Pharmacotherapy for Adults With Alcohol Use Disorders in Outpatient Settings
A Systematic Review and Meta-analysis

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IMPORTANCE Alcohol use disorders cause substantial morbidity and early mortality yet remain greatly undertreated. Medications are considerably underused.

OBJECTIVE To conduct a systematic review and meta-analysis of the benefits and harms of medications (US FDA-approved and others) for adults with alcohol use disorders.


STUDY SELECTION Two reviewers selected randomized clinical trials (RCTs) with at least 12 weeks' duration that reported eligible outcomes and head-to-head prospective cohort studies reporting health outcomes or harms.

DATA EXTRACTION AND SYNTHESIS We conducted meta-analyses using random-effects models and calculated numbers needed to treat for benefit (NNTs) or harm (NNHs).

MAIN OUTCOMES AND MEASURES Alcohol consumption, motor vehicle crashes, injuries, quality of life, function, mortality, and harms.

RESULTS We included 122 RCTs and 1 cohort study (total 22 803 participants). Most assessed acamprosate (27 studies, n = 7519), naltrexone (53 studies, n = 9140), or both. The NNT to prevent return to any drinking for acamprosate was 12 (95% CI, 8 to 26; risk difference [RD], −0.09; 95% CI, −0.14 to −0.04) and was 20 (95% CI, 11 to 500; RD, −0.05; 95% CI, −0.10 to −0.002) for oral naltrexone (50 mg/d). The NNT to prevent return to heavy drinking was 12 (95% CI, 8 to 26; RD −0.09; 95% CI, −0.13 to −0.04) for oral naltrexone (50 mg/d). Meta-analyses of trials comparing acamprosate to naltrexone found no statistically significant difference between them for return to any drinking (RD, 0.02; 95% CI, −0.03 to 0.08) or heavy drinking (RD, 0.01; 95% CI, −0.05 to 0.06). For injectable naltrexone, meta-analyses found no association with return to any drinking (RD, −0.04; 95% CI, −0.10 to 0.03) or heavy drinking (RD, −0.01; 95% CI, −0.14 to 0.13) but found an association with reduction in heavy drinking days (weighted mean difference [WMD], −4.6%; 95% CI, −8.5% to −0.56%). Among medications used off-label, moderate evidence supports an association with improvement in some consumption outcomes for nalmefene (heavy drinking days per month: WMD, −2.0; 95% CI, −3.0 to −1.0; drinks per drinking day: WMD, −1.02; 95% CI, −1.77 to −0.28) and topiramate (% heavy drinking days: WMD, −9.0%; 95% CI, −15.3% to −2.7%; drinks per drinking day: WMD, −1.0; 95% CI, −1.6 to −0.48). For naltrexone and nalmefene, NNHs for withdrawal from trials due to adverse events were 48 (95% CI, 30 to 112) and 12 (95% CI, 7 to 50), respectively; risk was not significantly increased for acamprosate or topiramate.

CONCLUSIONS AND RELEVANCE Both acamprosate and oral naltrexone were associated with reduction in return to drinking. When directly compared with one another, no significant differences were found between acamprosate and naltrexone for controlling alcohol consumption. Factors such as dosing frequency, potential adverse events, and availability of treatments may guide medication choice.


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alcohol use disorders (AUDs) are common, cause substantial morbidity, and result in 3-fold increased rates of early mortality (eTable 1 in the Supplement).1-8 Treating AUDs is difficult but may be aided by using medications. Pharmacotherapy for AUDs was initiated in the 1950s and consisted only of disulfiram (Antabuse). In the 1990s, naltrexone (oral and intramuscular formulations) and acamprosate were approved by the US Food and Drug Administration (FDA) (eTable 2 in the Supplement).

Fewer than one-third of patients with AUDs receive treatment,6 and only a small percentage (<10%) receive medications to assist in reducing alcohol consumption. To evaluate the benefits and harms of medications for the treatment of adults with AUDs, we conducted a systematic review. A larger, more comprehensive technical report for the Agency for Healthcare Research and Quality was prepared (eTable 3 in the Supplement).9 This article summarizes findings from the larger report on the efficacy of various medications used for the treatment of AUDs in reducing alcohol intake or improving health outcomes and on the adverse effects of these medications.

Methods
We developed and followed a standard protocol. A technical report that details methods, search strategies, and additional information is available online.9

Data Sources and Searches
We searched PubMed, the Cochrane Library, PsycINFO, CINAHL, and EMBASE from January 1, 1970, to October 11, 2013, for the technical report; we updated searches through March 1, 2014, for this article. An experienced Evidence-based Practice Center (EPC) librarian ran all searches; another EPC librarian peer-reviewed them. We manually searched reference lists of pertinent reviews and trials for relevant citations that our searches missed.

We searched for unpublished studies using ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and the FDA website. In addition, the Scientific Resource Center of the Agency for Healthcare Research and Quality requested unpublished studies and data from manufacturers.

Study Selection
We included studies enrolling adults with AUDs that evaluated an FDA-approved medication or any of 23 off-label medications for at least 12 weeks in an outpatient setting. Studies were required to assess one of the following outcomes: (1) consumption—return to any drinking, return to heavy drinking, drinking days, heavy drinking days (≥4 drinks per day for women; ≥5 for men), drinks per drinking day; (2) health outcomes—accidents (ie, motor vehicle crashes), injuries, quality of life, function, and mortality; or (3) adverse effects.

Double-blind randomized clinical trials (RCTs) comparing one of the medications with placebo or another medication were eligible. Prospective cohort studies that compared 2 medications were eligible if they reported a health outcome. For adverse effects, the following designs were eligible if they compared 2 drugs of interest: nonrandomized or open-label trials, subgroup analyses from trials, prospective cohort studies, and case-control studies.

Two investigators independently reviewed each title and abstract. Studies marked for possible inclusion by either reviewer underwent dual, independent full-text review. If reviewers disagreed, we resolved conflicts by consensus.

Data Extraction and Risk of Bias Assessment
We used structured data extraction forms to gather relevant data from each article. All data extractions were reviewed for completeness and accuracy by at least 2 investigators.

To assess the risk of bias of studies, we used predefined criteria based on established guidance.10,11 We included questions about adequacy of randomization, allocation concealment, similarity of groups at baseline, blinding, attrition, validity and reliability of measures, whether intention-to-treat (ITT) analysis was used, methods of handling missing data, and fidelity. We rated the studies as low, medium, high, or unclear risk of bias.10,11 Two independent reviewers assessed risk of bias for each study. Disagreements were resolved by consensus.

Data Synthesis and Analysis
We conducted meta-analyses of RCTs using random-effects models.12 For continuous outcomes, we used weighted mean differences (WMDs) and 95% CIs. For binary outcomes, we calculated risk differences (RDs) between groups and 95% CIs. We did not include studies rated as high or unclear risk of bias in our main analyses but included them in sensitivity analyses. When possible, we conducted post hoc subgroup analyses to assess whether pooled results differed for studies rated as low risk of bias. We calculated the P statistic to assess statistical heterogeneity.13,14 We examined potential sources of heterogeneity by analysis of subgroups defined by patient population (eg, US vs non-US studies). Analyses were conducted using the metaan, metafunnel, and metabias commands in Stata version 11.1 (StataCorp). Statistical significance was assumed when 95% CIs of pooled results did not cross 0. All testing was 2-sided. We calculated numbers needed to treat (NNTs) and numbers needed to harm (NNHs) when pooled RDs found a statistically significant result. When appropriate15,16 (eg, ≥10 studies in a meta-analysis), we assessed for publication bias by visually examining funnel plots and using the Begg-Mazumdar17 test. None of the funnel plots or statistical tests indicated concern for publication bias. When quantitative synthesis was not appropriate (eg, insufficient numbers of similar studies), we synthesized the data qualitatively.

We graded the strength of evidence as high, moderate, low, or insufficient based on established guidance.18 The approach incorporates 4 key domains: risk of bias, consistency, directness, and precision. Two reviewers assessed each domain for each outcome and determined an overall grade. Differences were resolved by consensus.

We did not combine medications with similar mechanisms or in the same drug class in our analyses because we...
aimed to determine which medications (not classes) have evidence supporting associations with improved outcomes. For example, nalmefene is an opioid receptor antagonist like naltrexone, but we analyzed them separately.

Results

We included 151 articles reporting on 123 studies (Figure 1). Of these, one was a prospective cohort study29; the rest were RCTs; the total number of participants was 22,803. Characteristics of included studies are shown in eTable 4 in the Supplement. Most studies assessed acamprosate (27 studies, n = 7519), naltrexone (53 studies, n = 9140), or both. Sample sizes ranged from 21 to 1383. Treatment duration ranged from 12 to 52 weeks. Mean age was usually in the 40s. All participants met criteria for alcohol dependence in the vast majority of trials. Most studies enrolled patients after detoxification or required a period of sobriety (at least 3 days). Studies typically included psychosocial co-interventions; thus, effect sizes reflect the added benefits of medications beyond those of psychosocial interventions and placebo.

The largest trial, COMBINE,30 randomized 1383 treatment-seeking patients after detoxification or required a period of sobriety (at least 3 days). Studies typically included psychosocial co-interventions; thus, effect sizes reflect the added benefits of medications beyond those of psychosocial interventions and placebo.

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Consumption Outcomes

Acamprosate and naltrexone were associated with improvement in consumption outcomes (Table 1, Figure 2, and Figure 3). To prevent 1 person from returning to any drinking, the NNTs were 12 (95% CI, 8 to 26; 16 trials, n = 4847) and 20 (95% CI, 11 to 500; 16 trials, n = 2347) for acamprosate and oral naltrexone (50 mg/d), respectively. For return to heavy drinking, acamprosate was not associated with improvement, whereas oral naltrexone (50 mg/d) was associated with improvement with an NNT of 12 (95% CI, 8 to 26; 19 trials, n = 2875). For injectable naltrexone, our meta-analyses found no statistically significant association with return to any drinking or return to heavy drinking but found an association with reduction in heavy drinking days (WMD −4.6%; 95% CI, −8.5% to −0.56%; 2 trials, n = 926). Evidence from well-controlled trials of disulfiram does not adequately support an association with preventing return to any drinking or improvement in other alcohol consumption outcomes (Table 1). The largest disulfiram trial (n = 605) reported fewer drinking days for participants who returned to drinking and had a complete set of assessments. Results of sensitivity analyses that included studies rated as high or unclear risk of bias were similar to the results of our main analyses (eFigures 1 and 2 in the Supplement).
Table 1. Summary of Findings and Strength of Evidence From Trials Assessing Efficacy of FDA-Approved Medications for Alcohol Use Disorders

<table>
<thead>
<tr>
<th>Medication</th>
<th>Outcome</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>Results Effect Size (95% CI)</th>
<th>NNT (95% CI)</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acamprosate</td>
<td>Return to any drinking</td>
<td>16</td>
<td>4847</td>
<td>RD: −0.09 (−0.14 to −0.04)</td>
<td>12 (8 to 26)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Return to heavy drinking</td>
<td>7</td>
<td>2496</td>
<td>RD: −0.01 (−0.04 to 0.03)</td>
<td>NA</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>% DDs</td>
<td>13</td>
<td>4485</td>
<td>WMD: −8.8 (−12.8 to −4.8)</td>
<td>NA</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>% HDDs</td>
<td>1</td>
<td>100</td>
<td>WMD: −2.6 (−11.4 to 6.2)</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Drinks per DD</td>
<td>1</td>
<td>116</td>
<td>WMD: 0.4 (−1.8 to 2.6)</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Accidents or injuries</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Qol or function</td>
<td>1</td>
<td>612</td>
<td>NSD</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>8</td>
<td>2677</td>
<td>7 events (acamprosate) vs 6 events (placebo)</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Return to any drinking</td>
<td>2</td>
<td>492</td>
<td>RD: −0.04 (−0.11 to 0.03)</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Return to heavy drinking</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>% DDs</td>
<td>2</td>
<td>290</td>
<td>NSD</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>% HDDs</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Drinks per DD</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Accidents or injuries</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Qol or function</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Naltrexone, 50 mg oral</td>
<td>Return to any drinking</td>
<td>16</td>
<td>2347</td>
<td>RD: −0.05 (−0.10 to 0.002)</td>
<td>20 (11 to 500)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Return to heavy drinking</td>
<td>19</td>
<td>2875</td>
<td>RD: −0.09 (−0.13 to −0.04)</td>
<td>12 (8 to 26)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>% DDs</td>
<td>15</td>
<td>1992</td>
<td>WMD: −5.4 (−7.5 to −3.2)</td>
<td>NA</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>% HDDs</td>
<td>6</td>
<td>521</td>
<td>WMD: −4.1 (−7.6 to −0.61)</td>
<td>NA</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Drinks per DD</td>
<td>9</td>
<td>1018</td>
<td>WMD: −0.49 (−0.92 to −0.06)</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td>Naltrexone, 100 mg oral</td>
<td>Return to any drinking</td>
<td>3</td>
<td>946</td>
<td>RD: −0.03 (−0.08 to 0.02)</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Return to heavy drinking</td>
<td>2</td>
<td>858</td>
<td>RD: −0.05 (−0.11 to 0.01)</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>% DDs</td>
<td>2</td>
<td>858</td>
<td>WMD: −0.9 (−4.2 to 2.5)</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>% HDDs</td>
<td>2</td>
<td>423</td>
<td>WMD: −3.1 (−5.8 to −0.3)</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Drinks per DD</td>
<td>1</td>
<td>240</td>
<td>WMD: 1.9 (−1.5 to 5.2)</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Naltrexone injection</td>
<td>Return to any drinking</td>
<td>2</td>
<td>939</td>
<td>RD: −0.04 (−0.10 to 0.03)</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Return to heavy drinking</td>
<td>2</td>
<td>615</td>
<td>RD: −0.01 (−0.14 to 0.13)</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>% DDs</td>
<td>1</td>
<td>315</td>
<td>WMD: −8.6 (−16.0 to −1.2)</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>% HDDs</td>
<td>2</td>
<td>926</td>
<td>WMD: −4.6 (−8.5 to −0.56)</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Drinks per DD</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Naltrexone (any dose)</td>
<td>Accidents or injuries</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Qol or function</td>
<td>4</td>
<td>1513</td>
<td>Some conflicting results</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>6</td>
<td>1738</td>
<td>1 event (naltrexone) vs 2 events (placebo)</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

Abbreviations: DD, drinking day; FDA, US Food and Drug Administration; HDD, heavy drinking day; NA, not applicable; NNT, number needed to treat; NSD, no statistically significant difference; Qol, quality of life; RD, risk difference; WMD, weighted mean difference.

* Includes only studies rated as low or medium risk of bias that were included in the main analyses; these numbers do not include studies rated as high or unclear risk of bias that were only included in sensitivity analyses.

* Negative effect sizes favor intervention over placebo/control. For dichotomous outcomes, RDs show the absolute difference between groups for the outcome. For example, the RD of −0.09 for acamprosate compared with placebo for return to any drinking indicates that 9% fewer participants treated with acamprosate (than with placebo) returned to any drinking. For continuous outcomes, the WMDs represent the mean difference between groups; they are the same units as the outcome specified. For example, a WMD of −8.8 for acamprosate compared with placebo for percentage of drinking days indicates 8.8% fewer drinking days over the course of treatment for those treated with acamprosate than for those who received placebo.

* NA entry for NNT indicates that the RD (95% CI) was not statistically significant, so we did not calculate a NNT, or that the effect measure was not one that allows direct calculation of NNT (eg, WMD).

* One study (n = 128) reported similar percentages and no significant difference; the other reported that disulfiram was favored among the subset of participants (162/605 participants) who drank and had a complete set of assessment interviews, but it did not report this outcome for the full randomized sample. Overall, evidence was insufficient due to imprecision, inconsistency, and indirectness.

* Contains data from personal communication (B. Silverman, November 14, 2013).

* Unable to pool data. Two studies found no significant difference between naltrexone- and placebo-treated participants. One study reported that patients receiving injectable naltrexone, 380 mg/d, had greater improvement on the mental health summary score than those receiving placebo at 24 weeks (8.2 vs 6.2, P = .04). One study measured alcohol-related consequences and reported that more participants who received placebo (n = 34) had at least 1 alcohol-related consequence than those who received naltrexone (n = 34): 76% vs 45%, P = .02.
Post hoc subgroup analyses by risk of bias (separating studies rated as low risk of bias) did not reveal any notable differences or were underpowered to find differences for most outcomes and medications (eFigures 3 through 10 in the Supplement). However, the subgroup analysis for return to any drinking for acamprosate compared with placebo showed a decreasing effect size from high/unclear (RD, −0.13; 95% CI, −0.20 to −0.06; 3 trials, n = 757) or medium (RD, −0.11; 95% CI, −0.16 to −0.06; 12 trials, n = 3438) to low (RD, −0.20; 95% CI, −0.09 to 0.05; 4 trials, n = 1409) risk of bias (eFigure 3 in the Supplement).

**Figure 2. Return to Any Drinking for Selected Medications Compared With Placebo**

<table>
<thead>
<tr>
<th>Source</th>
<th>Duration, wk</th>
<th>Risk of Bias</th>
<th>Events, No.</th>
<th>Events, No.</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acamprosate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anton et al, 2006</td>
<td>16</td>
<td>Low</td>
<td>244</td>
<td>59</td>
<td>254</td>
</tr>
<tr>
<td>Baltieri et al, 2004</td>
<td>12</td>
<td>Med</td>
<td>15</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Berger et al, 2013</td>
<td>12</td>
<td>Med</td>
<td>48</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>Besson et al, 1998</td>
<td>51</td>
<td>Med</td>
<td>41</td>
<td>14</td>
<td>47</td>
</tr>
<tr>
<td>Chick et al, 2000</td>
<td>24</td>
<td>Med</td>
<td>254</td>
<td>35</td>
<td>260</td>
</tr>
<tr>
<td>Geerlings et al, 1997</td>
<td>26</td>
<td>Med</td>
<td>96</td>
<td>32</td>
<td>116</td>
</tr>
<tr>
<td>Guat et al, 2001</td>
<td>26</td>
<td>Med</td>
<td>92</td>
<td>49</td>
<td>109</td>
</tr>
<tr>
<td>Kiefer et al, 2003</td>
<td>12</td>
<td>Low</td>
<td>30</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>Mason et al, 2006</td>
<td>24</td>
<td>Low</td>
<td>12</td>
<td>38</td>
<td>240</td>
</tr>
<tr>
<td>Morley et al, 1996</td>
<td>12</td>
<td>Low</td>
<td>44</td>
<td>11</td>
<td>50</td>
</tr>
<tr>
<td>Pailie et al, 1995</td>
<td>51</td>
<td>Med</td>
<td>294</td>
<td>67</td>
<td>157</td>
</tr>
<tr>
<td>Pelt et al, 1997</td>
<td>13</td>
<td>Med</td>
<td>74</td>
<td>52</td>
<td>53</td>
</tr>
<tr>
<td>Polodrugo et al, 1997</td>
<td>26</td>
<td>Med</td>
<td>63</td>
<td>59</td>
<td>84</td>
</tr>
<tr>
<td>Sass et al, 1996</td>
<td>48</td>
<td>Med</td>
<td>75</td>
<td>61</td>
<td>102</td>
</tr>
<tr>
<td>Tempesta et al, 2000</td>
<td>26</td>
<td>Med</td>
<td>87</td>
<td>77</td>
<td>115</td>
</tr>
<tr>
<td>Whitworth et al, 1996</td>
<td>52</td>
<td>Med</td>
<td>183</td>
<td>41</td>
<td>208</td>
</tr>
<tr>
<td>Subtotal:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Naltrexone (100 mg/d oral) | | | | | | | |
| Alan et al, 2006 | 16 | Low | 241 | 68 | 254 | 55 | −0.04 (−0.10 to 0.02) |
| Oslin et al, 2008 | 24 | Med | 95 | 25 | 96 | 24 | −0.01 (−0.11 to 0.09) |
| Pettinini et al, 2010 | 14 | Med | 39 | 10 | 30 | 9 | 0.03 (−0.15 to 0.20) |

| Naltrexone injection | | | | | | | |
| Garbutt et al, 2005 | 26 | Med | 388 | 27 | 198 | 11 | −0.01 (−0.05 to 0.03) |
| Kranzler et al, 2004 | 12 | Med | 130 | 28 | 141 | 16 | −0.08 (−0.15 to 0.00) |

Weights are from random-effects analysis. Size of data markers reflects study weight. Med indicates medium.
ment). Although the confidence intervals for pooled estimates of all subgroup overlaps were significant, the pooled estimate for the low risk of bias subgroup was not statistically significant, and the 2 studies rated as low risk of bias that contributed the largest number of events found lack of efficacy for acamprosate.

Our meta-analyses of head-to-head RCTs comparing acamprosate with naltrexone found no statistically significant difference between the 2 medications (Table 2). COMBINE was one of the RCTs. It found that patients receiving medical management with naltrexone, a combined behavioral intervention, or both had better drinking outcomes than those who received placebo, but acamprosate showed no evidence of efficacy.

For the vast majority of medications used off-label, evidence was either insufficient to determine whether they are associated with reduced consumption or evidence suggested that they are not (eTable 5 in the Supplement). We found some exceptions (eTable 5, Figure 3). For topiramate, evidence sup-

### Table 2: Return to Heavy Drinking for Selected Medications Compared With Placebo

<table>
<thead>
<tr>
<th>Source</th>
<th>Duration, wk</th>
<th>Risk of Bias</th>
<th>Events, No.</th>
<th>No Events, No.</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acamprosate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anton et al, 2006</td>
<td>16</td>
<td>Low</td>
<td>211</td>
<td>92</td>
<td>226</td>
</tr>
<tr>
<td>Chick et al, 2000</td>
<td>24</td>
<td>Med</td>
<td>246</td>
<td>43</td>
<td>242</td>
</tr>
<tr>
<td>Kiefer et al, 2003</td>
<td>12</td>
<td>Med</td>
<td>25</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Mann et al, 2013</td>
<td>12</td>
<td>Med</td>
<td>89</td>
<td>83</td>
<td>41</td>
</tr>
<tr>
<td>Mason et al, 2006</td>
<td>24</td>
<td>Low</td>
<td>143</td>
<td>198</td>
<td>119</td>
</tr>
<tr>
<td>Morley et al, 2006</td>
<td>12</td>
<td>Low</td>
<td>40</td>
<td>15</td>
<td>43</td>
</tr>
<tr>
<td>Wolter et al, 2011</td>
<td>24</td>
<td>Med</td>
<td>65</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>Subtotal: $I^2=0.0%; P=0.67$</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Naltrexone (100 mg/d oral)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anton et al, 2006</td>
<td>16</td>
<td>Low</td>
<td>207</td>
<td>102</td>
<td>226</td>
</tr>
<tr>
<td>Oslin et al, 2008</td>
<td>24</td>
<td>Med</td>
<td>73</td>
<td>47</td>
<td>76</td>
</tr>
<tr>
<td>Subtotal: $I^2=0.0%; P=0.61$</td>
<td></td>
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</table>

<table>
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<tr>
<th>Naltrexone (50 mg/d oral)</th>
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<tbody>
<tr>
<td>Anton et al, 1999</td>
<td>12</td>
<td>Med</td>
<td>26</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>Anton et al, 2005</td>
<td>12</td>
<td>Med</td>
<td>33</td>
<td>48</td>
<td>46</td>
</tr>
<tr>
<td>Baldin et al, 2003</td>
<td>24</td>
<td>Low</td>
<td>53</td>
<td>3</td>
<td>58</td>
</tr>
<tr>
<td>Chick et al, 2000</td>
<td>12</td>
<td>Med</td>
<td>57</td>
<td>28</td>
<td>53</td>
</tr>
<tr>
<td>Gastpar et al, 2002</td>
<td>12</td>
<td>Med</td>
<td>34</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td>Guardia et al, 2002</td>
<td>12</td>
<td>Med</td>
<td>8</td>
<td>93</td>
<td>19</td>
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<tr>
<td>Kiefer et al, 2003</td>
<td>12</td>
<td>Low</td>
<td>20</td>
<td>20</td>
<td>30</td>
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<tr>
<td>Killeen et al, 2004</td>
<td>12</td>
<td>Med</td>
<td>21</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>Krystal et al, 2001</td>
<td>12</td>
<td>Med</td>
<td>183</td>
<td>235</td>
<td>105</td>
</tr>
<tr>
<td>Latt et al, 2002</td>
<td>12</td>
<td>Med</td>
<td>19</td>
<td>37</td>
<td>27</td>
</tr>
<tr>
<td>Mann et al, 2012</td>
<td>12</td>
<td>Med</td>
<td>86</td>
<td>83</td>
<td>41</td>
</tr>
<tr>
<td>Monti et al, 2001</td>
<td>12</td>
<td>Med</td>
<td>16</td>
<td>48</td>
<td>19</td>
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<tr>
<td>Morley et al, 2006</td>
<td>12</td>
<td>Low</td>
<td>39</td>
<td>14</td>
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<tr>
<td>Morris et al, 2001</td>
<td>12</td>
<td>Med</td>
<td>28</td>
<td>27</td>
<td>43</td>
</tr>
<tr>
<td>O'Malley et al, 1992</td>
<td>12</td>
<td>Med</td>
<td>24</td>
<td>28</td>
<td>34</td>
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<tr>
<td>O'Malley et al, 2007</td>
<td>12</td>
<td>Med</td>
<td>39</td>
<td>18</td>
<td>32</td>
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<tr>
<td>O'Malley et al, 2008</td>
<td>16</td>
<td>Med</td>
<td>22</td>
<td>12</td>
<td>28</td>
</tr>
<tr>
<td>Oslin et al, 1999</td>
<td>12</td>
<td>Med</td>
<td>3</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Volpicelli et al, 1997</td>
<td>12</td>
<td>Med</td>
<td>17</td>
<td>31</td>
<td>26</td>
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<td>Subtotal: $I^2=43.7%; P=0.02$</td>
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<table>
<thead>
<tr>
<th>Naltrexone injection</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>ALK21-01476</td>
<td>12</td>
<td>Med</td>
<td>90</td>
<td>62</td>
<td>78</td>
</tr>
<tr>
<td>Kranzler et al, 2004</td>
<td>12</td>
<td>Med</td>
<td>122</td>
<td>36</td>
<td>132</td>
</tr>
<tr>
<td>Subtotal: $I^2=72.2%; P=0.06$</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Valproic acid</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Brady et al, 2002</td>
<td>12</td>
<td>Med</td>
<td>5</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Salloum et al, 2005</td>
<td>24</td>
<td>Med</td>
<td>12</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Subtotal: $I^2=0.0%; P=0.33$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Weights are from random-effects analysis. Size of data markers reflects study weight. Med indicates medium.
ports an association with fewer drinking days (WMD, −6.5%; 95% CI, −12.0% to −1.0%; 2 trials, \(^{77,79} n = 541\)), heavy drinking days (WMD, −9.0%; 95% CI, −15.3% to −2.7%; 3 trials, \(^{77-79} n = 691\)), and drinks per drinking day (WMD, −1.0%; 95% CI, −1.6 to −0.48; 3 trials, \(^{77-79} n = 691\)). For nalmefene, evidence supports an association with fewer heavy drinking days per month (WMD, −2.0; 95% CI, −3.0 to −1.0; 2 trials, \(^{80,81} n = 806\)) and drinks per drinking day (WMD, −1.02; 95% CI, −1.77 to −0.28; 3 trials, \(^{41,82,83} p = 0.68\)). Finally, limited evidence from 2 small RCTs\(^{42,43}\) (total \(n = 88\)), one enrolling people with bipolar disorder, supports an association between valproic acid and improvement in some consumption outcomes.

Health Outcomes

We found insufficient direct evidence from RCTs to determine whether or not treatment with medications leads to improvement in health outcomes (Table 1 and eTable 5 in the Supplement). Very few trials reported health outcomes, and the included trials were not designed or powered to assess health outcomes: they typically focused on consumption outcomes. COMBINE reported some evidence of improvement in quality of life with naltrexone plus behavioral intervention (on the physical health scale from the 12-item Short Form health survey, version 2), but the difference between groups did not reach a clinically meaningful threshold.\(^{33}\)

Adverse Effects

There was insufficient evidence regarding many potential adverse events precluding determination of risks associated with these medications. In most cases, inadequate precision (ie, wide confidence intervals that contained clinically distinct conclusions) resulted in our inability to arrive at conclusions about medication risk. For most of the specific adverse events, point estimates favored placebo (ie, more adverse events with medications), but differences were not statistically significant. In head-to-head studies, the risk of withdrawal due to adverse events was not significantly different between acamprosate and naltrexone, but the risks of headache and vomiting were slightly higher for those treated with naltrexone (eTable 6 in the Supplement).

Compared with placebo, patients treated with naltrexone or nalmefene had a higher risk of withdrawal from trials due to adverse events (NNH, 48; 95% CI, 30 to 112; 17 trials, \(n = 2743\); and NNH, 12; 95% CI, 7 to 50; 5 trials, \(n = 2054\), respectively); we found no significant difference for acamprosate or topiramate. Compared with placebo, patients treated with acamprosate had a higher risk of anxiety (NNH, 7; 95% CI, 5 to 11; 2 trials, \(n = 624\)), diarrhea (NNH, 11; 95% CI, 6 to 34; 12 trials, \(n = 2978\)), and vomiting (NNH, 42; 95% CI, 24 to 143; 4 trials, \(n = 1817\))

Discussion

When used in conjunction with psychosocial co-interventions, addition of several medications resulted in better alcohol consumption outcomes. Acamprosate and oral naltrexone (50 mg/d) have the best evidence supporting their benefits. Trials comparing these medications have not established a difference in outcomes between them.

When clinicians decide to use one of the medications, a number of factors may help with choosing which medication to prescribe, including the medication’s efficacy, administration frequency, cost, adverse events, and availability. In some health systems, these medications may not be on the formulary. Acamprosate is given 3 times daily and is somewhat less convenient to use than oral naltrexone that only requires 1 daily tablet. Acamprosate is contraindicated with severe renal impairment and oral naltrexone is contraindicated with acute hepatitis, liver failure, concurrent opioid use, or an anticipated need for opioids.\(^{34}\)

Because of its long-standing availability, clinicians may be more familiar with disulfiram than naltrexone or acamprosate. However, well-controlled trials of disulfiram did not show overall reductions in alcohol consumption. In a subgroup analysis of the largest disulfiram trial,\(^{35}\) there were fewer drinking days for patients who returned to drinking and had a complete set of assessments. This suggests that disulfiram may benefit some AUD patients. However, none of the disulfiram trials

---

Table 2. Summary of Findings and Strength of Evidence From Double-Blind Randomized Clinical Trials Directly Comparing Acamprosate and Naltrexone

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>Results Effect Size (95% CI)</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to any drinking</td>
<td>3</td>
<td>800</td>
<td>RD: 0.02 (−0.03 to 0.08)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Return to heavy drinking</td>
<td>4</td>
<td>1141</td>
<td>RD: 0.01 (−0.05 to 0.06)</td>
<td>Moderate</td>
</tr>
<tr>
<td>% DDs</td>
<td>2</td>
<td>720</td>
<td>WMD: −2.98 (−13.4 to 7.5)</td>
<td>Low</td>
</tr>
</tbody>
</table>

Abbreviations: DD, drinking day; RD, risk difference; WMD, weighted mean difference.

* We did not include rows in this table for outcomes that we graded as insufficient strength of evidence (percentage heavy drinking days, drinks per DD, accidents or injuries, quality of life or function, and mortality).

** Includes only studies rated as low or medium risk of bias included in the main analyses; these numbers do not include studies rated as high or unclear risk of bias that were included in sensitivity analyses.

* Negative effect sizes favor acamprosate over naltrexone.
evaluated supervised medication delivery, potentially under-
estimating the benefits of the drug when used in supervised

treatment programs.

The evidence from trials was insufficient to make any con-
clusions about improved health outcomes attributable to
pharmacotherapy of AUDs. Epidemiologic studies con-
sistently relate high average alcohol consumption and
heavy per-occasion use to increased risks for health prob-
lems. These include cancers (eg, mouth, esophagus, colon,
liver, and breast); cognitive impairment; liver cirrhosis; chronic
pancreatitis; stroke; depression; suicide; and injuries and
violence.\(^5,85-93\) Given the epidemiologic evidence for adverse
health consequences of heavy alcohol use, improved health
outcomes should occur with AUD treatment. A recent model-
ing study estimated that increasing treatment coverage to 40%
of all people with alcohol dependence in the European Union
would reduce alcohol-attributable mortality by up to 13%.\(^92\)
Several AUD treatment combinations including pharma-
cotherapy, when compared with placebo plus medical manage-
ment, reduced costs from health care, arrests, and motor ve-
cicle accidents in a cost analysis of the COMBINE trial.\(^93\)

Applicability of Findings
All participants met criteria for alcohol dependence in most
of the studies we reviewed. Based on the studies’ time pe-
riod, they used Diagnostic and Statistical Manual of Mental Dis-
orders (DSM) Third Edition or Fourth Edition criteria for alco-
hol dependence. The Fifth Edition, DSM-5, was released in 2013
and describes a single AUD category measured on a con-
tinuum from mild to severe (eTable 1 in the Supplement).
DSM-5 no longer has separate categories for alcohol abuse and
dependence.\(^94,95\) Using DSM-5 terminology, most partici-
pants in the studies we reviewed likely had moderate to se-
vere AUDs. As a consequence, applicability of our findings re-
garding pharmacological treatment for AUDs to patients with
mild disorders is uncertain. The mean age of participants was
generally in the 40s. We did not find evidence to confirm or
refute whether treatments are likely to be more or less ben-
eficial for older or younger subgroups, different sex groups,
racial or ethnic minorities, smokers or nonsmokers, and those
with certain coexisting conditions.\(^9\)

The majority of placebo-controlled trials assessing acam-
prosate were conducted in Europe (16/22) and a minority were
conducted in the United States (4/22). In contrast, the op-
opposite occurred for naltrexone: 27 of 44 trials were conducted
in the United States and 8 of 44 were carried out in Europe.
The few US-based acamprosate studies did not find it to be effica-
cious. The European trials of acamprosate typically identi-
fied patients from inpatient settings or treatment programs,
whereas the US-based trials recruited patients using adver-
sitements and referrals. Differences in how patients were re-
cruited into the trials might have resulted in populations with
ting AUD severity and differing potential for benefit.

Most studies required patients to abstain for at least a few
days prior to initiating medication. Medications for AUDs are
generally recommended for maintenance of abstinence. Acam-
prosate and injectable naltrexone are only approved for use in
patients who have established abstinence. However, some

studies enrolled patients who were not yet abstinent and re-
ported reduced heavy drinking with naltrexone\(^44,96\) or
acamprosate.\(^45\)

Applicability to Primary Care Settings
The US Preventive Services Task Force recommends screen-
ing adults for alcohol misuse.\(^97\) Screening will inevitably iden-
tify some individuals with AUDs. Clinicians must then decide
whether to refer to specialized treatment or intervene within
their practice. Like primary care–based behavioral counsel-
ing interventions for risky drinking, implementing pharma-
cotherapy and psychosocial interventions for AUDs may re-
quire formal protocols, staffing (eg, multidisciplinary team-
based care), support systems, and additional provider and staff
training.\(^86,98\) Some experts advocate chronic care manage-
ment, a systematic approach to treatment and follow-up simi-
lar to how the health care system approaches heart failure, dia-
betes, and other chronic diseases.\(^79\)

Barriers to prescribing medications for AUDs in primary
care may include lack of familiarity with the medications,
lack of confidence in their effectiveness, or inability to provide suit-
able psychosocial co-interventions—eg, because of compet-
ding demands or insufficient practice resources, personnel, or
training. Historically, primary care providers have referred
patients with AUDs for specialized treatment. However, these
medications are underutilized,\(^100,101\) and many patients
may not be willing to pursue or may not have access to spe-
cialized treatment. Thus, offering treatment through pri-
mary care has the potential to reduce morbidity for many pa-
tients with AUDs.

We found scant evidence from primary care settings. One
trial (n = 100) that recruited participants primarily by adver-
sitement in 2 family medicine settings found no significant
treatment effect for acamprosate.\(^46\) The only other trial meet-
ing our inclusion criteria conducted in primary care settings
compared nalmefene with placebo in 15 sites (about half were
primary care) in Finland.\(^83\) It found no significant differ-
cence in percentage of drinking days but reported a lower per-
centage of heavy drinking days (18.1% vs 29.7%, \(P = .02\)) and fewer
drinks per drinking day (WMD, −1.0; 95% CI, −2.0 to −0.02) for
patients treated with nalmefene than for those who received
placebo.

Some included studies conducted in non–primary care set-
tings used interventions that could be adapted for delivery in
primary care. For example, in the COMBINE study,\(^39\) provid-
ers delivered a medical management intervention comprised
of up to 9 manual-guided counseling visits (at weeks 0, 1, 2, 4,
6, 8, 10, 12, and 16). The first visit was approximately 45 min-
utes, and follow-up visits were about 20 minutes each. Medi-
cal management included advice for reducing drinking, in-
quiries about medication adverse effects, and emphasis on the
importance of adherence. Participants were encouraged to at-
tend support groups available in the community (eg, Alcohol-
provides direction for clinicians to provide medical manage-
ment, a combined behavioral intervention, and medical treat-
ment with naltrexone or acamprosate as provided in the
COMBINE trial.\(^102\)
Regarding implementation of treatment programs for AUDs in primary care, we identified 4 other publications that did not meet our inclusion criteria (because of study design or comparators) that have important implications.103-106 Although these studies found conflicting results, they demonstrate approaches to managing AUDs in primary care. Further details of these studies are available in the eDiscussion in the Supplement. In general, the interventions involve formal clinic structure, staffing, and protocols. They used variations of chronic care management, multidisciplinary team-based care, and care coordination between primary care and mental health providers.

Limitations
We only considered trials with at least 12 weeks of treatment. Longitudinal studies have found that shorter treatment periods may yield misleading conclusions about benefits, due to fluctuations in drinking typical of the course of AUDs.107,108 Next, we did not assess how medications and psychosocial interventions compare with each other. Our review focused on studies assessing benefits and harms of medications and how they compare with other medications, and our findings reflect the added benefits of medications beyond those of psychosocial co-interventions. Studies used a variety of different psychosocial co-interventions. This heterogeneity limits our certainty about the benefits of medications when used alone (with no co-intervention) or when added to a particular psychosocial intervention. Further, we did not specifically assess benefits for patients without a goal of abstinence.

We combined studies that included populations with a dual diagnosis (eg, alcohol dependence and depression) and those that did not in our meta-analyses. To determine whether this potential population heterogeneity had a significant influence on our conclusions, we conducted sensitivity analyses for acamprosate and naltrexone, stratifying by whether or not studies reported enrolling a dual diagnosis population (data in full report9). Effect sizes did not change significantly.

Most studies were rated as medium risk of bias. We rated few studies as low risk of bias (8/123 included studies; 4/27 studies assessing acamprosate; and 4/53 studies assessing naltrexone). Most studies rated as medium, rather than low, risk of bias lacked complete reporting of information about several of the following: randomization sequence generation, allocation concealment, fidelity, adherence, or outcome assessor masking. For most outcomes and medications, our post hoc subgroup analyses separating studies rated as low risk of bias did not suggest notable differences or were underpowered to find differences. But a subgroup analysis for return to any drinking for acamprosate showed that the pooled effect of the studies rated as low risk of bias found no significant difference between acamprosate and placebo. Possible explanations include population differences (eg, severity, country), other heterogeneity, no true association between acamprosate and return to drinking (ie, the effect found in overall pooled analyses represents bias), random error, or a combination of these factors. The 2 studies (out of 4) rated as low risk of bias that contributed by far the largest number of events were both conducted in the United States and relied on advertisements and referrals to identify participants. In contrast, the vast majority of the 15 studies rated as medium, high, or unclear risk of bias were conducted in European countries (1 was in the United States and 1 in Brazil) and typically identified patients from inpatient settings or treatment programs. It is possible that this resulted in populations with differing AUD severity and differing potential for benefit or that having gone through a program may increase adherence to treatments and improve potential for benefit.

In addition, publication bias and selective reporting are potential limitations. However, funnel plots did not raise concern for publication bias, and we searched for unpublished studies and unpublished outcomes and did not find direct evidence of either of these biases.

Conclusions
Both acamprosate and oral naltrexone (50 mg/d) were associated with reduction in return to drinking. They have the best evidence for improving alcohol consumption outcomes for patients with AUDs. Head-to-head trials have not established superiority of either medication. Among medications used off-label, moderate evidence supports an association with improvement in some consumption outcomes for nalmefene and topiramate.
drafts of the manuscript. Approval from AHRQ was required before the manuscript could be submitted for publication, but the authors are solely responsible for its content and the decision to submit it for publication. AHRQ staff did not participate in the conduct of the review, data collection, data management, data analysis, interpretation of the data, or preparation of the manuscript.

Disclaimer: Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the US Dept of Health and Human Services.

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