.
18
19

20
21 318 *Chinese movement therapies*
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23
24 319 A low-quality meta-analysis on Chinese meditative movement therapies revealed 30 RCTs, of which 2
25
26 320 RCTs on *Qi Gong* and 3 RCTs on *Tai Chi* met inclusion criteria for patients with mild to severe
27
28 321 symptoms of primary depression.¹⁵¹ Very low quality of evidence suggested significant short-term
29
30 322 effects for *Qi Gong* but not for *Tai Chi* in comparison to TAU. The evidence had to be downgraded
31
32 323 due to very serious limitations of the quality of the RCTs and the meta-analysis, significant
33
34 324 heterogeneity, imprecision, and a possible high risk of publication bias.
35
36

37
38 325 *Yoga*
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41 326 A high-quality meta-analysis of complex *yoga* interventions for various depressive disorders found 12
42
43 327 RCTs,¹⁴⁵ of which 5 RCTs of mostly unclear risk of bias met the inclusion criteria of this overview. The
44
45 328 pooled short-term effect on depression severity was of large size in comparison to TAU and medium
46
47 329 size in comparison to standard exercises (Figure 2). However, the evidence was assessed as very low
48
49 330 due to serious limitations of quality of the RCTs, significant heterogeneity, imprecision, and a possible
50
51 331 high risk of publication bias.
52
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54
55 332 A further systematic review of *yoga* in major depressive disorder, revealed 5 newer *yoga* RCTs but did
56
57 333 not perform a meta-analysis because of high clinical heterogeneity. Risk of bias was comparably high
58
59 334 and evidence mostly conflicting.¹⁰⁷
60

335 ***Mindfulness-based interventions***

1
2 336 *Mindfulness-based Cognitive Therapy (MBCT)*

3
4
5 337 A low-quality meta-analysis of mindfulness-based interventions in patients with major depression

6
7 338 found 4 RCTs investigating the effects of MBCT and Cognitive Behavioural Therapy (CBT) on depression

8
9 339 severity.¹⁵⁹ It revealed a significant large short-term effect of MBCT in comparison to TAU and similar

10
11 340 effects in comparison to CBT (Figure 2). However, the quality of the evidence was considered as very

12
13 341 low due to the missing risk of bias assessment, inconsistency, and imprecision.

14
15
16 342 A further moderate-quality systematic review on MBCT meta-analysed 9 RCTs on an individual patient

17
18 343 data level.¹⁴⁹ The sample consisted of patients with recurrent major depression currently in remission.

19
20 344 After a period of 60 weeks, MBCT showed a significantly reduced risk of depressive relapse compared

21
22 345 to those receiving antidepressant drugs (Figure 5). No serious adverse events were reported. The

23
24 346 evidence was assessed as moderate due to a possibly serious risk of publication bias.

25
26
27
28 347 *Mindfulness-based stress reduction (MBSR)*

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30
31 348 RCTs of MBSR and MBSR-like interventions were meta-analysed by a recent review¹⁴⁴ showing a

32
33 349 significant large short-term effect on depression severity in comparison to TAU and enhanced TAU

34
35 350 (Figure 2). The quality of the evidence was assessed as low because of the overall unclear risk of

36
37 351 selection and performance bias and significant heterogeneity.

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40
41 352 *Music therapy*

42
43
44 353 Studies on active and receptive *music therapy* in older patients with a diagnosis of depression were

45
46 354 summarized by a recent moderate-quality meta-analysis.¹⁶³ Out of 19 RCTs, 8 met the inclusion

47
48 355 criteria for this overview. Pooled analyses of 5 of them revealed a significant medium effect size on

49
50 356 depression severity against TAU up to 52 weeks, however with bigger short-term than long-term

51
52 357 effects, considerable heterogeneity and overall unclear risk of selection, performance and detection

53
54 358 bias resulting in very low quality of evidence. Further 3 RCTs of the same review revealed low quality

55
56 359 evidence for a significant large consistent and precise effect of music therapy as an adjunctive

57
58
59 360 treatment to antidepressants (Figure 2).

1
2 361 A newer Cochrane review¹³⁹ found 8 different RCTs showing a significant large pooled effect of music
3
4 362 therapy on depression severity against TAU and similar effects as CBT (Figure 2). However, both
5
6 363 analyses revealed very low quality of evidence due to mostly unclear selection, performance,
7
8 364 detection and reporting bias, significant heterogeneity, and imprecision.

11 365 ***Nutrition therapy***

14 366 No meta-analyses on specific diets for patients with depression were published to date. A systematic
15
16 367 review of 11 RCTs on whole-diet interventions in mostly healthy patients with subthreshold physical
17
18 368 conditions revealed conflicting evidence on the effectiveness of those intervention for the reduction
19
20 369 of depressive symptoms.¹¹⁵

24 370 A further systematic review on fasting in patients with chronic pain and inflammatory diseases¹¹¹
25
26 371 included 1 RCT and 7 observational studies, which showed promising short-term but questionable
27
28 372 longer-term anti-depressive effects.

31 373 ***Religious/spiritual Interventions***

34 374 Very low to low quality of evidence was found by a moderate-quality systematic review of 9 RCTs on
35
36 375 Christian, Muslim, and spiritual CBT adaptations.¹⁴¹ The analyses showed significant greater medium
37
38 376 effects on depression severity against TAU and standard CBT (Figure 2). Safety data were not
39
40 377 reported.

44 378 ***Supplements***

47 379 *Inositol*

50 380 A low quality meta-analysis of 2 RCTs in patients with major depression¹⁵⁴ revealed very low quality
51
52 381 evidence for inositol as adjective to standard antidepressants versus placebo in combination to standard
53
54 382 antidepressants (Figure 2).

57 383 *Magnesium*

59 384 No meta-analysis of magnesium supplementation was found. A recent systematic review detected no
60
385 RCTs in patients with a primary diagnosis of depression¹⁰⁸.

1
2 386 *Omega-3 fatty acids*
3

4
5 387 A high-quality Cochrane review¹⁴³ of 26 RCTs found conflicting evidence of the effectiveness of
6
7 388 supplementation with omega-3 fatty acids versus placebo in patients with major depression as
8
9 389 depression severity significantly improved while response and remission rates did not so (Figure 2-4).
10
11 390 One additional RCT with a very low sample size showed similar effects of omega-3 fatty acids on
12
13 391 severity and response rates in comparison to antidepressant drug treatment (Figure 2 and 4).
14
15 392 However, all meta-analyses were based on very low quality of evidence because of limitations of the
16
17 393 study quality, significant heterogeneity, imprecision and a possibly high risk of publication bias.
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21 394 *Probiotics*
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24 395 The effectiveness of the supplementation with probiotics on depression severity was analysed by a
25
26 396 moderate-quality meta-analysis of 5 RCTs, of which only one RCT with overall low risk of bias was
27
28 397 carried out on patients with major depression.¹⁴⁸ The analysis of the RCT revealed a significant
29
30 398 medium but imprecise short-term effect in comparison to placebo (Figure 2). This led to overall very
31
32 399 low quality of evidence for probiotics supplementation.
33
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35
36 400 *S-adenosyl methionine (SAME)*
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38
39 401 A high-quality Cochrane review¹⁴⁶ of the effectiveness and safety of SAME supplementation on
40
41 402 depression severity revealed 2 RCTs of low risk of bias that showed no significant pooled effects for
42
43 403 SAME monotherapy versus placebo. One RCT, also of low risk of bias showed a significant medium
44
45 404 short-term effect as adjunctive to standard antidepressant medication, both for depression severity.
46
47 405 Further 5 RCTs, which were rated as having overall unclear risk of bias, showed similar pooled effects
48
49 406 of SAME monotherapy on depression severity compared to standard antidepressant medication
50
51 407 (Figure 2). Original RCTs reported safety issues insufficiently. For all meta-analyses, the evidence was
52
53 408 assessed as low to very low quality because of limitations of the study quality, heterogeneity,
54
55 409 imprecision, and a possibly high risk of publication bias.
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59 410 *Tryptophan*
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1
2 411 A moderate-quality Cochrane review found 2 RCTs investigating the effectiveness and safety of
3
4 412 tryptophan supplementation on depression severity.¹⁵⁸ Pooling the effects led to significant greater
5
6 413 short-term response rates (Figure 4) as well as significant more adverse events in the tryptophan
7
8 414 group than in the placebo group. The evidence was assessed as very low quality because of an
9
10 415 unclear risk of detection, attrition and other bias, imprecision, and a possible risk for publication bias.

13 416 *Vitamins*

16 417 For Vitamin B6, no meta-analysis was available. A systematic review without meta-analysis revealed
18 418 2 RCTs showing no significant effects when compared to placebo.¹²⁰

21 419 Two further moderate to high-quality meta-analyses examined the effects of vitamin B9 (Folate) for
23 420 major depressive patients. While a Cochrane review¹⁶⁰ calculated a significant medium effect size of
25 421 folate-intake as an adjunctive intervention to standard drug treatment on depression severity, a
27 422 more recent review¹⁴⁰ revealed non-significant differences on severity and response rates (Figure 2
30 423 and 3). In contrast, a long-term combined intake of Vitamin B6, B9, and B12 was found to be
32 424 effective for relapse prevention after remission of symptoms as a result of one RCT (Figure 5).¹⁴⁰
35 425 However, all comparisons were based on very low quality of evidence mostly due to significant
37 426 heterogeneity, imprecision, and possible high risk of publication bias.

40 427 Another moderate-quality meta-analysis revealed evidence of the effectiveness of vitamin D-intake
42 428 on depression severity in comparison to placebo.¹⁵⁷ The analysis of the two included RCTs revealed a
44 429 significant medium short-term effect in favour of vitamin D in major depressed patients up to 8
46 430 weeks (Figure 2). The quality of evidence was rated as very low due to limitations of the study
48 431 quality, missing values of heterogeneity, imprecision, a high risk of publication bias as well as
50 432 insufficient reporting of adverse events.

54 433 *Zinc*

57 434 The effectiveness of zinc for major depression was meta-analysed by a low-quality review of 3
59 435 RCTs.¹⁵⁶ It revealed a significant pooled short-term effect of medium size and low heterogeneity
436 436 when zinc was taken as an adjunctive to standard antidepressant drug treatment (Figure 2).

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2 437 However, the available evidence had to be assessed as very low as the meta-analysis did not perform
3
4 438 risk of bias assessments and did not report adverse events.
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8 439 **Discussion**

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10 440 This systematic review provided a comprehensive overview of the evidence of CAM treatments for
11
12 441 patients with a diagnosis or clinical symptoms of depression. Moderate quality evidence suggested
13
14 442 the efficacy, comparative effectiveness to standard antidepressants, and safety of St. John's wort on
15
16 443 depression severity and response rates. For remission and relapse rates, the evidence was conflicting
17
18 444 and of lower quality. Moreover, moderate quality evidence showed that MBCT was superior to
19
20 445 standard antidepressant drug treatment for the prevention of depression relapse in patients with
21
22 446 recurrent major depression. Low quality evidence suggested significant greater effects in favour of
23
24 447 electroacupuncture in comparison to standard antidepressants alone and in adjunction to standard
25
26 448 antidepressants for depression severity. For remission rates, low quality evidence revealed
27
28 449 comparable effects of electroacupuncture and standard antidepressants. Further significant greater
29
30 450 effects, which based on low quality evidence, were found for MBSR versus TAU, music therapy in
31
32 451 adjunction to standard antidepressants, faith-adapted CBT versus CBT, and SAME versus standard
33
34 452 antidepressants. Other treatments such as manual acupuncture, aromatherapy, biofeedback, herbs
35
36 453 (crocus sativus, curcuma longa, traditional Chinese herbs, lavandula angustifolia, echium amoenum,
37
38 454 rhodiola rosea), Homoeopathy, hypnosis, bright light therapy, massage, meditative movement
39
40 455 therapies (dance therapy, Qi Gong, Tai Chi, yoga), whole-diet interventions, fasting, and
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42 456 supplementation with inositol, magnesium, omega-3 fatty acids, probiotics, tryptophan, B- and D-
43
44 457 vitamins, and zinc were based on very low quality of evidence or no level-1 evidence.
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51 458 The strengths of the review process included the comprehensive literature search based on a
52
53 459 structured list of CAM specific topics, which had been operationalized for the Cochrane
54
55 460 Collaboration.⁴² It therefore included evidence for more than the previously considered CAM
56
57 461 approaches and provided systematic information where further high-quality studies are required. In
58
59 462 addition, we only included results of RCTs of patients with a diagnosis of depression or clinical
60
463 relevant depressive symptoms and excluded RCTs on samples with minor or secondary symptoms of

1
2 464 depression by newly calculating effect sizes. Finally, we rated AMSTAR and considered the quality of
3
4 465 the meta-analyses as well when grading the quality of the evidence.
5
6

7 466 The conclusions derived from this overview are limited due to possibly missing evidence from newer
8
9 467 RCTs, which have not been summarized by the included systematic reviews and meta-analyses. As it
10
11 468 was not within the scope of this overview, we did not separately search for individual RCTs. We also
12
13 469 did not include meta-analyses on studies of lower evidence levels, which may include bigger samples
14
15 470 and may provide additional information about further possible treatment approaches. Moreover, we
16
17 471 did not search online registries or conference proceedings for unpublished or ongoing meta-analyses,
18
19 472 which may limit the conclusions. Another reason that limits the quality of evidence consists in the
20
21 473 unsatisfactory methodological quality of some of the included meta-analyses. Although the
22
23 474 methodological quality of the original RCTs might be acceptable, the bad reporting of some meta-
24
25 475 analyses led to downgraded evidence. In particular, meta-analyses often missed to search for grey
26
27 476 literature, cite excluded studies, adequately assess risk of bias of the original studies, and report
28
29 477 complete I^2 statistics. As the latter are known to be unstable in meta-analyses with a small numbers
30
31 478 of studies,¹⁶⁴ calculating confidence intervals for I^2 should be standard. Moreover, RCTs as well as
32
33 479 meta-analyses often missed to systematically report on occurred adverse events, which also limits
34
35 480 the significance of the conclusions. In RCTs of non-pharmacological interventions, there is always a
36
37 481 high or unclear risk of performance bias and possibly high placebo effects. As such, adding credible
38
39 482 sham interventions, controlling for patients' expectancies, and performing of ITT analyses is
40
41 483 indispensable. However, meta-analyses mostly did not systematically assess these issues. In meta-
42
43 484 analyses of pharmacological interventions, the influence of industrial funding sources was often not
44
45 485 adequately analysed. Here, subgroup analyses of studies having received no funding/non-industrial
46
47 486 funding versus those having received industrial funding are needed. Results of meta-analyses that
48
49 487 missed to report funding issues completely should interpreted with caution. In general, it should be
50
51 488 noticed that all evidence is based on short-term pooled effects, except for meta-analyses of St. John's
52
53 489 wort, MBCT, music therapy, and B- and D-vitamins that also provided longer-term follow-up data.
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1
2 490 Clinical recommendations for patients should follow the country-specific clinical practice guidelines
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4 491 considering the quality of evidence, the accessibility of the treatment, costs, and the preferences of
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6 492 the patients. While the guidelines agree^{31 32 34-36 165 166} that clinicians should select between either CBT
7
8 493 or second-generation antidepressant drugs for the treatment of major depression, the restricted
9
10 494 search strategy of some of the guidelines might limit their recommendations for CAM treatments.
11
12
13 495 For patients who do reject or do not tolerate standard antidepressant drugs, one alternative
14
15 496 treatment option may be St. John's wort. It is also recommended by the American Psychiatric
16
17 497 Association Task Force report⁴³ and the CANMAT Depression Work Group³³ as being proven
18
19 498 sufficiently for the short-term by placebo-controlled and equivalence trials with standard
20
21 499 antidepressants for mild to moderate major depression. Particularly for bridging the gap between
22
23 500 diagnosis and getting access to psychotherapy and meanwhile reducing/not-worsening depression
24
25 501 severity, St. John's wort may be considered as a possibly better tolerated alternative to standard
26
27 502 antidepressant drugs.¹⁶⁷ As St. John's wort is accessible without prescription and currently not
28
29 503 regulated by the US Food and Drug Administration, we agree with the ACP guidelines³¹ that it
30
31 504 remains difficult for patients to obtain quality-controlled remedies. Moreover, St. John's wort is
32
33 505 associated with numerous herb-to-drug interactions.¹⁶⁸ Therefore, we would recommend clinicians
34
35 506 to educate their patients about possible effects, side effects and interactions who in turn should not
36
37 507 take St. John's wort without professional advise.³⁴ Despite those limitations, we would not
38
39 508 discourage a general therapeutic attempt with St. John's wort, even if we disagree with the NICE
40
41 509 guideline in this point.³⁵ Clinicians may also inform patients with recurrent major depression
42
43 510 currently in remission about the superiority of MBCT in comparison to standard antidepressants for
44
45 511 relapse prevention.³²⁻³⁵ Finally, patients should also be informed that many other CAM treatments
46
47 512 might show promising effects but cannot be recommended until further higher-quality studies will
48
49 513 confirm their effectiveness and safety.
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56 514 Further research is needed, particularly for interventions that have shown preliminary evidence for
57
58 515 reducing secondary symptoms of depression, promising short-term but no longer-term effects, or
59
60 516 insufficient evidence due to low methodological quality of the original RCTs and/or the performed

1
2 517 meta-analyses. Reporting of clinical trials and meta-analyses should necessarily follow the
3
4 518 CONSORT¹⁶⁹ and PRISMA guidelines,³⁷ respectively, including rigorous documentation and analysis of
5
6 519 adverse events. Especially Chinese and Indian trials are still found to be poorly reported and tended
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8 520 to present more positive conclusions than those from western countries.^{170 171} Moreover, 7 of the
9
10 521 included meta-analyses showed no more than poor methodological quality. All were published in
11
12 522 peer-reviewed journals in the past 5 years. One complementary journal is among them, while 6 of
13
14 523 the journals are conventional psychiatric journals with impact factors ranging from 2.419 to 4.369.
15
16 524 Thus, particularly the review process as well as the editorial work need to be improved. Further
17
18 525 clinical practice guidelines should extend their search strategies and include standard search terms
19
20 526 for CAM. This is also important for CAM therapies that do not show consistent evidence or that are
21
22 527 not yet investigated. This information might be equally interesting for physicians as well as for
23
24 528 patients to make an informed decision about the treatment for clinical depression.
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29 529 **Conclusion**

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31 530 This overview of systematic reviews on CAM treatments for clinical depression aimed to provide a
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33 531 systematic search strategy and evidence base, on which further clinical practice guidelines may build
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35 532 their recommendations. To improve quality of trials and meta-analyses, researchers, reviewers as
36
37 533 well as editors are asked to ensure that future articles strictly adhere the CONSORT and PRISMA
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39 534 guidelines.
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12
13
14 540 **Competing interests**

15
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17
18 542 association that might create a conflict of interest regarding the submitted manuscript.

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21
22 543 **Author contribution statement**

23
24 544 HH was responsible for the conception and design of the study, the collection and analysis of the
25
26 545 study data and for drafting the manuscript. DA participated in the analysis of the study data and
27
28 546 drafting the manuscript. HC participated in the conception and design of the study and the analysis
29
30 547 of the study data, and critically revised the manuscript. GD participated in the conception and design
31
32 548 of the study, and critically revised the manuscript. All authors approved the final manuscript.

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36 549 **Data Availability**

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39 550 All data relevant to the study are included in the article or uploaded as supplementary information.
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2 **Figure legends**
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5 **Figure 1. Study flow diagram.**
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8 **Figure 2. Quality of evidence for depression severity.** ADM: Antidepressant medication, CBT:
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10 Cognitive Behavioural Therapy, CI: Confidence Interval, I²: Heterogeneity, MBCT: Mindfulness-based
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12 Cognitive Therapy, MBSR: Mindfulness-based Stress Reduction, N.c.: Not calculable because of only
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14 one included RCT, N.r.: Not reported, S-adenosyl methionine, Tau: Treatment as Usual
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18 **Figure 3. Quality of evidence for depression remission rates.** ADM: Antidepressant medication, CI:
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20 Confidence Interval, I²: Heterogeneity, N.c.: Not calculable because of only one included RCT, OR:
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22 Odds Ratio, RR: Risk Ratio, Tau: Treatment as Usual
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26 **Figure 4. Quality of evidence for depression response rates.** ADM: Antidepressant medication, CI:
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28 Confidence Interval, I²: Heterogeneity, N.c.: Not calculable because of only one included RCT, OR:
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30 Odds Ratio, RR: Risk Ratio
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33 **Figure 5. Quality of evidence for depression relapse rates.** ADM: Antidepressant medication, CI:
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35 Confidence Interval, HR: Hazard Ratio, I²: Heterogeneity, MBCT: Mindfulness-based Cognitive
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37 Therapy, N.c.: Not calculable because of only one included RCT, OR: Odds Ratio, RR: Risk Ratio, Tau:
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39 Treatment as Usual
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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)

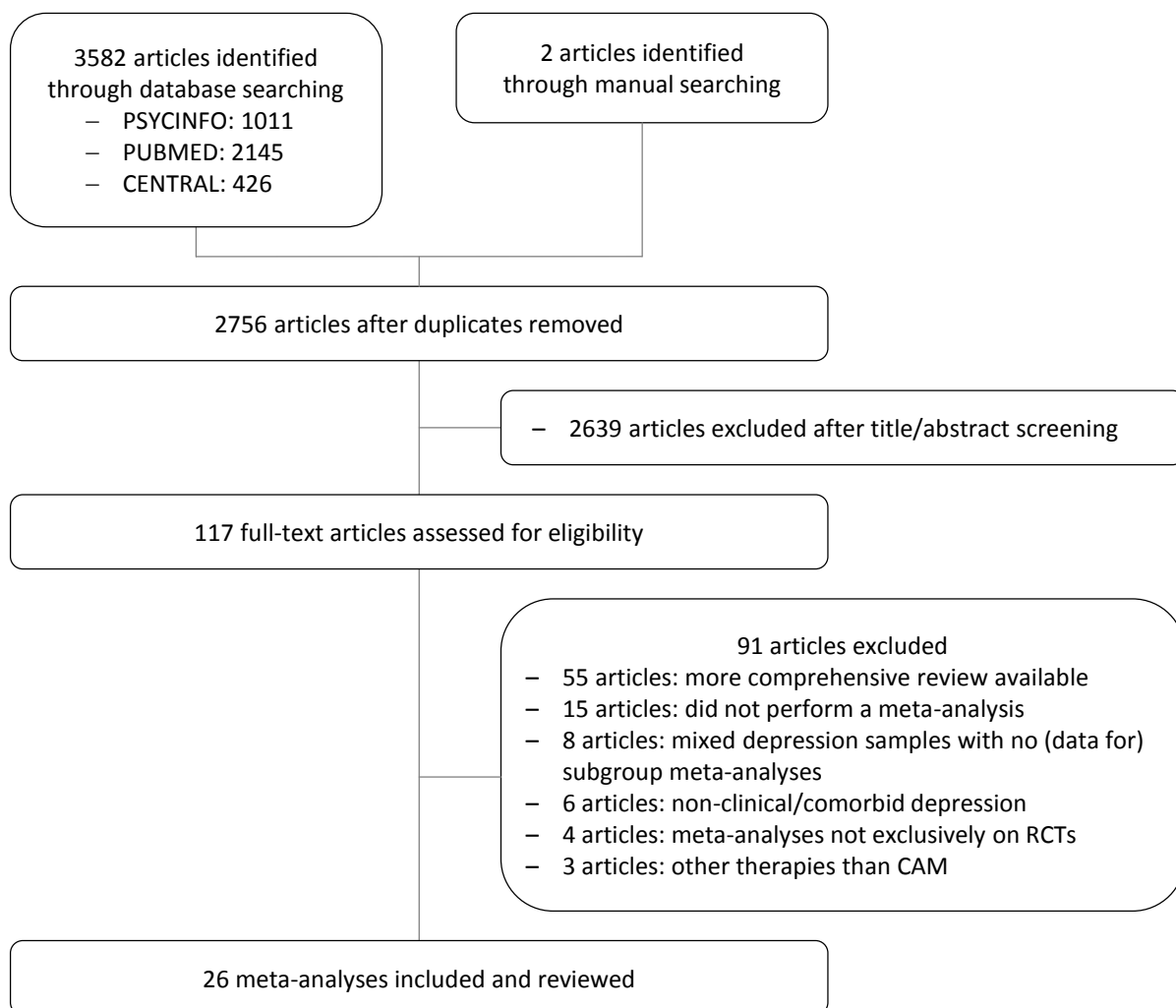
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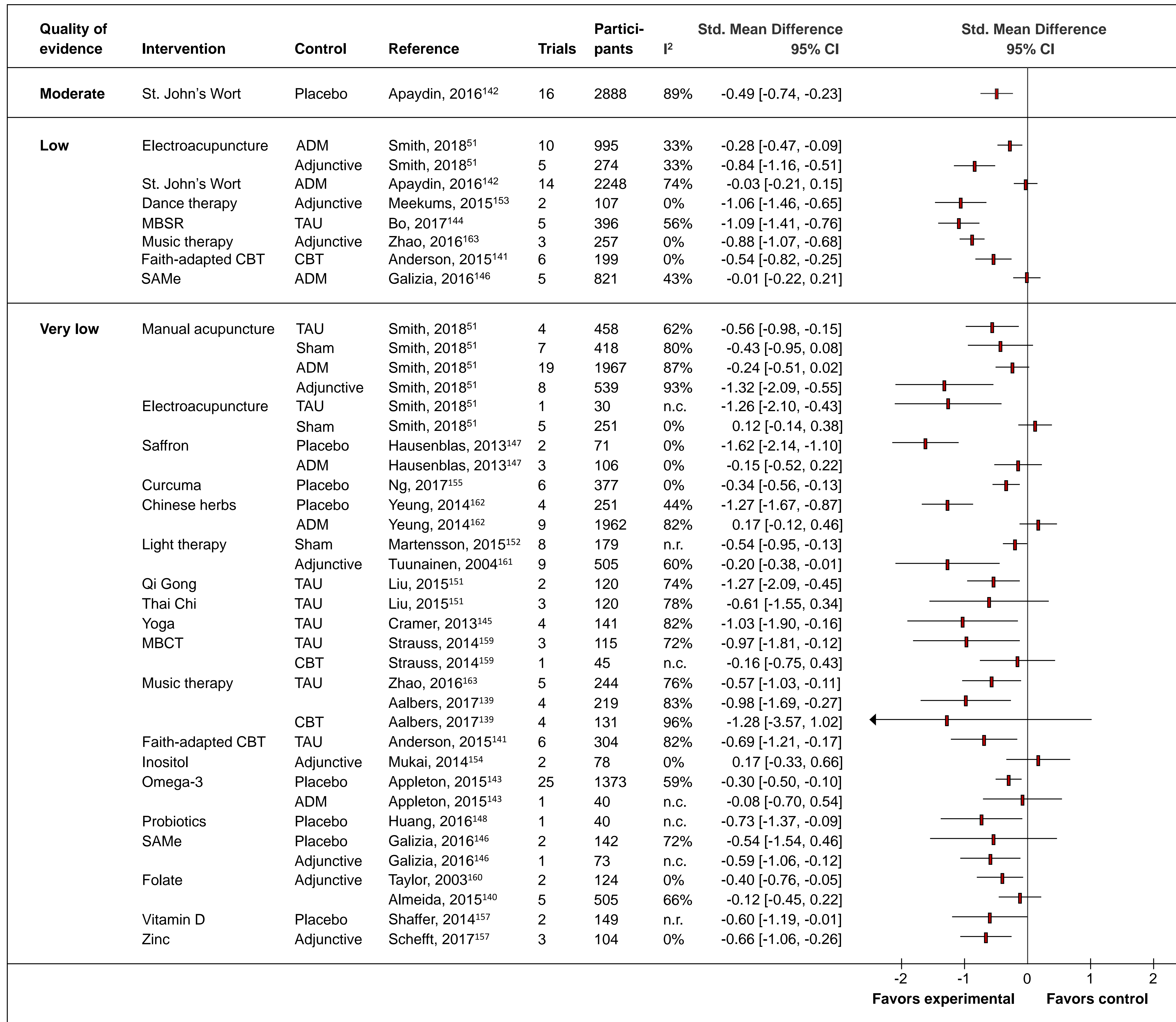
Supplementary data

Supplementary table 1: Detailed AMSTAR ratings.

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

For peer review only

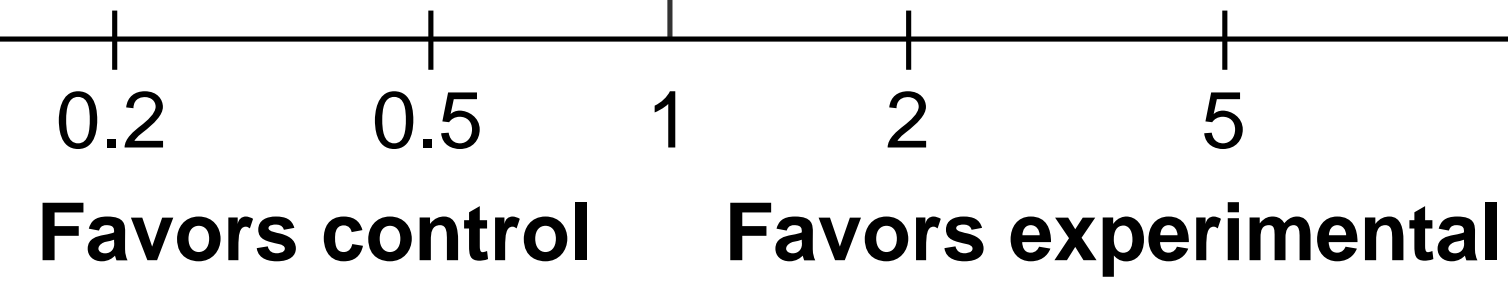




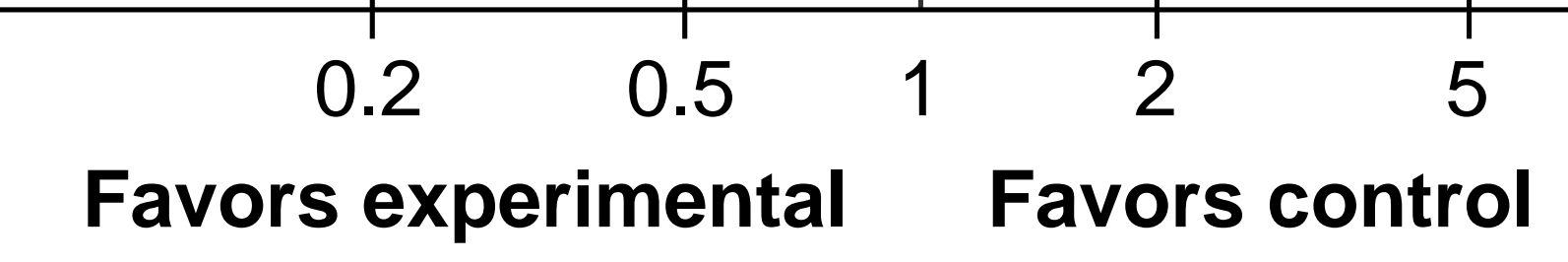
Quality of evidence	Intervention	Control	Reference	Trials	Partici- pants	I ²	Risk/Odds Ratio 95% CI	Risk/Odds Ratio 95% CI
Moderate	St. John's Wort	ADM	Apaydin, 2016 ¹⁴²	7	787	29%	RR: 1.17 [0.84, 1.62]	
Low	Manual acupuncture	ADM	Smith, 2018 ⁵¹	19	1967	87%	RR: 1.21 [1.06, 1.39]	
	Electroacupuncture	ADM	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	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	Participants	I ²	Risk/Odds/Hazard Ratio 95% CI	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]	



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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	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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

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	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
Electroacupuncture	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	<p>Severity:</p> <ul style="list-style-type: none"> – Sign. greater effects than TAU (1 RCT; SMD=-1.26; 95%CI=[-2.10,-0.43]; I²=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]; I²=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]; I²=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]; I²=33%; p=.20; N=274; ⊕⊕○○ low^{a,e}) <p>Remission:</p> <ul style="list-style-type: none"> – No sign. effects versus invasive SHAM (2 RCTs; RR=1.23; 95%CI=[0.35,4.29]; I²=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]; I²=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]; I²=49%; p=.10; N=273; ⊕○○○ very low^{a,d,e}) 	<ul style="list-style-type: none"> – Similar AEs as invasive SHAM (4 RCTs; RR=1.79; 95%CI=[0.99,3.25]; I²=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]; I²=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	<p>Response (50%):</p> <ul style="list-style-type: none"> – Sign. greater effects than PLACEBO (18 RCTs; RR=1.48; 95%CI=[1.23,1.77]; I²=75%; p<.001; N=3064; ⊕⊕⊕○ moderate^c) – Similar effects as SSRI/TCA/TECA (17 RCTs; RR=1.01; 95%CI=[0.93,1.09]; I²=17%; p=.25; N=2810; ⊕⊕⊕○ moderate^a) 	<ul style="list-style-type: none"> – Similar AEs as PLACEBO (14 RCTs; OR=0.98; 95%CI=[0.78,1.23]; I²=n.r.; N=2496), – Sign. less than ADMs (14 RCTs; OR=0.56; 95%CI=[0.43,0.74]; I²=n.r.; N=2663)

Supplementary table 1: continued

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety	
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	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)
37 38 39 40 41 42 43 44 45 46	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

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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,cj} #	– 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	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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 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 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

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments 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.

^aDowngraded one level because of study limitations (overall unclear or high risk of bias);

^bDowngraded two levels because of study limitations (overall unclear or high risk of bias) and limitations of the meta-analysis (AMSTAR ≤ 5);

^cDowngraded one level because of inconsistency (significant heterogeneity or no replication of the results);

^dDowngraded one level because of imprecision (confidence interval includes negligible or no effects or fewer than 250 participants were included in total);

^eDowngraded one level because of a probably high risk of publication bias.

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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 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

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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

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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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