AHRQ Systematic Review Surveillance Report

CER # <u>xxx</u>: Title, Month, YYYY

<u>Surveillance Report Date:</u> Month YYYY

<u>Summary of Key Findings:</u>
- Key Question 1: [insert]
  - o Original Conclusions are [likely current, may not be current, out of date] for ….[details of this KQ]
  - o *[Brief supporting details such as:*
    - *New evidence suggests ….*
    - *We identified NN new studies which provided additional evidence for …*
    - *Consistent with original review*
    - *Inconsistent/variable results*
    - *Likely/unlikely to change report conclusions.]*

- Key Question 2: [insert]
  - o Original Conclusions are [likely current, may not be current, out of date] for ….[details of this KQ]
  - [Repeat for each KQ, or sub-questions as needed]

Other considerations: [Example: Two large RCTs may have data in the next two years; FDA black box warning, new medication pending approval]

<u>Overall Assessment of Currency:</u>
[Summarize: for example- While some new evidence is available, Overall, the conclusions of the original review are [likely current, may not be current, out of date].

Authors:
[Name, Degree]

Reviewers/Subject Matter Experts

[Name, Degree
[Position / Title
Institution
City, State]

[Name, Degree
[Position / Title
Institution
City, State]

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Introduction

The purpose of the surveillance process for the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Center (EPC) Program is to determine whether the conclusions of a systematic review (SR) are current. The surveillance process examines the conclusions to the key questions as written, and does not evaluate the currency of the original scope (i.e., key questions, included interventions).

Comparative Effectiveness Review (CER) #NNN titled **"[Title]"** was originally released in [Month YYYY].[1] Since then, it has been cited NN times by PubMed articles, and downloaded [NN] times.

The **Key Questions** (KQ) are:

Key Question 1: [insert]

Key Question 2: [insert]

Key Question 3: [insert]

Key Question 4: [insert]

Key Question 5: [insert]

Key Question 6: [insert]

Methods

Our surveillance assessment began in [Month YYYY]. Briefly, we searched for literature published since the last search date in the original SR [Month Year]. Then, we asked content experts involved in the original SR for their input. We compiled these opinions, discussed as a group, and determined our conclusions.

Literature Searches

We limited our search to six months before the last search date in the original SR [Month Year] through the present [Month YYYY through Month YYYY]. We used the Simplified Search Strategy method described by Rice et al. [5] [One reviewer] selected a purposive sample [4] of key articles from the original SR to detect any signals, that is, new data that would change the results. The purposive sample yielded NN key articles, of the [total NN] included in the original SR. For each key article, [Author] entered the PMID into PubMed, and then selected the 'similar articles' feature in PubMed. [She] downloaded the results, deleted duplicates, and selected those published in the search window.

Study Selection

Using the same inclusion and exclusion criteria as the original systematic review (see Appendix B), one investigator (Initials) reviewed the titles, abstracts [and full reports] of the search results. We included systematic reviews and meta-analyses, whether or not they were included (as a study design) in the original systematic review. For systematic reviews and meta-analyses, we considered findings only if all included studies met inclusion criteria. . Reviews for which one or more study did not meet our criteria were used to identify potentially relevant primary research. [include any other exceptions or background articles selected].

Expert Opinion

We developed a findings matrix by summarizing new evidence alongside the original SR key questions and conclusions. We sent the findings matrix to subject matter experts. (Appendix C) We requested their comments on whether the SR conclusions were current and if we had missed any relevant new studies.

FDA Black Box Warnings. We searched the FDA Medwatch online database website for black box warnings for [list applicable drugs/devices] mentioned in the original systematic review.

Compilation of Findings and Assessment of Currency

To assess whether individual SR conclusions were current, we constructed a summary table (Appendix D) that compared the key questions and conclusions from the original SR, findings of the new literature searches, and the expert opinion. We qualitatively compared original SR conclusions with the new input from the literature and experts, and categorized whether each conclusion was current as follows:

New Evidence	Responding Experts	Assessment of Original Conclusion
None, or supports the original finding	Concur	Likely current

Some new or conflicting evidence	Disagree	May not be current
Major change in evidence (groundbreaking study, FDA warning)	Concur	Out of date

To assess whether the entire systematic review was current, we considered the strength of the original conclusion, and how new evidence contributed to the number of studies, number of participants, and consistency of results.

[Other considerations. *For example: We weighted conclusions for the FDA-approved medications more heavily than evidence for off-label medications, as these were the main points of the original review. Further, we prioritized results for KQ1, KQ2, and KQ3, because the original review found insufficient evidence for all comparisons and outcomes for KQ4, KQ5, and KQ6.]*

Results

Literature Search

We found nn articles that had potential to change the results of the original systematic review. The PubMed similar article search identified nnn unique citations. Of these, nn were excluded at title/abstract review, and nn at full review. In addition, experts contributed nn citations [cite here]. Thus nn studies were included as new evidence.[cite here]

[Optional: Of the nn of articles examined for potential to change the results of the original systematic review, the number that pertained to each key question was unevenly distributed. There were n for KQ1, n for KQ2, etc].

[Optional: For background, we also included [studies that did not fit includsion/exclusion] *For example: we included a recent meta-analysis of disulfiram efficacy that we found in the PubMed related articles search[49] and preliminary descriptions of two new trials on AUD treatment in primary care: STEP[50] and CHOICE trials.[51] Finally, we note that the Cochrane Collaboration has published a protocol for a systematic review of baclofen efficacy.[52]]*

Detailed findings from these studies are found in Appendix C.

FDA Black Box Warnings: We found no FDA black box warnings

Expert Opinion

We contacted nn subject matter experts (N original authors and N technical expert panel (TEP) members) for their opinions and recommendations. N experts responded with a completed matrix; one provided comments by email.

[Optional : reviewer general impressions. *For example: All reviewers concurred that overall, the systematic review did not need updating, or that updating was premature. One commented that AHRQ might consider a smaller update for newer/off-label medications. He noted that evidence on baclofen, in particular, is accumulating rapidly.]*

Compilation of Findings

Appendix D shows the original key questions, the conclusions of the original systematic review with strength of evidence (SOE), the results of the literature search, expert opinion, and the assessment of the currency of the systematic review. Details of each study are in this appendix. Below, we provide additional narrative support.

- Key Question 1: [insert verbatim]
    - Original Conclusions are [likely current, may not be current, out of date] for ….[details of this KQ]
    - [Expand on the supporting details listed in the face page:
        - New evidence suggests ….
        - We identified NN new studies which provided additional evidence for …
        - Consistent with original review
        - Inconsistent/variable results
        - Likely/unlikely to change report conclusions.]
    - *[Example: Efficacy conclusions are likely current for medications approved for use. We found one study each on disulfiram (n=109)[29], acamprosate (n=327)[13] which supported the SR conclusions and were too small to likely change the SOE. A single small trial of a lower dose of naltrexone (n=128)[24] with conflicting results is unlikely to change prior conclusions that were based on >10 trials with >2000 participants in the systematic review.]*
    [Example: Baclofen conclusions may not be current. Prior conclusions (insufficient SOE) were based on 2 trials (164 participants). We identified three new RCTs with 440 participants, but efficacy results are inconsistent.[23,26,43] A Cochrane review is planned.[52]]

- Key Question 2: [insert verbatim]
    - [repeat above format]

We identified no new large ground-breaking studies and no FDA boxed warnings since the original systematic review was published.

Overall Assessment of Currency

New evidence examined in this surveillance assessment suggests that the original review [is likely current/ may not be current/ is out of date].
[Supporting details] *For example ; For three approved medications, there is very little new data on efficacy or comparative effectiveness for alcohol consumption, health outcomes, or harms. Thus the major conclusions for KQ1 (alcohol consumption), KQ2 (health outcomes), and KQ3 (harms) are likely current. Similarly, conclusions for the efficacy of six of the eight off-label medications that were originally included are unlikely to change with the limited new data that has been published, with two exceptions. For citalopram, a single large RCT reports that treatment worsened drinking outcomes compared with placebo. Evidence for baclofen now includes five studies (over 600 patients) with mixed results for efficacy, and five studies (three RCTs, two observational studies) for harms. The reports of intentional overdose with baclofen are concerning. The Cochrane group plans a systematic review of the safety and efficacy of*

baclofen for alcohol use disorders. New information for KQ4, KQ5 and KQ6 is limited by the small number of studies, and heterogeneity of comparisons and outcomes.] Thus, overall, we conclude that the original systematic review [is likely current/ may not be current/ is out of date].

Appendix A: Methods

Appendix A: Methods- Purposive Sample of Key Articles

The simplified search strategy described by Rice et al recommends selecting two-six key articles that were "most recently published" or "largest sample size" from the original review.

[Describe additional selection criteria and justification] For details of the sample and reasons for inclusion, see (Purposive Citations, Table 1)

 For example: *However, the AUD report included six key questions and more than ten medications. Therefore, we adapted these approaches for the breadth of the AHRQ report. We designed a purposive sample [4] of citations to detect any signals, that is, new data that would change the results of the existing SR. To do this, I searched the full AUD report and identified all articles published in 2013 as the "recent" sample. Additionally, we identified the largest two articles for two FDA-cleared drugs (acamprosate and naltrexone), and for the named studies (COMBINE, PREDICT, SENSE). To assure that I did not miss a signal from newer or off-label drugs, weidentified the largest study for each off-label drug. If studies were the same size, we chose the most recent. If a single study had more than one publication, we included those with different outcomes pertinent to key questions (ie, consumption or health outcomes or genetics). We included the single study (a prospective cohort, high risk of bias) that was cited for harms. Of 167 citations (135 studies) in full AUD report, we selected 17 (10%) to inform this update.*

[Optional: We confirmed the purposive sample with [expertise]].

Appendix A: Methods

Table 1: Purposive Sample: Key Articles selected to inform update, and number of articles retrieved for each method [example of studies and reasons]

First Author	Publication Year	Drug	RoB [1]	Size (n)	Reason to include:	
					Primary	**Secondary**
Kranzler[54]	2013	naltrexone	Medium	150	Most recent	Genetic
Mann[56]	2013	nalmefene	Medium	600	Most recent	Named study- ESENSE
Gual[57]	2013	nalmefene	Medium	710	Most recent	
Mann[58]	2013	naltrexone, acamprosate	Medium	420	Named study-PREDICT	compares NTX and ACA
Kranzler[60]	2012	sertraline	Medium	130	Largest for drug	
Anton[61]	2011	naltrexone, acamprosate, gabapentin	Medium	150	Largest for drug	only 3 drug comparison; includes gabapentin
Garbutt[62]	2010	baclofen	Medium	80	Largest for drug	
Stedman[63]	2010	quetiapine	High	350	Largest for drug	
Anton[64]	2008	naltrexone	Medium	600	Largest genetic	Named study-COMBINE
Narayana[65]	2008	any	High	75	Harms	
Johnson[66]	2007	topiramate	Low	160	Largest for drug	
Salloum[67]	2005	valproic acid	Medium	60	Largest for drug	
Fawcett[68]	2000	buspirone	Medium	150	Largest for drug	
Naranjo[69]	1995	citalopram	High	150	Largest for drug	
Kranzler[70]	1995	fluoxetine	Medium	138	Largest for drug	

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[1] RoB: Risk of Bias, as listed in original AUD report

Appendix B: Inclusion and Exclusion Criteria from Original Systematic Review

Appendix B: Inclusion and Exclusion Criteria from Original Systematic Review

[Insert table from original SR]

Example:

Category	Inclusion	Exclusion
Population		
Interventions		
Comparators		
Outcomes		
Timing/ Length of follow-up		
Settings		
Publication Language		
Admissible evidence (study design and other criteria)		

Appendix C: Materials sent to expert reviewers

Appendix C: Materials sent to expert reviewers

We sent each reviewer a cover letter and Findings Matrix. Examples are included here.

Example: Cover Letter (email)
[Insert text]

Appendix C: Materials sent to expert reviewers

Example: Findings Matrix: [Insert page one text and a few rows of KQ-1 matrix as an example. Do not insert the entire Findings matrix] *Example:*

Findings Matrix for "Pharmacotherapy for Alcohol Use Disorders"

The first column contains the original findings/conclusion from the Executive Summary of the original Systematic Review "Pharmacotherapy for Alcohol Use Disorders" published in May 2014. Each row refers to a separate conclusion/finding from the full report. In the second column we summarized results of our recent targeted literature search.

Please **add your answer:**
Column 3: Is the original conclusion still supported by the evidence? (yes/no/don't know)
Column 4: Is there any other new evidence that may change this conclusion? (Author/date)

Tables are divided by Key questions. Key questions are modified for brevity; all are limited to: adults with AUDs in outpatient settings.

The findings matrix contained the first two columns of the Currency Assessment Summary Tables (Appendix D) two columns for their responses, a reference list, and the following directions**:**

An example of the difference in formatting between the findings matrix and the Currency Assessment **(Appendix D)** is shown below. To assist reviewers, citations were formatted as (Author, Year), and the reference list (in author order) contained hyperlinks directly to the articles in PubMed. Contents of column 1 (Conclusions from the Original Systematic Review) and column 2 (New Literature Search – [date range]) are contained in the Currency Assessment. The entire matrix is not repeated to decrease repetition in this document.

Appendix C: Materials sent to expert reviewers

Findings matrix: Example from Key Question 1:

<table>
<tr><td colspan="4">**Key Question 1a: Which medications effectively reduce alcohol consumption*?**
*Variably defined as: abstinence, return to any/heavy drinking; number of any/heavy drinking days, drinks per drinking day</td></tr>
<tr>
<th>KQ1a:
Conclusions from the Original Systematic Review – Link to Report</th>
<th>KQ1a:
New Literature Search –
(Dec 2013-Jul 2017)</th>
<th>Conclusion still supported?
(Yes/No/Unsure)</th>
<th>Any other new evidence?
(Author/Date)</th>
</tr>
<tr>
<td>**Disulfiram**
No significant differences were found between disulfiram and placebo on return to any drinking (3 studies; SOE: low) and number of drinking days (2 studies; SOE: insufficient).

No data were reported on percentage returning to heavy drinking, number of heavy drinking days, or drinks per drinking days.</td>
<td>**Disulfiram**
One study reported no significant difference between disulfiram and placebo in abstaining from alcohol (n=109). (Yoshimura et al. 2014)

A systematic review and metanalysis that included open label trials concluded that supervised disulfiram was superior to acamprosate, naltrexone and placebo. (Skinner et al. 2014)</td>
<td></td>
<td></td>
</tr>
</table>

Appendix D: Currency Assessment Summary Tables

Appendix D: Currency Assessment Summary Tables

The Summary table is built from the findings matrix. The first column contains the original findings/conclusion from the Systematic Review, cross-walked with the Evidence Tables from Appendix D of the original Systematic Review "Pharmacotherapy for Alcohol Use Disorders". Each row refers to a separate conclusion/finding from the full report. In the **second column**, we summarized results of our recent targeted literature searches.

Column 3 contains expert response to "is this conclusion still supported?" When expert responses differ, they are coded as expert 1, expert 2.

Column 4 contains the AHRQ assessment of currency.

Tables are divided by Key questions (modified for brevity); in this example, all KQs are limited to adults with AUDs in outpatient settings.

Key Question 1a: Which medications effectively reduce alcohol consumption*?

*Variably defined as: abstinence, return to any/heavy drinking; number of any/heavy drinking days, drinks per drinking day

KQ1a: Conclusions from the Original Systematic Review – **Link to Report;** (See Appendix D, Strength of Evidence Tables)	KQ1a: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert 1 Expert 2	AHRQ assessment (comment)
Disulfiram (Table D-2, Appendix D. Full Report) No significant differences were found between disulfiram and placebo on return to any drinking (3 studies, n=492; SOE: low) and number of drinking days (2 studies; SOE: insufficient). No data were reported on other outcomes.	**Disulfiram** One study reported no significant difference between disulfiram and placebo in abstaining from alcohol (n=109).[29]	1. May be worthwhile to update vis a vis open trials. 2. Yes (debate about how to interpret findings and ROB for older disulfiram studies is not new; the JAMA letters to the editor and our responses address that issue)	Likely current (One small study is consistent with previous conclusions)
Acamprosate (Table D-1, Appendix D, Full report) A meta-analysis of 19 studies found patients treated with acamprosate significantly decreased return to any drinking (SOE: moderate) and number of drinking days	**Acamprosate** One study reported that acamprosate was significantly more effective over placebo in return to any drinking	Yes	Likely current (One small study is consistent with previous

Appendix D: Currency Assessment Summary Tables

KQ1a: Conclusions from the Original Systematic Review – Link to Report; (See Appendix D, Strength of Evidence Tables)	KQ1a: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert 1 Expert 2	AHRQ assessment (comment)
compared to placebo (SOE: moderate). No significant differences were found between acamprosate and placebo on return to heavy drinking (SOE: moderate), heavy drinking days or drinks per drinking day (SOE: insufficient for both).	(n=327). [13]		conclusions)
Naltrexone *Any dose* **(Table D-3, Appendix D, Full report)** In subjects treated with naltrexone, 4% fewer subjects returned to any drinking, 7% fewer subjects returned to heavy drinking, the treatment group had 4.6% fewer drinking days, the treatment group had 3.8% fewer heavy drinking days, and the treatment group had 0.5% fewer drinks per drinking day than the placebo group.(SOE: moderate for each) *50 mg oral* **(Table D-4, Appendix D, Full report)** A meta-analysis showed subjects treated with 50 mg of naltrexone were significantly less likely to return to any drinking (SOE: moderate) or heavy drinking (SOE: moderate), and had a fewer number of drinking days (SOE: moderate). *100 mg oral* **(Table D-5, Appendix D, Full report)** A meta-analysis showed subjects treated with 100 mg of naltrexone showed no significant difference for returning to any drinking (SOE: low) or heavy drinking (SOE: low), or having fewer of drinking days (SOE: low). *Injection* **(Table D-6, Appendix D, Full report)** A meta-analysis showed subjects treated with an injection of naltrexone showed significantly fewer drinking days. Subjects treated with an injection of	**Naltrexone** One study [24] using 25-50 mg Naltrexone showed no significant difference between naltrexone and placebo on return to heavy drinking or the percentage of drinking days. However, compared to placebo, naltrexone significantly decreased the number of drinks per drinking day (n=128).	Yes	Likely current; (A single small trial of a lower dose is unlikely to change prior conclusions that were based on >10 trials with >2000 participants).

Appendix D: Currency Assessment Summary Tables

KQ1a: Conclusions from the Original Systematic Review – **Link to Report;** (See Appendix D, Strength of Evidence Tables)	KQ1a: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert 1 Expert 2	AHRQ assessment (comment)
naltrexone showed no significant difference in returning to any drinking (SOE: low) or heavy drinking (SOE: low).			
Off-Label Therapies			
Baclofen **(Table D-13, Appendix D, Full report)** There were conflicting findings for return to any drinking—1 study suggested only 29% of baclofen users returned to any drinking, and another suggests 90% of baclofen users returned to any drinking. There were no significant differences in baclofen vs placebo for heavy drinking (1 study), drinking days (1 study), and heavy drinking days (1 study). No studies were identified other outcomes. SOE: insufficient for all outcomes.	*Baclofen* One study [23] reported a significantly higher percentage of alcohol-abstinent days with baclofen compared to placebo (n=56). Another study [26] (n=64) reported no significant difference in consumption (percentage of alcohol-abstinent days or heavy drinking days) between baclofen and placebo groups. The ALDAPIR study (n=320) showed no difference between baclofen (180 mg) and placebo in percent reaching abstinence or alcohol consumption. However, there was a trend towards reduced daily consumption on baclofen. (p=.09). [43] Cochrane published a protocol for a new systematic review of the effectiveness of baclofen for AUD. [52] (Included for background).	1. Should be updated. 2. Unsure. This is the main drug that I've been hearing a lot more about for treating AUD (as far as one with potential to be really beneficial and used more). Synthesis of all the baclofen trials (old and new) might change conclusions for baclofen, and would be a useful contribution for an update	May not be current. (Prior conclusions were based on 2 trials (164 participants). We identified three new RCTs with 440 participants, but results are conflicting. A Cochrane review is planned.)

Appendix E: References

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