Comparative Effectiveness Review Disposition of Comments Report

Title: *Pharmacotherapy for Adults With Alcohol Use Disorder in Outpatient Settings: Systematic Review*

Draft report available for public comment from November 7, 2022, to December 7, 2022.

Citation: McPheeters M, O'Connor EA, Riley S, Kennedy SM, Voisin C, Kuznacic K, Coffey CP, Edlund M, Bobashev G, Jonas DE. Pharmacotherapy for Adults With Alcohol Use Disorder in Outpatient Settings: Systematic Review. Comparative Effectiveness Review No. 262. (Prepared by the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center under Contract No. 75Q80120D00007.) AHRQ Publication No. 23(24)-EHC011. Rockville, MD: Agency for Healthcare Research and Quality; November 2023. DOI: https://doi.org/10.23970/AHRQEPCCER262. Posted final reports are located on the Effective Health Care Program search page.

Comments to Draft Report

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This document includes the responses by the authors of the report to comments that were submitted for this draft report. 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.

Peer Reviewer, Technical Expert, and Public Comments and Author Response

Commentator & Affiliation	Section	Comment	Response
Technical Expert #1	General	Quality of report: Superior No Comments.	Thank you.
Peer Reviewer #1	General	Overall, this is an excellent review of the literature on this important topic that will help clinicians better utilize medications for alcohol use disorder. The target population and audience were well defined. The inclusion and exclusion criteria were appropriate.	Thank you.
Peer Reviewer #1	Introduction	Appropriate level of detail.	Thank you.
Peer Reviewer #1	Methods	The methods seem appropriate, including the inclusion/exclusion criteria and statistical methods.	Thank you.
Peer Reviewer #1	Results	The only criticism I have of the results is to be sure to be consistent with either referring to the evidence of disulfiram as "insufficient evidence" or "lower quality of evidence." The former implies that this could be an effective treatment but we just need more research. The latter seems to imply that there is some evidence (albeit low quality) that disulfiram is ineffective. The first phrasing seems more accurate to me	We agree that insufficient evidence is more accurate and have confirmed that is the language used in the section on disulfiram.
Peer Reviewer #1	Discussion and Conclusions	See comment above about contextualizing disulfiram findings. The discussion does a terrific job of discussing the ways in which many clinicians find this medication useful, despite the lack of evidence (and the complications of doing placebo controlled trials with this medication, given that much of it's likely mechanism of action is the participants belief that they will experience aversive consequences if they drink alcohol)	Thank you.
Technical Expert #2	General	Report is very clinically meaningful, target population is explicitly defined. Audience can be inferred but is not directly stated. Key questions are highly appropriate and explicitly stated. Please define SOE when it first appears in the abstract.	Thank you.

Source: https://effectivehealthcare.ahrq.gov/products/alcohol-use-disorders/research
Published Online: November 7, 2023

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Technical Expert #2	Introduction	Minor Points: Please define NNT when it first appears in the Main Points. Page 18, lines 24-31: Points 3 and 4 need to be rephrased for consistency with the rest of the sentence, e.g., Treatment outcomes can be affected by many factors, including the following (1) AUDs severity; (2) co-occurring conditions and challenges, including physical and mental health disorders that make treatment more challenging; (3) type of treatment, which can include multiple psychosocial interventions and several pharmacotherapies; (4) pathway to treatment, ranging from voluntary care seeking to legally mandated treatment; and (5) patient motivation Page 19, line 40: Please, specify if the 2011 UK clinical guideline was also specifically focused on pharmacotherapy or focused on AUD treatment more broadly.	Added number needed to treat in main points. Thank you, revised points 3 and 4. The 2011 UK Guideline focused on treatment more broadly and we have added language to clarify this.
Technical Expert #2	Methods	Methods are fully appropriate. Inclusion/exclusion criteria are well-defined and justifiable. The search strategy is explicitly stated and logical. Definitions of diagnosis and outcome measures are appropriate. Statistical methods, including descriptions of when statistical (quantitative) vs. qualitative analysis methods were utilized, are appropriate	Thank you.
Technical Expert #2	Results	Overall, the Results are well-presented. Study characteristics are clearly defined. Key messages are clear and applicable. Decisions about tables to include in the report itself vs. information to present in appendices is well balanced with key information presented in the main report. Minor points: Page 29, lines 46-49: The Summary of Findings for disulfiram does not comment on the drinking days outcome. Page 32, line 45: Missing “placebo” from the end of the first sentence. Page 47: A brief description of the arms and results of the COMBINE trial (such as that presented on page 55 under the Health Outcomes section) should be provided in the Head-to-Head Trial: Acamprosate Versus Disulfiram section to orient the reader to the trial before stating the results under Heavy Drinking Days which are hard to follow without being oriented to the study. Page 55, line 14: Please define RoB	Revised summary of findings. Thank you, we have added the word “placebo.” We have added a description of COMBINE to Section 3.1.3, acamprosate versus naltrexone. We have reviewed the report to ensure that acronyms are defined.
Technical Expert #2	Discussion and Conclusions	Major findings are clearly stated. Limitations are described. Implications for future research in the area are clear from the results and discussion sections.	Thank you.
Technical Expert #3	General	As a practicing clinician, I find this report to be very meaningful. I appreciate the specific question into primary care settings.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Technical Expert #3	Introduction	I would consider a more explicit call-out regarding the role of medications to reduce alcohol use (rather than just promote abstinence). I appreciate that this is mentioned, but feel it could be more strongly emphasized.	Thank you for your comment. We have edited to ensure a balance of focus on the potential role of medications in reduction of alcohol use and promotion of abstinence.
Technical Expert #3	Methods	Yes this is clear	Thank you.
Technical Expert #3	Results	Yes this is clear, I agree with what was included	Thank you.
Technical Expert #3	Discussion and Conclusions	Yes this is clear, I agree with the limitations and major implications	Thank you.
Technical Expert #3	Results	Pg 11 line 8 Alcohol use disorder is not usually hyphenated and not usually pluralized	Thank you for your comment. We have removed the hyphenation throughout.
Technical Expert #3	Results	Pg 11 line 12 Please clarify if NNT is for abstinence or reduction in days of alcohol use	Thank you, we have added language to clarify.
Technical Expert #3	Results	Pg 11 line 21 Please clarify NNT (similar to above)	Thank we have added language to clarify.
Technical Expert #3	Results	Pg 12 line 35 When feasible, please substitute the term “drinking” to instead be “alcohol use” as it is a clearer and more medically accurate term	We have made this revision where feasible. Notably, we did not revise the language used in our predefined key outcomes: return to any drinking, return to heavy drinking, drinking days, heavy drinking days, and drinks per drinking day.
Technical Expert #3	Results	Pg 13 line 30 Please consider using person-first language “person who smokes” rather than “smoker”	Thank you, we have revised “smokers” to “persons who smoke.”

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Technical Expert #3	Results	Pg 17 line 44 Is this list exhaustive? Consider listing all the alcohol-related malignancies. Consider changing “liver cirrhosis” to “liver disease including cirrhosis” and “fetal alcohol syndrome” to “fetal alcohol spectrum disorders”. “Sleep problems” and “insomnia” do not need to both be listed. “Osteopenia” could instead be osteoporosis” which is a more serious health risk and includes increased fracture risk.	We have clarified to note that this list is not necessarily exhaustive and, therefore, does not list all malignancies, though we have revised to note it is associated with several cancers. We have revised the language in the list as suggested.
Technical Expert #3	Results	Pg 18 line 5 Please avoid the term “alcoholism” Can instead use the term “addiction treatment center”	Thank you, we have revised this language.
Technical Expert #3	Results	Pg 18 line 6 Consider changing this sentence from “…abstinence to reducing alcohol use and/or harms related to alcohol use”	Thank you, we have revised this language.
Technical Expert #3	Results	Pg 18 line 9 “may be an appropriate goal” - please consider removing that language. I would advocate for stronger language re: reduction in alcohol use as an important goal/outcome, as there is evidence that some alcohol-associated adverse health outcomes are dose-related (for example in CV related outcomes), and certain outcomes such as accidents are likely positively impacted by reduction in alcohol use.	Thank you, we have revised this sentence as you suggest.
Technical Expert #3	Results	Pg 18 line 11 “Nonproblematic drinking” is not a term I’m familiar with and may need to be defined or a different term chosen	We have revised this sentence and removed this term.
Technical Expert #3	Results	Pg 18 line 24 (whole paragraph) - Please consider reworking this list; for example could include stigma either personal or from the medical profession, and lack of accessible treatment in traditional healthcare settings. Also recommend dropping “patient motivation” because it is reminiscent of the bias of AUD being related to “willpower” - patient motivation is likely always a factor in any chronic disease management, yet it is unlikely to be called out specifically as a treatment challenge for other medical conditions such as hyperlipidemia and diabetes.	We appreciate this comment and have revised that section to include stigma and lack of access and have revised “patient motivation” to “patient desires and preferences.”
Technical Expert #3	Results	Pg 22 figure 1 In general, the addiction field now prefers the term “return to use” instead of the term “relapse”	Thank you, we have revised the analytic framework to say return to use and removed any other use of the term “relapse.”

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	The report is clinically meaningful and the introduction clearly explains the clinical significance of this topic and how this is relevant to clinical care outside of specialty settings. The key questions are appropriate and the elimination of the one KQ from the 2014 clearly explained and justified.	Thank you.
Peer Reviewer #2	Executive Summary	Minor grammatical/stylistic comments: "Alcohol-use disorder" should be "alcohol use disorder" (first noted on pg v and then throughout) Need to have SOE spelled out in abstract (pg v) In the executive summary (ES-4), a period is missing in the 3rd to last sentence	We have revised "alcohol-use disorders" to "alcohol use disorder" throughout. Revised. Thank you! Revised.
Peer Reviewer #2	Introduction	The statistic that 4.3% receive any AUD treatment is the past year is misleading. This is receiving any AUD treatment from a "specialty setting." Also, the citation that is used indicates this number is actually 7.2%. Please update citation or percentage that is cited (pg 1)	Thank you, we have updated this to reflect data from 2021 in the abstract, ES and Introduction.
Peer Reviewer #2	Introduction	Not sure it is helpful to include the definitions of alcohol abuse and dependence (from DSM IV) in Table 1 since these are no longer used (pg 1-2)	The older definitions are included because they were used in older studies that are included in the report.
Peer Reviewer #2	Introduction	3rd paragraph in 1.1 (pg 2) seems out of place – could be better placed in context of 1st paragraph which contains other AUD statistics	We agree and have moved this up.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Methods	Search strategies stated logically and explicitly - Inclusion/exclusion criteria makes sense (although may have considered including adolescents since UAU can be a problem in this population as well. For example, the cited NICE recommendations include evidence for adolescents ages 10-17) - For KQ3 on adverse effects, I'm assuming the trials of the off-label/investigational medications included are exclusively trials where AUD outcomes are examined (and not other conditions' outcomes) but this is not explicitly stated. Would be helpful to state this explicitly in the methods or in the results.	We agree that AUD among adolescents is a problem, but this population was out of scope for the current review. To be included, the studies must have been conducted in adults with AUD, but we would have included a study that only reported adverse effects and no other AUD-related outcomes if all other criteria were met. It is correct that studies of medications that were being studied to affect other outcomes outside of AUD would not have been included. We have added a sentence in the methods section to clarify.
Peer Reviewer #2	Results	- Results well organized by KQ and tables are easy to follow and understand - Table 21 includes mortality data form acamprosate health outcome studies but a similar table is not provided for naltrexone. Please consider adding (p 36). - Otherwise, tables and description are adequate and descriptive	Thank you. We have created the requested table for naltrexone.
Peer Reviewer #2	Discussion and Conclusions	- Implications/findings are clearly discussed - Would recommend retitling 4.1.9 as "Areas for future research" instead of "Limitations of Evidence Base" (follows on limitations of the review so seems to suggest that it is part of 4.1.8) - Appreciate the inclusion of NNT in the conclusions	Thank you and thank you for this suggestion. We have retitled section 4.1.9 to be "Areas for Future Research"
Peer Reviewer #3	Introduction	Page 2, Line2 44-48- Alcohol use not just AUD can contribute to pancreatitis, gastritis, fetal alcohol spectrum disorders, sleep problems and hypertension	Yes, we agree but this report and introduction are focused specifically on AUD.
Peer Reviewer #3	Introduction	Page 4, Table 2 It would be helpful to include units for CrCl milliliters per minute (mL/min)	We have added these units.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Introduction	Page 5 Consider mentioning, the minimal transfer of naltrexone in breast milk. Chan CF, Page-Sharp M, Kristensen JH, O'Neil G, Ilett KF. Transfer of naltrexone and its metabolite 6,beta-naltrexol into human milk. J Hum Lact. 2004 Aug;20(3):322-6. doi: 10.1177/0890334404266881. PMID: 15296587.	The purpose of this section is to review at a high level existing guidelines and recommendations, so we did not provide details from individual studies.
Peer Reviewer #3	Methods	The inclusion and exclusion criteria was justifiable. the review approach is clearly stated.	Thank you.
Peer Reviewer #3	Methods	Page 17 line 45; is there a word missing between receiving and stratify? The result section is very detailed.	Yes, the word "placebo" was missing, and we have revised.
Peer Reviewer #3	Discussion/ Conclusion	The discussion section is the highlight of this review. Helps put the data in perspective aside from the results. Frames details in the clinical context. Very easy to read and understand.	Thank you.
Technical Expert #4	ES	Page v line 11 it would be helpful to include the year data were collected regarding how many patients with AUD received treatment and/or medications.	We have updated this to report data collected in 2021.
Technical Expert #4	ES	Page v line 49 As a clinician I do not find contraindication to acamprosate (severe renal impairment) to be a major challenge. I would probably take out mention of the contraindication as a major decision maker in this section, or if it stays in, specify that the contraindication is severe renal impairment. See my more extensive comments on the potential contraindications of acamprosate and naltrexone in the Discussion section.	Thank you for your comment. We have revised the conclusions of the abstract accordingly.
Technical Expert #4	ES	Page ES-1 lines 10-13 are extremely relevant to clinicians—naltrexone at 50 mg daily has the strongest SOE of all meds reviewed, is easy to use (once daily dosing) and NNT is 11. Consideration should be given to adding this information to the abstract.	Although naltrexone had moderate SOE for benefit, both acamprosate and topiramate did as well, albeit with considerations for harms and contraindications as well as ease of use. We have added a note that naltrexone had the lowest NNT to the abstract to address this comment.
Technical Expert #4	ES	ES-2 line 19—please cite the full report with a reference and let readers know where it is available	We have added the reference to the 2014 report here.

Commentator & Affiliation	Section	Comment	Response
Technical Expert #4	ES	ES-4 lines 19-20—the evidence summary does not include information on the potential contraindications of acamprosate (severe renal impairment), and the concern with topiramate is frequent side effects rather than any specific contraindication. This needs to be reworded. Again, see my comments in the Discussion area on this topic.	We have revised the text in the implications and conclusions of the ES to reflect this more clearly.
Technical Expert #4	General	The report is clinically meaningful. The target population and audience are explicitly defined. Key questions are clear. The section outlining the major changes since the previous report is particularly helpful and useful, and this is actually summarized in two places, which adds emphasis.	Thank you.
Technical Expert #4	Introduction	Page 3 lines 8-9 I find the term "nonproblematic drinking outcomes" awkward and unclear; would use of a term such as "outcomes related to reduced alcohol consumption" be useful here?	We agree and have revised this language.
Technical Expert #4	Methods	Page 6 lines 32-33 states medications with off-label uses were limited to those "currently in use in the United States," then provides a list of medications from the previous review that were not considered in this review. Many of the medications excluded from this review are currently in use in the U.S. Should the statement above be changed to those "currently in frequent use off-label for alcohol use disorder in the U.S."? This appears to be the intent, and it is clearly stated as such in the first paragraph of the Discussion.	We have revised this language to note off-label use but refrained from commenting on frequency.
Technical Expert #4	Results	Page 17 line 46 the end of the sentence is incomplete; it appears a word is missing (placebo?).	Yes, we have revised.
Technical Expert #4	Results	Page 24 line 23 should state percent drinking days, rather than percent drinking	Revised.
Technical Expert #4	Results	Page 30 lines 50-51 please add the number of patients in the study in which only 3 patients completed treatment	We have added this information to the report.
Technical Expert #4	Results	Page 31 lines 38-39 please note the number of patients in the study where only 2 patients in the treatment group completed the study	We have added this information to the report.
Technical Expert #4	Results	Page 40 lines 46-51 this nice summary of the COMBINE study should appear earlier in the Results section, at the first citation of COMBINE results, rather than here. Unfortunately, COMBINE data on health outcomes of interest are missing here. Any such outcomes should be inserted here.	We have added the summary earlier as requested. Data on the health outcomes of interest from COMBINE are reported in the outcome-specific sections of the report.
Technical Expert #4	Results	Page 49 line 35 should indicate here the number of serious adverse events in the varenicline group, as the number of such events among placebo patients was already included later in this sentence.	Thank you, we have added in text that there were three serious adverse events in the varenicline group.

Commentator & Affiliation	Section	Comment	Response
Technical Expert #4	Results	Page 51 Section 3.4.1 Since this is the only primary care study, I would suggest a bit more detail on the quality of the study, study procedures, and risk of bias, especially since a medication with evidence of efficacy in other studies showed no efficacy in this instance.	The only eligible trial was one reviewed in the 2014 report to which this is an update. Given that it adds very little additional information to the overall body of literature, we do not think it is appropriate to provide substantial detail at this time because we would not do so with other studies.
Technical Expert #4	Discussion/ Conclusion	Page 54 Table 29 is a very useful summary and a highlight of the report.	Thank you.
Technical Expert #4	Discussion/ Conclusion	**Contraindications.** Comments about contraindications are unclear throughout the manuscript, beginning with Page v line 29, then ES4 lines 19-20, and Page 60 line 10. I am unable to find a the "Harms" section described on Page 60 line 27 in relation to injectable NTX, though perhaps I overlooked it. The authors did finally include a nice, concise summary of contraindication information on Page 60, lines 25-29. This should be moved up much earlier in the manuscript, perhaps by creation of a paragraph or section entitled "Medication Contraindications and Concerns." Contraindications for disulfiram should also be included in this section, as well as the potential for inappropriate or nonmedical use of gabapentin.	We have ensured that contraindications are mentioned early in the report. Contraindications are not systematically reviewed per our Key Question 3 and are provided for context The section on harms is titled "Adverse Events". . We have ensured that the reference is correct.
Technical Expert #4	Discussion/ Conclusion	Conclusions about medication choice and use. (Page 60, lines 5-19). Overall, I think the authors have done an excellent job in summarizing the 3 medications with moderate SOE. I disagree inclusion of "potential contraindications" as a negative regarding acamprosate and topiramate. They never list contraindications to topiramate. I think a better approach would be a statement such as, "Clinicians should be careful to respect contraindications of each individual medication (for acamprosate, severe renal impairment, and for naltrexone, acute hepatitis, liver failure, current use of opioids or anticipated need for opioids), as well as the less desirable side effect profile of topiramate."	Thank you. This statement was unclear, and we have revised it to reflect these comments.

Commentator & Affiliation	Section	Comment	Response
Technical Expert #4	Discussion/ Conclusion	**Mention of all medications with low SOE. (Page 60, lines 11-12)** Specific mention is made in the discussion/summary of low SOE for injectable naltrexone, but other medications with low SOE are not mentioned here. Since the report is designed to summarize the evidence reviewed, I suggest that mention should be made here of the other two medications with low SOE, as follows: "Baclofen has low SOE for reduction in drinking days, heavy drinking days, drinks per drinking day and return to heavy drinking. Gabapentin has low SOE for return to heavy drinking." I like the subsequent comments about making medication decisions related to desired outcomes and the next paragraph's comments about collaborative decision making with patients	Thank you, we have added this language.
Technical Expert #4	Discussion/ Conclusion	**Future research. (Page 62, line 9)** I suggest stronger, more emphatic wording that more attention needs to be given to research regarding women, people of color/racial and ethnic minorities, and older adults and to research in primary care	We have added statements to this effect.
Public Comment #1 (NCHR)	Introduction	We agree with the AHRQ analysis of the data regarding treatments, and expect this will provide very useful information to providers and patients. We have questions regarding the presentation of information on the draft Research Protocol. In Table 1 of the "Backgrounds and Objectives" section, we do not understand why rows 1 & 2 are presented separately, despite having the same definition. The same is true for rows 5 & 6, which have the same definition and the numbered content continues as if it were one topic.	Thank you. Regarding Table 1, row 1 details the DSM-5 definition of AUD, and row 2 defines risky or hazardous use, which is not the same as a DSM-5-defined AUD. Row 5 defines alcohol **abuse** from the DSM-IV, and row 6 defines alcohol **dependence** from the DSM-IV; these are included for historical context because they are terms used in older papers included in the review and have different definitions, specifically those with alcohol abuse did not meet the criteria for alcohol dependence.

Commentator & Affiliation	Section	Comment	Response
Public Comment #1 (NCHR)	Results	For the "Results" section of the Draft Comparative Effectiveness Review, we encourage AHRQ to create a summary table for each subsection under "Key Question 1: Efficacy and Comparative Effectiveness for Improving Consumption Outcomes". There is a plethora of vital information in this review that prescribers, therapists, and patients should know about medications to treat AUD. There is so much information that it may be overwhelming for some readers to find the information they require to make informed choices. Providing summary tables will enable readers to more easily find the appropriate information and know where to go for additional information.	The summary tables in KQ 1 are only included for sections with meta-analyses and present the findings of the meta-analysis. We agree that there is a lot of information; we have included Tables 30 and 31 in the discussion, which summarize all the efficacy outcomes. We hope this both addresses the comment and provides readers with a much-needed quick summary.
Public Comment #1 (NCHR)	General	We agree with AHRQ that there is a lack of data "for measures of quality of life and function, accidents, and mortality" as well as adverse events, and particular subpopulations. We encourage AHRQ to emphasize the lack of information throughout the presentation of data, so that it is clear that even the medications that seem effective may have unknown risks or may not be suitable for all types of AUD.	We have attempted to ensure that this information carries throughout the report.
Public Comment #2 (IQVIA)	Methods	I know EPC methods consider only evidence from RCTs at the moment; that the EPC program recently issued a challenge to explore how to integrate real world evidence into systematic literature reviews in the future; and that it will take a while before the EPC program can update its methods to factor in real world evidence. Do you want to mention this in the methods or discussion section?	Although this is a potential shift in the field, we do not feel that it belongs in this report, but is certainly an important potential new approach for the future.
Public Comment #2 (IQVIA)	Methods	I also wonder if you consult with the FDA when you do EPC systematic literature reviews with a focus on prescription medication use? If not, do you want to consider it in the future?	We did not specifically consult with FDA, but FDA is welcome to submit comments as are all federal agencies.
Public Comment #3 (APA)	ES	ES-1 last pg Change "update" to "updated"	Revised.
Public Comment #3 (APA)	ES	ES-3 1st pg For "taste perversion", is this how it's typically expressed in the papers rather than dysgeusia or taste abnormalities?	The papers used a variety of terms, including "taste perversion," "dysgeusia," and "changes in taste." We have revised to "taste abnormalities" as an umbrella term.

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Public Comment #3 (APA)	ES	ES-4 2nd pg "while" should be "whereas"	Revised.
Public Comment #3 (APA)	ES	ES-4 last pg missing period in 3rd sentence	Revised.
Public Comment #3 (APA)	Introduction	Table 1: I just noticed that you use the hyphen throughout the document; DSM does not, however.	We have revised alcohol-use to alcohol use.
Public Comment #3 (APA)	Introduction	p. 2 pg after the table If there is evidence suggesting further increases in AUD during the pandemic, that may be worth mentioning.	We have added a sentence to mention this.
Public Comment #3 (APA)	Introduction	p. 3 Delete extra period.	Revised.
Public Comment #3 (APA)	Introduction	p. 3 1st pg "number of abstinent days" as an outcome still seems consistent with a focus on abstinence. Perhaps it would be better written as "number of heavy drinking episodes or number of drinking or heavy drinking days." If that is the language in the studies, then this makes sense to me. Number of episodes or days doesn't seem equivalent to me as days with no drinking. The next sentence though mentions non-abstinent outcomes.	We have revised this language to clarify.
Public Comment #3 (APA)	Introduction	Pg. 3 Delete s. Don't think it should be plural. Treatment outcomes can be affected by many factors, including the following (1) AUD**s**	Agreed and revised.
Public Comment #3 (APA)	Introduction	p. 3 2nd pg points 3 and 4 are not phrased in a fashion that is parallel to the other items. They seem like they would fit better as independent sentences rather than being included in this list. However, other factors that often influence outcomes include psychosocial factors (most recently subsumed under social determinants of health), insurance status, treatment availability, and prior treatment experiences	Yes, we have revised points 3 and 4.
Public Comment #3 (APA)	Introduction	p. 3 last pg in the info on disulfiram would add "for many patients" to the end of the sentence. For highly motivated people such as health professionals, it can still be very useful.	Revised.
Public Comment #3 (APA)	Introduction	p. 3 last pg Suggest changing "a successful withdrawal" to "withdrawing". This may be a matter of personal preferences, but in the APA guidelines, we try not to frame treatment in terms or "success" or "failure".	Revised.
Public Comment #3 (APA)	Introduction	p. 4 table disulfiram Suggest changing "at the acetaldehyde stage" to "by aldehyde dehydrogenase".	Revised.

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Public Comment #3 (APA)	Introduction	p. 4 Table naltrexone entries Suggest changing ", showing" to "and has". As written the phrase beginning with showing seems to apply to opioid receptor sites and not to naltrexone. It would also be helpful to say something more specific about how action through the HPA axis modifies alcohol consumption. Though I know that it can affect cortisol and other responses especially in animal models, I'm not familiar with specific mechanisms related to suppression of alcohol use. If this is well-established, it would be helpful to know the mode of action.	Replaced “showing” with “and has.” After discussing with subject matter experts, we have elected to leave this as is because it reflects what is understood about naltrexone and its mechanism.
Public Comment #3 (APA)	Introduction	p. 4 Table May wish to specify that it is a long-acting intramuscular injectable though this is implied by the monthly administration frequency.	Revised.
Public Comment #3 (APA)	Introduction	p. 4 table 3 delete parenthesis after agonist	Revised.
Public Comment #3 (APA)	Introduction	Pg. 4 change update review to updated review	Revised
Public Comment #3 (APA)	Results	p. 9 discussion of RoB, were all studies in the current report assess with RoB 2.0 or just the new studies identified in the update? If there was a mix of RoB criteria used, that seems problematic. If all (new and old) were done with RoB 2.0, it may be worth noting that specifically.	Because this was an update, we did not update the RoB assessments from the previous report but accepted them as previously assessed. RoB 2.0 was only done for the newly included studies.

Commentator & Affiliation	Section	Comment	Response
Public Comment #3 (APA)	Results	p.11 key point on disulfiram is that blinded RCTs may not be optimal for detecting an effect of disulfiram. Since the effect is apparently due to a wish to avoid an unpleasant experience and not a direct effect of the drug, per se. Since the research subject does not know whether they've received placebo or active drug, both treatment arms should be associated with a comparable effect. Although the Skinner meta-analysis (https://pubmed.ncbi.nlm.nih.gov/24520330/) also included consideration of open label trials, which showed benefit of disulfiram, these would not need to be mentioned since they would be inconsistent with the rest of the review inclusion criteria. But I think it is crucial to include some methodological caveat about RCTs in studying disulfiram. Otherwise, I'm concerned that the conclusions from the RCT data will be misleading.	We have slightly revised our discussion related to this, but we have not revised the key points. We do not have any new eligible studies to change it. Our evaluation (published in a reply to a *JAMA* letter to the editor) about evaluating disulfiram and the open-label studies found that none of those studies disentangled whether benefits were attributable to disulfiram (beyond the benefits of additional counseling or therapeutic relationships). Those small open-label trials might, at best, allow a conclusion that programs offered might help patients interested in taking the medication and who get all those other parts of the program, but it is not clear that any of the benefit is actually attributable to disulfiram. Differences between groups in motivation and goals may also underlie the findings.
Public Comment #3 (APA)	Results	Pg 13. delete s Although the statistical heterogeneity was fairly high, findings were largely consistent in finding**s** an effect in the direction of benefit, and the pooled result was reasonably precise.	Revised.

Commentator & Affiliation	Section	Comment	Response
Public Comment #3 (APA)	Results	Pg 13, change on to by? No differences in effect were observed when stratifying **on** risk-of-bias or treatment duration, but studies conducted in the United States tended to have smaller effect sizes. None of the three studies conducted in the United States showed a benefit for acamprosate	Revised.
Public Comment #3 (APA)	Results	p. 14 Disulfiram see comment above on RCTs and disulfiram	We have slightly revised our discussion related to this, but we have not revised the key points. We do not have any new eligible studies to change it. Our evaluation (published in a reply to a *JAMA* letter to the editor) about evaluating disulfiram and the open-label studies found that none of those studies disentangled whether benefits were attributable to disulfiram (beyond the benefits of additional counseling or therapeutic relationships). Those small open-label trials might, at best, allow a conclusion that programs offered might help patients interested in taking the medication and who get all those other parts of the program, but it is not clear that any of the benefit is actually attributable to disulfiram. Differences between groups in motivation and goals may also underlie the findings.
Public Comment #3 (APA)	Results	p. 14 Disulfiram trial characteristics Change "update search" to "updated search".	Revised.

Commentator & Affiliation	Section	Comment	Response
Public Comment #3 (APA)	Results	Pg 15 Characteristics of trials - delete period	Revised.
Public Comment #3 (APA)	Results	Pg 15, Fix comma in superscript second paragraph	Revised.
Public Comment #3 (APA)	Results	p. 17 table abbreviations should I2 be included? Also, double check that the 2 is superscripted in all of the tables/columns.	Updated I^2 on repeated header.
Public Comment #3 (APA)	Results	Table 7 footer. Font should match other footers or other footers should match this. Remove indent.	Revised this footnote to match the others.
Public Comment #3 (APA)	Results	Table 8 bottom row last cell change to 12.0	Revised.
Public Comment #3 (APA)	Results	p. 17 return to any drinking Something is missing at the end of the 1st sentence. Assume it's "than those receiving placebo"	Yes, we have added "placebo" to the end of the sentence.
Public Comment #3 (APA)	Results	p. 18 Drinking days Here and elsewhere consider changing "subjects" to "participants". This is now done in a number of publications to emphasize the collaborative nature of research.	Revised throughout.
Public Comment #3 (APA)	Results	p. 18 Drinking days 3rd sentence Can you change "our" here and elsewhere to "the"? If we use this information to update our guideline, it wouldn't actually be our meta-analysis.	Revised throughout.
Public Comment #3 (APA)	Results	p. 19 Summary of findings 2nd pg The sentence on evidence being low or insufficient and the reference to Appendix D, don't seem relevant to sensitivity analysis. Also, the sentence on the percent drinking days outcome may be better placed in the first paragraph. Although it does relate to removing a high risk of bias study, its current positioning makes it harder to read the section and get a straightforward "take home" message from the text. The preceding paragraph say there was no difference between baclofen and placebo except for return to any drinking, but this sentence suggests that there is probably an effect on percent drinking days as well once the study with significant concerns was removed. In the summary table if the results with all studies are what is shown, it may be worth adding an asterisk and note in the table footer that the results differ with removal of the high RoB study.	We have added a footnote to table 9 and moved the location of the sentence about Appendix D and SOE grades.
Public Comment #3 (APA)	Results	Table 9, third row last column change 46 to 46.0	Revised.
Public Comment #3 (APA)	Results	p. 20 Heavy Drinking Days Can the sentence on the 2 RCTs that weren't included be split into two sentences. It would be helpful to know the sample sizes of each and which trial had insufficient data vs. both groups having zero heavy drinking days. These seem like two different scenarios.	Thank you, we have revised this to two sentences and added the sample sizes for both trials.
Public Comment #3 (APA)	Results	p. 21 top of the page Suggest "change in drinks" should be "change in the number of drinks".	Revised.

Commentator & Affiliation	Section	Comment	Response
Public Comment #3 (APA)	Results	p. 22 Drinking days Consider rephrasing as "Evidence for a reduction in drinking days was insufficient, with no statistically significant difference in drinking days (p=0.2) reported in one trial conducted in Thailand that was rated as high risk of bias."	Revised.
Public Comment #3 (APA)	Results	p. 22 Heavy drinking days "while" should be "whereas" This is probably true in many places throughout the document.	Revised.
Public Comment #3 (APA)	Results	p. 24 Summary of findings "drinks per day" seems to be included twice.	Revised.
Public Comment #3 (APA)	Results	p. 24 Summary of findings The last sentence seems overly detailed for inclusion in a summary.	We have revised this sentence. A new study of ondansetron was identified during the bridge search, and this section now includes a more general summary.
Public Comment #3 (APA)	Results	p, 24 Drinks per Drinking Day Double check second sentence. Is this the first time standard deviation is mentioned? Also, the SD for both groups is 4.1. This is certainly possible but just double check.	We have confirmed this is the first instance of standard deviation in the text and confirmed both SDs are 4.1.
Public Comment #3 (APA)	Results	In some places it's mentioned why a study is rated as high risk of bias, which domains, but in other places it's not. Should it be consistent throughout or is there some way to know which items were being highlighted?	We highlighted which domains when we thought it was particularly meaningful. All RoB ratings are available in the appendix.
Public Comment #3 (APA)	Results	p. 25 Drinking days Need to state number of drinking days over what time period. It obviously can't be per week or per month, but unclear what it is. Similarly for the number of heavy drinking days.	We have added that this was over a 90-day period.
Public Comment #3 (APA)	Results	p. 27 Next to the last sentence Consider putting "in general populations" at the end of the sentence. Also, does it matter that they were by the same author?	We have rephrased as suggested and removed “by the same author.”
Public Comment #3 (APA)	Results	p. 28 Heavy drinking days Suggest changing the second sentence to the following "However, only five studies, which all reported the percent of heavy drinking days in the study observation period, 141, 145, 148, 149, 151 could be combined in a meta-analysis."	Revised.
Public Comment #3 (APA)	Results	Table 16, first row last column - This looks bolded.	Yes, revised.

Commentator & Affiliation	Section	Comment	Response
Public Comment #3 (APA)	Results	p. 29 Drinks per drinking day last sentence Verify that the standard error is the same in both groups -- possible but not necessarily the case in a study of 170 individuals.	These standard errors were rounded and correct as reported. The paper reported them as 5.21 (se=0.58) and 6.1 (se=0.61).
Public Comment #3 (APA)	Results	Delete one period.	Revised.
Public Comment #3 (APA)	Results	p. 29 Characteristics 3rd pg "mannually" is misspelled but it may be better to say manual-guided rather than manually-guided.	Revised to manual-guided.
Public Comment #3 (APA)	Results	p. 30 1st sentence It's not clear what is meant by "in a model" here and in subsequent sections.	Revised here and elsewhere to “in the meta-analysis.”
Public Comment #3 (APA)	Results	p. 30 Drinking days Unclear what "proportion" is referring to here. If it's percent of drinking days, it would be better to say that.	We have changed this to percentage as suggested.
Public Comment #3 (APA)	Results	p. 31 Heavy drinking days Proportion is clearer here but would be consistent in using the word percentage rather than proportion as not everyone will appreciate that a percentage is a proportion. Would also be specific that this is "a percentage of heavy drinking days" even though it seems redundant so that there's no confusion with the percentage of drinking days measures.	We have modified as suggested throughout the report.
Public Comment #3 (APA)	Results	p. 32 table N HDD N seems to mean something other than sample size here. Double check.	This was a typo and should have said % HDD.
Public Comment #3 (APA)	Results	p. 33 Heavy drinking days The phrasing naltrexone by CBI interaction sounds like statistical jargon. Can it be rewritten as "a significant interaction between naltrexone and CBI"? Similarly for the next section.	Revised.
Public Comment #3 (APA)	Results	p. 34 Topiramate vs. Naltrexone In the last sentence consider rephrasing as "Across alcohol-use outcomes, SOE was insufficient to determine whether effects are comparable between topiramate and naltrexone."	Revised.
Public Comment #3 (APA)	Results	p. 34 Key points Change "quality of life and function" to "quality of life, function," both here and below. Also be consistent in whether quality of life is separated by hyphens.	Rephrased and replaced all instances of “quality-of-life” with “quality of life” and removed the extra “and” in the key points for Section 3.2.
Public Comment #3 (APA)	Results	p. 35 3rd pg suggest changing "3 g" to "3000 mg" for consistency in units with the other discussion of acamprosate. Also the acamprosate pills are in mg.	Revised.
Public Comment #3 (APA)	Results	p. 35 3rd pg delete extra period after benzodiazepines.	Revised.
Public Comment #3 (APA)	Results	p. 36 table foot note Change to mg per LF comment above?	Revised.

Commentator & Affiliation	Section	Comment	Response
Public Comment #3 (APA)	Results	Pg 36, beginning of naltrexone characteristics of trials This was just stated previously.	Yes, but we were stating new studies at each section for consistency.
Public Comment #3 (APA)	Results	p. 37 Quality of Life Miller reference didn't format correctly. Once fixed, double check sentence wording. It seems like it should read "an alcohol-specific..." after the cite.	Thank you for noting this. We have revised the reference and phrasing.
Public Comment #3 (APA)	Results	First row page 38 Needs a space after reference	Revised.
Public Comment #3 (APA)	Results	p. 39 Topiramate characteristics Change "the remaining reported" to "the remaining studies reported" or "the remaining trials reported".	Revised.
Public Comment #3 (APA)	Results	Pg. 39 first sentence of accident or injury. This sentence doesn't make sense as it is or where it is. The first half says injury was included but it doesn't say in which group or how much. That doesn't demonstrate that topiramate may help prevent injuries. The info in the next statements does though. So maybe reorder.	We have revised the accident or injury section for topiramate.
Public Comment #3 (APA)	Results	p. 39 Quality of Life 3rd sentence put semicolon rather than comma after (N=106)	Revised.
Public Comment #3 (APA)	Results	Pg 40, first sentence in QoL section: “just say was”	Revised.
Public Comment #3 (APA)	Results	Pg 41, analyses? analysis of variances?	We have revised to analyses of variance.
Public Comment #3 (APA)	Results	Pg 41, See LF comments earlier about rewriting this type of phrasing.	We revised the previous section; however, we think this instance is clear.
Public Comment #3 (APA)	Results	p. 41 mortality Change "one person committed suicide" to "one person died by suicide". The phrasing "committed suicide" is no longer recommended for use.	Thank you, we have updated this language.
Public Comment #3 (APA)	Results	Pg 42 accidents or injuries OR accident or injury	Revised to “accidents or injuries.”
Public Comment #3 (APA)	Results	Pg. 42 In one study rated high risk of bias, quality of life was measured with...	Revised.
Public Comment #3 (APA)	Results	p. 43 Quality of life Is Psychiatric part of the actual scale title? I've usually seen it written WHODAS or WHO DAS without the slash.	Revised to remove psychiatric and abbreviated as WHODAS.
Public Comment #3 (APA)	Results	p. 43 Quality of life 3rd sentence Does it matter that it's by the same author? (also next paragraph)	We have deleted this phrase.
Public Comment #3 (APA)	Results	p. 43 Quality of life 1st pg Suggest changing "dosed topiramate" to "adjusted topiramate doses"	Revised.
Public Comment #3 (APA)	Results	p. 43 key points see prior comment about the phrase "taste perversion"	We have updated to taste abnormalities.

Commentator & Affiliation	Section	Comment	Response
Public Comment #3 (APA)	Results	p. 43 key points It's interesting that concentration and attention were the only cognitive effects noted, perhaps because of the design of the trials. More significant cognitive impairment is often a reason that patients report discontinuing topiramate, especially at higher doses.	We agree that this is interesting and is a reflection of the design and conduct of the trials.
Public Comment #3 (APA)	Results	p. 44 Summary May wish to specify that these are Study withdrawals. It's implied by the rest of the sentence but in an alcohol and medication treatment context, there's always a possibility of people thinking it refers to alcohol withdrawal or medication withdrawal side effects.	Agreed and revised.
Public Comment #3 (APA)	Results	P 45 Earlier tables did not have heterogeneity in the header.	Removed “heterogeneity” from the header for Table 22.
Public Comment #3 (APA)	Results	Table 22 0 throughout should probably be 0.0	Revised.
Public Comment #3 (APA)	Results	Pg 46, I just caught this here and see it's elsewhere. Is it really 1mg/day? That just seems non existent when the comparison is 250mg	Yes, it is correct. The study intentionally compared a dose considered potentially clinically useful vs. a dose that would be more like placebo but that would carry a possible threat of a disulfiram-ethanol reaction (the study had three arms: 250 mg, 1 mg, and also vs. no disulfiram)
Public Comment #3 (APA)	Results	Pg 46 after 2nd sentence in ntx section Add space	Revised.
Public Comment #3 (APA)	Results	Pg 46, first sentence: Delete apostrophe and shouldn't it just be 100-108?	Revised.
Public Comment #3 (APA)	Results	Table 23 The superscripted 2 seems in the wrong place.	Revised.
Public Comment #3 (APA)	Results	Table 23 All 0's should be 0.0	Revised.

Commentator & Affiliation	Section	Comment	Response
Public Comment #3 (APA)	Results	p. 47 Baclofen harms Elsewhere, a possible dose response effect was mentioned in terms of baclofen harms (p. 39 in the section on mortality). It would be important to include that information here as well in case people just look at parts of the document rather than the whole thing.	We did not repeat the assessment for mortality in this section (for baclofen or for other drugs). The dose response issue we found was in the mortality assessment (not in the assessment for other AEs). We have added a note to this section stating that findings related to mortality are in Section 3.2.2.
Public Comment #3 (APA)	Results	Table 24 0s to 0.0	Revised.
Public Comment #3 (APA)	Results	p. 47 Gabapentin Is the cognitive dysfunction risk rated low SOE as well?	Yes, and we have added this to the text.
Public Comment #3 (APA)	Results	Table 25 0.0	Revised.
Public Comment #3 (APA)	Results	Table 25, numbness I'm guessing these aren't ranges because there was only one RCT but this format is different than later table that only lists the percentage for the 1 RCT. Need to be consistent.	Thank you, we have revised to make the rows with one RCT consistent.
Public Comment #3 (APA)	Results	p. 48 ondansetron Change "update report" to "updated report" here and throughout the document.	Revised and searched for “update report” to revise any other instances.
Public Comment #3 (APA)	Results	Pg. 48 Update report to updated report	Revised.
Public Comment #3 (APA)	Results	p. 48 topiramate see prior comments on the phrase "taste perversion" and on the cognitive effects.	We have updated this to “taste abnormalities” throughout.
Public Comment #3 (APA)	Results	Table 26, 0.0	Revised.
Public Comment #3 (APA)		Table 26 Insomnia row Should there be something in this row and next in the I2 column?	Yes, thank you for noting this; we have added 0.0 in both places.

Commentator & Affiliation	Section	Comment	Response
Public Comment #3 (APA)	Results	p. 49 Varenicline The FDA's imposition of a black box warning for varenicline in 2009 led to significant decreases in its use for smoking cessation. Subsequent meta-analyses (e.g., https://pubmed.ncbi.nlm.nih.gov/25767129/) did not show significant differences in rates of suicide or other suicide-related behaviors. I don't know if that is worth noting even though it's not in alcohol specific studies.	We have elected not to note this. It is interesting, but it is our practice to restrict our evidence to that within the population/outcomes of interest for the report and including this one study would not be consistent.
Public Comment #3 (APA)	Results	Table 27 0s to 0.0	Revised.
Public Comment #3 (APA)	Results	Table 27 This layout is different than tables above.	We have revised Table 27 (now Table 28) and made additional edits to confirm the layout is consistent.
Public Comment #3 (APA)	Results	p. 52 characteristics 3rd line parenthesis is followed by a comma, which should be deleted.	Revised.
Public Comment #3 (APA)	Results	Pg. 52 Most of the discussions mention gender and not sex. Not sure if we know if people identified by their gender or assigned biological sex. Just stood out here and wonder if it should be gender.	We have left this section as sex because that reflects the current state of the literature. We do, however, recognize and note that no studies included any information on gender beyond male or female, and studies themselves referred to sex.
Public Comment #3 (APA)	Discussion	p. 55 2nd pg This may be another location where it would be appropriate to note that RCT design may not be optimal for showing whether disulfiram is effective or not.	We have edited the text to reflect this challenge.

Commentator & Affiliation	Section	Comment	Response
Public Comment #3 (APA)	Discussion	p. 58 Harms 3rd pg see prior comments re: topiramate and question of greater mortality with high dose baclofen.	For mortality, we routinely list this outcome under potential benefits because we want to look for evidence regarding whether the treatments would reduce deaths compared with the placebo/control group. And in this instance, The purpose of treatment for AUD is to reduce morbidity and mortality; therefore, it makes sense to think of reduced mortality under potentially beneficial health outcomes. But, we also understand that it's possible that it could be a harm – e.g., if a medication has some severe adverse event that could lead to more deaths than in the placebo group. So, when we analyze mortality data, we must always have an open mind about what the data is showing (were there more deaths or fewer deaths in the medication group than in the placebo group?) and then need to interpret it appropriately. In the case of baclofen, we do have a section on Mortality (with its own header) in the harms KQ of the report, and we detail the pertinent information there.

Commentator & Affiliation	Section	Comment	Response
Public Comment #3 (APA)	Discussion	Pg. 58 on perversion - See previous comments.	We have changed this to taste abnormalities.
Public Comment #3 (APA)	Discussion	p. 59 section 4.1.5 It would be useful to note the specific guidelines that describe naltrexone and/or acamprosate as first line and include the appropriate citations at the end of the 2nd sentence.	We have added reference to the specific guidelines.
Public Comment #3 (APA)	Discussion	p. 59 Section 4.1.6. Mention should also be made of the gender and race/ethnicity distributions in the studies, with many having relative low numbers of women or non-white participants and none (that I could tell) that specified gender other than male or female.	We have added more language to this effect.
Public Comment #3 (APA)	Discussion	Pg. 59 did not find that it demonstrated a	Revised.
Public Comment #3 (APA)	Discussion	p. 59 Applicability pg 3 last sentence. The comment about differences not being due to differences in healthcare systems is unclear. One of the issues with other countries is that they are more likely to provide inpatient treatment for significant periods of time during which alcohol withdrawal has abated and medications begun prior to discharge. This could impact the efficacy of the medication alone or in combination with psychotherapeutic interventions for AUD and would, in fact, seem to result from health care system differences.	We have revised this text.
Public Comment #3 (APA)	Discussion	Pg. 60 see taste perversion comment above	We have updated this to “taste abnormalities throughout.”
Public Comment #3 (APA)	Discussion	Pg. 60, delete extra space and comma (end of 3rd paragraph)	Revised.
Public Comment #3 (APA)	Appendices	A-19 Data synthesis pg 2 sentence 2. This statement on I2 seems odd because the ranges overlap. Thus 35% could be both unimportant and represent moderate heterogeneity. Also, considerable heterogeneity seems less pronounced than substantial heterogeneity yet is listed as being higher on the percentage scale (though with significant overlap).	We’ve removed the sentence describing the overlapping ranges to avoid confusion.
Public Comment #3 (APA)	Appendices	A-19 Data synthesis pg 2 last sentence The items in parentheses seem like they should be marked as e.g., rather than i.e.,	We have replaced i.e. with e.g.
Public Comment #3 (APA)	Appendices	A-19 Grading line 2 I've not seen the phrase "short GRADE" before. Is there any other way to describe this? May wish to add "to grade the overall strength of a body of evidence." after Program and start the next sentence with "This approach..." The last two sentences of this 1st pg are a bit unclear. If the studies are consistent, of high quality, direct, and clinically relevant, then the statistical significance of a finding would be expected to be more meaningful. The sample size issues addressed in the last sentence seem like less of a focus of the GRADE and EBPC approaches than incorporating RoB and SOE determinations. Although the sample sizes are factored into the meta-analytic weightings, not all of the studies were able to be incorporated into a meta-analysis.	We’ve incorporated the suggested change to the phrasing. This is standard language used in reports that apply the same methods but we have deleted the last two sentences to avoid confusion.

Commentator & Affiliation	Section	Comment	Response
Public Comment #3 (APA)	Appendices	p. A20 last of bullet points. May wish to add to the end of the sentence "particularly in terms of side effects and other potential harms of medications."	We have added this phrase.
Public Comment #3 (APA)	Appendices	A-21 1st sentence spell out FT (presumably full text)	Revised to full text.
Public Comment #3 (APA)	Appendices	p. B3 Is any information on funding sources and/or investigator conflict of interest? It's never been clear to me why AHRQ, GRADE, and RoB determinations don't incorporate those factors into potential considerations of bias, but we do discuss it, where relevant, in guideline group deliberations.	We did not abstract this information and the information in this table is consistent with the 2014 report.
Public Comment #3 (APA)	Appendices	p. B40 pg on gabapentin May wish to include (DRESS) after the full wording since this is how it's typically referred to in clinical practice.	We have added this acronym.
Public Comment #3 (APA)	Appendices	B-40 Ondansetron would add the following to the first sentence "due to reports of severe hypotension and loss of consciousness of unclear mechanism."	We have added this phrase.
Public Comment #3 (APA)	Appendices	B-40 Ondansetron pg the other listed items in the 2nd sentence are potential side effects but phenylketonuia may be better split into its own sentence. That warning applies to the dissolving tablet preparation of ondansetron, which contains phenylalanine and which contributes to neurological damage in individuals with phenylketonuria (PKU).	We have added a sentence with this information on phenylketonuria.
Public Comment #3 (APA)		B-40 topiramate Again this section seems to understate the various cognitive effects of topiramate.	We have added cognitive effects to this list.
Public Comment #3 (APA)		B-41 The baclofen paragraph mentions concerns related to withdrawal in neonates if there is maternal use in pregnancy but comments on use of the other medications in pregnancy are not included.	We've removed this language for consistency.
Public Comment #3 (APA)		C-16 in terms of the column headers that ask about masking, I recognize that this is commonly used and likely preferable to the word "blinded", which can be misleading to patients in vision related studies. In the pandemic era, however, questions about people being masked may be misinterpreted. Perhaps a footnote that says that in this context masking refers to whether outcome assessors, providers, or patients were aware of the treatment arm to which the participant was assigned.	We have added a footnote to define masked. Thank you for noting this. This table was developed for the 2014 report when this confusion would have been much less likely.