*Comparative Effectiveness Review Disposition of Comments Report*

**Research Review Title:** Treatment of Depression in Children and Adolescents: A Systematic Review

Draft review available for public comment from June 6, 2019, to July 5, 2019.

**Research Review Citation:** Viswanathan M, Kennedy SM, McKeeman J, Christian R, Coker-Schwimmer M, Cook Middleton J, Bann C, Lux L, Randolph C, Forman-Hoffman V. Treatment of Depression in Children and Adolescents: A Systematic Review. Comparative Effectiveness Review No. 224. (Prepared by the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center under Contract No. 290-2015-00011-I.) AHRQ Publication No. 20-EHC005-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2020. DOI: https://doi.org/10.23970/AHRQEPCCER224.

## Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site or AHRQ Web site in draft form for public comment for a 3- to 4-week period. Comments can be submitted via the Web site, mail, or email. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the 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 |
|---|---|---|---|
| **Public reviewer: American Psychological Association (APA)** | Title | For title, consider revising to include "and Adolescents" as follows: "Treatment of Depression in Children and Adolescents: A Systematic Review" | Revised as suggested |
| **Public reviewer: APA** | | Consider expanding a little more on "Treatments as Usual" and examine whether TAU was defined differently in these studies. | Added text to study characteristics.<br><br>"A minority of studies offered an active comparator: most compared treatments with placebo, usual care, or wait-list controls. Usual care participants were free to initiate or continue nonstudy mental health or other health care services.[1-3] For pharmacotherapy studies, usual care participants may have received the index medication.[3] For psychotherapy studies, therapists offered treatment that they believed to be effective.[4] Usual care could include therapy, medications, or combined therapy and medications.[5]" |
| **Public reviewer: APA** | Evidence Summary | On page ES-8, Table B- please change the title of this table to reflect that interventions that are not psychotherapy, such as exercise, are also included. | Updated table and revised text of section to be consistent. |
| **Public reviewer: APA** | Abstract and Evidence Summary | Suggest highlighting more prominently for the reader in the abstract and evidence summary the point that much of the available evidence for non-pharmacological interventions was based on single (as opposed to pooled) RCTs with small sample size. | Added text to the abstract and the executive summary.<br><br>"Abstract: Evidence on benefits of psychotherapy arose from single small studies. Regarding pharmacological interventions, pooled evidence suggests that selective serotonin reuptake inhibitors (SSRIs) as a class may improve response and functional status among adolescents and children."<br><br>Executive summary/Main report:<br>"Broadly speaking, the evidence base is characterized by large areas of uncertainty or lack of information; these large gaps in the evidence occur more frequently in the nonpharmacological evidence base where the evidence on benefits comes from single studies and few studies examined harms." |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Public reviewer: APA** | Introduction | In the introduction, please consider including the recently released APA Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts in the discussion of available clinical practice guidelines on treatment of depression in children and adolescents as well as including it in the list of available guidelines in Table 1. This guideline and associated materials can be found here:<br>• Guideline document: https://www.apa.org/depression-guideline/guideline.pdf<br>• Guideline appendices: https://www.apa.org/depression-guideline/appendices.pdf<br>• Associated materials: https://www.apa.org/about/offices/directorates/guidelines/clinical-practice | This guideline has been added to Table 1. |
| **Public reviewer: APA** | Evidence Summary | On page ES-8 and elsewhere in document (such as after the final summary of findings for KQ1b on page 49) where findings about psychotherapy are discussed, in addition to noting that insufficient evidence was found for particular, specified treatments, please consider adding language indicating that no evidence that met quality criteria was found for a broad range of psychotherapy interventions and therefore no statements are made about these treatments. | Added to ES and discussion.<br>"We found no eligible evidence on a range of other psychotherapies, including play therapy and psychodynamic therapy, and therefore cannot comment on their effectiveness." |
| **Public reviewer: APA** | Evidence Summary | Readers unfamiliar with the term "insufficient evidence" may be confused to read "insufficient evidence" for treatments such as CBT and IPT with no mention of other common treatments such as play therapy or psychodynamic psychotherapy. Lack of evidence does not mean lack of efficacy but it certainly means that treatments have not been adequately evaluated and therefore no conclusions can be drawn. Specifying this (without specifying all possible interventions or psychotherapy types) could be helpful. | Added to ES.<br>We graded the evidence on many interventions as insufficient because of imprecision, inconsistency, or bias; in other words, no conclusion can be drawn on benefits or harms |
| **Public reviewer: APA** | Evidence Summary | On p. vi, insert the highlighted word in the following sentence towards the bottom of the page:<br>"…we did not, however, find the same results for SSRIs as a drug class, owing to insufficient evidence." | Revised. |
| **Public reviewer: APA** | Evidence Summary | On p. ES-1, beginning third paragraph, insert a period at the end of this sentence:<br>"Uncertainty persists regarding their overall efficacy and variations in efficacy by age and disorder." | Revised. |
| **Public reviewer: APA** | Evidence Summary | On p. 51, toward the end of the page, fluoxetine is misspelled | Revised |
| **Public reviewer: APA** | Evidence Summary | On p. 59, first bullet, replace "Appendixes (SAE)" with "Adverse Events (SAE)" | Revised |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Public reviewer: APA** | Evidence Summary | On p. 83, perhaps explain the difference between “chronic” and “transient” depression. | Added.<br><br>**“Depression Chronicity:** In a sample with comorbid depression and substance use disorder, those with “chronic” (as compared with transient) depression (defined as episodes lasting 9 months or longer) showed significant decreases in depressive symptoms in the fluoxetine versus placebo group when compared with those with “transient” depression (episodes lasting less than 9 months).[6]” |
| **Public reviewer: AACAP** | Clearly Defined Use of Terms | The Review mentions “serious adverse events” but does not include its definition. Therefore, it is not clear how serious adverse events are defined or qualified for the purpose of the Review. If the serious adverse events aren’t defined by industry standards, AACAP recommends that the term “adverse event” be used instead. | Added.<br><br>“Studies that defined serious adverse events generally use the Food and Drug Administration’s definition, that is, events resulting in death, life-threatening events, new or prolonged hospitalization, disability or permanent damage, congenital anomalies, or other serious events.[7-9] In some instances, authors did not specify SAE.” |
| **Public reviewer: AACAP** | Clearly Defined Use of Terms | In the Key Message section on the effective healthcare website: the term “mixed depression diagnoses” is used. This term is not defined and unfamiliar. We recommend that the term mixed depression diagnoses is removed our more clearly defined | Replaced throughout the document. |
| **Public reviewer: AACAP** | Measure-ment of Adverse Outcomes/ Events | The Review brings attention to adverse outcomes due to the side effects of medicine. AACAP recommends more research and review concerning the adverse outcomes of untreated depression | Added to the document.<br><br>“Our findings on harms in treatment and placebo arms of studies are very limited. Studies that did report harms were generally not powered to do so, furthering limiting our conclusions on harms. The interpretation of the harms from treatment is hindered by inadequate information on untreated depression. Information on the rate of harms of untreated depression is particularly important in the context of rising suicidality following the black box warning among depressed children and adolescents.” |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Public reviewer: AACAP** | Missed References | We bring to your attention two scientific articles that were not included in the Review. We recommend that they be included and have provided citations below. If the following citations were intentionally left out of the Review because they did not meet the Review's parameters for inclusion, please describe why.<br><br>The first article discusses sertraline vs. placebo:<br>Wagner et al., 2003<br>https://jamanetwork.com/journals/jama/fullarticle/197174<br><br>The second article discusses two double-blind placebo controlled studies on venlafaxine ER:<br>Emslie et al., 2007<br>https://www.sciencedirect.com/science/article/pii/S0890856709616993?via%3Dihub | Wagner et al. 2003 [10] and Emslie et al. 2007 [11] were both initially excluded for wrong study design. Wagner et al present pooled analyses of RCTs (ineligible design) and did not present individual estimates from each trial for inclusion so it continues to be excluded for wrong design. On closer review., we identified eligible study-level results for depression symptoms and response alone (other outcomes are pooled) from Emslie et al and have updated the report to add these two studies. Thank you for identifying these articles. |
| **Public reviewer: AACAP** | Analysis of Number Needed to Harm or Treat | For other conditions, epidemiological measures are used that indicate the number needed to harm (NNH) and number needed to treat. AACAP recommends inclusion of NNH and NNT data in the Review's analysis | Added in the discussion section. |
| **Technical Expert Panel (TEP) member #1** | General | Overall, I believe this was an excellent report. The target audience was explicitly stated, and the key questions appropriate. | Thank you. |
| **TEP member #1** | Introduction | Overall, the introduction is clearly written and understandable. There is a period missing on line 17, page 14. The introduction lays out the concerns that many clinicians have as they are making decisions, specifically concerns about harms of SSRIs and psychotherapies. | Thank you. |
| **TEP member #1** | | p. 45, line 15 "of" should be changed to "or" | Revised. |
| **TEP member #1** | Scope and key question | Regarding the interventions, was dialectical behavior therapy (DBT) also looked at? Since this is commonly used treatment for adolescents with depressive disorders (and personality issues), this intervention could also be considered. | We did not exclude any particular type of psychotherapy a priori. All forms of interventions were eligible (the inclusion/exclusion criteria list several types but this list is not comprehensive). The absence of particular interventions from the evidence base was because studies did not meet the other criteria for inclusion in the review. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **TEP member #1** | Methods | The methods are consistent with established standards for systematic reviews. For the literature search strategy, I am glad that Psychinfo was included. Would you also consider searching via EMBASE as my understanding is that this will access more of the literature published in Europe. Particularly considering the table on page 20 which shows that very few studies were found from Europe and Canada, this might be worthwhile. | Our experience with EMBASE has been that it results in a large search with few final inclusions. In this particular review, we conducted exhaustive hand searches of various systematic reviews in addition to dedicated searches in PsycINFO and CINAHL, increasing our confidence in the sensitivity of our searches. |
| **TEP member #1** | Results | The results are clearly laid out by key question with generally an appropriate level of detail. Regarding the subpopulations examined (page 24, line 24), was it considered to examine effects by gender or race/ethnicity for the psychotherapies? If there were inadequate numbers/data, it might be worthwhile stating this explicitly. | We added this to limitations<br><br>"Some studies evaluated several demographic, clinical, caregiver, and study characteristics and found evidence of moderation for a subset of variables only. These findings could be explained by chance; we could not arrive at conclusions as a result." |
| **TEP member #1** | Results | I am glad that there was an explicit discussion about suicidality as a harm on page 25. | Thank you. |
| **TEP member #1** | Results | Regarding moderators, for example on p 32 line 25, it might be helpful to specify how the variable moderated the outcome. For example, ADHD was a moderator for benefit of CBT vs. fluoxetine. Did those with ADHD do better with this treatment, or worse? It would be more useful for clinicians to know this. (This is clarified later on p. 88, but would be good to see earlier as well) | Revised<br><br>"Three companion publications to a single trial of adolescents with MDD found that CBT was inferior to fluoxetine in groups with lower family income, marked/severe baseline depressive symptom severity, and comorbid ADHD. CBT plus fluoxetine was superior to fluoxetine in groups with ADHD, higher treatment expectations, or mild to moderate baseline depression symptoms. In addition, for those with treatment-resistant depression, when compared with no CBT plus new medication, CBT plus new medication increased response rates among those with no abuse history, who had at least one comorbid condition, and those with low levels of hopelessness.[67-69] |
| **TEP member #1** | Discussion/ Conclusion | On page 36, the authors do a good job of talking about gaps. I still wanted to know more about the direction of the moderators' impact in the subgroups. | The text has been revised |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **TEP member #1** | Discussion/ Conclusion | On page 36, I was confused by the following sentence: "Fourth, we found no evidence on minimally important differences to help us interpret some of the results." Could this be explained differently? | Revised.<br><br>"Fourth, we had difficulty interpreting the clinical significance of some reported changes in continuous scales in the absence of evidence on minimally important differences for patients on those scales." |
| **TEP member #1** | Discussion/ Conclusion | In terms of gaps, it might also be worthwhile to acknowledge gaps in other subpopulations such as specific ethnic and minority groups, as well as by sex/gender | We wrote more text in the future research section on gaps in moderator analyses<br><br>"Third, we found preliminary evidence for moderators of efficacy and effectiveness such as baseline depression severity and comorbid conditions. These subgroup analyses, when available, were generally hypothesis generating because studies were rarely designed to measure differences in moderating variables. Some studies evaluated several demographic, clinical, caregiver, and study characteristics and found evidence of moderation for a subset of variables only. These findings could be explained by chance. The paucity of evidence limits our ability to support recommendations tailored by underlying patient characteristics. A robust trial focusing on sequencing treatments would help provide patient-centered evidence that accounts for underlying patient characteristics." |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **TEP member #1** | Discussion/ Conclusion | There is some confusing information about the moderating role of ADHD for CBT. On page 127, it stats that the efficacy of CBT was higher for children and adolescents with comorbid ADHD (line 55). In the results section, it is noted that the combined treatment (CBT plus treatment) was superior in the group with ADHD. However, on p. 171 line 15 it is noted that CBT was inferior to fluoxetine in the presence of comorbid ADHD. It might be worthwhile to pull out a separate paragraph on the various findings related to the subpopulation of children and adolescents with depressive disorders and ADHD. Pulling it out will be helpful to clinicians reading it who are attempting to understand what might work best for their patients with depressive disorders and ADHD. | We made some corrections and edits for clarity for the subsection on combined CBT and fluoxetine. The key points now state:<br><br>"We found no clear evidence that family income, depression severity, or ADHD moderated outcomes for combination therapy when compared with placebo."<br><br>We added this text.<br><br>"As an example, a single study found that monotherapy (CBT or fluoxetine) may offer benefits similar to combination therapy for those with ADHD, but monotherapy may not match combined therapy for those without ADHD but these findings arise from small samples and post-hoc analyses and require confirmation from larger preplanned analyses." |
| **TEP member #1** | Discussion/ Conclusion | I would like to see a more fleshed out discussion about the findings for children and adolescents with comorbid ADHD. | Revised we added this text.<br><br>"As an example, a single study found that monotherapy (CBT or fluoxetine) may offer benefits similar to combination therapy for those with ADHD, but monotherapy may not match combined therapy for those without ADHD but these findings arise from small samples and post-hoc analyses and require confirmation from larger preplanned analyses." |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **TEP member #2** | General | In the Key Messages (lines 25-32) and in the body of the report (KQ 2a; pages 24-27), some caution might be warranted in presenting the harms associated with SSRIs, given evidence regarding higher risk of SAEs needs to be considered in the context of the overall base-rate of SAEs (particularly regarding emergent suicidality) and the risk associated with untreated depression. | We added this text.<br><br>"Our findings on harms in treatment and placebo arms of studies are very limited. Studies that did report harms were generally not powered to do so, furthering limiting our conclusions on harms. In interpreting the available data on harms from treatment, clinicians also need to account for the profound harms of untreated depression. Information on the rate of harms of untreated depression is particularly important in the context of rising suicidality following the black box warning among depressed children and adolescents" |
| **TEP member #2** | General | It might be useful to clearly operationalize what is meant by "mixed depression." For example, is this used to referred to studies that included children with DD/PDD or MDD, or is this is used primarily to refer to tx of dysthymia/PDD in the presence of MDD (i.e., 'dual depression')? | Revised. We removed the phrase "mixed depression" and specified diagnoses throughout the text. |
| **TEP member #2** | Introduction | The introduction clearly presents the key questions. However, the summary of challenges faced by families and clinicians seems potentially overly simplistic and does not address common concerns about how to select among interventions based on clinical presentation, family preferences, and /likely benefit or how to address non-response. | We added this text<br><br>"Treatment recommendations also need to account for patient and family preferences and prior experience with depression that has not responded to treatment. Comparatively little is known about these issues that influence treatment selection." |
| **TEP member #2** | Methods | Procedures for the literature search strategy, study selection, and assessment of methodological quality are clearly operationalized. It might be useful to briefly operationalize the anchors (high, medium, low) for the "Strength of Evidence" rating (i.e., for readers less familiar with the Evidence-based Practice Center Program). | Table 5 offers this detail in the full report. We added this detail to the summary.<br><br>"Grades represent the degree of confidence that the evidence reflects the true effect and the likelihood that further research will change the estimate of effect. Insufficient grades are assigned when evidence is either is unavailable or does not permit estimation of an effect." |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **TEP member #2** | Methods | Regarding the inclusion of studies addressing collaborative care: While inclusion of these studies was part of the original scope of work, on the basis of (a) limited evidence and (b) the fact that collaborative care is a service delivery strategy comprised of multiple and variable therapeutic modalities, the rationale for including collaborative care in this report might be reconsidered. | Given that the inclusion of collaborative care was decided a priori, we are electing to retain these results. |
| **TEP member #2** | Results | The results are reported in a manner that is comprehensive and clear, in general. | Thank you. |
| **TEP member #2** | Results | The Tables that list the results of studies include the study reference number (superscript reference number in the "study design and sample size" column). It would be helpful if the list of studies that were included in the table footnote or could be accessed via hyperlink. | The final version released by AHRQ will have hyperlinked references. |
| **TEP member #2** | Discussion/ Conclusion | Conclusions regarding relatively less evidence for children vs adolescents might be considered in the context of what is known the developmental epidemiology of depression. For example, MDD onset increases with age and increases sharply around adolescence. Given the base rate among younger children, we would expect fewer studies, and prior reviews of the literature suggest that studies that focus on younger samples tend to involve youth with clinically elevated symptoms and not necessarily those with diagnosable depression. The implications if the inclusions criteria for studies (i.e., only studies involving youth with "a confirmed diagnosis of MDD, PDD, or Depression NOS) in the present review might be directly addressed. | Added under limitations.<br><br>"As noted previously, we found limited evidence on children. National estimates from 2017 suggest that 13.3% (3.2 million) of adolescents aged 12-17 have had one major depressive episode. Estimates for younger children are less well understood; in one review, an aggregated estimate of 2.8% of children under 13 had depression.[145, 146] Our inclusion criteria required a diagnosed DD; the evidence base in this review is therefore not representative of interventions for children with clinically elevated symptoms but not mood disorders. The same inclusion criterion also limited our ability to synthesize the evidence on some treatments, including collaborative care.[147] |
| **TEP member #2** | Clarity and Usability | The review process was clearly very rigorous and comprehensive. The review considered multiple therapeutic modalities; harms, benefits, and moderators of interventions; and multiple outcomes (e.g., symptomatic outcomes, functioning) across indices/time (e.g., acute response, remission). Naturally, the review constitutes a comprehensive technical report that can at somewhat difficult to distill into clinical/practical implications. | We have added a table for numbers needed to treat and harm, and we hope that this table will help focus attention on the most actionable parts of our review. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **TEP member #2** | Clarity and Usability | The overall discussion/conclusion might benefit from additional commentary/input from researchers who are specifically steeped in the child/adolescent treatment literature (e.g., including the broader literature including studies with symptomatic, but not necessarily diagnosed youth) and who are actively involved in developing and implementing guidelines for treating youth. For example, while empirically derived, conclusions about insufficient or limited evidence would need to be put in context to have value for informing practice (including the context of what we know about the potential consequences of untreated depression). The implications of the review findings for selecting and/or sequencing interventions might also be addressed (although perhaps this task is more appropriate for those who are actually developing and disseminating practice guidelines). | Regarding the issue of untreated depression, we added this text, as noted above.<br><br>"Our findings on harms in treatment and placebo arms of studies are very limited. Studies that did report harms were generally not powered to do so, furthering limiting our conclusions on harms. In interpreting the available data on harms from treatment, clinicians also need to account for the profound harms of untreated depression. Information on the rate of harms of untreated depression is particularly important in the context of rising suicidality following the black box warning among depressed children and adolescents."<br><br>Regarding the issue of sequencing, unfortunately, this evidence base does not offer clear insight. We have added text to indicate our recommendation for future research.<br><br>"A robust trial focusing on sequencing treatments would help provide patient-centered evidence that accounts for underlying patient characteristics." |
| **Peer reviewer #1** | General | The report is clinically meaningful. Its target population and audience is explicitly defined. Key questions are appropriate and explicitly stated. Inclusion and exclusion criteria are justifiable. Search strategies are explicitly stated and logical. | Thank you. |
| **Peer reviewer #1** | Introduction | no concerns | Thank you. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Peer reviewer #1** | Methods | Definitions and diagnostic criteria for the outcome measures are generally appropriate. There were discrepancies in the definition of child versus adolescent (e.g., p. 49-age split for child/adolescent is listed as > 12 and <= 12—this differs from elsewhere in the text, such as p. 52)—please clarify.<br>Statistical methods are appropriate. The amount of detail presented in the results section are appropriate (and the summary section is greatly appreciated). | Added text.<br><br>"We elected to use age categories as defined by study authors (adolescents as defined by study authors [typically age 11 or 12 years or older], children as defined by study authors [typically age 10 or 11 years or younger], and mixed adolescent and child samples [typically age 7 or 8 to 17 or 18 years]) rather than our own a priori definitions (adolescents [sample age >12 and ≤18]: RCTs, children [sample age ≤12]) to capture all available evidence." |
| **Peer reviewer #1** | Results | Characteristics of the studies are for the most part clearly described. I may have missed where sample sizes were characterized—so was surprised in Table 7 to learn that Ns of 176 and 223 (and p. 121—N of 304) were considered "small". There is no distinction between sample sizes in the hundreds and those with 10 or so per group- all are referred to as "small", which does not lend clarity to the relative strength of the studies. | Added this text to methods.<br><br>"This approach requires looking beyond statistical significance alone, even when studies are consistent and of high quality and outcomes are direct and clinically relevant. It emphasizes the adequacy of the sample size to rule out spurious associations and results that are not clinically relevant." |
| **Peer reviewer #1** | Results | Not all relevant articles were included (see citation below).<br>Pilot Randomized Controlled Trial of Omega-3 and Individual–Family Psychoeducational Psychotherapy for Children and Adolescents With Depression Mary A. Fristad, Anthony T. Vesco, Andrea S. Young, K. Zachary Healy, Elias S. Nader, William Gardner, Adina M. Seidenfeld, Hannah L. Wolfson & L. Eugene Arnold Journal of Clinical Child & Adolescent Psychology, Volume 48, 2019 - Issue sup1 Published Online: 07 Nov 2016 | This paper was retrieved by the updated search and included in the review. |
| **Peer reviewer #1** | Discussion/ Conclusion | Key messages are explicit and applicable. Figures, tables and appendices are adequate and descriptive. Implications of the major findings are clearly stated. Limitations of the review/studies are described adequately, although more attention to the definition of "small sample", imprecision, and risk of bias throughout the document (intro/method/results/discussion0 would aid the reader. The future research section is clear and easily translated into new research, if only someone would fund it. | Thank you. |
| **Peer reviewer #1** | Discussion/ Conclusion | p. 32 l. 38 replace "found" with "find", next line, delete space before . | Revised (page ES-21). |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Peer reviewer #1** | Discussion/ Conclusion | p. 119—Key Points- should reference TCAs, not SNRIs p. 173 l. 40—should be “Fifth” not “Fourth” | Corrected, thank you. |
| **Peer reviewer #1** | Clarity and Usability | Yes to all questions (with attention to points made above). | Thank you. |
| **Peer reviewer #2** | General | The authors should be commended for addressing this important topic. They provide a very thorough and comprehensive review of the treatment of depression in children in this report. All AHRQ evidence-based reports are typically long. Although this report addresses five KQs, it is summarized well and is actually shorter than other evidence-based reports (such as, Psychological and Pharmacological Treatments for Adults With Post-traumatic Stress Disorder: A Systematic Review Update, 616 pgs; Anxiety in Children, 278 pgs). The inclusion of KQ 4: Collaborative care interventions is especially welcome as this topic has received increasing interest from clinicians and funders. | Thank you. |
| **Peer reviewer #2** | General | This report is clinically relevant and serves as a comprehensive resource document. The report's potential impact on clinical/patient care or even whether any of the information in this report will be implemented into practice guidelines is less clear. The SOE on many of the interventions is already known. For example, the evidence on short term treatments of MDD in adolescents is probably well known in the mental health community but possibly less so with primary care clinicians. Even so, statements such as “Little evidence exists for children, depressive disorders other than MDD, long-term outcomes, comparative effectiveness, and potential moderators” are valuable in helping highlight and reinforce the limitations of knowledge in this area. This report may serve to increase awareness of the treatment issues (or reinforce clinical practice) but it's direct impact on changing clinical practices remains to be seen. | Thank you, and we agree that impact is yet to be determined. |
| **Peer reviewer #2** | Evidence Summary | ES-1, lines 39-40: The sentence reads “In sum, clinicians contend with numerous challenges in treating childhood depression appropriately.” The authors may consider changing to “In sum, clinicians contend with numerous challenges in appropriately treating childhood depression.” | We checked with our editor and elect to keep our original text |
| **Peer reviewer #2** | Evidence Summary | ES-2, lines 6-10: Under Scope of Review it may be more appropriate to insert the word “efficacy” in the following paragraph: “This systematic review (SR) addresses the efficacy, comparative effectiveness and harms of commonly used types of nonpharmacological and pharmacological treatments for childhood depression.” | Added as suggested |
| **Peer reviewer #2** | Evidence Summary | ES-17, lines 41-42 – Appears to be a typo (head-to-har”) | Revised. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Peer reviewer #2** | Introduction | P 60, line 50- Please review formatting; specifically the need to close parenthesis in this sentence: "The evidence suggests an increased risk of withdrawals with SSRIs as a class for adolescents with depression (risk difference, 26/1,000; 95% CI, 6 fewer cases to 45 more cases." | Corrected as suggested |
| **Peer reviewer #2** | Introduction | Introduction: Two clinical practice guidelines addressing the treatment of depression in youth were just released in June 2019. Inclusion of the content with updated references from these guidelines appears warranted. | Thank you, these guidelines have been added to Table 1 in the Introduction. |
| **Peer reviewer #2** | Introduction | The NICE, 2015 Depression in children and young people: identification and management guideline was updated in June 2019 with new recommendations on psychological therapies added. Accessed at https://www.nice.org.uk/guidance/ng134). | Thank you, the reference to the NICE guideline has been updated to reflect the 2019 publication. |
| **Peer reviewer #2** | Introduction | Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts American Psychological Association Guideline Development Panel for the Treatment of Depressive Disorders, Version 6/4/2019. Accessed at: https://www.apa.org/depression-guideline/guideline.pdf | Thank you, this guideline was added to Table 1. |
| **Peer reviewer #2** | Methods | By convention, findings are clustered by age as children and/or adolescents. The groups are generally defined by the study authors as – " typically 11 or 12 years of age or older as adolescents and 10 or 11 years of age or younger as children." A quick sampling of pharmacological intervention references reveals that different study authors defined adolescents as beginning at 11 yo (Atkinson, 2014; Emslie, 2014); 12 yo (Emslie, 2009; Le Noury, 2015; Durgan, 2018) and 13 yo (Berard, 2006). One could speculate that a subgroup of adolescent subjects ages 11-12 overlap with the child group. | We agree that a subgroup of adolescents overlap with the child group. Unfortunately, studies did not separately present results for this group, in order for us to be able to pool with the child results. The alternative was to strictly adhere to a priori age definitions, which would have resulted in loss of informative studies. |
| **Peer reviewer #2** | Methods | In addition, KQ2b (P 82, lines 43-46) examines pharmacological interventions for child and adolescent depressive disorders by age groups with children defined as being between the ages of 8 to 12 years and adolescents between 13 to 17 years. The authors might address why they investigated subgroup differences with a different, potentially confounding grouping of age. | Revised KQ 2b text to say<br><br>"(defined as children ages 8 to 12 years versus adolescents ages 13 to 17 years in two of three studies,[72, 82] undefined in third study[125])" |
| **Peer reviewer #2** | Results | Although the review is very thorough, the detailed results (tables?) would have benefitted from reporting the age range and median age for the defined population groups (child and adolescent). | The specifics are reported in the evidence tables |
| **Peer reviewer #2** | Discussion/ Conclusion | The report clearly highlights the key messages from this review (eg, insufficient evidence of the potential harms of psychosocial and pharmacologic interventions for childhood depression). | Thank you. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Peer reviewer #2** | Evidence Summary | ES-22, lines 40-53 contains the future research section and the authors generally summarize well their recommendations. This section may be targeted to researchers in the field but since it is contained in the Evidence Summary section it may likely be read by clinicians (clinicians being less likely to read the full text). Lines 50-53 contain the following sentence: "In addition, new research should establish minimally important differences to help understand the trade-offs between benefits and harms." Although an academic or scientific professional may understand the meaning of the term "minimally important differences" the average clinician may not. If the report is intended to be read by clinicians, this term should be briefly explained (possibly something like "the smallest amount an outcome must change to be meaningful to patients."). | Added text to explain minimally important differences as suggested |
| **Peer reviewer #2** | Clarity and Usability | This report is consistently structured with the AHRQ's methodologies for systematic reviews (eg, defining the PICOTS for each KQ in the specific text; assessment of bias). | Thank you. |
| **Peer reviewer #2** | Clarity and Usability | The Evidence Summary provides a comprehensive summary of the report's findings. Most clinicians will probably only read the Key Messages, Abstract and/or Evidence Summary sections of this reports. | We concur with the reviewer. |
| **Peer reviewer #2** | Clarity and Usability | ES 20-23 – Table F (& pp 132-155 - Table 64): Evidence map for interventions for childhood depression. The table is very comprehensive, long and especially busy. The structure and format make it extremely difficult to read (especially the use "+, I, 0"). The authors might consider reformatting the table to make it more reader friendly, especially for those individuals who are only reading the Evidence Summary section. | We have conducted some reformatting and added some bolding to the text to improve readability |
| **Peer reviewer #2** | Clarity and Usability | ES-23, lines 34-53 provide a well written paragraph summarizing the findings. This part of the Discussion section basically includes the summary and/or conclusion as well. Since the text follows a relatively long table, the authors might consider a better way to highlight the information in this important paragraph. | We added a header "conclusion" above the closing paragraph. |
| **Peer reviewer #2** | Clarity and Usability | P 50, line 33: "The evidence for SSRIs as a class suggested now benefit for remission among adolescents with MDD" Please clarify "now benefit." | Corrected to say "no benefit." |
| **TEP member #3** | General Comments | Although I was unable to review the entire report in detail, I am impressed with its clarity and comprehensiveness. | Thank you. |
| **TEP member #3** | Introduction | Good | Thank you. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **TEP member #3** | Methods | Good, but wish it could also have included some more recent publications. | We have updated the search and included more recent publications. |
| **TEP member #3** | Results | Yes | Thank you. |
| **TEP member #3** | Discussion/ Conclusion | Yes | Thank you. |
| **TEP member #3** | Clarity and Usability | Yes | Thank you. |
| **TEP member #4** | General Comments | Clear | Thank you. |
| **TEP member #4** | Introduction | Well written | Thank you. |
| **TEP member #4** | Methods | The age cut off , 18, left out trials that used broader definition of adolescence. While I understand the decision not to include in review, I would have preferred some notation to indicate that when studies with broader age group are included there is some support for value of models such as collaborative care that integrate evidence based depression care within primary care (Asarnow et al; Richardson et al.) | We updated the table with inclusion/exclusion criteria with a footnote to explain why we did not include studies using screeners rather than clinical diagnoses. We also updated the Limitations section to call out our criteria as a reason for excluding relevant interventions. |
| **TEP member #4** | Results | Misses important information on treatment for child depression, may be after date cut off, but that being said- having a big report come out so long after the date cut off for review does make the report "dated."; and this needs to be clear at beginning of report and throughout, it is now July 2019. | We ran an update search through May 2019 and have updated the review with new eligible publications. |
| **TEP member #4** | Discussion/ Conclusion | Important when looking at suicidality as an outcome to note that SI and attempts, and deaths, and NSSI are different outcomes; and depression studies are generally not powered to look at these outcomes which would clearly lead to insufficient evidence. Point applies to many of the outcomes examined, I wonder whether better to leave these analyses out as they really are a bit questionable given lack of statistical power to address the issues. | We concur and added this sentence to Limitations.<br><br>“Studies that did report harms were generally not powered to do so, furthering limiting our conclusions on harms.” |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **TEP member #4** | Clarity and Usability | Very thorough in what report does. Important to note that:<br>1) studies often not powered to look at some of the outcomes examined in this report<br>2) some newer work is not included<br>3) some important work with broader patient populations (e.g. age, diagnostic criteria) not included<br>4) conclusions would have differed had this additional work been reviewed.<br><br>Without these comments, it seems that the review could be misinterpreted: it is what it is. | Thank you, we concur.<br><br>1. We added text about the lack of statistical power as a limitation.<br>2. We updated the search and the report through May 2019.<br>3. Agreed, and we added this fact as a limitation "The same inclusion criterion also limited our ability to synthesize the evidence on some treatments, including collaborative care.". |
| **TEP member #5** | General Comments | Yes, I think it is incredibly clear! Although the results are troubling, the implications are well articulated. | Thank you. |
| **TEP member #5** | Introduction | This did a great job of situating the review in the context of current clinical practice and need, as well as what the evidence landscape looked like. The KQs and PICOS all seemed clear and intuitive. | Thank you. |
| **TEP member #5** | Methods | I didn't see Pediatric Symptom Checklist or Strengths and Difficulties Questionnaire internalizing subscale on the list of instruments that could indicate DD. That might be relevant to studies in children. | We required a clinical diagnosis for inclusion but included all measured outcomes, as long as the authors used a validated scale. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **TEP member #5** | Methods | Why at least six weeks of treatment? There's evidence for even single session interventions, and I worry this makes it look like we should focus on moderate/severe. Especially if you wanted to pick up things like motivational interviewing. | We chose an inclusion criterion of treatment for six weeks after consultation with our technical experts. The rationale was to be able to attribute the effect to the intervention, rather than to regression to the mean.The following five studies were excluded for time frame:<br><br>1. Avci, A., Diler, R. S., Kibar, M., & Sezgin, F. (1999). Comparison of moclobemide and placebo in young adolescents with major depressive disorder. Annals of medical sciences, 8(1), 31-40. X5 [12]<br><br>2. Findling, R. L., Robb, A. S., DelBello, M., Huss, M., McNamara, N., Sarkis, E., . . . Auby, P. (2017). Pharmacokinetics and safety of vortioxetine in pediatric patients. Journal of Child and Adolescent Psychopharmacology, 27(6), 526-534. doi: 10.1089/cap.2016.0155 X5 [13]<br><br>3. Harrington, R., Whittaker, J., & Shoebridge, P. (1998). Psychological treatment of depression in children and adolescents. A review of treatment research. British Journal of Psychiatry, 173(OCT.), 291-298. X5 [14]<br><br>4. Niederhofer, H., & von Klitzing, K. (2011). Bright light treatment as add-on therapy for depression in 28 adolescents: a randomized trial. Primary Care Companion for CNS Disorders, 13(6), 9p-9p. X5 [15]<br><br>5. Stark, K. D., Reynolds, W. M., & Kaslow, N. J. (1987). A comparison of the relative efficacy of self-control therapy and a behavioral problem-solving therapy for depression in children. Journal of Abnormal Child Psychology, 15(1), 91-113. X5 [16] |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **TEP member #5** | Methods | Is there a good reason for separating out modalities of the same intervention? Recent research seems to be suggesting that the modality (tele v in-person) might not really have much of an effect. Where separating out the modalities makes it seem like there isn't s much evidence for an intervention, this could be problematic. | We separated modalities to try to get more homogenous sets of interventions. Looking across these interventions, they rated as insufficient because these single studies for each modality were small and likely underpowered, the effects generally spanned the null. A claim of no evidence of effect would require larger and more numerous studies for each modality to make conclusions above insufficient. |
| **TEP member #5** | Results | I thought this was great! It gave access to the amount of detail you could want, while still giving understandable syntheses for the findings in each table. | Thank you. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **TEP member #5** | Discussion/ Conclusion | It might be helpful to contextualize the fact that everything had low SOE in a discussion of other reviews that AHRQ has done that involved mental health or children. There are probably general methodologic problems that make it hard to get to high SOE for multi-week behavioral interventions, and testing anything in kids is always tough. Does adult depression have high SOE for particular interventions? If so, what made a difference there? | The methodological problems associated with multiweek interventions typically have to do with poor adherence and attrition. Because we intended to evaluate studies for the effect of the intervention as randomized rather than as received, we generally did not downgrade studies for poor adherence in the risk of bias assessment as long as the study continued to track outcomes. We did, however, mark down studies with high and/or differential attrition for risk of bias. However, problems associated with attrition are not limited to behavioral intervention studies.<br><br>More generally, we used methods consistent with AHRQ guidance. There are no standard methods specific to interventions for adolescents and children.<br><br>Regarding the question on the results from reviews of adult depression, the evidence for adults is also largely low strength of evidence or insufficient strength of evidence (using AHRQ methods).[17] We have listed the limitations of the evidence base in the report and in the future research section.<br><br>"First, we found insufficient evidence on many interventions and outcomes. Greater certainty in the estimate of effect will require more and better evidence for nearly all evaluated interventions. In some instances, we found no eligible evidence of benefits or harms in our specified populations, as with of collaborative care." |
| **TEP member #5** | Discussion/ Conclusion | For future research needs, both the table and the summary statements of specific directions were very well done and make it easy to understand where to head next. | Thank you. |
| **TEP member #5** | Clarity and Usability | Yes, while I was sad that there wasn't a higher SOE for the treatments, I thought it was extremely well done and makes it clear where we need to go to build the evidence for treating such a disabling condition. | Thank you. |

*Source: https://effectivehealthcare.ahrq.gov/products/childhood-depression/research*
*Published Online: April 10, 2020*

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Peer reviewer #3** | General Comments | This systematic review is an important addition to the literature on the treatment of childhood depression. The key questions are clearly addressed in the beginning and throughout the review. They did a good job of examining the efficacy and comparing both benefits and harms of non-pharmacological and pharmacological treatments. | Thank you. |
| **Peer reviewer #3** | Introduction | The introduction gives the necessary background of the topic and then clearly addresses the key questions throughout the paper.<br>The inclusion and exclusion criteria were described using table 4 | Thank you. |
| **Peer reviewer #3** | Methods | The search strategies were clearly stated. They identified their literature search strategy. They graded the strength of the evidence based on the guidance established for the Evidence-Based Practice center program. | Thank you. |
| **Peer reviewer #3** | Results | In the results section the amount of detail is appropriate. They addressed the key questions 1-5 a,b. The results were clearly laid out for each KQ. | Thank you. |
| **Peer reviewer #3** | Discussion/ Conclusion | The major findings for each key question were clearly stated. The limitations of the study were addressed. | Thank you. |
| **Peer reviewer #3** | Clarity and Usability: | The report is well structured and organized. The main points are clearly presented. The conclusions are relevant to practice decisions. The findings confirmed the effectiveness of some treatments for adolescents with major depressive disorder. Unfortunately they found little evidence for the treatments of children with depressive disorders other than major depressive disorder, The opportunities for new research were identified. | Thank you. |
| **Peer reviewer #4** | General Comments | The content area of the report is of great clinical relevance, and key questions addressed by the systematic review are explicitly stated. The target audience for the report is not well described. | We acknowledge the American Academy of Child and Adolescent Psychiatry in our final report but do not call out a specific audience because EPC reports are intended for a broad audience. |
| **Peer reviewer #4** | Introduction | The manuscript does not read well, and is diminished by repeated use of imprecise language and typographical errors. Some terms are not well-defined such as “mixed depressive disorders” and “serious adverse events”. | We corrected typographical errors We have replaced the term “mixed depression” and have specified “serious adverse events” in methods in our revisions. |
| **Peer reviewer #4** | Methods | Study methods, including inclusion and exclusion criteria, are not well described. | The study inclusion and exclusion criteria are described in detail in the methods section of the main report |
| **Peer reviewer #4** | Results | The detail presented appeared excessive and overwhelming, potentially distracting from the core message. Greater attention should be paid to synthesizing and presenting summary findings in a clear and consistent manner. | We have edited the document to address peer reviewer and public comments to increase the clarity of the report. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Peer reviewer #4** | Results | Clinically relevant findings from the systematic review are not well organized, summarized, or presented. The presentation is unwieldy and unsatisfying. Greater attention to consistently and clearly summarizing study findings and conclusions might reduce the likelihood of the report generating confusion among clinical providers. That said, study key questions are well presented and the Figure describing the analytic framework is useful and clear. Greater efforts on summary sections and key points<br>would benefit the presentation. | We have edited the document to address peer reviewer and public comments and correct typographical errors and hope that these edits help with clarity. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Peer reviewer #4** | Results | The manuscript does not read well, and is diminished by repeated use of imprecise language and typographical errors. Some terms are not well-defined such as “mixed depressive disorders” and “serious adverse events”. Additional proofreading and editing is in order. Specific examples include:<br>• Line 15 in the Introduction to the Evidence Summary (“…treatment options to treat childhood DDs are available to clinicians”).<br>• Substituting “of” for “or” (line 42, ES-1)<br>• “head to har comparisons…” (line 43, ES-17)<br>• “we did found insufficient evidence” (line 38, ES-19)<br>• “poor functional impairment” (line 9, Chapter 1, page 1)<br>• “companion” instead of “comparison (e.g., line 39, page 14; line 38, page 15)<br>• “suggested now benefit for remission” (line 33, page 50) | We replaced the term “mixed depression” with specifics of the depressive disorders for each study. We also added text to methods section on “serious adverse events.”<br><br>Thank you for identifying these typographical errors; we have corrected them.<br><br>Specific examples include:<br>• Line 15 in the Introduction to the Evidence Summary (“…treatment options to treat childhood DDs are available to clinicians”).<br>- We corrected this to say “treatment options for childhood DD”<br>• Substituting “of” for “or” (line 42, ES-1)\<br>- Corrected<br>• “head to har comparisons…” (line 43, ES-17)\\<br>- Corrected<br>• “we did found insufficient evidence” (line 38, ES-19)<br>- Corrected to “we found”<br>• “poor functional impairment” (line 9, Chapter 1, page 1)<br>- Thank you, corrected<br>• “companion” instead of “comparison (e.g., line 39, page 14; line 38, page 15)<br>- This was intentional and meant to point to companion articles. We have specified what we mean in this and in every other instance that we call out companions by clarifying “companion publication.”<br>• “suggested now benefit for remission” (line 33, page 50)<br>- Corrected to say “no benefit” |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Peer reviewer #4** | Results | It is unclear why some studies were included and others were not. For example, while the authors chose to address collaborative care interventions, no available studies met their inclusion criteria. Specifically, I wondered why the Asarnow YPIC study and the Richardson ROAD study were not included. What were the inclusion/exclusion criteria here? The statement in the discussion that "intervention delivered in collaborative care settings" were addressed by the review is misleading. | The study by Asarnow et al. reporting data from The Youth Partners-in-Care (YPIC) study was excluded for wrong study design and because data were reported for those aged 13 to 21 years with no subanalysis for those 18 years or younger.<br><br>The study by Richardson et al. reporting data from the Reaching Out to Adolescents in Distress (ROAD) Study was excluded for wrong population. Participant inclusion was based on screening questionnaire cutpoints rather than an MDD diagnosis.<br><br>The reasons for exclusion for both studies are reported in Appendix C.<br><br>The search included collaborative care settings, so this is described but, unfortunately, no studies in this setting met inclusion criteria of the review. |
| **Peer reviewer #4** | Results | It was unclear if the degree of attention paid to subgroup analysis was especially helpful or enlightening. | We hope that the paucity of evidence on subgroup analysis prompts consideration of new funding. |
| **Peer reviewer #4** | Results | In the section entitled "TCAs Versus Placebo: Harms" on page 77, the Key Points address SNRIs rather than TCAs. | Corrected. |
| **Peer reviewer #4** | Results | The authors focused on RCTs to address potential benefits of treatments and RCTs or observational studies to address potential harms. Why not be consistent across potential benefits and harms of treatments? | We typically include observational studies for harms in order to capture the widest possible range of eligible and useful evidence for harms. Observational data could potentially offer a signal of rare harms, in particular, that trials may not be able to capture. |
| **Peer reviewer #4** | Discussion/ Conclusion | Note: Reviewer referred to above results comments. | See above. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Peer reviewer #4** | Clarity and Usability | Clinically relevant findings from the systematic review are not well organized, summarized, or presented. The presentation is unwieldy and unsatisfying. Greater attention to consistently and clearly summarizing study findings and conclusions might reduce the likelihood of the report generating confusion among clinical providers. That said, study key questions are well presented and the Figure describing the analytic framework is useful and clear. Greater efforts on summary sections and key points would benefit the presentation. | We have edited the document to address peer reviewer and public comments and correct typographical errors and hope that these edits help with clarity. |

# References


1. Clarke GN, Hornbrook M, Lynch F, et al. Group cognitive-behavioral treatment for depressed adolescent offspring of depressed parents in a health maintenance organization. J Am Acad Child Adolesc Psychiatry. 2002 Mar;41(3):305-13. doi: 10.1097/00004583-200203000-00010. PMID: 11886025.
2. Storch EA, Wilhelm S, Sprich S, et al. Efficacy of Augmentation of Cognitive Behavior Therapy With Weight-Adjusted d-Cycloserine vs Placebo in Pediatric Obsessive-Compulsive Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2016 Aug 1;73(8):779-88. doi: 10.1001/jamapsychiatry.2016.1128. PMID: 27367832.
3. Clarke G, Debar L, Lynch F, et al. A randomized effectiveness trial of brief cognitive-behavioral therapy for depressed adolescents receiving antidepressant medication. J Am Acad Child Adolesc Psychiatry. 2005 Sep;44(9):888-98. PMID: 16113617.
4. Shirk SR, Deprince AP, Crisostomo PS, et al. Cognitive behavioral therapy for depressed adolescents exposed to interpersonal trauma: an initial effectiveness trial. Psychotherapy (Chic). 2014 Mar;51(1):167-79. doi: 10.1037/a0034845. PMID: 24377410.
5. Israel P, Diamond GS. Feasibility of Attachment Based Family Therapy for depressed clinic-referred Norwegian adolescents. Clin Child Psychol Psychiatry. 2013;18(3):334-50. doi: 10.1177/1359104512455811. PMID: 108668356. Language: English. Entry Date: 20160426. Revision Date: 20160426. Publication Type: Article.
6. Hirschtritt ME, Pagano ME, Christian KM, et al. Moderators of fluoxetine treatment response for children and adolescents with comorbid depression and substance use disorders. J Subst Abuse Treat. 2012 Jun;42(4):366-72. doi: 10.1016/j.jsat.2011.09.010. PMID: 22116008.
7. Kennard BD, Emslie GJ, Mayes TL, et al. Sequential treatment with fluoxetine and relapse--prevention CBT to improve outcomes in pediatric depression. Am J Psychiatry. 2014 Oct;171(10):1083-90. doi: 10.1176/appi.ajp.2014.13111460. PMID: 24935082.



*Source: https://effectivehealthcare.ahrq.gov/products/childhood-depression/research*
*Published Online: April 10, 2020*

8. Weihs KL, Murphy W, Abbas R, et al. Desvenlafaxine versus placebo in a fluoxetine-referenced study of children and adolescents with major depressive disorder. J Child Adolesc Psychopharmacol. 2018 Feb;28(1):36-46. doi: 10.1089/cap.2017.0100. PMID: 29189044.
9. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. JAMA. 2004 Aug 18;292(7):807-20. doi: 10.1001/jama.292.7.807. PMID: 15315995.
10. Wagner KD, Ambrosini P, Rynn M, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. JAMA. 2003 Aug 27;290(8):1033-41. doi: 10.1001/jama.290.8.1033. PMID: 12941675.
11. Emslie GJ, Findling RL, Yeung PP, et al. Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. J Am Acad Child Adolesc Psychiatry. 2007 Apr;46(4):479-88. doi: 10.1097/chi.0b013e31802f5f03. PMID: 17420682.
12. Avci A, Diler RS, Kibar M, et al. Comparison of moclobemide and placebo in young adolescents with major depressive disorder. Annals of medical sciences. 1999;8(1):31-40. PMID: CN-00214555.
13. Findling RL, Robb AS, DelBello M, et al. Pharmacokinetics and safety of vortioxetine in pediatric patients. J Child Adolesc Psychopharmacol. 2017 Aug;27(6):526-34. doi: 10.1089/cap.2016.0155. PMID: 28333546.
14. Harrington R, Whittaker J, Shoebridge P. Psychological treatment of depression in children and adolescents. A review of treatment research. Br J Psychiatry. 1998;173(OCT.):291-8. PMID: CN-01755513.
15. Niederhofer H, von Klitzing K. Bright light treatment as add-on therapy for depression in 28 adolescents: a randomized trial. Primary Care Companion for CNS Disorders. 2011;13(6):9p-p. PMID: 108174096. Language: English. Entry Date: 20120518. Revision Date: 20150712. Publication Type: Journal Article.
16. Stark KD, Reynolds WM, Kaslow NJ. A comparison of the relative efficacy of self-control therapy and a behavioral problem-solving therapy for depression in children. J Abnorm Child Psychol. 1987 Mar;15(1):91-113. PMID: 3571741.
17. Gartlehner G, Wagner G, Matyas N, et al. Pharmacological and non-pharmacological treatments for major depressive disorder: review of systematic reviews. BMJ Open. 2017 Jun 14;7(6):e014912. doi: 10.1136/bmjopen-2016-014912. PMID: 28615268.