Appendix 16e: pharmacological interventions study characteristics table

Study characteristics for acamprosate ................................................................. 1
Study characteristics for naltrexone ................................................................. 15
Study characteristics for acamprosate + naltrexone ....................................... 37
Study characteristics for disulfiram (oral) ....................................................... 41
Characteristics of studies excluded from all clinical questions ....................... 46
### Study characteristics for acamprosate

**Acamprosate vs Naltrexone**
- ANTON2006
- KIEFER2003
- MORLEY2006
- RUBIO2001

**Acamprosate vs Placebo**
- ANTON2006
- BALTIER2003
- BARRIAS1997
- BESSON1998
- CHICK2000A
- GEERLINGS1997
- GUAL2001
- KIEFER2003
- LADEWIG1993
- MORLEY2006
- NAMKOONG2003
- PAILE1995
- PELC1992
- PELC1997
- POLDRUGO1997
- ROUSSEAU1996
- SASS1996
- TEMPESTA2000
- WHITWORTH1996

<table>
<thead>
<tr>
<th>Study Type: RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Analysis: ITT- as long as baseline data</td>
</tr>
<tr>
<td>Blindness: Double blind</td>
</tr>
<tr>
<td>Duration (days): Mean 112</td>
</tr>
<tr>
<td>Followup: 1 year</td>
</tr>
<tr>
<td>Setting: recruited from 11 sites, by advertisements or clinical referrals.</td>
</tr>
</tbody>
</table>

Notes: Randomisation: permuted block design, using blocks of 9 stratified by site. Implemented via central telephone-based interactive voice response system.

Info on Screening Process: Approximately n=5000 were screened by telephone or in person, but only n=1383 were eligible after assessment.

#### ANTON2006
- n = 1383
- Age: Median 44
- Sex: 955 males, 428 females
- 100% Alcohol Dependence by DSM IV

Exclusions: <18 years of age, no DSM diagnosis of alcohol dependence, drinking less than 14 drinks a week if female, less than 21 drinks a week if male, less than 4 consecutive days abstinent or more than 21. Further criteria: meeting DSM criteria for major psychiatric disorder or psychological disorder requiring medication, current dependence on any drug except nicotine, cannabis or alcohol, meeting DSM criteria for opioid dependence in past 6 months, significant medical disorder, abnormal AST or ALT(3 times upper limit), participants who are pregnant, nursing or not using adequate birth control, individuals intending to engage other treatments for alcohol problems, individuals with previous

#### Data Used
- Relapse
- % days abstinent
- Leaving due to adverse events
- Leaving study early

#### N = 154
- Naltrexone. Mean dose 100mg/day - Dose of 25mg over first 4 days, dose of 50mg over next 4 days and then 100mg a day for the rest of the study. Placebo acamprosate also taken.
- Medication management - Delivered by licensed healthcare professional over 9 sessions in which pills were dispensed. Initial visit was for 45 minutes, professional recommended abstinence and provided education about alcohol and the study medications. Encouraged AA.

Study was supported by grants from the NIAAA. Acamprosate, Naltrexone and matching placebos were donated by Lippa Pharmaceuticals.

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**Appendix 16e**
Acamprosate. Mean dose 3g/day - Two 500mg tablets taken three times daily (6 tablets in total daily). Could be lowered if required. Placebo naltrexone also taken. Medication management - Delivered by licensed healthcare professional over 9 sessions in which pills were dispensed. Initial visit was for 45 minutes, professional recommended abstinence and provided education about alcohol and the study medications. Encouraged AA.

Naltrexone + Acamprosate - Combines the dosing schedule for naltrexone and acamprosate alone interventions. Medication management - Delivered by licensed healthcare professional over 9 sessions in which pills were dispensed. Initial visit was for 45 minutes, professional recommended abstinence and provided education about alcohol and the study medications. Encouraged AA.

Placebo - Inactive placebo tablets identical in appearance to active acamprosate and naltrexone taken on the same dosing schedule as the active interventions. Medication management - Delivered by licensed healthcare professional over 9 sessions in which pills were dispensed. Initial visit was for 45 minutes, professional recommended abstinence and provided education about alcohol and the study medications. Encouraged AA.

Naltrexone - Dose of 25mg over first 4 days, dose of 50mg over next 4 days and then 100mg a day for the rest of the study. Placebo acamprosate also taken. Combined behavioural intervention + MM - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement. Medication management also provided.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Naltrexone (mg)</th>
<th>Acamprosate (g)</th>
<th>Placebo</th>
<th>Combined Behavioural Intervention (sessions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLB+MM</td>
<td>148</td>
<td>12.6 (7.67)</td>
<td>18.9 (24.74)</td>
<td>44.4</td>
<td>18.9 (24.74)</td>
</tr>
<tr>
<td>NALX+MM</td>
<td>148</td>
<td>12.7 (7.69)</td>
<td>19.1 (24.70)</td>
<td>38.3</td>
<td>19.1 (24.70)</td>
</tr>
<tr>
<td>ACAM+MM</td>
<td>148</td>
<td>12.2 (7.77)</td>
<td>16.3 (24.76)</td>
<td>36.2</td>
<td>16.3 (24.76)</td>
</tr>
<tr>
<td>ACAM+MM</td>
<td>148</td>
<td>12.4 (7.66)</td>
<td>18.6 (24.70)</td>
<td>42.6</td>
<td>18.6 (24.70)</td>
</tr>
<tr>
<td>ACAM+MM</td>
<td>148</td>
<td>12.4 (7.72)</td>
<td>18.6 (24.76)</td>
<td>37.4</td>
<td>18.6 (24.76)</td>
</tr>
<tr>
<td>ACAM+MM</td>
<td>148</td>
<td>12.2 (7.77)</td>
<td>18.3 (24.68)</td>
<td>43.3</td>
<td>18.3 (24.68)</td>
</tr>
<tr>
<td>ACAM+CBI</td>
<td>148</td>
<td>12.2 (7.77)</td>
<td>18.3 (24.5)</td>
<td>41.4</td>
<td>18.3 (24.5)</td>
</tr>
<tr>
<td>CBI only</td>
<td>148</td>
<td>11.8 (7.66)</td>
<td>17.7 (25.35)</td>
<td>69.4</td>
<td>17.7 (25.35)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>12.4 (7.66)</td>
<td>18.6 (24.70)</td>
<td>43.3</td>
<td>18.6 (24.70)</td>
</tr>
</tbody>
</table>

Notes: Participants were required to acknowledge a desire to stop drinking. They were also required to be drinking at least 21 drinks a week if male, 14 drinks a week if female. Recommended abstinence.
<table>
<thead>
<tr>
<th>N</th>
<th>Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>N= 151</td>
</tr>
<tr>
<td></td>
<td>Acamprosate - Two 500mg tablets taken three times daily (6 tablets in total daily). Could be lowered if required. Placebo naltrexone also taken. Combined behavioural intervention + MM - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement. Medication management also provided.</td>
</tr>
<tr>
<td>7</td>
<td>N= 157</td>
</tr>
<tr>
<td></td>
<td>Naltrexone + Acamprosate - Combines the dosing schedule for naltrexone and acamprosate alone interventions Combined behavioural intervention + MM - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement. Medication management also provided.</td>
</tr>
<tr>
<td>8</td>
<td>N= 156</td>
</tr>
<tr>
<td></td>
<td>Placebo - Inactive placebo tablets identical in appearance to active acamprosate and naltrexone taken on the same dosing schedule as the active interventions. Combined behavioural intervention + MM - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement. Medication management also provided.</td>
</tr>
<tr>
<td>9</td>
<td>N= 157</td>
</tr>
<tr>
<td></td>
<td>Combined behavioural intervention - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement.</td>
</tr>
</tbody>
</table>

**BALTIERI2003**

**Study Type:** RCT

**Type of Analysis:** ITT - all taking one dose of study medication

- n= 75
- Age: Mean 44 Range 18-59
- Sex: all males
- 100% Alcohol Dependence by ICD-10

**Data Used**

- Abstinent at endpoint
- Leaving study early

- Acamprosate. Mean dose 1998mg/day - No details on dosing schedule.

**Funding:** no details
<table>
<thead>
<tr>
<th>Study Type: RCT</th>
<th>Study Type: RCT</th>
<th>Study Type: RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Analysis: ITT - all taking one dose of study medication</td>
<td>Type of Analysis: ITT - all taking one dose of study medication</td>
<td>Type of Analysis: ITT - all taking one dose of study medication</td>
</tr>
<tr>
<td>Blinding: Double blind</td>
<td>Blinding: Double blind</td>
<td>Blinding: Double blind</td>
</tr>
<tr>
<td>Duration (days): Mean 365</td>
<td>Duration (days): Mean 365</td>
<td>Duration (days): Mean 365</td>
</tr>
<tr>
<td>Setting: Awaiting translation</td>
<td>Setting: Awaiting translation</td>
<td>Setting: Awaiting translation</td>
</tr>
<tr>
<td>Notes: No details</td>
<td>Notes: No details</td>
<td>Notes: No details</td>
</tr>
<tr>
<td>Exclusions: &lt;18 or &gt;59 years of age, Female, no diagnosis of alcohol dependence (ICD-10 criteria), weighing less than 60kg. Further criteria: clinical and psychiatric pathologies who needed treatment and previous psychotic, as well as use of psychiatric and non-psychiatric medications.</td>
<td>Exclusions: &lt;18 or &gt;59 years of age, Female, no diagnosis of alcohol dependence (ICD-10 criteria), weighing less than 60kg. Further criteria: clinical and psychiatric pathologies who needed treatment and previous psychotic, as well as use of psychiatric and non-psychiatric medications.</td>
<td>Exclusions: &lt;18 or &gt;59 years of age, Female, no diagnosis of alcohol dependence (ICD-10 criteria), weighing less than 60kg. Further criteria: clinical and psychiatric pathologies who needed treatment and previous psychotic, as well as use of psychiatric and non-psychiatric medications.</td>
</tr>
<tr>
<td>Baseline:</td>
<td>Baseline: Acam</td>
<td>Baseline: PLB</td>
</tr>
<tr>
<td>Average daily alcohol intake (g/day)</td>
<td>370.1 (164.9)</td>
<td>348.5 (132.46)</td>
</tr>
<tr>
<td>In UK units:</td>
<td>46.26</td>
<td>43.56</td>
</tr>
<tr>
<td>Data Used</td>
<td>% continuously abstinent</td>
<td>% continuously abstinent</td>
</tr>
<tr>
<td>Data Not Used</td>
<td>Relapse</td>
<td>Relapse</td>
</tr>
<tr>
<td>Abstinent at endpoint</td>
<td>Abstinent at endpoint</td>
<td></td>
</tr>
<tr>
<td>Abstinent at assessment</td>
<td>Abstinent at assessment</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>CAD</td>
<td></td>
</tr>
<tr>
<td>Leaving study early</td>
<td>Leaving study early</td>
<td></td>
</tr>
<tr>
<td>GGT - Not relevant</td>
<td>GGT - Not relevant</td>
<td></td>
</tr>
<tr>
<td>Notes: Relapse: any alcohol consumption. ONLY CAD is recorded for acamprosate vs acamprosate + Disulfiram, all other variables report acamprosate including disulfiram users and non-users.</td>
<td>Notes: Relapse: any alcohol consumption. ONLY CAD is recorded for acamprosate vs acamprosate + Disulfiram, all other variables report acamprosate including disulfiram users and non-users.</td>
<td>Notes: Relapse: any alcohol consumption. ONLY CAD is recorded for acamprosate vs acamprosate + Disulfiram, all other variables report acamprosate including disulfiram users and non-users.</td>
</tr>
<tr>
<td>Data Not Used</td>
<td>Not relevant</td>
<td>Not relevant</td>
</tr>
<tr>
<td>Notes: Not relevant</td>
<td>Notes: Not relevant</td>
<td></td>
</tr>
<tr>
<td>Notes: Majority of the outcomes are reported for Acamprosate vs Placebo, including disulfiram participants in each group.</td>
<td>Notes: Majority of the outcomes are reported for Acamprosate vs Placebo, including disulfiram participants in each group.</td>
<td>Notes: Majority of the outcomes are reported for Acamprosate vs Placebo, including disulfiram participants in each group.</td>
</tr>
<tr>
<td>Baseline:</td>
<td>Acamprosate</td>
<td>Placebo</td>
</tr>
<tr>
<td>MAST score:</td>
<td>30.5</td>
<td>32.7</td>
</tr>
<tr>
<td>Craving (VAS score):</td>
<td>42.4</td>
<td>37.4</td>
</tr>
</tbody>
</table>

**BARRIAS1997**

- Study Type: RCT
- Blindness: Double blind
- Duration (days): Mean 365
- Followup: six months
- Setting: Awaiting translation
- Exclusions: Awaiting translation

**BESSION1998**

- Study Type: RCT
- Blindness: Double blind
- Duration (days): Mean 360
- Setting: 3 psychiatric centres that treat participants on a voluntary basis for short to medium periods.
- Notes: Randomisation: stratified for voluntary intake of disulfiram
- Info on Screening Process: No details

---

**Notes:**

- Double blind
- Mean 84 days
- 2 N= 35
- Placebo - Inactive control intervention, no details on dosing schedule
- Psychosocial program - GREA - behavioural orientation, clinical assessment and encouragement to join AA (not mandatory)
- 2 N= 150
- Acamprosate - Awaiting translation
- 2 N= 152
- Placebo - Awaiting translation
- Funding: supported in part by state funds and Lipha, Inc.
- Relapse: any alcohol consumption.
- ONLY CAD is recorded for acamprosate vs acamprosate + Disulfiram, all other variables report acamprosate including disulfiram users and non-users.
- Mean 40 Range 21-64
- Sex: 278 males 24 females
- n= 302
- Age: Mean 42 Range 18-65
- Sex: 88 males 22 females
- n= 110
- Age: Mean 42 Range 18-65
- Sex: 88 males 22 females
- 100% Alcohol Dependence by DSM-III

---

**Baseline: Acam PLB**

<table>
<thead>
<tr>
<th>Alcohol intake (g/day)</th>
<th>Acamprosate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average daily</td>
<td>370.1 (164.9)</td>
<td>348.5 (132.46)</td>
</tr>
<tr>
<td>In UK units:</td>
<td>46.26</td>
<td>43.56</td>
</tr>
</tbody>
</table>

**Followup:** 12 weeks

**Setting:** Participants were enrolled as outpatients in a treatment clinic for drug dependence at the university of Sao Paulo.

**Duration (days): Mean 84**

**Blindness:** Double blind

**Info on Screening Process:** n=80 participants were screened, but n=5 were excluded because of coexisting diseases.

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**Notes:**

- Randomisation: stratified for voluntary intake of disulfiram.
<table>
<thead>
<tr>
<th>Study Type: RCT</th>
<th>n = 581</th>
<th>Data Used</th>
<th>CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Analysis: ITT - all taking one dose of study medication</td>
<td>Age: Mean 43 Range 18-65</td>
<td>% continuously abstinent</td>
<td>Leaving study early</td>
</tr>
<tr>
<td>Blindness: Single blind</td>
<td>Sex: 485 males 96 females</td>
<td>Data Not Used</td>
<td>HAM-A - Not relevant</td>
</tr>
<tr>
<td>Duration (days): Mean 168</td>
<td>100% Alcohol Dependence by DSM-III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Followup: 4 weeks</td>
<td>Exclusions: &lt;18 or &gt;65 years of age, no DSM-III diagnosis of alcohol dependence with at least a 12 month history, had not undertaken withdrawal in past 5 weeks, abstinent for &lt;5 days. Further exclusion: if receiving disulfiram, calcium carbimide, drugs known to induce hepatic enzymes (except oral contraceptives) or tranquilizers, abusing drugs in previous 12 months, had a serious medical or psychiatric disorder, were pregnant or at risk of becoming pregnant.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: 20 UK clinics, connected with psychiatric services and a general hospital.</td>
<td>Baseline: Acamprosate Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes: Randomisation: blocks of eight. Info on Screening Process: n=684 screened, n=83 dropped out (n=24 lost to follow-up, n=40 failed to meet inclusion criteria, n=3 worsening condition, n=10 changed minds about medication and n=6 gave no reason), n=581 randomised.</td>
<td>Prior weekly consumption: 188 units/week 168 units/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Married (%): 57 55</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Employed (%): 49 54</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CHICK2000A**

<table>
<thead>
<tr>
<th>Study Type: RCT</th>
<th>n = 289</th>
<th>Data Used</th>
<th>CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Analysis: ITT - all taking one dose of study medication</td>
<td>Age: Mean 43 Range 18-65</td>
<td>% continuously abstinent</td>
<td>Leaving study early</td>
</tr>
<tr>
<td>Blindness: Single blind</td>
<td>Sex: 485 males 96 females</td>
<td>Data Not Used</td>
<td>HAM-A - Not relevant</td>
</tr>
<tr>
<td>Duration (days): Mean 168</td>
<td>100% Alcohol Dependence by DSM-III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Followup: 4 weeks</td>
<td>Exclusions: &lt;18 or &gt;65 years of age, no DSM-III diagnosis of alcohol dependence with at least a 12 month history, had not undertaken withdrawal in past 5 weeks, abstinent for &lt;5 days. Further exclusion: if receiving disulfiram, calcium carbimide, drugs known to induce hepatic enzymes (except oral contraceptives) or tranquilizers, abusing drugs in previous 12 months, had a serious medical or psychiatric disorder, were pregnant or at risk of becoming pregnant.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: 20 UK clinics, connected with psychiatric services and a general hospital.</td>
<td>Baseline: Acamprosate Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes: Randomisation: blocks of eight. Info on Screening Process: n=684 screened, n=83 dropped out (n=24 lost to follow-up, n=40 failed to meet inclusion criteria, n=3 worsening condition, n=10 changed minds about medication and n=6 gave no reason), n=581 randomised.</td>
<td>Prior weekly consumption: 188 units/week 168 units/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Married (%): 57 55</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Employed (%): 49 54</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GEERLING1997**

<table>
<thead>
<tr>
<th>Study Type: RCT</th>
<th>n = 262</th>
<th>Data Used</th>
<th>CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Analysis: ITT - all taking one dose of study medication</td>
<td>Age: Mean 41 Range 18-65</td>
<td>Time to first relapse</td>
<td>Relapse</td>
</tr>
<tr>
<td>Blindness: Single blind</td>
<td>Sex: 199 males 63 females</td>
<td>Abstinent at assessment</td>
<td>CAD</td>
</tr>
<tr>
<td>Duration (days): Mean 168</td>
<td>100% Alcohol Dependence by DSM-III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Followup: 4 weeks</td>
<td>Exclusions: &lt;18 or &gt;65 years of age, no DSM-III diagnosis of alcohol dependence with at least a 12 month history, had not undertaken withdrawal in past 5 weeks, abstinent for &lt;5 days. Further exclusion: if receiving disulfiram, calcium carbimide, drugs known to induce hepatic enzymes (except oral contraceptives) or tranquilizers, abusing drugs in previous 12 months, had a serious medical or psychiatric disorder, were pregnant or at risk of becoming pregnant.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: 20 UK clinics, connected with psychiatric services and a general hospital.</td>
<td>Baseline: Acamprosate Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes: Randomisation: blocks of eight. Info on Screening Process: n=684 screened, n=83 dropped out (n=24 lost to follow-up, n=40 failed to meet inclusion criteria, n=3 worsening condition, n=10 changed minds about medication and n=6 gave no reason), n=581 randomised.</td>
<td>Prior weekly consumption: 188 units/week 168 units/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Married (%): 57 55</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Employed (%): 49 54</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Leaving study early

**Data Not Used**

CDT - Not relevant

2 N= 134

Placebo - inactive control intervention, dosing schedule identical to the active intervention

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GUAL2001

**Study Type:** RCT

**Type of Analysis:** ITT - all receiving one dose of study medication

**Blindness:** Double blind

**Duration (days):** Mean 180

**Followup: 12 weeks**

**Setting:** 11 outpatient hospital centres in Spain.

**Notes:** Randomisation: no details

Exclusions: <18 or >65 years of age, not meeting DSM-III criteria for alcohol dependence, <5 days abstinence before study start, participants potentially pregnant, had a serious somatic pathology (diabetes, hypertension, etc), impaired renal function, hypercalcaemia, use of psychotropic medication.

Baseline:
- **Acamprosate:** Placebo
- % of population drinking >10 drinks/day: 77 70

**Notes:** Randomisation: no details

**Setting:** 22 outpatient treatment centres in Benelux region

**Notes:** Randomisation: no details

**Exclusions:** <18 or >65 years of age, not meeting DSM-III criteria for alcohol dependence, <5 days abstinence before study start, participants potentially pregnant, had a serious somatic pathology (diabetes, hypertension, etc), impaired renal function, hypercalcaemia, use of psychotropic medication.

Baseline: Acamprosate Placebo
- % of population drinking >10 drinks/day: 77 70

**Setting:** 22 outpatient treatment centres in Benelux region

**Notes:** Randomisation: no details

**Data Used**

- Recorded craving
- Stable recovery duration
- CAD
- Abstinent at endpoint
- Leaving study early

**Data Not Used**

- CDT - Not relevant
- GGT - Not relevant

**Funding:** study sponsored by Merck Liphra Spain.

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KIEFER2003

**Study Type:** RCT

**Type of Analysis:** ITT

**Blindness:** Double blind

**Duration (days):** Mean 84

**Followup: 12 weeks**

**Setting:** All patients with alcoholism admitted to an inpatient alcohol withdrawal program in Hamburg

**Notes:** Randomisation: according to a computer-generated code. Allocation codes in sealed envelopes

**Info on Screening Process:** n=196 registered, n=16 excluded due to medical issues, n=9 due to concurrent treatment and n=11 declined study participation. n=160 randomised.

Exclusions: <18 or >65 years of age, <5 DSM-IV criteria for alcohol dependence, body weight <60 kg or >90 kg, abstinence for <12 days, displaying withdrawal symptoms, positive drug screening. Further exclusions: current mental/psychiatric impairment/disease that required medication or inpatient treatment, history of cocaine/opiate abuse, history of psychosis, current use of psychotropic medication, evidence of severe neurological/physical disorders, history of cirrhosis, homeless, pregnancy or refusal to use reliable birth control.

Baseline:
- OCDS VAS Married Partnership score (%)
- Placebo 18.2 (12.1) 23.7 (26.7) 30 55
- Acamprosate 20.1 (10.6) 23.6 (28.0) 23 48
- Naltrexone 17.9 (13.2) 18.6 (27.7) 25 58

**Notes:** Relapse was defined as 5 or more drinks for a man, 4 or more for a woman.

**Funding:** medication donated by DuPont (nalox) and Merck (Acam)

---

**Notes:**
- Randomisation: according to a computer-generated code. Allocation codes in sealed envelopes
- Relapse defined as 5 or more drinks for a man, 4 or more for a woman.
- Funding: study sponsored by Merck Liphra Spain.
- Medication dose constant throughout 12 week study period. 1998mg/day given in form of 2 tablets three times a day.
<table>
<thead>
<tr>
<th>Study</th>
<th>n= 61</th>
<th>Data Used</th>
<th>n= 29</th>
<th>Data Used</th>
<th>n= 169</th>
<th>Data Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>LADEWIG1993</td>
<td></td>
<td>% continuously abstinent</td>
<td></td>
<td></td>
<td>Time to first drink</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age: Mean 47 Range 26-70</td>
<td></td>
<td>Acamprosate</td>
<td></td>
<td>Relapse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex: 47 males 14 females</td>
<td></td>
<td>Placebo</td>
<td></td>
<td>Abstinent at endpoint</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exclusions: Awaiting translation</td>
<td></td>
<td>Awaiting translation</td>
<td></td>
<td>Drinks per drinking day</td>
<td></td>
</tr>
<tr>
<td>MORLEY2006</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td>Acamprosate. Mean dose 1998mg/day -</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study Type: RCT</td>
<td></td>
<td>N= 55</td>
<td></td>
<td>Participants took six 333mg tablets daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blindness: Double blind</td>
<td></td>
<td></td>
<td></td>
<td>Funding: supported by</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration (days): Mean 180</td>
<td></td>
<td></td>
<td></td>
<td>grants from the National</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Followup: six months</td>
<td></td>
<td></td>
<td></td>
<td>Health and Medical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Setting: Awaiting translation</td>
<td></td>
<td></td>
<td></td>
<td>Research Council of</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Australia and the University</td>
<td></td>
</tr>
</tbody>
</table>

- **Acam + Naix**
  - N= 40
  - Naltrexone. Mean dose 50mg/day - Medication dose constant throughout 12 week study period. 50mg/day given as 1 capsule in the morning.
  - Group therapy - Weekly abstinence orientated sessions, including coping skills and relapse prevention based on the cognitive behavioural model of substance abuse. Groups were of between 8 and 14 participants and sessions lasted 90mins.

- **Acam + Nalx**
  - N= 40
  - Naltrexone + Acamprosate - Medication dose constant throughout 12 week study period. Same dosage and tablet numbers as the single pharmacological interventions.
  - Group therapy - Weekly abstinence orientated sessions, including coping skills and relapse prevention based on the cognitive behavioural model of substance abuse. Groups were of between 8 and 14 participants and sessions lasted 90mins.

- **Placebo**
  - N= 40
  - Placebo - Inactive control, same dosing procedure as with active pharmacological intervention
  - Group therapy - Weekly abstinence orientated sessions, including coping skills and relapse prevention based on the cognitive behavioural model of substance abuse. Groups were of between 8 and 14 participants and sessions lasted 90mins.
Appendix 16e

**Data Used**

**PAILLE1995**

Study Type: RCT

Type of Analysis: ITT - all taking one dose of study medication

Blindness: Double blind

Duration (days): Mean 56

Setting: Recruited through newspaper adverts or as patients seeking treatment at one of 12 outpatient clinics with alcohol treatment programs

Notes: Randomisation: Computer-generated random number list in groups of 12 for each study site.

Info on Screening Process: n=328 screened, n=159 excluded (n=113 refused to participate, n=36 did not meet inclusion criteria, n=10 had severe medical/psychiatric concerns). This left n=169 to be randomised.

Blinding: Double blind

Duration (days): Mean 56

Setting: Recruited through newspaper adverts or as patients seeking treatment at one of 12 outpatient clinics with alcohol treatment programs

Notes: Randomisation: Computer-generated random number list in groups of 12 for each study site.

Info on Screening Process: Of people screened, n=153 met the eligibility criteria but refused treatment (n=3), refused to take medication (n=2).

Baseline: Acam

Drinks per drinking day 16.0 (8.2) 14.1 (7.4) 14.3 (8.0)

UK units 21 18 19

ADS score 20.3 (8.3) 20.0 (9.4) 21.0 (8.6)

Married (%) 38.9 34 33.3

Partnership (%) 53.3 48.2 47.2

Employed (%) 67 70 58

**NAMKOONG2003**

Study Type: RCT

Type of Analysis: ITT - all taking one dose of study medication

Blindness: Double blind

Duration (days): Mean 56

Setting: Recruited through newspaper adverts or as patients seeking treatment at one of 12 outpatient clinics with alcohol treatment programs

Notes: Randomisation: Computer-generated random number list in groups of 12 for each study site.

Info on Screening Process: Of people screened, n=153 met the eligibility criteria but refused treatment (n=3), refused to take medication (n=2).

Baseline: Acamp PLB

Drinks per drinking day 18.4 (12.5) 17.5 (10.9)

In UK units: 27.6 26.25

Married (%) 77.8 74.3

Employed (%) 62.5 57.1

Total ADS score 20.4 (8.2) 22.7 (8.6)

**Data Not Used**

**NAMKOONG2003**

Data Used

Drinks per drinking day

% days abstinent

% without heavy drinking during study

% never relapsed

% continuously abstinent

Leaving study early

Data Not Used

VAD - Not relevant

Craving - OCDS - Not relevant

GTT - Not relevant

Notes: Relapse: defined as 5 or more drinks in a day for males, 4 or more for females.

1 N= 72

Acamprosate. Mean dose 1998mg/day - Visited clinic weekly for first 4 weeks, then biweekly for last 4. Given 1998mg/day if bodyweight >60kg (1332mg/day given if <60kg).

Psychosocial program - Outpatient psychosocial treatment program. Included medical counselling, brief psychotherapy and encouragement to attend AA or CBT.

2 N= 70

Placebo - Identically presented, inactive placebo tablet, given in the same dosing schedule to active intervention

Psychosocial program - Outpatient psychosocial treatment program. Included medical counselling, brief psychotherapy and encouragement to attend AA or CBT.

**Funding:**

- 1 N= 72
  - Acamprosate. Mean dose 1998mg/day - Visited clinic weekly for first 4 weeks, then biweekly for last 4. Given 1998mg/day if bodyweight >60kg (1332mg/day given if <60kg).
  - Psychosocial program - Outpatient psychosocial treatment program. Included medical counselling, brief psychotherapy and encouragement to attend AA or CBT.

- 2 N= 70
  - Placebo - Identically presented, inactive placebo tablet, given in the same dosing schedule to active intervention
  - Psychosocial program - Outpatient psychosocial treatment program. Included medical counselling, brief psychotherapy and encouragement to attend AA or CBT.

**PAILLE1995**

Study Type: RCT

Type of Analysis: ITT - all taking one dose of study medication

Blindness: Double blind

Duration (days): Mean 56

Setting: Recruited through newspaper adverts or as patients seeking treatment at one of 12 outpatient clinics with alcohol treatment programs

Notes: Randomisation: Computer-generated random number list in groups of 12 for each study site.

Info on Screening Process: Of people screened, n=153 met the eligibility criteria but refused treatment (n=3), refused to take medication (n=2).

Baseline: Acamp PLB

Drinks per drinking day 18.4 (12.5) 17.5 (10.9)

In UK units: 27.6 26.25

Married (%) 77.8 74.3

Employed (%) 62.5 57.1

Total ADS score 20.4 (8.2) 22.7 (8.6)

**Data Used**

Drinks per drinking day

% days abstinent

% without heavy drinking during study

% never relapsed

% continuously abstinent

Leaving study early

Data Not Used

VAD - Not relevant

Craving - OCDS - Not relevant

GTT - Not relevant

Notes: Relapse: defined as 5 or more drinks in a day for males, 4 or more for females.

1 N= 188

Acamprosate. Mean dose 1.3g/day - Participants took four 333mg tablets + 2

**Funding:**

- 1 N= 188
  - Acamprosate. Mean dose 1.3g/day - Participants took four 333mg tablets + 2

**NAMKOONG2003**

Study Type: RCT

Type of Analysis: ITT - all taking one dose of study medication

Blindness: Double blind

Duration (days): Mean 56

Setting: Recruited through newspaper adverts or as patients seeking treatment at one of 12 outpatient clinics with alcohol treatment programs

Notes: Randomisation: Computer-generated random number list in groups of 12 for each study site.

Info on Screening Process: Of people screened, n=153 met the eligibility criteria but refused treatment (n=3), refused to take medication (n=2).

Baseline: Acamp PLB

Drinks per drinking day 18.4 (12.5) 17.5 (10.9)

In UK units: 27.6 26.25

Married (%) 77.8 74.3

Employed (%) 62.5 57.1

Total ADS score 20.4 (8.2) 22.7 (8.6)

**Data Used**

Drinks per drinking day

% days abstinent

% without heavy drinking during study

% never relapsed

% continuously abstinent

Leaving study early

Data Not Used

VAD - Not relevant

Craving - OCDS - Not relevant

GTT - Not relevant

Notes: Relapse: defined as 5 or more drinks in a day for males, 4 or more for females.

1 N= 72

Acamprosate. Mean dose 1998mg/day - Visited clinic weekly for first 4 weeks, then biweekly for last 4. Given 1998mg/day if bodyweight >60kg (1332mg/day given if <60kg).

Psychosocial program - Outpatient psychosocial treatment program. Included medical counselling, brief psychotherapy and encouragement to attend AA or CBT.

2 N= 70

Placebo - Identically presented, inactive placebo tablet, given in the same dosing schedule to active intervention

Psychosocial program - Outpatient psychosocial treatment program. Included medical counselling, brief psychotherapy and encouragement to attend AA or CBT.

**Funding:**

- 1 N= 72
  - Acamprosate. Mean dose 1998mg/day - Visited clinic weekly for first 4 weeks, then biweekly for last 4. Given 1998mg/day if bodyweight >60kg (1332mg/day given if <60kg).
  - Psychosocial program - Outpatient psychosocial treatment program. Included medical counselling, brief psychotherapy and encouragement to attend AA or CBT.

- 2 N= 70
  - Placebo - Identically presented, inactive placebo tablet, given in the same dosing schedule to active intervention
  - Psychosocial program - Outpatient psychosocial treatment program. Included medical counselling, brief psychotherapy and encouragement to attend AA or CBT.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Analysis</th>
<th>Study Type</th>
<th>Setting</th>
<th>Duration (days)</th>
<th>Exclusions</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>PELC1992</td>
<td>ITT - all receiving one dose of study medication</td>
<td>RCT</td>
<td>Awaiting translation</td>
<td>Mean 180</td>
<td>Randomisation: no details</td>
<td></td>
</tr>
<tr>
<td>PELC1997</td>
<td>ITT - all receiving one dose of study medication</td>
<td>RCT</td>
<td>Awaiting translation</td>
<td>Mean 90</td>
<td>Randomisation: no details</td>
<td></td>
</tr>
</tbody>
</table>

**PELC1992**

- **Study Type**: RCT
- **Setting**: Awaiting translation
- **Exclusions**: Awaiting translation
- **Notes**: Awaiting translation

**PELC1997**

- **Study Type**: RCT
- **Setting**: 11 outpatient centres in Belgium and France, after 14-day inpatient detox.
- **Notes**: Randomisation: no details

---

**Baseline: Alcohol consumption In UK Live with Employed (g/day) units family (%) (%)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Consumption</th>
<th>Units</th>
<th>Family</th>
<th>% Male</th>
<th>% Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>192 (108)</td>
<td>24</td>
<td>74</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Acamp 1.3g/day</td>
<td>189 (161)</td>
<td>23.63</td>
<td>77</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Acamp 2g/day</td>
<td>180 (89.5)</td>
<td>22.5</td>
<td>77</td>
<td>66</td>
<td></td>
</tr>
</tbody>
</table>

---

**Abstinent at endpoint**

- **Abstinent at assessment**
- **% continuously abstinent**
- **Leaving study early**
- **Data Not Used**

**PELC1997**

- **Study Type**: RCT
- **Setting**: 11 outpatient centres in Belgium and France, after 14-day inpatient detox.
- **Notes**: Randomisation: no details

---

**Notes: Any alcohol consumption was considered relapse.**

**CGI assessment data given at days 8,15,30,45,60,75,90.**

---

**Funding**: Lipha Belgium
### POLDRUGO1997

**Study Type:** RCT  
**Type of Analysis:** ITT - all receiving one dose of study medication  
**Blindness:** Double blind  
**Duration (days):** Mean 180  
**Followup:** 6 months  
**Setting:** Study carried out in 5 alcohol treatment units in Italy.  
**Notes:** Randomisation: no details  
**Info on Screening Process:** n=923 alcohol dependent patients were screened, but only n=246 met inclusion criteria.

<table>
<thead>
<tr>
<th>n</th>
<th>246</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age:</strong></td>
<td>Mean 44 Range 18-65</td>
<td></td>
</tr>
<tr>
<td><strong>Sex:</strong></td>
<td>179 males 67 females</td>
<td></td>
</tr>
<tr>
<td><strong>100% Alcohol Dependence by DSM-III</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exclusions:</strong></td>
<td>&lt;18 or &gt; 65 years of age, no DSM-III diagnosis of alcohol dependence, GGT less than twice upper limit or MCV &lt;95fl, less than 5 days abstinence before study commenced. Further criteria: pregnant/breast feeding, major psychiatric or somatic pathology, failure to cooperate during the alcohol withdrawal treatment, no fixed residence and absence of relative/friends to supply information on participant progress.</td>
<td></td>
</tr>
<tr>
<td><strong>Notes:</strong></td>
<td>Participants suffering a severe relapse could be admitted to hospital for another withdrawal treatment while continuing medication.</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline:</strong></td>
<td>Amount of population drinking &gt;10 drinks/ drinking day (%): Acamprosate 94 (77) Placebo 91 (73)</td>
<td></td>
</tr>
</tbody>
</table>

### ROUSSEAUX1996

**Study Type:** RCT  
**Blindness:** Double blind  
**Duration (days):** Mean 90  
**Followup:** no follow-up  
**Setting:** Country: Belgium, Outpatient clinic at the Belgian Institute of Neurology, in the Psychiatric Department.  
**Notes:** Randomisation method: not mentioned.  
**Info on Screening Process:** None mentioned.

<table>
<thead>
<tr>
<th>n</th>
<th>127</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age:</strong></td>
<td>Mean 42 Range 23-64</td>
<td></td>
</tr>
<tr>
<td><strong>Sex:</strong></td>
<td>89 males 38 females</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol Dependence or Abuse by DSM-III</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exclusions:</strong></td>
<td>Patients were excluded if they did not meet DSM-III criteria for alcohol dependence, episodic or chronic alcoholism, or alcohol abuse, or if they had not had a problem with alcohol in the previous year. Additional exclusions include pregnant women, severe psychiatric conditions which required additional medication or treatment, chronic physical comorbidities, if they required inpatient treatment, conditions, or required additional residential treatment.</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline:</strong></td>
<td>Number of patients meeting diagnostic criteria for dependence (43 in placebo, 39 in acamprosate), and alcohol abuse (21 in placebo, 24 in acamprosate)</td>
<td></td>
</tr>
</tbody>
</table>

### RUBIO2001

**Study Type:** RCT  
**Type of Analysis:** ITT  
**Blindness:** Single blind  
**Duration (days):** Mean 365

<table>
<thead>
<tr>
<th>n</th>
<th>157</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age:</strong></td>
<td>Mean 43 Range 18-65</td>
<td></td>
</tr>
<tr>
<td><strong>Sex:</strong></td>
<td>all males</td>
<td></td>
</tr>
</tbody>
</table>

**Data Used**  
- Time to first drink  
- Time to first relapse  
- Craving - subjective desire  
- % days abstinent

**Data Used**  
- Naltrexone. Mean dose 50mg/day - 50mg of Naltrexone taken once daily.

---

**Appendix 16e**

**1 N= 122**  
Acamprosate. Mean dose 1998mg/day - Participants took six 333mg tablets daily if body weight above 60kg, if <80 kg then 1332mg taken per day (4 tablets).  
Psychosocial program - Alcohol rehabilitation program, offering psychological support including: group sessions, family therapy, education on alcoholism, community meetings.

**2 N= 124**  
Placebo - Inactive placebo taken in same frequency as active intervention.  
Psychosocial program - Alcohol rehabilitation program, offering psychological support including: group sessions, family therapy, education on alcoholism, community meetings.

**Notes:** Randomisation method: not mentioned.  
**Followup:** no follow-up  
**Setting:** Country: Belgium, Outpatient clinic at the Belgian Institute of Neurology, in the Psychiatric Department.  
**Duration (days):** Mean 90  
**Blindness:** Double blind  
**Study Type:** RCT  
**Type of Analysis:** ITT Age: Mean 43 Range 18-65  
**Sex:** all males  
**n= 157**  
**Data Used**  
- Naltrexone. Mean dose 50mg/day - 50mg of Naltrexone taken once daily.

**Notes:** Participants suffering a severe relapse could be admitted to hospital for another withdrawal treatment while continuing medication.
<table>
<thead>
<tr>
<th>Setting: All participants were patients requesting detoxification in the Addictive Behaviour Unit of 'Doce de Octubre' Hospital. Notes: Randomisation: using random number table. Info on Screening Process: n=356, were considered for inclusion but only n=160 were selected, the others did not meet the inclusion criteria for a number of reasons. n=3 then refused to participate, therefore n=157 were randomised.</th>
<th>100% Alcohol Dependence by DSM-III Exclusions: &lt;18 and &gt;65 years of age, no DSM-III-R diagnosis of alcohol dependence, unstable family environment. Further criteria: another substance use disorder (except nicotine), another psychiatric disorder, a medical condition that could hinder treatment compliance, impaired living function (AST or ALT value more than 3 times normal value, previous treatment with naltrexone or acamprosate. Notes: Abstinence was positively reinforced Baseline: Nalx Acamp % days drinking (over 6 months): 87 (20) 87 (21) drinks/drinking day (in UK units): 12.3 (5.0) 12.2 (5.1) Married (%): 95 92 Employed (%): 75 75</th>
<th>Drinks per drinking day Relapse Abstinent at endpoint Leaving study early Notes: Relapse: defined as &gt;5 drinks or 40g of alcohol per day. * % days heavy drinking has no SDs</th>
<th>Supportive psychotherapy - Weekly group relapse prevention programmes.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SASS1996 Study Type: RCT Type of Analysis: ITT - all taking one dose of study medication Blindness: Double blind Duration (days): Mean 336 Setting: Newly detoxified from one of 12 psychiatric outpatient clinics in Germany Notes: Randomisation: sealed envelope randomisation. Info on Screening Process: No details</td>
<td>n= 272 Age: Mean 41 Sex: 211 males 61 females 100% Alcohol Dependence by DSM-III Exclusions: Meeting &lt;5 DSM criteria for alcohol dependence and not classified as alcohol-dependent on the Munich alcoholism test. Further exclusion: mental or psychiatric impairment or disease requiring psychotropic medication or a stay in a psychiatric clinic, multiple-drug misuse, or severe neurological or physical disorders (eg liver cirrhosis, hyperparathyroidism). Notes: Participants had to abstain for alcohol for minimum of 14 days and maximum of 28 days and be free of withdrawal symptoms before admitted to the study. Baseline: Acamp Plb Married (%): 50 43 Living with anyone: 66 58 Employed (%) 73 74</td>
<td>Data Used Relapse Abstinent at endpoint Abstinent at assessment CAD Time to first relapse Leaving study early Data Not Used MCV - Not relevant CDT - Not relevant GGT - Not relevant Notes: Abstinence= no alcohol consumption during study period</td>
<td>N= 136 Acamprosate. Mean dose 1998mg/day - Participants took six 333mg tablets daily if body weight above 60kg, if &lt;60 kg then 1332mg taken per day (4 tablets). Counselling or psychotherapy - counselling or psychotherapy was not standardised between centres. Supportive group or individual therapy was behavioural in approach with a mean frequency of 1 hour per session for 18 weeks. Thereafter patients joined contact groups meeting fortnightly.</td>
<td></td>
</tr>
<tr>
<td>TEMPESTA2000 Study Type: RCT Type of Analysis: ITT - all taking one dose of study medication Blindness: Double blind Duration (days): Mean 180 Followup: 3 months</td>
<td>n= 330 Age: Mean 46 Range 18-65 Sex: 273 males 57 females 100% Alcohol Dependence by DSM-III</td>
<td>Data Used Relapse Abstinent at endpoint Abstinent at assessment CAD Leaving study early</td>
<td>N= 164 Acamprosate. Mean dose 1998mg/day - Participants took six 333mg tablets daily during 6 month study period.</td>
<td>Funding: Lipha, France.</td>
</tr>
</tbody>
</table>
Setting: 18 out-patient centres in Italy (11 internal medicine or neurology, 4 addiction units and 3 psychiatry units).

Notes: Randomisation: by sealed envelope, balanced by blocks of eight.

Info on Screening Process: n=340 screened, but n=10 did not comply with inclusion criteria. n=330 were randomised.

Exclusions: <18 or >65 years of age, no DSM-III-R diagnosis of alcohol dependence with history >12 months, GGT value <twice upper limit or MCV <93fl, abstinent for <5 days before study start and no partner/relatives to supply post-detoxification outcome. Further criteria: pregnancy, psychotic disorders requiring drug treatment, epilepsy unrelated to alcohol, cardiac or renal failure, hypercalcaemia, hyperparathyroidism, neoplasm, cholelithiasis, poorly controlled diabetes and decompensated liver disease.

Baseline: Acamprosate Placebo
MAST score: 22.23 (10.59) 23.24 (10.68)
Amount of population drinking >10
drinks/ day (%): 90 (55) 85 (51)
Married (%): 67.7 68.7

Notes: Relapse: any alcohol consumption. Relapse severity also recorded, based on amount of drinks during the relapse.

Psychosocial program - Post-detoxification program including weekly medical counselling on alcohol-related problems. Individual-behaviour-orientated supportive counselling (1-2 sessions per week, 1-hour sessions) and AA attendance (2-3 times a week) were available to all.

1 N= 224
Acamprosate. Mean dose 1998mg/day - Participants took six 333mg tablets daily if body weight above 60kg, if <60 kg then 1332mg taken per day (4 tablets).

2 N= 224
Placebo - Inactive control intervention, dosing schedule identical to the active intervention

Psychosocial program - Post-detoxification program including weekly medical counselling on alcohol-related problems. Individual-behaviour-orientated supportive counselling (1-2 sessions per week, 1-hour sessions) and AA attendance (2-3 times a week) were available to all.

WHITWORTH1996

Study Type: RCT

Type of Analysis: ITT - all taking one dose of study medication
Blindness: Double blind
Duration (days): Mean 365

Followup: 1 year
Setting: 5 Austrian hospitals that treat inpatients with alcohol dependence.

Notes: Randomisation: Computer generated list organised into blocks of eight, allocation codes in sealed envelopes.

Info on Screening Process: n=496 screened, n=41 excluded due to pregnancy, coexisting disease or lack of contraception, leaving n=455 recruited.

n= 448
Age: Mean 42 Range 18-65
Sex: 353 males 95 females

100% Alcohol Dependence by DSM-III

1 N= 224
Acamprosate. Mean dose 1998mg/day - Participants took six 333mg tablets daily if body weight above 60kg, if <60 kg then 1332mg taken per day (4 tablets).

2 N= 224
Placebo - Inactive control intervention, dosing schedule identical to the active intervention

Data Used
CAD
Abstinent at endpoint
Relapse
Death
Leaving study early

Notes: Randomisation: Computer generated list organised into blocks of eight, allocation codes in sealed envelopes.

BALTIERI2003  (Published Data Only)

BARRIAS1997  (Published Data Only)

BESSON1998  (Published Data Only)

CHICK2000A  (Published Data Only)

GEERLINGS1997  (Published Data Only)

GUAL2001  (Published Data Only)

KIEFER2003  (Published Data Only)

LADEWIG1993  (Published Data Only)

MORLEY2006  (Published Data Only)
Richardson, K., Baillie, A., Reid, S., et al. (2008). Do acamprosate or naltrexone have an effect on daily drinking by reducing craving for alcohol? Addiction, 103, 953-959.

NAMKOONG2003  (Published Data Only)

PAILLE1995  (Published Data Only)
PELC1992 (Published Data Only)

PELC1997 (Published Data Only)

POLDUGO1997 (Published Data Only)

ROUSSEAUX1996 (Published Data Only)

RUBIO2001 (Published Data Only)

SASS1996 (Published Data Only)

TEMPESTA2000 (Published Data Only)

WHITWORTH1996 (Published Data Only)
### Study characteristics for naltrexone

<table>
<thead>
<tr>
<th>Comparisons Included in this Review Question</th>
<th>Naltrexone + Sertraline vs Naltrexone</th>
<th>Naltrexone vs Acamprosate</th>
<th>Naltrexone vs Placebo</th>
<th>Naltrexone vs Topiramate</th>
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<tr>
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<td>KIEFER2003</td>
<td>ANTON1999</td>
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<td>MORLEY2006</td>
<td>ANTON2005</td>
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<td>RUBIO2001</td>
<td>ANTON2006</td>
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<td>BALLDIN2003</td>
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<td>HEINALA2001</td>
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<td>KRAZNYLER2000</td>
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<td>MOLLIS2001</td>
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<td>OMALELY1992</td>
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<td>VOLPICELLI1992</td>
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<tr>
<td></td>
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<td>VOLPICELLI1997</td>
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</table>

### Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Methods</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Interventions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AHMADI2002</strong></td>
<td>n= 116</td>
<td>Data Used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Type: RCT</td>
<td>Age: Mean 43  Range 23-56</td>
<td>Relapsed by endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Analysis: ITT</td>
<td>Sex: all males</td>
<td>Leaving study early</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blindness: Double blind</td>
<td>Diagnosis: 100% Alcohol Dependence by Undefined diagnosis tool</td>
<td>Notes: Relapse: defined as five or more standard drinks in one drinking occasion or drinking on 5 or more days in the week (drink = 10g of alcohol)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Duration (days): Mean 252 | Exclusions: Female, no diagnosis of alcohol dependence, maintenance of <3 or >30 days of sobriety. Further criteria: current drug abuse or dependence (except tobacco), current
| Setting: Conducted in Iran, participants were self-referrals. | **Group 1 N= 58** | Naltrexone. Mean dose 50mg/day - 50mg of naltrexone taken daily |
| Notes: Randomisation: stratified to dose and duration of drinking alcohol. | Relapse prevention - weekly 0.5 hour counselling sessions, providing training in relapse prevention through identifying situations, places and people that cue drinking. | No details on funding/sponsorship |
| Info on Screening Process: no details | Notes: |
**ANTON1999**

**Study Type:** RCT  
**Type of Analysis:** ITT  
**Blindness:** Double blind  
**Duration (days):** Mean 84  
**Followup:** 14 weeks  
**Setting:** Participants were seeking outpatient treatment for alcoholism, and were either referred to the clinic or responded to advertisements.  
**Notes:** Randomisation: no details  
**Info on Screening Process:** n=1094 were screened over the telephone, n=440 were invited for in-person screening. Of these n=338 were screened, n=190 gave informed consent and eventually n=132 entered treatment. Details for those dropping out not given.

**Diagnosis:** 100% Alcohol Dependence by DSM-III  
**Exclusions:** <21 and >65 years of age, no DSM-III-R diagnosis of alcohol dependence, drinking <5 drinks a day in 30 days before for men (<4 if female), residence >1 hour from the clinic, unstable living condition, unavailability of collateral reporter, unable to maintain abstinence for at least 5 days before the study start. Further criteria: previous inpatient detoxification in which medication was taken, current drug abuse or dependence, having ever abused opiates, current major psychiatric disorder, serious or unstable medical condition, current use of psychotropic or antiseizure medications or disulfiram, pending legal charges except for drinking while intoxicated, liver function test results (ALT & AST) greater than 2.5 times normal.  
**Notes:** Participants were required to be consuming >5 drinks per day if male (>4 if female) in the 30 days before start.  
They were also required to be abstinent for at least 5 days before the study started.  
**Baseline:**  
<table>
<thead>
<tr>
<th>Married(%)</th>
<th>Employed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td>70</td>
</tr>
</tbody>
</table>

**Data Used**  
<table>
<thead>
<tr>
<th>Relapse</th>
<th>Abstinent at endpoint</th>
<th>Time to first relapse</th>
<th>Time to first drink</th>
<th>Drinks per drinking day</th>
<th>% days abstinent</th>
<th>Leaving study early</th>
</tr>
</thead>
</table>

**Data Not Used**  
<table>
<thead>
<tr>
<th>CDT</th>
<th>GGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not relevant</td>
<td>Not relevant</td>
</tr>
</tbody>
</table>

**Notes:**  
Supported by a grant from the National Institute on Alcohol Abuse and Alcoholism. DuPont pharmaceuticals supplied the study drug and placebo for this research.

**ANTON2005**

**Study Type:** RCT  
**Type of Analysis:** ITT  
**Blindness:** Double blind  
**Duration (days):** Mean 84  
**Setting:** Participants were seeking outpatient treatment for alcoholism and were either referred to the clinic service or responded to advertisements.  
**Notes:** Randomisation: no details  
**Info on Screening Process:** No details  
**Appendix 16e**

**Diagnosis:** 100% Alcohol Dependence by DSM IV  
**Exclusions:** <21 or >70 years of age, no DSM-IV diagnosis of alcohol dependence (including criteria 2 - loss of control over drinking), >1 previous inpatient detox, consumption of <5 drinks/day for men (<4 for women) in 90 days before study entry, residence >50 miles from centre, unstable living condition, no collateral reporter, unable to maintain abstinence for at least 5 days before the study start.  
**Notes:** Participants were required to be consuming >5 drinks per day if male (>4 if female) in the 30 days before start.  
They were also required to be abstinent for at least 5 days before the study started.  
**Baseline:**  
<table>
<thead>
<tr>
<th>Married(%)</th>
<th>Employed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>71</td>
<td>81</td>
</tr>
</tbody>
</table>

**Data Used**  
<table>
<thead>
<tr>
<th>Total drinks</th>
<th>Time to first relapse</th>
<th>Time to first drink</th>
<th>Drinks per drinking day</th>
<th>% days abstinent</th>
<th>Leaving study early</th>
</tr>
</thead>
</table>

**Notes:** Supported by grants from the National Institute on Alcohol Abuse and Alcoholism.
Appendix 16e

Study Type: RCT

Type of Analysis: ITT - as long as baseline data

Blindness: Double blind

Duration (days): Mean 112 Range 18 -100

Followup: 1 year

Setting: recruited from 11 sites, by advertisements or clinical referrals.

Notes: Participant's were required to abstain for 5 consecutive days for inclusion.

Baseline: Drinks/ % days %

% drinking drinking Married Married

Baseline: Drinks/ % days %

% drinking drinking Married Married

Notes: Participants needed to abstain for 5 consecutive days for inclusion.

Notes: Randomisation: permuted block design, using blocks of 9 stratified by site. Implemented via central telephone-based interactive voice response system.

Info on Screening Process: Approximately n=5000 were screened by telephone or in person, but only n=1383 were eligible after assessment.

Notes: Relapse/heavy drinking day= >5 drinks in 1 day for men (>4 for women).

Notes: Relapse/heavy drinking day= >5 drinks in 1 day for men (>4 for women).

Notes: Participants were required to acknowledge a desire to stop drinking. They were also required to be drinking at least 21 drinks a week if male, 14 drinks a week if male. Recommended abstinence

Baseline: Drinks/ % days %

% drinking drinking Married Married

Baseline: Drinks/ % days %

% drinking drinking Married Married

ANTON2006

Study Type: RCT

Type of Analysis: ITT - as long as baseline data

Blindness: Double blind

Duration (days): Mean 112

Followup: 1 year

Setting: recruited from 11 sites, by advertisements or clinical referrals.

Notes: Randomisation: permuted block design, using blocks of 9 stratified by site. Implemented via central telephone-based interactive voice response system.

Info on Screening Process: Approximately n=5000 were screened by telephone or in person, but only n=1383 were eligible after assessment.

Notes: Relapse/heavy drinking day= >5 drinks in 1 day for men (>4 for women).

Notes: Participants were required to acknowledge a desire to stop drinking. They were also required to be drinking at least 21 drinks a week if male, 14 drinks a week if male. Recommended abstinence

Baseline: Drinks/ % days %

% drinking drinking Married Married

Baseline: Drinks/ % days %

% drinking drinking Married Married

Notes: Participants needed to abstain for 5 consecutive days for inclusion.

Notes: Randomisation: permuted block design, using blocks of 9 stratified by site. Implemented via central telephone-based interactive voice response system.

Info on Screening Process: Approximately n=5000 were screened by telephone or in person, but only n=1383 were eligible after assessment.

Notes: Relapse/heavy drinking day= >5 drinks in 1 day for men (>4 for women).

Notes: Participants were required to acknowledge a desire to stop drinking. They were also required to be drinking at least 21 drinks a week if male, 14 drinks a week if male. Recommended abstinence

Baseline: Drinks/ % days %

% drinking drinking Married Married

Baseline: Drinks/ % days %

% drinking drinking Married Married

Data Used

Relapse % days abstinent

Leaving due to adverse events

Leaving study early

Group 1 N= 154

Naltrexone. Mean dose 100mg/day - Dose of 25mg over first 4 days, dose of 50mg over next 4 days and then 100mg a day for the rest of the study. Placebo acamprosate also taken. Medication management - Delivered by licensed healthcare professional over 9 sessions in which pills were dispensed/ Initial visit was for 45 minutes, professional recommended abstinence and provided education about alcohol and the study medications. Encouraged AA.

Group 2 N= 152

Acamprosate. Mean dose 3g/day - Two 500mg tablets taken three times daily (6 tablets in total daily). Could be lowered if required. Placebo naltrexone also taken. Medication management - Delivered by licensed healthcare professional over 9 sessions in which pills were dispensed/ Initial visit was for 45 minutes, professional recommended abstinence and provided education about alcohol and the study medications. Encouraged AA.

Study was supported by grants from the NIAAA. Acamprosate, Naltrexone and matching placebos were donated by Liphra Pharmaceuticals.
<table>
<thead>
<tr>
<th>Group</th>
<th>N=</th>
<th>Medication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>148</td>
<td>Naltrexone + Acamprosate</td>
<td>Combines the dosing schedule for naltrexone and acamprosate alone interventions.</td>
</tr>
<tr>
<td>2</td>
<td>153</td>
<td>Placebo</td>
<td>Inactive placebo tablets identical in appearance to active acamprosate and naltrexone taken on the same dosing schedule as the active interventions.</td>
</tr>
<tr>
<td>3</td>
<td>155</td>
<td>Naltrexone</td>
<td>Dose of 25mg over first 4 days, dose of 50mg over next 4 days and then 100mg a day for the rest of the study. Placebo acamprosate also taken.</td>
</tr>
<tr>
<td>4</td>
<td>151</td>
<td>Acamprosate</td>
<td>Two 500mg tablets taken three times daily (6 tablets in total daily). Could be lowered if required. Placebo naltrexone also taken.</td>
</tr>
</tbody>
</table>

**Table: ACAM+CBI, NALX+**

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<thead>
<tr>
<th></th>
<th>ACAM+CBI</th>
<th>NALX+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>13.2 (7.74)</td>
<td>12.2 (7.77)</td>
</tr>
<tr>
<td>25.3 (24.70)</td>
<td>26.8 (24.68)</td>
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</tr>
<tr>
<td>44.4</td>
<td>43.3</td>
<td></td>
</tr>
<tr>
<td>70.9</td>
<td>70.7</td>
<td></td>
</tr>
<tr>
<td>CBI only</td>
<td>11.8 (7.66)</td>
<td>17.7</td>
</tr>
<tr>
<td>23.5 (25.35)</td>
<td>25.3 (24.70)</td>
<td></td>
</tr>
<tr>
<td>41.4</td>
<td>44.4</td>
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</table>

**Group 3 N= 148**
Naltrexone + Acamprosate - Combines the dosing schedule for naltrexone and acamprosate alone interventions. Medication management - Delivered by licensed healthcare professional over 9 sessions in which pills were dispensed. Initial visit was for 45 minutes, professional recommended abstinence and provided education about alcohol and the study medications. Encouraged AA.

**Group 4 N= 153**
Placebo - Inactive placebo tablets identical in appearance to active acamprosate and naltrexone taken on the same dosing schedule as the active interventions. Medication management - Delivered by licensed healthcare professional over 9 sessions in which pills were dispensed. Initial visit was for 45 minutes, professional recommended abstinence and provided education about alcohol and the study medications. Encouraged AA.

**Group 5 N= 155**
Naltrexone - Dose of 25mg over first 4 days, dose of 50mg over next 4 days and then 100mg a day for the rest of the study. Placebo acamprosate also taken. Combined behavioural intervention + MM - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement. Medication management also provided.

**Group 6 N= 151**
Acamprosate - Two 500mg tablets taken three times daily (6 tablets in total daily). Could be lowered if required. Placebo naltrexone also taken. Combined behavioural intervention + MM - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement. Medication management also provided.
<table>
<thead>
<tr>
<th>Study Type: RCT</th>
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</thead>
<tbody>
<tr>
<td>Type of Analysis: ITT</td>
</tr>
<tr>
<td>Blindness: Double blind</td>
</tr>
<tr>
<td>Duration (days): Mean 180</td>
</tr>
<tr>
<td>Setting: Study performed at 10 different investigation centres in Sweden, mostly university hospitals. Patients recruited from outpatients or advertisement.</td>
</tr>
<tr>
<td>Notes: Randomisation : Patients assigned unique sequential numbers stratified by study site.</td>
</tr>
<tr>
<td>Info on Screening Process: n=154 patients met inclusion and were eligible for placebo run-in period for 1 week. n=120 patients compliant with abstinence and n=2 patients excluded. n=1 patient died, n=1 included but liver enzyme activity was too high.</td>
</tr>
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<thead>
<tr>
<th>Data Used</th>
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<tbody>
<tr>
<td>Time to first relapse</td>
</tr>
<tr>
<td>Leaving study early</td>
</tr>
<tr>
<td>% heavy drinking days</td>
</tr>
<tr>
<td>Drinks per day</td>
</tr>
<tr>
<td>CBT</td>
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<td>% drinking days</td>
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<tr>
<th>Data Not Used</th>
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</thead>
<tbody>
<tr>
<td>GGT - Not relevant</td>
</tr>
<tr>
<td>Craving - OCDS - Not relevant</td>
</tr>
<tr>
<td>AST - Not relevant</td>
</tr>
<tr>
<td>ALT - Not relevant</td>
</tr>
<tr>
<td>Notes: Alcohol per drinking day measured in g.</td>
</tr>
</tbody>
</table>

| Notes: Obligatory for men to consume at least 5 drinks and women to have consumed at least 4 (one drink = 12 g of alcohol). |

| Study supported and medication provided by DuPont Pharma (UK) and Meda AB (Sweden). |

| Group 1 N= 25 |
| Naltrexone. Mean dose 50mg/day - patients ingested one 50 mg naltrexone tablet daily. |
| Coping skills - 9 sessions, lasting approximately 40-60 minutes each. Coping skills delivered using the Project MATCH manual (referred to as CBT in the paper). |

| Group 2 N= 31 |
| Naltrexone. Mean dose 50mg/day - patients ingested one 50 mg naltrexone tablet daily. |
| Supportive psychotherapy - 9 sessions, lasting approx 40-60 minutes each. Referred to as ‘treatment as usual’ in the paper, the main task of the therapist was to support and motivate the patient into sobriety without teaching specific coping skills. |

| Group 7 N= 157 |
| Naltrexone + Acamprosate - Combines the dosing schedule for naltrexone and acamprosate alone interventions |
| Combined behavioural intervention + MM - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement. Medication management also provided. |

| Group 8 N= 156 |
| Placebo - Inactive placebo tablets identical in appearance to active acamprosate and naltrexone taken on the same dosing schedule as the active interventions. |
| Combined behavioural intervention + MM - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement. Medication management also provided. |

| Group 9 N= 157 |
| Combined behavioural intervention - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement. |
pure alcohol) on at least 20 of last 60 days before screening. No more than 14 days of sobriety prior to screening was allowed.

Baseline: NLT+CBT NLT+ST PLB+CBT PLB+ST
% Days heavy drinking - 56 (19) 56 (22) 59 (23) 61 (24)
% days with drinking 60 (22) 63 (23) 66 (23) 66 (24)
consumption/day of alcohol (g) - 81 (38) 94 (41) 92 (49) 96 (41)
Consumption/day in UK units: 10.13 11.75 11.5 12
Married/cohabiting (%): 60 48 63 53
Employed (%): 80 65 77 66

Group 3 N= 25
Placebo - Inactive intervention, identical in appearance and dosing schedule to the active intervention
Coping skills - 9 sessions, lasting approximately 40-60 minutes each. Coping skills delivered using the Project MATCH manual (referred to as CBT in the paper)

Group 4 N= 30
Placebo - Inactive intervention, identical in appearance and dosing schedule to the active intervention
Supportive psychotherapy - 9 sessions, lasting approximately 40-60 minutes each. Referred to as 'treatment as usual' in the paper, the main task of the therapist was to support and motivate the patient into sobriety without teaching specific coping skills.

BALTIERI2008
Study Type: RCT
Type of Analysis: ITT - all taking one dose of study medication
Blindness: Double blind
Duration (days): Mean 84
Setting: Clinical hospital of the University of Sao Paulo, Brazil. Patients were enrolled as out-patients in the assistance sector.
Notes: Randomisation: no details on procedure, medication codes were revealed only after all participants had completed the study.
Info on Screening Process: n=175 screened, n=14 refused participation, n=6 did not meet eligibility criteria, so n=155 were randomised.

n= 155
Age: Mean 44 Range 18-65
Sex: all males
Diagnosis:
100% Alcohol Dependence by ICD-10
Exclusions: Female, <18 and >60 years of age, no ICD-10 criteria for alcohol dependence. Further criteria: current diagnosis of dependence or abuse of other substances except nicotine, serious coexisting diseases (e.g. inadequately controlled diabetes, cardiac failure, alcoholic cirrhosis), previous treatment with naltrexone or topiramate within 6 months of study start, concomitant psychiatric disorders that might require specific drug treatment.

Baseline: Ethanol per day (g) UK units Married(%)
Placebo 288.4 (175.4) 36.05 51.9
Naltrexone 203.7 (158.5) 36.71 49
Topiramate 321.8 (187.9) 40.23 53.9

Data Used
Heavy drinking weeks
% continuously abstinent CAD
Time to first drink Leaving due to adverse events
Leaving study early
Data Not Used
Craving - OCDS - Not relevant
GGT - Not relevant

Group 1 N= 49
Naltrexone. Mean dose 50mg/day - Participants one tablet of naltrexone (50mg) to be taken daily over the 12 weeks
Brief 'cognitive-behavioural' intervention - At each appointment, participants received a brief 'cognitive-behavioural' intervention from their doctor - the goal was to increase the person's ability to cope with high-risk situations. Also referred to as relapse prevention counselling.

Group 2 N= 54
Placebo - Inactive intervention, took one placebo tablet daily for 12 weeks.
Brief 'cognitive-behavioural' intervention - At each appointment, participants received a brief 'cognitive-behavioural' intervention from their doctor - the goal was to increase the person's ability to cope with high-risk situations. Also referred to as relapse prevention counselling.

Supported by grants from Fundacao de Amparo a Pesquisa do Estado de Sao Paulo.
### CHICK2000

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Analysis:</td>
<td>ITT - all taking one dose of study medication</td>
</tr>
<tr>
<td>Blindness:</td>
<td>Double blind</td>
</tr>
<tr>
<td>Duration (days):</td>
<td>Mean 84</td>
</tr>
<tr>
<td>Setting:</td>
<td>Conducted in 6 sites in the UK, all participants had/were about to enrol in an outpatient alcohol rehabilitation program or routine follow-up</td>
</tr>
<tr>
<td>Notes:</td>
<td>Randomisation: was stratified according to DSM diagnosis of alcohol dependence or abuse</td>
</tr>
<tr>
<td>Info on Screening Process:</td>
<td>No details</td>
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#### Data Used

<table>
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<th>Group 1 N= 90</th>
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</thead>
<tbody>
<tr>
<td>Naltrexone. Mean dose 50mg/day - 50mg of naltrexone taken daily</td>
</tr>
<tr>
<td>Psychosocial program - Each centre entered participants into its usual psychosocial treatment program. There were no protocol constraints on this. Patients were free to attend alternative facilities, such as AA or other support groups.</td>
</tr>
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#### Data Not Used

<table>
<thead>
<tr>
<th>Group 2 N= 85</th>
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</thead>
<tbody>
<tr>
<td>Placebo - Inactive intervention, same appearance and dosing schedule as the active intervention.</td>
</tr>
<tr>
<td>Psychosocial program - Each centre entered participants into its usual psychosocial treatment program. There were no protocol constraints on this. Patients were free to attend alternative facilities, such as AA or other support groups.</td>
</tr>
</tbody>
</table>

### FARRENS2009

<table>
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<tr>
<th>Study Type:</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Analysis:</td>
<td>ITT</td>
</tr>
<tr>
<td>Blindness:</td>
<td>Double blind</td>
</tr>
<tr>
<td>Duration (days):</td>
<td>Mean 84</td>
</tr>
<tr>
<td>Setting:</td>
<td>Participants responded to local</td>
</tr>
</tbody>
</table>

#### Data Used

<table>
<thead>
<tr>
<th>Group 1 N= 57</th>
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</thead>
<tbody>
<tr>
<td>Naltrexone + Sertraline. Mean dose 50 + 100mg/day - Participants started on 12.5mg/day of naltrexone for first 3 days, this was increased to 25mg/day for 4 days, then 50mg/day for next 11 weeks. Sertraline was dosed at 50mg/day for two</td>
</tr>
</tbody>
</table>

#### Data Not Used

<table>
<thead>
<tr>
<th>Group 3 N= 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate. Mean dose 300mg/day - Participants started with 25 mg/day during week 1, which was increased to 300mg/day by week 8. This dose was maintained until week 12.</td>
</tr>
<tr>
<td>Brief 'cognitive-behavioural' intervention - At each appointment, participants received a brief 'cognitive-behavioural' intervention from their doctor - the goal was to increase the person's ability to cope with high-risk situations. Also referred to as relapse prevention counselling.</td>
</tr>
</tbody>
</table>

### Notes

- **Age**: Mean 43 Range 18-65
- **Sex**: 131 males 44 females
- **Diagnosis**: 97% Alcohol Dependence by DSM-III
- **Exclusions**: <18 and >65 years old, no DSM diagnosis of alcohol dependence or abuse, being abstinent for <5 or >30 days, not enrolled or not about to enrol in outpatient alcohol treatment. Further exclusions: psychiatric condition requiring medication, polysubstance abuse, AST or ALT greater than 3 times the upper reference range, total serum bilirubin concentration greater than twice the upper limit, significant physical illness (ischaemic heart disease, chronic obstructive airways disease, insulin dependent diabetes). Patients using opioids in any form, opioid antagonists, or other psychotropics (except hypnotics for sleeping) were also excluded.
- **Notes**: Primary goal of each patient's treatment was to support abstinence from alcohol and to reduce risk of relapse.

#### Baseline:

<table>
<thead>
<tr>
<th>Group</th>
<th>NALX</th>
<th>PLB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinks/day</td>
<td>10.1 (9.1)</td>
<td>10.3 (7.5)</td>
</tr>
<tr>
<td>DD in UK units</td>
<td>15.15</td>
<td>15.45</td>
</tr>
<tr>
<td>Years drinking</td>
<td>22.6 (8.7)</td>
<td>25.9 (10.6)</td>
</tr>
<tr>
<td>Married/ Cohabiting (%)</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Living alone(%)</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>Employed(%)</td>
<td>21</td>
<td>32</td>
</tr>
</tbody>
</table>

#### 97% Alcohol Dependence by DSM-IV

- **Sex**: 91 males 20 females
- **Diagnosis**: 100% Alcohol Dependence by DSM IV
### GUARDIA2002

<table>
<thead>
<tr>
<th>Study Type: RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Analysis: ITT - LOCF</td>
</tr>
<tr>
<td>Blindness: Double blind</td>
</tr>
<tr>
<td>Duration (days): Mean 84</td>
</tr>
<tr>
<td>Setting: Conducted in 7 centres in Spain, all participants were seeking outpatient treatment.</td>
</tr>
<tr>
<td>Notes: Randomisation: no details</td>
</tr>
<tr>
<td>Info on Screening Process: no details</td>
</tr>
</tbody>
</table>

Exclusions: <18 and >64 years of age, no DSM-IV diagnosis of alcohol dependence, <5 or >30 days of abstinence before the start of the study. Further criteria: met criteria for current abuse or dependence on any substance other than nicotine or alcohol, had a current Axis I disorder in addition to alcohol dependence (including major depression), or reported any past opioid use, significant liver disease (AST or ALT >300% upper limit of normal or bilirubin >110% of upper limit of normal), a positive blood-alcohol level during evaluation, or any major physical illness.

Notes: Participants required to be abstinent for at least 5 days (but less than 30), before study started.

Baseline: Naltrexone taken once daily for first 3 days, this was increased to 25mg/day for 4 days, then 50mg/day for next 11 weeks.

Group 1 N= 101
Naltrexone. Mean dose 50mg/day - 50mg of naltrexone taken once daily. Supportive relapse prevention psychotherapy (Project MATCH), for 12 weeks. Participants were also encouraged to attend AA meetings.

Group 2 N= 54
Naltrexone. Mean dose 50mg/day - Participants started on 12.5mg/day of naltrexone for first 3 days, this was increased to 25mg/day for 4 days, then 50mg/day for next 11 weeks.

Group relapse prevention - Weekly group relapse prevention psychotherapy (Project MATCH), for 12 weeks. Participants were also encouraged to attend AA meetings.

**Data Used**

- Abstinent at assessment
- Leaving due to adverse events
- Leaving study early

### GASTPAR2002

<table>
<thead>
<tr>
<th>Study Type: RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Analysis: ITT - LOCF</td>
</tr>
<tr>
<td>Blindness: Double blind</td>
</tr>
<tr>
<td>Duration (days): Mean 84</td>
</tr>
<tr>
<td>Setting: Study was conducted at 7 sites in Germany. Participants were recently detoxified.</td>
</tr>
<tr>
<td>Notes: Randomisation: no details</td>
</tr>
<tr>
<td>Info on Screening Process: no details</td>
</tr>
</tbody>
</table>

Exclusions: No DSM diagnosis of alcohol dependence or abuse; psychiatric condition requiring medication, polysubstance abuse, or relevant medical conditions; current use of benzodiazepines, lithium, disulfiram, neuroleptics, or antidepressants.

Baseline: Total sample
Drinks per day: 7.1 (5.5) in UK units: 10.65

**Data Used**

- Abstinent at assessment
- Leaving due to adverse events
- Leaving study early

### Appendix 16e

- 1 N= 101 Group
- 2 N= 87 Group

- Group 1 N= 84
Naltrexone. Mean dose 50mg/day - 50mg of naltrexone taken once daily. "Standard" outpatient treatment - Usual psychosocial alcohol treatment program for each one of 7 sites used. At least 1 hour of psychosocial treatment delivered each week. The exact type and amount of treatment was not constrained by the protocol.

- Group 2 N= 87
Placebo - Inactive intervention, identical in appearance and dosing schedule to active intervention.
"Standard" outpatient treatment - Usual psychosocial alcohol treatment program for each one of 7 sites used. At least 1 hour of psychosocial treatment delivered each week. The exact type and amount of treatment was not constrained by the protocol.

**Data Used**

- Time to first relapse
- Time to first drink
- % days abstinent
- Drinks per drinking day
- % days abstinent
- With partner

**Notes**

- Randomisation: within site according to a computerised schedule.

**Info on Screening Process:** n=605 screened, n=113 randomised. The majority of participants were eligible for randomisation because of the presence of depressive symptoms or failure to follow-up.
## HEINALA2001

### Study Type: RCT

**Type of Analysis:** ITT  
**Blindness:** Double blind  
**Duration (days):** Mean 84

**Setting:** Participants were people seeking treatment for alcoholism, who responded to advertisements for the study.  
**Notes:** Randomisation: no details  
**Info on Screening Process:** n=326 were interviewed over the telephone, n=137 were invited to be screened in person, of which n=121 gave informed consent and were randomised to treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>N=</th>
<th>Study Group Details</th>
</tr>
</thead>
</table>
| 1     | 50 | Supportive psychotherapy - Supportive group therapy for relapse prevention once per week, alongside individual supportive counselling.  
**Placebo:** Inactive control taken on same schedule as active treatment. |
| 2     | 101| Supportive psychotherapy - Supportive group therapy for relapse prevention once per week, alongside individual supportive counselling.  
**Placebo:** Inactive control taken on same schedule as active treatment. |
| 3     | 29 | Supportive psychotherapy - Supportive group therapy for relapse prevention once per week, alongside individual supportive counselling.  
**Placebo:** Inactive control taken on same schedule as active treatment. |
| 4     | 25 | Supportive psychotherapy - Supportive group therapy for relapse prevention once per week, alongside individual supportive counselling.  
**Placebo:** Inactive control taken on same schedule as active treatment. |

### Data Used

<table>
<thead>
<tr>
<th>Group</th>
<th>N=</th>
<th>Data Used Details</th>
</tr>
</thead>
</table>
| 1     | 50 | Relapse  
**Notes:** Relapse to heavy drinking: drinking 5 or more drinks in one occasion.  
**Drink= 12 g of alcohol**  
**Coping skills:** Supported slips if controlled/stop binging  
**Supportive therapy:** supported complete abstinence. |
| 2     | 101| Relapse  
**Notes:** Relapse to heavy drinking: drinking 5 or more drinks in one occasion.  
**Drink= 12 g of alcohol**  
**Coping skills:** Supported slips if controlled/stop binging  
**Supportive therapy:** supported complete abstinence. |
| 3     | 29 | Relapse  
**Notes:** Relapse to heavy drinking: drinking 5 or more drinks in one occasion.  
**Drink= 12 g of alcohol**  
**Coping skills:** Supported slips if controlled/stop binging  
**Supportive therapy:** supported complete abstinence. |
| 4     | 25 | Relapse  
**Notes:** Relapse to heavy drinking: drinking 5 or more drinks in one occasion.  
**Drink= 12 g of alcohol**  
**Coping skills:** Supported slips if controlled/stop binging  
**Supportive therapy:** supported complete abstinence. |

### Notes:

- **Relapse:** defined as >5 drinks per day for men (>4 drinks for women)  
- **Baseline:**  

<table>
<thead>
<tr>
<th>N= 121</th>
</tr>
</thead>
</table>
| Age: Mean 45 Range 21-65  
**Sex:** 86 males 35 females  
**Diagnosis:** 100% Alcohol Dependence by DSM IV  
**Exclusions:** <21 or >65 years of age, no DSM-IV diagnosis of alcohol dependence, consumption of <5 drinks per day in last 30 days, unstable living condition and no collateral reporter available. Further criteria: other current drug abuse or dependence (including marijuana), ever having used opiates, current major psychiatric disorder as determined by the SCID, current use of psychotropic or antiseizure medications or disulfiram, and liver function test results (ALT and AST) greater than 250 IU.  
**Notes:** Coping skills: supported slips if controlled/stop binging  
**Supportive therapy:** supported complete abstinence.  
**Baseline:** Total sample  
**Married (%):** 72.7  
**Employed (%):** 79.4 |

### Notes:

- **Baseline:**  

<table>
<thead>
<tr>
<th>N= 121</th>
</tr>
</thead>
</table>
| Age: Mean 45 Range 21-65  
**Sex:** 86 males 35 females  
**Diagnosis:** 100% Alcohol Dependence by DSM IV  
**Exclusions:** <21 or >65 years of age, no DSM-IV diagnosis of alcohol dependence, consumption of <5 drinks per day in last 30 days, unstable living condition and no collateral reporter available. Further criteria: other current drug abuse or dependence (including marijuana), ever having used opiates, current major psychiatric disorder as determined by the SCID, current use of psychotropic or antiseizure medications or disulfiram, and liver function test results (ALT and AST) greater than 250 IU.  
**Notes:** Coping skills: supported slips if controlled/stop binging  
**Supportive therapy:** supported complete abstinence.  
**Baseline:** Total sample  
**Married (%):** 72.7  
**Employed (%):** 79.4 |

## HUANG2005

### Study Type: RCT

**Type of Analysis:** ITT  
**Blindness:** Double blind  
**Duration (days):** Mean 98

**Setting:** Alcoholism treatment unit of a Alcoholism treatment unit of a

<table>
<thead>
<tr>
<th>Group</th>
<th>N=</th>
<th>Study Group Details</th>
</tr>
</thead>
</table>
| 1     | 20 | Supportive psychotherapy - Supportive group therapy for relapse prevention once per week, alongside individual supportive counselling.  
**Placebo:** Inactive control taken on same schedule as active treatment. |
| 2     | 34 | Supportive psychotherapy - Supportive group therapy for relapse prevention once per week, alongside individual supportive counselling.  
**Placebo:** Inactive control taken on same schedule as active treatment. |
| 3     | 33 | Supportive psychotherapy - Supportive group therapy for relapse prevention once per week, alongside individual supportive counselling.  
**Placebo:** Inactive control taken on same schedule as active treatment. |
| 4     | 25 | Supportive psychotherapy - Supportive group therapy for relapse prevention once per week, alongside individual supportive counselling.  
**Placebo:** Inactive control taken on same schedule as active treatment. |

### Data Used

<table>
<thead>
<tr>
<th>Group</th>
<th>N=</th>
<th>Data Used Details</th>
</tr>
</thead>
</table>
| 1     | 20 | Relapse  
**Notes:** Relapse to heavy drinking: drinking 5 or more drinks in one occasion.  
**Drink= 12 g of alcohol**  
**Coping skills:** Supported slips if controlled/stop binging  
**Supportive therapy:** supported complete abstinence.  
**Baseline:** Total sample  
**Married (%):** 72.7  
**Employed (%):** 79.4 |
| 2     | 34 | Relapse  
**Notes:** Relapse to heavy drinking: drinking 5 or more drinks in one occasion.  
**Drink= 12 g of alcohol**  
**Coping skills:** Supported slips if controlled/stop binging  
**Supportive therapy:** supported complete abstinence.  
**Baseline:** Total sample  
**Married (%):** 72.7  
**Employed (%):** 79.4 |
| 3     | 33 | Relapse  
**Notes:** Relapse to heavy drinking: drinking 5 or more drinks in one occasion.  
**Drink= 12 g of alcohol**  
**Coping skills:** Supported slips if controlled/stop binging  
**Supportive therapy:** supported complete abstinence.  
**Baseline:** Total sample  
**Married (%):** 72.7  
**Employed (%):** 79.4 |
| 4     | 25 | Relapse  
**Notes:** Relapse to heavy drinking: drinking 5 or more drinks in one occasion.  
**Drink= 12 g of alcohol**  
**Coping skills:** Supported slips if controlled/stop binging  
**Supportive therapy:** supported complete abstinence.  
**Baseline:** Total sample  
**Married (%):** 72.7  
**Employed (%):** 79.4 |

### Notes:

- **Baseline:**  

<table>
<thead>
<tr>
<th>N= 40</th>
</tr>
</thead>
</table>
| Age: Mean 41 Range 20-60  
**Sex:** all males  
**Diagnosis:** 100% Alcohol Dependence by DSM-III |

### Notes:

- **Baseline:**  

<table>
<thead>
<tr>
<th>N= 40</th>
</tr>
</thead>
</table>
| Age: Mean 41 Range 20-60  
**Sex:** all males  
**Diagnosis:** 100% Alcohol Dependence by DSM-III |

### Financially supported by the Finnish Alcohol Research Foundation and the National Public Health Institute.
Notes: Relapse: defined as having more than 5 drinks per day or 5 days drinking per week, blood alcohol concentration standing at >100mg/dl and any situation requiring inpatient detoxification treatment.

Supportive psychotherapy - Weekly, 30 minute individual psychotherapy sessions, focused on abstinence and compliance enhancement, conducted in outpatients department.

Group 1 N= 40
Group therapy - Weekly abstinence orientated sessions, including coping skills and relapse prevention based on the cognitive behavioural model of substance abuse. Groups were of between 8 and 14 participants and sessions lasted 90 minutes.

Acamprosate. Mean dose 1998mg/day - Medication dose constant throughout 12 week study period. 1998mg/day given in form of 2 tablets three times daily.

Group 2 N= 40
Naltrexone. Mean dose 50mg/day - Medication dose constant throughout 12 week study period. 50mg/day given as 1 capsule in the morning.

Group therapy - Weekly abstinence orientated sessions, including coping skills and relapse prevention based on the cognitive behavioural model of substance abuse. Groups were of between 8 and 14 participants and sessions lasted 90 minutes.

Group 3 N= 40
Naltrexone + Acamprosate - Medication dose constant throughout 12 week study period. Same dosage and tablet numbers as the single pharmacological interventions.

Group therapy - Weekly abstinence orientated sessions, including coping skills and relapse prevention based on the cognitive behavioural model of substance abuse. Groups were of between 8 and 14 participants and sessions lasted 90 minutes.

Funding: medication donated by DuPont (nalx) and Merck (Acamp)
<table>
<thead>
<tr>
<th>Study Type: RCT</th>
<th>Controlled Clinical Trial</th>
<th>Double-blind study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Analysis: ITT- all having at least 1 follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blindness: Double blind</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (days): Mean 84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: recruitment was from individuals who entered treatment at an outpatient community treatment program for an alcohol use disorder. US.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes: Randomisation: Urn randomisation used to balance gender, comorbidities, severity of dependence (ADS) and treatment intensity across groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Info on Screening Process: n=191 screened, n=145 enrolled. No details on reasons for exclusion.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline: Nalx Plb TAU</td>
<td>Married (%): 39 29 23</td>
<td>Employed(%): 43 56 67</td>
</tr>
</tbody>
</table>

**KILLEEN2004**

- **Group 1 N= 51**: Naltrexone. Mean dose 50mg/day - 50 mg of naltrexone taken daily
  - Psychosocial program: Program delivered at study centre. Treatment intensity ranged from 1 to 2 hours per week group and/or individual therapy to intensive group programs for 3 to 4 hours, 4 days per week. Therapy was eclectic, including 12-step and relapse prevention.

- **Group 2 N= 36**: Placebo - inactive intervention, identical in appearance and dosing schedule to active intervention.
  - Psychosocial program: Program delivered at study centre. Treatment intensity ranged from 1 to 2 hours per week group and/or individual therapy to intensive group programs for 3 to 4 hours, 4 days per week. Therapy was eclectic, including 12-step and relapse prevention.

- **Group 3 N= 46**: Psychosocial program - Program delivered at study centre. Treatment intensity ranged from 1 to 2 hours per week group and/or individual therapy to intensive group programs for 3 to 4 hours, 4 days per week. Therapy was eclectic, including 12-step and relapse prevention.

**Data Used**

- Relapse
- Leaving study early

**Data Not Used**

- Craving - OCDS - Not relevant

**Notes:** Supported by grants from the NIAAA.

---

<table>
<thead>
<tr>
<th>Study Type: RCT</th>
<th>Controlled Clinical Trial</th>
<th>Double-blind study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Analysis: ITT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blindness: Double blind</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (days): Mean 77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: recruited through advertisements in local news media and referrals from area clinicians, US.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes: Randomisation: no details</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Info on Screening Process: no details</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**KRAZLNER2000**

- **Group 1 N= 61**: Naltrexone. Mean dose 50mg/day - 50 mg of naltrexone taken daily
  - Coping skills: 12-session treatment based on McCrady et al (1985). Designed to foster problem solving, interpersonal skills, relaxation and skills for coping with cravings.

**Data Used**

- % heavy drinking days
- Drinks per day
- % drinking days
- Abstinent at endpoint
- Leaving study early

**Data Not Used**

- Craving - OCDS - Not relevant

**Notes:** Supported by grants from the National Institute of Health.
4% Social phobia by DSM-III

Exclusions: <18 or >60 years of age, no desire for abstinence, no DSM-III diagnosis of alcohol dependence, maintaining abstinence for less than 3 days before baseline assessments, unable to read English. Further exclusion: homeless, currently dependent on psychoactive substance other than nicotine and alcohol, past diagnosis of opioid dependence, regularly used psychoactive medications or disulfiram, currently suicidal, manic or psychotic, had significant uncontrolled medical illness or were abstinent for more than 28 days.

Notes: Participants required to desire abstinence from alcohol for inclusion.

Baseline: Nalx  Nef  Plb
MAST score: 25.7 (11.2) 26.9 (11.9) 26.8 (10.6)
Married (%): 39.3 49.2 46
Employed (%): 73.8 71.2 69.8

KRYSTAL2001

Study Type: RCT
Type of Analysis: ITT- all providing some outcome data.
Blindness: Double blind
Duration (days): Mean 365
Followup: 6 months
Setting: Recruited outpatients from veteran affairs medical centres
Notes: Randomisation: no details
Info on Screening Process: n=3372 screened, n=627 patients included in study. No details on reasons for exclusions.

Data Used
Drinks per drinking day
% drinking days
Time to first relapse
Relapse
Leaving study early

Notes: Outcomes for both naltrexone groups recorded together at 3 months, but reported separately at 1 year.
Relapse: 6+ drinks for men, 4+ for women in one occasion.

Group 1 N= 209
Naltrexone (3 months). Mean dose 50mg/day - 50mg of naltrexone taken daily for 3 months, placebo given for next 9 months.
12-step facilitation counselling - Individual therapy for 13 months, and encouraged to join AA. Counselling aimed at reinforcing abstinence and providing basic relapse-prevention information. Visits were weekly for first 16 weeks, bi-weekly until week 36 and monthly to week 56.

Group 2 N= 209
Naltrexone (12 months). Mean dose 50mg/day - 50mg of naltrexone taken daily for 12 months.
12-step facilitation counselling - Individual therapy for 13 months, and encouraged to join AA. Counselling aimed at reinforcing abstinence and providing basic relapse-prevention information. Visits were weekly for first 16 weeks, bi-weekly until week 36 and monthly to week 56.

Group 3 N= 209
Placebo - Inactive intervention, identical in appearance and dosing schedule to active intervention.
12-step facilitation counselling - Individual therapy for 13 months, and encouraged to join AA. Counselling aimed at reinforcing abstinence and providing basic relapse-prevention information. Visits were weekly for first 16 weeks, bi-weekly until week 36 and monthly to week 56.

Supported by the cooperative studies program of the Department of Veteran Affairs Office of Research and Development. Naltrexone and placebo were donated by DuPont pharmaceuticals, which also analysed blood naltrexone levels.
Appendix 16e

Partial hospital treatment program in a private setting: Recruited from a substance abuse treatment programme in a inpatient treatment centre, having completed detoxification and primary rehabilitation in setting. Participants were presenting to drug and alcohol services at four Sydney hospitals.

Notes: Randomisation: by random numbers.

Info on Screening Process: n=238 were assessed, n=15 excluded as they did not meet inclusion criteria, n=42 refused or did not re-attend, leaving n=107 to be randomised.

n=107
Age: Mean 45 Range 18-70
Sex: 74 males 33 females
Diagnosis: 100% Alcohol Dependence by DSM IV

Exclusions: <18 and >70 years of age, no DSM-IV diagnosis of alcohol dependence. Further criteria: pregnant women and women of child bearing age not using contraception, patients using either illicit or prescribed opioids, patients with significant liver disease (GGT, AST, ALT more than twice normal), patients with any other concomitant major medical or psychiatric illness, untreated major depression or a recent suicide attempt.

Baseline: Alcohol intake (g/week) UK units
Nalx: 1200.3 (1075-1365.7) 150
PLB: 1152.2 (1025.9-1277.5) 144.03

Data Used
Drinking days per week
Relapse
Drinks per week
Leaving due to adverse events
Leaving study early

Data Not Used
GTT - Not relevant
Craving - OCDS - Not relevant
Notes: * Time to first relapse no SDs

Relapse: drinking to previous heavy levels, in excess of the National Health and Medical Research Council Recommendations.

Group 1 N=56
Naltrexone. Mean dose 50mg/day - 50mg of Naltrexone taken once daily.

Group 2 N=51
Placebo - Inactive intervention, same appearance and dosing schedule as the active intervention

This study received financial support from Northern Sydney Health, Orphan Australia, DuPont Pharma and the Kim and Kris Morris Trust Fund for Drug & Alcohol Services.

Lee2001

Study Type: RCT
Type of Analysis: ITT
Blindness: Double blind
Duration (days): Mean 84

Setting: Recruited individuals with drinking problems admitted to the alcohol treatment centre at a psychiatric institution, in Singapore. Notes: Randomisation: no details.

Info on Screening Process: n=238 were assessed, n=35 refused or did not re-attend, n=15 excluded as they did not meet inclusion criteria, leaving n=107 to be randomised.

n=53
Age: Mean 45 Range 21-65
Sex: all males
Diagnosis: 100% Alcohol Dependence by DSM IV

Exclusions: <21 and >65 years of age, no DSM-IV diagnosis of alcohol dependence, not mentally competent, not completing detoxification and primary rehabilitation programme in the inpatient treatment centre, having marked impairment of liver function. Further criteria: dementia or major cognitive deficit, comorbid major mental illness, other concurrent illicit drug use or dependence, judged by the treating clinician as quite unlikely to be compliant with medication.

Baseline: NALX PLB
AUQ 19.4 (15.3) 16.1 (9.1)
ADS 16.5 (6.6) 17.9 (9.2)
Married(%): 71.4 77.8
Employed(%): 429 38.9

Data Used
Returned to drinking
Leaving study early

Data Not Used
Alcohol urge questionnaire - Not relevant

Relapse: drinking to previous heavy levels, in excess of the National Health and Medical Research Council Recommendations.

Group 1 N=35
Naltrexone. Mean dose 50mg/day - 50 mg tablet taken daily
Psychosocial program - Total abstinence, 12-step based primary rehabilitation programme for 1 month, included daily lectures, twice-weekly psychotherapy, thrice-weekly support group meetings. After 1 month, (until study end), outpatient group therapy, AA and support meetings.

Group 2 N=18
Placebo - Vitamin C, appeared identical to placebo tablet, taken at same dosing schedule.
Psychosocial program - Total abstinence, 12-step based primary rehabilitation programme for 1 month, included daily lectures, twice-weekly psychotherapy, thrice-weekly support group meetings. After 1 month, (until study end), outpatient group therapy, AA and support meetings.

Monti2001

Study Type: RCT
Type of Analysis: ITT
Blindness: Double blind
Duration (days): Mean 84

Followup: one year

Setting: Recruited from a substance abuse partial hospital treatment program in a private setting. Participants were presenting to drug and alcohol services at four Sydney hospitals.

Notes: Randomisation: by random numbers.

Info on Screening Process: n=164 assessed, n=15 excluded as they did not meet inclusion criteria, n=42 refused or did not re-attend, leaving n=107 to be randomised.

n=128
Age: Mean 39
Sex: 97 males 31 females
Diagnosis: 100% Alcohol Dependence by DSM-IV SCID

Exclusions: No DSM-IV diagnosis of alcohol abuse or dependence, current opiate abuse, opiate use 2 weeks

Data Used
Relapsed by endpoint
Drinks per drinking day
% heavy drinking days

Relapse: drinking to previous heavy levels, in excess of the National Health and Medical Research Council Recommendations.

Group 1 N=64
Naltrexone. Mean dose 50mg/day - 50mg taken daily.

Group 2 N=64
Placebo - Inactive control, same appearance and dosing procedure as with active pharmacological intervention

Supported by grants from the NIAAA. Medication and placebo supplies were supplied by DuPont-Merck Pharmaceutical Company.
before study start, urine screen positive for opiates, current psychiatric symptoms or organic impairment, pregnant, nursing, or not using reliable birth control if female, currently suicidal or symptomatic of post-traumatic stress disorder, medical condition or liver function tests that contraindicate naltrexone, disulfiram use during the medication trial.

Baseline: Total sample (N=111 before treatment)
- Days drinking (%): 68.1 (28.3)
- Days heavy drinking (%): 48.7 (32.1)
- Drinks per drinking day: 12.0 (7.5)
- Days heavy drinking (%): 48.7 (32.1)
- Drinks per drinking day: 12.0 (7.5)
- DDD in UK units: 18
- Married/cohabiting (%): 46
- Employed (%): 84

MORLEY2006

Study Type: RCT
Type of Analysis: ITT - all taking one dose of study medication
Blindness: Double blind
Duration (days): Mean 84
Setting: Subjects had attended an in-patient detoxification program, out-patient treatment or follow-up or who responded to live or print advertisements.
Notes: Randomisation: random number list in 12 groups of 12 for each study site.

In Info Screening Process: n=328 screened, n=159 excluded (n=113 refused to participate, n=10 had severe medical/psychiatric concerns). This left n=169 to be randomised.

<table>
<thead>
<tr>
<th>Data Used</th>
<th>Time to first drink</th>
<th>Relapse</th>
<th>Abstinent at endpoint</th>
<th>Drinks per drinking day</th>
<th>Time to first relapse</th>
<th>CAD</th>
<th>Leaving study early</th>
<th>ADS score - Not relevant</th>
<th>Notes: Relapse: 4 or more drinks for women, 6 or more for men. Lapse: 1 drink</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 N=55</td>
<td>Acamprosate. Mean dose 1998mg/day - Participants took six 333mg tablets daily</td>
<td>Medication compliance therapy - four to six sessions of manualised compliance therapy were offered. This was a brief intervention targeting treatment compliance issues.</td>
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<tr>
<td>Group 2 N=53</td>
<td>Naltrexone. Mean dose 50mg - Participants took 50mg in one tablet daily</td>
<td>Medication compliance therapy - four to six sessions of manualised compliance therapy were offered. This was a brief intervention targeting treatment compliance issues.</td>
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</tr>
<tr>
<td>Group 3 N=61</td>
<td>Placebo - Inactive control, tablets appeared identical to either naltrexone or acamprosate and were taken in the same dosing schedule.</td>
<td>Medication compliance therapy - four to six sessions of manualised compliance therapy were offered. This was a brief intervention targeting treatment compliance issues.</td>
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</tr>
</tbody>
</table>

MORRIS2001

Study Type: RCT
Type of Analysis: ITT
Blindness: Double blind
Duration (days): Mean 84
Setting: Participants were recruited from a medical centre in Melbourne, Australia.
Notes: Randomisation: no details provided.

In Info Screening Process: n=137 were screened, but only n=111 were included, n=26 were screened, but only n=111 were included, n=26 were screened, but only n=111 were included.

Data Used

Relapse
Leaving due to adverse events
Leaving study early

Group 1 N=55
Naltrexone. Mean dose 50mg/day - 50mg tablet taken daily
Group relapse prevention - Weekly, 1.5 hour relapse prevention training developed by Turning Point. Group session also provided education and social support, through information on alcohol use and abuse, and it's consequences.

TurningPoint developed the 12-week group therapy programme, and DuPont Pharmaceutical Company supplied the active naltrexone tablets and matching placebos.
were excluded for not meeting eligibility criteria or relapsing before randomisation.

7% major depression by DSM-III
25% Post-traumatic stress disorder by DSM-III
25% Social phobia by DSM-III
14% dysthymia by DSM-III

Exclusions: <18 and >65 years of age, no current DSM-III diagnosis of alcohol dependence, score of <5 on the MAST, living >1.5 hours drive from the hospital, <3 and >30 days abstinent before study. Further criteria: other current drug abuse or dependence (except nicotine), current use of opiates or disulfiram, bilirubin level above normal laboratory range, and AST >5 times normal. Dementia, acute psychotic illness or suicidal behaviour were also excluded.

Notes: Participants needed to maintain abstinence for at least 3 days (but no more than 30).

Baseline: NALX PLB
Drinking days per week: 5 (2) 5 (2)
Std drinks per week: 89 (55) 74 (35)
D per week in UK units: 115.7 96.2
days of sobriety (before study): 8 (5) 9 (6)
Married (%): 45 50

Data Used
Relapse
Total drinks
% drinking days
Drinks per drinking day
% continuously abstinent
Leaving study early
Notes: Relapse: drinking 5 or more drinks for men, 4 or more for women.

Notes: "TIME TO FIRST DRINK AND HEAVY DRINKING REPORTED, BUT NO SDs.
Relapse: defined as (1) drinking 5 or more drinks (1 drink = 10g alcohol) on one occasion, (2) drinking for 5 or more days in the week, (3) BAC >100mg/dl.

Group 1 N= 29
Naltrexone. Mean dose 50mg/day - 50mg, in one pill taken daily.
Relapse prevention - Weekly, manual guided therapy, using didactic presentations, cognitive and behavioural rehearsal within sessions, and homework exercises. Patients learn to identify and handle situations that place them at high risk of drinking.

Group 2 N= 25
Naltrexone. Mean dose 50mg/day - 50mg, in one pill taken daily.
Relapse prevention - Weekly, manual guided therapy, using didactic presentations, cognitive and behavioural rehearsal within sessions, and homework exercises. Patients learn to identify and handle situations that place them at high risk of drinking.

Group 3 N= 56
Placebo - inactive control intervention, dosing schedule identical to the active intervention.
Group relapse prevention - Weekly, 1.5 hour relapse prevention training developed by Turning Point. Group session also provided education and social support, through information on alcohol use and abuse, and its consequences.

Study supported in part by grants from the National Institute on Alcohol Abuse and Alcoholism and a grant from the National Institute on Drug Abuse. DuPont pharmaceuticals provided the naltrexone and placebo.

Study Type: RCT
Type of Analysis: ITT - all taking one dose of study medication
Blindness: Double blind
Duration (days): Mean 84
Setting: recruited through advertisements in local newspapers and from patients seeking treatment at the outpatient alcohol treatment unit. (USA)

Notes: Randomisation: no details
Info on Screening Process: n=194 screened, n=19 dropped before eligibility could be attained, n=21 excluded for medical reasons, n=8 excluded for diagnostic or current psychotropic medication use, n=8 inadequate abstinence length. n=104 randomised.

OMALLEY1992
Study Type: RCT
Type of Analysis: ITT - all taking one dose of study medication
Blindness: Double blind
Duration (days): Mean 84
Setting: recruited through advertisements in local newspapers and from patients seeking treatment at the outpatient alcohol treatment unit. (USA)

Notes: Randomisation: no details
Info on Screening Process: n=194 screened, n=19 dropped before eligibility could be attained, n=21 excluded for medical reasons, n=8 excluded for diagnostic or current psychotropic medication use, n=8 inadequate abstinence length. n=104 randomised.

n= 104
Age: Mean 41 Range 18-65
Sex: 77 males 27 females

Diagnosis: 100% Alcohol Dependence by DSM-III-R

Exclusions: <18 and >65 years of age, no DSM-III-R diagnosis of alcohol dependence. Further criteria: current DSM-III-R diagnosis of dependence on other substances except nicotine, history of opioid abuse, history of psychosis, current suicidality, homicidality, or psychiatric symptoms that require other medications, current use of disulfiram, evidence of significant cerebral, renal, thyroid or cardiac disease, history of cirrhosis, pregnancy, nursing or refusal to use a reliable method of birth control.

Notes: Participants had to have achieved abstinence for 7-30 days before study start.

Baseline: whole sample
drinks per drinking occasion: 11.2 (9.2)
DDD in UK units: 16.8
days drinking (60 days pre-study): 60%
Married : 34%
Employed : 73%
### O'MALLEY2003

| Study Type: RCT |
| Type of Analysis: ITT- all attending first session of treatment |
| Blindness: Double blind |
| Duration (days): Mean 168 |
| Setting: Recruited through newspaper advertisements or from patients seeking treatment at the outpatient alcohol treatment unit of a mental health centre. |
| Notes: Randomisation: computer generated schedule by the pharmacist. |
| Info on Screening Process: n=425 met initial eligibility criteria, n=107 of these were excluded after more thorough screening, n=121 declined participation or dropped out before randomisation, n=197 were randomised to open label initiation study, n=84 dropped out before maintenance |

| n= 113 |
| Age: Mean 44  Range 18-65 |
| Sex: 79 males  34 females |
| Diagnosis: 100% Alcohol Dependence by DSM-III |

Exclusions: <18 and >65 years of age, no current DSM-III diagnosis of alcohol dependence, abstinence from alcohol for <5 or >30 days at treatment initiation. Further criteria: no telephone or stable residence, current DSM-III criteria for cocaine abuse or dependence on other substances other than alcohol, current DSM-III criteria for opiate or currently using opiates, significant psychiatric problems (e.g. suicidal, psychosis, and current manic episode) or unstable pharmacological treatment for psychiatric disorders, unstable or significant medical conditions, evidence of severe hepatocellular injury (AST or ALT >3 times upper limit of normal), required more intensive treatment, more than 5 previous treatment episodes. Participant also had to respond to naltrexone treatment in the initiation study before moving into maintenance treatment. |

Notes: Study 1 = initiation study, all participants received naltrexone, but were randomised to CBT or PCM. Study 2 was randomised all PCM responders to naltrexone or placebo with continued PCM. Study 3 was randomised CBT responders to CBT & naltrexone or placebo. |

Baseline: CBT (study 1)  PCM (study 1)  Drinks per drinking day (in 90 days): 9.2 (5)  9.6 (6.4)  In UK units: 13.8  14.4  Days without heavy drinking: 46.9 (29.4)  42.1 (32.4)  %days abstinent: 40.2 (23.1)  35.1 (23.2)  Married (%): 46  44  Employed (%): 81  74

### O'MALLEY2008

| Study Type: RCT |
| Type of Analysis: ITT |
| Appendix 16e |

| n= 101 |
| Age: Mean 40  Range 18-65 |
| Sex: 67 males  34 females |

Data Used: Leaving due to adverse events  % heavy drinking days  Drinks per drinking day

| Group 1 N= 27 |
| Placebo - inactive placebo tablet, identical in appearance to active naltrexone |
| Primary care management - Individual sessions, first was 45 minutes, following sessions were 15-20 minutes in length (held monthly during maintenance). Based around advice and clinical management techniques used in primary care settings. All patients referred to AA. |
| Group 2 N= 30 |
| Naltrexone. Mean dose 50mg/day - 50mg of naltrexone taken daily |
| Primary care management - Individual sessions, first was 45 minutes, following sessions were 15-20 minutes in length (held monthly during maintenance). Based around advice and clinical management techniques used in primary care settings. All patients referred to AA. |
| Group 3 N= 30 |
| Placebo - inactive placebo tablet, identical in appearance to active naltrexone |
| Coping skills - Individual sessions, 1.25 hour sessions, held weekly during initiation study, but biweekly in first month of maintenance, then monthly thereafter. From project MATCH manual (referred to as 'CBT' in paper). AA recommended. |
| Group 4 N= 26 |
| Naltrexone. Mean dose 50mg/day - 50mg of naltrexone taken daily |
| Coping skills - Individual sessions, 1.25 hour sessions, held weekly during initiation study, but biweekly in first month of maintenance, then monthly thereafter. From project MATCH manual (referred to as 'CBT' in paper). AA recommended. |

Supported by grants from the National Institute of Health, Bethesda, and by Veterans Administration New England Mental Illness Research Education and Clinical Center (MIRECC). Naltrexone and placebo supplied by DuPont pharmaceuticals.

Funded by the National Institute on Alcohol Abuse and Alcoholism and the National Centre on Minority.

---

**Data Used**

| responders |
| % continuously abstinent |
| Drinks per drinking day |
| % days abstinent |
| Leaving study early |

**Data Not Used**

| Craving - OCDS - Not relevant |

**Notes:** Responders: individuals with 2 or less heavy drinking days during any 28-day period during discontinuation study.


### OSLIN1997

**Study Type:** RCT  
**Type of Analysis:** ITT  
**Blindness:** Double blind  
**Duration (days):** Mean 84

**Setting:** Participants recruited from the Baltimore Veterans Affairs Medical Center.  
**Notes:** Randomisation: no details  
**Info on Screening Process:** no details

<table>
<thead>
<tr>
<th>Data Not Used</th>
<th>Data Used</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relapse</strong></td>
<td><strong>Relapse</strong></td>
</tr>
<tr>
<td>% drinking days</td>
<td>% drinking days</td>
</tr>
<tr>
<td>Leaving due to adverse events</td>
<td>Leaving due to adverse events</td>
</tr>
<tr>
<td>Notes:</td>
<td>Notes:</td>
</tr>
<tr>
<td>Relapse defined as either (1) reporting five or more drinks per drinking occasion, (2) reporting drinking 5 or more days within 1 week, (3) coming to treatment with a blood alcohol concentration (BAC) of 100mg/dL.</td>
<td>Relapse defined as either (1) reporting five or more drinks per drinking occasion, (2) reporting drinking 5 or more days within 1 week, (3) coming to treatment with a blood alcohol concentration (BAC) of 100mg/dL.</td>
</tr>
</tbody>
</table>

**Diagnosis:** 100% Alcohol Dependence by DSM-III

**Exclusions:** <50 and >70 years of age, no DSM-II-R diagnosis of alcohol dependence. Further criteria: unstable or serious medical problem, diagnosis of severe dementia, seizure disorder, mental retardation, or psychosis, being judged by physician as being a danger to self or others, use of psychoactive substance other than alcohol, caffeine, or nicotine within the 6 weeks prior to the study, use of an opiate within 7 days before initiation of naltrexone; having a positive drug screen for opiates, amphetamine, cocaine, benzodiazepines, or barbiturates at the end of the study; having active hepatitis or severe hepatic disease

**Baseline:** Nalx PLB  
**Drinks per drinking day:** 11.4 (6.4) 10.0 (8.1)  
**In UK units:** 17.1 15  
**Married (%):** 17.4 14.3

**OSLIN2008**

**Study Type:** RCT  
**Type of Analysis:** ITT  
**Blindness:** Double blind  
**Duration (days):** Mean 168

**Setting:** recruited through advertisements in the local media.  
**Notes:** Randomisation: no details  
**Info on Screening Process:** no details

<table>
<thead>
<tr>
<th>Data Not Used</th>
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<tbody>
<tr>
<td><strong>Relapse</strong></td>
<td><strong>Relapse</strong></td>
</tr>
<tr>
<td>% drinking days</td>
<td>% drinking days</td>
</tr>
<tr>
<td>Leaving due to adverse events</td>
<td>Leaving due to adverse events</td>
</tr>
<tr>
<td>Notes:</td>
<td>Notes:</td>
</tr>
<tr>
<td>Relapse defined as either (1) reporting five or more drinks per drinking occasion, (2) reporting drinking 5 or more days within 1 week, (3) coming to treatment with a blood alcohol concentration (BAC) of 100mg/dL.</td>
<td>Relapse defined as either (1) reporting five or more drinks per drinking occasion, (2) reporting drinking 5 or more days within 1 week, (3) coming to treatment with a blood alcohol concentration (BAC) of 100mg/dL.</td>
</tr>
</tbody>
</table>

**Diagnosis:** 100% Alcohol Dependence by DSM-IV SCID

**Exclusions:** <18 years of age, no DSM-IV diagnosis of alcohol dependence. Further criteria: schizophrenia, bipolar disorder, depression, dysthymia, panic attack or disorders, anxiety disorder, obsessive-compulsive disorder, or psychosis, use of psychoactive substances other than alcohol or caffeine, use of any medical condition that would contraindicate the use of sertraline or naltrexone

**Baseline:** Nalx PLB  
**Drinks per drinking day:** 17.6 (12.7) 16.5 (8.44) 19.6 (13.10)  
**In UK units:** 26.4 24.75 29.4  
**% days abstinent:** 43.6 (25.5) 40.6 (26.86) 43.2 (25.29)  
**Married (%):** 47 35 27  
**Employed (%):** 62 59 58

**Group 2 N=34**  
Naltrexone + Sertraline - 12.5 mg given for one day, 25 mg for 2 days, 50 mg thereafter for 16 weeks. Sertraline dose was 50 mg a day for two weeks, and afterwards dose was increased to 100 mg daily.

**Group 3 N=33**  
Naltrexone + Sertraline - 12.5 mg given for one day, 25 mg for 2 days, 50 mg thereafter for 16 weeks. Sertraline dose was 50 mg a day for two weeks, and afterwards dose was increased to 100 mg daily.

**Group 1 N=21**  
Naltrexone. Mean dose 50mg/day - Naltrexone was given at 100mg on Mondays and Wednesdays, and 150mg was given on Fridays (equivalent to 50mg/day).

**Group 4 N=40**  
Naltrexone. Mean dose 100mg/day - Naltrexone was taken daily, but if not tolerated, dose was decreased to 50mg/day.

**Data Used**  
**Relapse**  
**% drinking days**  
**Leaving due to adverse events**  
**Notes:** Relapse defined as either (1) reporting five or more drinks per drinking occasion, (2) reporting drinking 5 or more days within 1 week, (3) coming to treatment with a blood alcohol concentration (BAC) of 100mg/dL.

**Data Not Used**  
**Alcohol urge questionnaire - Not relevant**  
**GGT - Not relevant**

**Medication and placebo were supplied by DuPont Merck pharmaceutical company.**

**Supported by grants from the NIAAA, the National Institute on Mental Health and the National Institute on Drug Abuse.**

This information is intended for educational purposes only and should not be used as a substitute for professional medical advice.
Notes: Outcomes reported for naltrexone vs placebo, regardless of psychosocial intervention.

Coping skills - Coping skills delivered in 50-60 minute sessions. Allowed up to 18 sessions in first 12 weeks of the study, then bi-weekly for last 12 weeks. Purpose of therapy was to identify triggers and life problems using a problem-solving/skills training format.

Group 2 N= 40
Placebo - Inactive intervention, identical in appearance and dosing schedule to active intervention
Coping skills - Coping skills delivered in 50-60 minute sessions. Allowed up to 18 sessions in first 12 weeks of the study, then bi-weekly for last 12 weeks. Purpose of therapy was to identify triggers and life problems using a problem-solving/skills training format.

Group 3 N= 39
Naltrexone - 100mg of naltrexone taken daily, but if not tolerated, dose was decreased to 50mg/day.
BRENDA - Up to 18, 20-30 minute sessions available for participants in first 12 weeks, sessions bi-weekly thereafter. Therapy was manualised and included motivational enhancement counselling.

Group 4 N= 40
Placebo - Inactive intervention, identical in appearance and dosing schedule to active intervention
BRENDA - Up to 18, 20-30 minute sessions available for participants in first 12 weeks, sessions bi-weekly thereafter. Therapy was manualised and included motivational enhancement counselling.

Group 5 N= 41
Naltrexone - 100mg of naltrexone taken daily, but if not tolerated, dose was decreased to 50mg/day.
Medication management - Total of 9, 5-10 minute meetings with a research physician over 24 weeks.

Group 6 N= 40
Placebo - Inactive intervention, identical in appearance and dosing schedule to active intervention
Medication management - Total of 9, 5-10 minute meetings with a research physician over 24 weeks.

The Fundacion Cerebro y Mente funded this research.

### Baseline:

<table>
<thead>
<tr>
<th></th>
<th>Drinks per day</th>
<th>Uk units drinking</th>
<th>% days Married</th>
<th>% Days Married</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaLx+BDA</td>
<td>9.1 (6.6)</td>
<td>13.65</td>
<td>74.3 (27.6)</td>
<td>30 87.5</td>
</tr>
<tr>
<td>Plb+BDA</td>
<td>9.1 (6.6)</td>
<td>13.65</td>
<td>74.3 (27.6)</td>
<td>30 87.5</td>
</tr>
<tr>
<td>NaLx+BRENDA</td>
<td>7.2 (6.0)</td>
<td>10.8</td>
<td>65.7 (29.0)</td>
<td>41 84.6</td>
</tr>
<tr>
<td>Plb+BRENDA</td>
<td>8.0 (5.1)</td>
<td>12</td>
<td>70.9 (28.5)</td>
<td>35.9 87.5</td>
</tr>
<tr>
<td>NaLx+Doctor</td>
<td>10.1 (6.5)</td>
<td>15.15</td>
<td>76.3 (22.1)</td>
<td>31.7 85.4</td>
</tr>
<tr>
<td>Plb+Doctor</td>
<td>8.0 (5.6)</td>
<td>12</td>
<td>70.0 (30.0)</td>
<td>38.5 85</td>
</tr>
</tbody>
</table>

### Data Used:

- Time to first drink
- Time to first relapse
- Craving - subjective desire

### Study Type:

RCT (Randomized Controlled Trial)

### Type of Analysis:

ITT (Intention to Treat)
Appendix 16e

Notes: Randomisation: Computer number.
Center.

Setting: Admitted alcohol-dependent patients receiving outpatient treatment at the University of Pennsylvania/Veterans Affairs Treatment Center.

Duration (days): Mean 365

Notes: Randomisation: using random number

Substance abuse treatment unit of Philadelphia.

Setting: Recruited newly admitted patients in

Duration (days): Mean 84

Blindness: Double blind

Study Type: RCT

Notes: Randomisation: no details

VOLPICELLI1992

Data Not Used

Diagnosis:
100% Alcohol Dependence by DSM-III

Exclusions: <18 and >65 years of age, no DSM-III-R
diagnosis of alcohol dependence, unstable family
environment. Further criteria: another substance use
disorder (except nicotine), another psychiatric disorder, a
medical condition that could hinder treatment compliance,

Notes: Abstinence was positively reinforced

Baseline:

Na1x Acamp

% days drinking (over 6 months):
87 (20) 87 (21)
drinks/drinking day (in UK units):
12.3 (5.0) 12.2 (5.1)
Married (%): 95 92
Employed (%): 75 75

VOLPICELLI1997

Data Not Used

Diagnosis:
100% Alcohol Dependence by DSM-III

Exclusions: No DSM-III-R criteria diagnosis for alcohol
dependence, no recent completion of medical detoxification
for alcohol withdrawal. Further criteria: major psychiatric
illness associated with psychosis or dementia at the time of
evaluation, history of unstable/serious medical condition,

Notes: Randomisation : Computer number

Appendix 16e

Data Not Used

Diagnosis:
100% Alcohol Dependence by DSM-III

Exclusions: <18 and >65 years of age, no DSM-III-R
diagnosis of alcohol dependence, unstable family
environment. Further criteria: another substance use
disorder (except nicotine), another psychiatric disorder, a
medical condition that could hinder treatment compliance,

Baseline:

Naltrexone Placebo

Drinking days:
0.02 (0.07) 0.06 (0.13)
Years heavy drinking:
20.4 (8.6) 19.4 (9.5)
Married (%): 42.8 45.7
Employed (%): 34.2 48.9

Group 1 N= 35
Naltrexone.

Psychosocial program - First month
consisted of 6 hours of day treatment,
made up of group therapy, individual
counselling, educational classes and
health education. Afterwards, patients
entered after-care treatment, consisting of
group therapy, twice a week for 11
months.

Group 2 N= 80
Acamprosate.

Supported by a National
Institute of Drug Abuse
Research Center grant,
National Institute of Alcohol
Abuse and Alcoholism
grant, and the Penn
Veterans Affairs Addiction
Research Center,
Philadelphia.

Group 1 N= 49
Naltrexone - Received 50 mg/day
per day for 12 weeks.
Counselling - Received relapse
prevention counselling (based on Gorski
& Miller) for 12 weeks. For the first
month of treatment, subject met twice per week. Remainder of
treatment, subjects met counsellors once per week.

Supported by grant from the
National Institute on
Alcoholism and Alcohol
Abuse, Rockville, MD, and
by Uni of Pennsylvania/Vet
Affairs Medical centre, from
National institute on drug
abuse center and veterans
affairs merit review
research funds
generated blocks of 20 subjects
Info on Screening Process: n=127 screened for initial interview, 12 initially dropped out, 1 dropped out because of work related problems, 13 inadequate/excessive duration of abstinence, 1 incarcerated, 1 relocated. 1 declined participation, 1 dropped from analysis due to medical error.

<table>
<thead>
<tr>
<th>Group 2 N= 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo - initial 1 week placebo lead in to establish baseline measures. 1 identical looking tablet to naltrexone prescribed once daily for 12 weeks.</td>
</tr>
<tr>
<td>Counselling - Received relapse prevention counselling (based on Gorski &amp; Miller) for 12 weeks. For the first month of treatment, subject met twice per week. Remainder of treatment, subjects met counsellors once per week.</td>
</tr>
</tbody>
</table>

Characteristics of Excluded Studies - see final section

References of Included Studies

**AHMADI2002** (Published Data Only)

**ANTON1999** (Published Data Only)

**ANTON2005** (Published Data Only)

**ANTON2006** (Published Data Only)

**BALLDIN2003** (Published Data Only)

**BALTIERI2008** (Published Data Only)

**CHICK2000** (Published Data Only)
FARREN2009 (Published Data Only)

GASTPAR2002 (Published Data Only)

GUARDIA2002 (Published Data Only)

HEINALA2001 (Published Data Only)

HUANG2005 (Published Data Only)

KIEFER2003 (Published Data Only)

KILLEEN2004 (Published Data Only)

KRANZLER2000 (Published Data Only)

KRYSAL2001 (Published Data Only)

LATT2002 (Published Data Only)

LEE2001 (Published Data Only)

MONTI2001 (Published Data Only)
MORLEY2006  (Published Data Only)
Richardson, K., Baillie, A., Reid, S., et al. (2008). Do acamprosate or naltrexone have an effect on daily drinking by reducing craving for alcohol? Addiction, 103, 953-959.

MORRIS2001  (Published Data Only)

OMALLEY1992  (Published Data Only)

OMALLEY2003  (Published Data Only)

OMALLEY2008  (Published Data Only)

OSLIN1997  (Published Data Only)

OSLIN2008  (Published Data Only)

RUBIO2001  (Published Data Only)

VOLPICELLI1992  (Published Data Only)

VOLPICELLI1997  (Published Data Only)

References of Excluded Studies - see final section.

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### Comparisons Included in this Review Question

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acamprosate + Naltrexone vs acamprosate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANTON2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIEFER2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acamprosate + Naltrexone vs naltrexone</td>
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<tr>
<td>ANTON2006</td>
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<tr>
<td>KIEFER2003</td>
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<tr>
<td>Acamprosate + Naltrexone vs placebo</td>
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<td></td>
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<tr>
<td>ANTON2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIEFER2003</td>
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</tr>
</tbody>
</table>

### Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Methods</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Interventions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTON2006</strong></td>
<td>n = 1383</td>
<td>Data Used</td>
<td>Medication management - Delivered by licensed healthcare professional over 9 sessions in which pills were dispensed. Initial visit was for 45 minutes, professional recommended abstinence and provided education about alcohol and the study medications. Encouraged AA.</td>
<td></td>
</tr>
<tr>
<td>Type of Analysis: ITT - as long as baseline data</td>
<td>Age: Mean 44 Range 18-</td>
<td>Relapse</td>
<td>Naltrexone. Mean dose 100mg/day - Dose of 25mg over first 4 days, dose of 50mg over next 4 days and then 100mg a day for the rest of the study. Placebo acamprosate also taken.</td>
<td></td>
</tr>
<tr>
<td>Blindness: Double blind</td>
<td>Sex: 955 males 428 females</td>
<td>% days abstinent</td>
<td>Medication management - Delivered by licensed healthcare professional over 9 sessions in which pills were dispensed. Initial visit was for 45 minutes, professional recommended abstinence and provided education about alcohol and the study medications. Encouraged AA.</td>
<td></td>
</tr>
<tr>
<td>Duration (days): Mean 112</td>
<td>Diagnosis: 100% Alcohol Dependence by DSM IV</td>
<td>Leaving due to adverse events</td>
<td>Group 1 N= 154</td>
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<tr>
<td>Followup: 1 year</td>
<td>Exclusions: &lt;18 years of age, no DSM diagnosis of alcohol dependence, drinking less than 14 drinks a week if female, less than 21 drinks a week if male, less than 4 consecutive days abstinent or more than 21. Further criteria: meeting DSM criteria for major psychiatric disorder or psychological disorder requiring medication, current dependence on any drug except nicotine, cannabis or alcohol, meeting DSM criteria for opioid dependence in past 6 months, significant medical disorder, abnormal AST or ALT(3 times upper limit), participants who are pregnant, nursing or not using adequate birth control, individuals intending to engage other treatments for alcohol problems, individuals with previous treatment with the study interventions.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: recruited from 11 sites, by advertisements or clinical referrals.</td>
<td>Notes: Randomisation: permuted block design, using blocks of 9 stratified by site. Implemented via central telephone-based interactive voice response system.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes: Studies were supported by grants from the NIAAA. Acamprosate, Naltrexone and matching placebos were donated by Lipha Pharmaceuticals.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Info on Screening Process: Approximately n=5000 were screened by telephone or in person, but only n=1383 were eligible after assessment.</td>
<td>Blinding: Double blind</td>
<td>Leaving study early</td>
<td>Group 2 N= 152</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acamprosate. Mean dose 3g/day - Two 500mg tablets taken three times daily (8 tablets in total daily). Could be lowered if required. Placebo naltrexone also taken.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Medication management - Delivered by licensed healthcare professional over 9 sessions in which pills were dispensed. Initial visit was for 45 minutes, professional recommended abstinence and provided education about alcohol and the study medications. Encouraged AA.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 3 N= 148</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Naltrexone + Acamprosate - Combines the dosing schedule for naltrexone and acamprosate alone interventions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Medication management - Delivered by licensed healthcare professional over 9 sessions in which pills were dispensed. Initial visit was for 45 minutes, professional recommended abstinence and provided education about alcohol and the study medications. Encouraged AA.</td>
<td></td>
</tr>
</tbody>
</table>

### Baseline

<table>
<thead>
<tr>
<th></th>
<th>Drinks/ UK</th>
<th>% days abstinent</th>
<th>%</th>
<th>Married</th>
<th>Employed</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLB+MM</td>
<td>12.6 (7.67)</td>
<td>18.9</td>
<td>24.3 (24.74)</td>
<td>44.4</td>
<td>79.7</td>
</tr>
<tr>
<td>NALX+MM</td>
<td>12.7 (7.69)</td>
<td>19.1</td>
<td>29.8 (24.70)</td>
<td>38.3</td>
<td>72.7</td>
</tr>
<tr>
<td>ACAM+MM</td>
<td>12.2 (7.77)</td>
<td>18.3</td>
<td>24.6 (24.78)</td>
<td>36.2</td>
<td>71.7</td>
</tr>
<tr>
<td>NALX+ACAM+MM</td>
<td>12.4 (7.66)</td>
<td>18.6</td>
<td>22.9 (24.70)</td>
<td>42.6</td>
<td>70.9</td>
</tr>
<tr>
<td>PLB+ACAM</td>
<td>12.6 (7.74)</td>
<td>18.9</td>
<td>24.3 (24.73)</td>
<td>50.0</td>
<td>71.8</td>
</tr>
<tr>
<td>NALX+CBI</td>
<td>12.4 (7.72)</td>
<td>18.6</td>
<td>23.7 (24.78)</td>
<td>37.4</td>
<td>76.8</td>
</tr>
<tr>
<td>ACAM+CBI</td>
<td>13.2 (7.74)</td>
<td>19.8</td>
<td>25.3 (24.70)</td>
<td>44.4</td>
<td>70.9</td>
</tr>
<tr>
<td>NALX+ACAM+CBI</td>
<td>12.2 (7.77)</td>
<td>18.3</td>
<td>26.8 (24.68)</td>
<td>43.3</td>
<td>70.7</td>
</tr>
<tr>
<td>CBI only</td>
<td>11.8 (7.66)</td>
<td>17.7</td>
<td>23.5 (25.35)</td>
<td>41.4</td>
<td>69.4</td>
</tr>
</tbody>
</table>
Group 4  N= 153
Placebo - Inactive placebo tablets identical in appearance to active acamprosate and naltrexone taken on the same dosing schedule as the active interventions.
Medication management - Delivered by licensed healthcare professional over 9 sessions in which pills were dispensed. Initial visit was for 45 minutes, professional recommended abstinence and provided education about alcohol and the study medications. Encouraged AA.

Group 5  N= 155
Naltrexone - Dose of 25mg over first 4 days, dose of 50mg over next 4 days and then 100mg a day for the rest of the study. Placebo acamprosate also taken. Combined behavioural intervention + MM - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement. Medication management also provided.

Group 6  N= 151
Acamprosate - Two 500mg tablets taken three times daily (6 tablets in total daily). Could be lowered if required. Placebo naltrexone also taken. Combined behavioural intervention + MM - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement. Medication management also provided.

Group 7  N= 157
Naltrexone + Acamprosate - Combines the dosing schedule for naltrexone and acamprosate alone interventions Combined behavioural intervention + MM - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement. Medication management also provided.

Appendix 16e
Placebo - Inactive placebo tablets identical in appearance to active acamprosate and naltrexone taken on the same dosing schedule as the active interventions.

Combined behavioural intervention + MM - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement. Medication management also provided.

Combined behavioural intervention - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement.

Funding: medication donated by DuPont (nalx) and Merck (Acamp)

Data Used
Relapse
Leaving study early
Data Not Used
GGT - Not relevant
Notes: Relapse was defined as 5 or more drinks for a man, 4 or more for a woman.

Group 1 N= 40
Group therapy - Weekly abstinence orientated sessions, including coping skills and relapse prevention based on the cognitive behavioural model of substance abuse. Groups were of between 8 and 14 participants and sessions lasted 90 minutes.
Acamprosate. Mean dose 1998mg/day - Medication dose constant throughout 12 week study period. 1998mg/day given in form of 2 tablets three times daily.

Group 2 N= 40
Naltrexone. Mean dose 50mg/day - Medication dose constant throughout 12 week study period. 50mg/day given as 1 capsule in the morning.
Group therapy - Weekly abstinence orientated sessions, including coping skills and relapse prevention based on the cognitive behavioural model of substance abuse. Groups were of between 8 and 14 participants and sessions lasted 90 minutes.

Notes: Randomisation: according to a computer-generated code. Allocation codes in sealed envelopes
Followup: 12 weeks
Setting: All patients with alcoholism admitted to an inpatient alcohol withdrawal program in Hamburg

Age: Mean 46 Range 18-65
Sex: 118 males 42 females

100% Alcohol Dependence by DSM IV

Exclusions: <18 or > 65 years of age, <5 DSM-IV criteria for alcohol dependence, body weight <60kg or >90kg, abstinence for <12 days, displaying withdrawal symptoms, positive drug screening. Further exclusions: current mental/psychiatric impairment/disease that required medication or inpatient treatment, history of cocaine/opiate abuse, history of psychosis, current use of psychotropic medication, evidence of severe neurological/physical disorders, history of cirrhosis, homelessness, pregnancy or refusal to use reliable birth control.

Baseline: OCDS VAS Married Partnership score (%) (%) Placebo 18.2 (12.1) 23.7 (26.7) 30 55 Acamprosate 20.1 (10.6) 23.6 (28.0) 23 48 Naltrexone 17.9 (13.2) 18.6 (27.7) 25 58 Acamp + Nalx 14.1 (11.8) 17.9 (27.7) 33 43

Diagnosis:

KIEFER2003

Study Type: RCT
Type of Analysis: ITT
Blindness: Double blind
Duration (days): Mean 84
Followup: 12 weeks
Setting: All patients with alcoholism admitted to an inpatient alcohol withdrawal program in Hamburg
Notes: Randomisation: according to a computer-generated code. Allocation codes in sealed envelopes
Info on Screening Process: n=196 registered, n=15 excluded due to medical issues, n=9 due to concurrent treatment and n=11 declined study participation. n=160 randomised.

n = 160

Funding: medication donated by DuPont (nalx) and Merck (Acamp)

Data Used
Relapse
Leaving study early
Data Not Used
GGT - Not relevant
Notes: Relapse was defined as 5 or more drinks for a man, 4 or more for a woman.

Group 8 N= 156
Placebo - Inactive placebo tablets identical in appearance to active acamprosate and naltrexone taken on the same dosing schedule as the active interventions.

Combined behavioural intervention + MM - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement. Medication management also provided.

Group 9 N= 157
Combined behavioural intervention - Up to 20 sessions of 50 minutes delivered by health specialists. Integrated aspects of coping skills (project MATCH), 12-step facilitation, motivational interviewing and support system involvement.

Notes: Randomisation: according to a computer-generated code. Allocation codes in sealed envelopes
Followup: 12 weeks
Setting: All patients with alcoholism admitted to an inpatient alcohol withdrawal program in Hamburg
Notes: Randomisation: according to a computer-generated code. Allocation codes in sealed envelopes

Age: Mean 46 Range 18-65
Sex: 118 males 42 females

100% Alcohol Dependence by DSM IV

Exclusions: <18 or > 65 years of age, <5 DSM-IV criteria for alcohol dependence, body weight <60kg or >90kg, abstinence for <12 days, displaying withdrawal symptoms, positive drug screening. Further exclusions: current mental/psychiatric impairment/disease that required medication or inpatient treatment, history of cocaine/opiate abuse, history of psychosis, current use of psychotropic medication, evidence of severe neurological/physical disorders, history of cirrhosis, homelessness, pregnancy or refusal to use reliable birth control.

Baseline: OCDS VAS Married Partnership score (%) (%) Placebo 18.2 (12.1) 23.7 (26.7) 30 55 Acamprosate 20.1 (10.6) 23.6 (28.0) 23 48 Naltrexone 17.9 (13.2) 18.6 (27.7) 25 58 Acamp + Nalx 14.1 (11.8) 17.9 (27.7) 33 43

Diagnosis:
<table>
<thead>
<tr>
<th>Group 3</th>
<th>N= 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone + Acamprosate - Medication dose constant throughout 12 week study period. Same dosage and tablet numbers as the single pharmacological interventions.</td>
<td></td>
</tr>
<tr>
<td>Group therapy - Weekly abstinence orientated sessions, including coping skills and relapse prevention based on the cognitive behavioural model of substance abuse. Groups were of between 8 and 14 participants and sessions lasted 90 minutes.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 4</th>
<th>N= 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo - Inactive control, same dosing procedure as with active pharmacological intervention</td>
<td></td>
</tr>
<tr>
<td>Group therapy - Weekly abstinence orientated sessions, including coping skills and relapse prevention based on the cognitive behavioural model of substance abuse. Groups were of between 8 and 14 participants and sessions lasted 90 minutes.</td>
<td></td>
</tr>
</tbody>
</table>

**Characteristics of Excluded Studies - see final section.**

**References of Included Studies**

**ANTON2006**
(Published Data Only)

**KIEFER2003**
(Published Data Only)

**References of Excluded Studies - see final section.**

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## Study characteristics for disulfiram (oral)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Type of Analysis</th>
<th>Age</th>
<th>Sex</th>
<th>Exclusions</th>
<th>Data Used</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Chicks 1992 | RCT | Completers | Mean 43 Range 18-67 | 106 males 20 females | Not having relapsed after previous therapy or other support, pregnant women, cardiac disease, psychosis, or habitual drug use. Also, all those showing abnormally high levels of serum bilirubin, AST or ALT were also excluded. | Disulfiram Placebo
SADQ: 31.6 (13.6) 33.1 (13.3)
Units per week: 207 190 | Disulfiram (witnessed). Mean dose 200mg/day - 200mg of disulfiram taken daily under supervision of informant. Counselling or psychotherapy - varied between centres but not defined. A few patients were offered day-patient places. Marital therapy, relaxation therapy, AA, vitamin B supplements, and supportive group therapy were also used by some patients. |
| Chicks 2008 | RCT | ITT | Mean 44 Range 18-65 | All males | Other substance use and dependence excluding nicotine dependence, any comorbid psychiatric disorder that | Naltrexone - 50mg of naltrexone taken at breakfast daily. Compliance was enhanced by asking family member to view participant taking drug in the morning. |

### Data Used
- **Units per week**
- **Days since last drink**
- **Total drinks**
- **Leaving due to adverse events**
- **Leaving study early**

### Notes
- Randomisation: by a pharmacist who randomly placed treatments against numbers, which in turn were given to participants entering treatment.
- Setting: Participants were attending one of seven outpatient alcoholism treatment centres. All participants had already relapsed after previous therapy/support.
- Duration (days): Mean 180
- Exclusions: Not having relapsed after previous therapy or other support, pregnant women, cardiac disease, psychosis, or habitual drug use. Also, all those showing abnormally high levels of serum bilirubin, AST or ALT were also excluded.
- Baseline: Total sample: 35
- Lived with spouse: 46
- Disulfiram Placebo
SADQ: 31.6 (13.6) 33.1 (13.3)
Units per week: 207 190

### Data Used
- **Units per week**
- **Days since last drink**
- **Total drinks**
- **Leaving due to adverse events**
- **Leaving study early**

### Notes
- Randomisation: list provided by qualified statistician. Participants were allocated.
- Setting: Participants were alcohol-dependent patients undergoing detoxification in a private psychiatric hospital in Mumbai, India.
- Duration (days): Mean 365
- Exclusions: <18 or >65 years of age, no DSM-IV diagnosis of alcohol dependence, unstable family environment. Further criteria: other substance use and dependence excluding nicotine dependence, any comorbid psychiatric disorder that
## DESOUUSA2008

<table>
<thead>
<tr>
<th>Study Type: RCT</th>
<th>Type of Analysis: ITT</th>
<th>Blindness: Open</th>
<th>Duration (days): Mean 252</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting: Participants were undergoing inpatient detoxification in a psychiatric hospital. The centre had facilities for inpatient and outpatient treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes: Randomisation: performed by qualified statistician, with treatment allocated by clinic staff according to serial number on the list</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Baseline

<table>
<thead>
<tr>
<th>Disulfiram</th>
<th>Naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinks per drinking day: 10 (3.2)</td>
<td>9.6 (3.3)</td>
</tr>
<tr>
<td>Days of drinking in month: 87 (20)</td>
<td>87 (22)</td>
</tr>
<tr>
<td>ADS severity: 29 (5)</td>
<td>28 (6)</td>
</tr>
<tr>
<td>ASI: 0.71 (0.12)</td>
<td>0.71 (0.12)</td>
</tr>
<tr>
<td>Typical drinks per day: 12.5 (5)</td>
<td>12.2 (5.1)</td>
</tr>
</tbody>
</table>

### Data Used

<table>
<thead>
<tr>
<th>n = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: Range 18-65</td>
</tr>
<tr>
<td>Sex: all males</td>
</tr>
</tbody>
</table>

### Exclusions

- <18 or >65 years of age, no DSM diagnosis of alcohol dependence, unstable family environment. Further criteria: other substance use disorders, comorbid psychiatric disorder, medical condition that would interfere with treatment compliance or be a contraindication of the drugs in the study, any liver function test values more than three times upper limit.

### Notes

- Stable family environment required so that family could ensure compliance and provide follow up information.
- Randomisation: computer generated.

## FULLER1979

<table>
<thead>
<tr>
<th>Study Type: RCT</th>
<th>Type of Analysis: ITT</th>
<th>Blindness: Double blind</th>
<th>Duration (days): Mean 365</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting: All participants attended Cleveland VA hospital and were requesting treatment for alcoholism or were admitted for one or more alcohol-related illnesses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes: Randomisation: computer generated</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Baseline

<table>
<thead>
<tr>
<th>Disulfiram</th>
<th>Topiramate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinks per drinking day: 9.6 (3.3)</td>
<td>10.4 (4.4)</td>
</tr>
<tr>
<td>Days of drinking in month: 86 (12)</td>
<td>82 (14)</td>
</tr>
<tr>
<td>ADS severity: 26 (5)</td>
<td>28 (4)</td>
</tr>
<tr>
<td>ASI: 0.69 (0.08)</td>
<td>0.73 (0.10)</td>
</tr>
<tr>
<td>Married (%): 98</td>
<td>98</td>
</tr>
<tr>
<td>Employed (%): 68</td>
<td>76</td>
</tr>
</tbody>
</table>

### Data Used

<table>
<thead>
<tr>
<th>n = 43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: Mean 43</td>
</tr>
<tr>
<td>Sex: all males</td>
</tr>
</tbody>
</table>

### Exclusions

- Individuals not living with a relative, were 60 years old or older, had any of the following contraindications to disulfiram: heart disease, history of psychosis, idiopathic seizure disorder, cirrhosis with portal hypertension, or

### Notes

- Randomisation: computer generated.
<table>
<thead>
<tr>
<th>Study Type: RCT</th>
<th>Data Used</th>
<th>Notes: Placebo group were aware of their allocation to inactive medication. Disulfiram and disulfiram 'placebo' groups unaware of allocation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Analysis: ITT</td>
<td>% continuously abstinent</td>
<td>Placebo - Participants were instructed to take one tablet of riboflavin (50mg) daily. Participants were aware they were not taking active medication.</td>
</tr>
<tr>
<td>Blindness: Double blind</td>
<td>Leaving study early</td>
<td>Placebo group were aware of their allocation to inactive medication. Disulfiram and disulfiram 'placebo' groups unaware of allocation.</td>
</tr>
<tr>
<td>Duration (days): Mean 365</td>
<td></td>
<td>Notes: Abstinence: designated if there was no evidence, from patients self-reports, reports for family/friends or detected through urine or blood specimens.</td>
</tr>
<tr>
<td>Setting: Patients presented for treatment at a participating alcoholism treatment unit. VA hospital.</td>
<td></td>
<td>Setting: Outpatient alcoholism clinic at Boston city hospital.</td>
</tr>
<tr>
<td>Notes: Randomisation: Sequentially numbered envelopes based on a randomisation list.</td>
<td></td>
<td>Notes: Abstinence was the goal of the rehabilitation program.</td>
</tr>
<tr>
<td>Info on Screening Process: n=6629 screened, n=5011 were excluded for not meeting inclusion criteria or refusing to participate in the trial. Leaving n=605 to be randomised.</td>
<td></td>
<td>Notes: Randomisation: no details.</td>
</tr>
<tr>
<td>Full Details:</td>
<td></td>
<td>Setting: Outpatient alcoholism clinic at Boston city hospital.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Notes: Randomisation: no details.</td>
</tr>
<tr>
<td>Fuller1986</td>
<td>Disulfiram: Mean dose 250mg/day - 250mg of disulfiram taken daily.</td>
<td>Supported by National Institute of Alcohol Abuse and Alcoholism grant.</td>
</tr>
<tr>
<td>N= 605</td>
<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
<td>Supported by National Institute of Alcohol Abuse and Alcoholism grant.</td>
</tr>
<tr>
<td>Age: Mean 42</td>
<td>1 N= 202</td>
<td></td>
</tr>
<tr>
<td>Sex: all females</td>
<td>2 N= 204</td>
<td></td>
</tr>
<tr>
<td>100% Alcohol Dependence by National Council on alcoholism diagnostic criteria</td>
<td>3 N= 199</td>
<td></td>
</tr>
<tr>
<td>Exclusions: &lt;60 years of age, Not meeting national council on alcoholism diagnostic criteria. Further exclusion: lived alone, had a condition that contraindicated the use of disulfiram (heart disease, organic brain syndrome, etc), history indicating compulsive destructive behaviour, uncooperativeness, or abuse of psychoactive drugs, had been abstinent for over one month, or lived more than 80km from the hospital.</td>
<td>Placebo - No disulfiram - participants told they were not taking disulfiram and instead were taking riboflavin. This group was a control group for the counselling delivered.</td>
<td></td>
</tr>
<tr>
<td>Notes: Abstinence was the goal of the rehabilitation program.</td>
<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
<td></td>
</tr>
<tr>
<td>Baseline: 250 Disulf 1mg Disulf No Disulf</td>
<td>Data Used</td>
<td>Notes: Abstinence: designated if there was no evidence, from patients self-reports, reports for family/friends or detected through urine or blood specimens.</td>
</tr>
<tr>
<td>Days drinking in previous month: 20.3 (0.7) 20.8 (0.7) 20.0 (0.7)</td>
<td>% continuously abstinent</td>
<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
</tr>
<tr>
<td>Employed (%): 51 56 54</td>
<td>Leaving study early</td>
<td>1 N= 13</td>
</tr>
<tr>
<td>Married (%): 73 71 66</td>
<td></td>
<td>Disulfiram. Mean dose 250mg/day - 250mg of disulfiram taken daily.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
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<tr>
<td></td>
<td></td>
<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
</tr>
<tr>
<td>GERREIN1973</td>
<td></td>
<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
</tr>
<tr>
<td>Study Type: RCT</td>
<td></td>
<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
</tr>
<tr>
<td>Type of Analysis: ITT</td>
<td></td>
<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
</tr>
<tr>
<td>Blindness: Open</td>
<td></td>
<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
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<tr>
<td>Duration (days): Mean 56</td>
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<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
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<tr>
<td>Setting: Outpatient alcoholism clinic at Boston city hospital.</td>
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<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
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<td>Notes: Randomisation: no details.</td>
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<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
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<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
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<td>n= 121</td>
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<td>Counselling - Defined as any interaction between the patient and member of the outpatient alcohol rehabilitation staff, which didn't exceed 3 hours a week. Most sessions were in groups, and occurred at least weekly for first 6 months, biweekly for the next 6 months.</td>
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<tr>
<td>n</td>
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<td>Details</td>
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<tr>
<td>1</td>
<td>Disulfiram. Mean dose 150mg/day - 100-200mg taken daily or 400mg taken twice a week.</td>
<td>Dose was decided by the study doctor based on the participants weight. Brief 'cognitive-behavioural' intervention - Psychosocial treatments were matched to the medications used - total abstinence was goal of disulfiram, reducing heavy drinking or abstinence for naltrexone and acamprosate. Manual contained elements of problem-solving, motivation and relapse prevention.</td>
</tr>
<tr>
<td>2</td>
<td>Disulfiram (witnessed) - Participants received disulfiram twice a week in the clinic, witnessed by a nurse, and received 5 tablets to take alone during the week. 250mg was taken daily. Counselling - Weekly individual visits to a counsellor as well as a open discussion group on Mondays and Thursdays.</td>
<td>Study medications were purchased from Dumex-Alpharma, Bristol-Myers Squibb and Merck.</td>
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<tr>
<td>3</td>
<td>Counselling - Weekly individual visits to a counsellor. No further details.</td>
<td>Setting: Voluntary seeking outpatient treatment for alcohol problems at 3 different A-clinics in Finland. Notes: Randomisation: Assigned by an independent person in a 1:1:1 ratio - using random number permuted blocks.</td>
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<tr>
<td>4</td>
<td>Counselling - Same as counselling only group, but with additional invitation to the open discussion groups weekly.</td>
<td>Notes: All interventions were taken under supervision of friend/family of participant. For the first 12 weeks, medication was taken daily. From the 13th week, medication was taken only on drinking days.</td>
</tr>
<tr>
<td>5</td>
<td>Counselling - Refused to take disulfiram but allowed to attend counselling on a weekly basis at the clinic.</td>
<td>Notes: Standard drink = 12g of ethanol. Relapse: defined as 5 or more drinks in a day or men, 4 or more for women.</td>
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<td>6</td>
<td>Counselling - Refused to take disulfiram but allowed to attend counselling on a weekly basis at the clinic as well as open-group discussion.</td>
<td>Notes: Randomisation: Assigned by an independent person in a 1:1:1 ratio - using random number permuted blocks.</td>
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<tr>
<td>Baseline: Disulfiram</td>
<td>Naltrexone</td>
<td>Acamprosate</td>
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<tr>
<td>----------------------</td>
<td>------------</td>
<td>-------------</td>
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<tr>
<td>Alcohol (g/week)</td>
<td>Min: 120</td>
<td>50 mg/day</td>
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<tr>
<td></td>
<td>Max: 1848</td>
<td>50 mg/day</td>
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<td>240</td>
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<td>Married(%)</td>
<td>62.5</td>
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<td>58.4</td>
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<td>48.0</td>
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<tr>
<td></td>
<td>Employed(%)</td>
<td>70.4</td>
</tr>
<tr>
<td></td>
<td>56.6</td>
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<td>71.4</td>
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N= 81

Acamprosate. Mean dose 1998mg/day - 666mg of acamprosate taken three times daily if body weight was more than 60kg, if less then 1333mg was taken daily. Brief 'cognitive-behavioural' intervention - Psychosocial treatments were matched to the medications used - total abstinence was goal of disulfiram, reducing heavy drinking or abstinence for naltrexone and acamprosate. Manual contained elements of problem-solving, motivation and relapse prevention.

N= 81

Naltrexone. Mean dose 50mg/day - 50 mg of naltrexone taken daily. Brief 'cognitive-behavioural' intervention - Psychosocial treatments were matched to the medications used - total abstinence was goal of disulfiram, reducing heavy drinking or abstinence for naltrexone and acamprosate. Manual contained elements of problem-solving, motivation and relapse prevention.

Weeks 13-52, medication was taken in 'targeted' basis - in response to craving situation.

Baseline: Disulfiram Naltrexone Acamprosate

<table>
<thead>
<tr>
<th>Alcohol (g/week)</th>
<th>Min: 120</th>
<th>132</th>
<th>240</th>
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<tr>
<td>Max: 1848</td>
<td>1880</td>
<td>2520</td>
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<tr>
<td>Married(%)</td>
<td>62.5</td>
<td>58.4</td>
<td>48.0</td>
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<tr>
<td>Employed(%)</td>
<td>70.4</td>
<td>56.6</td>
<td>71.4</td>
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### References

**CHICK1992** (Published Data Only)

**DESOUSA2004** (Published Data Only)

**DESOUSA2008** (Published Data Only)

**FULLER1979** (Published Data Only)

**FULLER1986** (Published Data Only)


**GERREIN1973** (Published Data Only)

**LAASKONEN2008** (Published Data Only)
### Characteristics of Studies Excluded from All Clinical Questions

<table>
<thead>
<tr>
<th>Reference ID</th>
<th>Reason for Exclusion</th>
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<tbody>
<tr>
<td>ANSOMS2000</td>
<td>Open-label</td>
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<tr>
<td>ANTON2004</td>
<td>less than 10 participants in intervention group.</td>
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<tr>
<td>BAEEKLAND1971</td>
<td>Non RCT</td>
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<td>BALTIERI2009</td>
<td>No relevant outcomes</td>
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<tr>
<td>BOEIJINGA2004</td>
<td>No relevant outcomes</td>
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<tr>
<td>BORUP1994</td>
<td>Non RCT</td>
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<td>BRASSE2004</td>
<td>Cross-over trial</td>
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<td>BUDZYNISKI2000</td>
<td>No relevant outcomes</td>
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<td>CAPUTO2003</td>
<td>Open-label</td>
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<td>CAPUTO2007</td>
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<tr>
<td>CARROLL1993</td>
<td>less than 10 participants in intervention group</td>
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<td>CARROLL1998</td>
<td>All participants were also cocaine dependent</td>
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<tr>
<td>CHRISTENSEN1984</td>
<td>No relevant outcomes</td>
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<td>CROISSANT2006</td>
<td>Open-label</td>
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<td>CROOP1997</td>
<td>No usable outcomes</td>
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<tr>
<td>DAVIDSON1996</td>
<td>Cross over study, participants were healthy, social drinkers.</td>
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<td>DAVIDSON1999</td>
<td>Crossover study.</td>
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<td>DAVIDSON2004</td>
<td>No relevant diagnostic criteria.</td>
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<td>DAVIDSON2007</td>
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<td>DESOUSA2008A</td>
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<td>DOTY1995</td>
<td>Participants were healthy, social drinkers.</td>
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<tr>
<td>DROBES2003</td>
<td>Clinical laboratory experiment.</td>
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<td>DROBES2004</td>
<td>No relevant outcomes, clinical laboratory experiment</td>
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<td>FARREN1999</td>
<td>Crossover study, n=6.</td>
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<td>FEENEU2001</td>
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<td>FEENEU2002</td>
<td>Non-RCT</td>
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<td>FEENEU2004</td>
<td>Non RCT</td>
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<td>FEENEU2006</td>
<td>Non RCT (participants were matched across groups).</td>
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<td>FLANNERY2004</td>
<td>Open-label</td>
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<td>FLOREZ2008</td>
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<tr>
<td>GEERA1992</td>
<td>Cross-over trial</td>
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<tr>
<td>GOYER1984</td>
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<tr>
<td>HAMMARBERG2004</td>
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<td>HAN2008</td>
<td>Non RCT, no relevant outcomes.</td>
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<td>HERMOS2004</td>
<td>Non RCT</td>
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<td>Reference</td>
<td>Description</td>
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<tr>
<td>JOHNSON2004</td>
<td>Placebo group has &lt;10 participants (n=5)</td>
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<td>KING2002</td>
<td>Participants were healthy, social drinkers</td>
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<tr>
<td>KIRITZETOPOR2004</td>
<td>Open-label</td>
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<tr>
<td>KOFOED1987</td>
<td>No relevant comparators</td>
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<tr>
<td>KRANZLER1990</td>
<td>Non RC</td>
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<td>KRANZLER1997</td>
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<td>Placebo group has &lt;10 participants (n=5)</td>
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<tr>
<td>KRANZLER2003</td>
<td>Sample of problem drinkers, not dependent on alcohol. Moderate and severe drinkers were excluded.</td>
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<tr>
<td>KRISTAL2006</td>
<td>Participants were 'healthy' subjects.</td>
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<td>LEEMAN2008</td>
<td>Non RCT</td>
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<tr>
<td>LHUINTE1985</td>
<td>No details on diagnosis tool or drinking behaviour, no relevant outcomes.</td>
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<tr>
<td>LHUINTE1990</td>
<td>No details on diagnosis or consumptions on study intake. No usable outcomes.</td>
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<td>LING1983</td>
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<td>MARTIN2003</td>
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<td>MARTINOTTI2007</td>
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<td>MASON2006</td>
<td>Subanalysis of COMBINE study, no useful outcomes</td>
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<td>MCCCAUL2000</td>
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<td>MIRANDA2007</td>
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<td>MONTEROSSO2001</td>
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<td>MONTI1999</td>
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<td>MORGAN2004</td>
<td>Not randomised</td>
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<td>MUESER2003</td>
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<td>NAMKOONG1999</td>
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<tr>
<td>NIEDERHOFER2003</td>
<td>Participants were all under 18 years of age</td>
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<td>NIEDERHOFER2003E</td>
<td>Participants were all under 18 years of age</td>
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<tr>
<td>omalley2002</td>
<td>less than 10 participants in intervention group</td>
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<td>OMALLEY2007</td>
<td>Outcomes not extractable, large amount of participants had comorbid eating disorder.</td>
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<td>OOTEMAN2007</td>
<td>No relevant outcomes</td>
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<td>OSLIN1997A</td>
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<td>PAJADE1990</td>
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<td>PANTALON2002</td>
<td>All participants were also cocaine dependent</td>
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<td>PEACHEY1983</td>
<td>Social drinkers, less than 10 participants in treatment groups.</td>
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<td>PELC2002</td>
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<td>PETERSON2006</td>
<td>Crossover design</td>
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<td>All participants have at least one comorbid psychiatric disorder</td>
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<td>PETTINATI2008</td>
<td>All participants had comorbid cocaine dependence</td>
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<td>ROBICHAUD1979</td>
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<td>STELLA2008</td>
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<td>SWIFT1998</td>
<td>Participants were healthy, social drinkers.</td>
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<td>TIDEY2008</td>
<td>No details on diagnostic criteria</td>
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<tr>
<td>WEINSTEIN2003</td>
<td>Non-RCT</td>
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References to Studies Excluded from All Clinical Questions

ANSOMS2000

ANTON2004

BAEKELAND1971

BALTIERI2009
BOEIJINGA2004

BORUP1994

BRASSER2004

BUDZYNISKI2000

CAPUTO2003

CAPUTO2007

CROISSANT2006

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DAVIDSON1999

DAVIDSON2004
DAVIDSON2007

DESOUSA2008A

DOTY1995

DROBES2003

DROBES2004

FARREN1999

FEENEY2001

FEENEY2001B

FEENEY2002

FEENEY2004

FEENEY2006

FLANNERY2004

FLOREZ2008
GEERA1992
Gerra, G., Caccavari, R., Delsignore, R., Bocchi, R., Fertonati, G., & Passeri, M. Effects of fluoxetine and ca-acetyl-homotaurinate on alcohol intake in familial and nonfamilial alcoholic patients. Current Therapeutic Research, 52 (2), 291-295

GOYER1984

HAMMARBERG2004

HAN2008

HERMOS2004

JOHNSON2003B

JOHNSON2004

KING2002

KIRITZETOPO2004

KOFOEDE1987

KRANZLER1990

KRANZLER1997

KRANZLER1998

KRANZLER2003
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MCCAUL2001

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OMALLEY2007

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RUBIO2004
RUBIO2005

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