Appendix 16e: pharmacological interventions study characteristics table

Study characteristics for acamprosate

Acamprosate vs Naltrexone
ANTON2006
KIEFER2003
MORLEY2006
RUBIO2001

Acamprosate vs Placebo
ANTON2006
BALTIERI2003
BARRIAS1997
BESSON1998
CHICK2000A
GEERLINGS1997
GUAL2001
KIEFER2003
LADEWIG1993
MORLEY2006
NAMKOONG2003
PAILLE1995
PELC1992
PELC1997
POLDRUGO1997
ROUSSEAUX1996
SASS1996
TEMPESTA2000
WHITWORTH1996

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

	treatment with the study interventions. 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/ drinking day; UK units; % days abstinent; Married %; Empl-oyed % PLB+MM 12.6 (7.67) 18.9 24.3 (24.74) 44.4 79.7 NALX+MM 12.7 (7.69) 19.1 29.8 (24.70) 38.3 72.7 ACAM+MM 12.2 (7.77) 18.3 24.6 (24.78) 36.2 71.7 NALX+ ACAM+MM 12.4 (7.66) 18.6 22.9 (24.70) 42.6 70.9 PLB+CBI 12.6 (7.74) 18.9 24.3 (24.73) 50.0 71.8 NALX+CBI 12.4 (7.72) 18.6 23.7 (24.78) 37.4 76.8 ACAM+CBI 13.2 (7.74) 19.8 25.3 (24.70) 44.4 70.9 NALX+ ACAM+CBI 12.2 (7.77) 18.3 26.8 (24.68) 43.3 70.7 CBI only 11.8 (7.66) 17.7 23.5 (25.35) 41.4 69.4		**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. **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. **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. **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.	

			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. **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. **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. **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.	
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	**1 N= 40** Acamprosate. Mean dose 1998mg/day - No details on dosing schedule.	Funding: no details

Blindness: Double blind Duration (days): Mean 84 Followup: 12 weeks Setting: Participants were enrolled as outpatients in a treatment clinic for drug dependence at the university of Sao Paulo. Notes: No details Info on Screening Process: n=80 participants were screened, but n=5 were excluded because of coexisting diseases.	Exclusions: <18 or >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. Baseline: Acam PLB Average daily alcohol intake (g/day) 370.1 (164.9) 348.5 (132.46) In UK units: 46.26 43.56		Psychosocial program - GREA - behavioural orientation, clinical assessment and encouragement to join AA (not mandatory) **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)	
BARRIAS1997 Study Type: RCT Blindness: Double blind Duration (days): Mean 365 Followup: six months Setting: Awaiting translation	n= 302 Age: Mean 40 Range 21-64 Sex: 278 males 24 females Exclusions: Awaiting translation	**Data Used** % continuously abstinent	**1 N= 150** Acamprosate - Awaiting translation **2 N= 152** Placebo - Awaiting translation	
BESSON1998 Study Type: RCT Type of Analysis: ITT - all taking one dose of study medication 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	n= 110 Age: Mean 42 Range 18-65 Sex: 88 males 22 females 100% Alcohol Dependence by DSM-III Exclusions: <18 or >65 years of age, no DSM-III diagnosis of alcohol dependence with at least a 12-month history, GGT <twice upper limit, MCV <95fl, <5 days abstinent before study start. Further criteria: pregnancy or women not practicing contraception, psychiatric disorders needing drug treatment, systemic diseases (poorly controlled diabetes, heart failure, active tuberculosis, cancer), epilepsy unrelated to alcoholism, renal failure, hypoglycaemia, participants with no fixed residence, hospitalised patients and patients residing in posttreatment institutions. Notes: Majority of the outcomes are reported for Acamprosate vs Placebo, including disulfiram participants in each group. Baseline: Acamprosate Placebo MAST score: 30.5 32.7 Craving (VAS score): 42.4 37.4	**Data Used** Relapse Abstinent at endpoint Abstinent at assessment CAD Leaving study early **Data Not Used** GGT - Not relevant 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.	**1 N= 31** Acamprosate. Mean dose 1998mg/day - 1998mg/day divided into 6 tablets for participants weighing 60kg or more, or 1332mg/day for participants under 60kg. Supportive psychotherapy - Non-standardised supportive treatment, generally consisted of short sessions (15-20 minutes) of psychological assessment and support approximately twice a month. **2 N= 33** Placebo - Inactive control intervention, dosing schedule identical to the active intervention Supportive psychotherapy - Non-standardised supportive treatment, generally consisted of short sessions (15-20 minutes) of psychological assessment and support approximately twice a month.	Funding: supported in part by state funds and Lipha, Inc.

			3 N= 24 Acamprosate + Disulfiram. Mean dose 1998mg/day - 1998mg/day divided into 6 tablets for participants weighing 60kg or more, or 1332mg/day for participants under 60kg. Disulfiram dispensed daily, no further details. Supportive psychotherapy - Non-standardised supportive treatment, generally consisted of short sessions (15-20 minutes) of psychological assessment and support approximately twice a month. **4 N= 22** Placebo + Disulfiram - Inactive control intervention, dosing schedule identical to the active intervention. Disulfiram dispensed daily, no further details. Supportive psychotherapy - Non-standardised supportive treatment, generally consisted of short sessions (15-20 minutes) of psychological assessment and support approximately twice a month.	
CHICK2000A Study Type: RCT Type of Analysis: ITT - all taking one dose of study medication Blindness: Single blind Duration (days): Mean 168 Followup: 4 weeks Setting: 20 UK clinics, connected with psychiatric services and a general hospital. Notes: Randomisation: blocks of eight. Info on Screening Process: n=664 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.	n= 581 Age: Mean 43 Range 18-65 Sex: 485 males 96 females 100% Alcohol Dependence by DSM-III Exclusions: <18 or >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 <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. Baseline: Acamprosate Placebo Prior weekly consumption: 188 units/week 168 units/week Married (%): 57 55 Employed (%): 49 54	**Data Used** CAD % continuously abstinent Leaving study early **Data Not Used** HAM-A - Not relevant	**1 N= 289** Acamprosate. Mean dose 1998mg/day - 1998mg/day divided into 6 tablets for participants weighing 60kg or more, or 1332mg/day for participants under 60kg. 'Standard' outpatient treatment - Usual psychosocial out-patient treatment programme. **2 N= 292** Placebo - Inactive control intervention, dosing schedule identical to the active intervention 'Standard' outpatient treatment - Usual psychosocial out-patient treatment programme.	Funding: Lipha pharmaceuticals.
GEERLINGS1997 Study Type: RCT Type of Analysis: ITT - all taking one dose of study medication	n= 262 Age: Mean 41 Range 18-65 Sex: 199 males 63 females 100% Alcohol Dependence by DSM-III	**Data Used** Time to first relapse Relapse Abstinent at assessment CAD	**1 N= 128** Acamprosate. Mean dose 1998mg/day - 1998mg/day divided into 6 tablets for participants weighing 60kg or more, or 1332mg/day for participants under 60kg.	Funding: Study sponsored by Lipha Belgium.

Blindness: Double blind Duration (days): Mean 180 Followup: 6 months Setting: 22 outpatient treatment centres in Benelux region Notes: Randomisation: no details Info on Screening Process: no details	Exclusions: <18 or >65 years of age, not meeting DSM-III criteria for alcohol dependence, <5 days abstinent 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	Leaving study early **Data Not Used** CDT - Not relevant	**2 N= 134** Placebo - Inactive control intervention, dosing schedule identical to the active intervention	
GUAL2001 Study Type: RCT Type of Analysis: ITT - all receiving one dose of study medication Blindness: Double blind Duration (days): Mean 180 Setting: 11 outpatient hospital centres in Spain. Notes: Randomisation: no details	n= 288 Age: Mean 41 Range 18-65 Sex: 229 males 59 females 100% Alcohol Dependence by DSM-III Exclusions: <18 or >65 years of age, not meeting DSM-III criteria for alcohol dependence for at least 12 months. Further criteria for exclusion: psychiatric illness requiring specific drug treatment during the trial, history of abusing other substances (except nicotine) in last 6 months. Baseline: Acamprosate Placebo Amount of population drinking >10 drinks/ drinking day (%): 90 (64) 101 (69)	**Data Used** Recorded craving Stable recovery duration CAD Abstinent at endpoint Leaving study early **Data Not Used** CDT - Not relevant GGT - Not relevant	**1 N= 141** Acamprosate. Mean dose 1998mg/day - two 333mg tablets taken three times a day. **2 N= 147** Placebo - inactive control taken on same schedule as active treatment.	Funding: study sponsored by Merck Lipha Spain.
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.	n= 160 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, abstinent 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 score Married (%) Partnership (%) 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	**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.	**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 90mins. Acamprosate. Mean dose 1998mg/day - Medication dose constant throughout 12 week study period. 1998mg/day given in form of 2 tablets three times daily.	Funding: medication donated by DuPont (nalx) and Merck (Acam)

	Acam + Nalx 14.1 (11.8) 17.9 (27.7) 33 43		**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 90mins. **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 90mins. **4 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.	
LADEWIG1993 Study Type: RCT Blindness: Double blind Duration (days): Mean 180 Followup: six months Setting: Awaiting translation	n= 61 Age: Mean 47 Range 28-70 Sex: 47 males 14 females Exclusions: Awaiting translation	**Data Used** % continuously abstinent	**1 N= 29** Acamprosate - Awaiting translation **2 N= 32** Placebo - Awaiting translation	
MORLEY2006 Study Type: RCT Type of Analysis: ITT - all taking one dose of study medication	n= 169 Age: Mean 45 Range 18-65 Sex: 118 males 51 females	**Data Used** Time to first drink Relapse Abstinent at endpoint Drinks per drinking day	**1 N= 55** Acamprosate. Mean dose 1998mg/day - Participants took six 333mg tablets daily	Funding: supported by grants from the National Health and Medical Research Council of Australia and the University

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 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.	100% Alcohol Dependence or Abuse by DSM IV Exclusions: <18 or >65 years of age, no DSM-IV diagnosis of alcohol dependence or abuse, had been abstinent from alcohol for <3 or >21 days and insufficient understanding of English. Further criteria: advanced liver disease, previous treatment with naltrexone or acamprosate within 3 months of randomisation, any other drug dependence (other than nicotine or low-potency benzodiazepine for sleep), or severe current psychiatric disorder associated with psychosis and significant suicide risk. Pregnant or breast feeding women also excluded. Baseline: Acamp Nalx Plb 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	Time to first relapse CAD Leaving study early **Data Not Used** ADS score - Not relevant Notes: Relapse: 4 or more drinks for women, 6 or more for men. Lapse: 1 drink	Medication compliance therapy - four to six sessions of manualised compliance therapy were offered. This was a brief intervention targeting treatment compliance issues. **2 N= 53** Naltrexone. Mean dose 50mg - Participants took 50mg in one tablet daily Medication compliance therapy - four to six sessions of manualised compliance therapy were offered. This was a brief intervention targeting treatment compliance issues. **3 N= 61** Placebo - Inactive control, tablets appeared identical to either naltrexone or acamprosate and were taken in the same dosing schedule. Medication compliance therapy - four to six sessions of manualised compliance therapy were offered. This was a brief intervention targeting treatment compliance issues.	of Sydney Sesqui Fund.
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 schedule. Info on Screening Process: Of people screened, n=153 met the eligibility criteria but n=11 dropped out prior to randomisation due to: unable to abstain (n=2), lost to follow-up (n=4), refused treatment (n=3), refused to take medication (n=2).	n= 142 Age: Mean 44 Range 21-65 Sex: 136 males 6 females 100% Alcohol Dependence by DSM IV Exclusions: <21 or >65 years of age, no DSM-IV diagnosis of alcohol dependence, not able to read and write in Korean, unstable residence and no telephone. Further exclusion criteria: current misuse/dependence on substance except alcohol or nicotine, acute major psychiatric illness, liver cirrhosis or renal problems, unstable medical condition, current use of disulfiram or psychotropic medication, previous acamprosate treatment, pregnancy, nursing or refusal to take reliable birth control. Baseline: Acam 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** VAS - Not relevant Craving - OCDS - Not relevant GGT - 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 present inactive placebo tablet, given in 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: Financed by Whan-In Pharmaceutical Co.
PAILLE1995 Study Type: RCT Type of Analysis: ITT- all receiving one dose of study medication	n= 538 Age: Mean 43 Range 18-65 Sex: 430 males 108 females	**Data Used** CAD Time to first relapse	**1 N= 188** Acamprosate. Mean dose 1.3g/day - Participants took four 333mg tablets + 2	Funding: no details

Blindness: Double blind Duration (days): Mean 365 Setting: 31 specialist alcohol centres in France. Notes: Randomisation: predetermined list Info on Screening Process: No details	100% Alcohol Dependence by DSM-III Exclusions: <18 or >65 years of age, no DSM-III-R diagnosis of alcohol dependence, not undergone detoxification and not currently abstinent. Further criteria: Severe psychiatric or organic disease, renal failure or hypercalcaemia, pregnancy, nursing mothers, non-permitted concomitant medication, attempted detoxification on three previous occasions in the last 2 years and having no fixed address. Notes: Study medication started 7-28 days after last drink, mean duration of abstinence was 18 days. Baseline: Alcohol consumption (g/day); In UK units; Live with family (%); Employed (%) Placebo 192 (108) 24 74 65 Acamp 1.3g/day 189 (161) 23.63 77 73 Acampr 2g/day 180 (89.5) 22.5 77 66	Abstinent at endpoint Abstinent at assessment % continuously abstinent Leaving study early **Data Not Used** MCV - Not relevant GGT - Not relevant	placebo tablets per day. Supportive psychotherapy - Supportive psychotherapy given as required (no further details) **2 N= 173** Acamprosate. Mean dose 2g/day - Participants took six 333mg tablets per day Supportive psychotherapy - Supportive psychotherapy given as required (no further details) **3 N= 177** Placebo - Participants took 6 inactive placebo tablets per day Supportive psychotherapy - Supportive psychotherapy given as required (no further details)	
PELC1992 Study Type: RCT Blindness: Double blind Duration (days): Mean 180 Followup: six months Setting: Awaiting translation	n= 102 Age: Mean 43 Range 23-64 Sex: 70 males 32 females Exclusions: Awaiting translation	**Data Used** % continuously abstinent	**1 N= 55** Acamprosate - Awaiting translation **2 N= 47** Placebo - Awaiting translation	
PELC1997 Study Type: RCT Type of Analysis: ITT - all receiving one dose of study medication Blindness: Double blind Duration (days): Mean 90 Setting: 11 outpatient centres in Belgium and France, after 14-day inpatient detox. Notes: Randomisation: no details	n= 188 Age: Range 18-65 Sex: no information 100% Alcohol Dependence by DSM-III Exclusions: <18 or >65 years of age, no DSM-III-R diagnosis of alcohol dependence, weighing less than 60kg, drinking history less than 12 months. Further exclusion criteria: Pregnant women, premenopausal women not practising contraception, major psychiatric or somatic disease, hypercalcaemia or having received prior treatment with acamprosate.	**Data Used** Time to first relapse Abstinent at endpoint Relapse CAD Leaving study early **Data Not Used** CGI - Not relevant Craving - subjective desire - Not relevant Notes: Any alcohol consumption was considered relapse. CGI assessment data given at days 8,15,30,45,60,75,90.	**1 N= 63** Acamprosate. Mean dose 1332mg/day - Four 333mg tablets taken daily alongside two placebo tablets. Supportive counselling + social support - Offered to all participants, who received intervention when needed. No specific psychotherapeutic model was used. **2 N= 63** Acamprosate. Mean dose 1998mg/day - six 333mg tablets taken daily. Supportive counselling + social support - Offered to all participants, who received intervention when needed. No specific psychotherapeutic model was used. **3 N= 62** Placebo - six placebo tablets taken daily. Supportive counselling + social support - Offered to all participants, who received intervention when needed. No specific psychotherapeutic model was used.	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.	n= 246 Age: Mean 44 Range 18-65 Sex: 179 males 67 females 100% Alcohol Dependence by DSM-III Exclusions: <18 or > 65 years of age, no DSM-III diagnosis of alcohol dependence, GGT less than twice upper limit or MCV <95fl, less than 5 days abstinent 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. Notes: Participants suffering a severe relapse could be admitted to hospital for another withdrawal treatment while continuing medication. Baseline: Acamprosate Placebo Amount of population drinking >10 drinks/ drinking day (%): 94 (77) 91 (73)	**Data Used** Relapse Abstinent at endpoint Abstinent at assessment CAD Leaving study early **Data Not Used** GGT - Not relevant Notes: Abstinence, relapse and GGT assessments at months 1,3 and 6. Relapse = any alcohol consumption.	**1 N= 122** 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). 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.	Funding: Sponsored by Lipha France
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.	n= 127 Age: Mean 42 Range 23-64 Sex: 89 males 38 females Alcohol Dependence or Abuse by DSM-III Exclusions: 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. Baseline: Number of patients meeting diagnostic criteria for dependence (43 in placebo, 39 in acamprosate), and alcohol abuse (21 in placebo, 24 in acamprosate)	**Data Used** % continuously abstinent	**1 N= 63** Acamprosate - Daily dose for those weighing less than 60kgs: 2 pills twice daily each at 333mg (1332 mg/day) and for those weighing more than 60kg, 3 pills twice daily each at 333mg (1, 998mg/day). **2 N= 64** Placebo - Same dosage regimen and placebos were placed in the same box. The patient received the pills necessary at each consultation.	
RUBIO2001 Study Type: RCT Type of Analysis: ITT Blindness: Single blind Duration (days): Mean 365	n= 157 Age: Mean 43 Range 18-65 Sex: all males	**Data Used** Time to first drink Time to first relapse Craving - subjective desire % days abstinent	**1 N= 77** Naltrexone. Mean dose 50mg/day - 50mg of Naltrexone taken once daily.	The Fundacion Cerebro y Mente funded this research.

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 met the inclusion criteria for a number of reasons. n=3 then refused to participate, therefore n=157 were randomised.	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, 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	Drinks per drinking day Relapse Abstinent at endpoint Leaving study early Notes: Relapse: defined as >5 drinks or 40g of alcohol per day. * % days heavy drinking has no SDs	Supportive psychotherapy - Weekly group therapy, less structed than classical relapse prevention programmes. **2 N= 80** Acamprosate. Mean dose 1998mg/day - six tablets of acamprosate taken daily (5 tablets - 1665mg - if lower body weight). Supportive psychotherapy - Weekly group therapy, less structured than classical relapse prevention programmes.	
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	n= 272 Age: Mean 41 Sex: 211 males 61 females 100% Alcohol Dependence by DSM-III Exclusions: Meeting <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	**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	**1 N= 136** 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). 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. **2 N= 136** Placebo - Inactive control intervention, dosing schedule identical to the active intervention. 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.	Funding: Sponsored by the Lipha Company, Essen, Germany.
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	n= 330 Age: Mean 46 Range 18-65 Sex: 273 males 57 females 100% Alcohol Dependence by DSM-III	**Data Used** Relapse Abstinent at endpoint Abstinent at assessment CAD Leaving study early	**1 N= 164** Acamprosate. Mean dose 1998mg/day - Participants took six 333mg tablets daily during 6 month study period.	Funding: Lipha, France.

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 <95fl, abstinent for <5 days before study start and no partner/relatives to supply post-detoxification outcome. Further criteria: pregnancy, psychiatric 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. **2 N= 166** 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 Exclusions: <18 or > 65 years of age, no DSM-III diagnosis of alcohol dependence (chronic or episodic) with at least a 12 month history, abstinent for <5 days before study start, GGT value <twice upper limit and a MCV of <93fl. Further criteria: serious coexisting disease (renal failure, poorly controlled diabetes, cardiac failure, septicaemia, active tuberculosis, epilepsy unrelated to alcohol and psychiatric disorders requiring drug treatment), pregnant women, and women not using contraception. Baseline: Acamprosate Placebo MAST score: 32.7 (8.63) 32.4 (8.87) Amount of population drinking >121 g of alcohol daily: 140 (of 224) 141 (of 224)	**Data Used** CAD Abstinent at endpoint Relapse Death Leaving study early	**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	Funding: Groupe LIPHA, France.

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Study characteristics for naltrexone

Comparisons Included in this Review Question

Naltrexone + Sertraline vs Naltrexone
FARREN2009
OMALLEY2008

Naltrexone vs Acamprosate
ANTON2006
KIEFER2003
MORLEY2006
RUBIO2001

Naltrexone vs Placebo
AHMADI2002
ANTON1999
ANTON2005
ANTON2006
BALLDIN2003
BALTIERI2008
CHICK2000
GASTPAR2002
GUARDIA2002
HEINALA2001
HUANG2005
KIEFER2003
KILLEEN2004
KRANZLER2000
KRYSTAL2001
LATT2002
LEE2001
MONTI2001
MORLEY2006
MORRIS2001
OMALLEY1992
OMALLEY2003
OMALLEY2008
OSLIN1997
OSLIN2008
VOLPICELLI1992
VOLPICELLI1997

Naltrexone vs Topiramate
BALTIERI2008

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
AHMADI2002 Study Type: RCT Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 252 Setting: Conducted in Iran, participants were self-referrals. Notes: Randomisation: stratified to dose and duration of drinking alcohol. Info on Screening Process: no details	n= 116 Age: Mean 43 Range 23-56 Sex: all males Diagnosis: 100% Alcohol Dependence by Undefined diagnosis tool 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	**Data Used** Relapsed by endpoint Leaving study early 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)	**Group 1 N= 58** Naltrexone. Mean dose 50mg/day - 50mg of naltrexone taken daily 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

	use of opioids or disulfiram, bilirubin level and ALT higher than 5 times normal and intake of neuroleptic drugs. Baseline: Married(%) Employed (%) Total sample: 87 83.6		**Group 2 N= 58** Placebo - Inactive intervention, identical in appearance and dosing schedule to active intervention. Relapse prevention - weekly 0.5 hour counselling sessions, providing training in relapse prevention through identifying situations, places and people that cue drinking.	
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.	n= 131 Age: Mean 42 Range 21-65 Sex: 92 males 39 females 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: Nalx PLB % days drinking: 82 (21) 82 (21) Drinks/drinking day: 11.8 (4.9) 11.9 (5.1) UK units DDD: 17.7 17.85 Married(%): 66 70 Employed (%)full-time: 81 81	**Data Used** Relapse Abstinent at endpoint Time to first relapse Time to first drink Drinks per drinking day % days abstinent Leaving study early **Data Not Used** CDT - Not relevant GGT - Not relevant	**Group 1 N= 68** Naltrexone. Mean dose 50mg/day - 50mg of naltrexone taken daily Coping skills - Weekly individual sessions of coping skills, using the Project MATCH manual (referred to as CBT in the paper). **Group 2 N= 63** Placebo - Inactive intervention, identical in appearance to active intervention. Coping skills - Weekly individual sessions of coping skills, using the Project MATCH manual (referred to as CBT in the paper).	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	n= 160 Age: Mean 44 Range 21-70 Sex: 121 males 39 females 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	**Data Used** Total drinks Time to first relapse Time to first drink Drinks per drinking day Relapse % days abstinent Leaving study early	**Group 1 N= 39** Naltrexone. Mean dose 50mg/day - 50mg of naltrexone taken daily. Coping skills - Weekly coping skills delivered using the manual from Project MATCH. Referred to as 'CBT' in the paper.	Supported by grants from the National Institute on Alcohol Abuse and Alcoholism.

	abstinence for 5 days before study. Further criteria: current dependence or abuse of other psychoactive substances (except nicotine and marijuana misuse allowed), history of opiate abuse/dependence, current major psychiatric disorder, serious or unstable medical condition, current use of psychoactive medication including antiseizure medications, current use of disulfiram, pending legal charges for any violent crime, use of any opioid antagonist in the month before study entry, pregnancy, nursing or lack of reliable birth control and liver function test results (ALT and AST) greater than 2.5 times the upper limit of normal. Notes: Participants needed to abstain for 5 consecutive days for inclusion. Baseline: Drinks/ drinking day(US) (UK) % days drinking (out of 90) % Married % Employed Nalx+CBT 11.1 (4.9) 16.65 72 (16) 33 92 Nalx+MET 13.0 (7.0) 19.57 78 (12) 46 73 Plb+CBT 11.7 (5.4) 17.33 71 (22) 41 93 Plb+MET 11.9 (6.5) 17.85 77 (14) 35 92	Notes: Relapse/heavy drinking day= >5 drinks in 1 day for men (>4 for women).	**Group 2 N= 41** Naltrexone. Mean dose 50mg/day - 50mg of naltrexone taken daily. MET - Motivational enhancement therapy, delivered weekly using the manual from Project MATCH **Group 3 N= 41** Placebo - Inactive intervention identical in appearance to active intervention Coping skills - Weekly coping skills delivered using the manual from Project MATCH. Referred to as 'CBT' in the paper. **Group 4 N= 39** Placebo - Inactive intervention identical in appearance to active intervention MET - Motivational enhancement therapy, delivered weekly using the manual from Project MATCH	
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.	n= 1383 Age: Mean 44 Range 18- Sex: 955 males 428 females Diagnosis: 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 my 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. Notes: Participant's 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/ drinking day UK units % days abstinent % Married % Employed PLB+MM 12.6 (7.67) 18.9 24.3 (24.74) 44.4 79.7 NALX+MM 12.7 (7.69) 19.1 29.8 (24.70) 38.3 72.7 ACAM+MM 12.2 (7.77) 18.3 24.6 (24.78) 36.2 71.7 NALX+ ACAM+MM 12.4 (7.66) 18.6 22.9 (24.70) 42.6 70.9 PLB+CBI 12.6 (7.74) 18.9 24.3 (24.73) 50.0 71.8 NALX+CBI 12.4 (7.72) 18.6 23.7 (24.78) 37.4 76.8	**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 Lipha Pharmaceuticals.

	ACAM+CBI NALX+	13.2 (7.74)	19.8	25.3 (24.70)	44.4	70.9		**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.	
	ACAM+CBI	12.2 (7.77)	18.3	26.8 (24.68)	43.3	70.7			
	CBI only	11.8 (7.66)	17.7	23.5 (25.35)	41.4	69.4			

			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.	
BALLDIN2003 Study Type: RCT Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 180 Setting: Study performed at 10 different investigation centres in Sweden, mostly university hospitals. Patients recruited from outpatients or advertisement. Notes: Randomisation : Patients assigned unique sequential numbers stratified by study site. 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.	n= 118 Age: Mean 49 Sex: 100 males 18 females Diagnosis: Alcohol Dependence by DSM IV Exclusions: <18 and 65> years of age, no DSM-IV criteria for alcohol dependence, no permanent place of residence. Further criteria : clinical evidence of cerebral, cardiovascular, hepatic, renal, gastrointestinal, metabolic or other systemic (e.g. cancer) disease or taking medication for it if such a medical condition exists. Signs of liver disease (defined by ALT or AST activities), past/current psychiatric disorder, suicide liability, brain damage, aggressive impulses, abuse or dependence criteria for any other psychoactive substance disorder during 6 months preceding the study, currently taking disulfiram, calcium carbamide, naltrexone, acamprosate, benzodiazepines, lithium, buspirone, pregnant/breast-feeding women. Notes: Obligatory for men to consume at least 5 drinks and women to have consumed at least 4 (one drink = 12 g of	**Data Used** Time to first relapse Leaving study early % heavy drinking days Drinks per day CBT % drinking days **Data Not Used** GGT - Not relevant Craving - OCDS - Not relevant AST - Not relevant ALT - Not relevant Notes: Alcohol per drinking day measured in g.	**Group 1 N= 25** Naltrexone. Mean dose 50mg/day - patients ingested one 50 mg naltrexone tablet daily. Coping skills - 9 sessions, lasting approx-imately 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.	Study supported and medication provided by DuPont Pharma (UK) and Meda AB (Sweden).

	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 approx-imately 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 293.7 (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.

			Group 3 N= 52 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. 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.	
CHICK2000 Study Type: RCT Type of Analysis: ITT - all taking one dose of study medication Blindness: Double blind Duration (days): Mean 84 Setting: Conducted in 6 sites in the UK, all participants had/were about to enrol in an outpatient alcohol rehabilitation program or routine follow-up Notes: Randomisation: was stratified according to DSM diagnosis of alcohol dependence or abuse. Info on Screening Process: No details	n= 175 Age: Mean 43 Range 18-65 Sex: 131 males 44 females Diagnosis: 97% Alcohol Dependence by DSM-III 3% Alcohol Abuse 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: NALX PLB Drinks/day: 10.1 (9.1) 10.3 (7.5) DD in UK units: 15.15 15.45 Years drinking: 22.9 (8.7) 25.9 (10.6) Married/ Cohabiting (%): 41 41 Living alone(%): 31 22 Employed(%): 21 32	**Data Used** Total drinks % continuously abstinent Leaving due to adverse events Leaving study early Notes: Heavy drinks: defined as >5 drinks in single occasion for men (>4 for women). Drink = 13g of ethanol. Total drinks: total drinks in last 4 weeks of the study.	**Group 1 N= 90** Naltrexone. Mean dose 50mg/day - 50mg of naltrexone taken daily 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. **Group 2 N= 85** Placebo - Inactive intervention, same appearance and dosing schedule as the active intervention. 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.	DuPont pharmaceuticals supplied Naltrexone and placebo medication, as well as giving funds to participating clinics.
FARREN2009 Study Type: RCT Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 84 Setting: Participants responded to local	n= 111 Age: Mean 43 Range 19-64 Sex: 91 males 20 females Diagnosis: 100% Alcohol Dependence by DSM IV	**Data Used** % days abstinent Drinks per drinking day Leaving due to adverse events Leaving study early **Data Not Used**	**Group 1 N= 57** 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	Study was supported by the Mount Sinai GCRC, grants from the National Institute of Health & the State of Connecticut Department of Mental Health and Addiction Services, plus a small grant

advertisements. Study carried out at two sites, Yale university and Mount Sinai school of medicine. 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.	Exclusions: <19 and >64 years of age, no DSM-IV diagnosis of alcohol dependence, <5 or >30 days of abstinent 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: Nalx+Sert Nalx Drinks per drinking Day (in past 90 days): 7.3 (4.82) 7.4 (4.78) % days abstinent: 29.3 (19.13) 25.6 (18.66) % Married/living with partner: 33.9 46.2	GGT - Not relevant Craving - OCDS - Not relevant	weeks, then this was increased to 100mg/day for final 10 weeks. Group relapse prevention - Weekly group 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.	from Pfizer. Medication was supplied by DuPont Pharm and by Pfizer.
GASTPAR2002 Study Type: RCT Type of Analysis: ITT - LOCF Blindness: Double blind Duration (days): Mean 84 Setting: Study was conducted at 7 sites in Germany. Participants were recently detoxified. Notes: Randomisation: no details	n= 171 Age: Mean 43 Sex: 124 males 47 females Diagnosis: 98% Alcohol Dependence by DSM-III 2% Alcohol Abuse by DSM-III 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	**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.	Study was designed, monitored and sponsored by DuPont Pharmaceuticals, USA.
GUARDIA2002 Study Type: RCT Type of Analysis: ITT - all taking one dose of study medication Blindness: Double blind Duration (days): Mean 84 Setting: Conducted in 7 centres in Spain, all participants were seeking outpatient treatment. Notes: Randomisation: no details Info on Screening Process: no details	n= 202 Age: Mean 42 Range 18-60 Sex: 150 males 52 females Diagnosis: 100% Alcohol Dependence by DSM IV Exclusions: <18 and 60> years of age, no DSM-IV criteria for alcohol dependence. Further criteria : pregnant or breastfeeding women, severe organic disorders, serum aspartate (AST) or alanine aminotransferase (ALT) > 150 U/litre, severe psychiatric disorders, other current substance abuse or dependence disorder (except for nicotine) that was	**Data Used** Time to first relapse Time to first drink % days abstinent Drinks per drinking day Relapsed by endpoint Leaving study early	**Group 1 N= 101** Supportive psychotherapy - Supportive group therapy for relapse prevention once per week, alongside individual supportive counselling. Naltrexone. Mean dose 50mg/day - Given 50mg/day for 12 weeks.	Pharmazam/Zambon S.A. provided financial support to contract a research assistant physician and supplied the naltrexone and matching placebo.

	not in sustained remission Notes: Nurses encouraged participants to remain abstinent. Baseline: Nalx Plb Recent daily alcohol intake, Standard units : 17.67 (9.49) 17.65 (8.95) DD in UK units: 23 22.95 Married (%): 64 53 Employed (%): 46 44	Notes: Relapse: defined as >5 drinks per day for men (>4 drinks for women)	**Group 2 N= 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.	
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	n= 121 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	**Data Used** Relapse Notes: Relapse to heavy drinking: drinking 5 or more drinks in one occasion. Drink= 12 g of alcohol	**Group 1 N= 34** Naltrexone. Mean dose 50mg/day - 50mg of naltrexone taken daily Coping skills - Four group sessions over 12 week study period. Cognitive behavioural therapy emphasised coping with a slip when the patient samples alcohol so that the slip doesn't become a binge. **Group 2 N= 33** Placebo - Inactive intervention, identical in appearance and dosing schedule to active intervention Coping skills - Four group sessions over 12 week study period. Cognitive behavioural therapy emphasised coping with a slip when the patient consumes alcohol so that the slip does not become a a binge. **Group 3 N= 29** Naltrexone. Mean dose 50mg/day - 50mg of naltrexone taken daily Supportive psychotherapy - Four group sessions over 12 week study period. Supportive therapy emphasised the support of complete abstinence from all drinking. **Group 4 N= 25** Placebo - Inactive intervention, identical in appearance and dosing schedule to active intervention Supportive psychotherapy - Four group sessions over 12 week study period. Supportive therapy emphasised the support of complete abstinence from all drinking.	Financially supported by the Finnish Alcohol Research Foundation and the National Public Health Institute.
HUANG2005 Study Type: RCT Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 98 Setting: Alcoholism treatment unit of a	n= 40 Age: Mean 41 Range 20-60 Sex: all males Diagnosis: 100% Alcohol Dependence by DSM-III	**Data Used** Relapse Leaving due to adverse events Leaving study early	**Group 1 N= 20** Naltrexone. Mean dose 50mg/day - 50mg taken daily.	No details on funding/sponsorship.

psychiatric hospital in Taipei city. Notes: Randomisation: no details Info on Screening Process: No details	Exclusions: <20 and >60 years of age, not meeting DSM-IV criteria for alcohol dependence. Further exclusion criteria: current other substance abuse/dependence (except nicotine), suffering from significant physical illness such as ischaemic heart disease or diabetes mellitus, suffering from severe psychiatric disorders such as schizophrenia or bipolar disorders, or displayed AST and ALT levels >3 times laboratory reference levels. Notes: Underwent inpatient detoxification treatment for at least 2 weeks Baseline: Nalx Plb Married (%): 70 60	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 2 N= 20** Placebo - Inactive control intervention, dosing schedule identical to the active intervention Supportive psychotherapy - Weekly, 30 minute individual psychotherapy sessions, focused on abstinence and compliance enhancement, conducted in outpatients department.	
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.	n= 160 Age: Mean 46 Range 18-65 Sex: 118 males 42 females Diagnosis: 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, abstinent 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 score Married (%) Partnership (%) 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	**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. **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)

			Group 4 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.	
KILLEEN2004 Study Type: RCT Type of Analysis: ITT- all having at least 1 follow-up Blindness: Double blind Duration (days): Mean 84 Setting: recruitment was from individuals who entered treatment at an outpatient community treatment program for an alcohol use disorder. US. Notes: Randomisation: Urn randomisation used to balance gender, comorbidities, severity of dependence (ADS) and treatment intensity across groups Info on Screening Process: n=191 screened, n=145 enrolled. No details on reasons for exclusion.	n= 133 Age: Mean 37 Sex: 84 males 49 females Diagnosis: 100% Alcohol Dependence by DSM IV 51% Any axis I disorder by DSM IV 35% Other substance use disorder by DSM IV Exclusions: No current DSM-IV diagnosis of alcohol dependence, not drinking in 30 days before the trial. Further criteria: current addiction to opiates, women who were pregnant, breastfeeding, or of child-bearing age and not using effective birth control, serious medical conditions or liver enzymes more than 3 times the normal range, cognitive dysfunction to an extent that would impair the understanding of informed consent or assessments, having >10 days of outpatient treatment in past 3 months. Baseline: Nalx Plb TAU Married (%): 39 29 23 Employed(%): 43 56 67	**Data Used** Relapse Leaving study early	**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.	Supported by grants from the NIAAA.
KRANZLER2000 Study Type: RCT Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 77 Setting: recruited through advertisements in local news media and referrals from area clinicians, US. Notes: Randomisation: no details Info on Screening Process: no details	n= 183 Age: Mean 40 Range 18-60 Sex: 142 males 41 females Diagnosis: 100% Alcohol Dependence by DSM-III 12% dysthymia by DSM-III 6% major depression by DSM-III	**Data Used** % heavy drinking days Drinks per day % drinking days Abstinent at endpoint Leaving study early **Data Not Used** Craving - OCDS - Not relevant	**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.	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 Nefa Plb MAST score: 25.7 (11.2) 26.9 (11.9) 26.8 (10.8) Married (%): 39.3 49.2 46 Employed(%): 73.8 71.2 69.8		**Group 2 N= 59** Nefazodone. Mean dose 200mg/day - Dose started at 100mg daily but was gradually increased to 200mg. Participants showing no response were raised to 300mg/day. 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. **Group 3 N= 63** Placebo - Inactive intervention, identical in appearance and dosing schedule to active intervention. 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.	
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.	n= 627 Age: Mean 49 Range 18- Sex: 615 males 12 females Diagnosis: 100% Alcohol Dependence by DSM IV Exclusions: <18 years of age, no DSM diagnosis of alcohol dependence, heavy drinking less than twice in one week in month before screening, abstinent for <5 days before randomisation. Further criteria: previous use of naltrexone, liver disease, a psychiatric diagnosis other than alcoholism requiring current psychotropic medication, homelessness, other substance dependence or abuse (excluding nicotine and occasional cannabis use), any past illicit opiate use. Patients with pending legal charges with potential for jail or those receiving disability pension related to alcoholism were also excluded. Baseline: LT Nalx ST Nalx Plb % drinking days in in previous 90 days: 65.9 (30) 68.3 (29) 65.6 (29) Drinks/drinking day: 13.1 (8) 14.1 (9) 13.0 (7) In UK units: 19.65 21.15 19.5 Married / living with partner (%): 33.5 36.9 33	**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 to naltrexone tablets, taken 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.	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.

LATT2002

Study Type: RCT

Type of Analysis: ITT

Blindness: Double blind

Duration (days):

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= 107

Age: Mean 45 Range 18-70

Sex: 74 males 33 females

Diagnosis:
100% Alcohol Dependence by DSM IV

Exclusions: <18 and >70 years, 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 (1026.9-1277.5)	144.03

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

Data Not Used
GGT - 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 admitted to the hospital, but only n=53 were included in the study, others were excluded as they didn't meet eligibility criteria or they refused to participate.

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

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), out-patient 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), out-patient group therapy, AA and support meetings.

Naltrexone was provided by Boots Healthcare.

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

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

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

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

Supported by grants from the NIAAA. Medication and placebo supplies were supplied by DuPont-Merck Pharmaceutical Company.

psychiatric hospital. Program lasted 7-27 days, 6 hours daily. Notes: Randomisation: Stratified for sex and socialisation scale scores from the California psychology inventory. Info on Screening Process: n=1549 screened, only n=384 eligible and of these, n=196 declined participation. n=165 patients entered psychosocial treatment, but n=18 left the program quickly, and then n=37 dropped out of the hospital program. n=128 were randomised to medication.	before study start, urine screen positive for opiates, current psychotic 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 (180 days before treatment) Days drinking (%): 66.1 (28.3) 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 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.	n= 169 Age: Mean 45 Range 18-65 Sex: 118 males 51 females Diagnosis: 100% Alcohol Dependence or Abuse by DSM IV Exclusions: <18 or >65 years of age, no DSM-IV diagnosis of alcohol dependence or abuse, had been abstinent from alcohol for <3 or >21 days and insufficient understanding of English. Further criteria: advanced liver disease, previous treatment with naltrexone or acamprosate within 3 months of randomisation, any other drug dependence (other than nicotine or low-potency benzodiazepine for sleep), or severe current psychiatric disorder associated with psychosis and significant suicide risk. Pregnant or breast feeding women also excluded. Baseline: Acamp Nalx Plb 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	**Data Used** Time to first drink Relapse Abstinent at endpoint Drinks per drinking day Time to first relapse CAD Leaving study early **Data Not Used** ADS score - Not relevant Notes: Relapse: 4 or more drinks for women, 6 or more for men. Lapse: 1 drink	**Group 1 N= 55** Acamprosate. Mean dose 1998mg/day - Participants took six 333mg tablets daily Medication compliance therapy - four to six sessions of manualised compliance therapy were offered. This was a brief intervention targeting treatment compliance issues. **Group 2 N= 53** Naltrexone. Mean dose 50mg - Participants took 50mg in one tablet daily Medication compliance therapy - four to six sessions of manualised compliance therapy were offered. This was a brief intervention targeting treatment compliance issues. **Group 3 N= 61** Placebo - Inactive control, tablets appeared identical to either naltrexone or acamprosate and were taken in the same dosing schedule. Medication compliance therapy - four to six sessions of manualised compliance therapy were offered. This was a brief intervention targeting treatment compliance issues.	Funding: supported by grants from the National Health and Medical Research Council of Australia and the University of Sydney Sesqui Fund.
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 Info on Screening Process: n=137 were screened, but only n=111 were included, n=26	n= 111 Age: Mean 47 Range 18-65 Sex: all males Diagnosis: 100% Alcohol Dependence by DSM-III 4% panic disorder by DSM-III 35% Generalised anxiety disorder by DSM-III	**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	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 2 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.	
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 Exclusions: <18 and >65 years of age, no DSM-III-R diagnosis of alcohol dependence. Further criteria: current DSM-III 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%	**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.	**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= 23** Supportive psychotherapy - Weekly therapy. Therapist encouraged patient to remain abstinent without being taught specific coping skills. Naltrexone. Mean dose 50mg/day - 50mg, in one pill taken daily. **Group 3 N= 25** 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. Placebo - Inactive control intervention, dosing schedule identical to the active intervention	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.

			Group 4 N= 27 Placebo - Inactive control intervention, dosing schedule identical to the active intervention Supportive psychotherapy - Weekly therapy. Therapist encouraged patient to remain abstinent without being taught specific coping skills.	
OMALLEY2003 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, abstinent 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 opiates or currently using opiates, significant psychiatric problems (eg 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 = randomised all PCM responders to naltrexone or placebo with continued PCM Study 3 = 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	**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.	**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.
OMALLEY2008 Study Type: RCT Type of Analysis: ITT	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= 34** Naltrexone - 12.5 mg given for one day, 25 mg for 2 days, 50 mg thereafter for 16 weeks.	Funded by the National Institute on Alcohol Abuse and Alcoholism and the National Centre on Minority

Blindness: Double blind Duration (days): Mean 112 Setting: Recruited over a span of 3 years for participation within Alaska. Notes: Randomisation : Conditions in blocks of 12 within Native and non-Native groups and within study site. Info on Screening Process: n=365 screened, n=264 did not meet inclusion criteria or withdrew, leaving n=101 to be randomised.	Diagnosis: Alcohol Dependence by DSM IV Exclusions: <18 to 65>years of age, drinking <21 drinks a week if male (<14 drinks if female),no DSM-IV alcohol dependence diagnosis. Further criteria : presence of DSM-IV diagnosis for cocaine, opioid, or amphetamine abuse or dependence, current opiate use, psychiatric conditions that required use of psychotropic medications, a condition jeopardising safety (suicidality, psychosis), medical conditions contraindicate the use of sertraline or naltrexone. Notes: >4 and <30 days abstinence were required before study start. Patients must be absent from detoxification medications for at least 4 days prior to randomisation. Baseline: PLB NX NX+SER 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	% days abstinent Relapse % continuously abstinent Leaving study early **Data Not Used** Alcohol urge questionnaire - Not relevant GGT - Not relevant	Counselling - participants seen weekly for 4 weeks, bi-weekly for one month, and once a month for the final 2 months. **Group 2 N= 34** Placebo - one placebo pill per day (50mg) for two weeks, and afterwards the dose was increased to 100mg daily (two 50 mg placebo tablets). Counselling - participants seen weekly for 4 weeks, bi-weekly for one month, and once a month for the final 2 months. **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. Counselling - participants seen weekly for 4 weeks, bi-weekly for one month, and once a month for the final 2 months.	Health and Health Disparities. Pfizer pharmaceuticals donated study medications, but had no role in design, conduct or reporting of 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	n= 44 Age: Mean 58 Range 50-70 Sex: no information 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 before 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	**Data Used** Relapse % drinking days Leaving due to adverse events Leaving study early 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.	**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 therapy - Weekly group therapy and referral to a case manager, who they met at least twice a month. The goal of therapy was to achieve abstinence through peer support and education. **Group 2 N= 23** Placebo - Inactive control intervention, dosing schedule identical to the active intervention Group therapy - Weekly group therapy and referral to a case manager, who they met at least twice a month. The goal of therapy was to achieve abstinence through peer support and education.	Medication and placebo were supplied by DuPont Merck pharmaceutical
OSLIN2008 Study Type: RCT Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 168 Setting: recruited through advertisements in the local media.	n= 240 Age: Mean 43 Range 18- Sex: 173 males 67 females Diagnosis: 100% Alcohol Dependence by DSM- IV SCID Exclusions: <18 years of age, no DSM-IV diagnosis of	**Data Used** Drinks per day % heavy drinking days % drinking days % without heavy drinking during study Abstinent at endpoint Leaving study early	**Group 1 N= 40** Naltrexone. Mean dose 100mg/day - 100mg of naltrexone taken daily, but if not tolerated, dose was decreased to 50mg/day.	Supported by grants from the NIAAA, the National Institute on Mental Health and the National Institute on Drug Abuse

Info on Screening Process: No details	alcohol dependence, <3 consecutive days of abstinence before the study started. Further criteria: any psychoactive substance dependence other than alcohol or had opioid misuse in past 30 days (measured by self-report and urine analysis), taking psychotropic medications or evidence of severe psychiatric symptoms such as psychosis, mania, or PTSD; severe medical illness such as active hepatitis; pregnancy, nursing or not using reliable birth control. Baseline: Drinks per day / Uk units / % days drinking / Married (%) / Empl-oyed (%) Nalx+CBT 9.4 (9.1) 14.1 72.5 (27.4) 20 80 Plb+CBT 9.1 (6.6) 13.65 74.3 (27.6) 30 87.5 Nalx+ BRENDA 7.2 (6.0) 10.8 65.7 (29.0) 41 84.6 Plb+ BRENDA 8.0 (5.1) 12 70.9 (28.5) 35.9 87.5 Nalx+ Doctor 10.1 (6.5) 15.15 76.3 (22.1) 31.7 85.4 Plb+ Doctor 8.0 (5.6) 12 70.0 (30.0) 38.5 85	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.	
RUBIO2001 Study Type: RCT Type of Analysis: ITT	n= 157 Age: Mean 43 Range 18-65 Sex: all males	**Data Used** Time to first drink Time to first relapse Craving - subjective desire	**Group 1 N= 77** Naltrexone. Mean dose 50mg/day - 50mg of Naltrexone taken once daily.	The Fundacion Cerebro y Mente funded this research.	

Blindness: Single blind Duration (days): Mean 365 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 other did not met the inclusion criteria for a number of reasons. n=3 then refused to participate, so n=157 were randomised.	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, 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	% days abstinent Drinks per drinking day Relapse Abstinent at endpoint Leaving study early Notes: Relapse: defined as >5 drinks or 40g of alcohol per day. * % days heavy drinking has no SDs	Supportive psychotherapy - Weekly group therapy, less structured than classical relapse prevention programmes. **Group 2 N= 80** Acamprosate. Mean dose 1998mg/day - six tablets of acamprosate taken daily (5 tablets - 1665mg - if lower body weight). Supportive psychotherapy - Weekly group therapy, less structured than classical relapse prevention programmes.	
VOLPICELLI1992 Study Type: RCT Blindness: Double blind Duration (days): Mean 84 Setting: Recruited newly admitted patients in outpatient rehabilitation treatment at the Substance abuse treatment unit of Philadelphia medical center. Notes: Randomisation: no details	n= 70 Age: Mean 43 Range 21-65 Sex: all males Diagnosis: 100% Alcohol Dependence by DSM-III Exclusions: <21 and >65 years of age, no DSM-III-R diagnosis of alcohol dependence (at least 5 criteria met), score =<5 on the MAST,incapable of understanding requirements of the study. Further criteria: having a major psychiatric illness associated with psychosis or dementia at the time of evaluation, being judged by psychiatrist as a danger to self/others, history of unstable or serious medical illness, using narcotics in past 30 days, having positive drug screen (opiates, amphetamine, cocaine or barbiturates), laboratory evidence of significant hepato-cellular failure as evidenced by bilirubin levels. Baseline: Naltrxone 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	**Data Used** Leaving study early days drinking (during study) Relapse **Data Not Used** SCL-90 - Not relevant GGT - Not relevant Notes: Relapse: defined as (1) more than 5 days drinking within 1 week, (2) reporting >5 drinks on one occasion (3) coming to treatment appointment with a blood alcohol concentration above 100mg/dL.	**Group 1 N= 35** Naltrexone. Mean dose 50mg/day - 50mg, in one pill taken daily. 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= 35** Placebo - inactive intervention, identical in appearance to active intervention, taken in same dosing schedule. 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.	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.
VOLPICELLI1997 Study Type: RCT Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 84 Setting: Admitted alcohol-dependent patients receiving outpatient treatment at the University of Pennsylvania/veterans Affairs Treatment Center. Notes: Randomisation : Computer number	n= 97 Age: Mean 38 Range 21-65 Sex: 70 males 27 females 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,	**Data Used** Leaving study early Relapse Lapse % drinking days **Data Not Used** GGT - Not relevant Craving - subjective desire - Not relevant	**Group 1 N= 49** Naltrexone - Received 50 mg naltrexone 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.	narcotic use in past 30 days, lab evidence of significant hepatocellular injury, current disulfiram treatment, pregnant female patients (or nursing), or not using a reliable method of contraception, and abstinence from alcohol for longer than 21 days. Baseline: Naltrexone Placebo drinking days 13.3(8.9) 14.8(8.9) Married (%): 42.9 46 Employed (%): 71.4 64	Notes: Craving assessed on a 10 point scale (0, not at all, 10 would have had a drink if one were available). Relapse defined as at least 5 drinks during 1 drinking occasion or a documented breath alcohol level greater than 100 mg/dL.	**Group 2 N= 48** Placebo - initial 1 week placebo lead in to establish baseline measures. 1 identical looking tablet to naltrexone prescribed once daily 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.	

Characteristics of Excluded Studies - see final section

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References of Excluded Studies - see final section.

Study characteristics for acamprosate + naltrexone

Comparisons Included in this Review Question

Acamprosate + Naltrexone vs acamprosate
ANTON2006
KIEFER2003

Acamprosate + Naltrexone vs naltrexone
ANTON2006
KIEFER2003

Acamprosate + Naltrexone vs placebo
ANTON2006
KIEFER2003

Characteristics of Included Studies

ANTON2006

Methods

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.

Participants

n= 1383

Age: Mean 44 Range 18-

Sex: 955 males 428 females

Diagnosis:
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 treatment with the study interventions.

Notes: Participant's 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/ drinking day	UK units	% days abstinent	Married %	Empl-oyed %
PLB+MM	12.6 (7.67)	18.9	24.3 (24.74)	44.4	79.7
NALX+MM	12.7 (7.69)	19.1	29.8 (24.70)	38.3	72.7
ACAM+MM	12.2 (7.77)	18.3	24.6 (24.78)	36.2	71.7
NALX+ ACAM+MM	12.4 (7.66)	18.6	22.9 (24.70)	42.6	70.9
PLB+CBI	12.6 (7.74)	18.9	24.3 (24.73)	50.0	71.8
NALX+CBI	12.4 (7.72)	18.6	23.7 (24.78)	37.4	76.8
ACAM+CBI	13.2 (7.74)	19.8	25.3 (24.70)	44.4	70.9
NALX+ ACAM+CBI	12.2 (7.77)	18.3	26.8 (24.68)	43.3	70.7
CBI only	11.8 (7.66)	17.7	23.5 (25.35)	41.4	69.4

Outcomes

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

Interventions

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.

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.

Notes

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

			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.	

			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.	
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.	n= 160 Age: Mean 46 Range 18-65 Sex: 118 males 42 females Diagnosis: 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, abstinent 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 score / Married (%) / Partnership (%) 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	**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.	Funding: medication donated by DuPont (nalx) and Merck (Acamp)

			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. **Group 4 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 90 minutes.	

Characteristics of Excluded Studies - see final section.

References of Included Studies

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References of Excluded Studies - see final section.

Study characteristics for disulfiram (oral)

Disulfiram + Counselling Vs Counselling
GERREIN1973

Disulfiram Vs Acamprosate
LAAKSONEN2008

Disulfiram Vs Naltrexone
DESOUSA2004
LAAKSONEN2008

Disulfiram Vs Placebo
CHICK1992
FULLER1979
FULLER1986

Disulfiram Vs Topiramate
DESOUSA2008

CHICK1992 Study Type: RCT Type of Analysis: Completers Blindness: Single blind Duration (days): Mean 180 Setting: Participants were attending one of seven outpatient alcoholism treatment centres. All participants had already relapsed after previous therapy/support Notes: Randomisation: by a pharmacist who randomly placed treatments against numbers, which in turn were given to participants entering treatment.	n= 126 Age: Mean 43 Range 18-67 Sex: 106 males 20 females 100% Alcohol Dependence by Undefined diagnosis tool 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: Employed%: 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	**1 N= 64** 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. **2 N= 62** Placebo - Vitamin C, 100mg daily taken under supervision of designated 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.	
DESOUSA2004 Study Type: RCT Type of Analysis: ITT Blindness: Open Duration (days): Mean 365 Setting: Participants were alcohol-dependent patients undergoing detoxification in a private psychiatric hospital in Mumbai, India. Notes: Randomisation: list provided by qualified statistician. Participants were allocated	n= 100 Age: Mean 44 Range 18-65 Sex: all males 100% Alcohol Dependence by DSM IV 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	**Data Used** GGT Drinks per drinking day Time to first relapse Time to first drink Relapse Abstinent at assessment Leaving due to adverse events Leaving study early	**1 N= 50** Naltrexone - 50mg of naltrexone taken at breakfast daily. Compliance was enhanced by asking family member to view participant taking drug in the morning.	No details on financial support

according to serial number on list. Info on Screening Process: n=182 participants were screened, n=114 met inclusion criteria. Of these n=105 gave consent, but n=5 dropped out before randomisation.	met DSM-IV criteria, any medical condition that would interfere with treatment compliance, liver function tests elevated above three times normal limit and previous treatment with naltrexone and/or disulfiram. Notes: Detoxification was either in the hospital setting or in community. Compliance enhanced by asking family member to view participant taking medication. Baseline: Naltrexone Disulfiram Days of drinking in last 6 months: 87 (20) 87 (22) ADS severity: 29 (5) 28 (6) ASI: 0.7 (.14) 0.71 (.12) Typical drinks per day: 12.5 (5) 12.2 (5.1)		**2 N= 50** Disulfiram - 250mg of disulfiram taken daily at breakfast. Compliance was enhanced by asking family member to view participant taking drug in the morning.	
DESOUSA2008 Study Type: RCT Type of Analysis: ITT Blindness: Open Duration (days): Mean 252 Setting: Participants were undergoing inpatient detoxification in a psychiatric hospital. The centre had facilities for inpatient and outpatient treatment Notes: Randomisation: performed by qualified statistician, with treatment allocated by clinic staff according to serial number on the list. Info on Screening Process: n=171 patients were screened, n=103 met inclusion criteria and the first 100 (in serial order) were randomised to treatment.	n= 100 Age: Range 18-65 Sex: all males 100% Alcohol Dependence by DSM IV 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. Baseline: Disulfiram Topiramate Drinks per drinking day: 9.6 (4.3) 10.4 (4.4) Days of drinking in month: 86 (12) 82 (14) Severity on ADS: 26 (5) 28 (4) ASI: 0.69 (0.08) 0.73 (0.10) Married (%): 98 98 Employed (%): 68 76	**Data Used** Time to first relapse Time to first drink Relapse Leaving due to adverse events Leaving study early Notes: Relapsed: defined as >5 drinks/40g of alcohol in 24 hours.	**1 N= 50** Disulfiram (witnessed). Mean dose 250mg/day - 250mg of disulfiram taken daily at breakfast. Family members observed participants while taking their medication. Supportive psychotherapy - Weekly supportive group psychotherapy was offered to all participants. Less structured, abstinence was positively reinforced. **2 N= 50** Topiramate. Mean dose 150mg/day - 50mg of topiramate taken three times daily. Family members observed participants while taking their medication. Supportive psychotherapy - Weekly supportive group psychotherapy was offered to all participants. Less structured, abstinence was positively reinforced.	
FULLER1979 Study Type: RCT Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 365 Setting: All participants attended Cleveland VA hospital and were requesting treatment for alcoholism or were admitted for one or more alcohol-related illnesses Notes: Randomisation: computer generated.	n= 128 Age: Mean 43 Sex: all males 100% Alcohol Dependence by Undefined diagnosis tool 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	**Data Used** % continuously abstinent	**1 N= 43** Disulfiram. Mean dose 250mg/day - Participants were instructed to take one 500mg tablet of disulfiram daily for the first week of treatment, and this was then reduced to 250mg per day thereafter. **2 N= 43** Disulfiram. Mean dose 1mg/day - Inactive treatment identical in appearance to active disulfiram but containing only 1mg of disulfiram. Taken in same dosing schedule as 'active' disulfiram.	

	chronic renal disease. Notes: Placebo group were aware of their allocation to inactive medication. Disulfiram and disulfiram 'placebo' groups unaware of allocation.		**3 N= 42** Placebo - Participants were instructed to taken one tablet of riboflavin (50mg) daily. Participants were aware they were not taking active medication.	
FULLER1986 Study Type: RCT Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 365 Setting: Patients presented for treatment at a participating alcoholism treatment unit. VA hospital. Notes: Randomisation: Sequentially number envelopes based on a randomisation list. 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.	n= 605 Age: Mean 42 Sex: all females 100% Alcohol Dependence by National Council on alcoholism diagnostic criteria Exclusions: <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. Notes: Abstinence was the goal of the rehabilitation program. Baseline: 250 Disulf 1mg Disulf No Disulf Days drinking in previous month: 20.3 (0.7) 20.8 (0.7) 20.0 (0.7) Employed (%): 51 56 54 Married (%): 73 71 66	**Data Used** % continuously abstinent Leaving study early Notes: Abstinence: designated if there was no evidence, from patients self-reports, reports for family/friends or detected through urine or blood specimens.	**1 N= 202** Disulfiram. Mean dose 250mg/day - 250mg of disulfiram taken daily. 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 month, biweekly for the next 6 months. **2 N= 204** Disulfiram. Mean dose 1mg - 'clinically insufficient' 1mg of disulfiram taken daily. 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 month, biweekly for the next 6 months. **3 N= 199** 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. 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 month, biweekly for the next 6 months.	
GERREIN1973 Study Type: RCT Type of Analysis: ITT Blindness: Open Duration (days): Mean 56 Setting: Outpatient alcoholism clinic at Boston city hospital. Notes: Randomisation: no details.	n= 121 Age: Mean 42 Sex: 107 males 14 females 100% Alcohol Dependence by Undefined diagnosis tool Baseline: Total sample: With spouse(%): 10	**Data Used** Leaving study early % continuously abstinent	**1 N= 13** Disulfiram. Mean dose 250mg/day - Participants were given a 7-day supply of disulfiram once a week, to take at home. 250mg dose taken daily. Counselling - Weekly individual visits to a counsellor. No further details	Supported by National Institute of Alcohol Abuse and Alcoholism grant.

	Employed(%): 49		**2 N= 13** Disulfiram (witnessed) - Particpants 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. **3 N= 12** Counselling - Weekly individual visits to a counsellor. No further details. In addition - participants were told they may receive disulfiram in the future depending on 'how they were doing'. **4 N= 11** Counselling - Same as counselling only group, but with additional invitation to the open discussion groups weekly. **5 N= 36** Counselling - Refused to take disulfiram but allowed to attend counselling on a weekly basis at the clinic. **6 N= 36** Counselling - Refused to take disulfiram but allowed to attend counselling on a weekly basis at the clinic as well as open-group discussion.	
LAAKSONEN2008 Study Type: RCT Type of Analysis: Completers Blindness: Open Duration (days): Mean 365 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 permutated blocks. Info on Screening Process: n=277 screened, n=14 refused to participate, n=20 did not meet inclusion criteria, leaving n=243 to be randomised.	n= 243 Age: Mean 43 Range 25-65 Sex: 172 males 71 females 100% Alcohol Dependence by ICD-10 Exclusions: No ICD-10 diagnosis of alcohol dependence, clinically significant symptoms of alcohol withdrawal, significant recently diagnosed psychiatric disease (psychosis, personality disorder, or suicidal tendency that appeared during the initial interview), current psychiatric disease demanding special treatment or medication including DSM-IV determined drug dependence other than alcohol or nicotine dependence, current use of any opioids within the 4 weeks before screening, significant brain, thyroid, kidney disease, uncompensated heart disease, clinically significant liver disease (cirrhosis, alcoholic hepatitis or alanine transaminase (ALT) >200), pregnancy, nursing, or women who refused to use a reliable birth control. Notes: All interventions were taken under supervision of friend/family of participant. For the first 12 weeks, medication was taken daily. From	**Data Used** Average alcohol (g) per week Abstinent days per week Time to first relapse Time to first drink Leaving study early Notes: Standard drink = 12g of ethanol. Relapse: defined as 5 or more drinks in a day or men, 4 or more for women.	**1 N= 81** Disulfiram. Mean dose 150mg/day - 100-200mg taken daily or 400mg taken twice a week. 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.	Study medications were purchased from Dumex-Alpharma, Bristol-Myers Squibb and Merck.

	weeks 13-52, medication was taken in 'targeted' basis - in response to craving situation. Baseline: Disulfiram Naltrexone Acamprosate Alcohol (g/week) Min: 120 132 240 Max: 1848 1680 2520 Married(%): 62.5 58.4 48.0 Employed(%): 70.4 56.6 71.4		**2 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. **3 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.	

CHICK1992 (Published Data Only)

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Characteristics of Studies Excluded from All Clinical Questions

Reference ID	Reason for Exclusion
ANSOMS2000	Open-label
ANTON2004	less than 10 participants in intervention group.
BAEKELAND1971	Non RCT
BALTIERI2009	No relevant outcomes
BOEIJINGA2004	No relevant outcomes
BORUP1994	Non RCT
BRASSER2004	Cross-over trial
BUDZYNSKI2000	No relevant outcomes
CAPUTO2003	Open-label
CAPUTO2007	Open-label
CARROLL1993	less than 10 participants in intervention group
CARROLL1998	All participants were also cocaine dependent
CHRISTENSEN1984	No relevant outcomes
CROISSANT2006	Open-label
CROOP1997	No usable outcomes
DAVIDSON1996	Cross over study, participants were healthy, social drinkers.
DAVIDSON1999	Crossover study.
DAVIDSON2004	No relevant diagnostic criteria.
DAVIDSON2007	No relevant outcomes
DESOUSA2008A	Open-label.
DOTY1995	Participants were healthy, social drinkers.
DROBES2003	Clinical laboratory experiment.
DROBES2004	No relevant outcomes, clinical laboratory experiment
FARREN1999	Crossover study, n=6.
FEENEY2001	Non RCT
FEENEY2001B	Non RCT
FEENEY2002	Non-RCT
FEENEY2004	Non RCT
FEENEY2006	Non RCT (participants were matched across groups).
FLANNERY2004	Open-label
FLOREZ2008	Open-label
GEERA1992	Cross-over trial
GOYER1984	No relevant outcomes
HAMMARBERG2004	Open-label.
HAN2008	Non RCT, no relevant outcomes.
HERMOS2004	Non RCT

JOHNSON2004	Placebo group has <10 participants (n=5)
KING2002	Participants were healthy, social drinkers
KIRITZETOPOR2004	Open-label
KOFOED1987	No relevant comparators
KRANZLER1990	Non RC
KRANZLER1997	Non RCT
KRANZLER1998	Placebo group has <10 participants (n=5)
KRANZLER2003	Sample of problem drinkers, not dependent on alcohol. Moderate and severe drinkers were excluded.
KRYSTAL2006	Participants were 'healthy' subjects.
LEEMAN2008	Non RCT
LHUINTRE1985	No details on diagnosis tool or drinking behaviour, no relevant outcomes.
LHUINTRE1990	No details on diagnosis or consumptions on study intake. No usable outcomes.
LING1983	No relevant outcomes
MARTIN2003	Non RCT
MARTINOTTI2007	Open-label
MASON2006	Subanalysis of COMBINE study, no useful outcomes
MCCAUL2000	Crossover study.
MCCAUL2001	Crossover design
MCGEARY2006	No relevant outcomes
MIRANDA2007	Non-RCT
MONTEROSSO2001	Data is not extractable
MONTI1999	No relevant outcomes
MORGAN2004	Not randomised
MUESER2003	Non RCT
NAMKOONG1999	Open label
NIEDERHOFER2003	Participants were all under 18 years of age
NIEDERHOFER2003E	Participants were all under 18 years of age
OMALLEY2002	less than 10 participants in intervention group
OMALLEY2007	Outcomes not extractable, large amount of participants had comorbid eating disorder.
OOTEMAN2007	No relevant outcomes
OSLIN1997A	No relevant outcomes
OSLIN1999	Open-label.
PALEAI1999	Crossover trial

PANTALON2002	All participants were also cocaine dependent
PEACHEY1983	Social drinkers, less than 10 participants in treatment groups.
PELC2002	Non RCT
PETERSON2006	Crossover design
PETRAKIS2005	All participants have at least one comorbid psychiatric disorder
PETTINATI2008	All participants had comorbid cocaine dependence
RAY2007	Crossover study
ROBICHAUD1979	Non RCT
ROHSENOW2000	No relevant outcomes
ROHSENOW2000A	No relevant outcomes
ROMACH2002	Open-label
ROTHSTEIN	No relevant outcomes
RUBIO2002	Open label.
RUBIO2004	Non-RCT
RUBIO2005	open label trial
STANER2006	No relevant outcomes
STELLA2008	Open-label.
SWIFT1998	Participants were healthy, social drinkers.
TIDEY2008	No details on diagnostic criteria
WEINSTEIN2003	Non-RCT

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Borup, C., & Unden, M. (1994). Combined fluoxetine and disulfiram treatment of alcoholism with comorbid affective disorders. A naturalistic outcome study, including quality of life measurements. European Psychiatry, 9, 83-89.

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