PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Complementary therapies for clinical depression: an overview of systematic reviews
AUTHORS	Haller, Heidemarie; Anheyer, Dennis; Cramer, Holger; Dobos, Gustav

VERSION 1 - REVIEW

REVIEWER	David Mischoulon Massachusetts General Hospital, Boston, MA, USA Dr Mischoulon has received research support from Nordic Naturals. He has provided unpaid consulting for Pharmavite LLC and Gnosis USA, Inc. He has received honoraria for speaking from the Massachusetts General Hospital Psychiatry Academy, Blackmores, and PeerPoint Medical Education Institute, LLC. He has received royalties from Lippincott Williams & Wilkins for published book “Natural Medications for Psychiatric Disorders: Considering the Alternatives.”
REVIEW RETURNED	27-Jan-2019

GENERAL COMMENTS	This is a very interesting, well designed and thorough systematic review of previous systematic reviews and meta-analyses of CAM therapies for depression. The authors selected 26 meta-analyses examining treatments for major, minor, and seasonal depression. Findings showed moderate quality evidence for benefit of St John's wort for mild-moderate MDD. In recurrent MDD, MBCT showed moderate quality evidence compared to standard antidepressants for prevention of depression relapse. All other treatments were not supported as having quality evidence. Overall, the findings will be a good cautionary tale for the field, as well as for clinicians who use or are considering using these therapies in their practices. The article is well written, the data clearly presented, and the conclusions solid, with proper acknowledgment of limitations of the work. One particular question I want to raise is that in other similar reviews of meta-analyses, the authors also consider the role of industry sponsorship as a factor for downgrading the quality of the evidence. In particular there is the concern that when private companies fund (or even provide medication/placebo) in such studies, there is an automatic concern about bias. This is likely not an issue with therapies such as MBCT or massage, but could be a concern with herbal remedies or supplements. The authors should examine this, particularly in view that the one herbal remedy that their analysis supports is SJW, which has historically had much support from different

	manufacturers. At a minimum, they should address this issue in the Discussion as a potential concern or limitation.

REVIEWER	Lifeng Lin Florida State University
REVIEW RETURNED	10-Feb-2019

GENERAL COMMENTS	This manuscript performed an interesting overview of meta-analyses on the effects of complementary therapies for clinical depression. I have focused on the statistical analyses. I have several suggestions as follows. First, on page 5, the inclusion criteria required that all included meta-analyses must be published on peer-reviewed journals. I was wondering if this inclusion criterion might induce publication bias in the overview's conclusion? Did the authors obtain any unpublished meta-analyses (e.g., in conference proceedings, dissertations, etc.) on complementary therapies for clinical depression? The flowchart in Figure 1 does not clearly show that the authors found and exclude such meta-analyses. I think such meta-analyses may be still included in this overview to reduce the potential risk of publication bias; their quality could be graded as low. A related suggestion that the authors focused only on meta-analyses of RCTs, and they excluded meta-analyses that contained studies with designs other than RCTs and did not present the separate meta-analyses of RCTs. Is this exclusion a kind of waste of information? The authors could also present meta-analyses of non-RCTs (with specifying their design types) and downgrade their evidence. On page 7 in data synthesis, the authors transformed effect sizes in all meta-analyses of MDs to SMDs. I think if the original meta-analyses used MDs, then the studies in these meta-analyses were likely on the same scale and comparable. This transformation looks unnecessary to me. By transforming MDs to SMDs, the authors might obtain different conclusions from the original meta-analyses. Did the authors obtain the results of meta-analyses of SMDs by re-performing the analyses? Did the results (e.g., significance of treatment effects) change compared with those in the original meta-analyses? In addition, I'm wondering what methods were used by the authors to assess publication bias in each included meta-analysis? I think Figure 1 may also include the information about the p-value of the chi-squared test for heterogeneity and the p-value of publication bias. The I^2 statistic may only inform the magnitude of heterogeneity, not its significance. Minor comments: On page 4, line 59, did "both therapies" refer to the separate antidepressants and psychotherapy, not their combination, right? Was there any study showing the effectiveness of the combination?

	On page 7, change “Chi^2 statistics” to “chi-squared statistic” and “I^2 statistics” to “I^2” statistic. Specify the extent of SMD if SMD < 0.2 and the extent of heterogeneity if I^2 < 25%. Also, I believe the categorization of SMD’s extent should be on absolute magnitude (e.g., SMD < -0.8 also indicates large effects), and the authors should mention this.

REVIEWER	Jesus Montero-Marin University of Zaragoza, Spain
REVIEW RETURNED	16-Feb-2019

GENERAL COMMENTS	In general, I am positive with the work developed in this paper that aims to summarize the evidence of CAM for patients with clinical diagnosis of depression. However, in my oppinion and previous to publication, three points should be improved (and that is why I have ticked the points number 1, 8 and 12 in the check-list): 1) the CAM definition used should be explicitly explained in the text (and not only referred); 2) one more database should be included in the search to be more confident of studies obtained; and 3) more enphasis in the study limitations should be done in the discussion section (not only those due to the limitations of included studies, but also those of the own present study according to deffinitions, methods and procedures used to generate evidence regarding the research question).

VERSION 1 – AUTHOR RESPONSE

Reply to Reviewer 1:

This is a very interesting, well designed and thorough systematic review of previous systematic reviews and meta-analyses of CAM therapies for depression. The authors selected 26 meta-analyses examining treatments for major, minor, and seasonal depression. Findings showed moderate quality evidence for benefit of St John's wort for mild-moderate MDD. In recurrent MDD, MBCT showed moderate quality evidence compared to standard antidepressants for prevention of depression relapse. All other treatments were not supported as having quality evidence. Overall, the findings will be a good cautionary tale for the field, as well as for clinicians who use or are considering using these therapies in their practices. The article is well written, the data clearly presented, and the conclusions solid, with proper acknowledgment of limitations of the work. One particular question I want to raise is that in other similar reviews of meta-analyses, the authors also consider the role of industry sponsorship as a factor for downgrading the quality of the evidence. In particular there is the concern that when private companies fund (or even provide medication/placebo) in such studies, there is an automatic concern about bias. This is likely not an issue with therapies such as MBCT or massage, but could be a concern with herbal remedies or supplements. The authors should examine this, particularly in view that the one herbal remedy that their analysis supports is SJW, which has historically had much support from different manufacturers. At a minimum, they should address this issue in the Discussion as a potential concern or limitation.

 HH: Dear Dr. Mischoulon, thank you very much for your valuable comments on our manuscript. You are right that industrial funding is always possible risk of bias when conducting clinical studies. We considered funding issues in our manuscript two times. First, at the individual study level under the category “other risk of bias”. Second, at the level of meta-analyses when applying AMSTAR. As we used the GRADE approach for rating the quality of evidence, it was not possible to downgrade the evidence due to funding concerns in addition to the standard domains. For the special case of St. John’s Wort, we included two meta-analyses: One Cochrane review, which did not reach the highest possible AMSRAR-rating, but was conducted by authors of the Cochrane collaboration. Therefore, the results presented by this review should most likely be free of bias due to funding interests. The second meta-analysis assessed the funding issues of all individual studies as well as the own funding source that was not related to the private drug sector. With our conclusions for St. John’s wort, we followed the conclusions of both meta-analyses. Never¬theless, we included a sentence into the limitation section of our manuscript that addresses the special problem of industrial funding for pharmacological interventions. We also added that results of meta-analyses that did not address funding issues should be interpreted with caution (page 20, line 474ff).

Reply to Reviewer 2:

This manuscript performed an interesting overview of meta-analyses on the effects of complementary therapies for clinical depression. I have focused on the statistical analyses. I have several suggestions as follows. First, on page 5, the inclusion criteria required that all included meta-analyses must be published on peer-reviewed journals. I was wondering if this inclusion criterion might induce publication bias in the overview’s conclusion? Did the authors obtain any unpublished meta-analyses (e.g., in conference proceedings, dissertations, etc.) on complementary therapies for clinical depression? The flowchart in Figure 1 does not clearly show that the authors found and exclude such meta-analyses. I think such meta-analyses may be still included in this overview to reduce the potential risk of publication bias; their quality could be graded as low.

 HH: Dear Dr. Lin, thank you very much for your comments and effort while reviewing our manuscript. With regard to our inclusion criteria, we decided to consider only peer-reviewed meta-analyses, as the peer-review procedure should ensure high quality scientific work. Meta-analyses only published as conference abstracts could not be assessed for their quality, etc. and could therefore not be included in our overview. However, 15 of the included meta-analysis also searched for unpublished and grey literature. In addition, we assessed the risk of publication bias for all CAM treatments while grading the evidence. Thus, there should be no further risk of publication bias, except for newer RCT, not included in one of the analysed meta-analyses. This limitation was already discussed.

A related suggestion that the authors focused only on meta-analyses of RCTs, and they excluded meta-analyses that contained studies with designs other than RCTs and did not present the separate meta-analyses of RCTs. Is this exclusion a kind of waste of information? The authors could also present meta-analyses of non-RCTs (with specifying their design types) and downgrade their evidence.

 HH: You are right; we most likely missed evidence from several studies of lower level of evidence. However, the scope of this overview was to systematically summarize the level-1 evidence of CAM for depression. Therefore, we decided to not include study designs of lower level of evidence. We discussed this issue in the limitations (page 19-20, line 459ff).

On page 7 in data synthesis, the authors transformed effect sizes in all meta-analyses of MDs to SMDs. I think if the original meta-analyses used MDs, then the studies in these meta-analyses were likely on the same scale and comparable. This transformation looks unnecessary to me. By transforming MDs to SMDs, the authors might obtain different conclusions from the original meta-analyses. Did the authors obtain the results of meta-analyses of SMDs by re-performing the analyses? Did the results (e.g., significance of treatment effects) change compared with those in the original meta-analyses?

 HH: It is correct that it is the better way to calculate MDs when the included studies all used the same instrument. However, it makes it difficult to compare those results with MDs of other instruments or SMDs. Therefore, we decided to newly calculate SMDs in cases where only MDs were available. We again checked all analyses with the result that the significance did not change.

In addition, I'm wondering what methods were used by the authors to assess publication bias in each included meta-analysis? I think Figure 1 may also include the information about the p-value of the chi-squared test for heterogeneity and the p-value of publication bias. The I^2 statistic may only inform the magnitude of heterogeneity, not its significance.

 HH: For the assessment of publication bias, we strictly followed the assessments of the included meta-analyses (we added this also to the manuscript (page 8, line 157f). If a meta-analysis did not assess publication bias, the meta-analysis received a lower AMSTAR-rating and the quality of evidence according to GRADE was downgraded by one grade. Due to the complexity of the figures, we refer to the supplementary table 1, where we reported all p-values for all I^2 statistics. Moreover, the significance of the heterogeneity is also reflected by the GRADE-ratings, which are presented in all the figures.

Minor comments:

On page 4, line 59, did "both therapies" refer to the separate antidepressants and psychotherapy, not their combination, right? Was there any study showing the effectiveness of the combination?

 HH: Yes, both therapies refer to antidepressants and psychotherapy as single interventions, but also the combi¬nation was found to be effective. Thus, we changed the sentence so that it better to understand (page 4, line 59f).

On page 7, change "Chi^2 statistics" to "chi-squared statistic" and "I^2 statistics" to "I^2" statistic. Specify the extent of SMD if SMD < 0.2 and the extent of heterogeneity if I^2 < 25%. Also, I believe

the categorization of SMD's extent should be on absolute magnitude (e.g., SMD < -0.8 also indicates large effects), and the authors should mention this.

 HH: Thank you very much for these helpful suggestions. We changed it all and highlighted the changes in grey (page 7, line 141 – 149).

Reply to Reviewer 3:

In general, I am positive with the work developed in this paper that aims to summarize the evidence of CAM for patients with clinical diagnosis of depression. However, in my opinion and previous to publication, three points should be improved (and that is why I have ticked the points number 1, 8 and 12 in the check-list): 1) the CAM definition used should be explicitly explained in the text (and not only referred); 2) one more database should be included in the search to be more confident of studies obtained; and 3) more emphasis in the study limitations should be done in the discussion section (not only those due to the limitations of included studies, but also those of the own present study according to definitions, methods and procedures used to generate evidence regarding the research question).

 HH: Dear Dr. Montero-Marin, thank you very much for your valuable comments. You are right the definition of CAM treatments is a central issue of this overview. Therefore, we provided a detailed search term list of all CAM treatments in table 1. According to your second concern, we agree with you that sometimes a more comprehensive search in more than the recommended number of databases is better. However, for this overview, we decided to include the three most important databases for meta-analyses of studies of depressions. For possible missing meta-analyses, we also searched all available practice guidelines manually. Thus, we hope that we did not miss an important high-quality meta-analysis. Third, we added sentences to the discussion that complement the limitations of our own review process (page 19-20, line 457ff).

VERSION 2 – REVIEW

REVIEWER	David Mischoulon Massachusetts General Hospital, USA Dr Mischoulon has received research support from Nordic Naturals. He has provided unpaid consulting for Pharmavite LLC and Gnosis USA, Inc. He has received honoraria for speaking from the Massachusetts General Hospital Psychiatry Academy, Blackmores, Harvard Blog, and PeerPoint Medical Education Institute, LLC. He has received royalties from Lippincott Williams & Wilkins for published book "Natural Medications for Psychiatric Disorders: Considering the Alternatives."
REVIEW RETURNED	20-Mar-2019

GENERAL COMMENTS	The authors have adequately addressed the concerns of this reviewer and the other ones. The manuscript has been greatly

	strengthened by the revisions. No further modifications are requested.

REVIEWER	Lifeng Lin Florida State University
REVIEW RETURNED	12-Apr-2019

GENERAL COMMENTS	I thank the authors for responding to my previous comments in detail, and I do not have further comments on this manuscript.

REVIEWER	Jesus Montero-Marin University of Zaragoza Spain
REVIEW RETURNED	04-Apr-2019

GENERAL COMMENTS	Please, provide a comprehensive CAM definition in the introduction as a framework able to integrate all the different types of therapies included in the study under the CAM umbrella beyond the mere presentation of the search term list in table 1.

VERSION 2 – AUTHOR RESPONSE

Dear reviewers,

Thank you very much for reviewing our manuscript again. We added the requested defintion of CAM to the introduction and highlighted the changed paragraph in grey. Again, thank you very much for all your effort while reviewing our manuscript.