
MANAGEMENT OF SUBSTANCE DEPENDENCE
REVIEW SERIES

**A SYSTEMATIC REVIEW OF OPIOID
ANTAGONISTS FOR ALCOHOL
DEPENDENCE**



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ABSTRACT

The results from animal studies suggest that opioid antagonists may prevent the reinforcing effects of alcohol consumption. This systematic review was carried out to determine the effectiveness of opioid antagonists for attenuating or preventing the recommencement of alcohol consumption in patients with alcohol dependence. Electronic searches of MEDLINE, EMBASE, CINAHL, and Cochrane Controlled Trials Register were undertaken. Du Pont Pharmaceutical and Ivax Corporation were contacted for information regarding unpublished trials. The reference lists of the identified papers were also examined. All relevant randomized controlled trials (RCTs) and clinical control trials (CCTs) were included. Participants were people with alcohol dependence, diagnosed by any set of criteria, except, alcohol dependence with currently abstinent. Naltrexone (NTX), nalmefene (NMF), and other opioid antagonists with/without other biological or psychosocial treatments were examined. A variety of clinical outcomes, for example alcohol consumption, duration of abstinence, were considered. The dichotomous data were extracted on an intention-to-treat basis. The Peto Odds Ratio was used to assess the dichotomous data. The Weighted Mean Difference was used to assess the continuous data. The results indicate that the short-term (< 3 months) benefits of NTX were shown in three respects, which were number of patients who return to drinking, percentage or number of drinking days and the number of standard drinks of alcohol. However, 6 months after the completion of 12-week NTX treatment, the benefit of decreasing the number of patients who return to drinking were lost. The evidence from small sample-size studies suggested that disulfiram and NTX plus an aversive agent were more effective than NTX in some respects. From two short-term and small sample-size studies, the benefit of NMF was shown only in the respect of number of patients who return to drinking. The limited evidence suggests that NTX has some benefits for patients with alcohol dependence, but patients' adherence to treatment should be of concern. Psychosocial treatments should be concurrently given with NTX. The optimal duration of NTX treatment is not yet known. Due to the dearth of evidence, at present, the combination of NTX and disulfiram or NMF alone should not be used in everyday clinical practice.

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INTRODUCTION

RATIONALE FOR THE SYSTEMATIC REVIEW OF OPIOID ANTAGONISTS FOR ALCOHOL DEPENDENCE

Healthcare providers, consumers, researchers, and policy makers are inundated with unmanageable amounts of information. Systematic review is an application of scientific strategies that limit bias to the systematic assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. High quality systematic reviews can provide a basis for rational decision making. Meta-analysis, the use of statistical methods to summarize the results of independent studies, can provide more precise estimates of the effects of healthcare those derived from the individual studies included in a review. The need for systematic reviews of healthcare has grown rapidly and continues to grow, as reflected by the number of articles about review methods and empirical studies of the methods used in reviews, the number of systematic reviews published in healthcare journals, and the rapid growth of the Cochrane Collaboration.

The Cochrane Collaboration is a not-for-profit organization that aims to help people make well-informed decisions about healthcare by preparing, maintaining, and promoting the accessibility of systematic reviews of the effects of healthcare interventions. Cochrane reviews (the principal output of the Collaboration) are published electronically in successive issues of *The Cochrane Database of Systematic Reviews*.

Because of the high prevalence of alcohol dependence and its social, psychological, and physical morbidity, a systematic review of treatment for alcohol dependence is needed. As opioid antagonists, for example naltrexone (NTX), is a new technology for the treatment of alcohol dependence, a systematic review in this issue would be of helpful for healthcare providers, consumers, researchers, and policy makers in making a clinical judgment.

This systematic review was conducted by using the Cochrane Collaboration standards. An electronic version of this report will be published as a Cochrane Review and will be updated as the new evidence emerges.

ALCOHOL DEPENDENCE, ITS PHARMACOLOGICAL TREATMENT, AND OPIOID ANTAGONISTS

Alcohol dependence is a prevalent psychiatric disorder. Its 1-year and lifetime prevalence rates are about 7% and 14% of general population, respectively (Regier 1993, Kessler 1994). Its health, social, and economic consequences are usually devastating. Although many individuals do achieve long-term sobriety with treatment, others continue to relapse and deteriorate despite multiple courses of treatment.

Since psychosocial treatment programs for alcohol dependence have had only limited success, several pharmacological agents for treating this problem have been studied.

Many pharmacological adjuncts to alcohol rehabilitation treatment programs have been investigated. For example, disulfiram, lithium, selective serotonin reuptake inhibitors (SSRIs), and acamprosate have been investigated. Disulfiram has been shown to have limited clinical utility. Highly motivated alcohol-dependent patients taking disulfiram may partially improve in some respects, e.g., drinking frequency, amount of alcohol consumption (Garbutt 1999). While the results of some studies showed that lithium reduced drinking in alcohol-dependent patients with mood disorders (Merry 1976; Fawcett 1984), a randomized controlled trial failed to demonstrate any benefit for lithium in either depressed or non depressed patients (Dorus 1989). The efficacy of SSRIs in alcohol-dependent patients remains to be tested in randomized, double-blind studies with large sample sizes. Acamprosate is considered to be an effective treatment for attenuating alcohol consumption (Garbutt 1999).

While the results of many studies have suggested that opioid agonists increase alcohol consumption, others have shown that mu-opioid antagonists and partial agonists reduce alcohol consumption (Volpicelli 1986; George 1991).

No current theoretical model explains how endogenous opioids and opiate antagonists are related to alcohol consumption. However, studies conducted in both rodents and monkeys have demonstrated that naloxone and naltrexone (NTX) attenuate voluntary self-administration of alcohol and stress-induced increases in alcohol consumption. This suggests that these agents may prevent the reinforcing effects of alcohol consumption (O'Brien 1996).

Based on the results of these animal studies, opioid antagonists such as NTX and nalmefene (NMF) have been studied to determine their benefits in treating alcohol dependence.

OBJECTIVES

To determine the relative effectiveness of opioid antagonists in comparison to placebo, other medications, and psychosocial treatments for attenuating or preventing the recommencement of alcohol consumption in people with alcohol dependence. In addition, discontinuation rate, mortality, patient satisfaction, degree of functioning, health-related quality of life, and economic outcomes were also evaluated.

METHODS

SEARCH STRATEGY

Electronic searches:

The searches of MEDLINE (1966 – May 1999), EMBASE (1980 – May 1999), CINHL (1982 – March 1999), and Cochrane Controlled Trials Register were undertaken.

MEDLINE search strategies for optimal sensitivity in identifying randomized clinical trials as recommended by Cochrane Collaboration were used in conjunction with the following phrases and words

#1 (exp naltrexone) or (nalmefene) or (exp narcotic antagonists) or (opioid antagonist)

#2 (exp alcohols) or (exp ethanol)

#3 #1 and #2

An EMBASE search was undertaken by using the above-mentioned strategies applied for a MEDLINE search.

A CINHL search was undertaken by using the following strategies:

#1 (exp alcohols) or (exp alcohol, ethyl)

#2 (naltrexone) or (exp narcotic antagonists) or (nalmefene) or (opiate antagonist)

#3 #1 and #2

The Cochrane Controlled Trials Register was searched by using the words: (NALTREXONE OR NALMEFENE OR NACROTIC ANTAGONIST OR OPIATE ANTAGONIST) AND (ALCOHOL OR ETHANOL).

Additional searches

Du Pont Pharmaceutical and Ivax Corporation were contacted for information regarding unpublished trials. In addition, references of the articles obtained by any means were searched.

TYPES OF STUDIES

All relevant randomized controlled trials (RCTs) clinical control trials (CCTs) were included. As far as possible, missing information relevant to randomization, blinding, etc. was sought by contacting the study's author.

TYPES OF PARTICIPANTS

The participants were people with alcohol dependence, diagnosed by any set of criteria. However, the information of patients whose clinical

conditions were in concordance with the ICD-10 diagnosis of alcohol dependence with current abstinence was excluded.

TYPES OF INTERVENTIONS

1. NTX with/without other biological or psychosocial treatments,
2. NMF with/without other biological or psychosocial treatments,
3. Other opioid antagonists with/without other biological or psychosocial treatments.

TYPES OF OUTCOME MEASURES

The primary outcomes of interest were:

1. Dichotomous data
 - 1.1 Number of patients who relapse to alcohol dependence (as priori criteria),
 - 1.2 Number of patients who return to drinking (but not meet the priori criteria for alcohol dependence),
 - 1.3 Discontinuation rate,
 - 1.4 Death
2. Continuous data
 - 2.1 Number of abstinent days prior to the recommencement of drinking,
 - 2.2 Percentage or number of drinking days,
 - 2.3 Number of standard drinks of alcohol (as priori criteria),
 - 2.4 Number of episodes of heavy drinking (as priori criteria),
 - 2.5 Craving,
 - 2.6 Amount of alcohol consumed,
 - 2.7 Duration of adherence to treatment,
 - 2.8 Patient satisfaction,
 - 2.9 Functioning,
 - 2.10 Health-related quality of life, and
 - 2.11 Economic outcomes.

All outcomes were reported for the short term (less than 3 months), medium term (3 to 12 months), and long term (over 1 year). If any outcome was assessed more than once in a particular term, only the results of the longest duration in that term were considered.

SELECTION OF TRIALS

Reports identified by the electronic searches were assessed for relevance. Two reviewers (MS & NJ) independently inspected all study citations identified by the electronic searches and full reports of the studies of agreed relevance were obtained. Where disputes arose the full report were acquired for more detailed scrutiny. The reviewers then independently inspected all these full study reports. Similarly, all of the full study reports obtained from the pharmaceutical companies were independently inspected by the reviewers, and the studies of agreed relevance were identified.

The correspondence author was contacted if the necessary information was not available in the reports. Where it was not possible to obtain that necessary information, the study was added to the awaiting assessment list.

QUALITY ASSESSMENT

The quality of methodology of each selected study was independently rated (MS & NJ) using the Cochrane Collaboration Handbook (Mulrow 1997). The trial quality was based on the evidence of a strong relationship among the potential for bias in the results and the allocation concealment (Schulz 1995) and was defined as below:

- A. Low risk of bias (adequate allocation concealment)
- B. Moderate risk of bias (unclear allocation concealment)
- C. High risk of bias (inadequate allocation concealment).
- D. No allocation concealment used

DATA COLLECTION

Data were extracted independently by MS and NJ onto data extraction forms. Again, if the disputes arose these were resolved either by discussion between the two reviewers or the correspondence author of the paper.

DATA SYNTHESIS

In conducting a meta-analysis, a fixed effect model, an analysis that ignores the between-study variation, can give a narrower confidence interval than a random effect model. It is generally agreed that the fixed effect model is valid as a test of significance of the overall null hypothesis (i.e. 'no effect in all studies'). A statistically significant result obtained by the use of this model indicated that there is an effect in at least one of the studies. Because of these advantages, the fixed effect model was used for the synthesis of a group of data with homogeneity. Although a random effect model can be applied for the synthesis of a group of data with significant heterogeneity, the results obtained by the synthesis of this group of data have to be interpreted with great caution. The reviewers, therefore, decided to disregard the groups of data with significant heterogeneity.

The Peto Odds Ratio (OR), the ratio of the odds of an event in the experimental (intervention) group to the odds of an event in the control group, with the 95% confidence interval (95% CI) was used for the synthesis of dichotomous data. Odds are the ratio of the number of people in a group with an event to the number without an event. An odds ratio of one indicates no difference between comparison groups. For undesirable outcomes an OR that is less than one indicates that the intervention was effective in reducing the risk of that outcome. In addition, as a measure of efficacy, the number needed to treat (NNT) was also calculated. The reviewers applied the following guidelines to

analyze data from included studies: (i) the analysis included all those who entered the trial; and (ii) the analysis maintained the study groups according to the original randomization procedure. The reviewers assigned people lost to follow-up to the worst outcome.

The Weighted (or Standardized) Mean Difference (WMD), the difference between two means divided by an estimate of the within-group standard deviation, with 95% CI was used for the synthesis of continuous data. When an outcome (such as pain) is measured in a variety of ways across studies (using different scales) it may not be possible directly to compare or combine study results in a systematic review. By expressing the effects as a standardized value the results can be combined since they have no units. Whenever possible we took the opportunity to make direct comparison between trials that used the same instrument of measurement to quantify specific outcomes. For the studies that the treatment and/or controlled groups were divided into subgroups because of the differences of concurrent treatment, the continuous data of the subgroups receiving more rigorous treatment, e.g., higher doses of drug treatment, more intensive psychotherapy, would be extracted.

To be included in a parametric test, the data had to be fulfil the following criteria: (i) standard deviations and means were reported in the paper or were obtainable from the author; (ii) when a scale starts from a finite number (such as 0), the standard deviation, when multiplied by 2, was less than the mean (Altman 1996). Otherwise such data are skewed and not appropriate to be presented in graphical form within RevMan. Skewed data of this sort were entered into the 'Other data types' tables.

SENSITIVITY ANALYSIS

Sensitivity analysis is an analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used. We applied this technique to examine whether our decision to include the unpublished papers or the studies conducted in patients with polysubstance dependence affected the results of review compared to an analysis that excluded those papers or studies.

TEST FOR HETEROGENEITY

Test of heterogeneity is important to ask whether the results of studies are similar within each comparison. The reviewers checked whether differences between the results of trials were greater than could be expected by chance alone. This was done by looking at the graphical display of the results but also by using tests of heterogeneity.

DESCRIPTION OF STUDIES

CHARACTERISTICS OF INCLUDED STUDIES

This review includes the results of 11 studies that were presented in 17 articles. The main characteristics of included studies were summarized in Table 1. Those studies that were presented more than once are as follows:

1. Hersh 1998 presented in the other publication (Modesto-Lowe 1997),
2. O'Malley 1992 presented in the other three publications (Jaffe 1996, O'Malley 1996a, O'Malley 1996b),
3. Oslin 1997a presented in the other publication (Oslin 1997b),
4. Volpicelli 1992 presented in the other publication (Volpicelli 1995).

Table 1: The main characteristics of included studies

STUDY ID	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES	NOTES	QUALITY
Carroll 1993	Randomized, double-blind, 12-week study	Dual cocaine and alcohol dependence or abuse (DSM-III-R); no age specified	NTX 50 mg/day (n = 9) vs disulfiram 250 mg/day (n = 9); all participants received weekly individual psychotherapy	Discontinuation rate, no. of abstinent days; % or no. of drinking days, no. of standard drinks of alcohol	Both % and no. of drinking days presented but the priority was given to % of drinking day	B
Croop 1997	Nonrandomized, open-label, 12-week study	Patients who were entering or participating in the alcohol rehabilitation programs; > 18 years of age	NTX 50 mg/day (n = 570) vs no biological treatment (n = 295); all participants received psychosocial treatment program	Discontinuation rate	Other outcomes mainly relevant to the safety profile of naltrexone	D
Galarza 1997	Randomized, double-blind, placebo-controlled, 4-week study	Alcohol dependence (DSM-IV); 21-75 years of age; male only	NTX (no dose specified) (n = 10) vs placebo (n = 10); all participants received regular psychosocial treatments	Discontinuation rate	Other outcomes relevant to psychopathology of the participants, including, anxiety, depression, somatization, obsessive-compulsive symptoms, cognitive impairment, craving were presented as dichotomous data	B

Table 1: The main characteristics of included studies (continue)

STUDY ID	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES	NOTES	QUALITY
Hersh 1998	Randomized, double-blind, placebo-controlled, 8-week study	Dual cocaine and alcohol dependence or abuse (DSM-III-R); 18-45 years of age	NTX 50 mg/day (n = 31) vs placebo (n = 33); all participants received individual relapse prevention psychotherapy	Discontinuation rate, no. of abstinent days, % or no. of drinking days, no. of standard drinks of alcohol	Two mentioned outcomes (no. of patients who return to drinking and craving)*	B
Landabaso 1999	Randomized, open-label, 24 month study	Alcohol dependence (DSM-IV); mean = 30.6 years of age	NTX 25 mg/day plus an aversive agent (n = 15) vs an aversion agent alone (n = 15); NTX was given for 6 months; aversion agent was given for 12 months	No. of patients who return to drinking	Two mentioned outcomes (% or no. of drinking days and no. of standard drinks of alcohol)*; no specified for the aversion agent	B
Mason 1994	Randomized, double-blind, placebo-controlled, 12-week study	Alcohol dependence (DSM-III-R); 18-65 years of age	NMF 10 mg/day (n = 7) vs 40 mg/day (n = 7) vs placebo (n = 7); no psychosocial treatment provided	Discontinuation rate, no. of abstinent days, no. of standard drinks of alcohol, craving	One mentioned outcome (no. of episode of heavy drinking)*	B
Mason 1999	Randomized, double-blind, placebo-controlled, 12-week study	Alcohol dependence (DSM-III-R); 18-65 years of age	NMF 20 mg/day (n = 35) vs 80 mg/day (n = 35) vs placebo (n = 35); all participants received individual cognitive-behavioral therapy	No. of patients who return to drinking, discontinuation rate, no. of standard drinks of alcohol	Four mentioned outcomes (no. of abstinent days, % or no. of drinking days, craving, amount of consumed alcohol)*	B

Table 1: The main characteristics of included studies (continue)

STUDY ID	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES	NOTES	QUALITY
O'Malley 1992	Randomized, double-blind, placebo-controlled, 12-week study	Alcohol dependence (DSM-III-R); 18-68 (mean = 40.5) years of age	NTX 50 mg/day (n = 52) vs placebo (n = 52); all participants received either coping skills or relapse prevention therapy	No. of patients who return to drinking, discontinuation rate, % or no. of drinking day, no. standard drinks of alcohol, craving	Two mentioned outcomes (amount of consumed alcohol and patient satisfaction)*	B
O'Malley 1996a	Randomized, double-blind, placebo-controlled, 6-month follow-up study after the completion of 12-week study in O'Malley 1992	As O'Malley 1992	No interventions after the completion of 12-week study in O'Malley 1992	No. of patients who return to drinking	Three mentioned outcomes (% or no. of drinking days, no. of standard drinks of alcohol, no. of episodes of heavy drinking)*	B
Oslin 1997a	Randomized, double-blind, placebo-controlled 12-week study	Alcohol dependence (DSM-III-R); 50-70 (mean = 57.8) years of age	NTX 100 mg on Monday & Wednesday and 150 mg on Friday (n = 21) vs placebo (n = 23); all participants received group therapy (once per week) and case management (twice per month)	No of patients who return to drinking, discontinuation rate, duration of adherence to treatment	Two mentioned outcomes (% or no. of drinking days, craving)*	B

Table 1: The main characteristics of included studies (continue)

STUDY ID	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES	NOTES	QUALITY
Volpicelli 1992	Randomized, double-blind, placebo-controlled, 12-week study	Alcohol dependence (DSM-III-R); 21-65 years of age	NTX 50 mg/day (n = 35) vs placebo (n = 35); all participants received standard rehabilitation treatment	No. of patients who return to drinking, discontinuation rate	Two mentioned outcomes (% or no. of drinking days, craving)*	B
Volpicelli 1997	Randomized, double-blind, placebo-controlled, 12-week study	Alcohol dependence (DSM-III-R); 21-65 years of age	NTX 50 mg/day (n = 48) vs placebo (n = 49); all participants received individual psychotherapy and met their counselors twice per week	No. of patients who return to drinking, discontinuation rate, % or no. of drinking days, craving, amount of consumed alcohol	One mentioned outcome (amount of consumed alcohol)*	A

* data not presented, data not completely presented, data not presented in figures or data presented in graph.

It should be noted that the O'Malley 1996a article presents the follow-up results of the O'Malley 1992 article. This is a 6-month follow-up study following the completion of 12-week intervention study reported in O'Malley 1992. No intervention was provided in the O'Malley 1996a study.

According to the type of interventions, the 11 included studies investigated four comparisons (see Table of comparisons). Those are:

1. NTX vs placebo (short- and medium-term outcomes) (7 studies),
2. NTX vs disulfiram (short-term outcomes) (1 study)
3. NTX plus an aversive agent vs an aversive agent alone (short-, medium-, and long-term outcomes) (1 study),
4. NMF vs placebo (short-term outcomes) (2 studies).

It should be noted that all studies, except one (Mason 1994), stated clearly that the some types of psychosocial treatment were concurrently given with NTX or NMF.

The total number of participants in the eleven included studies was 1438. Most of them were adults with alcohol dependence (DSM-III-R or DSM-IV). The participants in two studies were diagnosed as both cocaine and alcohol dependence or abuse (DSM-III-R) (Carroll 1993, Hersh 1998). The diagnoses of the participants were not presented in a study (Croop 1997). One study did not specify the age of participants (Carroll 1993), another was carried out in the elderly (Oslin 1997a).

Each study presented only 1-5 outcomes of interest. The outcomes and the number of studies presenting those outcomes are as follows:

1. NTX vs placebo (short-term outcomes)
 - 1.1 discontinuation rate: 7 studies
 - 1.2 number of patients who return to drinking: 4 studies
 - 1.3 number of abstinent days prior to the recommencement of drinking: 1 study
 - 1.4 percentage or number of drinking days: 3 studies
 - 1.5 number of standard drinks of alcohol: 2 studies
 - 1.6 craving: 2 studies
 - 1.7 duration of adherence to treatment: 1 study
 - 1.8 discontinuation rate (without Hersh 1998): 6 studies
 - 1.9 percentage or number of drinking days (without Hersh 1998): 2 studies
 - 1.10 number of standard drinks of alcohol (without Hersh 1998): 1 studies
2. NTX vs placebo (medium-term outcomes)
 - 2.1 number of patients who return to drinking: 1 study
3. NTX vs disulfiram (short-term outcomes)
 - 3.1 discontinuation rate: 1 study
 - 3.2 number of abstinent days prior to the recommencement of drinking: 1 study
 - 3.3 percentage or number of drinking days: 1 study
 - 3.4 number of standard drinks of alcohol: 1 study

4. NTX plus an aversive agent vs an aversive agent alone (short-term outcomes)
 - 4.1 number of patients who return to drinking: 1 study
5. NTX plus an aversive agent vs an aversive agent alone (medium-term outcomes)
 - 5.1 number of patients who return to drinking: 1 study
6. NTX plus an aversive agent vs an aversive agent alone (long-term outcomes)
 - 6.1 number of patients who return to drinking: 1 study
7. NMF vs placebo (short-term outcomes)
 - 7.1 discontinuation rate: 2 studies
 - 7.2 number of patients who return to drinking: 1 study
 - 7.3 number of abstinent days prior to the recommencement of drinking: 1 study
 - 7.4 number of standard drinks of alcohol: 1 study
 - 7.5 craving: 1 study

CHARACTERISTICS OF EXCLUDED STUDIES

- Bohn 1994: participants were alcohol abuse (DSM-III-R)
- Davidson 1996: participants were social drinkers
- Davidson 1999: participants were heavy drinkers
- King 1997: participants were healthy nonalcoholic male social drinkers
- Oslin 1999: no controlled group

CHARACTERISTICS OF ONGOING STUDIES

The main characteristics of ongoing studies are summarized in Table 2

Table 2: The main characteristics of included studies

STUDY ID	TRIAL NAME	PARTICIPANTS	INTERVENTIONS	OUT-COMES	STARTING DATE	CONTACT INFO	NOTES
Brady	Effectiveness of NTX in a community setting	Alcohol dependence; 18 years of age and above	NTX	N/A	14 January, 2000	Dr. Kathleen Brady, Medical University of South Carolina, 171 Ashley Avenue, Charleston, USA 1-843-792-5215	Searched from www.clinicaltrials.gov
Farren	Sertaline and NTX for alcohol dependence	Alcohol dependence; 18-55 years of age	NTX and sertraline	N/A	28 October, 1999	Dr. Conor Farren, Mount Sinai School of Medicine, One Gustave Levy Place, New York, New York, USA 1-718-584-9000	Searched from www.clinicaltrials.gov
Kranzler	Targeted NTX for early problem drinkers	Alcohol dependence; 18-60 years of age	NTX	N/A	28 October, 1999	Dr. Henry Kranzler, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, Connecticut, USA 1-860-679-4151	Searched from www.clinicaltrials.gov
Mason	Role of tobacco dependence in alcoholism treatment	Alcohol dependence and smoking; 18-65 years of age	NTX and nicotine replacement patch	N/A	28 October, 1999	Dr. Barbara Mason, University of Miami School of Medicine, 1400 N.W. 10th Avenue, Miami, Florida, USA 1-305-355-9105	Searched from www.clinicaltrials.gov
Pettinati	Sertaline for alcohol dependence and depression	Alcohol dependence and depression; 21-65 years of age	NTX and sertraline	N/A	14 January, 2000	Dr. Helen Pettinati, University of Pennsylvania 3900 Chestnut Street, Philadelphia, Pennsylvania, 19104 USA 1-215-222-3200	Searched from www.clinicaltrials.gov

Table 2: The main characteristics of included studies (continue)

STUDY ID	TRIAL NAME	PARTICIPANTS	INTERVENTIONS	OUT-COMES	STARTING DATE	CONTACT INFO	NOTES
Robin	NTX and SSRI therapy for alcohol dependence in Alaska natives	Alcohol dependence; 18-65 years of age	NTX and sertaline	N/A	14 January, 2000	Dr. Robert Robin, 222 Tongass Drive Sitka, Alaska USA 1-907-966-2411	Searched from www.clinicaltrials.gov
Schmitz	Behavioral/ pharmacological treatments for alcohol-nicotine dependence	Alcohol dependence and smoking; 18-50 years of age	NTX and nicotine replacement patch	N/A	14 January, 2000	Dr. Joy Schmitz, University of Texas, 1300 Moursun Avenue, Houston, Texas, USA 1-713-500-2874	Searched from www.clinicaltrials.gov
USA	Project Combine	Alcohol dependence; 21 years of age and above	NTX and acamprosate	N/A	28 October, 1999	N/A	Searched from www.clinicaltrials.gov
Volpicelli	NTX treatment of alcohol dependence	Alcohol dependence; 18-75 years of age	NTX, compliance enhancement techniques, and cognitive behavioral therapy	N/A	28 October, 1999	Dr. Joseph Volpicelli, University of Pennsylvania, 3900 Chestnut Street, Philadelphia, Pennsylvania, 19140 USA 1-215-898-4746	Searched from www.clinicaltrials.gov

N/A: not available

METHODOLOGICAL QUALITY OF INCLUDED STUDIES

The techniques of randomization and double-blindness were applied in 9 studies. One study is a clinical controlled trial without randomization (Croop 1997). In addition, 2 studies are open-label design (Croop 1997, Landabaso 1999). Of the nine randomized controlled trials, only one study stated the method used for randomization (Volpicelli 1997).

The duration of nine studies was less than 3 months. Two studies presented the medium-term results (Landabaso 1999, O'Malley 1996a). Only one study presented the long-term results (Landabaso 1999). It should be noted that all participants receiving NTX alone took the drug for less than 3 months. There was a small sample-size (N = 30) study giving naltrexone plus an aversive agent to participants for 6 months (Landabaso 1999).

While the discontinuation rates were presented in most studies, 5 of the total 15 outcomes were not assessed, presented or presented in figures in any study. They were the numbers of patients who relapse to alcohol dependence, patient satisfaction, functioning, health-related quality of life, and economic outcomes.

RESULTS

(All of the graphs mentioned in this section can be seen in Appendix)

NTX VS PLACEBO (SHORT-TERM OUTCOMES)

The numbers of patients in NTX and placebo groups were 767 and 497, respectively. Because the participants in Hersh 1998 were patients with both cocaine and alcohol dependence or abuse, the reviewers conducted a sensitivity analysis by excluding the results of Hersh 1998 from the meta-analyses of 3 outcomes, including discontinuation rate, percentage or number of drinking days, and number of standard drinks of alcohol. After the exclusion the Peto OR and the WMD were different from those obtained by including the results of Hersh 1998 with respect to discontinuation rate and the number of standard drinks of alcohol. Therefore the meta-analyses of discontinuation rate and the number of standard drinks of alcohol were performed by excluding the results of Hersh 1998 (graph 01.08 and 01.10). Graphs 01.01 and 01.05 were disregarded. The WMD for the percentage and number of drinking days was not significantly different from that obtained when including the results of Hersh 1998. Therefore, the meta-analysis of the percentage or number of drinking days was performed by including the results of Hersh 1998 (graph 01.04). Graph 01.09 was disregarded.

Due to the significant heterogeneity of data the craving outcome was disregarded (chi-square = 58.16, df = 1, $p < 0.05$) (see graph 01.06).

After performing the sensitivity analyses and heterogeneity tests, only six outcomes were taken into consideration (see graph 01.02-01.04, 01.07-01.08, and 01.10). The benefits of NTX were shown in three outcomes, which were number of patients who return to drinking [Peto OR (95%CI) = 0.50 (0.32 to 0.79), chi-square = 1.95, df = 3, $p = 0.58$] (see graph 01.02), percentage or number of drinking days [WMD (95%CI) = -4.59 (-5.36 to -3.82), chi-square = 0.51, df = 2, $p = 0.77$] (see graph 01.04), and the number of standard drinks of alcohol [WMD (95%CI) = -24.30 (-41.91 to 6.69), chi-square = 0.00, df = 0] (see graph 01.10). In the respect of harm, the discontinuation rate of naltrexone group was significantly higher than that of placebo group [Peto OR (95%CI) = 1.30 (1.02 to 1.65), chi-square = 6.08, df = 5, $p = 0.30$] (see graph 01.08). In comparison to placebo, 2 outcomes showed no benefits of NTX in increasing the number of abstinent days prior to the recommencement of drinking [WMD (95%CI) = -0.40 (-1.68 to 0.88), chi-square = 0.00, df = 0] (see graph 01.03), and the duration of adherence to treatment [WMD (95%CI) = 0.800 (-1.18 to 2.78), chi-square = 0.00, df = 0] (see graph 01.07).

NTX VS PLACEBO (MEDIUM-TERM OUTCOMES)

The numbers of patients in NTX and placebo groups were 40 and 40, respectively. No benefit of NTX was found with respect to number of patients who return to drinking [Peto OR (95%CI) = 0.61 (0.20 to 1.88), chi-square = 0.00, df = 0] (see graph 02.01). It should be reiterated that the results were obtained from a 6-month follow-up study after the completion of 12-week intervention study comparing NTX and placebo treatment. Therefore, no intervention was given during the follow-up period.

NTX VS DISULFIRAM (SHORT-TERM OUTCOMES)

The numbers of patients given NTX and disulfiram for less than 3 months were nine in both groups. Disulfiram was better than NTX in the respects of number of abstinent days prior to recommencement of drinking [WMD (95%CI) = -5.60 (-7.94 to -3.26), chi-square = 0.00, df = 0] (see graph 03.02), percentage or number of drinking days [WMD (95%CI) = 22.30 (22.18 to 22.42), chi-square = 0.00, df = 0] (see graph 03.03), and number of standard drinks of alcohol [WMD (95%CI) = 24.70 (0.51 to 48.89), chi-square = 0.00, df = 0] (see graph 03.04). No difference was found with respect to discontinuation rates for both treatment groups [Peto OR (95%CI) = 2.57 (0.38 to 17.27), chi-square = 0.00, df = 0] (see graph 03.01).

NTX PLUS AN AVERSIVE AGENT VS AN AVERSIVE AGENT ALONE (SHORT-, MEDIUM-, AND LONG-TERM OUTCOMES)

The numbers of patients given NTX plus an aversive agent and an aversive agent alone were 15 in both groups. NTX plus an aversive agent was more beneficial than an aversive agent alone in the respect of number of patients who return to drinking in short- [Peto OR (95%CI) = 0.13 (0.03-0.52), chi-square = 0.00, df = 0] (see graph 04.01), medium- [Peto OR (95%CI) = 0.06 (0.01-0.24) chi-square = 0.00, df = 0] (see graph 05.01), and long-term treatment [Peto OR (95%CI) = 0.09 (0.02-0.52), chi-square = 0.00, df = 0] (see graph 06.01).

NMF VS PLACEBO (SHORT-TERM OUTCOMES)

The numbers of patients given NMF and placebo groups were 84 and 42, respectively. Since there was no significant heterogeneity of any data set, all 5 outcomes were taken into consideration.

The benefit of NMF was shown in the respect of number of patients who return to drinking [Peto OR (95%CI) = 0.40 (0.18 to 0.90), chi-square = 0.00, df = 0] (see graph 07.02). The benefits of NMF were not found in respect of discontinuation rates [Peto OR (95%CI) = 0.95 (0.44 to 2.05), chi-square = 0.39, df = 1, p = 0.53] (see graph 07.01), number of abstinent days prior to the recommencement of drinking [WMD (95%CI) = 0.70 (-1.74 to 3.138), chi-square = 0.00, df = 0] (see graph 07.03), number of standard drinks of alcohol [WMD

(95%CI) = -1.20 (-2.91 to 0.51), chi-square = 0.00, df = 0] (see graph 07.04), and cravings [WMD (95%CI) = 0.30 (-0.13 to 0.73), chi-square = 0.00, df = 0] (see graph 07.05).

DISCUSSION

The findings in this review should be considered as tentative because of two reasons. Firstly, no patient included in this review received NTX or NMF alone for longer than 3 months. Only 15 patients in a single trial took NTX plus an aversive agent for 6 months. As alcohol dependence is a chronic relapsing disorder, the evidence from medium- and long-term treatment of these agents is very important in making clinical decisions. Secondly, because of the high discontinuation rate (53% for NTX and 39% for NMF within 3 months), the results of this review should be viewed with caution.

NTX has some short-term benefits in the treatment of alcohol dependence. It appears to decrease the number of patients who return to drinking, the percentage or number of drinking days and the amount of alcohol consumed. However, these benefits may be lost after the patients stop using the agent for 6 months. With the lack of studies to provide evidence of efficacy for medium- and long-term NTX treatment, physicians have a dilemma. Although effectiveness of NTX does not endure following cessation there is currently no evidence to support prescribing NTX for longer than 3 months. Clinical trials determining the optimum duration of NTX treatment are needed to solve this problem.

Apart from these three respects no other benefit of NTX has been shown. It is of interest to note the high discontinuation rate of 53% in 3 months of NTX treatment. This was significantly higher than those in placebo group. Patients' adherence to NTX treatment, therefore, should be of concern.

The result of a small sample-size study have shown disulfiram to be superior to NTX in three respects, including number of abstinent days prior to the recommencement of drinking, percentage or number of drinking days, and number of standard drinks of alcohol (Carroll 1993). Despite the small sample-size ($N = 18$), the results are still of interest. In addition, the discontinuation rates of both treatments are not significantly different. However, the results of this study should be viewed with caution due to the small sample size, short duration of study, and the participants' diagnoses of both cocaine and alcohol dependence.

The use of NTX with an aversive agent may be a promising approach (Landabaso 1999). This treatment may be able to decrease the number of patients who return to drinking for several months. However this study had a small sample size ($N = 30$) and was an open-label study.

Although NMF may be able to decrease the number of patients who return to drinking, very few studies could be found. The efficacy and safety of NMF have been studied in only 126 patients with alcohol dependence. Moreover, no trial longer than 3 months has been conducted.

The above-mentioned conclusions are limited to patients with alcohol dependence. Whether NTX will be of benefit for people with alcohol abuse or heavy drinkers is out of the scope of this review.

IMPLICATIONS FOR PRACTICE

Due to the limited evidence, the following conclusions should be viewed as tentative. The evidence regarding the benefits and adherence to treatment suggests that NTX has some benefits for patients with alcohol dependence, but patients' adherence to treatment should be of concern. For three reasons, psychosocial treatments should be concurrently given with NTX. Firstly, in all NTX studies, some psychosocial treatments or an aversive agent was concurrently given. Secondly, psychosocial treatments may help maintaining the adherence to NTX treatment. Lastly, NTX has only some benefits in treating alcohol dependence.

The optimal duration of NTX treatment is not yet known. The benefit of 12-week treatment of NTX appears to be lost within 6 months of cessation and only 15 patients in a trial had taken NTX plus an aversive agent for 6 months.

The evidence so far does not support that NTX is more effective or more acceptable than disulfiram in the treatment of alcohol dependence. Although NTX is available for treating alcohol dependence in many countries, in the respect of cost-effectiveness, disulfiram should still remain as an alternative.

Due to the dearth of evidence, at present, the combination of NTX and disulfiram or NMF alone should not be used in everyday clinical practice.

IMPLICATIONS FOR RESEARCH

Randomized, double-blind, placebo-controlled trials of NTX treatment in patients with alcohol dependence are still needed. The trials should be conducted over a longer period of time and measure several important outcomes, including, alcohol consumption, patient satisfaction, functioning, health-related quality of life, and economic outcomes.

The techniques used for randomization and double-blindness should be described clearly in presentation of a study. In addition, all outcomes should be presented in figures. All of these should be done as clearly as possible. So, the journal readers can recompute the data or draw the conclusions by themselves.

The comparisons of NTX and other treatments for alcohol dependence, both biological and psychosocial, should be investigated. Regarding biological treatments, disulfiram and acamprosate should be compared with NTX. Moreover, the relative efficacy of NTX compared with psychosocial treatments such as cognitive-behavioral therapy should also be investigated.

According to the results of a small randomized controlled trial, the combination of NTX and disulfiram appears to be a promising approach for treating alcohol dependence (Landabaso 1999). A randomized, double-blind, placebo-controlled of combined NTX and disulfiram in a large number of patients should be conducted. The investigators should be encouraged to apply the strategy of 24 months follow-up as in the study of Landabaso 1999.

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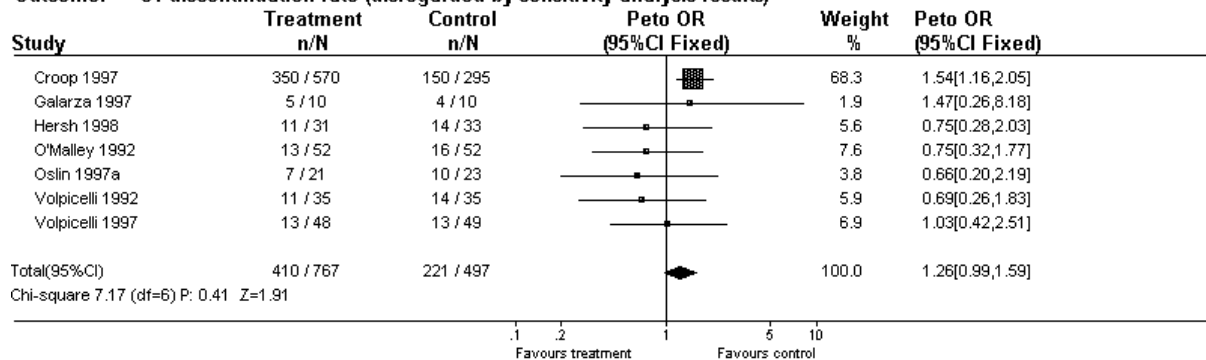
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APPENDIX

Comparison: 01 NTX vs Placebo (short-term outcomes)

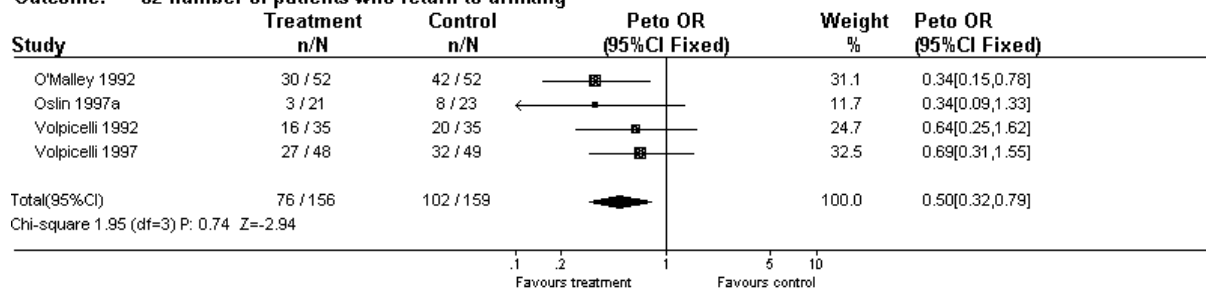
Outcome: 01 discontinuation rate (disregarded by sensitivity-analysis results)



Graph 01.01

Comparison: 01 NTX vs Placebo (short-term outcomes)

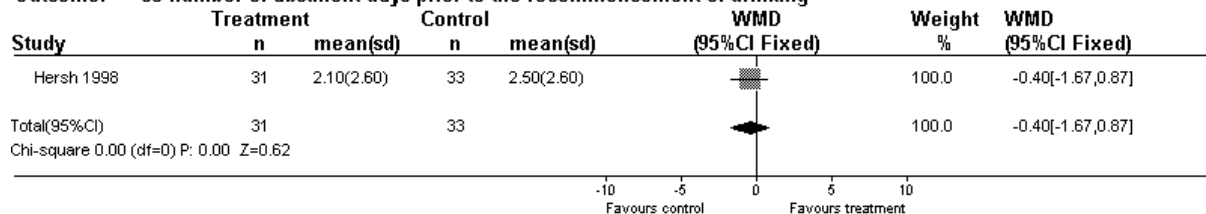
Outcome: 02 number of patients who return to drinking



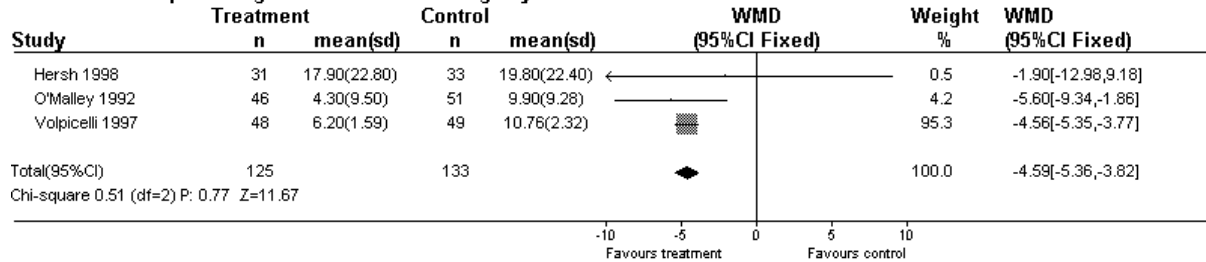
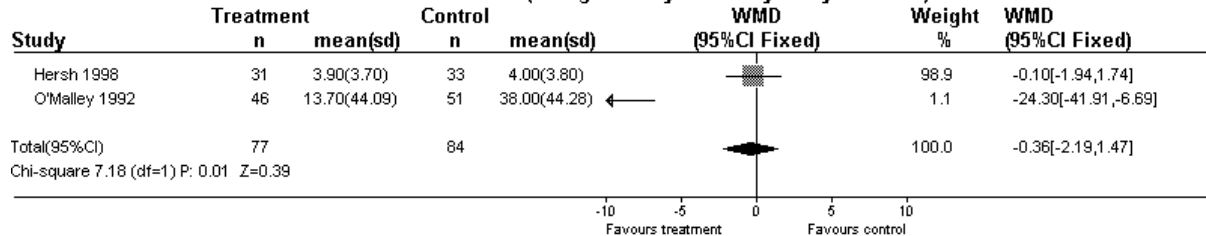
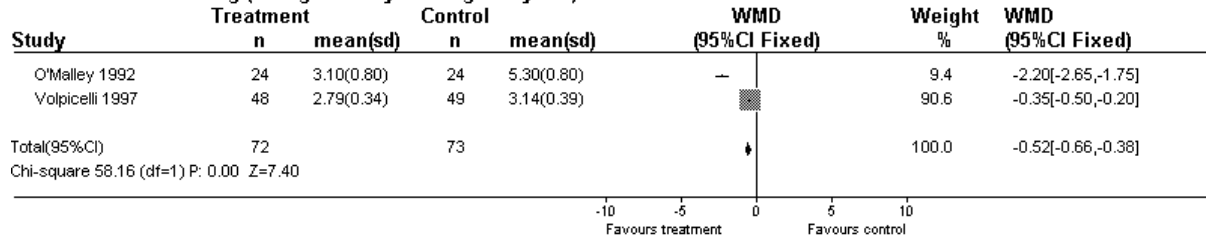
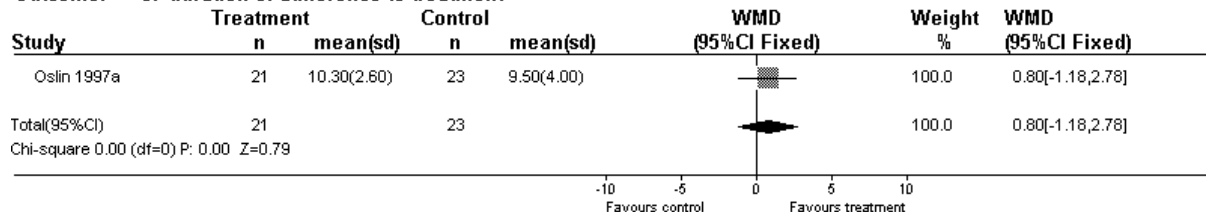
Graph 01.02

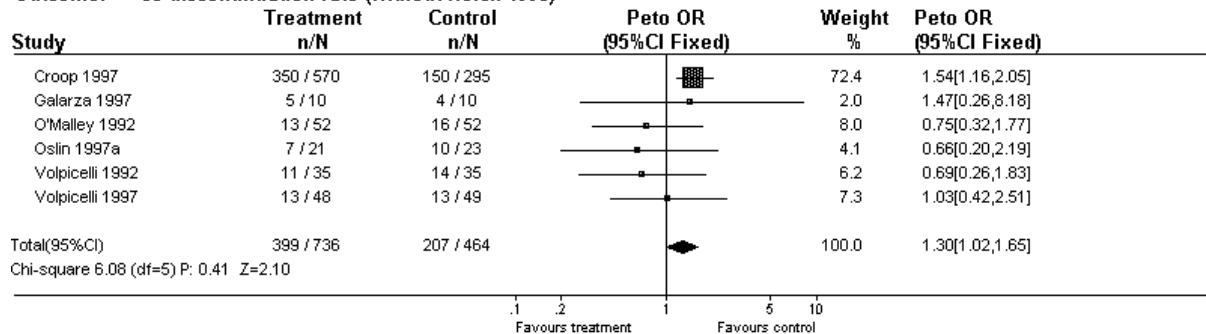
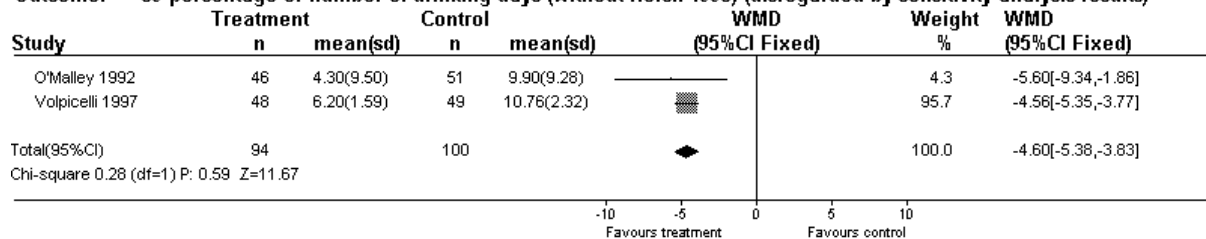
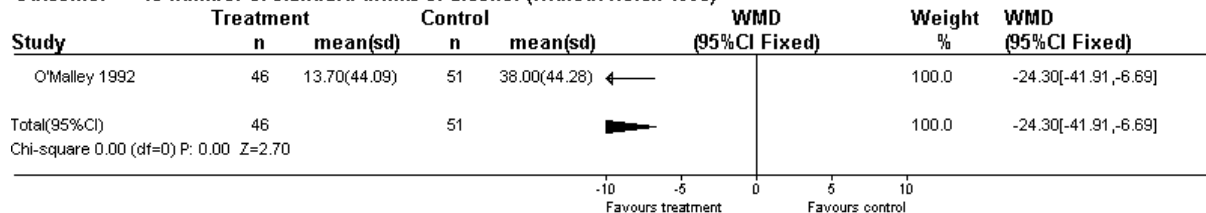
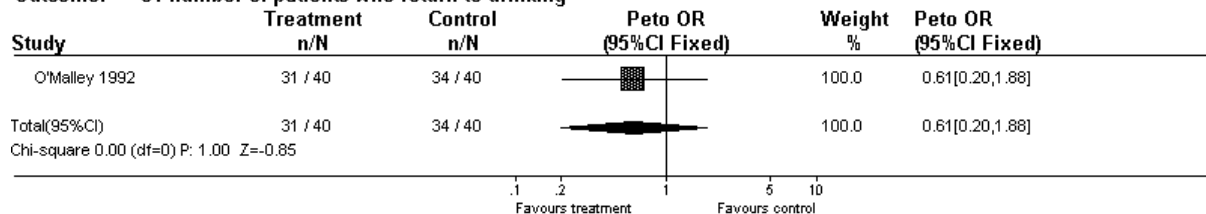
Comparison: 01 NTX vs Placebo (short-term outcomes)

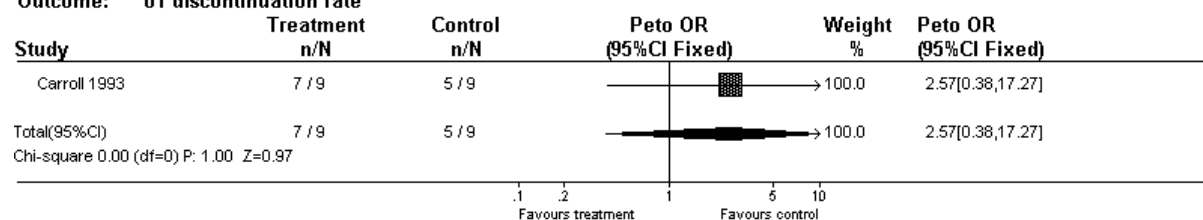
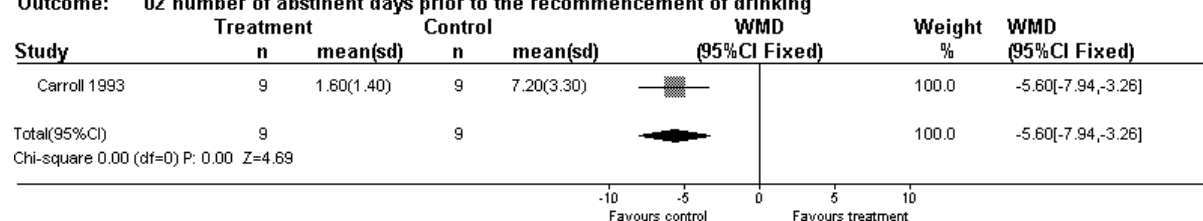
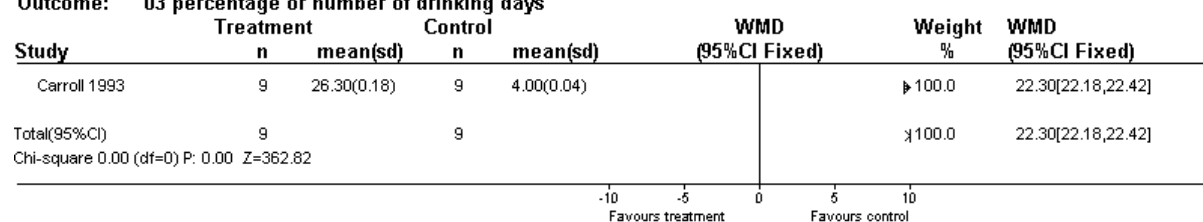
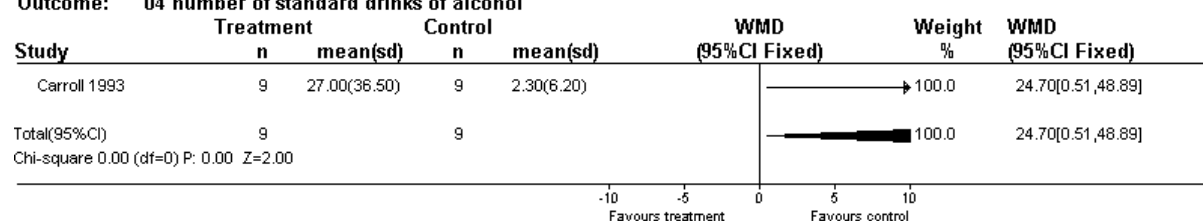
Outcome: 03 number of abstinent days prior to the recommencement of drinking

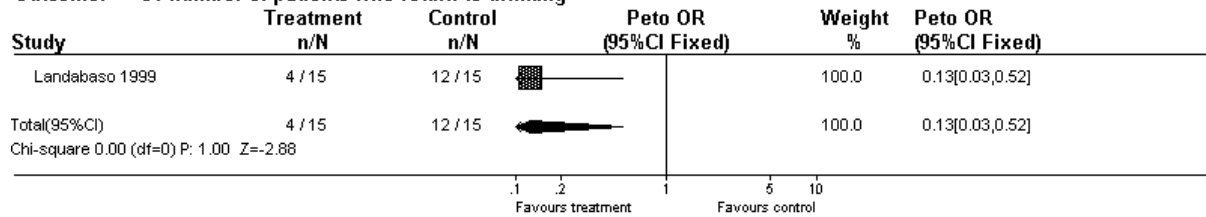
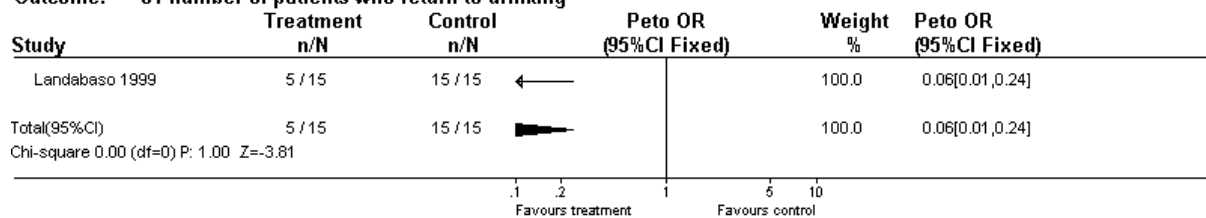
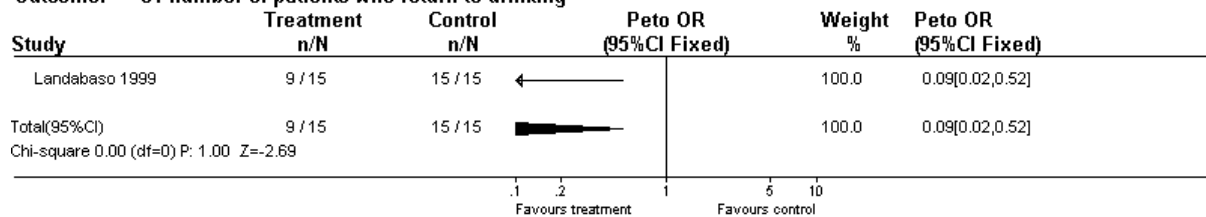
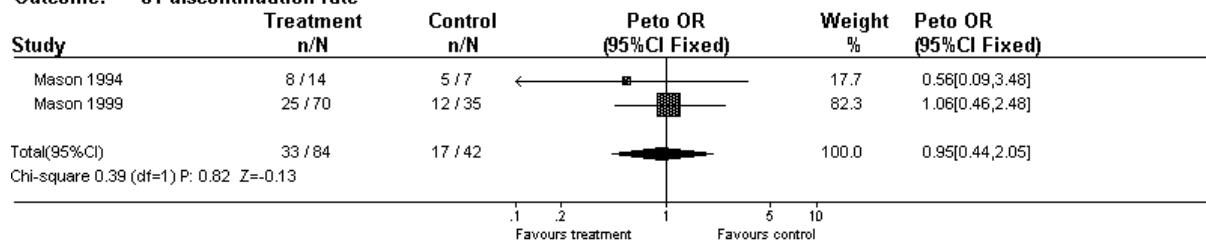


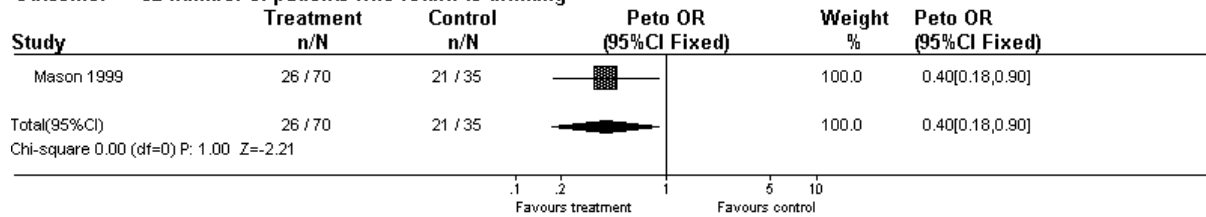
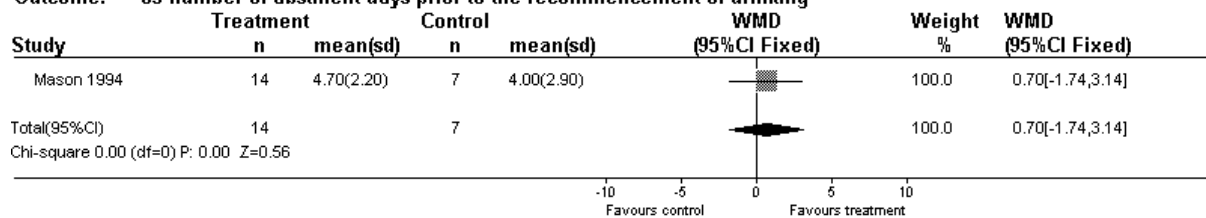
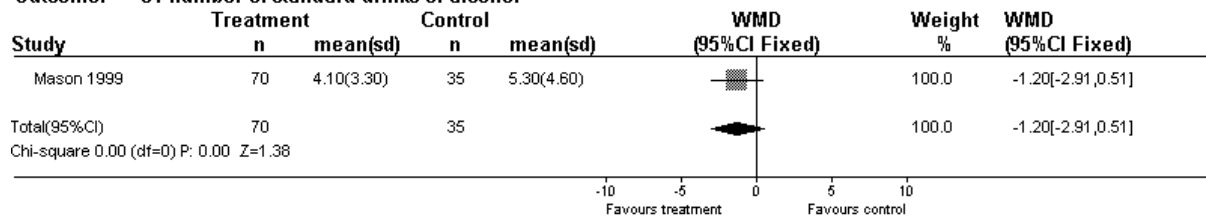
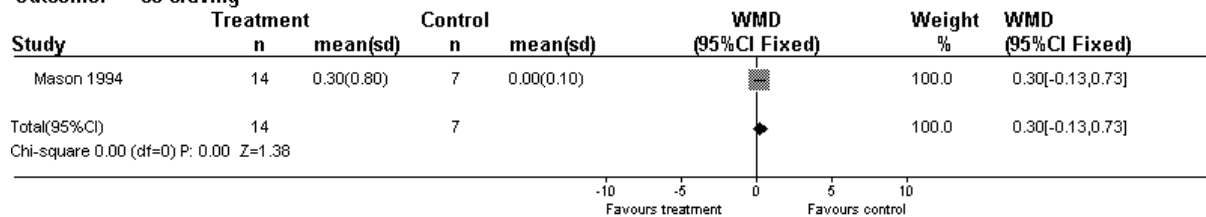
Graph 01.03

Comparison: 01 NTX vs Placebo (short-term outcomes)
Outcome: 04 percentage or number of drinking days

Graph 01.04
Comparison: 01 NTX vs Placebo (short-term outcomes)
Outcome: 05 number of standard drinks of alcohol (disregarded by sensitivity-analysis results)

Graph 01.05
Comparison: 01 NTX vs Placebo (short-term outcomes)
Outcome: 06 craving (disregarded by heterogeneity test)

Graph 01.06
Comparison: 01 NTX vs Placebo (short-term outcomes)
Outcome: 07 duration of adherence to treatment

Graph 01.07

Comparison: 01 NTX vs Placebo (short-term outcomes)
Outcome: 08 discontinuation rate (without Hersh 1998)

Graph 01.08
Comparison: 01 NTX vs Placebo (short-term outcomes)
Outcome: 09 percentage or number of drinking days (without Hersh 1998) (disregarded by sensitivity-analysis results)

Graph 01.09
Comparison: 01 NTX vs Placebo (short-term outcomes)
Outcome: 10 number of standard drinks of alcohol (without Hersh 1998)

Graph 01.10
Comparison: 02 NTX vs Placebo (medium-term outcomes)
Outcome: 01 number of patients who return to drinking

Graph 02.01

Comparison: 03 NTX vs Disulfiram (short-term outcomes)**Outcome: 01 discontinuation rate****Graph 03.01****Comparison: 03 NTX vs Disulfiram (short-term outcomes)****Outcome: 02 number of abstinent days prior to the recommencement of drinking****Graph 03.02****Comparison: 03 NTX vs Disulfiram (short-term outcomes)****Outcome: 03 percentage or number of drinking days****Graph 03.03****Comparison: 03 NTX vs Disulfiram (short-term outcomes)****Outcome: 04 number of standard drinks of alcohol****Graph 03.04**

Comparison: 04 NTX plus an aversive agent vs an aversive agent alone (short-term outcomes)
Outcome: 01 number of patients who return to drinking

Graph 04.01
Comparison: 05 NTX plus an aversive agent vs an aversive agent alone (medium-term outcomes)
Outcome: 01 number of patients who return to drinking

Graph 05.01
Comparison: 06 NTX plus an aversive agent vs an aversive agent alone (long-term outcomes)
Outcome: 01 number of patients who return to drinking

Graph 06.01
Comparison: 07 NMF vs Placebo (short-term outcomes)
Outcome: 01 discontinuation rate

Graph 07.01

Comparison: 07 NMF vs Placebo (short-term outcomes)
Outcome: 02 number of patients who return to drinking

Graph 07.02
Comparison: 07 NMF vs Placebo (short-term outcomes)
Outcome: 03 number of abstinent days prior to the recommencement of drinking

Graph 07.03
Comparison: 07 NMF vs Placebo (short-term outcomes)
Outcome: 04 number of standard drinks of alcohol

Graph 07.04
Comparison: 07 NMF vs Placebo (short-term outcomes)
Outcome: 05 craving

Graph 07.05