

## *Comparative Effectiveness Review Disposition of Comments Report*

**Research Review Title:** *Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder*

Draft review available for public comment from January 13, 2015 to February 11, 2015.

**Research Review Citation:** Gartlehner G, Gaynes BN, Amick HR, Asher G, Morgan LC, Coker-Schwimmer E, Forneris C, Boland E, Lux LJ, Gaylord S, Bann C, Pierl CB, Lohr KN. Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder. Comparative Effectiveness Review No. 161. (Prepared by the RTI International–University of North Carolina Evidence-based Practice Center under Contract No. 290-2012-00008-I.) AHRQ Publication No. 15(16)-EHC031-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2015. [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

### **Comments to Research Review**

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

| Commentator & Affiliation | Section | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| #2 Peer Reviewer          | General | <p>The authors did a very good job reviewing the literature , but one of the real "take home" messages is that we do not have enough evidence to make any definitive statement about comparative efficacy. I am very worried by the assertion that SJW is as effective as SGAs and CBT. Most of the positive studies with SJW are from German speaking countries where for years there was a strong bias favoring SJW as a first line therapy for MDD. Most of the data from the rest of the world has been unable to replicate these findings. Another issue that needs to be more explicitly discussed is that there may well be sample bias depending on how subjects are ascertained for trials. Furthermore, subjects interested in entering trials that compare and contrast an SGA with a CAM therapy are likely not to be representative of the larger cohort of patients suffering from MDD- this should at least be mentioned as a possible challenge with this analysis.</p> | <p>In our meta-analysis on treatment response, eight studies were included, four of which were conducted in Germany. Individually, two of the German studies favored SJW while two found no difference but tilted in favor of SSRIs. Of the other four studies (non-German), none found a difference although the estimates for two favored SSRI while the other two favored SJW. For treatment remission, only one of four included studies was from Germany.</p> <p>In short, the studies we have included do not support the contention of an overwhelming presence of German studies biased towards supporting SJW.</p> <p>The reviewer makes a good point about sampling bias, which may affect the generalizability of the study results. It is possible that patients self-selected based on their interest in taking a dietary supplement. Unfortunately, expectancy and credibility were not measured in any of the included studies so we cannot make any estimates for the magnitude and effect of sampling bias. We have noted this problem in the discussion section.</p> <p>The data in our meta-analyses does demonstrate similar comparative effectiveness between SJW and SGA. However, we changed our SOE rating from moderate to low for the SJW analyses to reflect our concern about dose range issues.</p> |

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| Commentator & Affiliation          | Section | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| #1 Technical Expert Panel Reviewer | General | <p>The report is clinically meaningful and should be of use to its intended audience. That being said I do have several concerns:</p> <p>1) By focusing exclusively on the second-generation antidepressants (SGAs) the report understates the efficacy of some of the older psychosocial approaches like interpersonal psychotherapy (IPT) that were largely established in comparisons to the tricyclic antidepressants. While I have no ties to IPT it is the psychosocial intervention that has done the most consistently well in comparisons to medications and there is no reason to think that it would not continue to do the same in direct comparisons to the SGAs.<br/> <b>[Continued on the next row]</b></p> | <p>The nominator chose SGAs as the intervention of interest because SGAs are the most commonly used pharmacological intervention for the treatment of depression. We appreciate the concern of the reviewer. In the report, we identified four trials (872 participants) that compared SGA monotherapy with interpersonal psychotherapy alone. Overall, response and remission rates did not lead to statistically different response or remission rates with low SOE.</p>                                                                                                                                                                                                                                                                                                                                 |
| #1 Technical Expert Panel Reviewer | General | <p><b>[Continued from previous row]</b></p> <p>2) By focusing exclusively on acute response the report understates what I think is the key advantage for the cognitive and (perhaps) behavioral interventions; namely that they appear to reduce risk for subsequent relapse (and perhaps recurrence) by about a half (see Cuijpers et al., 2013, BMJ Open, attached). In a chronically recurrent disorder like depression that is a very large advantage and might well lead patients (and health care systems as is the case in the UK) to prefer starting with a psychosocial intervention over medication (SGA or otherwise).<br/> <b>[Continued on the next row]</b></p>                                              | <p>We thank the reviewer for this comment and appreciate that reviews of chronically recurrent conditions like MDD should assess relapse and recurrence.</p> <p>We included relapse and recurrence as an outcome of interest, though few eligible studies reported it. As stated in the text for KQ 1a (full report), we reported relapse rates during off-treatment follow-up for 2 CBT vs. SGA comparisons. We also reported the rate and significance of relapse as reported in one of the third-wave CBT trials.</p> <p>In the Cuijpers et al. paper referenced by the reviewer, 3 of the 9 studies that reported relapse compared CBT with an SGA arm. One of those is already included in our review and is in the text referenced above (David et al.); we examined the other 2 studies (Dobson</p> |

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|                                    |         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <p>et al., and Hollon et al.) for inclusion in this study.</p> <p>We reviewed the design and results of Dobson et al. and feel that the post-acute followup design renders the relapse results ineligible for our purpose. During followup, patients initially treated with psychotherapy received no further treatment; patients initially treated with SGA, however, were either continued on the medication or withdrawn to pill placebo. Because only one half of one group continued to receive active treatment and the others did not, we cannot compare the effectiveness of treatments beyond the acute phase.</p> <p>For the suggested Hollon paper, we were only able to use data from the first 8 weeks of the acute treatment phase of the DeRubeis study (of which Hollon et al, cited by the reviewer, is an extension). Continuation results are not eligible for this review because patients in the SGA arm of the study were allowed to augment or switch medications if response was not achieved after 8 weeks.</p> |
| #1 Technical Expert Panel Reviewer | General | <p><b>[Continued from previous row]</b></p> <p>3) Given that most patients first approach their primary care physician regarding possible treatment and given that most primary care physicians are only competent to provide medication treatment (especially the SGAs) I doubt that even a balanced review as the one provided in this report will do much to change current practice. That is not so much a critique of the systematic review (which I think did a nice</p> | <p>Thank you. We appreciate the reviewer's observations.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

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|                                    |         | <p>job overall) as an indictment of our existing health care system. The UK has recently allotted 700 million pounds in training therapists in the empirically supported psychotherapies (like the cognitive and behavioral interventions and interpersonal psychotherapy) and those therapists are embedded in the primary care practices where they work on a daily basis with primary care physicians who can refer to a trusted colleague across the hall rather than an unknown psychotherapist across town. The upshot is that high quality psychosocial interventions (especially those with long-term enduring effects) are more readily accessible to the typical patient with depression in the UK than they are in the US.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| #3 Technical Expert Panel Reviewer | General | <p>The primary focus of this review is on nonpharmacological approaches to MDD. Within that domain the terms complementary and alternative medicine are used. This reviewer recommends that if possible it might be better to use the terms complementary and integrative medicine. That National Center for Complementary and Alternative Medicine at the National Institutes of Health just recently changed its name to the National Center for Complementary and Integrative Health. I believe that the approaches being discussed in this review are better described as complementary or integrative medicine. Indeed each of the treatment approaches, such as acupuncture is discussed in conjunction with SGA, so the assumption is that these are complementary - that is can be used to "complement" or be integrated with conventional care.</p> <p>I think this change would make this review be more "current" and not get caught in some of the stigma associated with "alternative medicine."</p> <p>This terminology is throughout the report from the Executive Summary to the Discussion and it presents a problem. The terminology is in the Tables and the Figures. From ES -3 to ES -6 referring to "CAM" therapies. This terminology is "dated."</p> <p>In the Executive Summary the Sections on Research Gaps and the review of the Discussion are particularly well written.</p> | <p>The primary focus of the report is a comparisons of pharmacologic vs. nonpharmacologic approaches. Although we recognize the recent change in name of the NCCAM to NCCIH, indeed, a number of our research questions pertained to alternative medicine (eg. SGA vs acupuncture monotherapy or SJW monotherapy), whereas the combination therapies fit the complementary medicine definition (eg. SGA vs SGA + Acupuncture combination therapy). Therefore, at least as pertains to this review, the term CAM appears more fitting than any other terminology.</p> |
| #4 Technical Expert Panel Reviewer | General | <p>The key questions, target population and audience are explicitly defined. The key questions are appropriate in terms of trying to help primary care clinicians decide among treatment options for patients with depression. Unfortunately, since the scope of the review needed to be limited to head-to-head trials, many of the conclusions are uninformative for</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <p>Thank you. For all outcomes that were deemed relevant for decisionmaking, we provide the strength of the evidence for these findings. Strength of evidence grades</p>                                                                                                                                                                                                                                                                                                                                                                                             |

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|                                                       |         | clinical decision-making. Many of the conclusions that can be made need to be framed in the context of study limitations and confounding effects if readers are to understand the relevance of the findings to policy making, guideline development or patient care.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | reflect various aspects of study limitations. We made these limitations explicit in Appenix E, the summary of findings tables.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Public Commenter:<br>American Psychiatric Association | General | One issue is that many of the trials, particularly with acupuncture and with St. John's wort, used doses of second generation antidepressants (SGAs) that were at the low end of the recommended dose range. This is likely to have affected primary outcome measures as well as influencing reported rates of response and remission. Loss of information known from placebo controlled studies may also affect readers' inferences about treatment efficacy. Based on the head-to head trial data, for example, SGAs and St. John's wort may appear to be equally efficacious. However, two large U.S. based placebo controlled trials of St. John's wort (Hypericum Depression Trial Study Group, JAMA. 287(14):1807-14, 2002; Shelton et al., JAMA. 285(15):1978-86, 2001) showed no benefit of St. John's wort relative to placebo. | <p>Five of eight trials of SJW used the lowest SSRI dose, two trials used moderate SSRI dose, and one trial used the majority of the appropriate dose range. The commenter is correct that low dosages may affect the treatment outcomes. We address this issue by conducting sensitivity analyses based on SGA dose, re-evaluate our SOE rating, and report those findings in the results and discussion sections. We also noted these issues in the abstract and executive summary.</p> <p>Additionally, we changed our SOE rating from moderate to low for the SJW analyses primarily due to the dose range issue.</p> <p>The HDTRG( Hypericum Depression Trial Study Group)study was a 3-arm study comparing SJW, moderate-dose sertaline, and placebo. Neither of the treatment groups separated from placebo, which reported 32% response in placebo-treated pts, so it is challenging to interpret the SJW vs placebo results. However, a Cochrane review of SJW vs placebo clearly demonstrates SJW efficacy.</p> |
| Public Commenter:<br>American                         | General | Overall, we think that the draft review discusses many important aspects of treatment options for major depressive disorder. The methodology used for conducting the systematic literature review, appraising                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Thank you. Direct head-head (H-H) evidence provides the strongest information about the comparative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

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| Psychiatric Association                               |         | the individual studies, and performing meta-analyses is well-delineated and comprehensive. However, we do have concerns that limiting the review to head-to-head trials may have affected the report's conclusions in several key areas.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | benefits and risks of competing interventions. Because H-H evidence was sparse or entirely missing in many cases, we conducted network meta-analyses for which we also included placebo controlled trials.                                                                                                     |
| Public Commenter:<br>American Psychiatric Association | General | Similarly, the most recent meta-analysis of sham-controlled trials of acupuncture in depression (Smith et al., Cochrane Database Syst Rev. 20(1):CD004046, 2010) found insufficient evidence for benefits of acupuncture in treating individuals with depression. The lack of inclusion of placebo-controlled trials in the review may also have influenced conclusions about the impact of depression severity on the choice of a treatment strategy. Because severely depressed individuals have a significantly increased risk of suicide, it is particularly important to institute a treatment with known efficacy as soon as possible. We understand that analysis of placebo-controlled and head-to-head trials was not possible given the scope of the review, but we think readers should be made aware that these factors should be considered before making decisions about treatment. | We addressed this issue in the Discussion chapter.                                                                                                                                                                                                                                                             |
| Public Commenter:<br>American College of Physicians   | General | This may be a semantic point, but I still don't understand the term "subthreshold depression". From their inclusion criteria, they included studies of patients with MDD of any severity. So is subthreshold depression just depression with a low score on one of the depression scales, or is it used to refer to patients who don't even have depression? May be important to clarify in terms of applicability again.                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | "Subthreshold depression" is the presence of depressive symptoms that may be clinically distressing but do not severe enough to meet criteria for a major depressive episode. We have made this change in the Applicability section of the Executive Summary and of the Discussion section in the full report. |
| Public Commenter:<br>American College of Physicians   | General | The question of applicability will be central to crafting recommendations. The authors address this in numerous places, but it may be worth knowing more about study entry criteria. Specifically, did the studies typically screen out patients with any hint of suicidal ideation? This has important implications for recommendations in primary care practice because we could say that you can choose either SGAs or CBT depending on pt preference, resources etc, but it would be important to specify which types of patients this applied to. It might also be helpful to know the range of HAM-D scores in the trials (I believe only the means are reported - might be useful to know the SD).                                                                                                                                                                                         | In general, studies excluded patients with suicidal ideation at the screening phases of the trials. We added text about this limitation to the chapter on applicability in the Executive Summary and the Discussion.                                                                                           |

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| Public<br>Commenter:<br>American College of Physicians | General | Where are the network meta-analysis results? Was this data incorporated into all the KQ's (if so, it seems like the number of trials reported is small)? Or were these data reported elsewhere?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | In the revised report, we provided all NWMA results in an appendix. We viewed network meta-analyses (NWMA) as an additional analytic tool in cases where direct evidence was missing or insufficient. If we had H-H studies, we did not report results from NWMA.                                                                                                                                                                             |
| Public<br>Commenter:<br>American College of Physicians | General | What about the option of no treatment/watchful waiting? This is obviously most relevant to those with mild-moderate MDD, but I think it is a relevant question since depression screening is occurring widely. I realize this review focused on comparative effectiveness, but their network meta-analysis would include all the placebo controlled trials. Is it possible to use these data to explore the question of whether or not there was good evidence supporting treatment effects compared to placebo in patients with lower HAM-D scores?                                                                                                                                                                                                                                 | For the current report, the question, unfortunately, is outside its scope. But we collected the data on placebo and other inactive comparisons. In a subsequent project we could analyze this question.                                                                                                                                                                                                                                       |
| Public<br>Commenter:<br>Maryalice JordanMarsh          | General | Overall a very valuable document for widely varying levels of audience. However a bit too mired in the past see notes on games interactive media telehealth including programmed phone calls social media as complements if not monotherapy. Tools in wide use by clinicians such as PHQ9 deserve at least a mention for future research. Furthermore Cochrane reviews on multiple intervention topics note the lack of information on training provided prior to delivery of an intervention suggesting that the target intervention was not truly delivered. So dose made available may be inadequate whether pharma or alternative and adherence to any regimen is rarely assessed in the detail required to guide clinical application. Thank you for the opportunity to comment | These are insightful comments about the current state of depression research in general, but the points about telehealth and PHQ9 use are not directly relevant to the focus of our comparative effectiveness review. We agree that the point about the risk of not receiving an adequate course of treatment is important, and we have already mentioned this point in our section on "Implications for Clinical and Policy Decisionmaking". |
| Public<br>Commenter:<br>Carol Alter                    | General | We have concerns regarding Key Question 2a. It appears from this question that the intent is to examine the role of a variety of pharmacologic and nonpharmacologic treatments when used to augment the effects of an SGA in the setting of nonresponsiveness to the SGA alone. The pharmacologic studies included in the analysis do not appear to contain any of the data related to FDA approved and commonly employed strategies such as antipsychotic medications indicated for use in this setting. Therefore it is unclear what the usefulness of this information might be for clinical practice. It would be helpful to offer clinically focused rationale for why those treatments or                                                                                      | Atypical antipsychotic use is a common practice with treatment resistant depression (usually defined as 2 or more treatment failures), with a number of atypical antipsychotics having FDA-approval as augmentation agents, and our inclusion criteria lists atypical antipsychotics as eligible for inclusion as an augmentation agent. However,                                                                                             |

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|                                                         |                                     | the studies which include evidence for their use were not included for consideration in this report.                                                                                                                                                                                                                                                                                                                                                                                                                                        | we identified no comparative effectiveness data involving augmentation with an atypical antipsychotic compared to a treatment involving an SGA that involved a population with only one failed treatment in the current episode, so we were not able to include any atypical antipsychotic data in our results.      |
| Public Commenter:<br>American Psychological Association | Abstract                            | little unclear whether authors are referring to the combination of CBT and John's Wort or whether authors are referring to them as individual therapies.                                                                                                                                                                                                                                                                                                                                                                                    | In the revised report we graded the strength of evidence as moderate for only one effectiveness outcome of one comparison: SGAs compared with cognitive behavioral therapy (CBT). Results indicate that SGAs and CBT had similar effectiveness regarding symptomatic relief in patients with moderate to severe MDD. |
| Public Commenter:<br>American Psychiatric Association   | Abstract,<br>page vi<br>Conclusions | Suggested edits: Given no clear differences in beneficial treatment effect among treatment options, the choice of the initial treatment of MDD should be strongly based on <i>results of previous treatment trials</i> , patient preferences and the feasibility (e.g., costs, likely adherence) following a discussion of the 2 advantages and disadvantages of each treatment option, <i>including risks of particular adverse effects and potential drug interactions</i> . [Note: Due to 508 compliance, red text converted to italics] | We appreciate this suggestion. We added " <i>results of previous treatment trials</i> " to the text                                                                                                                                                                                                                  |
| #4 Technical Expert Panel Reviewer                      | Abstract,<br>p. 7 line 30           | Without information about the low SGA dosing in many of these trials and without consideration of the results of two large U.S. RCTs in which St. John's Wort did not separate from placebo, one would infer from these statements that CBT and St. John's Wort are preferable to SGAs (due to comparable benefit but less harm). I don't think the subsequent evidence review and discussion would be consistent with that conclusion for St. John's wort.                                                                                 | Due to the low SGA doses used in many SJW trials, we have rated the SOE for SJW as low.                                                                                                                                                                                                                              |
| #4 Technical Expert Panel Reviewer                      | Abstract,<br>p. 7 line 38-40        | It may be helpful to specify what the comparators actually were. Also, the apparent increase in benefit of SGA + interpersonal therapy vs. SGA alone may be worth noting in this section. Alternatively, since the                                                                                                                                                                                                                                                                                                                          | Because of word limitations, we deleted the low/insufficient comparisons of different treatments                                                                                                                                                                                                                     |

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|                                    |                            | evidence is low/insufficient, one could end the paragraph after the initial sentence.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | from the abstract.                                                                                                                                                                                                                                             |
| #4 Technical Expert Panel Reviewer | Abstract, p. 7 line 41     | Emphasizing the effectiveness of combination SGA plus acupuncture in the abstract seems to overstate the evidence and its limitations, even with the caveats in the final sentence. Of the two studies that looked at combination treatment, one showed no difference in response and did not measure remission. The other combined findings from the groups with manual and electroacupuncture and used a range of medication doses that included low doses of SGA. That study also showed no difference in remission rates despite a reported difference in response rates. Many people are likely to read the abstract and not the remainder of the review and may be misled by the apparent superiority of SGA + acupuncture as a treatment approach. | We agree with the reviewer. Without context this could be misleading. We deleted all low/insufficient comparisons from the abstract                                                                                                                            |
| #4 Technical Expert Panel Reviewer | Abstract , p.7 lines 48-50 | The wording of this sentence seems a bit unclear. Is it intended to mean that there is no benefit to any of these approaches versus continuing on an ineffective first-line treatment? Or does it intend to mean that any of these approaches would be reasonable based on the available evidence? I think it would be clearer to readers to state ""For second-line therapies (i.e., ...), evidence is limited. However, available data suggests that switching to another SGA, switching to CBT, augmenting with a particular medication (e.g., ..... ) or augmenting with CBT are all options.                                                                                                                                                         | We agree, and we have modified the wording as suggested in the Abstract, in the last paragraph of the Executive Summary, and, and in the last paragraph of the Discussion.                                                                                     |
| #4 Technical Expert Panel Reviewer | Abstract, p. 7 lines 52-54 | The wording of this statement, specifically the phrase "does not support the superiority", may be somewhat confusing to readers. Also, by focusing the conclusions on the comparison of the treatment options, the abstract may inappropriately imply that there is limited benefit of treatment in general. The second sentence "Given no clear differences" also seems framed as a negative (e.g. rather than saying "Given comparable benefits").                                                                                                                                                                                                                                                                                                      | We revised the text. We removed "does not support the superiority", and changed to "Given comparable benefits the choice of the initial treatment of MDD should be strongly based on results of previous treatments, patient preferences, and the feasibility" |
| #4 Technical Expert Panel Reviewer | Abstract, p. 7 line 58     | Since these are not the only considerations and since other considerations such as drug interactions are important, it may be preferable to phrase this as "Factors such as adverse effects, drug interactions, costs, availability and personal preferences may be taken into consideration..." (The meaning of "personal engagement" in this context is not clear to me.)                                                                                                                                                                                                                                                                                                                                                                               | We revised the text and added factors to be considered selecting the treatment option.                                                                                                                                                                         |

| Commentator & Affiliation                          | Section                                                                                                        | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Response                                                                                                                                                                                                                                                                                                                                                               |
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| #4 Technical Expert Panel Reviewer                 | Abstract, p. 8 line 4-7                                                                                        | Although this statement is not unreasonable, it emphasizes a topic (i.e., shared decisionmaking) that was not a focus of the review. Rather than including this last sentence, it may be preferable in the conclusions to emphasize the facts that the head-to-head comparison data is quite limited and that data from other types of studies (particularly placebo-controlled trials of these treatment options) should also be taken into consideration by policy makers and guideline developers. | <p>We think that it is important to emphasize the importance of shared decision-making in the abstract, particularly because patient preference can become the decisive factor for which treatment will be chosen.</p> <p>With our NWMA we have taken placebo-controlled trials into consideration, however, the focus of this report is on head-head comparisons.</p> |
| Public Commenter: American College of Physicians   | Executive Summary, p.13, para 6                                                                                | clarify difference between “initial” and “first-line” treatment.                                                                                                                                                                                                                                                                                                                                                                                                                                      | Thank you. We changed the text of the report to replace “initial” with “first-step treatment”                                                                                                                                                                                                                                                                          |
| Public Commenter: American Psychiatric Association | Executive Summary, page ES-1, at the end of the first paragraph, under Condition and Therapeutic Strategies    | Suggested edits: Approximately one-third of patients with MDD are severely depressed, which is associated with <i>a harder to treat depression more difficulty in achieving treatment response and remission.</i> [Note: Due to 508 compliance, red text converted to italics]                                                                                                                                                                                                                        | We have added this part to the sentence in the Executive Summary and in the Background fo the report, to read, “a harder to treat depression, as evidenced by more difficulty in achieving treatment response and remission.”                                                                                                                                          |
| Public Commenter: American Psychiatric Association | Executive Summary, page ES-3, Table A. Inclusion/exclusion criteria: Interventions, Second-Gen Antidepressants | Because this list does not include other SGAs that are available outside of the US, we would suggest that this be indicated in some fashion such as "Second-Generation Antidepressants available in the United States" or with a footnote.                                                                                                                                                                                                                                                            | We agree, and we have added this clarification into Table A and in the Introduction where Table 1 is called out.                                                                                                                                                                                                                                                       |

| Commentator & Affiliation               | Section                             | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Response                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----------------------------------------|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Public Commenter: Maryalice JordanMarsh | Executive Summary- Methods, ES-3, 4 | The methodology for this review excludes placebo controlled trials from consideration. However we believe that there are two studies which should have been included in consideration of Key Question 2A see comment in references. In both of these studies the comparison was between an SGA vs. placebo SGA alone compared to an SGA augmented with quetiapine. Based on the draft report this comparison SGA plus minus augmenting agent should be considered. Additional information regarding Seroquel XR is contained in the product insert which is included in this comment.                                                                  | These references are important, but they use a placebo control and are not relevant for our direct comparative effectiveness results. Also, we did not perform a network meta-analysis because we did not have a sufficient number of studies. Most trials did not connect through common comparators; furthermore, trials did not report on the same efficacy outcome. Therefore, we did not have sufficient data to run NWMA for KQ2. |
| Public Commenter: Maryalice JordanMarsh | Executive Summary – Methods, ES-4   | I thought that quality of life was a common measure of success for depression related treatments yet this is not in the Outcomes table on p.ES4 please provide more links for example to TEP and Key Informant details.                                                                                                                                                                                                                                                                                                                                                                                                                                | Quality of life is included as an outcome and listed in Table A                                                                                                                                                                                                                                                                                                                                                                         |
| #4 Technical Expert Panel Reviewer      | Executive Summary, p. 13 line16-17  | The wording "harder to treat depression" is unclear. It would be helpful to be more specific depending upon the point made in the cited reference.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | We agree and have clarified this sentence to read, "a harder to treat depression, as evidenced by more difficulty in achieving treatment response and remission."                                                                                                                                                                                                                                                                       |
| #4 Technical Expert Panel Reviewer      | Executive Summary, p. 13 line 34-36 | Commenting on the benefit of exercise seems out of place in this part of the document.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | We agree and have removed the text, but we still feel it is important to briefly describe exercise treatment in the Background section..                                                                                                                                                                                                                                                                                                |
| #4 Technical Expert Panel Reviewer      | Executive Summary, p. 13 line 28    | Commenting on the length of psychological treatment seems out of place since the parameters of treatment are not discussed for the other treatment options.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | We agree and have removed this text.                                                                                                                                                                                                                                                                                                                                                                                                    |
| #4 Technical Expert Panel Reviewer      | Executive Summary, p.16 line 6      | The lack of inclusion of placebo comparison groups in the literature review is obviously an outgrowth of the way in which the key questions were framed. However it may make the conclusions of the review harder to interpret, particularly for clinicians and policy makers. It may be helpful to explicitly discuss the reasons that the key questions (and thus the exclusion criteria) were crafted in this fashion. It may also be worth stating, in an explicit fashion, that this document begins with the assumption that a major depressive episode has been identified and has been determined to be of sufficient duration and severity to | The focus of the report was on head-head comparisons of various treatment options. Key questions and eligibility were developed through a process involving the public and key informants who deemed a comparative effectiveness questions as more clinically relevant than comparisons with placebo.                                                                                                                                   |

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| Commentator & Affiliation                        | Section                           | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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|                                                  |                                   | warrant treatment. An additional assumption is presumably that the patient has not had prior trials of treatment for this episode (and does not meet criteria for treatment resistance), given the focus on treatment of depression in primary care. However, the literature does not always address the degree of treatment resistance in designing trials of antidepressant treatments despite the evidence that treatment resistance has a clear impact on outcome.                                                                                                        | One of our basic assumptions was that FDA approval of SGAs for the treatment of MDD is an indication for general efficacy of these treatments.                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Public Commenter: Maryalice JordanMarsh          | Executive Summary – Methods, ES-5 | There are problems with the risk of bias instrument used when applied to studies of psychological treatments. Two of the criteria are Care provider masked Patient masked These criteria are not applicable to studies of psychotherapy because you blind the provider of a psychological treatment and the patient is an active participant in whatever treatment they receive. When applied these criteria artificially inflate the risk of bias in studies of psychological treatments. Please eliminate these irrelevant risk categories and reevaluate the risk of bias. | We recognize that in studies of psychological interventions, masking of patients and providers is not usually possible. While we noted whether patients and providers were masked to treatment, we did not consider these factors in our assessments: no psychological studies were deemed at increased risk of bias for those reasons alone. As a result, reevaluation of the studies of psychological treatments is not necessary.                                                                                                                                                                         |
| Public Commenter: American College of Physicians | Executive Summary, p. 18, para 6  | Many studies report remission rates. How much variability was there in the definition of remission rates across studies?                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <p>Of the studies that compared SGA with psychotherapy that reported remission, nearly all defined it as HAM-D-17 &lt; 7 or ≤ 7. Of the 2 that deviated from that definition, 1 defined it as HAM-D-17 ≤ 10 and 1 defined it as MADRS ≤ 12. One study required both HAM-D-17 ≤ 7 and BDI ≤ 10 for remission.</p> <p>The study that used the higher cutoff on the HAM-D-17 (Segal, 2006) was rated high risk of bias and only included in sensitivity analysis. Literature suggests that the most appropriate MADRS definition for remission is 7. The higher MADRS value used by Lam et al. could result</p> |

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| Commentator & Affiliation                        | Section                          | Comment                                                                                                                                                                                                                                                                  | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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|                                                  |                                  |                                                                                                                                                                                                                                                                          | <p>in higher remission rates compared with the other studies, but the remission rate was similar for both groups (53% vs, 56%; p=0.74).</p> <p>Because of those reasons and the fact that we used a relative measure for meta-analyses, we are confident that the effect of the variability on pooled estimates is small.</p>                                                                                                                                            |
| #4 Technical Expert Panel Reviewer               | Executive Summary, p. 19 line 4  | Although technically correct as phrased, the concept of a "risk of response" may be confusing to some readers.                                                                                                                                                           | We have rephrased the title to "Response of SGAs compared with other eligible interventions (relative risks).                                                                                                                                                                                                                                                                                                                                                            |
| Public Commenter: American College of Physicians | Executive Summary, p.20, para 1  | What about "third wave" CBT (Figure A)? Oops! Appears below. Why not have this paragraph follow CBT?                                                                                                                                                                     | We changed the order of presentation of the Third Wave by making it CBT-Third Wave –because all of the interventions are in alphabetical order.                                                                                                                                                                                                                                                                                                                          |
| #4 Technical Expert Panel Reviewer               | Executive Summary, p. 20 line 48 | Were there any differences in remission rates with addition of CBT to SGA? Even if there was no data on this question, it would be useful to state.                                                                                                                      | Thank you. We have changed the relevant statement in the Executive Summary to read, "Adding CBT to SGA did not show any benefit in remission or response..."                                                                                                                                                                                                                                                                                                             |
| #4 Technical Expert Panel Reviewer               | Executive Summary, p. 20 line 52 | Since these studies all related to interpersonal psychotherapy, it would be clearer to include "interpersonal psychotherapy" in the title of this section. Also, I don't think most people would view interpersonal psychotherapy and integrative therapy as synonymous. | <p>Thank you; we recognize the inherent potential for confusion with the term "integrative.". However, in order to maintain consistency with how we categorize the other psychotherapeutic interventions (i.e., using the CCDAN terms), we have retained the term "integrative."</p> <p>Although the CCDAN guidelines do not provide an explanation or rationale for why these interventions are considered integrative therapies, it is likely because they combine</p> |

| Commentator & Affiliation          | Section                          | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|                                    |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <p>elements and concepts from more than one of the broader theoretical frameworks such as Cognitive Behavior Therapy or Psychodynamic Therapies.</p> <p>To address potential confusion, we have used “interpersonal psychotherapy” in as many places as it is appropriate to do so, and we have added further detail regarding Integrative Therapies to the Methods section, and we have clarified in several places that the only type of Integrative Therapy used in the included studies was interpersonal psychotherapy (IPT).</p> |
| #4 Technical Expert Panel Reviewer | Executive Summary, p. 21 line 21 | <p>It would be preferable to specify the specific symptoms and behaviors that were assessed.</p> <p>Although the use of the word "suicidality" has been common, it is also problematic in that it lumps together suicidal ideas, suicidal behaviors (including attempts) and suicide, per se. The demographic and clinical characteristics of individuals with suicidal ideas and attempts overlap with but are not identical to the characteristics of those who die by suicide. Lumping these together has given rise to confusion and misinterpretation in the literature with associated effects on clinical care. Thus, if the studies looked only at suicidal ideas or at suicidal attempts it would be preferable to state that. And if suicides occurred in the studies, it would be helpful to state that as well. It would be helpful to address the same issues of suicidal ideas, attempts and deaths in all of the comparisons if possible. (For example, the interpersonal therapy section does not mention "suicidality".)</p> | <p>We agree that it would be more informative to use an alternative to the composite “suicidality” measure. We have changed “suicidality” to “suicidal ideas or behaviors” in cases when studies do not specify which suicidality outcomes they report. If the information is available, we have identified when studies’ reporting focused on specific types of suicidal ideas or behaviors.</p>                                                                                                                                      |
| #4 Technical Expert Panel Reviewer | Executive Summary, p. 21 line 37 | <p>This is an example where the lack of inclusion of placebo controlled trials makes it difficult to know how to apply this information in a clinical context. The title "severity as a moderator of treatment effectiveness" leads the reader to expect information on whether treatment is more effective (or not) with more severe illness. Yet the available trials are</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <p>The question here is whether depressive severity moderates the comparative effectiveness of the interventions, not whether it moderates the effect of a specific</p>                                                                                                                                                                                                                                                                                                                                                                |

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| Commentator & Affiliation                           | Section                                | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Response                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----------------------------------------------------|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                     |                                        | only examining whether there were differences between treatments. The fact that there was insufficient evidence for this comparison is only partly germane to the clinical question of whether depression severity moderates effectiveness. At least in the executive summary, it is not clear whether the range of depression severities in the available trials is sufficient to show an effect of severity on responses, even if such an effect existed. (For example, if virtually all of the patients in the trials had moderate depression, then it would be hard to show any impact of severity on response.)                                                                                                                                                                                                                                                                                                                            | intervention. We have clarified this part by renaming the section, “Severity as a Moderator of Comparative Treatment Effectiveness” (adding “Comparative”) in both the Executive Summary and the Key Findings in Results, and have clarified this in the Key Findings section of the Discussion                                                                                                                                |
| Public Commenter:<br>American College of Physicians | Executive Summary,<br>p. 22, para 4    | First mention of a network meta-analysis result. Why here, as opposed to reporting the results of the network meta-analysis separately?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | In the revised report we present results from NWMA in an appendix. We viewed NWMA as an additional analytic tool in direct evidence was missing. In most cases, direct evidence is more reliable than results from NWMA. . We used results of NWMA when direct evidence was missing or unreliable for certain comparisons.<br>Eg:<br>SGA vs acupuncture<br>SGA vs Omega 3 FA<br>SGA vs SAME<br>SGA vs Exercise                 |
| #4 Technical Expert Panel Reviewer                  | Executive Summary,<br>p. 23 line 13 ff | In this section, when the various comparisons conclude the are "no substantial differences", it is not clear whether the comparison is between 2 second-line options (SGA 1 changed either to SGA 2 or SGA3 with response to SGA2 compared to SGA3) or whether the response rate to the 1st line SGA treatment is being compared to the 2nd line treatment. If there is a comparable response to first and second-line treatments, this suggests (as in the STAR-D study) that incremental increases in the overall response to treatment can be achieved by continuing to pursue trials of additional treatment if the initial trial or trials are unsuccessful. However, for augmentation studies a lack of difference between treatments suggests no benefits to augmenting with another treatment. Particularly in the SGA vs. SGA sections, it may be helpful to be explicit about the comparisons that showed no substantial differences. | The comparison is among second line therapies. We have clarified this point by adding “of second line therapies” in the text description of each of these results. Also, at the Executive Summary level, we are not mentioning specific names of medications if the findings are insignificant or insufficient because we do not want to emphasize specific compounds if the data do not clearly support one versus the other. |

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| Commentator & Affiliation                        | Section                              | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Response                                                                                                                                                                                                                                                                                                      |
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| #4 Technical Expert Panel Reviewer               | Executive Summary, p. 23 line 57     | Neither study seems to show a significant differences in the comparative response to second line treatment when stratified by depression severity. See prior comment in terms of the difficulties in interpreting severity effects on treatment response in the context of treatment comparisons.                                                                                                                                                                                       | As noted by the reviewer (and reported in the Executive Summary) in the comparative response (although the trends were in different directions). Also, we agree that this available evidence is difficult to interpret. Indeed, this information helped determine our rating of the evidence as insufficient. |
| Public Commenter: American College of Physicians | Executive Summary, p. 23-24          | Were the definitions of remission similar in the two studies examining severity as a predictor of remission?                                                                                                                                                                                                                                                                                                                                                                            | Yes, the definitions of remission used were similar, with total HAM-D score $\leq 7$ . Included studies had some variability in the way the defined response and remission. Because we used relative measure for meta-analyses, the effect of the variability on pooled estimates, however, should be small.  |
| #4 Technical Expert Panel Reviewer               | Executive Summary, p. 24 line 12     | It may help to specify the differences being addressed here (e.g., differences in benefits or harms of treatment).                                                                                                                                                                                                                                                                                                                                                                      | Thank you for this suggestion. We have revised the text to make these clarifications.                                                                                                                                                                                                                         |
| #4 Technical Expert Panel Reviewer               | Executive Summary, p. 24 line 18     | It may be helpful to remind readers here that psychotic depression was specifically excluded in the systematic review to alert them to the fact that this common accompanying symptom was not assessed. Given the primary care focus of the review, excluding psychotic depression was appropriate but it would help to be explicit here given the association of psychotic depression with increased depression severity and a tendency to be resistant to antidepressant monotherapy. | We added text. The sentence now reads:<br><br>We did not attempt to review literature on interventions for MDD in children or for patients with subthreshold depression, dysthymia, psychotic depression, or perinatal depression.                                                                            |
| #4 Technical Expert Panel Reviewer               | Executive Summary, p. 24 lines 46-47 | The information about a lower risk of adverse effects is hard to interpret without more details on whether these are minor side effects (e.g., occasional diarrhea, tolerable dry mouth), have significant effects or tolerability or have potentially life threatening consequences. The breadth of side effects or difference in their frequency would clearly influence clinical decision making related to these comparisons.                                                       | We agree that this is an important point to consider. However, clinically relevant information about overall adverse events, such as severity and frequency, was rarely reported in our included studies.                                                                                                     |

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| Commentator & Affiliation                          | Section                                                                                                                                            | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| #4 Technical Expert Panel Reviewer                 | Executive Summary, p. 24 lines 55-57                                                                                                               | This statement seems clearer than statements on preceding pages about the findings of studies vis a vis depression severity and the implications of those findings for clinicians.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Thank you                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Public Commenter: American Psychiatric Association | Executive Summary, ES-10, first paragraph, lines 2-3, "Indirect evidence, however, indicates lower adverse event rates for acupuncture than SGAs." | The meaning of "indirect evidence" in this sentence is not clear. It would be helpful to be more specific about the indirect evidence that is being used to make this conclusion.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | We deleted "indirect". The sentence now reads: "Evidence from meta-analyses of placebo controlled trials, however, indicated lower overall adverse event rates for acupuncture than SGAs."                                                                                                                                                                                                                                                                                                                             |
| #1 Technical Expert Panel Reviewer                 | Executive Summary, ES-12                                                                                                                           | I have several points with regard to wording:<br>1) In line 57 at the bottom of page ES-12 "data" is plural ("datum" is singular) and the sentence should read: "Overall, the available data do not indicate..."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | We changed to plural.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| #1 Technical Expert Panel Reviewer                 | Executive Summary, ES-13                                                                                                                           | 3) Line 26 on page ES-13 reads "Patients who strongly prefer one or the other therapy can be allowed freedom to choose among the available options, while under a physician's supervision and monitoring." Since these are non-psychotic patients I would think it is not so much a matter of allowing patients to choose (since the choice is always theirs) as the physician providing a summary of the extant scientific literature and the patient exercising his or her right to choose whatever he or she finds most congenial. Moreover, if the patient chooses to pursue a psychosocial intervention that is likely to occur outside of the physician's supervision or monitoring (although the patient may elect to keep the physician apprised of his or her progress). I would suggest rewording in each instance to make it clear that the patient exercises decisional control and may well elect to pursue treatment with some other professional. (The report does a nice job of framing that | We have revised the text to emphasize that patients exercise decisional control.<br>We added: "Physicians can provide a summary of the available evidence base indicating the advantages and disadvantages of these options, and patients can identify which intervention they would prefer. Some, such as medication and St. John's wort (SJW), would require physician supervision and monitoring given their potential side effects and drug interactions." We removed: the text about patients who strongly prefer |

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| Commentator & Affiliation          | Section                              | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Response                                                                                                                                                                                                                                                                                                                |
|------------------------------------|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    |                                      | recommendation in lines 49/50 on page ES-14.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | one or the other therapy can be allowed freedom to choose among available options                                                                                                                                                                                                                                       |
| #4 Technical Expert Panel Reviewer | Executive Summary, p. 25 lines 24-25 | It seems potentially misleading to base this decision purely on the SOE of available comparison studies without taking into consideration the SOE and magnitude of effect of placebo controlled trials of other interventions that just weren't subjected to well-designed comparative trials.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | For NWMA we do take effect estimates from placebo-controlled trials into consideration. NWMA's, however, provide indirect evidence and results from head-head trials are generally more reliable.                                                                                                                       |
| #4 Technical Expert Panel Reviewer | Executive Summary, p. 25 line 27     | This is an important caveat and worth emphasizing throughout the document including the abstract (which is all many people read). Most individuals who take St. John's wort do not do so under a physician's supervision and they may not even tell the physician that they are taking St. John's wort. Most such individuals also do not take a preparation that has a standardized ratio of potentially active components(e.g., hyperforin, hypericum). The manufacturing process for herbal preparations is not well regulated (PMID: 18415652); impurities are common and inconsistent amounts of active ingredient can be seen within and among batches of product. Given the documented effects of St. John's wort on metabolism of other drugs and the documented variations in effects on drug metabolism with different St. John's wort preparations (PMID: 15470332; 15179409; 16341856), inconsistencies in manufactured product are worrisome for patients on other medications. This is especially the case for medications with a narrow therapeutic window such as protease inhibitors, cyclosporin, digoxin, clozapine and others (including other psychotropic medications metabolized by the CYP 450 system or subjected to intestinal transport via Pglycoprotein. These drug drug interactions with St. John's wort are generally not included in drug-drug interaction checking software including electronic prescribing or electronic medical record systems. These factors should be considered prior to selection of St. John's wort, particularly given the greater likelihood of patients receiving concomitant medications in a primary care practice as compared to clinical trials (in which concomitant medications are often excluded). | Agreed – herb-drug interactions are a concern when considering SJW, which is why we have recommended it be used under physician supervision, and why we have mentioned the concern for HDI in both the introduction and discussion sections. Additionally, we have changed the SOE rating for SJW from moderate to low. |
| #4 Technical Expert Panel Reviewer | Executive Summary, p 25 lines        | If this was the case in the studies of St. John's wort and acupuncture, this would be worth noting elsewhere (including the abstract) as this would temper the strength of the conclusions that could be drawn from                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Five of eight trials of SJW used the lowest SSRI dose, two trials used moderate SSRI dose, and one trial                                                                                                                                                                                                                |

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|                                    | 46-49                                | these studies.                                                                                                                                                                                                                                                                                                                                                                | used the majority of the appropriate dose range. The commenter is correct that low dosages may affect the treatment outcomes. We addressed this issue by conducting sensitivity analyses based on SGA dose. Additionally, we have changed the SOE rating for SJW from moderate to low. |
| #4 Technical Expert Panel Reviewer | Executive Summary, p. 26 lines 7-10  | This is an excellent point and may be worth emphasizing elsewhere (including in the abstract).                                                                                                                                                                                                                                                                                | Thank you. We emphasize this point in the Discussion.                                                                                                                                                                                                                                  |
| #4 Technical Expert Panel Reviewer | Executive Summary, p. 26 lines 13-14 | The fact that many of the CAM trials were conducted outside of the US may also warrant mention in the abstract and elsewhere, particularly if done in cultures or countries in which significant differences might be expected (e.g., China, India). Differences from the U.S. might be less likely if studies were done in Western Europe, the UK, Australia or New Zealand. | Yes, there may be some differences in expectancy based on country of study. However, none of the studies systematically measured expectancy or credibility. We mention these issues in the discussion.                                                                                 |
| #4 Technical Expert Panel Reviewer | Executive Summary, p. 26 line 46     | See comment on this phrasing above.                                                                                                                                                                                                                                                                                                                                           | We revised the text.                                                                                                                                                                                                                                                                   |
| #4 Technical Expert Panel Reviewer | Executive Summary, p. 26 lines 49-52 | Other considerations would also be worth mentioning here including drug interactions, side effect profiles of specific medications, standardization of preparations (with St. John's wort), and availability of clinicians who are well trained in a specific therapeutic option (particularly with psychotherapies and acupuncture) among other considerations.              | Many of these are mentioned in the Discussion section of the report. We revised the text.                                                                                                                                                                                              |
| #4 Technical Expert Panel Reviewer | Executive Summary, p. 27 line 11     | This seems to address the point raised above, but it would be worth emphasizing this elsewhere in the document as well (including the abstract).                                                                                                                                                                                                                              | We also address this point in the Discussion.                                                                                                                                                                                                                                          |
| #1 Peer Reviewer                   | Introduction [No page # provided]    | The introduction is clearly written and appropriate for a report of this depth and length. Starting in the introduction and continuing throughout the report, there is a virtually unquestioned conclusion that St. John's Wort is as effective as SGAs. Because this CAM is recommended so infrequently in the USA, some note of the disparity between findings and          | We readdressed the SOE rating of SJW in the abstract, executive summary, results and discussion sections, which is now rated as low SOE.                                                                                                                                               |

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| Commentator & Affiliation                  | Section                                   | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                            |                                           | clinical practice would be in order in the Introduction - just a sentence or two. Then later in the report, the reasons for lack of use of St. John's Wort in clinical practice in USA could be explored. This reviewer suspects that most psychiatrists disbelieve the data from St. John's Wort studies done outside the USA.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| #2 Peer Reviewer                           | Introduction<br>[No page # provided]      | It is well written and thoughtful. It would be important to emphasize that the majority of the data included are from acute treatment trails and really do not informs us in terms of continuation or maintenance therapy.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | We have addressed this point in the Limitations of the Evidence Base section in the Discussion chapter.                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Public Commenter:<br>Maryalice JordanMarsh | Introduction<br>[no page number provided] | <p>in the inclusion and exclusion criteria were LGBTQ populations specifically searched were all populations English speaking</p> <p>The term psychoeducation is not used but masters level students love this term please explain exclusion see reference Psychoeducation for depression anxiety and psychological distress a metaanalysis Tara Donker<sup>1</sup> Kathleen M Griffiths<sup>2</sup> Pim Cuijpers<sup>1</sup> and Helen Christensen<sup>2</sup> See also Psychoeducation and Medication Better for Depression than Medication Alone May 19 2014 Posted in Current Treatments <a href="http://bipolarnews.org">http://bipolarnews.org</a> p2614 Editors Note There are now about a dozen controlled studies indicating the efficacy of psychoeducation. It is time that systematic delivery of psychoeducation either in a private practice setting a clinic or the home environment become a mandatory part of the treatment of bipolar disorder. Overall the introduction provides very useful information and perspectives.</p> <p>HOWever some of the epidemiological data is quite old ref 6 is 1996. assertion n p.1 of Introduction about burden is more that ensuing 10 years see ref 13. An organization such as AHRQ should have more recent data or should note that despite predicted severity of problem no more recent data were available even to this governmental agency</p> | <p>We appreciate the reviewer's comments. We did not specifically search for subpopulations. Instead, our searches were broad which allowed us to capture any publications in MDD populations. As a result, any studies in LGBTQ populations that met our broad search criteria (e.g., our pre-specified interventions and outcomes of interest) would be captured by our searches. We did not restrict our searches to English speaking populations.</p> <p>We have updated the 1996 reference with a 2013 reference.</p> |
| #1 Technical Expert Panel Reviewer         | Introduction, p 1, lines 52-60            | <p>I think that the introduction is generally nicely structured and makes a number of important points:</p> <p>1) I especially like the way you handle the moderating role of severity in lines 52-60 on the first page of the Introduction and your point on the subsequent page that while under-treatment is the biggest problem in the treatment of depression, we also overtreatment many patients with less severe depressions.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Thank you.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

| Commentator & Affiliation                               | Section                                            | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Response                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------------------------|----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Public Commenter:<br>American Psychological Association | Introduction, p. 1 second to last paragraph        | Unclear whether those who do not receive adequate treatment do not receive it due to them dropping out of treatment or due to providers not providing evidence based care in accordance with guidelines.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | We agree and have added this information in this introduction paragraph.                                                                                                                                                                                                                                                                                                           |
| Public Commenter:<br>American Psychiatric Association   | Introduction, p. 1, last paragraph, last two lines | It is true that patients treated in primary care settings may have less severe symptoms than individuals treated in psychiatric specialty settings or those enrolled in clinical antidepressant trials. However, clinical antidepressant trials tend to exclude individuals who are the most severely depressed as they generally do not include psychiatric inpatients or individuals with any significant suicide risk.                                                                                                                                                                                                                                                                                                                                                                 | The reviewer makes an important point, but clinical antidepressant trials also tend to enroll more severely depressed patients to increase the likelihood of finding an antidepressant signal. . Our review targets those likely to be seen in primary care settings, We believe the statement as currently reads effectively presents the context for our population of interest. |
| #2 Technical Expert Panel Reviewer                      | Introduction Pg. 2                                 | The authors do a good job reviewing pharmacotherapy issues, but the manuscript would benefit from more background on the use of psychotherapy and CAM.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Thank you. We have provided more background on the use of psychotherapy and CAM in the Introduction                                                                                                                                                                                                                                                                                |
| #1 Technical Expert Panel Reviewer                      | Introduction, p. 2, line 6-7                       | 2) In line 6/7 on the second page of the introduction you state that: “as baseline depressive symptoms increase, response to pharmacotherapy improves.” I am inclined to agree and think that this also holds for the specificity of response increases relative to pill-placebo. My reading of Fournier 2010 and studies like Dimidjian 2005 and Elkin 1989 from which it draws its data patients exhibit about the same amount of change in pill-placebo regardless of level of initial severity but that patients with more severe depressions need the extra “boost” provided by an active medication (or efficacious psychotherapy) to end treatment at about the same point that patients with less severe depressions reach with either active treatments or nonspecific controls. | This point is an insightful one, but it addresses a point different than the one we are making here, so we will not add it to the Introduction.                                                                                                                                                                                                                                    |
| Public Commenter:<br>American Psychiatric Association   | Introduction, p 4, first paragraph                 | Suggested edits: Only about 60 percent of patients treated with SGAs respond to treatment (meaning specifically that their depressive severity decreases by at least half, <i>as measured by a depression rating scale</i> , an improvement that may or may not meet criteria for remission); [Note: Due to 508 compliance, red text converted to italics]                                                                                                                                                                                                                                                                                                                                                                                                                                | We agree, and have made this change.                                                                                                                                                                                                                                                                                                                                               |
| Public Commenter:                                       | Introduction, p. 4                                 | “The American Psychological Association recently concluded that the general benefits of the major psychotherapies that have been studied                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Thank you. We have added this reference.                                                                                                                                                                                                                                                                                                                                           |

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| Commentator & Affiliation          | Section           | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| American Psychological Association |                   | <p>are significant and large.” -The references for this are listed as 38 and 39, noted below. This is from a resolution the American Psychological Association passed so it would be helpful to cite the resolution. The resolution is found at this link:<br/> <a href="http://www.apa.org/about/policy/resolution-psychotherapy.aspx">http://www.apa.org/about/policy/resolution-psychotherapy.aspx</a><br/>           Reference 38 is in APA's resolution but 39 is not.</p> <p>Associated references are:<br/>           38. Cuijpers P, van Straten A, Andersson G, et al. Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. J Consult Clin Psychol. 2008 Dec;76(6):909-22. Epub: 2008/12/03. PMID: 19045960.<br/>           39. Nieuwsma JA, Trivedi RB, McDuffie J, et al. Brief psychotherapy for depression: A systematic review and meta-analysis. Int J Psychiatry Med. 2012;43(2):129-51. PMID: 2012-17351-003. PMID: 22849036.<br/>           First Author &amp; Affiliation: Nieuwsma, Jason A.</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| #3 Technical Expert Panel Reviewer | Introduction, p 5 | Very well written with the exception of the concerns noted above about the dated and inappropriate terminology. In particular, on Page 5, change CAM and MDD to Complementary Approaches for MDD or Complementary and Integrative Approaches for MDD.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Although we recognize the recent change in name of the NCCAM to NCCIH, indeed, a number of our research questions pertained to alternative medicine (e.g., SGA vs acupuncture monotherapy or SJW monotherapy), whereas the combination therapies fit the complementary medicine definition (e.g., SGA vs SGA + Acupuncture combination therapy). Therefore, at least as it pertains to this review, the term CAM appears more fitting than any other terminology. The terms complementary and alternative, as used in this report, have been more clearly defined on page 5. |
| #3 Peer Reviewer                   | Introduction, p 5 | The Introduction is good and provides a nice overview. But let me introduce my first concern with St. John's Wort. On page 5, in the section headed "CAM for MDD" is the statement "Although the evidence base from high-quality RCTs is limited, sufficient placebo-controlled                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Yes, these are two different sets of studies that answer two separate questions (ie. Does SJW work? and How well does SJW work compared                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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| Commentator & Affiliation                            | Section                     | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------------------------------|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                      |                             | <p>evidence exists to support St. John's wort for mild to moderate MDD." This is a reasonable and accurate statement. But it seems to be contradicted in the Structured Abstract on page vi, which concludes "Overall, the available evidence does not support the superiority of SGAs over CBT and St. John's wort as first line treatments for patients with moderate to severe MDD." This is confusing! Perhaps different studies are being looked at here: SJW vs placebo and separately, SGA vs SJW. But it is misleading to use the latter to imply that SJW is an appropriate treatment for SEVERE depression, which I believe the field would concur is not the case.</p> | <p>to other treatments for MDD?).</p> <p>The studies of SJW vs SGA were done almost entirely in pts with severe MDD, and our results indicated little difference in effectiveness between the two treatments. However, our confidence that the treatment estimates are stable is low. Therefore some uncertainty remains as to whether SJW is comparable to SGA treatment. The issue as to whether SJW is an appropriate treatment for severe MDD is separate and depends on both the provider and patient involved. We have addressed some of those issues in the section on applicability in both the abstract and discussion section. We have revised the sentence about superiority in the abstract to make it clearer.</p> |
| #2 Technical Expert Panel Reviewer                   | Introduction Pg. 5, line 43 | <p>Their needs to be discussion about the limitations of adverse response measurement in psychotherapy; most medication side effects are not relevant, while some domains relevant to psychotherapy (e.g., increased conflict with partners, negative consequences of behavioral activation or exposure exercises), are not regularly measured.</p>                                                                                                                                                                                                                                                                                                                               | <p>We have added text that highlights the limitations associated with measuring adverse events in psychotherapy, both in our evidence base and in other research. This new text is located in the Applicability section of the Discussion because there, we already discuss how other limitations of our evidence base affect the usability of our findings.</p>                                                                                                                                                                                                                                                                                                                                                                |
| Public Commenter: American Psychological Association | Introduction, p. 6          | <p>"This review will examine the evidence base for primary care management of MDD for the first two treatment attempts, after which primary care clinicians would consider referral to or consultation by a mental health professional." – It is unclear the basis for the second half of this particular statement- is this based in a particular primary care guideline? Also, does primary care management of MDD include things</p>                                                                                                                                                                                                                                           | <p>The second part of this statement is based on the STAR*D data, which indicated that after two adequate trials that do not produced remission, the likelihood of remission drops from 30% to 15%. This rationale is</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| Commentator & Affiliation          | Section                         | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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|                                    |                                 | other than meds?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | provided at the end of the first section of the Introduction (“Context”).                                                                                                                                                                                                                                                                                                                                                                               |
| #1 Technical Expert Panel Reviewer | Introduction, p.7               | 3) In your analytic framework (Figure 2) I would reverse the order of the heading “Maintenance/Continuation” in the second box from the right to match the temporal sequence of relapse and recurrence below.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | We agree and have made this change.                                                                                                                                                                                                                                                                                                                                                                                                                     |
| #4 Technical Expert Panel Reviewer | Introduction, p. 30 lines 14-18 | It may be preferable to split the information on diagnostic criteria into a separate sentence from the information on prevalence.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | We carefully considered, and we believe the sentence reads well as is, so we will leave it this way.                                                                                                                                                                                                                                                                                                                                                    |
| #4 Technical Expert Panel Reviewer | Introduction, p. 30 line 22     | See prior comment on this phrasing.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | We have added the requested phrasing.                                                                                                                                                                                                                                                                                                                                                                                                                   |
| #4 Technical Expert Panel Reviewer | Introduction, p. 30 line 32     | I believe many suicidologists try to avoid using the phrase "commit suicide" (similarly avoiding phrases such as "completed suicide"). Though it seems somewhat redundant, the preferred language is "die by suicide."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | As requested, we have replaced the phrase “commit suicide” with “die by suicide”.                                                                                                                                                                                                                                                                                                                                                                       |
| #4 Technical Expert Panel Reviewer | Introduction, p. 30 line 33     | Suggest replacing this with "depression precedes about two-thirds of deaths due to suicide."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | We have made the change as requested.                                                                                                                                                                                                                                                                                                                                                                                                                   |
| #4 Technical Expert Panel Reviewer | Introduction, p. 30 line 40     | Suggest change to "individuals" -- if they haven't sought care, they technically would not be a patient.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | We have made the change as requested.                                                                                                                                                                                                                                                                                                                                                                                                                   |
| #4 Technical Expert Panel Reviewer | Introduction, p. 30 lines 57-58 | Most clinical trials of depression (with the exception of electroconvulsive therapy trials) do not enroll very severely depressed subjects and many enrolled subjects have depressive symptoms at the moderate end of the continuum. For example, in a recent analysis of pooled data from duloxetine trials (PMID: 22147842), the mean of the 17 item HAM-D was approximately 19. This enrollment pattern occurs for a number of reasons including the ambulatory setting for most such trials, the greater likelihood that severely depressed patients will be excluded for suicidal ideation or recent suicidal behaviors, the common need for non-protocol medications to control other distressing symptoms of severe illness (e.g., anxiety, agitation, insomnia, psychosis), and the desire of severely ill patients and their families for a rapid or more certain response than achievable via a clinical trial. Individuals in such trials may still have a greater symptom severity than individuals seen in primary care or they may exhibit a different pattern of symptoms, with greater degrees of somatic concerns in primary care populations. | We acknowledge that there are a variety of definitions for a “severe” depressive episode, but a mean of 19 on the HAM-D17 is commonly the threshold of what would be considered a severe MDD episode (Yonkers KA, Samson J. Mood disorders measures. In: Rush AJ, Pincus HA, First MB, et al, editors. Handbook of psychiatric measures, 1 <sup>st</sup> ed Washington (DC)7 American Psychiatric Association; 2000. P. 515-48), so we will keep as is. |

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| Commentator & Affiliation          | Section                         | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Response                                                                                                                                                                                                                                                                                                                    |
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| #4 Technical Expert Panel Reviewer | Introduction, p. 31 line 13     | This paragraph does a good job of emphasizing that severity of depression is an important consideration even though the available studies don't help in determining which of the studied interventions may be preferable in more severe depressions.                                                                                                                                                                                                                                                                                                                                                                                                         | We thank the reviewer for their kind comment.                                                                                                                                                                                                                                                                               |
| #4 Technical Expert Panel Reviewer | Introduction, p. 31 lines 16-17 | If this conclusion is based primarily on the analysis of the STAR-D data, it may not be generalizable to more typical primary care settings. Presumably in STAR-D, the use of measurement based care and feedback to clinicians would have had an impact on equalizing treatment adequacy across primary care and specialty settings.                                                                                                                                                                                                                                                                                                                        | Forty percent of STAR*D patients were from primary care clinics, where measurement-based care proved feasible and similarly effective to psychiatric settings. We have clarified that these outcomes assume an evidence-based treatment approach, so we believe the conclusion as written is accurate. We will leave as is. |
| #4 Technical Expert Panel Reviewer | Introduction, p. 31 line 23     | Consider changing this to "psychiatric specialty settings"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | We have made the change as requested.                                                                                                                                                                                                                                                                                       |
| #4 Technical Expert Panel Reviewer | Introduction, p. 31 line 28     | Suggest that this be changed to "would benefit from referral to a psychiatrist" or "would benefit from psychiatric referral". Not all psychiatrists practice in clinic settings.                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | We agree and have changed to "psychiatric referral" as suggested.                                                                                                                                                                                                                                                           |
| #4 Technical Expert Panel Reviewer | Introduction, p. 33 line 4      | May wish to change this to "Usual Range of Total Daily Doses" just to emphasize that this would not be given at the frequency listed in the next column                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | We agree and have changed this to "Usual total daily dosing range".                                                                                                                                                                                                                                                         |
| #4 Technical Expert Panel Reviewer | Introduction p. 34 lines 5      | Suggest replacing this with "psychotherapies".                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | It is unclear what term the reviewer suggests be changed. We assume it is "other talk therapies", and have changed it to "other psychotherapies."                                                                                                                                                                           |
| #4 Technical Expert Panel Reviewer | Introduction, p. 34 lines 5-8   | The fact that these different psychotherapies have different customary lengths of treatment is correct, but the implications of this are not made clear in the text as currently written. I would suggest ending the sentence just before "which" and replacing the highlighted sentence with the following:<br>Of note, the optimal frequency and duration of psychotherapy has not been rigorously studied in controlled trials and different forms of psychotherapy have different customary lengths of treatment. Consequently, there is no clear evidence for what might be considered an adequate or standard course of these therapeutic approaches." | Thank you, we have incorporated the reviewer's suggestion.                                                                                                                                                                                                                                                                  |

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| Commentator & Affiliation          | Section                         | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Response                                                                                                                                                                                                                                                                                                                                                        |
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| #4 Technical Expert Panel Reviewer | Introduction p. 34 line 33      | It would be important to know whether the preparations used in clinical trials were commonly available. If not, this would be a factor that might mitigate against use of St. John's wort.                                                                                                                                                                                                                                                                                                                                                                                                                               | Many of the preparations used in our selected studies are commercially available. Furthermore, many other standardized preparations are available with specifications similar to those of used in these studies, which we have noted in the discussion section.                                                                                                 |
| #4 Technical Expert Panel Reviewer | Introduction, p. 34 lines 44 ff | See additional information and caveats on St. John's wort noted above.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Herb-drug interactions are a concern when considering SJW, which is why we have recommended it be used under physician supervision, and why we have mentioned the concern for HDI in both the introduction and discussion sections. Because we have changed the SJW SOE rating to low, we have decided not to include this point in other places of the report. |
| #1 Peer Reviewer                   | Methods [No page # provided]    | Search criteria, inclusion and exclusion criteria are appropriate and adequate. Somewhere in the introduction or methods it would be useful to explain reasons for not including studies with TCAs and the advantages and disadvantages of doing so. For example, a wealth of data from very important studies comparing TCAs with CBT and combined TCAs and CBT is lost. If all of these studies were combined with the SGA literature in a meta-analysis, more knowledge may have been gained (for example regarding the possible advantages of combined ADs and CBT - other meta-analysis have found this advantage). | Based on discussion with the nominator and the technical expert panel we limited the antidepressants to SGAs because they are the most commonly used pharmaceutical interventions for the treatment of MDD. The scope of the review would have become too large to be manageable within the time limits.                                                        |
| #2 Peer Reviewer                   | Methods [No page # provided]    | I think that the overall methods employed were appropriate for the project. I do always worry when the data employed to answer a specific question are limited to studies performed in one country or region of the world. There may be expectancy and credibility biases that limit the generalizability of the findings. I have this fear about both the SJW and the acupuncture data.                                                                                                                                                                                                                                 | Thank you for the comment. We agree and have noted this concern in the discussion section                                                                                                                                                                                                                                                                       |
| #1 Technical Expert Panel Reviewer | Methods [No page # provided]    | I have several comments regarding the methods followed:<br><br>1) In your section on populations you indicate that you did not include patients with chronic depression or seasonal affective disorder or                                                                                                                                                                                                                                                                                                                                                                                                                | Many thanks for this comment. We changed the text accordingly.                                                                                                                                                                                                                                                                                                  |

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| Commentator & Affiliation          | Section                         | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|                                    |                                 | <p>treatment-resistant depression. I think it might be more accurate to say that you excluded trials that focused solely on those populations since many of the studies that you did include would not have screened out such patients (for example DeRubeis 2005 or Dimidjian 2006).</p> <p><b>[Continued on the next row]</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| #1 Technical Expert Panel Reviewer | Methods<br>[No page # provided] | <p><b>[Continued from previous row]</b></p> <p>2) While a useful convention to follow, the way in which risk of bias is assessed has at least two problems. First, the specific risks specified largely deal with internal validity (such as method of randomization and protection of the blind) and do not address what is perhaps the larger problem in the field namely allegiance effects. The outcomes of a trial can often be predicted by knowing who conducted the trial often not because the investigator intends to manipulate the findings but because he or she is not fully competent to execute the comparison condition(s). This is most likely to be a problem with respect to psychotherapy vs psychotherapy comparisons (see for example Dimidjian et al. 2006 in which behavioral activation was found to be superior to cognitive therapy at the home site of the behavioral intervention as provided by the authors of the treatment manual) but sometimes can be a problem with pharmacotherapy as well (see Moradveisi 2013 in which sertraline dosage was capped at only 100 mg/day).</p> <p><b>[Continued on the next row]</b></p> | <p>For this review we did not include psychotherapy vs. psychotherapy comparisons. As part of our risk of bias assessment, we assessed treatment fidelity for psychological interventions.</p> <p>We are grateful for the recognition that the sertraline dosage in Moradveisi was capped at 100mg. While that dosage is within the normal prescribing range, we understand how the upper limit could result in a more favorable outcome for the psychological intervention.</p> <p>As a result, we have added a sentence in several places that highlights the dosage cap and cautions the reader about interpreting the results.</p> |
| #1 Technical Expert Panel Reviewer | Methods<br>[No page # provided] | <p><b>[Continued from previous row]</b></p> <p>3) Earlier trials often followed adequate procedures with respect to randomization and the protection of the blind but did not report what was done in sufficient detail to pass muster with respect to risk of bias assessment. The decision not to contact authors regarding exactly how they handled such methodological details was tantamount to assuming that adequate safeguards were not in place when they simply may not have been adequately reported. One of the good things about the growing reliance on secondary reviews is that investigators have become more aware of reporting what they did in a manner that facilitates scoring for risk of bias but in at least some instances such practices were followed in earlier trials but not reported.</p>                                                                                                                                                                                                                                                                                                                                     | <p>In case methodological procedures were not well (or not at all) described we rated them as “unclear risk of bias”. Ratings of high risk of bias were reserved for studies for which it was clear from the manuscript that there have been methodological shortcomings.</p>                                                                                                                                                                                                                                                                                                                                                          |

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| Commentator & Affiliation          | Section                         | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Response                                                                                                                                                                                                                                                                                                                                       |
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| #2 Technical Expert Panel Reviewer | Methods<br>[No page # provided] | the focus on SGA's may have excluded several important studies comparing antidepressants and psychotherapy. Given the limited number of studies available, there may be justification for including earlier medications. While they will likely have more problematic side-effect profiles, the additional studies may increase SOE for some domains.<br><b>[Continued on the next row]</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | We appreciate the reviewer's comment. Based on discussion with the nominator and the technical expert panel we limited the antidepressants to SGAs because they are the most commonly used pharmaceutical interventions for the treatment of MDD. The scope of the review would have become too large to be manageable within the time limits. |
| #2 Technical Expert Panel Reviewer | Methods<br>[No page # provided] | <b>[Continued from previous row]</b><br><br>More detail about the design and limitations of the network meta-analysis is needed.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | We provide a detailed description of the methods of NWMA in the Methods section. We also provide references to key papers. A discussion of the statistical pros and cons of NWMA in the Methods section would probably go beyond the scope of the report.                                                                                      |
| #3 Peer Reviewer                   | Methods<br>[No page # provided] | For the most part, the descriptions of the methods are clear. I would have liked to see more comments on source of subjects and potential impact on results - e.g. those referred thru clinical channels vs advertising. In particular, it is not clear that individuals who volunteer for "alternative" treatments are representative of the patient population as a whole. Also, while the use of a 50% drop in Hamilton depression rating to indicate "response" is reasonable, many studies also add a stricter criterion of requiring that the FINAL Hamilton score be below a certain cutoff, e.g. below 10; the point here being that if an initial Hamilton was, say, over 30, a 50% drop would be meaningful but as the subject would still be quite depressed, it might be misleading to include that person in the "response" group.<br><b>[Continued on the next row]</b> | We present such details in the in-text tables. Aggregate data presented in studies, however, often provide limited information.                                                                                                                                                                                                                |
| #3 Peer Reviewer                   | Methods<br>[No page # provided] | <b>[Continued from previous row]</b><br><br>Caveats might be in order that information needed for the inclusion and exclusion criteria enumerated for this review were not always available in the published reports. For example, it is not always clear that no subjects in a given trial had "chronic" depression, or that diagnoses were ascertained through structured interview or other comprehensive method, as opposed to a checklist of DSM criteria only (which would fail                                                                                                                                                                                                                                                                                                                                                                                                 | We have added text to the Limitation of the Evidence Base in the Discussion chapter.                                                                                                                                                                                                                                                           |

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| Commentator & Affiliation          | Section                         | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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|                                    |                                 | to establish comorbid diagnoses).<br>[Continued on the next row]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| #3 Peer Reviewer                   | Methods<br>[No page # provided] | [Continued from previous row]<br>Although it is appreciated that comparisons with SGAs are the focus, in terms of second-line interventions this is quite restrictive and potentially misleading. In particular, augmentation studies of interventions added to SGAs with a placebo "augmentation" comparison, would be of considerable interest to clinicians but are ruled out. Two good examples (that make the "ineligible" reference list) are Papakostas et al (2010) and Trivedi et al (2011), using SAM-e and exercise respectively, in SGA nonresponders. The comparison of, for example, SGA + SAM-e versus SGA + placebo certainly would be of interest to the reader.<br>[Continued on the next row]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Our comparisons were informed by the wishes of the topic nominator, who was interested in comparative effectiveness of interventions that would be used by primary care physicians. While the comparison the reviewer mentioned would not be selected for the direct comparative effectiveness analysis, if it were otherwise eligible it would be included in the network meta-analysis.                                                                                                                                                                                                                                                                               |
| #3 Peer Reviewer                   | Methods<br>[No page # provided] | [Continued from previous row]<br>Also, it might be worth making clear that for the most part, the reviewed studies are "investigator-initiated," so that some comparisons have not been answered with a definitive trial simply because no one has taken the initiative and/or has had the time and resources to conduct every potentially useful or "missing" clinical trial.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | From the information that is available in the published manuscripts it is almost impossible to distinguish between "investigator-initiated" or "funder-initiated" studies.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| #4 Technical Expert Panel Reviewer | Methods<br>[No page # provided] | The inclusion and exclusion criteria were reasonable. As noted above, it was unfortunate that placebo-controlled trials could not be included in the review as this makes it hard to synthesize the findings in a meaningful way, particularly since the head-to-head comparison trials as so limited in number and quality. The search strategies are logical, explicit and well constructed. The statistical approaches and other systematic review methods are excellent. Definitions and diagnostic criteria are reasonable with the possible exception of the range of HAM-D scores used for defining moderate vs. severe depression. The Rush et al. paper that the review uses to set severity cutpoints uses a less conservative definition of severity than many other authors recommend. Thus, studies that were identified using the Rush criteria as having severely ill subjects would only have been said to have moderately ill subjects by other authors. This could cause a shift in the conclusions about treatment efficacy in relationship to illness severity.<br>p. 40 line 43<br>Other groups have suggested that the cut point between moderate and severe depression on the HAMD-17 is more appropriately defined as being greater than or equal to 24 (PMID: 23759278). | Thank you. Also, re the severity cut point: This point is a thoughtful one. We acknowledge that there are a variety of definitions for a "severe" depressive episode, but a mean of 19 on the HAM-D17 is commonly the threshold of what would be considered a severe MDD episode (Yonkers KA, Samson J. Mood disorders measures. In: Rush AJ, Pincus HA, First MB, et al, editors. Handbook of psychiatric measures, 1st ed. Washington (DC)7 American Psychiatric Association; 2000. p. 515- 48.). Also, the degree of severity involved in this patient population reflects the range seen in primary care populations (note that the very severe patients are likely |

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| Commentator & Affiliation          | Section                    | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Response                                                                                                                                                                                                                                                                                                                                                                                   |
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|                                    |                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | inpatients or are being managed in a psychiatric clinic). Accordingly, we will keep as is.                                                                                                                                                                                                                                                                                                 |
| #4 Technical Expert Panel Reviewer | Methods, p. 41 line 55     | The logic behind using the CCDAN framework is reasonable. All of the categories as outlined in Appendix B also seem reasonable with the exception of "Integrative Therapies". Interpersonal psychotherapy has a defined theory and methodology and has been "manualized" whereas the other types of "integrative therapies" are more nebulous (e.g., counseling, eclectic therapy). It seems unfortunate to lump it into a category that is so diverse. Also, I don't think most people are familiar with the "integrative therapy" term as used in this context. (The terminology of "third wave CBT" also seems non-standard.) | We appreciate the reviewer's concern, however in order to maintain consistency throughout the report, we need to adhere to the CCDAN categorization of interpersonal therapy as an integrative therapy. Where possible in the report we tried to specifically identify IPT accordingly                                                                                                     |
| #4 Technical Expert Panel Reviewer | Methods, p. 42 line 50     | See prior comments on use of the word "suicidality". Suggest replacing this word wherever it appears in the document.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | We agree that it would be more informative to use an alternative to the composite "suicidality" measure. We have changed "suicidality" to "suicidal ideas or behaviors" in cases when studies do not specify which suicidality outcomes they report. If the information is available, we have identified when studies' reporting focused on specific types of suicidal ideas or behaviors. |
| #4 Technical Expert Panel Reviewer | Methods, p. 43 lines 56-57 | The inclusion of placebo controlled trials for the network meta-analysis seems like an important point that may be deserving of greater emphasis in the executive summary and/or abstract in terms of interpreting the meta-analytic findings and the conclusions of the review. On the other hand, not all of the comparisons seem to have included placebo-controlled trial results, complicating interpretation of some of the findings of the review.                                                                                                                                                                        | We viewed NWMA as an additional analytic tool when reliable head-head evidence was not available. In the revised report, we provide results for all the low and medium risk of bias trials in an appendix                                                                                                                                                                                  |
| #4 Technical Expert Panel Reviewer | Methods, p. 46 lines 17-18 | Was this requirement also applied to acupuncture? If so, it would be important to mention; if not, some explanation of the rationale for this approach would be helpful to add.                                                                                                                                                                                                                                                                                                                                                                                                                                                  | For studies of acupuncture, like all studies evaluated in this review, we specifically looked at blinding of the outcome assessors when assessing risk of bias.                                                                                                                                                                                                                            |
| #4 Technical Expert Panel Reviewer | Methods, p. 46 line 23     | The phrase "rate of response" may be unclear as it could imply the rapidity of response rather than the proportion of individuals who responded. If there was a reason that response was chosen rather than                                                                                                                                                                                                                                                                                                                                                                                                                      | We added text to clarify this point.                                                                                                                                                                                                                                                                                                                                                       |

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| Commentator & Affiliation | Section                         | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|                           |                                 | remission, it may be useful to provide that information. (Presumably response was chosen because many studies report response rather than remission. But remission may be the more important outcome for patients/families and the results of network analysis may have differed if remission were used instead of response.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| #1 Peer Reviewer          | Results<br>[No page # provided] | The results are very comprehensive and well presented. But the repetitive nature of the report will make it hard for all but the most dedicated readers to digest the material and stay on task in reading it. Perhaps the Key Points (for example Key Points on page 22 and 23) could be presented in a more appealing way in a table with graphic design elements to key the reader in to the main findings. As currently presented, they appear in a sea of text.<br><b>[Continued on the next row]</b>                                                                                                                                                                                                                                                                                                                                                                   | We appreciate the reviewer's suggestion. In the Discussion we provide tables that summarize results and the respective strength of evidence.                                                                                                                                                                                                                                                                                                                                                                                                        |
| #1 Peer Reviewer          | Results<br>[No page # provided] | <b>[Continued from previous row]</b> In the presentation of results on St. John's Wort, insufficient attention is paid to quality of trials and the remarkable absence of any trends suggesting efficacy in the major USA trial by Davidson et al (reference 97) which appeared in JAMA. In this highly influential USA trial, neither St. John's Wort or sertraline were significantly better than placebo. Also, the response rate for St. John's Wort was considerably lower (23.9%) than the rates typically reported in European studies. This pivotal trial seems to have quashed enthusiasm for using St. John's Wort in clinical practice in the USA. The current report needs to acknowledge the issue of acceptance of St. John's Wort and do a better job of helping primary care physicians make a well-reasoned decision on recommending this treatment option. | All of the trials were rated for quality, and sensitivity analyses were conducted based on those ratings. Only 2 studies received our best rating, and the Davidson study was not one of them (due to its high attrition rate). In terms of influence, we agree the Davidson trial was pivotal. Here, however, we try to best assess the weight of evidence. Of note, we have modified the report to mention our concerns about risk of bias, which lower the strength of evidence to "low", and to note the caveats its use in clinical practice.. |
| #2 Peer Reviewer          | Results<br>[No page # provided] | I worry about the assessment of adverse effects because most of the tools used and most of how we conceptualize AEs is based on pharmacological trials and we could miss AEs that develop with CAM interventions. For example, I know that some of the subjects in the intervention trials developed muscle stiffness and soreness but unlike sexual side effects or constipation, it was not necessarily considered an AE by either participant or study team.                                                                                                                                                                                                                                                                                                                                                                                                              | Adverse events assessment is one of the great limitations of this body of literature. Only 1 study used an objective scale for adverse events assessment. We address this issue in the Discussion.                                                                                                                                                                                                                                                                                                                                                  |
| #2 Peer Reviewer          | Results<br>[No page # provided] | The results are presented in a thorough manner but I would if some type of Table summarizing analysis where there are insufficient data might not cut down on some of the redundancy.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | In the Discussion we provide tables that summarize results and the respective strength of evidence                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

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| #1 Technical Expert Panel Reviewer | Results<br>[No page # provided] | <p>In general I thought that the results were nicely done and clearly presented. I do have questions about several of the studies covered:</p> <p>1) Hollon 2014: Nice that you caught the recently published trial comparing combined treatment (with cognitive therapy) versus medication treatment alone (see attached). Please note that in that trial we treated to a fixed outcome (remission and then recovery) instead of for a fixed period of time and that although most patients started on an SGA that was not true for all and that we eventually took patients over to a tricyclic and then an MAOI if they did not respond to SGAs.</p> <p><b>[Continued on the next row]</b></p> | <p>We thank the reviewer for the additional information on the Hollon 2014 study. We reviewed this trial while the draft report was out for review, and we determined that it is not eligible for inclusion due to the information contained in this comment—the mix of eligible medications and the ability of patients to switch from one class to another.</p>                                                                                                                                |
| #1 Technical Expert Panel Reviewer | Results,<br>[pp. 26-29]         | <p><b>[Continued from previous row]</b></p> <p>2) Kennedy 2007/Segal 2006: I am not sure that it matters but studies done in Toronto by Sid Kennedy and Zindel Segal that were labeled CBT referred to the same treatment manual and likely followed the same procedures to those used in studies labeled CT by investigators like DeRubeis 2005 or Dimidjian 2006. It is something of a random walk through the literature with regard to whether investigators call CT by that name or CBT (since it is an example of a larger set) although there are clearly types of cognitive behavior therapy that are not CT.</p> <p><b>[Continued on the next row]</b></p>                               | <p>We thank the reviewer for this comment and agree that the terms “CT” and “CBT” are used in different ways by different researchers and practitioners (and that doing so can lead to confusion in the interpretation of study results). Rather than attempt to (re)classify included studies’ interventions, we deferred to the study authors’ treatment classifications; in the case of Kennedy/Segal, we used their term (“CBT”); with DeRubeis and Dimidjian, we used “CT” as they did.</p> |
| #1 Technical Expert Panel Reviewer | Results<br>[Pg. 26-29]          | <p><b>[Continued from previous row]</b></p> <p>3) Landenberger 2002: I could be wrong but I think that this report is based upon patients treated in DeRubeis 2005. Nana Landenberger was my advisee at Vanderbilt University and as such would have had access to the data from that trial. I would be very surprised if she generated another sample of randomized patients.</p> <p><b>[Continued on the next row]</b></p>                                                                                                                                                                                                                                                                      | <p>We thank the reviewer very much for bringing this to our attention. Although it is not explicit and we have found no reliable means of contacting Dr. Landenberger, upon review of the data from Landenberger and from the Vanderbilt site population in DeRubeis 2005, we agree that the patients are very likely the same. As a result, we have edited the report to consider Landenberger 2002 a</p>                                                                                       |

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| Commentator & Affiliation          | Section                         | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|                                    |                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | companion paper to DeRubeis 2005 and have made all of the appropriate edits to the results sections.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| #1 Technical Expert Panel Reviewer | Results<br>[No page # provided] | <p><b>[Continued from previous row]</b></p> <p>4) Dimidjian 2006: This trial typically is interpreted as providing strong support for the efficacy of behavioral activation (BA) in that it was found to be as efficacious as an SGA (paroxetine) and both superior to either cognitive therapy (CT) or pill-placebo (PLA) among patients with more severe depressions. That is because the authors of the article focused on ITT analyses of continuous symptom measures (the BDI and HRSD) as their primary outcomes of interest. However, nearly half of the patients assigned to active medication dropped out of treatment (a very high rate likely attributable to the very slow dosage escalation scheduled followed in that trial) such that only a minority of the patients randomized to SGA either responded to or remitted on medications. BA did well on either measure, but how CT did depends on whether one focuses on the continuous measures (with imputation for missing data for dropouts) that suggest that it did far less well than medication treatment or categorical indices of response or remission (in which dropouts are counted as nonresponders or non-remitters). This might be worth a comment.</p> <p><b>[Continued on the next row]</b></p> | <p>This is an excellent point by the reviewer. We noted the very high rate of both overall and differential attrition, and it contributed to the study's rating of a high risk of bias.</p> <p>That study was included in KQ 1b but mistakenly omitted from KQ 1a. We have pooled the reported dichotomous results of all eligible treatments, counting all dropouts as nonresponders or non-remitters, and we have added them to KQ 1a. Because we did not pool the continuous results for KQ 1a, we relied on the dichotomous results to describe the comparative effectiveness of CT (and all eligible interventions from this study for KQ 1a)</p> |
| #1 Technical Expert Panel Reviewer | Results<br>[No page # provided] | <p><b>[Continued from previous row]</b></p> <p>5) Moradveisi 2013: This trial conducted in Iran appeared to suggest that BA was superior to an SGA (sertraline) but capped the dosage of the latter at only 100 mg/day (about half the recommended maximum dosage). This should be noted.</p> <p><b>[Continued on the next row]</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <p>Thank you for the recognition that the sertraline dosage in Moradveisi was capped at 100mg. While that dosage is within the normal prescribing range, we understand how the upper limit could result in a more favorable outcome for the psychological intervention.</p> <p>As a result, we have added a sentence in several places that highlights the dosage cap and cautions the reader about interpreting the results.</p>                                                                                                                                                                                                                      |

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| #1 Technical Expert Panel Reviewer | Results<br>[No page # provided] | <b>[Continued from previous row]</b><br>6) Barber 2012: In Table 20 you list the maximum dosage of sertraline in that trial as 100 mg/day but the published study indicates that patients were taken as high as 200 mg/day and nonresponsive patients switched to venlafaxine up to 375 mg/day.<br><b>[Continued on the next row]</b>                                                                                                                                                                                                                                                                                    | We thank the reviewer for identifying the error in the dosage listed. We have corrected it in Table 20. Because nonresponsive patients were switched to venlafaxine after 8 weeks, we only report the 8-week outcomes from this study.                                                                                                                                                                                                                                                                                                                                   |
| #2 Technical Expert Panel Reviewer | Results<br>[No page # provided] | A review of the excluded studies leads to some concerns that relevant studies were potentially excluded. More detail regarding the reviewer's expertise around psychotherapy would be helpful.                                                                                                                                                                                                                                                                                                                                                                                                                           | We acknowledge the reviewer's comment.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| #3 Technical Expert Panel Reviewer | Results<br>[No page # provided] | <b>[Continued from previous row]</b><br>When discussing "psychological interventions," such as on page 22 of the Results, it would be better to not use the term "integrative therapies" for interpersonal psychotherapy (IPT). Integrative therapies is a term that applies to many different approaches in medicine. However, recently this term, is being combined with complementary medicine to characterize the new field of complementary and integrative medicine.<br><br>To avoid confusion, perhaps just refer to interpersonal psychotherapy since this is a well known term.                                 | We appreciate the reviewer's concern, however in order to maintain consistency throughout the report, we need to adhere to the CCDAN categorization of interpersonal therapy as an integrative therapy. Where possible in the report we tried to specifically identify IPT accordingly.                                                                                                                                                                                                                                                                                  |
| #3 Peer Reviewer                   | Results<br>[No page # provided] | For the most part, the Results are straightforward, although clearly much data of potential interest, e.g. functioning, quality of life, simply do not exist. It might be helpful to "import" some of the limitations described in general. Using St. John's wort, for example, the fact that much of the positive literature emanates from Germany is worth noting, as well as the general caveat that people who sign up for CAM treatment trials may not be representative of the MDD population as a whole, and may start off favorably disposed to a non-prescription option.<br><b>[Continued on the next row]</b> | We considered this point about country of origin carefully, and we found little difference between the literature emanating from Germany and non-German countries concerning SJW. We have added a sensitivity analysis based on country of origin to address this point<br><br>We think the key point concerning bias in the SJW literature is the concern about whether SGAs were adequately dosed, and we added text to the Executive summary, in addition to the existing text in the discussion section, on this topic. Additionally, we changed our SOE rating from |

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|                           |                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | moderate to low for the SJW analyses primarily due to the dose range issue.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| #3 Peer Reviewer          | Results<br>[No page # provided] | <p><b>[Continued from previous row]</b></p> <p>This reviewer has particular concerns about the presentation of the SJW results. The "Key Point" (page 23) states that "SGAs and St. John's wort monotherapy led to similar response (eight trials, moderate SOE) and remission rates (four trials, moderate SOE) in patients with moderate to severe MDD after 4 to 12 weeks of treatment." This does not pass a "reality check"! First, should it not arouse concern that no data are presented newer than 2006, when the literature through 2014 was surveyed -- although surely no one would suggest that the questions have been answered? (In other words, the only studies included were done when SJW was "popular"). Of particular concern, the reader might be misled into thinking that SJW is an appropriate treatment for SEVERE depression - an opinion surely not shared by the field. For reference, "Position Statement 41" of the Royal Australian &amp; New Zealand College of Psychiatrists (2009) flatly states, "The College does not recommend the use of St. John's Wort for the treatment of major depression or other psychiatric disorders on the evidence available" (and this was 3 years after the most recent study cited in the present review). A year later, in 2010, the American Psychiatric Association, in its updated (3rd edition) practice guidelines for the treatment of major depression (<a href="http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf">http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf</a>) states, "In patients who prefer complementary and alternative therapies, S-adenosyl methionine (SAME) or St. John's wort might be considered, although evidence for their efficacy is modest at best, and careful attention to drug-drug interactions is needed with St. John's wort ... Patients who are being treated with antiretroviral medications should be cautioned about drug-drug interactions with St. John's wort that can reduce the effectiveness of HIV treatments ... in the two largest controlled studies conducted in the United States, effects of St. John's wort did not differ from placebo, which somewhat limits confidence in the magnitude of the antidepressant actions of St. John's wort. In addition, preparations of St. John's wort are not regulated by the FDA as a drug and lack standardization of their ingredients, composition, and potency. Based on the evidence cited,</p> | <p>Thank you for these important comments. The purpose of this review was to assess the comparative effectiveness of the eligible interventions. Accordingly, the absence of literature following 2006 reflects the limited data on comparative effectiveness, in general. We report on what the comparative effectiveness of these studies show for these interventions, but do not propose guidelines. Indeed the report now identifies our concern about how dosing may effect these comparative data, which limits the strength of evidence data rating to "low", and we note the caveat of SJW prescription. The discussion of herb-drug interactions is in the introduction and discussion sections.</p> |

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|                                                      |                              | St. John's wort would not meet the FDA's minimum requirements to be declared an effective antidepressant and is not recommended for general use in treating depression." The potential for drug-drug interactions from St. John's wort's action in inducing the P450 enzyme 3A4 is overlooked in the Results section of current review - indeed, SGAs are described as having more adverse effects - and only appears in the Discussion on page 98. More importantly, the fact that practice guidelines in multiple countries reject St. John's wort as a reasonable treatment for major depression must be reconciled with the seemingly positive views expressed in this review.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                       |
| #4 Technical Expert Panel Reviewer                   | Results [No page # provided] | The authors provide an excellent level of detail in the text, tables and figures. Study characteristics are well described in the document. Appendices are extremely thorough and useful for interested readers. They also make the review process extremely transparent. The evidence that was included was extremely complete. The key messages are not always worded in a fashion that will be clear to readers; specific examples and suggestions for modification are included in the attached file. Another problem with the Key Statements under results is that they address the conclusions of the analysis (e.g., no difference in compared treatments) but do not place these conclusions in the context of the study limitations and other issues of applicability to clinical settings. This may lead to erroneous conclusions by many readers since few people will take the time to read the entire document and most will simply read the abstract or look for bulleted statements of key findings. Particularly given the limitations of the evidence, it would be important to provide additional context including discussion of limitations and need for medical supervision in conjunction with all interventions (including St. John's wort and acupuncture). | The intention of the key points is to provide a brief summary of the results. Adding more text would probably limit the readability. In the main report and also in the executive summary we address the limitations. |
| Public Commenter: American Psychological Association | Results, p. 23               | typo "Adding exercise with to SGA treatment did not..."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | This typo has been corrected.                                                                                                                                                                                         |
| Public Commenter: American Psychological             | Results, p. 25               | "In our syntheses, however, we place more emphasis on trials with low or medium risk of bias because of the presumed higher certainty of findings." – Further explain what you did to place more emphasis on those trials. For example, does this refer to only including high risk of                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | What we mean is that we describe them in more detail than high RoB studies. For meta-analysis we used high risk of bias trials for sensitivity                                                                        |

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| Commentator & Affiliation                          | Section                                                                                                                                                                  | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Response                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Association                                        |                                                                                                                                                                          | bias trials in sensitivity analyses or was there a different way you placed more emphasis on low/medium risk of bias trials?                                                                                                                                                                                                                                                                                                                                                                                                                                                            | analyses (see Methods)                                                                                                                                                                                                                                                                                                                                                                                 |
| Public Commenter: American Psychiatric Association | Results, p. 26, the last sentence under Description of Included Trials, “The total daily dose of each SGA medication was within the usual ranges prescribed for adults.” | Clinical trials almost always use daily doses of SGAs within the FDA approved dosing range. In addition, many studies chose doses at the low to mid-range of approved dosing to achieve statistically significant benefits while minimizing adverse effects and study withdrawals. As a result, these findings may not reflect usual prescribed doses as severely ill patients may require higher doses (above the dose on the FDA labeling) and some patients may require higher doses due to factors such as body weight, drug interactions or genetic influences on drug metabolism. | We agree, and this point is indicated by the range of daily dosing indicated.                                                                                                                                                                                                                                                                                                                          |
| Public Commenter: American College of Physicians   | Results, p.3 3, para 1                                                                                                                                                   | Comment on the definition of remission. How standard is it?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Remission is usually defined as we noted 1 page earlier (page 2 of the Introduction): “symptom remission (usually defined as a HAM-D score of $\leq 7$ )” and in the text of Figure 1. This definition is reasonably standard.                                                                                                                                                                         |
| Public Commenter: American College of Physicians   | Results, , Figures 10-12, [p. 41-2]                                                                                                                                      | To what extent might the heterogeneity reflected in the figures comparing the benefits of SGAs to St John wort reflect heterogeneity of the preparations?                                                                                                                                                                                                                                                                                                                                                                                                                               | We examined this in sensitivity analyses and reported these analyses in the results. Although some of the heterogeneity may be due to different preparations, it is difficult to conclude as such since several of the preparations were only used in a single study and there may be many factors contributing to the results of those single studies. We added this point to the discussion section. |

| Commentator & Affiliation                          | Section                                | Comment                                                                                                                                                                                                                                                                                                                                                                                                             | Response                                                                                                                                                                                                                                                                                |
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| #2 Technical Expert Panel Reviewer                 | Results, p. 44-45                      | Pg. 44-45: The report of the exercise trials can be edited to be more concise. Details about aerobic capacity seem beyond the scope of this report.                                                                                                                                                                                                                                                                 | This information has been removed from the text.                                                                                                                                                                                                                                        |
| #4 Technical Expert Panel Reviewer                 | Results, p. 51 line 19                 | This is a huge range of trial durations. Shorter durations (e.g., 4 weeks) would not typically be thought of as being an adequate trial whereas longer durations (certainly 96 weeks) would not be considered "acute-phase". It would be helpful to know, even in terms of a qualitative summary if there appeared to be any systematic differences in response or remission rates as a function of trial duration. | We thank the reviewer for raising this important point, and we have added detail to the Introduction directing the reader to the place in the report where she can find the results she mentions. We also edited several Key Points to clarify the time points used in those summaries. |
| #4 Technical Expert Panel Reviewer                 | Results, p. 51 lines 28 ff             | In outlining key points, it would be helpful to include information about the limitations of these conclusions along with the SOE related conclusions as these would provide some context to the statements being made.                                                                                                                                                                                             | We appreciate this comment but believe that including the number of studies and the SOE after each Key Point highlights adequately the need for caution when interpreting our conclusions.                                                                                              |
| #4 Technical Expert Panel Reviewer                 | Results, p. 51 line 33                 | As above, the range of trial durations is quite broad and it would be helpful to note if there was any systematic variations in response or remission as a function of trial duration.                                                                                                                                                                                                                              | We thank the reviewer for raising this important point, and we have added detail to the Introduction directing the reader to the place in the report where she can find the results she mentions. We also edited several Key Points to clarify the time points used in those summaries. |
| #4 Technical Expert Panel Reviewer                 | Results, p. 52 line 7                  | The type of acupuncture that was used may be worth stating (e.g., electroacupuncture vs. traditional needle based acupuncture). The same would be true elsewhere in the document and abstract where acupuncture is discussed.                                                                                                                                                                                       | Type of acupuncture for each trial is detailed in the main text under the acupuncture section.                                                                                                                                                                                          |
| Public Commenter: American Psychiatric Association | Results, p 52, Augmentation Strategies | It would be useful to note whether any studies compared augmentation strategies with increasing the dose of the initial SGA, including increases of the SGA dose above the dose noting in FDA labeling. This approach is common in clinical practice and often seems to be associated with enhanced clinical response.                                                                                              | We clarified these points in the text                                                                                                                                                                                                                                                   |
| Public Commenter: American                         | Results, p 61, Second-                 | It would be helpful to know more details about the exercise related trials, in terms of the way the design may have influenced this conclusion. In clinical practice, recommendations for exercise are typically                                                                                                                                                                                                    | Information has been added to the discussion under limitations.                                                                                                                                                                                                                         |

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| Commentator & Affiliation                        | Section                                           | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Response                                                                                                                                                                  |
|--------------------------------------------------|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Psychiatric Association                          | Generation Antidepressants Compared with Exercise | associated with very poor adherence. Thus, it would be helpful to know whether the trial duration (e.g., shorter trials fostering fewer dropouts due to early enthusiasm), compensation (e.g., direct finances, gym membership) or structure and support for exercise (e.g., personal trainer, weekly meetings to review progress) contributed to the apparent similarity in discontinuation rates. Individuals who agreed to be randomized to a study involving exercise may also have been more motivated to adhere to exercise than individuals in typical clinical practice. Exclusion criteria for exercise related studies may also have eliminated individuals who would have more difficulty in adhering to an exercise regimen due to factors such as poor health or obesity. |                                                                                                                                                                           |
| Public Commenter: American College of Physicians | Results, , Figures 16-17, 19-20 [p 64 on]         | Figures 16-17 have problems with formatting. Also Figures 19-20 and many subsequent Figures.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Our version has no formatting problems. It could have been a printer problem at the reviewer's end. However, the report will be further formatted prior to final posting. |
| #4 Technical Expert Panel Reviewer               | Results, p. 65 line 14                            | The fact that all of these trials were done in China would seem to be a potential limitation in terms of translating the findings into the U.S., both on the basis of cultural considerations and the availability of appropriately trained acupuncturists.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | We agree. This is mentioned in the discussion section under Applicability.                                                                                                |
| #4 Technical Expert Panel Reviewer               | Results, p. 65 lines 52-54                        | The heterogeneity in treatment type, points and frequency would also seem to be an important limitation in drawing conclusions from these studies as a body.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | We agree, and this heterogeneity contributed to the SOE rating for acupuncture as <i>low</i> or <i>insufficient</i> .                                                     |
| #4 Technical Expert Panel Reviewer               | Results, p. 69 Table 18                           | At least 5 of these studies seemed to use doses of SSRIs at the low end of the dosing spectrum. It would be helpful to know if there were systematic differences in the response to SSRI as compared to St. John's Wort in the low-dose studies as compared to the adequately dosed studies.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | This is an important point and we report on a sensitivity analysis that addresses this question.                                                                          |
| #4 Technical Expert Panel Reviewer               | Results, p. 70 lines 41-45                        | The fact that the subjects receiving SSRIs were underdosed in a significant number of studies may play a role in this finding. It is also not clear whether patients willing to be randomized to a complementary treatment such as St. John's wort differ from patients in other trials. The same consideration may also be true of psychotherapy-medication comparisons in which some individuals may not be willing to be randomized to psychotherapy.                                                                                                                                                                                                                                                                                                                               | We addressed the SSRI dosing using sensitivity analysis.                                                                                                                  |

| Commentator & Affiliation                            | Section                  | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Response                                                                                                                                                                                                                                                                                   |
|------------------------------------------------------|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| #4 Technical Expert Panel Reviewer                   | Results, p. 72 line 20   | These are important exclusion criteria that would impact the conclusion that dropout rates for exercise and medication are similar. Individuals willing to accept randomization to exercise may also have been more open to adhering to an exercise regimen than the typical clinical patient population.                                                                                                                                                                                                                                                                            | Information has been added under limitations.                                                                                                                                                                                                                                              |
| #4 Technical Expert Panel Reviewer                   | Results, p. 81 line 8 ff | See comment above; it would be helpful to include relevant limitations and confounds in the key points sections to aid in interpretation of the evidence rather than making the reader wait until the end of the document.<br><br>[THIS IS THE COMMENT ABOVE #7 REFERS TO: These are important exclusion criteria that would impact the conclusion that dropout rates for exercise and medication are similar. Individuals willing to accept randomization to exercise may also have been more open to adhering to an exercise regimen than the typical clinical patient population. | We have clarified and corrected the studies' exclusion criteria in the text.                                                                                                                                                                                                               |
| Public Commenter: American Psychological Association | Results, p. 83           | typo "St. John's wort did not lead to statistically different rates of rates compared with SGAs"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Thank you. We have made this correction.                                                                                                                                                                                                                                                   |
| #4 Technical Expert Panel Reviewer                   | Results, p. 88 line 22   | Given the broad range of durations of these trials, it may be helpful to know whether there was any difference in discontinuation rates with trial duration. At least in clinical practice, the ease of taking a medication vs. the need to attend more frequent appointments on a consistent basis often leads to greater dropout rates over time for psychotherapy. This is also consistent with the information in the next bullet point in terms of combination therapies.                                                                                                       | Thank you, we agree that it would be informative to know how trial duration affects discontinuation rates. We have stratified our meta-analyses of discontinuation outcomes for the SGA vs. any psychotherapy comparison by whether study durations were <12 weeks or 12 weeks or longer.  |
| #4 Technical Expert Panel Reviewer                   | Results, p. 89 line 21   | In terms of the discontinuation rates for acupuncture, did the studies specify if this was due to side effects or due to lack of efficacy? If the latter, this may temper the findings on acupuncture efficacy.                                                                                                                                                                                                                                                                                                                                                                      | No the studies did not specify the discontinuation rates. The one study providing overall discontinuation data reported that participants either withdrew for "no reason" or because they were frightened of having blood drawn for study purposes (see reference 96 by Sun et al., 2013). |

| Commentator & Affiliation          | Section                    | Comment                                                                                                                                                                                                                                                                                                                                                                                             | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| #4 Technical Expert Panel Reviewer | Results, p. 89 line 25     | Was indirect evidence considered for the other interventions? Did the studies in the metaanalysis have the same issues with heterogeneity of acupuncture methodology and potential cultural effects of study location as the studies done in patients with MDD? If so, this may limit the generalizability of the findings.                                                                         | <p>Only direct evidence was included to address KQ3, with the exception of indirect evidence based on a large systematic review of comparative harms from acupuncture and SGAs. In keeping with our pre-specified data synthesis plan, we restricted network meta-analyses to the rate of response on the HAM-D.</p> <p>We believe that the risk of harms results are probably more generalizable than our efficacy outcomes. Nevertheless, for the comparison of SGAs and acupuncture, we downgraded the strength of evidence about overall risk of adverse events based on the meta-analysis for indirectness..</p> |
| #4 Technical Expert Panel Reviewer | Results, p. 90 line 13     | However, the patients in these trials were preselected to include healthier and non-sedentary individuals who would be predicted to tolerate exercise without risk of musculoskeletal injury. It is not clear how generalizable this finding would be to a typical primary care or psychiatric population of depressed patients.                                                                    | Thank you, we agree that generalizability may be an issue. We have added the following text to the Discussion: “Additionally, their generalizability to a typical primary care or psychiatric population of depressed adults is unclear because these trials only included patients free of medical comorbidities that would restrict their ability to follow the prescribed exercise regimens.”                                                                                                                                                                                                                      |
| #4 Technical Expert Panel Reviewer | Results, p. 92 lines 41-42 | Was indirect evidence, such as that from placebo controlled trials considered here? Presumably, the data in patients with MDD from those trials would be expected to be similar (at comparable doses and trial durations) to the same treatment arms in a head-to-head trial and would be relevant to clinicians and guideline developers in balancing the benefits and harms of treatment choices. | As mentioned in a previous response, only direct evidence was included to address KQ3, with the exception of indirect evidence for the comparison of acupuncture and SGAs.                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| Commentator & Affiliation          | Section                     | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Response                                                                                                                                                                                                        |
|------------------------------------|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| #4 Technical Expert Panel Reviewer | Results, p. 92 line 46      | Although one can make the case that psychotherapy, particularly more insight-oriented therapies and exposure therapies (with PTSD) may cause a worsening of anxiety and other symptoms, it is less clear that the onset of new depression associated symptoms in someone being treated for depression is caused by the therapy vs the natural progression of the depressive episode that has not yet had a chance to be addressed by the therapy. It may be preferable to delete this latter phrase.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | While we agree with the reviewer's observation, we have left the last phrase intact to acknowledge that the onset of new depressive symptoms are a potential harm of psychotherapy for MDD.                     |
| #4 Technical Expert Panel Reviewer | Results, p. 93 line 12      | Typically psychodynamic and supportive therapies use different treatment approaches. The short-term nature of the intervention also should be taken into consideration in drawing conclusions for practice since psychodynamic approaches are not typically delivered in a short-term fashion.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Thank you for noting this distinction. We have deleted "supportive" to clarify that the intervention being evaluated was actually short-term psychodynamic therapy and not a form of supportive therapy per se. |
| #4 Technical Expert Panel Reviewer | Results, p. 106 lines 7-8   | As noted previously, it is problematic to lump these elements together into a composite "suicidality" measure. This is particularly true when discussing adverse outcomes since the term "suicidality" implies that an increase in this factor is associated with increases in suicides, per se. This is not necessarily the case and many clinical trials do not have any subjects with suicide as an adverse outcome. Conclusions drawn from any clinical trial findings on "suicidality" also need to be carefully presented as the highest risk individuals (e.g., those already reporting suicidal ideas or with recent suicide attempts) have typically been excluded from the trial. On the other hand, the fact that individuals with depression have significant rates of suicidal ideas, suicide attempts, and suicide in conjunction with their disorder makes it difficult to know whether emergence of these thoughts and behaviors is a result of the treatment or simply a manifestation of the underlying illness. The term "completed suicides" should be replaced with other language (e.g., "deaths due to suicide"). | In response to your previous comment, we have replaced "suicidality" with "suicidal ideas or behaviors". In addition, we have replaced "completed suicides" with "deaths due to suicide".                       |
| #4 Technical Expert Panel Reviewer | Results, p. 108 lines 11-16 | Distinguishing between short-term and long-term psychodynamic psychotherapy is helpful. Where possible these distinctions should be made elsewhere in the document.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | We appreciate the reviewer's input. We have added "short-term" and "long-term" descriptors throughout the report when that information was available.                                                           |

| Commentator & Affiliation          | Section                         | Comment                                                                                                                                                                                                                                                                                                                                                                                                              | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| #4 Technical Expert Panel Reviewer | Results, p. 109 line 17         | It is helpful that this level of detail has been included so that the reader can gain an appreciation for the specific adverse events that were reported. Some of these (e.g., lesion of brachial plexus, lower arm fracture) seem unlikely to be related to the treatment.                                                                                                                                          | Thank you for your comment. We reported serious adverse events as described in our included studies, even when their relationships to the treatments being evaluated were unclear or questionable.                                                                                                                                                                                                                                                                                                                            |
| #4 Technical Expert Panel Reviewer | Results, p. 109 line 20         | Were the study authors any more specific about this? It's hard to know how this would have been identified or even what it means.                                                                                                                                                                                                                                                                                    | No, this was as much detail as the study authors provided.                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| #4 Technical Expert Panel Reviewer | Results, p. 109 line 24         | The risk of treatment emergent mania is a common concern when treating patients with MDD given that a proportion will have had an unrecognized history of hypomania (consistent with bipolar disorder) or will go on to develop episodes of mania or hypomania later in life. In the other comparisons, it may be worth specifically noting whether emergence of mania or hypomania was reported or assessed.        | We appreciate this insight. Rather than specify which serious adverse events were not reported, with the exception of suicidal ideas or behaviors, we have opted to describe specific events only when they occurred, such as emergent mania or hypomania.                                                                                                                                                                                                                                                                    |
| #4 Technical Expert Panel Reviewer | Results, p. 111 line 23 ff      | As with the analysis of harms, one would expect that specific benefits/harms of treatment for patient subgroups would be related to the treatment arm and would not differ if the study comparison group happened to be placebo vs. an active comparator. The lack of inclusion of placebo controlled trial data, particularly given the paucity of evidence, makes it hard to know how to interpret these findings. | We appreciate the reviewer's point. However, our focus in this review is on <i>comparative</i> efficacy and harms. General efficacy and harms are beyond the scope of this review. We considered including placebo comparisons for the purposes of indirect comparisons in network meta-analyses. In the case of subgroups, we would have conducted meta-regression within NWMA had data been sufficient to do so. Unfortunately, we did not have enough evidence addressing subgroups of interest to conduct such analyses.. |
| #1 Peer Reviewer                   | Discussion [No page # provided] | The discussion is also well done. As noted above, the problem with understanding and using the St. John's Wort literature needs to be taken into account. Because the report is so lengthy and uses a repetitive style, I wonder if graphic design elements could also be used in the discussion and conclusion to help primary care physicians see the main                                                         | We acknowledge the reviewer's comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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| Commentator & Affiliation          | Section                            | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Response                                                                                                                                        |
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|                                    |                                    | take aways and remember them to use in clinical practice.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                 |
| #2 Peer Reviewer                   | Discussion<br>[No page # provided] | In general the discussion is reasonable and thoughtful It might be wise to remind the readers that the CBT employed was performed by trained therapists who had regular supervision, fidelity checks, and in most cases were using a manualized form of CBT. It would also be important to mention that the studies discussed tended to employ individual rather than group CBT.<br><b>[Continued on the next row]</b>                                                                                                                                                                                                                                                                                                                                                             | Thank you for the comment. We have updated the text.                                                                                            |
| #2 Peer Reviewer                   | Discussion<br>[No page # provided] | <b>[Continued from previous row]</b><br>It might also be reasonable to discuss the fact that MDD is a syndrome and that we need to dissect this syndrome into more homogeneous subgroups so that we can tailor therapies more appropriately. I think that one of the very important caveats that should be present in the abstract as well as emphasized even more strongly in the discussion is that, a finding of no statistical difference does not mean equivalence.<br><b>[Continued on the next row]</b>                                                                                                                                                                                                                                                                     | We address this point in various places in the Discussion. In the revised report we tried to put more emphasis on this in the executive summary |
| #2 Peer Reviewer                   | Discussion<br>[No page # provided] | <b>[Continued from previous row]</b><br>I would suggest acknowledging how challenging it is to compare and contrast 2 different therapies- there are issues around expectancy bias, masking of raters, how to comprehensively measure both the positive and negative effects of 2 potentially quite dissimilar interventions. It requires investigators to be very thoughtful in understanding the complexity of such studies and how such a study cannot be "plugged into" the usual trial design.                                                                                                                                                                                                                                                                                | We acknowledge the reviewer's comment.                                                                                                          |
| #1 Technical Expert Panel Reviewer | Discussion<br>[No page # provided] | 2) It might be worthwhile to point out exactly where your recommendations diverge from both the American Psychiatric Association and the Department of Veterans Affairs/Department of Defense. It sounds like all agree that either medication or psychotherapy (or perhaps CAM) are sufficient for patients with less severe depressions (although I think a case can be made for preferring psychosocial interventions as the first line treatment for such patients since they have fewer side effects and for the cognitive and behavioral interventions may have enduring effects that reduce subsequent risk). Where I think they do diverge is with respect to what to recommend for patients with more severe depressions. If I recall correctly, the recent APA guideline | Thank you for the comment. We have incorporated the reviewer's suggestions into the text.                                                       |

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| Commentator & Affiliation          | Section                         | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Response                                                                                                                                                                                                             |
|------------------------------------|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    |                                 | <p>continues to assert that medications are necessary for such patients despite the absence of any strong empirical evidence for that claim. Moreover, it is not clear that the empirical literature (which you so ably review) supports the claim that combined treatment is necessarily to be preferred for such patients (see for example DeRubeis et al., 2005, Arch Gen Psych). Combined treatment typically shows a modest advantage over either monotherapy alone but a recent trial suggests that that effect is heavily moderated and may only apply to non-chronic patients with more severe depressions (see Hollon et al., 2014, JAMA Psychiatry, attached). Your review appears to suggest that there is no reason to prefer SGAs to the empirically supported psychotherapies (at least the cognitive behavior therapies and the older literature would suggest IPT as well) and it might be worthwhile stating that more explicitly at the end of the paragraph in which you describe the APA and DOD recommendations.</p> |                                                                                                                                                                                                                      |
| #2 Technical Expert Panel Reviewer | Discussion [No page # provided] | <p>The authors in general do a very good job in discussing the issues of the report. As noted above, there does need to be increased discussion of limitations around the assessment of adverse events.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <p>Adverse events assessment is one of the main limitations of this body of evidence. In the revised report we put more emphasis on this issue in the abstract and the executive summary</p>                         |
| #3 Technical Expert Panel Reviewer | Discussion [No page # provided] | <p>The discussion is very well written. I won't repeat my concern about the use of "alternative."</p> <p>Aside from the dated language, the manner in which the findings are presented, with the comparative benefits, and the implications for practice is excellent.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <p>Thank you for your comment</p>                                                                                                                                                                                    |
| #3 Peer Reviewer                   | Discussion [No page # provided] | <p>The Discussion is generally good, and is more nuanced, and appropriately so, than the rest of the review. Concerns about the uneven quality of the data are more spelled-out here, with some - but not enough - recognition that the review is reaching more positive conclusions about than those (possibly dated) ones reached by the field. The fact is that while SJW might have a role to play in the treatment of major depression, the field seems to have stopped studying it and has largely rejected its use in routine clinical practice. Certainly one could take issue with this, but the fact that the present review seems to accept 10 -15-year-old studies at face value is problematic (for openers, limitations of the trials should not wait until the Discussion section - e.g. whether comparison SGAs were being used optimally).</p>                                                                                                                                                                           | <p>We conducted additional sensitivity analyses on dosages and geographical location of studies for SJW. Based on these results we changed the strength of evidence to low for the comparisons of SGAs with SJW.</p> |

| Commentator & Affiliation               | Section                              | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| #4 Technical Expert Panel Reviewer      | Discussion [No page # provided]      | Although such preparations may be available, patients and/or physicians may not know where to find them and may not know how to distinguish between well-standardized and well-manufactured products and less consistent ones.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | In the US, standardized SJW preps are commonly available at most pharmacies, health food stores, and groceries. Standardization is no more difficult to assess (eg. 0.3% hypericin) than the dose of ibuprofen contained in a single capsule. Quality, however, is a more challenging issue. Although quality seals for extracts are available, such as those from the US Pharmacopeia, NSF, as well as certified Good Manufacturing Practices (cGMP), this is an ongoing challenge for patients and providers. We noted this problem in the discussion section on applicability. |
| #4 Technical Expert Panel Reviewer      | Discussion [No page # provided]      | Many portions of the document do a good job of discussing the implications of the findings including the limitations of the studies (individually and as a body). The attached document includes comments and suggestions for areas of the document that may benefit from more detailed or more explicit discussion of limitations and implications. For such a broad topic area, the future research section give a reasonable overview. Giving a more detailed explication of future research needs would be beyond the scope of a document such as this one.                                                                                                                                                                                                                                          | Thank you for your comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Public Commenter: Maryalice JordanMarsh | Discussion [No page number provided] | clear useful tables helped summary of lack of data about harms is very important. I would like to have seen a comment on social media sites like Patients Like Me Daily Bread and the lack of data on importance of data provided to researchers and the relationship of participation as a variable in success of treatment. finally a note should be made about the rapidly emerging field of games and other interactive media in managing depression and programmed phone calls such as those reported by Shiny Wu et al. It is important that this kind of a review serve not only to catalog the past but call attention to the emerging present games programmed calling telehealth etc and at least recommend how to improve understanding of what is happening in practice and related research | We appreciate the reviewer's comments. For this report, unfortunately, these interventions are outside the scope.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

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| Commentator & Affiliation                          | Section                                                                                                                                                             | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Response                                                                                                                                                                                                                                                               |
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| Public Commenter: American Psychiatric Association | Discussion, p. 96 in the last paragraph, "In particular, patients with higher severity MDD respond better to medication than those with lower severity depression." | This is not exactly the case. Rather those with low depression severity respond well to a placebo arm, and it is difficult to detect a statistically significant difference in treatment response between drug and placebo.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | We now have added this potential explanation in this section.                                                                                                                                                                                                          |
| Public Commenter: American Psychiatric Association | Discussion, p.99, Implications for Clinical and Policy Decision-making,                                                                                             | <p>In addition to those discussed in the review, we would like to point out that there are also other factors relevant in making a decision about treatment choice for depression. As with other disorders, such choices require an individualized approach, including a review of any previous treatments for that condition including dose and duration, and the clinical response and any adverse effects and their tolerability. There should also be a review of potential drug-drug interactions, including nonpsychotropic medications, herbal supplements and diet. There should be consideration of the cost of treatment, and whether the patient can reasonably pay for the treatment.</p> <p>With depression, consideration also needs to be given to a prior history of mania or hypomania (in the patient or in biological relatives) as this may affect the potential benefits and harms of treatment with an SGA. In terms of adverse event rates (and serious adverse event rates), there should also be consideration of the severity of the adverse effect (mild, moderate, severe), tolerability to a particular patient, and relationship to dose or treatment duration. Some adverse events may be idiosyncratic to a particular treatment (e.g., phototoxic rash with St. John's wort, lowering of seizure threshold with bupropion, liver failure with nefazodone, significant weight gain with several) whereas others may be related to a class of treatments (e.g., serotonergic versus noradrenergic adverse effects).</p> | <p>These are important comments, we added some of these factors about decision making to the conclusions.</p> <p>Drug-drug interactions were outside the scope of this review. In the Discussion, we point out the potential drug interactions of St. John's wort.</p> |

| Commentator & Affiliation                               | Section                        | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Response                                                                                                                                                                                                |
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| Public Commenter:<br>American Psychological Association | Discussion, p. 99              | “Health care reform around the world reflects a trend toward integrative care as a remedy for the current, fragmented delivery of health and social services common in many health care systems. Given that both SGAs and psychotherapies can have equal merit in treating MDD, locating clinicians who render mental health care in primary care settings needs to be part of this trend. Doing so would likely increase patient access to therapy and enhance coordination of care between primary care clinicians and therapists.” – This is a nice statement and supportive of views expressed by the American Psychological Association. | Thank you for your comment.                                                                                                                                                                             |
| #4 Technical Expert Panel Reviewer                      | Discussion, p. 115 lines 18-20 | The fact that data from placebo controlled trials was not part of the review is an important limitation as noted earlier. It may be more precise to insert "from head-to-head trials" after the phrase "available evidence".                                                                                                                                                                                                                                                                                                                                                                                                                  | See earlier reply. Placebo-controlled studies were included in NWMAs. In most cases, results from NWMAs were similar to those from direct head-head trials                                              |
| #4 Technical Expert Panel Reviewer                      | Discussion, p. 115 lines 33-34 | In the past, many trials didn't actually assess remission rates since the primary outcome for statistical analysis was typically a change in continuous variable such as a symptom based rating scale score. (That most studies do not report response rates, remission rates or rates of specific adverse events has made it hard to develop medical decision analyses that would facilitate shared-decision making by patients.)                                                                                                                                                                                                            | We acknowledge the reviewer's comment.                                                                                                                                                                  |
| #4 Technical Expert Panel Reviewer                      | Discussion, p. 115 line 41     | It may be more precise to say that there has been very little direct testing in head-to-head trials as there is some additional data from placebo controlled studies.                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | As suggested, we have added the phrasing here “in head to head trials”.                                                                                                                                 |
| #4 Technical Expert Panel Reviewer                      | Discussion, p. 115 lines 55-57 | The generalizability of this conclusion to primary care patients, however, may be an issue given the exclusion of individuals with significant medical conditions and multiple concomitant medications from these trials. This is most likely to be a factor with St. John's wort as noted above.                                                                                                                                                                                                                                                                                                                                             | We acknowledge the reviewer's comment.                                                                                                                                                                  |
| #4 Technical Expert Panel Reviewer                      | Discussion, p. 118 lines 26-29 | It is not clear if the trials in this meta-analysis also included the one trial described under direct evidence. In any case, it would seem that at least 20 of the trials would have included some other diagnoses besides MDD, otherwise they should have been a part of the studies included under direct evidence above. Including indirect evidence only for the acupuncture comparison but not for the others seems problematic.                                                                                                                                                                                                        | Many of the trials that were included in this meta-analysis were not eligible for our report. We believe, however, that the risk for adverse events probably is generalizable to a population with MDD. |
| #4 Technical Expert Panel Reviewer                      | Discussion, p. 121 lines 47-48 | Again, here and elsewhere (particularly in conclusions about results), it may be worth specifying that it is the evidence from head-to-head trials that is being used to draw conclusions and not the totality of evidence                                                                                                                                                                                                                                                                                                                                                                                                                    | To make this point clearer, we have clarified the word “comparative”, such that it now reads: “The evidence was                                                                                         |

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| Commentator & Affiliation          | Section                        | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Response                                                                                                                                                                             |
|------------------------------------|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    |                                | about the particular interventions.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | insufficient to draw any firm conclusions about comparative differences in benefits and harms among interventions of interest as a function of depressive severity.                  |
| #4 Technical Expert Panel Reviewer | Discussion, p. 124 lines 35-37 | The results are consistent in terms of the statements in the rest of the paragraph but not consistent in terms of recommendations on acupuncture and St. John's wort.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | This section is in reference to psychological treatments only.                                                                                                                       |
| #4 Technical Expert Panel Reviewer | Discussion, p. 125 lines 26-28 | Most of the studies of TCAs vs. St. John's Wort also used low doses of antidepressant and did not include TCA blood levels as a way to assess the adequacy of dosing.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Thank you for this comment.                                                                                                                                                          |
| #4 Technical Expert Panel Reviewer | Discussion, p. 126 lines 18-20 | May be worth specifying that "we did not find evidence in head-to-head trials..."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Thank you for this suggestion. We have added this specification to the text.                                                                                                         |
| #4 Technical Expert Panel Reviewer | Discussion, p. 126 lines 28-30 | There can also be differences in cultural explanatory models of illness that may make acupuncture more aligned with belief systems in China vs. in the US. Cultural belief systems can also influence reporting of psychiatric symptoms, insight into having a psychiatric condition such as MDD and acceptance of other treatment approaches (e.g., psychotherapy, pharmacotherapy). The availability of trained practitioners of acupuncture in China vs. the US is an additional factor that would significantly limit the applicability of these study results.                                                                                                               | Thank you for this comment, which we have addressed in the discussion section.                                                                                                       |
| #4 Technical Expert Panel Reviewer | Discussion, p. 126 lines 41-45 | This is an extremely important concept and needs to be emphasized in the abstract and elsewhere in a fashion that will make this limitation clear to policy-makers, guideline developers and typical readers of the report.                                                                                                                                                                                                                                                                                                                                                                                                                                                       | In the revised executive summary we emphasize more strongly that the lack of a statistically significant difference should not be equated with equivalence of two treatment options. |
| #4 Technical Expert Panel Reviewer | Discussion, p. 126 lines 46-48 | This is another extremely important point that is often a source of confusion and misinterpretation for payers, policy makers and clinicians. The fact that no difference is observed for the sample as a whole does not hold true for the individual patient. Thus a patient might respond to treatment A but not treatment B (or vice versa) and might respond to SGA 1 but not SGA 2. Yet decision makers who are setting policies about formularies and treatment authorizations often assume that "no difference in treatments" makes them equivalent and interchangeable for any patient, regardless of a patient's prior treatment history or current pattern of symptoms. | We acknowledge the reviewer's comment.                                                                                                                                               |

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| Commentator & Affiliation          | Section                        | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Response                                                                                                                                                                                     |
|------------------------------------|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| #4 Technical Expert Panel Reviewer | Discussion, p. 127 lines 11-13 | Clinician type, training, experience and degree of treatment fidelity are likely to be even less in routine clinical practice than in the studies reviewed in this document. Along with psychotherapist availability, these are important factors for clinicians to consider when deciding on psychological interventions.                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Thank you for the comment. We have modified the text to include this comment.                                                                                                                |
| #4 Technical Expert Panel Reviewer | Discussion, p. 127 lines 14-17 | This conclusion seems very appropriate based on the totality of the evidence. It should be made clear in the abstract as well as elsewhere in the document. Many of the other portions of the document would suggest that acupuncture is an appropriate substitute for antidepressants. This is problematic for the reasons discussed above.                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Thank you for the comment.                                                                                                                                                                   |
| #4 Technical Expert Panel Reviewer | Discussion, p. 127 line 23     | p. 127 lines 26-28 The effect of St. John's wort on levels of anti-rejection regimens in patients posttransplant may be worth mentioning here given the implications for patient safety. Oral contraceptives are also metabolized by CYP 3A4 (PMID: 15914127) and concomitant use of St. John's wort can reduce oral contraceptive effectiveness and would be important to keep in mind in primary care settings, particularly given the female preponderance of MDD.                                                                                                                                                                                                                                                                                                                            | We agree and we have noted many of these HDIs in the discussion section.                                                                                                                     |
| #4 Technical Expert Panel Reviewer | Discussion, p. 127 lines 45-46 | The fact that the trials excluded individuals who were sedentary and/or had significant medical conditions would also be important to note here in discussing the generalizability of results to typical primary care or psychiatric outpatient settings.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | It is not very clear from eligibility criteria but we think the studies included both sedentary and non-sedentary subjects. In most studies none of the 2 were explicit exclusion criteria.. |
| #4 Technical Expert Panel Reviewer | Discussion, p. 127 line 51     | May be better worded as "typical clinical settings" or something similar.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | We changed the wording                                                                                                                                                                       |
| #4 Technical Expert Panel Reviewer | Discussion, p. 128 line 2      | This paragraph makes an excellent (and appropriate) point that it is not possible to determine a comparative assessment of the balance of benefits and harms without accurate data on harms. This has a major (negative) impact on how useful the findings will be for guideline developers, policy makers, clinicians and others. However, this seems somewhat different from questions of applicability. Drawing conclusions about whether the data are applicable to typical clinical settings and patient populations would seem to be guided by considerations such as exclusion criteria, characteristics of the patient sample, or the location/ culture and setting in which the study was done. The "applicability" section should be examined closely to see if some portions are more | This paragraph is actually not under "applicability" anymore but rather under "Implications for clinical and policy decisionmaking" where we believe is the appropriate place.               |

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| Commentator & Affiliation          | Section                        | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Response                                                                                                                                                                                                                                                                                          |
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|                                    |                                | relevant to other sections of the document.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                   |
| #4 Technical Expert Panel Reviewer | Discussion, p. 128 lines 9-15  | This paragraph seems somewhat confusing as written. It might be more clear to frame it as follows: "Systematic review of head-to-head clinical trials with moderate SOE detected no statistically significant differences in effectiveness between an SGA medication or psychotherapy in treating MDD. The specific psychotherapeutic interventions studied included cognitive behavioral therapy, interpersonal therapy, psychodynamic therapy and behavioral activation. These findings suggest that either approach can serve as a reasonable starting place for treatment of MDD. We caution, however, that it remains unknown whether the severity of depression should influence decisions about the initial treatment strategy."                                                                                                                                                                                                                              | We have modified as suggested.                                                                                                                                                                                                                                                                    |
| #4 Technical Expert Panel Reviewer | Discussion, p. 128 lines 18-22 | As written, these sentences seem to imply support for a model in which pharmacotherapy for depression is provided by primary care clinicians and psychotherapy is provided by therapists, presumably non-psychiatrist therapists. This model of split treatment is one approach but it is not the only possible model of integrated care delivery and it would be helpful to note this. Particularly for patients with more complex medical conditions, having co-localization of a sychiatrist rather than a nonmedically trained therapist may have distinct advantages. For example, fatigue or hopelessness may relate to depression, medical illness or both and non-medically trained therapists may not be able to make those distinctions. Psychiatrists embedded in primary care settings can provide consultation about diagnosis and pharmacotherapy to primary care clinicians or can provide pharmacotherapy and/or psychotherapy directly to patients. | We agree, and we have modified to read as follows (added words in italics):<br>"Doing so would likely increase patient access to <i>psychiatric consultation and</i> therapy, and it would enhance coordination of care between primary care clinicians and <i>mental health professionals</i> ." |
| #4 Technical Expert Panel Reviewer | Discussion, p. 128 lines 25-26 | Interventions that have been studied to improve treatment adherence are not typically the same as those reviewed here. Although adherence and the need for interventions to improve adherence is an important topic, it is not clear to me that it fits into this paragraph. I do think it's fair to say that having access to non-pharmacological interventions for depression in the primary care setting may improve treatment outcomes.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | We think that adherence and improved downstream effects are notable potential benefits of this integrative approach, so we will keep as is.                                                                                                                                                       |

| Commentator & Affiliation          | Section                        | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Response                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------------------------|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    |                                | The "downstream effects" discussed in the final sentence seem related to the colocalization of mental health professionals in the primary care setting rather than being a direct effect of psychotherapy, per se. This sentence may need to be moved earlier in the paragraph or reworded slightly.                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| #4 Technical Expert Panel Reviewer | Discussion, p. 128 lines 33-39 | This paragraph is somewhat confusing as written. It is true that many managed care companies have traditionally "carved out" mental health benefits, including psychotherapy, and subjected mental health benefits to different payment and utilization review policies. Although laws and regulations related to mental health parity are beginning to change this, it remains a problem. However, psychotherapy is no more or no less a special type of care than neurosurgery, oncology or a multiplicity of other medical specialties. Thus, it may be clearer to write "Some insurance plans in the United States charge different rates for psychotherapy and other mental health services than they do for generalized medical care. Decision- and policy-makers ...." | We have modified as suggested.                                                                                                                                                                                                                                                                                                                                                                                                                |
| #4 Technical Expert Panel Reviewer | Discussion, p. 128 line 44     | The phrasing that "the weight of evidence favors efficacy for the CAM treatment" seemingly implies that St. John's wort is more efficacious than other treatments such as SGAs or psychotherapy when this is not the case. The example of ginger root doesn't seem germane for this context.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | The comment is about efficacy, not comparative efficacy (ie. when research has demonstrated efficacy, but insurance coverage does not support use.) For SJW, there are now two Cochrane reviews that support the efficacy of SJW for treatment of MDD. We clarified this point by having the phrase read, "the weight of evidence <i>addresses the efficacy of CAM treatment compared to placebo.</i> " (italics only identify the addition). |
| #4 Technical Expert Panel Reviewer | Discussion, p. 128 line 45-47  | At least for St. John's wort, this argument seems overblown since it can be purchased in large quantities (e.g., via Amazon) at a cost of about \$5/month, which is comparable to the co-payments on most non-CAM pharmacological treatments.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Thank you for the comment.                                                                                                                                                                                                                                                                                                                                                                                                                    |
| #4 Technical Expert Panel Reviewer | Discussion, p. 128 lines 48-54 | These sentences are appropriate in content but may be able to be written in a way that is clearer to readers.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | We will consider modifying this wording, but we believe that this sentence reads adequately.                                                                                                                                                                                                                                                                                                                                                  |
| #4 Technical                       | Discussion,                    | Even doses of 75-100 mg of sertraline are not sufficient for many                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | This point is true, but we are pointing                                                                                                                                                                                                                                                                                                                                                                                                       |

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| Commentator & Affiliation          | Section                        | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Response                                                                                                                                                                                              |
|------------------------------------|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Expert Panel Reviewer              | p. 129 line 55                 | patients.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | out here that the 50 mg dose use in these comparative trials was quite low and likely not sufficient. We have left as is.                                                                             |
| #4 Technical Expert Panel Reviewer | Discussion, p. 129 line 57     | The table of Rush et al. which compares depression rating scales and thresholds of depression severity does use this range for severe depression. However, others have defined higher cutoff scores on the HAM-D as distinguishing moderate from severe depression. For example, Roger McIntyre and Jay Nathanson in their book "Severe Depression" (Oxford University Press, 2010) note that "most trials employ a threshold score of 25 or 28 on the HAM-D 17 ... to define severe depression." They also note that studies that use sensitivity, specificity and ROC curves to define rating scale cut-points show that a MADRS score of 31 (corresponding to a HAM-D 17 of 25) gives the best discrimination between moderate and severe depression. Similarly Zimmerman et al. (PMID: 23759278) found a cutpoint of greater than or equal to 24 as the best threshold for severe depression. By comparison, large studies of electroconvulsive therapy typically have subjects with mean HAM-D scores of approximately 37 on the HAM-D 24, which corresponds to about 32 on the HAM-D 17. From this standpoint, a range of HAM-D scores from 19-23 would be more consistent with moderate depression. | We agree that there is general disagreement with how severity is defined per the HAM-D. Most references we identified defined it the way we had, so we continued with this severity categorization.   |
| #4 Technical Expert Panel Reviewer | Discussion, p. 130 lines 24-25 | For readers who are unfamiliar with the explanatory vs. pragmatic terminology, it might be useful to insert "(i.e., designed to show if a treatment could work in ideal circumstances rather than in everyday practice)"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Thank you. We inserted your suggested wording.                                                                                                                                                        |
| #4 Technical Expert Panel Reviewer | Discussion, p. 130 lines 34-35 | It would be useful to give examples of these factors (e.g., ....).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | We agree and have given examples and added a citation.                                                                                                                                                |
| #4 Technical Expert Panel Reviewer | Discussion, p. 130 line 43     | This seemingly contrasts with previous statements about the SOE and lack of superiority/inferiority to SGA for St. John's wort and for acupuncture.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | The statement in this section is not about SOE ratings (e.g., insufficient), but about which outcomes are reported (or not reported) overall. We changed the SOE rating for SJW from moderate to low. |
| #4 Technical Expert Panel          | Discussion, p. 132 line 4      | As a more dramatic treatment than taking a pill, acupuncture could have a differentially greater placebo response associated with its use.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | That is correct. We believe though that a fuller discussion of this problem                                                                                                                           |

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| Commentator & Affiliation               | Section    | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Response                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----------------------------------------|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reviewer                                |            | However, this would require a study with a placebo and sham acupuncture arms as well as active acupuncture and active SGA arms to test this hypothesis.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | is beyond the scope of our systematic review.                                                                                                                                                                                                                                                                                                                                                                                           |
| Public Commenter: Maryalice JordanMarsh | References | given purpose and mission of AHRQ should references have a code for those that are free to the public                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | We appreciate the reviewer's comment.                                                                                                                                                                                                                                                                                                                                                                                                   |
| Public Commenter: Maryalice JordanMarsh | References | Two randomized multicenter double blind parallel group placebo controlled studies conducted by E I Khalili et al <sup>1</sup> and Bauer et al <sup>2</sup> evaluated the efficacy and tolerability of once daily quetiapine extended release XR as an adjunct to antidepressant therapy in patients with major depressive disorder MDD single episode or recurrent who had an inadequate response to their current antidepressant treatment. In the E I Khalili study <sup>1</sup> a significant reduction in Montgomerysberg Depression Rating Scale MADRS total score at Week 6 was observed with quetiapine XR 300 mgday versus placebo but not with quetiapine XR 150 mgday. In the Bauer study <sup>2</sup> significant reductions in MADRS total score at Week 6 were observed with both quetiapine XR 300 mgday and 150 mgday versus placebo. The most common adverse events AEs reported in 5 or more of quetiapine XR treated patients in both studies included dry mouth somnolence sedation fatigue constipation nausea insomnia headache diarrhea increased appetite weight increased irritability and dizziness.<br><sup>1</sup> EIKhalili N Joyce M Atkinson S et al. Extended release quetiapine fumarate quetiapine XR as adjunctive therapy in major depressive disorder MDD in patients with an inadequate response to ongoing antidepressant treatment a multicentre randomized double blind placebo controlled study. Int J Neuropsychopharmacol. 201013917932.<br><sup>2</sup> Bauer M Pretorius HW Constant E et al. Extended release quetiapine fumarate as adjunct to an antidepressant in patients with major depressive disorder results of a randomised placebo controlled doubleblind study. J Clin Psychiatry. 200970540549. | These references are important, but they use a placebo control and are not relevant for our direct comparative effectiveness results. Also, we did not perform a network meta-analysis because we did not have a sufficient number of studies. Most trials did not connect through common comparators; furthermore, trials did not report on the same efficacy outcome. Therefore, we did not have sufficient data to run NWMA for KQ2. |
| Public Commenter: Maryalice JordanMarsh | Tables     | table demonstrates that games and other interactive media were not included                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | The reviewer is correct, they were not included.                                                                                                                                                                                                                                                                                                                                                                                        |

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| Commentator & Affiliation                               | Section               | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Response                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------------------------|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Public Commenter:<br>American Psychological Association | Appendix              | Could references be added to the summary of findings tables? Guideline development panel members often like to have the specific references on hand so they can refer back to the primary literature in case of questions.                                                                                                                                                                                                                                                                      | We added reference to the SOE tables.                                                                                                                                                                                                                                                                                              |
| Public Commenter:<br>Maryalice JordanMarsh              | Appendix              | 1 please include a lay summary appendix<br>2 in Appendix make note of where readers of final document will be able to post comments<br>3 describe reviews by real world practitioners patients and their families and critical policy people                                                                                                                                                                                                                                                    | We acknowledge the reviewer's comment. At this time, unfortunately, we do not have resources to write a lay summary appendix. The reviewers' comments and the replies of the author team will be posted on the AHRQ website. Limitations regarding real world population are addressed in the applicability section of the report. |
| #1 Peer Reviewer                                        | Clarity and Usability | As noted above, I have concerns that the report is so dense with detailed text that it may be difficult for the intended audience to read, digest, and use. Anything that can be done to use graphic design to guide the reader to key points would be helpful. Also, a brief companion article geared toward primary care physicians could make the huge effort in doing the report more accessible to clinicians.                                                                             | Thank you for your comment. We will also publish the report as a journal article which will be less dense.                                                                                                                                                                                                                         |
| #2 Peer Reviewer                                        | Clarity and Usability | In Tables 17 and 22 David Mischoulon's last name is misspelled.                                                                                                                                                                                                                                                                                                                                                                                                                                 | We have corrected this.                                                                                                                                                                                                                                                                                                            |
| #2 Technical Expert Panel Reviewer                      | Clarity and Usability | Overall, the report is clear and well presented, and can inform policy. The limited scope of comparisons reduces the overall applicability, but it adds to the usability.                                                                                                                                                                                                                                                                                                                       | Thank you for your comment.                                                                                                                                                                                                                                                                                                        |
| #3 Peer Reviewer                                        | Clarity and Usability | The report is well-structured and organized, with the main points clearly presented. Through no fault of the authors, the extant literature is quite uneven in every respect. The conclusions can be used to inform policy and/or practice decisions, but the limited scope of the review to studies that employed an SGA control arm is a limitation. Readers probably will want to consult other sources of information, e.g. practice guidelines, to complement the analysis presented here. | Thank you for your comment.                                                                                                                                                                                                                                                                                                        |
| #4 Technical Expert Panel Reviewer                      | Clarity and Usability | The report is generally well structured and clearly presented, with the caveats noted above. As already noted, some specific comments and suggestions for improvement are included in the attachment. Unfortunately, it is not clear to me whether the conclusions will be useful                                                                                                                                                                                                               | Thank you for your comment.                                                                                                                                                                                                                                                                                                        |

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| Commentator & Affiliation | Section | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Response |
|---------------------------|---------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
|                           |         | <p>or even appropriate to use in guiding decision making by primary care physicians, policy makers or guideline developers because of the issues with exclusion of placebo-controlled evidence. the limited breadth and quality of head-to-head trials and the paucity of studies on switch and augmentation strategies for 2nd line treatment. These limitations are not the fault of the authors who have done a very impressive job of compiling, synthesizing and organizing a significant body of complex and confusing literature.</p> |          |