Drug and Alcohol Services South Australia

Pharmacotherapies for Relapse Prevention in Alcohol Dependence

2nd Edition

Monograph No. 26
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Contents

Significance of alcohol dependence

In the *Australian guidelines to reduce health risks from drinking alcohol*[1] a range of diseases associated with alcohol consumption are identified, including:

> Cardiovascular disease (high blood pressure, increased risk of arrhythmias, shortness of breath, some types of cardiac failure, haemorrhagic stroke and other circulatory problems);

> Cancers, particularly in the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and breast;

> Nutrition-related conditions (malnutrition, Wernicke-Korsakoff syndrome, folate deficiency, Vitamin A depletion and pellagra);

> Liver diseases – alcohol consumption is the most common cause of cirrhosis of the liver, and drinking alcohol over many years can cause cirrhosis in the absence of other causes. The presence of conditions such as hepatitis B or C increases the effects of alcohol in contributing to development and course of cirrhosis;

> Mental health conditions

- alcohol increases the risk of highly prevalent mental health conditions such as depression and anxiety in some people, and may affect the efficacy of antidepressant medication;
- alcohol dependence increases the risk of having major depression one year later, and equally, the presence of major depression elevates the risk of having an alcohol dependence disorder one year later;
- the co-occurrence of major depression and alcohol-use disorders increases the risks of both violence and suicidal behaviour;

> Long-term cognitive impairment (drinkers who consume alcohol at harmful levels exhibit negative structural and metabolic brain changes, and have an increased risk of dementia);

> Self-harm (harmful drinking is a major risk factor for suicide and suicidal behaviour in both males and females across the lifespan).

Worldwide, around 3.7% of all deaths and 4.4% of the total burden of disease can be attributed to alcohol (based on 2001 data). Alcohol consumption accounted for 3.3% of the total burden of disease and injury in Australia in 2003; 4.9% in males and 1.6% in females. This compared with a contribution of 7.8% for tobacco smoking, 7.5% for high body mass, 7.6% for hypertension and 6.6% for physical inactivity[1]).

Drinking alcohol has been associated with injuries in many settings, including motor vehicle and bicycle accidents, incidents involving pedestrians, falls, fires, drowning, sports and recreational injuries, alcohol poisoning, overdose, suffocation, inhalation of vomit, assault, violence, and intentional self-harm. Alcohol accounts for 13% of all deaths among 14–17-year-old Australians[1]

Concerns to the community that are associated with alcohol use include noise, litter, offensive behaviour, vandalism, aggression, petty crime, assault and road safety issues. Many of these social consequences can result in affront, violence or injury to others.[1]

Alcohol is significantly associated with crime, with studies suggesting that alcohol is involved in up to half of all violent crimes. There is a link between drinking and domestic violence. In men who are already predisposed towards domestic violence, alcohol increases the risk of violence. Alcohol consumption also increases the risk of being a victim of domestic violence.[1]

The costs of alcohol-related problems accrue not only to government health and welfare systems, but also to industry through absenteeism, premature retirement, and impaired or lost productivity.[1]

Defining alcohol dependence

There are short-term risks of harm (associated with high levels of drinking on a single occasion) and long-term risks (associated with consistent high level consumption over a lengthy period of time). It is the latter pattern of consumption that is most likely to be associated with alcohol dependence, and it is sustained high-risk drinking that is the target of treatment services. Occasional high level consumption, or binge drinking, is associated with particular risks of acute intoxication, but it addressed more by prevention and educational approaches than treatment interventions.

A distinction between “alcohol abuse” and “alcohol dependence” was made for the first time in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*, published in 1980. The current version, DSM-IV, maintains the separation, but the fifth edition, DSM-V, is expected to adopt a single category of ‘alcohol-use disorder’.

A loss of control over alcohol consumption is central to the DSM-IV definitions of both alcohol abuse and alcohol dependence, and to the proposed DSM-V definition of alcohol-use disorder. This is reflected in the features of interference with major role obligations and continued consumption despite problems related to alcohol (see Appendix 2). The distinction between alcohol abuse and alcohol dependence made by DSM-IV is in the experience of tolerance and withdrawal, features that are attributed only to dependence. The proposed DSM-V definition adds craving as a possible criterion of alcohol-use disorder.

The definition of alcohol dependence in the current revision of the International Classification of Diseases (ICD-10) similarly identifies difficulties in controlling alcohol consumption, withdrawal, tolerance and persisting with alcohol use despite clear evidence of harmful consequences as features of the condition (see Appendix 2).

The National Drug Strategy Household Survey reports on the proportion of the population at risk of alcohol-related harm in the long term (equating to sustained drinking). For the purposes of the survey, males who consume 29 to 42 standard drinks per week are considered to be at risk of long term harm, while males who consume 43 or more drinks per week are at “High risk”. Females who consume 15 to 28 standard drinks per week are considered to be at risk of long term harm and females who consume 29 or more drinks per week are at “High risk”. Those considered at high risk of long-term harm would comprise the main target population for treatment.

In 2007, the majority (60.8%) of Australians over 14 years of age drank alcohol at levels that involved a low risk of harm. However, 10.3% drank at levels considered risky or high risk to health.[2]

Neurobiology of alcohol dependence

Certain areas of the brain have been implicated in the rewarding properties of all drugs of abuse including alcohol. This reward circuitry includes the mesocorticolimbic dopamine system that starts in the ventral tegmental area and projects to the nucleus accumbens and the forebrain including the dorsal striatum. The nucleus accumbens is associated with the motivational aspects of the circuit, and the dorsal striatum is associated with learning and the behavioural response.[3;4]

This system is normally activated by natural rewards (food, sex, exercise) that are basic to survival. The neurotransmitter dopamine, is central to the brain reward system. Activation of the ventral tegmental area results in the release of dopamine in the nucleus accumbens and limbic system and the prefrontal cortex. Drugs of dependence, including alcohol, directly or indirectly act on dopamine to activate the brain reward system. Activation of the brain reward system causes facilitation of learning about drug use and motivation to use drugs.

Dopamine functions as a signal for learning about experiences. It is important in identifying and remembering which activities or experiences are worth pursuing and repeating[4;5]. It is activation of the dopamine system that has been associated with feelings of euphoria[6]. The repeated use of drugs appears to reset the threshold for activating the reward system so that the nucleus accumbens becomes less sensitive to the rewarding effects of everyday activities in chronic drug users[5].

Dopamine release in the nucleus accumbens and the ventral tegmental area is mediated by excitatory and inhibitory inputs. These include excitatory glutamatergic projections from the cerebral cortex, the amygdale and hippocampus, and the inhibitory medium spiny projecting neurons which use the neurotransmitter GABA. The nucleus accumbens dopamine release is primarily influenced by GABA, whereas in the ventral tegmental area, dopamine release is primarily mediated by glutamate.[3;7]

Unlike stimulants which have a direct effect on dopamine, alcohol’s action is thought to be primarily through its indirect effects on modulating neurotransmitters. Acute alcohol suppresses the firing rate of ventral tegmental area GABA neurons, which leads to less suppression of ventral tegmental area dopamine neuronal activity. This disinhibition leads to ventral tegmental area dopamine neuronal firing and dopamine release in the nucleus accumbens[8]. Chronic alcohol sensitises the system leading to a relative dopamine deficiency. It has been suggests that a lower central dopaminergic tone may be a factor contributing to the vulnerability of some individuals to the development of alcohol use disorders.[3;4]

GABA is implicated in many behavioural effects of alcohol. In general, agents that increase brain GABA content or GABA receptor activity enhance acute sensitivity to ethanol and maintaine ethanol preference, whereas drugs that decrease GABAergic transmission attenuate many acute effects of alcohol and reduce alcohol preference in animals.[3]

The NMDA glutamate receptor plays a central role in the neuropharmacological effects of alcohol. Alcohol is an NMDA receptor antagonist or inhibitor. Changes in the NMDA receptor or its function may underlie the neurobiological changes associated with alcohol dependence, withdrawal, and related behavioural phenomena such as 'craving'. Increased glutamatergic tone is associated with chronic alcohol consumption and may in part be attributed to increased activity of NMDA as well as AMPA and kainite glutamate receptors.[3;4]

The expression of alcohol's reinforcing effects is mediated through the endogenous opioid system, particularly through interactions with the dopamine reward system.[4;9] Functional activity of beta-endorphin pathways can lead to increased dopamine release in the nucleus accumbens via two mechanisms. First, beta-endorphins can disinhibit the tonic inhibition of GABA neurons on dopamine cells in the ventral tegmental area. Second, beta-endorphins can stimulate dopamine cells in the nucleus accumbens directly. Both mechanisms may be important for alcohol reward. Alcohol stimulates beta-endorphin release in both the nucleus accumbens and ventral tegmental area. Mu-receptor antagonists such as naloxone and naltrexone block these central effects of beta-endorphins[8].

In animal studies serotonergic function has been consistently associated with the regulation of alcohol intake. Specifically, a central serotonergic deficiency correlates with high alcohol intake. However, abnormal serotonergic function has not been consistently detected in alcohol abuse and dependence in humans. Nonetheless it is possible that contributions of serotonin dysregulation may be selectively associated with a subtype of patients with alcohol dependence.[3] Johnson suggests that 5-HT3 receptors in the cortico-mesolimbic system are involved in mediation of alcohol's reinforcing effects[8].

Acute alcohol is also known to affect the hypothalamic-pituitary axis[10;11], possibly involving corticotrophin-releasing factor. This action probably underlies the stress-reducing effects of alcohol. The development of alcohol dependence, particularly after repeated cycles of alcohol exposure and withdrawal, is associated with increased anxiety and increased sensitivity to stress in animals. These changes, which appear to be long-lasting, result, at least in part, from adaptations in the corticotrophin-releasing factor system and contribute to increased alcohol consumption through negative reinforcement motivated by the ability of alcohol to eliminate a 'negative emotional state'.[4;5;12]

Typology and genetics of alcohol dependence

Knowledge of the genetic basis of alcohol dependence can help with understanding vulnerability to alcohol dependence and in the identification of high risk groups. Much of the interest in this area relates to the development of treatment approaches and matching individuals to the most effective treatment.

The likelihood of any individual developing drug dependence is determined by a balance of risk and protective factors which are both social and biological in nature.

Genes may affect:

> The way in which individuals respond to particular substances (eg. drug metabolism, absorption and excretion and activity or sensitivity to drugs);

> Behavioural traits that influence an individual's willingness to try drugs (eg. risk-taking behaviour, impulsivity, novelty-seeking);

> The likelihood of developing problem use or dependence if they use drugs (eg. how rewarding they find the effects of drugs)[5].

Family, twin and adoption studies indicate that there is a strong hereditary component in alcoholism. Genes explain about 50% of the vulnerabilities leading to heavy drinking and associated problems. It is likely that multiple genes influence a range of intermediate characteristics that subsequently interact with the environment to produce the condition. Most genetic influences appear to impact at least four prominent intermediate characteristics (phenotypes) that interact with environmental events to produce the alcoholism risk:

1. a flushing response to alcohol, related to the efficiency of aldehyde dehydrogenase, is most intense among individuals of Asian descent, 40-50% of whom are poor metabolisers of acetaldehyde, and is

associated with a lower risk of alcohol use disorders but does not significantly impact on the vulnerability to problems with other drugs;

2. a low level of response to alcohol, probably related to GABA and serotonin systems and second messenger mechanisms, which appears to enhance the probability of heavier drinking in order for the person to achieve the desired effects, and thus increases the risk for alcohol use disorders but not other major conditions;
3. personality characteristics that include impulsivity, sensation seeking, and neuronal and behavioural disinhibition – these conditions increase the risk for a wide range of problematic behaviours including most substance use disorders and are probably related to a range of polymorphisms; and
4. through psychiatric symptoms, including bipolar disorder, schizophrenia, and several anxiety disorders that are related to an enhanced risk of substance use disorders in general, and are also related to a range of polymorphisms.[13]

There are gender differences in the patterns of alcohol consumption, and women are at greater risk of alcohol-related damage. A number of neurotransmitters and growth factors may be partially involved, but it is likely that gender differences in alcoholism and complications are due to differences in all the factors influencing the development of this disorder.[14]

The effects of opioids are mediated through opioid receptors mu, kappa and delta, each a seven-transmembrane domain G-protein coupled receptor. Of the three receptor subtypes, the opioid receptor mu 1 (OPRM1) is thought to account for the most of the opioidergic effects. OPRM1 is the primary site of action of an endogenous opioid peptide, beta-endorphin, that is released in response to alcohol, and the mu-opioid receptor antagonist, naltrexone.[15]

Over 300 OPRM1 genetic variants have been identified. Most abundant of the missense variants is Asn40Asp or A118 which changes the amino acid sequence of the 40th residue from asparagine, which can be glycosylated, to aspartate, which cannot be glycosylated. [16] This change appears to be associated with functional difference. Beta-endorphin was reported in one study to have three-fold higher binding affinity at the Asp40 mutated receptor than at the receptor encoded by the Asn40 allele. However, follow-up studies have not found differences in binding affinities. The OPRM1 Asn40Asp polymorphism does not appear to affect risk for substance dependence, but may influence response to opioid antagonist treatment of alcohol dependence.[15] The frequency of the Asp40 allele varies considerably between populations, from less than 5% in African-Americans to 20% in European Americans, and as high as 58% among those of Asian descent.[17]

There is increasing recognition of the complexity of craving and relapse in alcohol dependence. It seems likely that different subtypes of alcohol-dependent people have different mechanisms at the basis of alcohol craving and relapse. [4;18;19] If several pathways of craving and relapse exist, it might be expected that different interventions may be appropriate to address craving and relapse in the different subtypes. One model identifies three types of craving:

> Reward craving, in which alcohol is sought for the euphoric effects. The physiological substrate for reward craving is stimulation of the mid-brain dopaminergic reward pathway, activation of which is regulated by the endogenous opioid system. The associated symptoms include the spontaneous search for alcohol, the inability to abstain, and binge drinking. Early development of alcoholism (“early-onset”) and a positive family history for alcoholism are features of reward craving.

> Relief craving, in which alcohol is consumed to avoid the negative feelings and mood states associated with withdrawal from alcohol, including cue-induced withdrawal. The basis of this craving is believed to be hyperactivity of GABAergic neurotransmission that occurs in alcohol withdrawal, through reactivity to stress or a combination of both.

> Obsessive craving which can be defined as a loss of control over intrusive thoughts about the intake of alcohol. At the basis of this craving there is a serotonergic dysregulation or a personality trait consisting of disinhibition or a combination of both factors. The main characteristic of obsessive craving is a loss of control; associated symptoms consist of compulsive drinking and alcohol-related damage.

Similarly relapse has been characterised as cue-, stress- and priming-induced, with different mechanisms likely to point to differing response to different forms of treatment.[4;20] The practical usefulness of these different models of craving and relapse are still to be proven, but they are aspects worthy of consideration in relation to heterogeneity of treatment response.

Various attempts have been made to identify subgroups of alcohol dependence that have therapeutic relevance. The typologies used most frequently are those of Cloninger and Barbor, plus Lesch's typology, particularly in Europe. There is a high correlation (overlapping but not identical) between the two most frequently cited alcoholic subtypes: early versus late onset (Cloninger) and Type A versus Type B.

Cloninger

> Type I alcoholics start abusing alcohol later in life (age of onset >25 years). Susceptibility to alcohol is provoked by environmental factors. They experience withdrawal symptoms and loss of control and often feel guilty about their drinking behaviour.

> Type 2 alcoholics are male, exhibit alcohol-seeking behaviour early in life (age of onset <25 years), tend to be impulsive and risk-taking, manifest antisocial behaviour and have strong heritable influences independent of the environment. These patients often have multiple attempts to give up alcohol.

While the Cloninger definition uses 25 years as the cut-off for early versus late onsent of alcohol abuse, Le Strat *et al*.[21] recommend a cut-off of 22 years based on an analysis of data from the US Epidemiologic Survey on Alcohol and Related Conditions.

Babor

> Type A – late onset, fewer childhood risks, less severe dependence, fewer alcohol-related physical and social consequences, less previous treatment for alcohol problems, less psychopathological dysfunction and less distress in the areas of work and family. Also referred to as low risk/less severe alcoholism.

> Type B –earlier onset, greater severity of dependence, stronger family history, more childhood risk factors, polydrug use, greater frequency of comorbid psychiatric disorders, more serious consequences.[22] Also referred to as high risk/severe alcoholism.[23]

Lesch

> Type I – no marked craving for alcohol during periods of abstinence, feel healthy in their psychosocial situation but develop strong and immediate craving in response to even small amounts of alcohol. Develop severe withdrawal at an early stage and use alcohol to suppress withdrawal symptoms. At risk of seizures during alcohol withdrawal. Postulated to have high ethanol metabolism with consequent high levels of acetaldehyde during drinking.

> Type II – alcohol used as self-medication and for conflict solving. Tend to have passive lifestyle and low self-esteem. Behavioural changes (eg. aggressive symptoms) may emerge with alcohol. Postulated to have disturbance of serotonin system.

> Type III – marked by affective disorders. Often a family history of both alcohol dependence and affective disorders. Frequently suffer from sleep disorders.

> Type IV – cerebral damage during brain development (before age 14) or negative familial and social circumstances, leading to behavioural problems during childhood. Epileptic seizures independent of alcohol consumption are possible. Compulsive traits and a loss of criticism concerning their alcohol intake lead to an inability to resist drinking pressure of their social surroundings.[24]

(See Vyssoki *et al*.[25] for a schematic representation of the diagnostic process of application of the Lesch typology.)

Scope

This review provides an overview and analysis of evidence from randomised controlled trials of the effectiveness of different pharmacotherapies for relapse prevention in alcohol dependence.

The review covers all pharmacotherapies for which a randomised controlled trial investigating effectiveness in treatment of alcohol dependence has been located.

Trials of different psychological approaches are included only where these therapies are delivered as adjuncts to a pharmacotherapy.

Method

Studies included in the review were randomised controlled trials comparing an active medication with placebo, no medication, or another active medication for treatment of alcohol abuse or dependence. Randomised controlled trials comparing different types or different intensities of psychological treatments as adjuncts to active medication were also considered.

Relevant studies were located by reference to recent systematic reviews, supplemented by searches of electronic databases, including Medline, Embase and PsycINFO, using alcoholism, alcohol dependence, and medication names and types as search terms.

Studies were excluded from analyses where:

> there was considered to be a significant risk of bias;

> medication was scheduled to be administered for less than one month;

> the focus of the study was on the pharmacokinetics of the medication, or the acute effect of medication on drinking behaviour; or

> there were insufficient data on retention in treatment, alcohol consumption or adverse effects.

Multiple publications derived from a single study were considered together to avoid double-counting of participants in analyses. To simplify in-text citations, particularly for studies with multiple publications, studies are generally identified by the last name of the first author of the most relevant report from each study.

Included studies were grouped for analysis on the basis of the primary intervention of interest – these groupings establish the major sections of this review. Brief information about the included studies is provided by Appendix 1. Studies are listed in this appendix in alphabetical order by the study identifier (generally the first author). Studies are not grouped by intervention as many studies fall into more than one grouping.

Treatment effectiveness is considered in terms of:

> retention in treatment
  - participants completing scheduled treatment#
  - average time in treatment#;

> alcohol consumption
  - participants continuously abstinent during treatment#;
  - participants abstinent at the end of the treatment period#;
  - participants relapsing to heavy drinking (usually based on five or more standard drinks for men, four or more for women, in a session, with consideration also of the number of drinking days in a week) during treatment#;
  - average drinks (calculated where necessary using 10g alcohol as a standard drink) per drinking day;
  - average drinks per week;
  - percent treatment days abstinent (cumulative abstinence duration, calculated where necessary from percent treatment days with drinking for consistency across all studies);
  - percent treatment days with heavy drinking;
  - average days to first drink#;
  - average days to relapse to heavy drinking#;
  - average craving scores; and

> adverse effects
  - participants requiring a dose reduction to manage adverse effects#;
  - participants experiencing gastrointestinal symptoms (abdominal pain, diarrhoea);
  - participants experiencing nausea or vomiting;
  - participants experiencing neuropsychiatric symptoms (tiredness, sleepiness, drowsiness, dizziness, headache);
  - participants withdrawn from treatment due to adverse effects#.

In assessing the evidence of effectiveness, greatest emphasis has been placed on the more objective outcomes (marked with #) as these outcomes are associated with a lower risk of bias. The other outcomes are relevant but constitute a secondary level of evidence because of the possible risk of bias.

The main source of bias is dropout (attrition bias). Participants who relapse to drinking during treatment are more likely to dropout. Hence any outcome that relies on data collected throughout the treatment period may be biased by this differential dropout. This is particularly the case with alcohol consumption data (drinks per drinking day, drinks per week).

Adverse effects are not always addressed and reported systematically and there is considerable variability between studies in the nature of adverse effects reported. Data on major types of adverse effects are included to provide an indication of the nature of adverse effects associated with different types of medication, but the primary data for considering effectiveness are the number of participants requiring a dose reduction and the number dropping out due to adverse effects.

Many laboratory tests vary with alcohol intake, but only a few show sufficient response to serve as biological markers and discriminate between acceptable and probably safe and excessive and probably harmful alcohol use. The best tests for assessing average alcohol intake over the previous 2-4 weeks are plasma gamma glutamyl transferase (GGT) and carbohydrate deficient transferrin (CDT). Factors such as age, gender,[26;27] and body mass index can affect GGT or CDT independent of alcohol intake. CDT is a comparatively expensive test and may provide no benefit when applied to women, at least in the context of population screening for at risk alcohol consumption.[28-31] It is best used in combination with GGT.[26]

People who are alcohol dependent are at high risk of liver disease. Alanine amino-transferase (ALT) is a primary marker for hepatotoxicity. Results of liver function tests were reported by many of the studies included in this review. Some narrative discussion of these data is included but there is no quantitative analysis as meta-analysis of the data is problematic. In the context of treatment of alcohol dependence, it is change in these markers, not the absolute values, that is most relevant. Interpretation of liver enzyme levels, as objective confirmation of change in alcohol consumption, would generally involve consideration of changes in all the markers from baseline, and such data is not readily presented as part of the results of a clinical trial, and variability in reporting of the data complicated any meta-analysis. Furthermore, there is a lag phase with these indicators taking 2 to 3 weeks to change, either in response to abstinence or relapse to heavy drinking.[29-32] This limits the value of these biological markers as outcome data in a meta-analysis.

Studies of the validity of self-report data on alcohol consumption have been undertaken.[33;34] Self-report validity is influenced by the time of last consumption, assured confidentiality, the participants' expectations of the use of alternate verification, as well as the use of objective events such as arrests for driving under the influence of alcohol. Collateral reports of use have been found to more consistently predict self-report data than biological indices.[34] In randomised controlled trials with assured confidentiality, and the use of alternate verification methods, self-report data can be expected to be reasonably accurate.

Statistical analyses of main outcomes were undertaken using Review Manager 4.2.10. For dichotomous outcomes (number completing treatment, number experiencing adverse effects), combined risk ratio and number needed to treat were calculated. For continuous outcomes (time in treatment, cumulative abstinence duration) weighted mean differences were used, unless there was diversity in outcome measures, in which case standardised mean differences were used. Combined statistics were calculated using a fixed effect statistical model, unless significant statistical heterogeneity was identified, in which case a random effects model was applied. All statistics are presented with 95% confidence intervals, and tests of statistical significance and statistical heterogeneity. (For explanation of these terms refer to the following section.)

In presenting the findings of analyses, the strength of evidence is rated as follows:

****	strong	further research is unlikely to substantially change the estimate of effect
***	moderate	further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate
**	low	further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate
*	very low	any estimate of effect is very uncertain

These ratings are based on the approach of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group (see www.gradeworkinggroup.org). The ratings incorporate an assessment of the quality of the evidence, taking into account factors such as study limitations (lack of allocation concealment, lack of blinding, incomplete accounting of participants and outcome events, selective outcome reporting), unexplained heterogeneity or inconsistency of results, indirectness of evidence, imprecision, and publication bias.

In addition to the analyses of relative effectiveness, this review also presents the rationale for effectiveness of the different medications and factors identified in research literature as possibly influencing treatment outcome.

Interpretation of Analyses

The **Relative Risk or Risk Ratio (RR)** is the probability of an event in the active group divided by the probability of the event in the comparison group. Hence, if the risk ratio is greater than 1, the probability of an event occurring is greater in the active group than in the comparison group. If the event is beneficial (e.g. the number of participants completing treatment), a relative risk greater than 1 indicates that the active intervention is more effective than the comparison intervention, at least with regards to that particular outcome. If the event is harmful (e.g. the number of participants experiencing adverse effects), a relative risk less than 1 indicates that the active intervention is more effective than the comparison intervention.

The **Absolute Risk Reduction**, or **Risk Difference**, is the difference between the event rates in the active and comparison groups. The absolute risk reduction is a decimal fraction, which is not easy to grasp. This review instead uses the **Number Needed to Treat (NNT)**, which is the inverse of the Absolute Risk Reduction. The NNT is the number needed to treat to prevent, or gain, one additional event in the active group relative to the comparison group. That is, the NTT indicates the number needed to treat to prevent one individual from experiencing adverse events, or to gain one additional person completing treatment, above the number for the comparison intervention.

The **Mean Difference (MD)** is the sum of the differences in the individual studies, weighted by the individual variances for each study. Hence the mean difference takes account of the precision of each study. The mean difference has the same units as the outcome being assessed and is a direct indication of the difference between the active and comparison groups for that outcome. It may be positive or negative, with the interpretation of the result depending on the outcome being considered. For example, in the case of time in treatment, a positive mean difference indicates a longer time in treatment in the active group, indicating greater effectiveness than the active group if this is the desirable outcome. In the case of mean withdrawal score, a lower score and hence a negative mean difference indicates greater effectiveness in the active group relative to the comparison group.

The **Standardised Mean Difference (SMD)** is the difference in mean outcome between groups divided by the standard deviation of outcome among participants. It is sometimes call an effect size. It is used when the same outcome is measured in a variety of ways (eg. different scales for rating withdrawal symptoms). The SMD standardises the results to a uniform scale before combining them. It is reported in units of standard deviation rather than in units of any of the measurement scales being combined.

The figures included in this topic review present the comparisons for each outcome of interest. Each figure presents data for the individual studies reporting for that outcome, and a combined result (if it is able to be calculated). The individual studies are listed in the far left column, with data for the active and comparison groups in the next two columns. The column headed “weight” indicates the contribution of each study to the combined result (studies are listed in order of increasing weight). The far right column gives the calculated statistic (RR, WMD or SMD) with 95% confidence interval for each study and the combined result at the bottom. The central portion of each figure presents these data graphically – the horizontal lines represent the 95% confidence intervals, and the square boxes represent the point estimates, with the size of the boxes representing the weighting for each individual study. The diamond at the bottom represents the combined result, with the length of the diamond indicating the 95% confidence interval. The vertical line indicates the value of the statistic representing no difference between the active and comparison groups (RR of 1 or WMD or SMD of 0). Where the 95% confidence interval includes the value representing no difference, the horizontal line will touch or cross the vertical line, indicating that the difference is not statistically significant. At the bottom left of each figure is a test for statistical heterogeneity – a P-value less than 0.05 indicates there is significant statistical heterogeneity, and the I^2 value indicates the extent to which this heterogeneity contributes to the combined variance. Below that is the test for overall effect – a P-value less than 0.05 indicates the difference is statistically significant.

Section 1: Opioid Antagonists

Overview

Rationale

The reinforcing effects of alcohol are thought to be modulated by the endogenous opioid system. Opioid antagonists by interfering with opioid activity should block the positive reinforcing properties of alcohol.

Type of opioid antagonist

Most data on the effectiveness of opioid antagonists for relapse prevention treatment of alcohol dependence comes from studies comparing oral preparations of naltrexone (50-100mg/day) with placebo, but some data are available for oral naltrexone compared with no medication, depot preparations of naltrexone, and also for oral preparations of nalmefene, an opioid antagonist with some different properties to naltrexone.

Retention in treatment

Treatment with an opioid antagonist is not associated with increased retention in treatment, relative to treatment with placebo.****

Treatment with oral naltrexone may slightly increase retention in treatment relative to treatment with no medication.* This suggests a small placebo effect that is related to the provision of medication and not the specific pharmacological properties of opioid antagonists.

Abstinence

Treatment with oral naltrexone significantly increases the probability of total abstinence from alcohol during treatment relative to placebo.**** However, the degree of benefit is relatively small (NNT=20, meaning that for every 20 people treated with oral naltrexone, one additional person can be expected to be continuously abstinent during treatment than would be the case with placebo).

Depot naltrexone may also promote abstinence but insufficient data are available to be conclusive.* No data are available on nalmefene.

Relapse to heavy drinking

Treatment with oral naltrexone significantly decreases the risk of relapse to heavy drinking.**** The difference translates to an NNT of 9, meaning that for every 9 people treated with oral naltrexone, one less person can be expected to relapse during treatment than would be the case with placebo.

The risk of relapse to heavy drinking is also significantly lower with oral naltrexone compared with no medication.*

Nalmefene and depot preparations of naltrexone may reduce the risk of relapse* but more data are needed to confirm this.

The different NNT values (NNT=20 for continuous abstinence and NNT=9 for relapse to heavy drinking) suggests that oral naltrexone is more effective at preventing relapse to heavy drinking than promoting total abstinence.

Amount of alcohol consumed

Compared with placebo, oral naltrexone reduces alcohol consumption by around one drink per drinking day.***

Oral naltrexone decreases alcohol consumption by around 2 drinks per week relative to placebo, but this difference is not statistically significant.**

Nalmefene and depot preparations of naltrexone may be associated with decreased alcohol consumption,** but available data are currently insufficient to determine this with any certainty. The dose delivered by depot preparations may be important.

Periods of abstinence or heavy drinking during treatment

Treatment with oral naltrexone is associated with more abstinent days compared to placebo (4% more treatment days****) or no medication (5% less treatment days).**

Depot naltrexone is also associated with more abstinent days compared to placebo.*

Treatment with oral naltrexone is associated with significantly less days of heavy drinking compared to placebo (4% less treatment days)*** or no medication.*

There is no significant difference in days of heavy drinking for depot naltrexone* but data are limited.

Insufficient data are available on nalmefene.

Time to first drink and time to relapse

Treatment with oral naltrexone does not prolong abstinence from alcohol,** but it does prolong the interval between recommencement of drinking and relapse to heavy drinking.** The additional time without relapse associated with oral naltrexone, relative to placebo, is around 7 days.

Nalmefene and depot preparations of naltrexone may prolong the time to relapse, but insufficient data are available to determine the degree of effect.

Objective indicators of alcohol consumption

Levels of GGT, or change in GGT, are not significantly different for groups treated with opioid antagonists compared to placebo. This may indicate limitations in the sensitivity of GGT for the detection of changes in alcohol consumption in the population of alcohol dependent people.

Craving

Oral naltrexone treatment is associated with significantly lower average craving scores compared to placebo,** but significant reductions in craving are not consistently observed.

High levels of craving may be predictive of a greater degree of response to treatment with an opioid antagonist.

More complex, or more specific, monitoring of craving may be needed to elucidate the effect of opioid antagonists on craving and the relationship between craving and alcohol consumption. Reward craving may be a more specific baseline indicator of likely response to opioid antagonists.

Adverse effects

Treatment with oral naltrexone is associated with an increased risk of adverse effects*** particularly nausea or vomiting.****

The increased risk of adverse effects is reflected in a greater likelihood of dose reductions to manage adverse effects for oral naltrexone compared to placebo,** and an increased risk of withdrawal from treatment due to adverse effects.*** However, the difference translates to an NNT of 33 which is not clinically significant.

Data on nalmefene and depot preparations of naltrexone are limited, but it appears that, compared to placebo, nalmefene* but not depot naltrexone,** may be associated with an increased risk of adverse effects and an increased risk of withdrawal from treatment due to adverse effects.

There is no significant difference between opioid antagonists and placebo in effect on serum levels of AST or ALT. Declines in AST and ALT reflect declines in alcohol consumption during treatment but also indicate that the incidence of hepatotoxic effects is not significant at the doses used in the studies included in this review.

Elevations of liver enzymes can occur, albeit rarely, making monitoring of liver function advisable. In reported cases, levels resolved following discontinuation of medication.

Factors affecting treatment response

(a) Adverse effects

Neuropsychiatric adverse effects (tiredness, sleepiness, drowsiness) directly reduce retention, while gastrointestinal effects (abdominal pain, nausea, dry mouth) reduce compliance.

It is the number and severity of adverse effects, and not just severity, that predicts early termination of treatment.

Taking medication with meals, taking the dose at bedtime, and taking an antacid daily are strategies suggested for managing nausea and fatigue associated with opioid antagonist treatment.

(b) Compliance with medication

A positive treatment response to naltrexone is more likely in those who are compliant to their medication regime (>80% tablets taken).

There appears to be a significant placebo effect in trials comparing naltrexone and placebo, probably associated with expectations about medications, regular contact with treatment providers and associated psychosocial treatment.

The effect of medication declines after cessation. Compliance needs to be maintained over a sufficiently long period for behavioural change to occur to increase the likelihood of sustained treatment effects.

Depot and implant preparations, through a sustained duration of effect, may increase the period of exposure to medication.

Targeted medication may increase compliance by linking administration of medication to awareness of a high risk of alcohol consumption occurring.

(c) Treatment goal

Naltrexone may be effective in supporting reduced alcohol consumption in controlled drinking programs as well as in treatment with a goal of total abstinence but there are insufficient studies to form a view on the effectivess of opioid antagonist treatment in the context of controlled drinking compared to a goal of total abstinence.

(d) Abstinence at commencement of treatment

A period of abstinence prior to treatment with naltrexone is predictive of a better response to treatment. Psychological aspects of preparedness for treatment, motivation, and support are likely to be factors underlying this outcome.

(e) Comorbid mental health disorder

There is no clear evidence to indicate that the presence or degree of depression, or prescription of antidepressants, is predictive of response to naltrexone.

One study has reported a greater response to naltrexone in people with more antisocial traits.

Naltrexone is well tolerated by people with schizophrenia or schizoaffective disorder or bipolar disorder.

(f) Age at entry to treatment

Naltrexone is suitable for a wide range of age groups.

(g) Gender

There may be gender differences in the response to naltrexone but more information is needed to confirm the significance of the difference and the implications for treatment decisions.

(h) Genetics, family history and typology of alcohol dependence

The underlying mechanism of addiction, as indicated by genetics, family history and typology of alcohol-related disorder, appears to be an important factor determining response to naltrexone treatment. However practical implications of this remain to be determined.

1.1 Rationale for effect

The reinforcing effects of alcohol are thought to be modulated by the endogenous opioid system. Opioid antagonists by interfering with opioid activity should block the positive reinforcing properties of alcohol.[4;35;36] Through this mechanism, opioid antagonists are seen as potentially useful in reducing the likelihood of heavy drinking following a slip.[37]

Naltrexone (ReVia® or Naltrexone QP) is the opioid antagonist that is approved in Australia for relapse prevention treatment of alcohol dependence. It has a rapid onset of action[36] and can be administered orally as a single daily dose. The standard dose for relapse prevention treatment of alcohol abuse or dependence has been 50mg/day but several studies have used higher doses, and the general adequacy of a dose of 50mg/day has been questioned.[8]

The COMBINE Study Research Group,[37] in developing the methodology for that study, noted that very little work had been done to establish the optimal dose of naltrexone. On the basis of preclinical studies, clinical experience, preliminary results of a clinical trial, and a controlled laboratory study, this group suggested that the suppressive effects of naltrexone on alcohol self-administration are dose dependent. They also suggested that higher doses may provide greater protection against the effects of missed doses. Hence they chose to test a dose of 100 mg per day.

Pettinati 2008A used naltrexone at a dose of 150mg/day as standard doses were considered unlikely to be adequate for the target population of people dependent on both cocaine and alcohol.

Six studies used oral naltrexone at doses of 100mg/day or more. With variability in the type of data reported by these studies it was not possible to compare outcomes for these six studies and those studies using 50mg/day.

The effectiveness of naltrexone is dependent on patients taking the medication and compliance has been problematic. Sustained-release depot or implantable preparations are seen as one possible means of overcoming the problem of patient compliance. Depot preparations typically contain naltrexone in biodegradable microcapsules that are injected subcutaneously[38] or intramuscularly.[39] Implants comprising tablets contained in a coating are inserted surgically into the abdominal area.[40] None of the studies included in this review used the implant preparation, but four studies used a depot preparation.

In addition to optimising compliance, depot preparations may be associated with less adverse effects due to a slower rate of increase in plasma levels following initial administration, compared to oral preparations. Relatively constant plasma levels may also facilitate good clinical outcome through greater exposure to therapeutic doses of medication[8].

Nalmefene is not available in Australia, but has been the subject of trials internationally. The half-life and mode of administration of nalmefene are similar to naltrexone, but nalmefene is a partial agonist at kappa-opioid receptors as well as a full antagonist at mu-opioid receptors. Nalmefene thus has a different mechanism of action from naltrexone. In particular nalmefene has no dose-dependent association with toxic effects to the liver.[41;42]

1.2 Evidence of effectiveness

Opioid antagonists have been compared with placebo or no medication for the treatment of alcohol dependence in 56 trials (see Table 1.1). The majority (45) of studies used oral naltrexone, but depot preparations of naltrexone have been used, as well as the longer-acting antagonist, nalmefene. Brief information on the design of these studies is included in Appendix 1.

Table 1.1: Studies involving the use of opioid antagonists for relapse prevention treatment of alcohol dependence.

Placebo comparison				No medication comparison
Oral naltrexone		Depot or implant naltrexone	Nalmefene	Oral naltrexone
Ahmadi 2002[43;44] Anton 1999[53;54] Anton 2005[64;65] Balldin 2003 [71] Baltieri 2008 [76] Brown 2009[79] Castro 2009 [82] Chick 2000 [87] Combine Pilot[52] Combine Study[15;22;37;59-63] Galarza 1997 [90] Gastpar 2002 [92] Guardia 2002 [95] Heinala 2001 [98] Hersh 1998 [101;102] Huang 2005 [105] Kiefer 2003[24;111-113] Killeen 2004 [70] Kranzler 2000 [117] Kranzler 2003 [119-121] Kranzler 2009 [123] Krystal 2001[126-128] Latt 2002 [130]	Lee 2001 [45] Monterosso 2001 [55] Monti 2001[66-68] Morley 2006 [72-74] Morris 2001 [77] Niederhofer 2003a [80] O'Malley 1992[83-86] O'Malley 2003-2[88] O'Malley 2003-3[88] O'Malley 2007[89] O'Malley 2008[91] Oslin 1997 [93;94] Oslin 2005 [96;97] Oslin 2008 [99;100] Petrakis 2004 [103;104] Petrakis 2005[106-110] Pettinati 2008 [114] Pettinati 2008A[115;116] Pettinati 2010[118] Schmitz 2009 [122] Volpicelli 1992[124;125] Volpicelli 1997 [129]	Garbutt 2005[46-50] Johnson 2004 [56] Kranzler 1998 [38] Kranzler 2004 [39]	Anton 2004 [51] Karhuvaara 2007 [57;58] Mason 1994 [69] Mason 1999 [41]	Combine Pilot[52] Combine Study[15;22;37;59-63] Killeen 2004 [70] Landabaso 1999 [75] Rubio 2002 [78] Rubio 2005 [81]

1.2.1 Retention in treatment

****	Treatment with an opioid antagonist is not associated with increased retention in treatment, relative to treatment with placebo.
*	Treatment with oral naltrexone may slightly increase retention in treatment, relative to treatment with no medication. This suggests there may be a small placebo effect encouraging retention in treatment that is related to the provision of medication and not the specific pharmacological properties of opioid antagonists.

Supporting evidence

There is no significant difference in the rates of completion of treatment for patients receiving:

> oral naltrexone compared to placebo (Figure 1.1: RR 1.03, 95% CI 0.98, 1.09, P=0.23);****

> depot naltrexone compared to placebo (Figure 1.1: RR 1.02, 95% CI 0.94, 1.12, P=0.58);** or

> nalmefene compared to placebo (Figure 1.1: RR 0.95, 95% CI 0.86, 1.05, P=0.33).**

Heinala 2001 did not report data suitable for inclusion in the analyses, but reported no significant difference between oral naltrexone and placebo groups in retention at 12 or 32 weeks, a finding that is consistent with the meta-analyses above.

Figure 1.1: Opioid antagonist compared with placebo, completion of treatment

Study or Subgroup	Antagonist Events	Antagonist Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Oral naltrexone						
Ahmadi 2002	46	58	25	58	1.4%	1.84 [1.33, 2.54]
Anton 1999	59	68	49	63	3.9%	1.12 [0.95, 1.31]
Anton 2005	64	80	66	80	4.3%	0.97 [0.84, 1.13]
Balldin 2003	44	56	47	62	3.1%	1.04 [0.85, 1.26]
Baltieri 2008	29	49	23	54	1.1%	1.39 [0.94, 2.05]
Brown 2009	14	23	12	27	0.6%	1.37 [0.80, 2.34]
Chick 2000	37	90	36	85	1.3%	0.97 [0.68, 1.38]
COMBINE Pilot	10	18	13	17	0.7%	0.73 [0.44, 1.19]
COMBINE Study	246	308	251	308	7.1%	0.98 [0.91, 1.06]
de Goes e Castro 2004	17	35	18	36	0.7%	0.97 [0.61, 1.56]
Galarza 1997	5	10	6	10	0.3%	0.83 [0.37, 1.85]
Gastpar 2002	56	84	54	87	2.6%	1.07 [0.86, 1.34]
Guardia 2002	61	101	59	101	2.5%	1.03 [0.82, 1.30]
Hersh 1998	20	31	19	33	1.0%	1.12 [0.76, 1.66]
Huang 2005	11	20	13	20	0.6%	0.85 [0.51, 1.41]
Kiefer 2003	22	40	10	40	0.5%	2.20 [1.20, 4.03]
Killeen 2004	27	51	24	36	1.3%	0.79 [0.56, 1.12]
Kranzler 2000	36	61	50	63	2.3%	0.74 [0.58, 0.95]
Kranzler 2003	66	75	64	75	5.1%	1.03 [0.91, 1.17]
Kranzler 2009	68	83	70	80	4.9%	0.94 [0.82, 1.07]
Latt 2002	33	56	34	51	1.7%	0.88 [0.66, 1.18]
Lee 2001	14	35	4	18	0.2%	1.80 [0.69, 4.68]
Morley 2006	36	53	40	61	2.1%	1.04 [0.80, 1.34]
Morris 2001	38	55	33	56	1.8%	1.17 [0.89, 1.55]
O'Malley 1992	37	52	31	52	1.8%	1.19 [0.90, 1.58]
O'Malley 2003-2	17	26	13	27	0.7%	1.36 [0.84, 2.20]
O'Malley 2003-3	19	30	24	30	1.4%	0.79 [0.57, 1.10]
O'Malley 2007	34	57	27	50	1.4%	1.10 [0.79, 1.54]
O'Malley 2008	26	34	21	34	1.4%	1.24 [0.90, 1.71]
Oslin 1997	14	21	13	23	0.7%	1.18 [0.74, 1.89]
Oslin 2005	30	37	33	37	3.2%	0.91 [0.75, 1.10]
Oslin 2008	89	120	96	120	4.7%	0.93 [0.81, 1.06]
Petrakis 2004	12	16	13	15	1.3%	0.87 [0.61, 1.22]
Petrakis 2005	46	59	40	64	2.4%	1.25 [0.99, 1.58]
Pettinati 2008	35	52	32	54	1.7%	1.14 [0.85, 1.52]
Pettinati 2008a	55	82	50	82	2.5%	1.10 [0.87, 1.38]
Pettinati 2010	29	49	23	39	1.3%	1.00 [0.71, 1.42]
Volpicelli 1992	24	35	21	35	1.3%	1.14 [0.80, 1.62]
Volpicelli 1997	35	48	36	49	2.3%	0.99 [0.78, 1.26]
Subtotal (95% CI)		**2258**		**2232**	**79.3%**	**1.03 [0.98, 1.09]**
Total events	1561		1493			
Heterogeneity: Tau² = 0.01; Chi² = 58.60, df = 38 (P = 0.02); I² = 35%						
Test for overall effect: Z = 1.19 (P = 0.23)						
Depot or implant naltrexone						
Garbutt 2005	250	415	128	209	4.8%	0.98 [0.86, 1.12]
Johnson 2004	17	25	4	5	0.6%	0.85 [0.51, 1.42]
Kranzler 2004	127	158	118	157	5.4%	1.07 [0.95, 1.20]
Subtotal (95% CI)		**598**		**371**	**10.8%**	**1.02 [0.94, 1.12]**
Total events	394		250			
Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.55 (P = 0.58)						
Nalmefene						
Anton 2004	151	202	49	68	3.8%	1.04 [0.88, 1.23]
Karhuvaara 2007	145	242	110	161	4.4%	0.88 [0.76, 1.02]
Mason 1994	6	14	2	7	0.1%	1.50 [0.40, 5.61]
Mason 1999	45	70	23	35	1.7%	0.98 [0.73, 1.32]
Subtotal (95% CI)		**528**		**271**	**9.9%**	**0.95 [0.86, 1.05]**
Total events	347		184			
Heterogeneity: Tau² = 0.00; Chi² = 2.69, df = 3 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Total (95% CI)		**3384**		**2874**	**100.0%**	**1.02 [0.98, 1.06]**
Total events	2302		1927			
Heterogeneity: Tau² = 0.01; Chi² = 63.23, df = 45 (P = 0.04); I² = 29%						
Test for overall effect: Z = 0.90 (P = 0.37)						

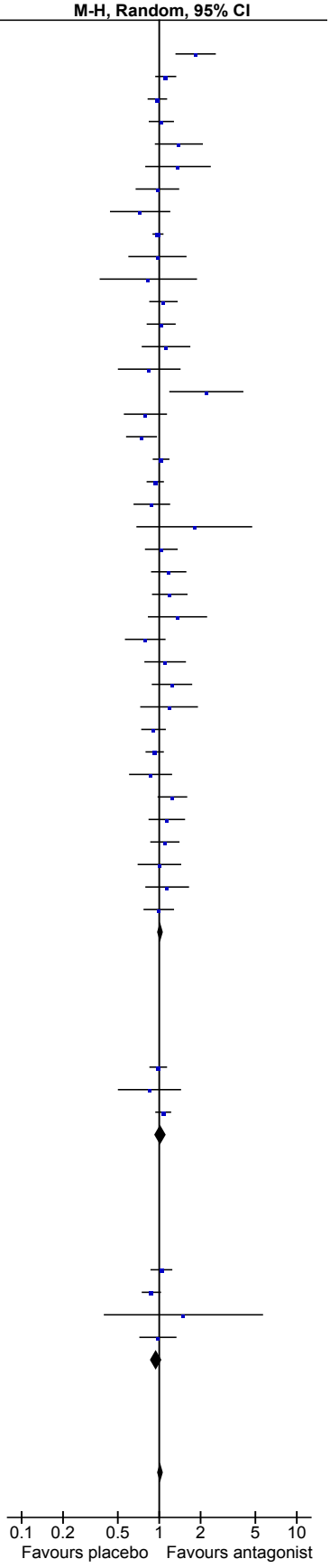
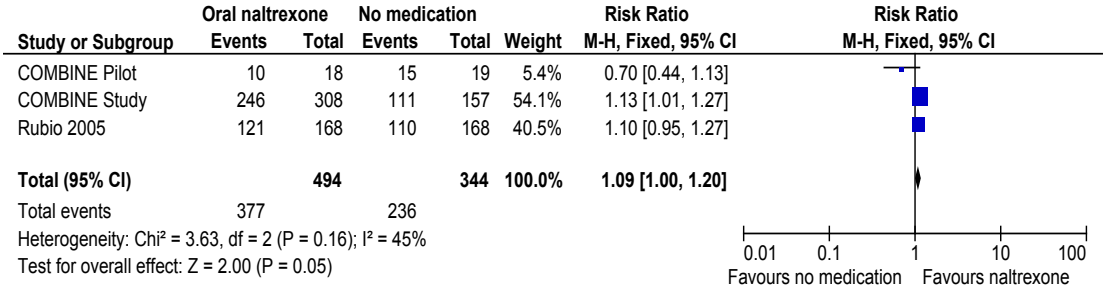


Figure 1.2: Oral naltrexone compared with no medication, completion of treatment



Based on three studies, completion of treatment is more likely with oral naltrexone compared to no medication, with the difference just achieving statistical significance (Figure 1.2: RR 1.09, 95% CI 1.00, 1.20, P=0.05)*.

A small number of studies reported retention in terms of time in treatment rather than the number of participants completing treatment. These data also indicate no significant difference in retention for patients receiving:

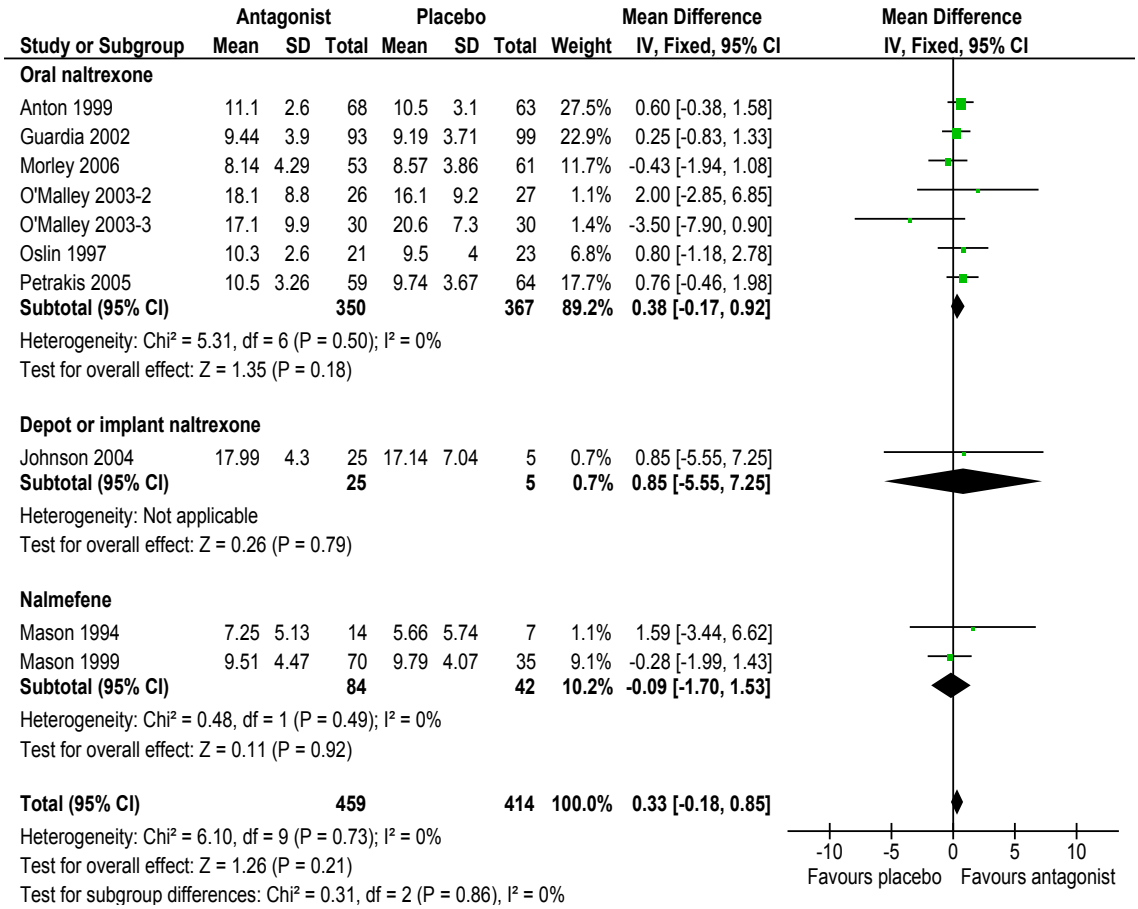
> oral naltrexone compared to those receiving placebo (Figure 1.3: mean difference 0.38, 95% CI -0.17, 0.92, P=0.18)***;

> depot naltrexone compared to placebo (Figure 1.3: mean difference 0.85, 95% CI -5.55, 7.25, P=0.79)*; or

> nalmefene compared to placebo (Figure 1.3: mean difference -0.09, 95% CI -1.70, 1.53, P=0.92)*.

Brown 2009 reported average retention of 9.6 weeks for naltrexone and 8.8 weeks for placebo (difference not significant). These data could not be included in the analyses above, but are consistent with the finding.

Figure 1.3: Opioid antagonist compared with placebo, average weeks in treatment



1.2.2 Effect on alcohol consumption

	Total abstinence
****	Treatment with oral naltrexone significantly increases the probability of total abstinence from alcohol during treatment relative to placebo. However the degree of benefit is small (NNT=20).
*	Depot naltrexone may also promote abstinence but insufficient data are available to be conclusive.
	No data are available on nalmefene.

Supporting evidence

Treatment with oral naltrexone is associated with significantly more participants being abstinent from alcohol during treatment, compared to those receiving placebo (Figure 1.4: RR 1.16, 95% CI 1.06, 1.27, P<0.001). **** This difference translates to an NNT of 20 (95% CI 50, 14), indicating that for every 20 people treated with oral naltrexone, one additional person will be continuously abstinent during treatment than would be the case with placebo. This is a relatively small degree of benefit.

Available data show a trend towards higher rates of continuous abstinence for depot naltrexone compared to placebo (Figure 1.4: RR 1.50, 95% CI 0.97, 2.32; P=0.07)*. However, depot preparations are still under development and as yet there are insufficient studies available to form a conclusive view on their effectiveness.

Based on two studies, there is no significant difference between oral naltrexone and no medication in rates of continuous abstinence from alcohol (Figure 1.5: RR 1.76, 95% CI 0.52, 5.97, P=0.36)*.

	Relapse to heavy drinking
***	Treatment with oral naltrexone significantly decreases the risk of relapse to heavy drinking. The difference translates to an NNT of 8 (95% CI 6, 13), meaning that for every 8 people treated with oral naltrexone, one less person can be expected to relapse during treatment than would be the case with placebo.
**	The risk of relapse to heavy drinking is also significantly lower with oral naltrexone compared with no medication.
*	Nalmefene and depot preparations of naltrexone may also reduce the risk of relapse but more data are needed to confirm this.
	Oral naltrexone is more effective at preventing relapse to heavy drinking than promoting total abstinence.

Supporting evidence

Most studies defined relapse as a resumption of heavy drinking (usually based on five or more standard drinks for men, four or more for women, in a session). By these criteria, rates of relapse are significantly lower for those treated with oral naltrexone, compared to those receiving placebo (Figure 1.6: RR 0.80, 95% CI 0.72, 0.88; P<0.001).**** The difference translates to an NNT of 9 (95% CI 7, 13) meaning that for every 9 people treated with oral naltrexone, one less person can be expected to relapse than would be the case with placebo. Rates of relapse to heavy drinking are also significantly lower for oral naltrexone compared to no medication (Figure 1.7: RR 0.84, 95% CI 0.75, 0.94; P=0.003)*.

Monterosso 2001 did not report data but reported that there was less incidence of clinical deterioration (effectively relapse to heavy drinking) among patients receiving naltrexone compared to those receiving placebo (P=0.003). Ahmadi 2002 also reported that naltrexone significantly reduced the rate of relapse to heavy drinking relative to placebo and Schmitz 2009 found that the probability of heavy drinking decreased with time for naltrexone but not placebo. These findings are consistent with the data above.

Two studies reported the number of participants relapsing during treatment with nalmefene and one study reported data for depot naltrexone compared to placebo (Figure 1.6). While the results favoured nalmefene* and depot naltrexone*, the differences did not achieve statistical significance.

Figure 1.4: Opioid antagonist compared with placebo, participants continuously abstinent during treatment

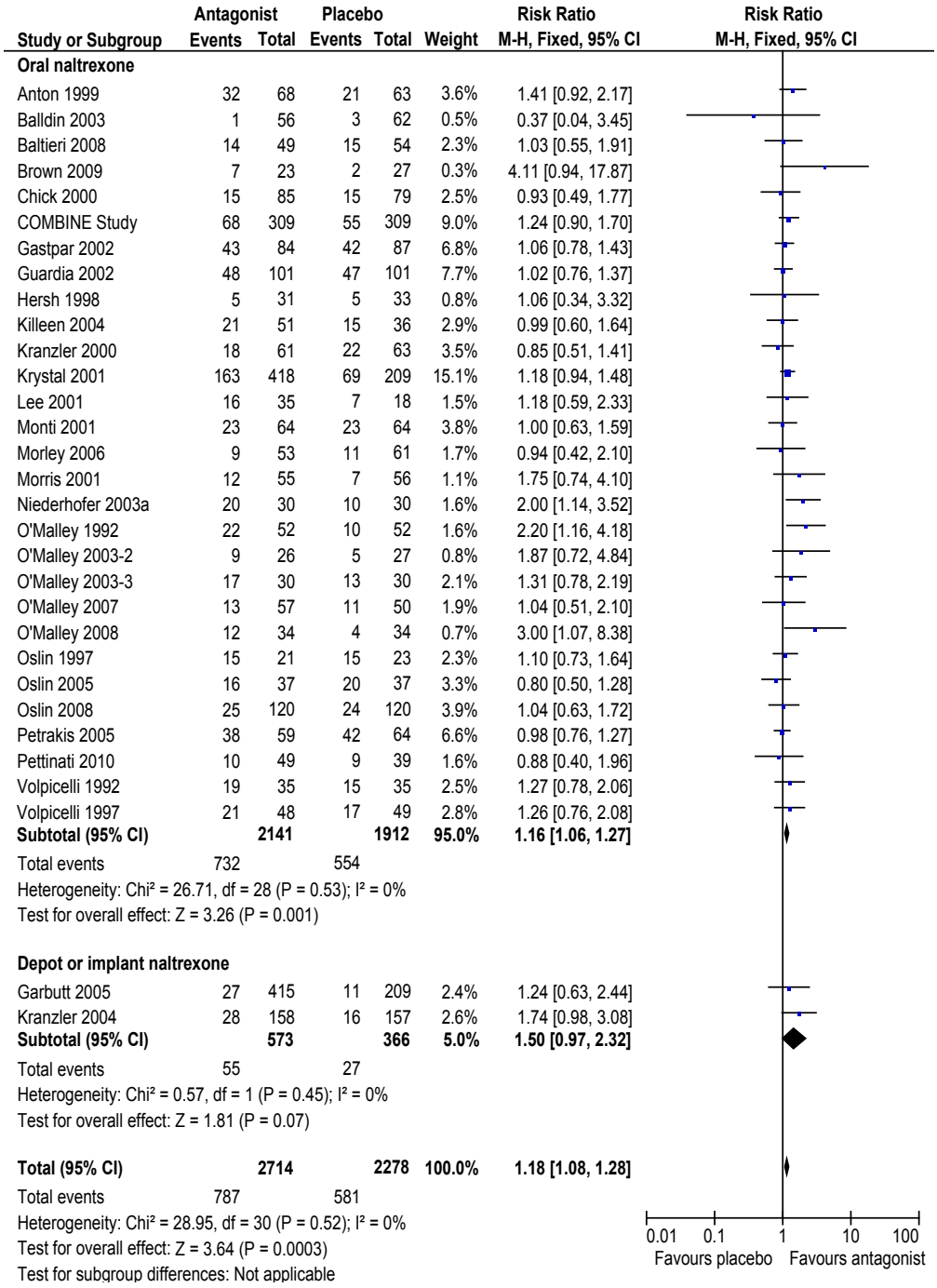


Figure 1.5: Oral naltrexone compared with no medication, participants continuously abstinent during treatment

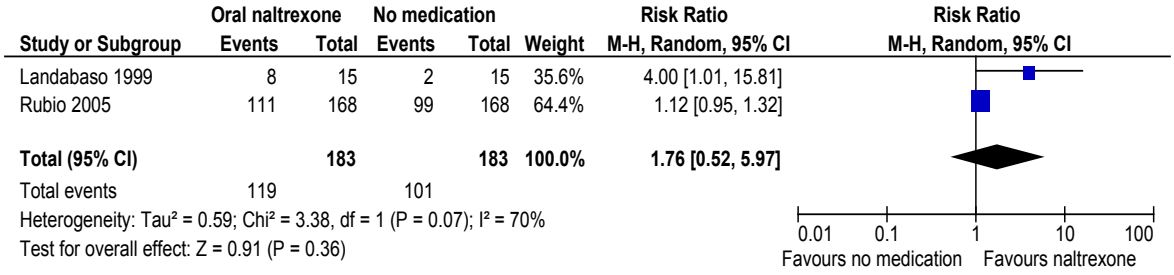


Figure 1.6: Opioid antagonist compared with placebo, participants relapsing during treatment

Study or Subgroup	Antagonist Events	Antagonist Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Oral naltrexone						
Ahmadi 2002	12	58	33	58	1.8%	0.36 [0.21, 0.63]
Anton 1999	26	68	38	63	3.2%	0.63 [0.44, 0.91]
Anton 2005	33	80	47	80	3.6%	0.70 [0.51, 0.97]
Balldin 2003	53	56	58	62	6.5%	1.01 [0.92, 1.11]
Brown 2009	5	23	12	27	0.9%	0.49 [0.20, 1.18]
Castro 2009	1	35	8	36	0.2%	0.13 [0.02, 0.98]
Chick 2000	57	85	53	79	4.9%	1.00 [0.81, 1.24]
COMBINE Study	207	308	226	308	6.4%	0.92 [0.83, 1.02]
de Goes e Castro 2004	3	35	10	36	0.5%	0.31 [0.09, 1.03]
Gastpar 2002	32	84	33	87	3.0%	1.00 [0.68, 1.47]
Guardia 2002	8	101	19	101	1.1%	0.42 [0.19, 0.92]
Heinala 2001	52	63	54	58	6.0%	0.89 [0.78, 1.01]
Hersh 1998	22	31	25	33	3.9%	0.94 [0.70, 1.26]
Huang 2005	4	20	3	20	0.4%	1.33 [0.34, 5.21]
Kiefer 2003	12	40	30	40	2.1%	0.40 [0.24, 0.66]
Killeen 2004	21	51	12	36	1.8%	1.24 [0.70, 2.18]
Kranzler 2000	29	61	32	63	3.2%	0.94 [0.65, 1.34]
Krystal 2001	143	378	83	187	5.0%	0.85 [0.69, 1.05]
Latt 2002	19	56	27	51	2.5%	0.64 [0.41, 1.00]
Lee 2001	8	24	8	15	1.2%	0.63 [0.30, 1.31]
Monti 2001	18	64	21	64	2.0%	0.86 [0.51, 1.45]
Morley 2006	39	53	43	61	4.7%	1.04 [0.83, 1.31]
Morris 2001	19	55	26	56	2.4%	0.74 [0.47, 1.18]
O'Malley 1992	20	52	34	52	2.9%	0.59 [0.40, 0.87]
O'Malley 2003-2	5	26	13	27	0.9%	0.40 [0.17, 0.96]
O'Malley 2003-3	5	30	9	30	0.7%	0.56 [0.21, 1.46]
O'Malley 2007	33	57	29	50	3.6%	1.00 [0.72, 1.38]
O'Malley 2008	22	34	28	34	3.9%	0.79 [0.59, 1.05]
Oslin 1997	3	21	8	23	0.5%	0.41 [0.13, 1.35]
Oslin 2005	13	37	12	37	1.5%	1.08 [0.57, 2.05]
Oslin 2008	73	120	76	120	5.1%	0.96 [0.79, 1.17]
Volpicelli 1992	8	35	19	35	1.3%	0.42 [0.21, 0.83]
Volpicelli 1997	17	48	26	49	2.3%	0.67 [0.42, 1.06]
Subtotal (95% CI)		**2289**		**2078**	**89.8%**	**0.80 [0.72, 0.88]**
Total events	1022		1155			
Heterogeneity: Tau² = 0.03; Chi² = 87.47, df = 32 (P < 0.00001); I² = 63%						
Test for overall effect: Z = 4.59 (P < 0.00001)						
Depot or implant naltrexone						
Kranzler 2004	122	158	132	157	6.3%	0.92 [0.82, 1.02]
Subtotal (95% CI)		**158**		**157**	**6.3%**	**0.92 [0.82, 1.02]**
Total events	122		132			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.54 (P = 0.12)						
Nalmefene						
Mason 1994	8	13	4	6	1.2%	0.92 [0.45, 1.88]
Mason 1999	26	70	20	35	2.7%	0.65 [0.43, 0.99]
Subtotal (95% CI)		**83**		**41**	**3.9%**	**0.71 [0.50, 1.02]**
Total events	34		24			
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 1.85 (P = 0.06)						
Total (95% CI)		**2530**		**2276**	**100.0%**	**0.81 [0.74, 0.88]**
Total events	1178		1311			
Heterogeneity: Tau² = 0.03; Chi² = 89.87, df = 35 (P < 0.00001); I² = 61%						
Test for overall effect: Z = 4.83 (P < 0.00001)						

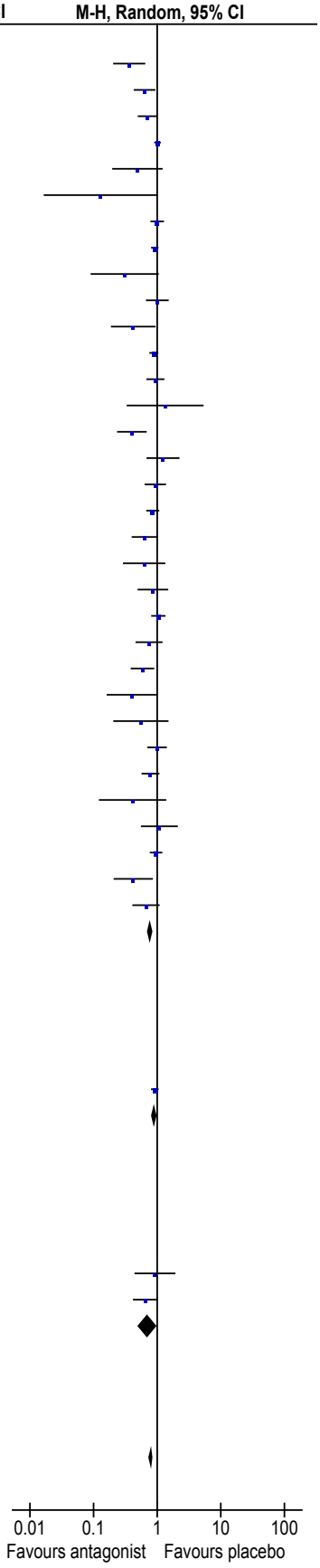
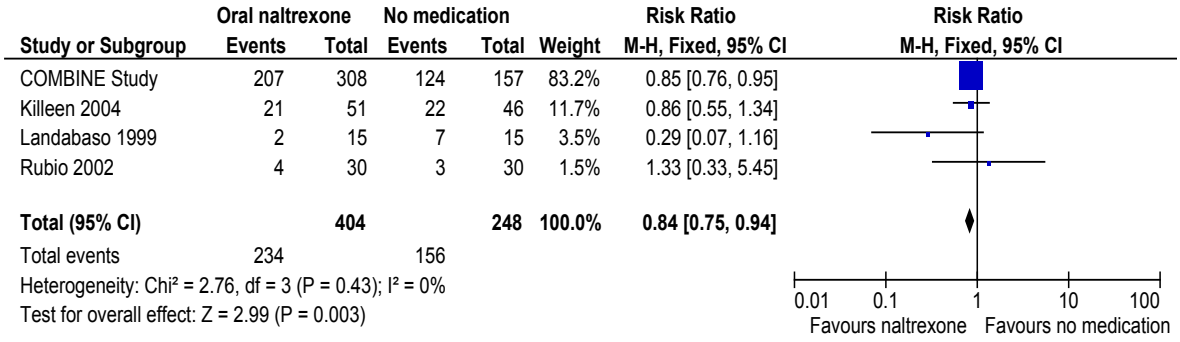


Figure 1.7: Oral naltrexone compared with no medication, participants relapsing during treatment



The limited effect of oral naltrexone on the promotion of continuous abstinence (NNT=20) and the greater effect on the prevention of relapse to heavy drinking (NNT=9) suggests that naltrexone is more effective at preventing relapse to heavy drinking than promoting total abstinence. Indeed individual studies and a previous review[131] have drawn similar conclusions, with Volpicelli 1992 noting that naltrexone did not stop participants from sampling alcohol (46% treated with naltrexone and 57% receiving placebo had at least one alcoholic drink) but decreased subsequent drinking once drinking occurred. Similarly in Morris 2001, 63% of naltrexone subjects who sampled alcohol relapsed to clinically significant drinking, compared with 90% of participants receiving placebo, and in Volpicelli 1992, 50% of naltrexone subjects who sampled alcohol progressed to relapse, compared to 95% of placebo subjects.

In reviewing the status of naltrexone for treatment of alcohol dependence, Pettinati *et al*.[131] noted that 19 of 27 (70%) clinical trials that measured reductions in 'heavy or excessive drinking' demonstrated an advantage for naltrexone over placebo, whereas only 9 of 25 (36%) clinical trials that measured abstinence or 'any drinking' found an advantage for medication over placebo.

	Amount of alcohol consumed
***	Compared with placebo, oral naltrexone reduces alcohol consumption by around one drink/ drinking day.
**	Oral naltrexone decreases alcohol consumption by around 2 drinks per week relative to placebo, but this difference is not statistically significant.
*	Nalmefene and depot preparations of naltrexone may be associated with decreased alcohol consumption, but available data are currently insufficient to determine this with any certainty and the dose delivered by the depot preparation may be important.

Supporting evidence

Studies included in this review reported significantly fewer drinks per drinking day for patients receiving:

> oral naltrexone compared to those receiving placebo (Figure 1.8: mean difference -0.83 drinks/drinking day, 95% CI -1.38, -0.28; P=0.003)***; and

> (from 1 study) depot naltrexone compared with placebo (Figure 1.8: mean difference -2.20 drinks/drinking day, 95% CI -3.19, -1.21; P<0.001)*

Three studies reported data on drinks per drinking day for nalmefene compared to placebo. While the overall result favoured nalmefene, the difference was not statistically significant (Figure 1.8, mean difference -0.78 drinks/drinking day, 95% CI -1.70, 0.13; P=0.09)*.

One study (Killeen 2004) reported drinks per drinking day for oral naltrexone compared with no medication, with no significant difference reported (mean difference -0.33 drinks/drinking day, 95% CI -2.80, 2.14; P=0.79)*. In addition, Rubio 2002 reported that, during the last two months of treatment, the naltrexone group drank for fewer days and took a smaller number of drinks than the no medication group, but the difference was not statistically significant.

Some studies reported alcohol consumption as average drinks per week. While the differences favoured oral naltrexone over placebo (Figure 1.9: mean difference -1.80 drinks/week, 95% CI -3.86, 0.26; P=0.09)** or no medication (Figure 1.10: mean difference -3.35 drinks/week, 95% CI -8.37, 1.67; P=0.19)*, the differences were not statistically significant. Gastpar 2002 also reported no significant difference between

oral naltrexone and placebo in the mean total standard drinks consumed. From one study there was also no significant difference for depot or implant naltrexone compared to placebo (Figure 1.9: mean difference -1.40 drinks/week, 95% CI -9.06, 6.26; P=0.72)* and it has been suggested that the dose delivered by the depot preparation may be important.[47]

Figure 1.8: Opioid antagonist compared with placebo, average drinks per drinking day

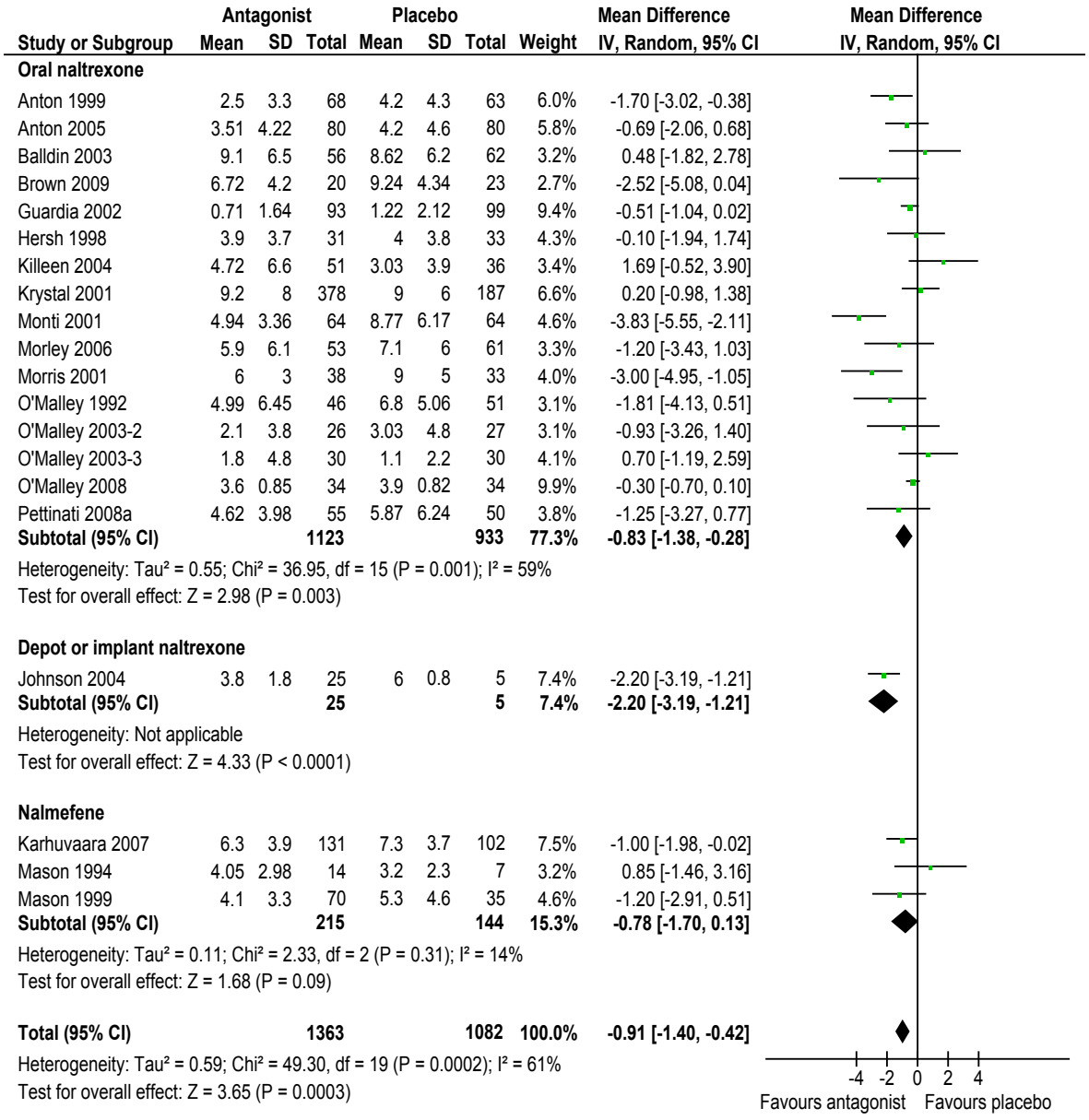


Figure 1.9: Opioid antagonist compared with placebo, average drinks per week

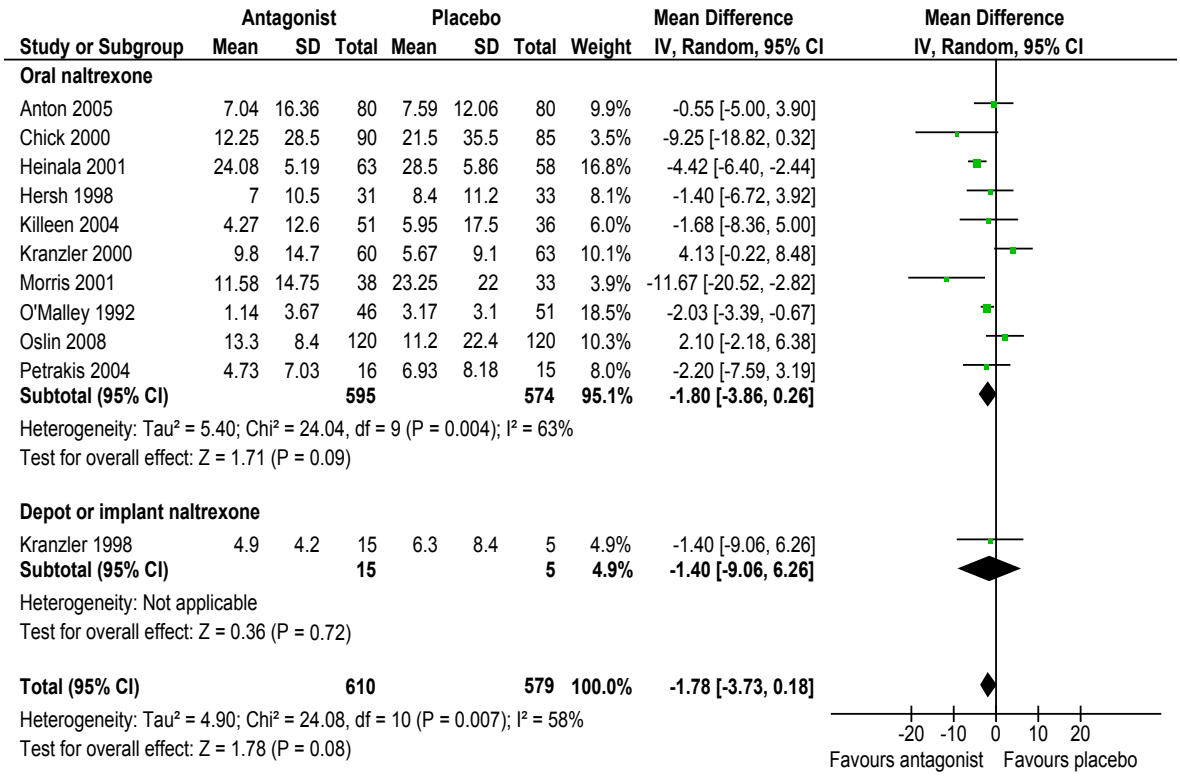
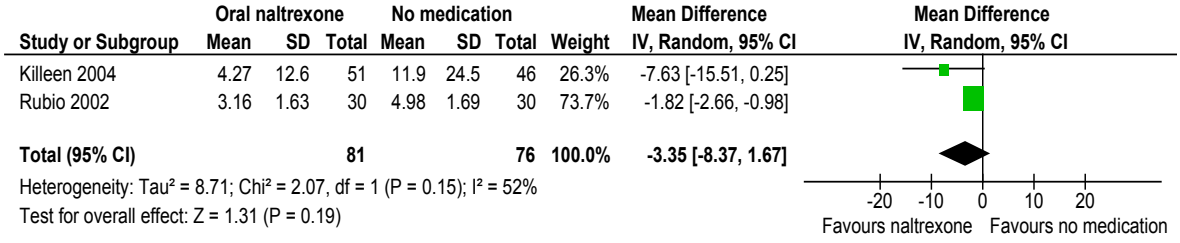


Figure 1.10: Oral naltrexone compared with no medication, average drinks per week



	Periods of abstinence or heavy drinking during treatment
**** **	Treatment with oral naltrexone is associated with significantly more abstinent days compared to placebo (4% more treatment days) or no medication (5% more treatment days).
*	Depot naltrexone is also associated with more abstinent days compared to placebo.
*** *	Treatment with oral naltrexone is associated with significantly less days of heavy drinking compared to placebo (4% less treatment days) or no medication.
*	There is no significant difference in days of heavy drinking compared to placebo, but data are limited.
	Insufficient data are available to form a view on the effect of nalmefene on days of abstinence or heavy drinking.

Supporting evidence

Data on percent of days with drinking were converted to percent of days of abstinence (cumulative abstinence duration) for consistency with studies of other medications covered by subsequent sections of this review. The available data showed significantly greater cumulative abstinence duration for:

> oral naltrexone compared with placebo (Figure 1.11: mean difference 4.33% days, 95% CI 2.10, 6.56; P<0.001)****; and

> oral naltrexone compared with no medication (Figure 1.12: mean difference 5.53% days, 95% CI 1.41, 9.66; P=0.009)**.

Participants treated with naltrexone in Volpicelli 1992 drank on an average of 1.6% of study days, whereas those receiving placebo drank on an average of 8.3% of study days (P<0.025 after controlling for drinking days during the baseline week of placebo treatment). Oslin 1997 reported that the naltrexone-treated group drank on an average of 1.9% of study days compared with 6.5% for the placebo group (P=0.275). Gastpar 2002 reported no significant difference between oral naltrexone and placebo in the number of non-abstinent days. These findings are consistent with the meta-analysis which shows no significant difference for the majority of individual studies, but a statistically significant difference for the combined estimate of overall effect.

Based on four studies, depot naltrexone is associated with significant greater cumulative abstinence duration compared to placebo (Figure 1.11: mean difference 8.50% days, 95% CI 1.36, 15.65; P=0.002.*

There is no significant difference in cumulative abstinence duration for nalmefene compared with placebo (Figure 1.11: mean difference 3.74% days, 95% CI -1.68, 9.17; P=0.18)*.

Two studies reported additional data on nalmefene:

> Anton 2004 reported an increase in overall abstinent days from about 5 per month at baseline to about 16 days per month during treatment, with no significant difference between nalmefene and placebo.

> In Mason 1999 the percent of days abstinent increased in both groups (+46% nalmefene, +39% placebo) with no significant difference between groups.

A minority of studies reported the percent of days during treatment on which heavy drinking occurred. There were significantly less days of heavy drinking associated with oral naltrexone compared to placebo (Figure 1.13: mean difference -2.50% days, 95% CI -4.14, -0.85; P=0.003)***.

Based on two studies, there were significantly less days of heavy drinking associated with oral naltrexone compared with no medication (Figure 1.14, mean difference -3.98% days, 95% CI -6.12, -1.84; P<0.001)*. In addition, participants treated with oral naltrexone in Monterosso 2001 reported heavy drinking on fewer days than did participants receiving placebo (marginal means of 5.0% and 8.9%, respectively, *P*=0.04), and Kranzler 2003 found that although oral naltrexone (targeted or daily administration) did not significantly reduce drinking days, naltrexone was better than placebo in reducing the frequency of heavy drinking during the treatment period. There was a 19% reduction in the overall likelihood of heavy drinking during treatment with naltrexone compared with placebo (P=0.029).

No studies reported data for nalmefene that were suitable for inclusion in meta-analyses but Anton 2004 reported that all subjects (nalmefene and placebo) had a reduction in heavy drinking days with no significant differences between groups. In Karhuvaara 2007, during the first month of treatment, the number of heavy drinking days decreased by 40% in the nalmefene group and 24% in the placebo group. For the whole study period, the risk of heavy drinking was 32.4% smaller in the nalmefene group, and the mean cumulative number of heavy drinking days was 58.2 in the nalmefene group and 86.1 for the placebo group.

Based on three studies, there is no significant difference for depot naltrexone compared to placebo in the proportion of treatment days with heavy drinking (Figure 1.13: mean difference -3.07% days, 95% CI -8.50, 2.37; P=0.27)*. Data from Garbutt 2005 was reported in the form of hazards ratios. The rate of any drinking was not significantly lower with either dose of long-acting naltrexone, but compared to those receiving placebo, the rate of heavy drinking was reduced by around 25% in those treated with 380mg of long-acting naltrxone (P=0.03), and around 17% in those treated with 190mg (P=0.07).

Figure 1.11: Opioid antagonist compared with placebo, % days abstinent (cumulative abstinence duration)

Study or Subgroup	Antagonist Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Oral naltrexone								
Anton 1999	90	18.9	68	82	22.9	63	3.6%	8.00 [0.78, 15.22]
Anton 2005	83.83	24.21	80	77.05	29.08	80	3.2%	6.78 [-1.51, 15.07]
Balldin 2003	61.4	25.7	56	51.5	33.1	62	2.4%	9.90 [-0.74, 20.54]
Baltieri 2008	55	40.8	49	46.7	40	54	1.4%	8.30 [-7.33, 23.93]
Brown 2009	54	31.3	20	52	30.5	23	1.1%	2.00 [-16.53, 20.53]
Castro 2009	92.6	12.6	35	96.4	8.7	36	4.6%	-3.80 [-8.85, 1.25]
COMBINE Study	77.94	26.04	309	76.83	25.96	308	5.0%	1.11 [-2.99, 5.21]
de Goes e Castro 2004	79.3	35.5	35	88.3	24.3	36	1.6%	-9.00 [-23.19, 5.19]
Guardia 2002	65.3	22.64	93	63	26.9	99	3.7%	2.30 [-4.72, 9.32]
Hersh 1998	82.1	22.8	31	80.2	22.4	33	2.3%	1.90 [-9.18, 12.98]
Killeen 2004	91.81	0.2	51	89.57	0.2	36	6.2%	2.24 [2.15, 2.33]
Kranzler 2000	78.8	28.9	61	84.3	21.3	63	2.9%	-5.50 [-14.46, 3.46]
Krystal 2001	88.7	21	378	86	23	187	5.1%	2.70 [-1.22, 6.62]
Latt 2002	68.6	8.6	56	67.7	10	51	5.3%	0.90 [-2.65, 4.45]
Morley 2006	57.8	29.2	53	56.7	31.4	61	2.3%	1.10 [-10.03, 12.23]
Morris 2001	75	28	38	64	30	33	1.7%	11.00 [-2.57, 24.57]
Niederhofer 2003a	69.8	27.5	30	22.8	9	30	2.5%	47.00 [36.65, 57.35]
O'Malley 1992	95.7	9.5	46	90.1	9.28	51	5.2%	5.60 [1.86, 9.34]
O'Malley 2003-2	89.8	17.9	26	78.4	33.4	27	1.6%	11.40 [-2.95, 25.75]
O'Malley 2003-3	93.8	13.4	30	93.5	16.4	30	3.4%	0.30 [-7.28, 7.88]
O'Malley 2008	94.8	3.09	34	85.7	2.96	34	6.1%	9.10 [7.66, 10.54]
Oslin 2008	82	22.4	120	81.6	23	120	4.2%	0.40 [-5.34, 6.14]
Petrakis 2004	92.62	9.52	16	83.93	18.57	15	2.4%	8.69 [-1.80, 19.18]
Petrakis 2005	95.4	11.8	59	93.5	14	64	4.8%	1.90 [-2.66, 6.46]
Pettinati 2008a	89.55	14.41	55	87.16	14.93	50	4.3%	2.39 [-3.23, 8.01]
Volpicelli 1997	93.8	11.02	48	89.24	16.24	49	4.4%	4.56 [-0.95, 10.07]
Subtotal (95% CI)			**1877**			**1695**	**91.2%**	**4.33 [2.10, 6.56]**
Heterogeneity: Tau² = 19.28; Chi² = 185.70, df = 25 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 3.81 (P = 0.0001)								
Depot or implant naltrexone								
Johnson 2004	69.4	33.7	25	62.6	51.4	5	0.2%	6.80 [-40.15, 53.75]
Kranzler 1998	79	25.5	15	71.6	34.5	5	0.4%	7.40 [-25.48, 40.28]
Kranzler 2004	62.9	33.6	158	54.3	33.5	157	3.5%	8.60 [1.19, 16.01]
Subtotal (95% CI)			**198**			**167**	**4.1%**	**8.50 [1.36, 15.65]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 2 (P = 0.99); I² = 0%								
Test for overall effect: Z = 2.33 (P = 0.02)								
Nalmefene								
Karhuvaara 2007	61.6	25.1	242	57.6	29.1	161	4.4%	4.00 [-1.50, 9.50]
Mason 1994	50.7	30.7	14	57.1	41.4	7	0.3%	-6.40 [-41.03, 28.23]
Subtotal (95% CI)			**256**			**168**	**4.7%**	**3.74 [-1.68, 9.17]**
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%								
Test for overall effect: Z = 1.35 (P = 0.18)								
Total (95% CI)			**2331**			**2030**	**100.0%**	**4.43 [2.34, 6.52]**
Heterogeneity: Tau² = 18.21; Chi² = 189.26, df = 30 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 4.15 (P < 0.0001)								

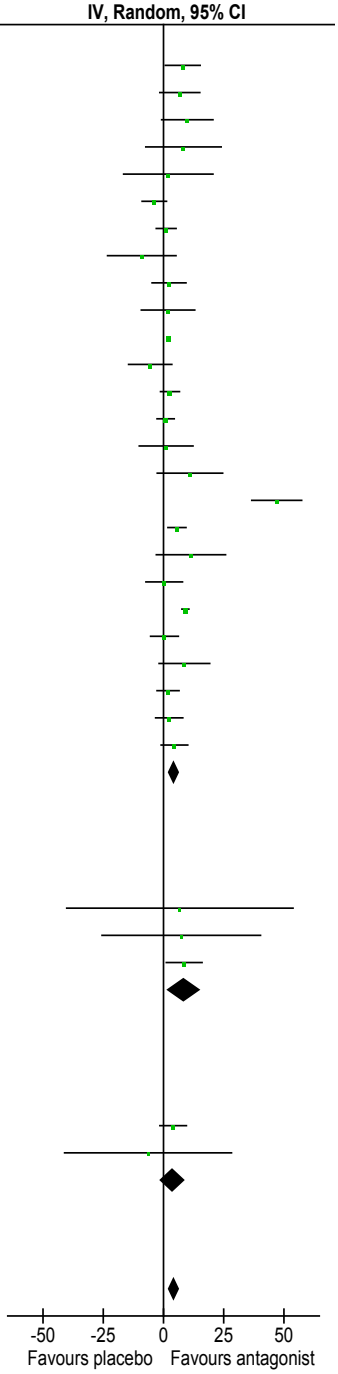


Figure 1.12: Oral naltrexone compared with no medication, % days abstinent (cumulative abstinence duration)

Study or Subgroup	Oral naltrexone Mean	SD	Total	No medication Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
COMBINE Study	77.94	26.04	309	66.6	27.14	157	16.7%	11.34 [6.20, 16.48]
Killeen 2004	91.81	0.2	51	83.62	0.3	46	22.6%	8.19 [8.09, 8.29]
Landabaso 1999	98.7	2.5	15	97.6	1.3	15	22.0%	1.10 [-0.33, 2.53]
Rubio 2002	73.83	9.67	30	69.5	6	30	18.5%	4.33 [0.26, 8.40]
Rubio 2005	98.57	9.43	168	94.9	18.51	168	20.0%	3.67 [0.53, 6.81]
Total (95% CI)			**573**			**416**	**100.0%**	**5.53 [1.41, 9.66]**
Heterogeneity: Tau² = 19.53; Chi² = 107.15, df = 4 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 2.63 (P = 0.009)								

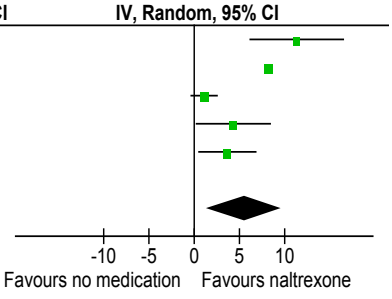


Figure 1.13: Opioid antagonist compared with placebo, % treatment days with heavy drinking

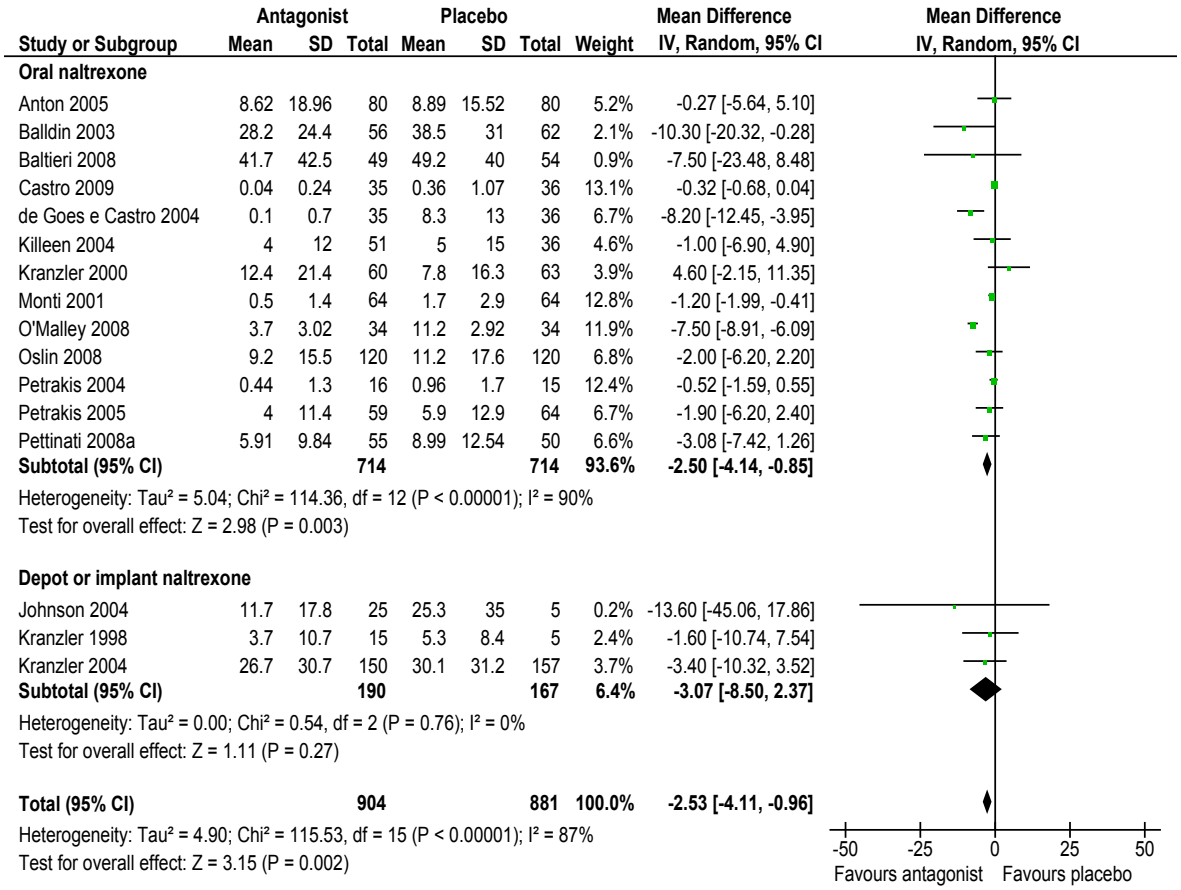
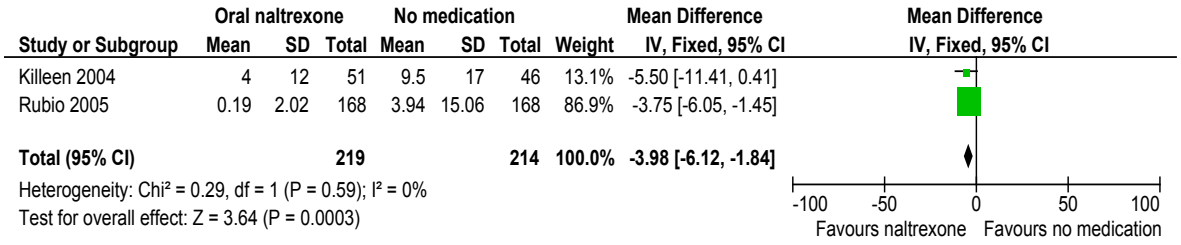


Figure 1.14: Oral naltrexone compared with no medication, % treatment days with heavy drinking



	Time to first drink and time to relapse
**	Treatment with oral naltrexone does not prolong abstinence from alcohol, but it does prolong the interval between recommencement of drinking and relapse to heavy drinking. The additional time without relapse associated with oral naltrexone, relative to placebo, is around 7 days.
	Nalmefene and depot preparations of naltrexone may also prolong the time to relapse, but insufficient data are available to determine the degree of effect.

Supporting evidence

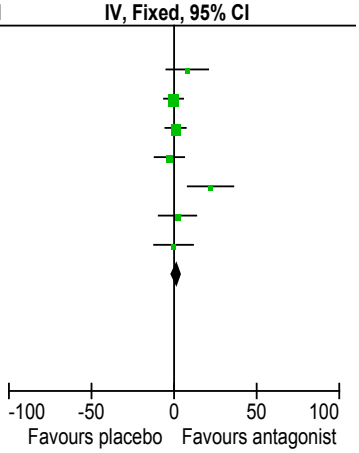
Seven studies reported the average time to first drink for oral naltrexone compared to placebo, with no significant difference (Figure 1.15: mean difference 1.69 days, 95% CI -1.55, 4.93; P=0.31)**.

No data were reported for depot preparations of naltrexone, or for nalmefene that were suitable for inclusion in meta-analyses, but Kranzler 2004 reported a median time to first drinking day of 5 days for those treated with naltrexone depot (95% CI 3, 9) compared with 3 days for those receiving placebo (95% CI 2, 4; P=0.003). In the case of nalmefene, Anton 2004 reported a median time to first drinking day of 9 days for nalmefene and 4 days for placebo (difference not significant).

Figure 1.15: Oral naltrexone compared with placebo, average days to first drink

	Antagonist			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Oral naltrexone								
Anton 1999	48	33	68	40	40	63	6.6%	8.00 [-4.61, 20.61]
Anton 2005	10.7	20.1	80	11	17.1	80	31.3%	-0.30 [-6.08, 5.48]
Guardia 2002	30.17	22.64	93	29.23	20.74	99	27.7%	0.94 [-5.21, 7.09]
Hersh 1998	14.7	18.2	31	17.5	18.2	33	13.2%	-2.80 [-11.72, 6.12]
Kiefer 2003	45.4	32.7	34	23.3	26.9	40	5.5%	22.10 [8.30, 35.90]
Kranzler 2000	42	32.9	61	39.9	31.5	63	8.1%	2.10 [-9.24, 13.44]
Morley 2006	24.3	31.7	53	24.6	32.1	61	7.6%	-0.30 [-12.04, 11.44]
Subtotal (95% CI)			**420**			**439**	**100.0%**	**1.69 [-1.55, 4.93]**

Heterogeneity: Chi² = 10.97, df = 6 (P = 0.09); I² = 45%
Test for overall effect: Z = 1.02 (P = 0.31)



Ten studies reported the average time to relapse to heavy drinking for oral naltrexone, with a significantly longer time for naltrexone compared to placebo (Figure 1.16: mean difference 7.35 days, 95% CI 2.18, 12.53; P=0.005)**.

In addition, six studies reported findings without data suitable for inclusion in meta-analyses:

> Morris 2001 reported significantly longer time to relapse for oral naltrexone compared with placebo;

> Latt 2002 and Volpicelli 1992 reported longer times to relapse for oral naltrexone with testing for statistical significance; and

> Gastpar 2002, Oslin 2005 and O'Malley 2008 reported found no significant difference between oral naltrexone and placebo in time to first heavy drinking episode or time to relapse.

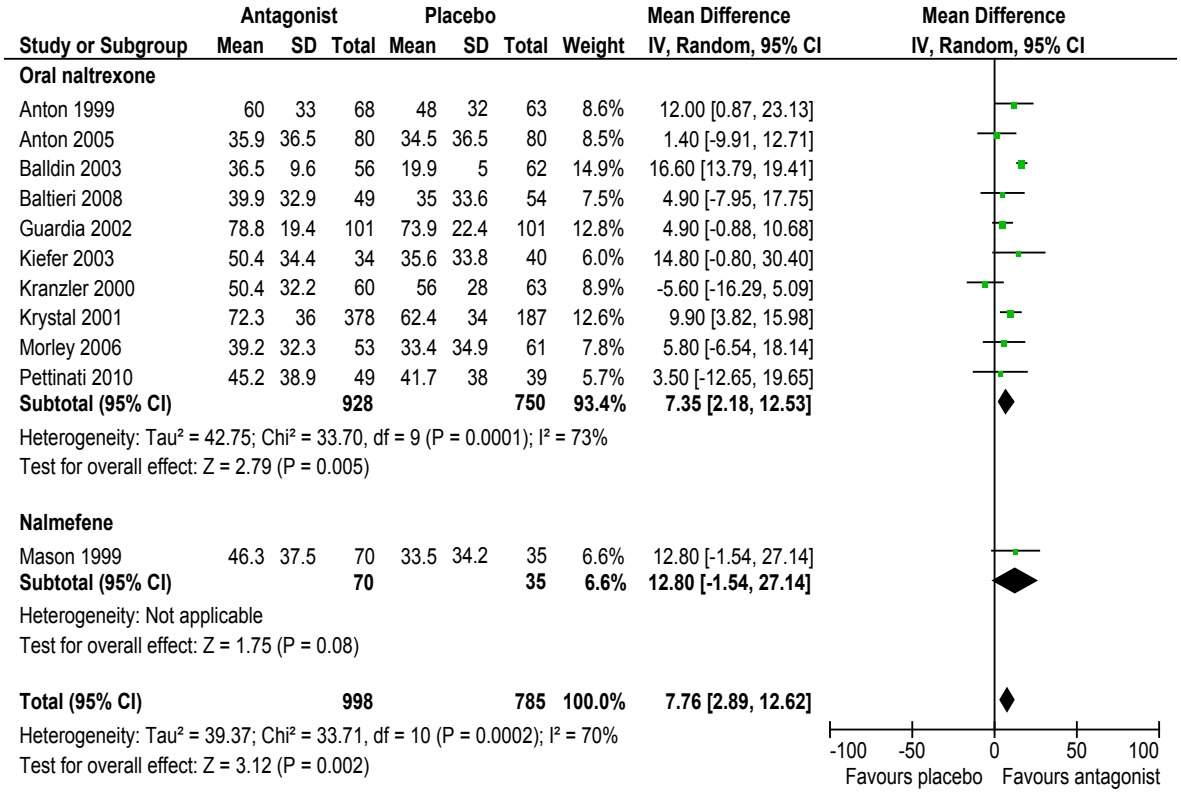
Like the meta-analysis (Figure 1.16) this suggests substantial variation between studies, with overall a small effect in favour of oral naltrexone.

Rubio 2005 reported a significantly longer time to relapse for oral naltrexone compared to no medication (mean difference 51 days, 95% CI 39.59, 62.41; P<0.001), and Landabaso 1999 reported a median survival to first relapse of 27 weeks for naltrexone, compared to 20 weeks for no medication (P<0.05)*.

One study reported a longer average time to relapse to heavy drinking for nalmefene compared with placebo, but the difference was not statistically significant (Figure 1.16: mean difference 12.80 days, 95% CI -1.54, 27.14; P=0.08)*. Anton 2004 reported similar findings for nalmefene compared with placebo, with a median

time to first heavy drinking day of 4 days for placebo and 9 days for nalmefene, and a median time to fourth heavy drinking day of 19 days for placebo and 31 days for nalmefene (P=0.14).

Figure 1.16: Opioid antagonist compared with placebo, average days to relapse



No data were reported for depot or implant preparations of naltrexone that were suitable for inclusion in meta-analyses. However, Kranzler 2004 reported a median time to first heavy drinking day of 11 days for naltrexone depot (95% CI 8, 17) compared with 6 days for placebo (95% CI 4, 10; P=0.05).

O'Malley 2007 looked at the effectiveness of naltrexone for alcohol dependent women (28% with an eating disorder). There were no significant differences in the time to the first drinking day, time to first day of heavy drinking, or the percentage of participants who continued to meet the criteria of alcohol dependence. However, naltrexone significantly delayed the time to second and third drinking days among those who did not maintain abstinence.

	Objective indicators of alcohol consumption
	Levels of GGT, or change in GGT are not significantly different for groups treated with opioid antagonists compared to those receiving placebo. This may indicate limitations in the sensitivity of GGT for the detection of changes in alcohol consumption in the population of alcohol dependent people.

Supporting evidence

Decreases in GGT or CDT over time with no significant difference between opioid antagonist and placebo were reported by 23 studies (Anton 2004; Brown 2009; Combine Study; Garbutt 2005; Hersh 1998; Kiefer 2003; Killeen 2004; Kranzler 1998; Kranzler 2000; Kranzler 2004; Lee 2001; Mason 1999; Monterosso 2001; Monti 2001; Morley 2006; Morris 2001; O'Malley 2003-3; O'Malley 2007; O'Malley 2008; Oslin 1997; Rubio 2002; and Volpicelli 1992).

Five studies reported that absolute levels of GGT were significantly lower, or decreased to greater extent, with opioid antagonist compared with placebo (Anton 2005; Balldin 2003; Chick 2000; Gastpar 2002; O'Malley 2003-2).

Karhuvaara 2007 reported that in the nalmefene group, GGT decreased, while levels increased in the placebo group despite the subjects reporting less drinking. At the time of study completion or discontinuation, 27% of placebo and 43% of nalmefene reported much or very much improvement.

Latt 2002 reported that 21 of 56 (37.5%) participants allocated to naltrexone and 11 of 51 (21.6%) allocated to placebo had abnormal (>65U/L) GGT levels at entry. At three months, 5 of 28 (17/9%) naltrexone and 4 of 30 (13.3%) placebo had abnormal GGT.

	Craving
**	Oral naltrexone treatment is associated with significantly lower average craving scores compared to placebo, but significant reductions in craving are not consistently observed.
	High levels of craving may be predictive of a greater degree of response to treatment with an opioid antagonist.
	More complex, or more specific, monitoring of craving may be needed to elucidate the effect of opioid antagonists on craving and the relationship between craving and alcohol consumption. Reward craving may be a more specific baseline indicator of likely response to opioid antagonist treatment.

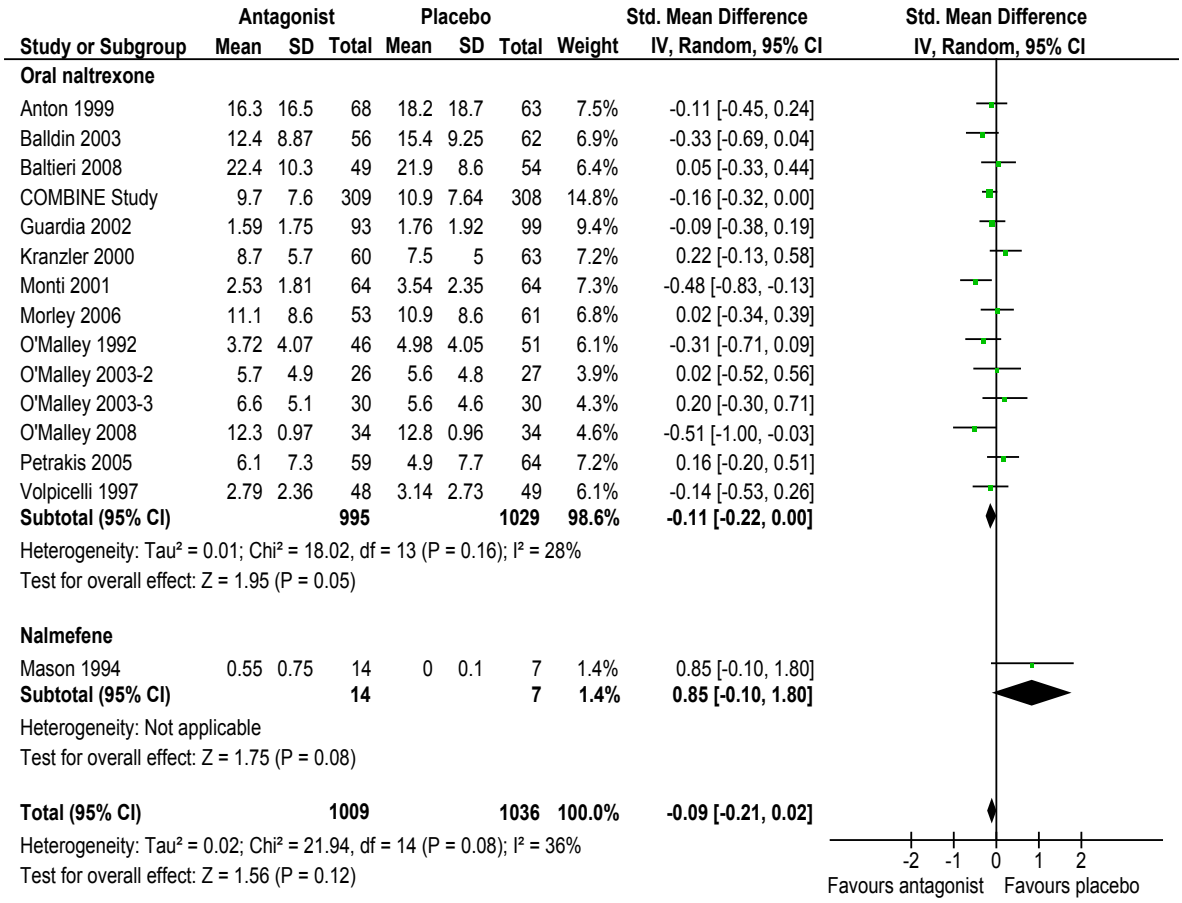
Supporting evidence

The effect of naltrexone on alcohol consumption may be due to reduction in craving and alteration of the sense of intoxication derived from alcohol consumption[132].

The only data on craving suitable for inclusion in meta-analyses was the average craving score, in most instances assessed with the Obsessive Compulsive Drinking Scale (OCDS).

The average craving scores during treatment were significantly lower with oral naltrexone compared with placebo (Figure 1.17: SMD -0.11, 95% CI -0.22, 0.00; P=0.05)**.

Figure 1.17: Opioid antagonist compared with placebo, average craving scores



One study reported significantly lower average craving scores for oral naltrexone compared with no medication (mean difference -6.00, 95% CI -10.58, -1.42; P=0.01)*. One study found no significant difference in average craving score for nalmefene compared with placebo (Figure 1.17: SMD 0.85, 95% CI -0.10, 1.80; P=0.08)*.

A number of studies reported on craving without reporting data suitable for inclusion in the above meta-analyses.

Six studies (Anton 2005; Chick 2000; Huang 2005; Lee 2001; Petrakis 2004; Volpicelli 1992) reported greater reductions in craving with opioid antagonist compared to placebo. In Anton 2005, all three factors of the OCDS decreased with time, but only the obsession factor decreased significantly more in participants treated with naltrexone.

Six studies (Anton 2004; Kiefer 2003; Killeen 2004; Mason 1999; Monterosso 2001; O'Malley 2001) reported decreases in craving over time with no significant differences between opioid antagonist and placebo. However, four studies (Gastpar 2002, Hersh 1998, Morley 2006, Oslin 1997) reported no significant difference in craving.

For the participants in O'Malley 1992 taking placebo, those with higher craving at baseline drank significantly more per occasion than those with lower baseline craving. However, for participants receiving naltrexone, level of baseline craving had no effect on the amount drunk per occasion.[83]

Volpicelli *et al*.[133] found significant interactions between naltrexone treatment, initial craving, and somatic distress and suggest that naltrexone may be useful for subjects who present with high levels of craving and somatic symptoms. Monterosso *et al*.[55] found greater medication efficacy among patients with higher levels of craving.

For a subset of participants from Morley 2006 with 80% compliance with medication[73], craving was a significant predictor of daily drinking and baseline levels of depression were the best predictor of daily craving (with no effect of treatment group). Daily alcohol consumption was best predicted by a model incorporating baseline dependence and depression scores and daily craving. However, Kiefer 2005A found no predictive value of baseline craving.

Secondary analysis of data from Petrakis 2005 have identified differences in responses to medication in terms of changes in craving according to the presence or absence of diagnoses of Antisocial Personality Disorder, Borderline Personality Disorder[110] and Post-Traumatic Stress Disorder.[109]

Participants in three studies (O'Malley 1992, Volpicelli 1992, Volpicelli 1997) reported a less-than-expected high when alcohol was consumed in conjunction with oral naltrexone indicating that this may be a factor. From Volpicelli 1992, 7 of 12 participants receiving naltrexone and 2 of 17 receiving placebo reported that the "high" produced by alcohol during the study was significantly less than usual.[125] In Volpicelli 1997, 11 of 22 NTX versus 7 of 28 placebo reported feeling a less-than-expected high from drinking.[129] Laboratory studies of social drinkers have also demonstrated that naltrexone decreases the reinforcing effects of alcohol.[131]

A subset of participants in O'Malley 1992 reported retrospectively on their subjective responses to their first episode of drinking. Compared to the subjects who received placebo, the subjects who received naltrexone reported lower levels of craving for alcohol and were more likely to give reasons for terminating drinking that were consistent with decreased incentive to drink. The authors consider this support for the hypothesis that a central effect of naltrexone is the modification of alcohol-induced craving.[85]

Overall, the findings of the studies included in this review point to greater reductions of craving associated with naltrexone treatment compared to placebo in some, but not all, people who are alcohol dependent.

It may be that average craving scores and the instruments used in these studies to assess craving are not sufficiently sensitive to the particular forms of craving that are responsive to opioid antagonist treatment (see *Typology and genetics of alcohol dependence*, pp3-5). The rationale for using opioid antagonists to treat alcohol dependence is that suppression of positive reinforcement mediated by opioid pathways will reduce alcohol consumption. The findings from three studies of a less-than-expected high from alcohol consumed in conjunction with oral naltrexone supports the validity of this mechanism. It may be that "reward craving"[18] would be a better baseline indicator of likely response to opioid antagonist treatment, and more complex monitoring of craving may be required to further elucidate responses to treatment.

1.2.3 Adverse effects

***	Treatment with oral naltrexone is associated with an increased risk of experiencing adverse effects, particularly nausea or vomiting, as well as neuropsychiatric symptoms (headache, daytime sleepiness).
**	The increased risk of adverse effects is reflected in a greater likelihood of dose reductions to manage adverse effects, and an increased risk of withdrawal from treatment due to adverse effects. However, the difference translates to an NNT of 33 which is not clinically significant.
*	Data on nalmefene and depot preparations of naltrexone are limited, but it appears that nalmefene, but not depot naltrexone, may also be associated with an increased incidence of adverse effects and an increased risk of withdrawal from treatment due to adverse effects.
	There is no significant difference between opioid antagonists and placebo in effect on serum levels of AST or ALT. Declines in AST and ALT reflect declines in alcohol consumption during treatment but also indicate that the incidence of hepatotoxic effects is not significant at the doses used in the studies included in this review.
	Elevations of liver enzymes can occur, albeit rarely, making monitoring of liver function advisable. In reported cases, levels resolved following discontinuation of medication.

Supporting evidence

The incidence of any adverse effects is significantly higher for participants who receive oral naltrexone compared to those receiving placebo (Figure 1.18: RR 1.11, 95% CI 1.02, 1.21; P=0.01)*** but there is no significant difference in the incidence of adverse effects for depot preparations of naltrexone (Figure 1.18: RR 1.02, 95% CI 0.91, 1.14; P=0.76)**. One study reported significantly more adverse effects with nalmefene compared to placebo (Figure 1.18: RR 1.18, 95% CI 1.09, 1.28; P<0.001)*.

In addition, five studies (Oslin 2005; Castro 2009; Niederhofer 2003A; Oslin 1997; Schmitz 2009) reported no significant differences in adverse effects. Oslin 2005 reported that new or worsening of adverse events during treatment was common, but none of the events were more common in the naltrexone compared to placebo group.

Oslin 1997 reported no significant differences in adverse effects for oral naltrexone compared to placebo in male veterans older than 50, and Niederhofer 2003A reported no significant difference in side effects of oral naltrexone compared to placebo for adolescents.

Petrakis 2004 reported no differences between groups on symptoms of psychosis and other adverse effects. This indicated that naltrexone was well tolerated in this group with comorbid schizophrenia and alcohol dependence.

Available data on reduction of doses of medication in response to adverse effects indicate that significantly more participants receiving oral naltrexone (Figure 1.19: RR 1.81, 95% CI 1.24, 2.64; P=0.002)** or nalmefene (Figure 1.19: RR 4.99, 95% CI 2.66, 9.36; P<0.001)* required a dose reduction, compared to those receiving placebo.

The occurrence of gastrointestinal symptoms is somewhat more likely with an opioid antagonist compared to placebo but the difference is not statistically significant (Figure 1.20: RR 1.29, 95% CI 0.97, 1.72; P=0.08)***. However, the occurrence of nausea or vomiting is significantly more likely with all forms of opioid antagonist compared to placebo (Figure 1.21: RR 1.96, 95% CI 1.75, 2.20; P<0.001)****. Neuropsychiatric symptoms (daytime sleepiness, headache, dizziness) are also significantly more likely with oral naltrexone compared to placebo (Figure 1.22: RR 1.20, 95% CI 1.00, 1.43; P=0.05)***.

Significantly more participants withdrew from treatment because of adverse effects with:

> oral naltrexone compared to placebo (Figure 1.23: RR 2.01, 95% CI 1.39, 2.91; P<0.001)***;

> nalmefene compared to placebo (Figure 1.23: RR 5.27, 95% CI 2.42, 11.48; P<0.001)*.

Only one study (COMBINE Study) reported data on withdrawal from treatment because of adverse effects for oral naltrexone compared to no medication, with no significant difference (RR 3.06, 95% CI 0.69, 13.50; P=0.14)*.

There was no significant difference in participants withdrawing from treatment because of adverse effects for depot naltrexone compared to placebo (Figure 1.23: RR 1.48, 95% CI 0.92, 2.39; P=0.11)**. In Garbutt 2005, 1% discontinued treatment due to injection site reactions.

Figure 1.18: Opioid antagonist compared with placebo, participants experiencing any adverse effects

Study or Subgroup	Antagonist Events	Antagonist Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Oral naltrexone						
Baltieri 2008	21	49	26	54	3.8%	0.89 [0.58, 1.36]
Chick 2000	81	85	71	78	11.3%	1.05 [0.96, 1.14]
Gastpar 2002	52	82	54	82	8.2%	0.96 [0.77, 1.21]
Heinala 2001	38	63	26	58	4.1%	1.35 [0.95, 1.91]
Kranzler 2000	55	61	51	63	7.6%	1.11 [0.96, 1.29]
Lee 2001	7	35	4	18	0.8%	0.90 [0.30, 2.67]
Morley 2006	37	53	29	61	4.1%	1.47 [1.07, 2.02]
Morris 2001	8	55	6	56	0.9%	1.36 [0.50, 3.66]
O'Malley 2003-2	14	56	16	57	2.4%	0.89 [0.48, 1.65]
O'Malley 2007	41	53	26	50	4.1%	1.49 [1.10, 2.02]
Petrakis 2004	16	16	15	15	2.4%	1.00 [0.89, 1.13]
Pettinati 2010	13	49	11	39	1.9%	0.94 [0.47, 1.86]
Subtotal (95% CI)		**657**		**631**	**51.6%**	**1.11 [1.02, 1.21]**
Total events	383		335			
Heterogeneity: Chi² = 16.38, df = 11 (P = 0.13); I² = 33%						
Test for overall effect: Z = 2.52 (P = 0.01)						
Depot or implant naltrexone						
Garbutt 2005	21	415	15	209	3.0%	0.71 [0.37, 1.34]
Johnson 2004	23	25	4	5	1.0%	1.15 [0.73, 1.81]
Kranzler 1998	7	15	2	5	0.5%	1.17 [0.35, 3.88]
Kranzler 2004	140	167	132	166	20.1%	1.05 [0.95, 1.17]
Subtotal (95% CI)		**622**		**385**	**24.7%**	**1.02 [0.91, 1.14]**
Total events	191		153			
Heterogeneity: Chi² = 2.06, df = 3 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.76)						
Nalmefene						
Karhuvaara 2007	230	242	130	161	23.8%	1.18 [1.09, 1.28]
Subtotal (95% CI)		**242**		**161**	**23.8%**	**1.18 [1.09, 1.28]**
Total events	230		130			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.96 (P < 0.0001)						
Total (95% CI)		**1521**		**1177**	**100.0%**	**1.11 [1.05, 1.17]**
Total events	804		618			
Heterogeneity: Chi² = 20.70, df = 16 (P = 0.19); I² = 23%						
Test for overall effect: Z = 3.59 (P = 0.0003)						

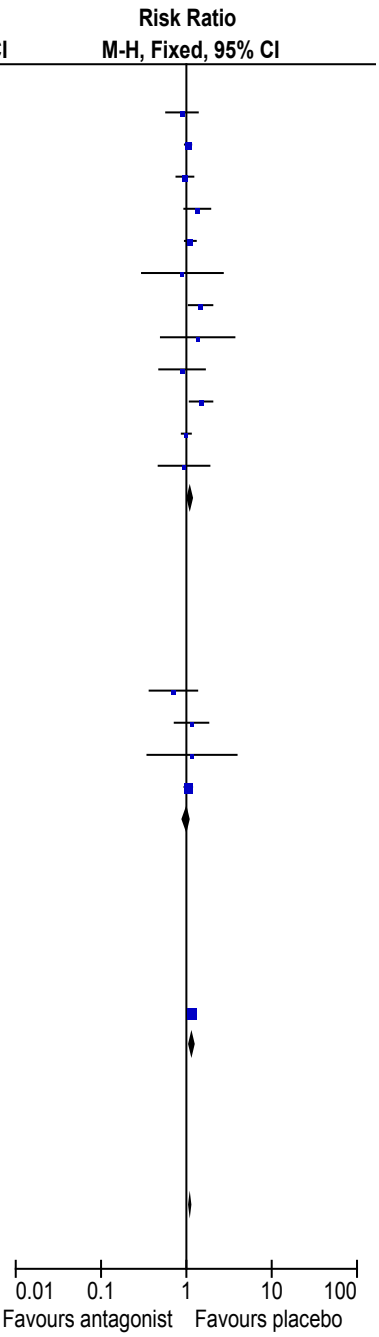


Figure 1.19: Opioid antagonist compared to placebo, participants requiring a dose reduction to manage adverse effects

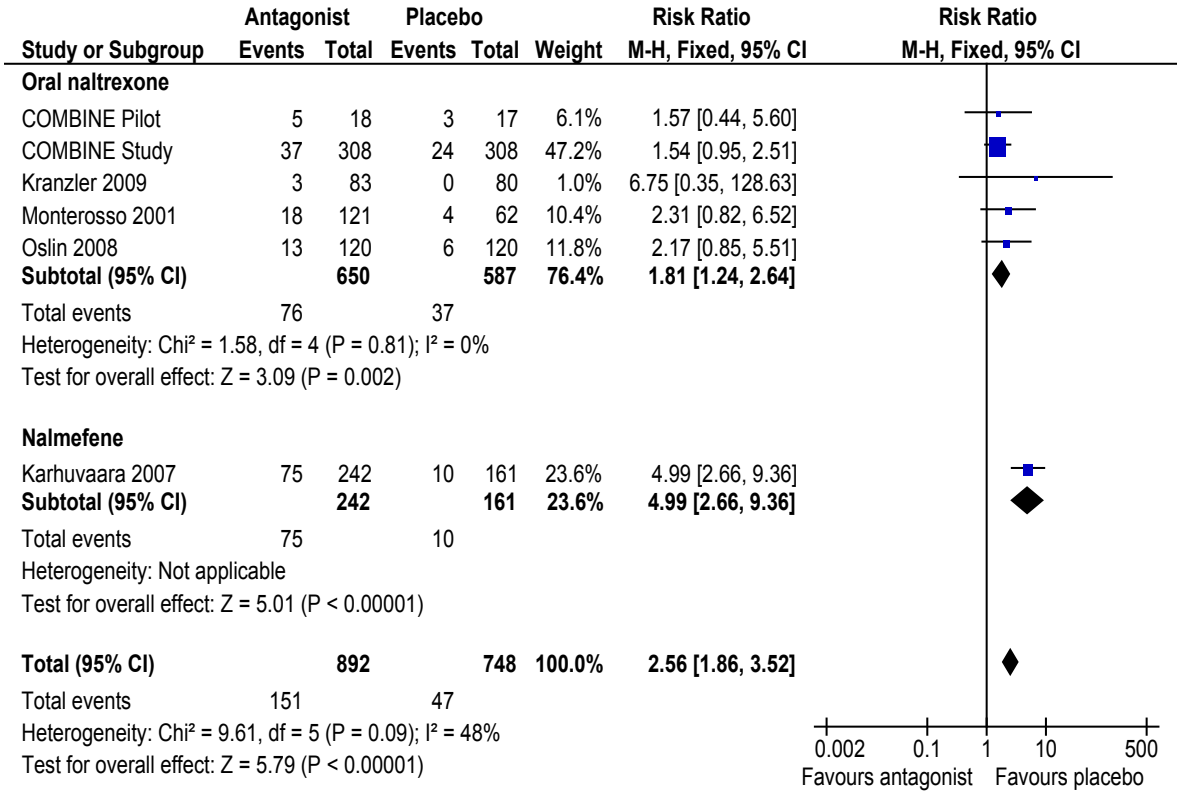


Figure 1.20: Opioid antagonist compared with placebo, participants experiencing gastrointestinal symptoms

Study or Subgroup	Antagonist Events	Antagonist Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Oral naltrexone						
Anton 1999	21	68	7	63	6.2%	2.78 [1.27, 6.09]
Balldin 2003	11	56	2	62	2.6%	6.09 [1.41, 26.29]
Baltieri 2008	0	49	3	54	0.8%	0.16 [0.01, 2.97]
COMBINE Pilot	10	18	10	17	8.3%	0.94 [0.53, 1.68]
COMBINE Study	92	308	108	308	12.4%	0.85 [0.68, 1.07]
Gastpar 2002	4	82	2	82	2.1%	2.00 [0.38, 10.62]
Guardia 2002	9	93	1	99	1.5%	9.58 [1.24, 74.16]
Kiefer 2003	1	40	3	40	1.3%	0.33 [0.04, 3.07]
Killeen 2004	4	51	2	36	2.2%	1.41 [0.27, 7.30]
Kranzler 2000	47	61	33	63	11.9%	1.47 [1.12, 1.93]
Morley 2006	7	53	1	61	1.5%	8.06 [1.02, 63.38]
O'Malley 2007	4	53	1	50	1.4%	3.77 [0.44, 32.62]
Petrakis 2004	8	16	9	15	7.6%	0.83 [0.44, 1.58]
Petrakis 2005	29	59	26	64	10.5%	1.21 [0.82, 1.79]
Pettinati 2008	4	52	6	54	3.6%	0.69 [0.21, 2.31]
Pettinati 2008a	21	82	18	82	8.6%	1.17 [0.67, 2.02]
Subtotal (95% CI)		**1141**		**1150**	**82.3%**	**1.29 [0.97, 1.72]**
Total events	272		232			
Heterogeneity: Tau² = 0.12; Chi² = 34.18, df = 15 (P = 0.003); I² = 56%						
Test for overall effect: Z = 1.77 (P = 0.08)						
Depot or implant naltrexone						
Garbutt 2005	49	415	18	209	9.0%	1.37 [0.82, 2.29]
Johnson 2004	6	25	0	5	0.9%	3.00 [0.19, 46.28]
Kranzler 2004	9	158	0	157	0.8%	18.88 [1.11, 321.63]
Subtotal (95% CI)		**598**		**371**	**10.7%**	**2.71 [0.59, 12.36]**
Total events	64		18			
Heterogeneity: Tau² = 0.94; Chi² = 3.77, df = 2 (P = 0.15); I² = 47%						
Test for overall effect: Z = 1.29 (P = 0.20)						
Nalmefene						
Karhuvaara 2007	13	242	16	161	6.9%	0.54 [0.27, 1.09]
Subtotal (95% CI)		**242**		**161**	**6.9%**	**0.54 [0.27, 1.09]**
Total events	13		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.71 (P = 0.09)						
Total (95% CI)		**1981**		**1682**	**100.0%**	**1.26 [0.97, 1.65]**
Total events	349		266			
Heterogeneity: Tau² = 0.13; Chi² = 43.52, df = 19 (P = 0.001); I² = 56%						
Test for overall effect: Z = 1.74 (P = 0.08)						

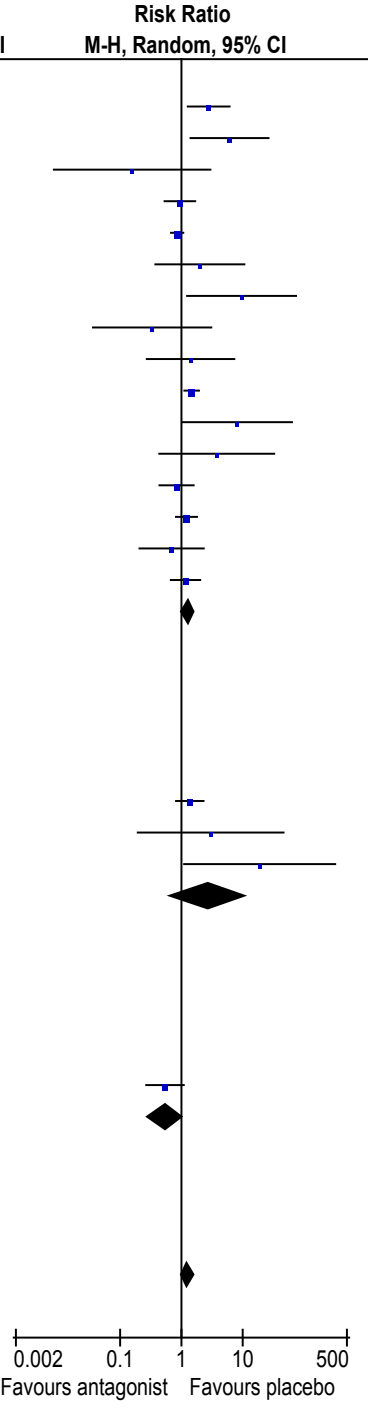


Figure 1.21: Opioid antagonist compared with placebo, participants experiencing nausea or vomiting

Study or Subgroup	Antagonist Events	Antagonist Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Oral naltrexone						
Ahmadi 2002	20	58	9	58	2.6%	2.22 [1.11, 4.46]
Anton 1999	23	68	9	63	2.7%	2.37 [1.19, 4.72]
Balldin 2003	2	49	4	54	1.1%	0.55 [0.11, 2.88]
Baltieri 2008	2	49	4	54	1.1%	0.55 [0.11, 2.88]
Chick 2000	27	85	13	78	3.9%	1.91 [1.06, 3.42]
COMBINE Pilot	10	18	8	17	2.3%	1.18 [0.62, 2.27]
COMBINE Study	101	308	65	308	18.5%	1.55 [1.19, 2.03]
de Goes e Castro 2004	8	35	3	36	0.8%	2.74 [0.79, 9.50]
Gastpar 2002	6	82	1	82	0.3%	6.00 [0.74, 48.74]
Heinala 2001	7	63	2	58	0.6%	3.22 [0.70, 14.89]
Kiefer 2003	1	40	1	40	0.3%	1.00 [0.06, 15.44]
Killeen 2004	10	51	3	36	1.0%	2.35 [0.70, 7.95]
Kranzler 2000	20	61	9	63	2.5%	2.30 [1.14, 4.64]
Kranzler 2009	31	83	3	80	0.9%	9.96 [3.17, 31.29]
Krystal 2001	32	418	9	209	3.4%	1.78 [0.86, 3.65]
Monti 2001	14	64	5	64	1.4%	2.80 [1.07, 7.32]
Morley 2006	8	53	3	61	0.8%	3.07 [0.86, 10.98]
Morris 2001	19	55	10	56	2.8%	1.93 [0.99, 3.78]
O'Malley 1992	17	52	7	52	2.0%	2.43 [1.10, 5.36]
O'Malley 2007	15	53	9	50	2.6%	1.57 [0.76, 3.26]
Oslin 1997	3	21	4	23	1.1%	0.82 [0.21, 3.25]
Oslin 2008	20	40	16	40	4.6%	1.25 [0.77, 2.04]
Petrakis 2004	7	16	6	15	1.8%	1.09 [0.48, 2.51]
Petrakis 2005	34	59	27	64	7.4%	1.37 [0.95, 1.96]
Pettinati 2008	20	52	14	54	3.9%	1.48 [0.84, 2.62]
Pettinati 2008a	44	82	22	82	6.3%	2.00 [1.33, 3.01]
Subtotal (95% CI)		**2015**		**1797**	**76.6%**	**1.82 [1.60, 2.07]**
Total events	501		266			
Heterogeneity: Chi² = 29.53, df = 25 (P = 0.24); I² = 15%						
Test for overall effect: Z = 9.06 (P < 0.00001)						
Depot or implant naltrexone						
Garbutt 2005	121	415	23	209	8.7%	2.65 [1.75, 4.01]
Johnson 2004	8	25	1	5	0.5%	1.60 [0.25, 10.11]
Kranzler 2004	23	158	17	157	4.9%	1.34 [0.75, 2.42]
Subtotal (95% CI)		**598**		**371**	**14.1%**	**2.16 [1.55, 3.01]**
Total events	152		41			
Heterogeneity: Chi² = 3.55, df = 2 (P = 0.17); I² = 44%						
Test for overall effect: Z = 4.58 (P < 0.00001)						
Nalmefene						
Anton 2004	36	197	7	68	3.0%	1.78 [0.83, 3.80]
Karhuvaara 2007	87	242	18	161	6.2%	3.22 [2.02, 5.13]
Mason 1999	9	70	0	35	0.2%	9.63 [0.58, 160.88]
Subtotal (95% CI)		**509**		**264**	**9.3%**	**2.89 [1.95, 4.27]**
Total events	132		25			
Heterogeneity: Chi² = 2.48, df = 2 (P = 0.29); I² = 19%						
Test for overall effect: Z = 5.31 (P < 0.00001)						
Total (95% CI)		**3122**		**2432**	**100.0%**	**1.96 [1.75, 2.20]**
Total events	785		332			
Heterogeneity: Chi² = 42.72, df = 31 (P = 0.08); I² = 27%						
Test for overall effect: Z = 11.44 (P < 0.00001)						

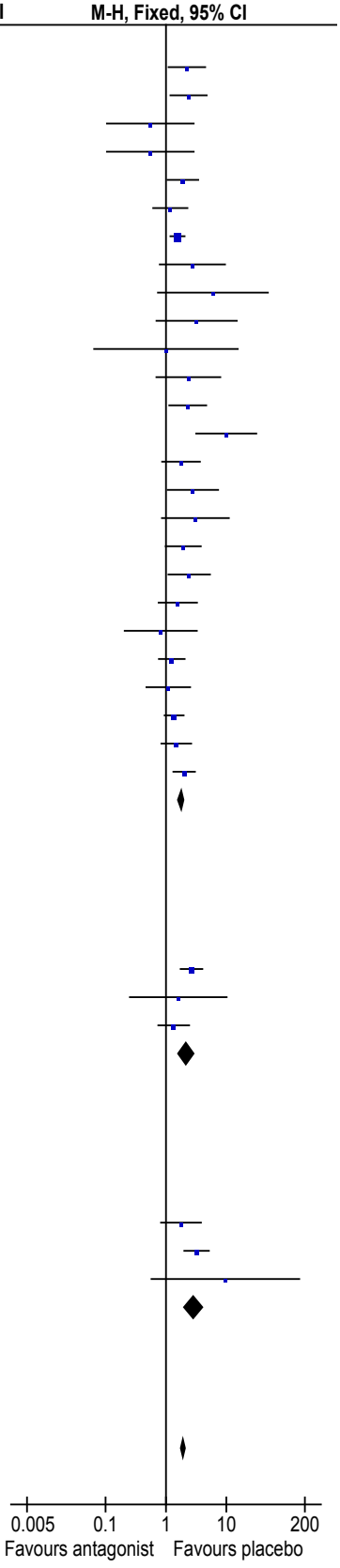


Figure 1.22: Opioid antagonist compared with placebo, participants experiencing neuropsychiatric symptoms

Study or Subgroup	Antagonist Events	Antagonist Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Oral naltrexone						
Ahmadi 2002	14	58	6	58	2.4%	2.33 [0.96, 5.65]
Anton 1999	31	68	17	63	5.2%	1.69 [1.04, 2.74]
Baltieri 2008	2	49	1	54	0.4%	2.20 [0.21, 23.56]
COMBINE Pilot	7	18	6	17	2.5%	1.10 [0.46, 2.62]
de Goes e Castro 2004	10	35	4	36	1.8%	2.57 [0.89, 7.44]
Gastpar 2002	9	82	10	82	2.6%	0.90 [0.39, 2.10]
Guardia 2002	8	93	1	99	0.5%	8.52 [1.09, 66.78]
Heinala 2001	6	63	10	58	2.2%	0.55 [0.21, 1.42]
Killeen 2004	10	51	2	36	1.0%	3.53 [0.82, 15.15]
Kranzler 2000	53	61	43	63	9.0%	1.27 [1.05, 1.55]
Kranzler 2009	11	83	0	80	0.3%	22.18 [1.33, 370.20]
Krystal 2001	53	418	24	209	5.6%	1.10 [0.70, 1.74]
Latt 2002	8	55	16	50	3.0%	0.45 [0.21, 0.97]
Morley 2006	5	53	12	61	2.0%	0.48 [0.18, 1.27]
Morris 2001	15	55	8	56	2.9%	1.91 [0.88, 4.14]
O'Malley 1992	18	52	8	52	3.1%	2.25 [1.07, 4.71]
O'Malley 2007	12	53	9	50	2.9%	1.26 [0.58, 2.73]
O'Malley 2008	20	34	16	34	5.5%	1.25 [0.79, 1.97]
Oslin 1997	6	21	6	23	2.1%	1.10 [0.42, 2.87]
Oslin 2008	16	40	21	40	5.3%	0.76 [0.47, 1.23]
Petrakis 2004	10	16	8	15	4.0%	1.17 [0.64, 2.15]
Pettinati 2008	33	52	29	54	7.2%	1.18 [0.86, 1.63]
Pettinati 2008a	49	82	52	82	8.4%	0.94 [0.74, 1.20]
Subtotal (95% CI)		**1592**		**1372**	**80.0%**	**1.20 [1.00, 1.43]**
Total events	406		309			
Heterogeneity: Tau² = 0.06; Chi² = 41.18, df = 22 (P = 0.008); I² = 47%						
Test for overall effect: Z = 1.97 (P = 0.05)						
Depot or implant naltrexone						
Garbutt 2005	78	415	34	209	6.6%	1.16 [0.80, 1.67]
Johnson 2004	8	25	1	5	0.7%	1.60 [0.25, 10.11]
Kranzler 1998	3	15	0	5	0.3%	2.63 [0.16, 43.63]
Kranzler 2004	37	158	33	157	6.0%	1.11 [0.74, 1.69]
Subtotal (95% CI)		**613**		**376**	**13.6%**	**1.15 [0.88, 1.51]**
Total events	126		68			
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 3 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.04 (P = 0.30)						
Nalmefene						
Anton 2004	54	197	8	68	3.4%	2.33 [1.17, 4.64]
Karhuvaara 2007	15	242	0	161	0.3%	20.67 [1.25, 342.97]
Mason 1999	12	70	7	35	2.6%	0.86 [0.37, 1.98]
Subtotal (95% CI)		**509**		**264**	**6.3%**	**2.07 [0.62, 6.98]**
Total events	81		15			
Heterogeneity: Tau² = 0.74; Chi² = 7.33, df = 2 (P = 0.03); I² = 73%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Total (95% CI)		**2714**		**2012**	**100.0%**	**1.22 [1.04, 1.42]**
Total events	613		392			
Heterogeneity: Tau² = 0.06; Chi² = 51.09, df = 29 (P = 0.007); I² = 43%						
Test for overall effect: Z = 2.49 (P = 0.01)						

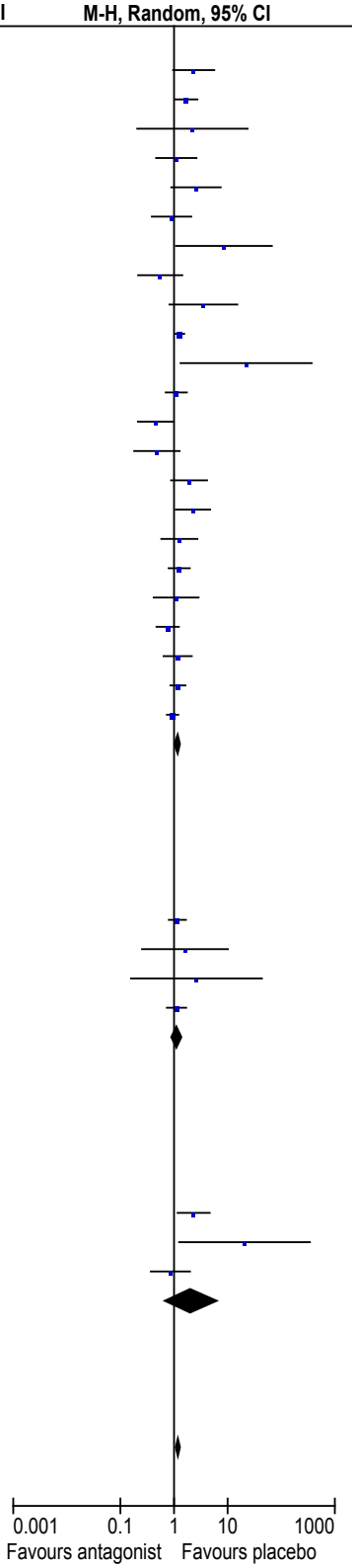
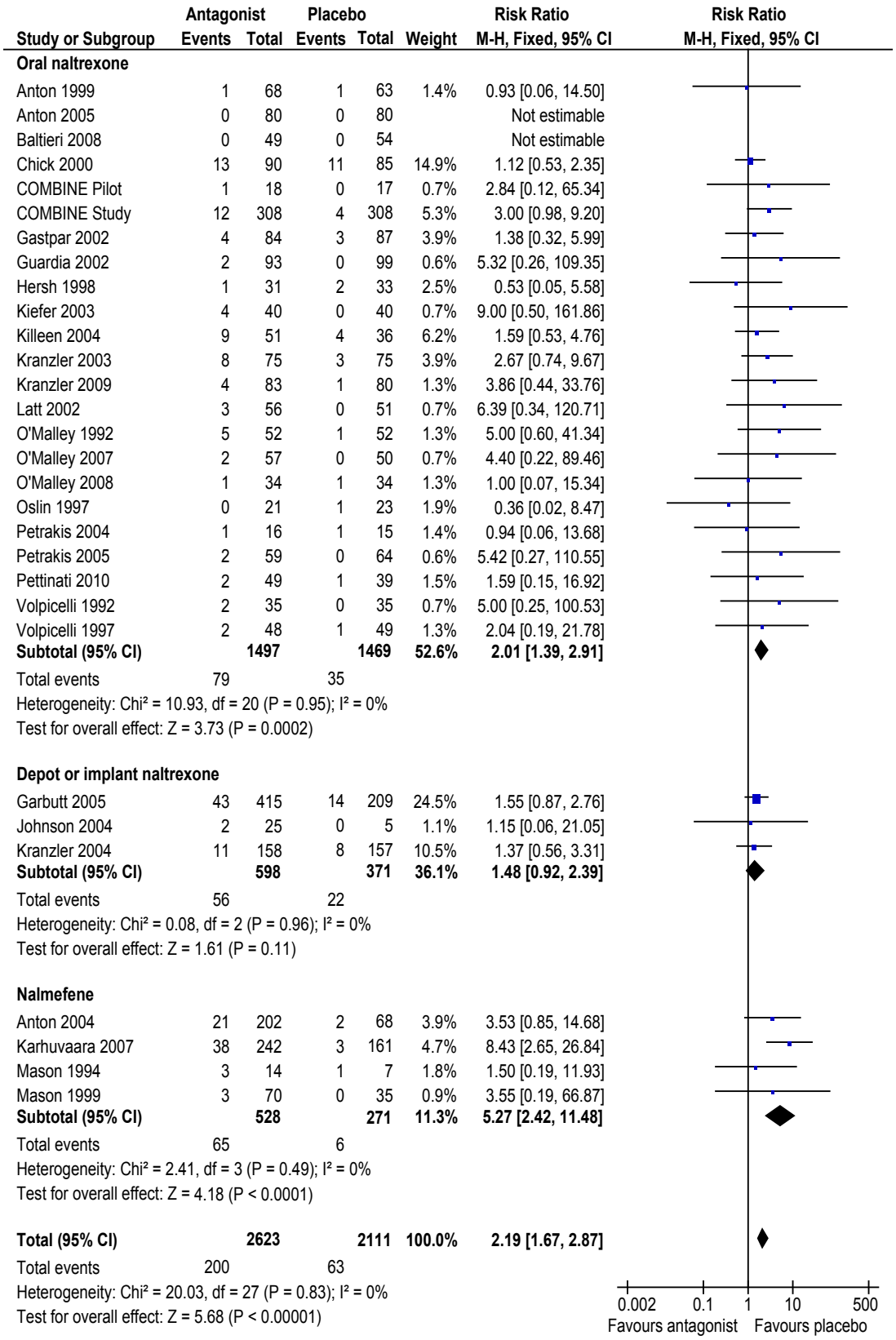


Figure 1.23: Opioid antagonist compared with placebo, Participants withdrawn from treatment due to adverse effects



The accuracy of estimates of the number of participants withdrawn from treatment due to adverse effects is reduced by the small numbers. Note that some studies reported no withdrawals in either group and were unable to be included in estimates of combined effect.

In addition to the adverse effects identified above, prescribing information warns of a potential risk of hepatotoxicity. This is based on a study in which naltrexone was administered to obese subjects at a dose of 300 mg/day. In that study, 5 of 26 naltrexone recipients, and none of the placebo group, developed elevations of serum transaminases after 3 to 8 weeks of treatment.[134]

This review uses data on AST and ALT levels as indicators of hepatotoxicity, with levels indicating both the effect of medication on hepatotoxicity, and reduced hepatotoxicity due to reduced alcohol consumption.

Twelve of 1383 participants (0.9%) in the Combine Study had treatment-emergent levels of liver enzymes (aspartate aminotransferase or alanine aminotransferase) greater than five times the upper limit of normal (most cases were in the naltrexone group). These effects resolved following discontinuation of medication. This is the only study large enough to detect an adverse effect at this low level of incidence.

No change, or a decline in AST and/or ALT levels with no significant group difference, was reported by 15 studies (Chick 2000; Garbutt 2005; Gastpar 2002; Hersh 1998; Johnson 2004; Killeen 2004; Latt 2002; Lee 2001; Monti 2001; Morley 2006; Morris 2001; Niederhofer 2003A; O'Malley 2003-3; O'Malley 2007; Oslin 1997).

A secondary analysis of data from Garbutt 2005[50] found that the administration of depot naltrexone to the subgroup of participants who continued to drink heavily throughout the study was not associated with increased levels of serum markers of liver injury. There was also no significant difference between depot naltrexone and placebo in rates of treatment-emergent liver chemistry tests in participants who were obese.

Three studies (Balldin 2003; Brown 2009; Karhuvaara 2007) reported greater reduction in AST and/or ALT associated with opioid antagonist treatment.

Mason 1994 reported only that the decrease in ALT in nalmefene groups paralleled the decrease in alcohol consumption.

Further discussion of adverse effects as a factor influencing treatment outcome, and approaches to management of adverse effects is provided in section 1.3.1.

1.3 Factors influencing treatment outcome

It has been noted that while the overall effectiveness of naltrexone is modest, for some individual patients the affect appears to be strong.[135] Factors that have been identified as potentially influencing the response to treatment with an opioid antagonist include:

- nature of adverse effects experienced;
- compliance with medication[8;35;131];
- type of adjunct psychosocial therapy[35;36] (considered in more detail in section 9)
- the treatment goal (total abstinence or controlled drinking);
- abstinence, or active drinking at commencement of treatment9
- comorbid mental health condition or use of other drugs[81];
- age of onset of drinking problems[81;135;136]
- gender[9;136]
- family history[81;135;136] and genetics[9;131;136].

It has not been possible to explore these factors through subgroup analyses of the studies that met the inclusion criteria for this review, but some qualitative analysis is presented in the following sections.

1.3.1 Adverse effects

	Neuropsychiatric adverse effects (tiredness, sleepiness, drowsiness) directly reduce retention, while gastrointestinal effects (abdominal pain, nausea, dry mouth) reduce compliance.
	It is the number and severity of adverse effects, and not just severity, that predicts early termination of treatment.
	Taking medication with meals, taking the dose at bedtime, and taking an antacid daily are strategies suggested for managing nausea and fatigue associated with opioid antagonist treatment.

Supporting evidence

Oncken *et al*.[137] looked at adverse effects experienced by participants in two randomised controlled trials who had been allocated to naltrexone. They found that neuropsychiatric adverse effects (tiredness, sleepiness, drowsiness) exerted little influence on medication compliance, but directly decreased the length of study retention. In contrast, the main effect of gastrointestinal effects was on medication compliance. Reduced compliance in turn negatively impacted on study retention, presumably due to a relapse to drinking.

Rohsenow *et al*.[67] looked at the impact of adverse effects on participants in Monti 2001. They found that the number and severity (but not severity alone) of side effects in the first week, particularly nausea and fatigue, predicted early termination.

Adverse effects are generally worst at the beginning of treatment. Anton 2004 reported a median time of 1-3 days to onset of adverse effects in active treatment groups. O'Malley 1992 also reported significant side effects were typically experienced immediately after the first dose, and Balldin 2003 indicated adverse effects were of short duration. Rohsenow *et al*.[67] reported the mean (±SD) duration of the four most common side effects: nausea 17.9±27.0 days; headache 10.1±14.8 days; dizziness 8.7±7.3 days; fatigue 17.7±20.8 days. They reported the most effective methods of managing nausea were advising patients to take their dose with meals, take their dose at bedtime, or take an antacid daily. Bedtime dosing was suggested to help with fatigue if side effects usually occur within two hours of a dose.

Wilkin and Hazelrigg[138] compared cohorts of oriental and white Americans in terms of response to naltrexone and alcohol. Abdominal discomfort and nausea associated with naltrexone pre-treatment (before an alcohol challenge) was reported by 8 of 20 oriental and 1 of 20 white Americans. It was therefore suggested that people of Asian ethnicity may be more susceptible to adverse effects than people of Caucasian background. Two studies included in this review (Huang 2005, Lee 2001) were undertaken in Asian countries. Huang 2005 did not report data on adverse effects; Lee 2001 was consistent with other studies in finding no significant difference between oral naltrexone and placebo in the number of participants experiencing any adverse effects. Lee 2001 described adverse effects as mild and self-limiting.

Budzynski *et al*.[139] note epidemiological studies suggesting that periods of abstinence in some patients with alcohol dependence may increase their cardiovascular risk via proatherogenic changes in plasma lipid levels. To investigate this aspect they looked at plasma lipid levels following a period of pharmacotherapy for relapse prevention in alcohol dependence. They found that naltrexone was associated with significant decreases in total cholesterol and triglycerides in plasma after 16 weeks. Budzynski *et al*. concluded that naltrexone, by its hypolipaemic effect, could decrease the cardiovascular risk in abstinent patients by lipid mechanisms. In contrast, carbamazepine, lithium and disulfiram had an unfavourable effect on lipids – the authors suggest these medications should be used with caution in patients with elevated lipid levels.

1.3.2 Compliance with medication

	A positive treatment response to naltrexone is more likely in those who are compliant to their medication regime (>80% tablets taken).
	There appears to be a significant placebo effect in trials comparing naltrexone and placebo, probably associated with expectations about medications, regular contact with treatment providers and associated psychosocial treatment.
	The effect of medication declines after cessation. Compliance needs to be maintained over a sufficiently long period for behavioural change to occur to increase the likelihood of sustained treatment effects.
	Depot and implant preparations, through a sustained duration of effect, may increase the period of exposure to medication.
*	Targeted medication may increase compliance by linking administration of medication to awareness of a high risk of alcohol consumption occurring.

Supporting evidence

Pettinati *et al*.[140], using data from Volpicelli 1992 and 1997, found that for patients who adhered to the prescribed treatment, relapse rates were lower with naltrexone than placebo (10% compared to 38.6%, P<0.001). For noncompliant patients, relapse rates were high and comparable between naltrexone- and placebo-treated patients (42.9% compared with 40%).

Chick *et al*.[87] found no significant difference between naltrexone and placebo in an intention-to-treat analysis, but reported a significant effect of naltrexone on alcohol consumption when analyses were based on compliant participants (80% tablet consumption and attendance at all follow-up appointments). Naltrexone patients who discontinued the trial during the first 6 weeks of the study had substantially higher rates of non-compliance with study medication than those who remained in treatment for more than 6 weeks. Oslin 2008 also reported a significant association between medication adherence and time to first relapse.

Regardless of medication or adjunct therapy, participants in Anton 2005 who were compliant with their medication did better than those who were not compliant. In Krystal 2001, patients who were more compliant with medication and those who attended more counselling or AA sessions had better outcomes, whether they took naltrexone or placebo. Davidson *et al*.[141] also found that greater compliance was a predictor of lower alcohol consumption independent of medication, and Oslin 2008 found that a low level of medication compliance was associated with poor outcome. Cramer *et al*.[142] from an analysis of data from an RCT comparing naltrexone with placebo[127], found that better control of drinking was demonstrated among higher compliers, but there was no significant effect of treatment at any compliance rate. Cramer *et al.* concluded that lack of treatment effect was not due to poor compliance.

There appeared to be a significant placebo effect in the COMBINE Study. Contributing factors to the placebo response may have included pill taking itself, the benefits of meeting with a medical professional, repeated advice to attend AA and optimism about a medication effect.[62]

The importance of the medication is indicated by follow-up data from one RCT[54]. This study found that once medication was discontinued, there was a gradual increase in relapse rates, heavy drinking days, and drinks per drinking day. By the end of the 14-week follow-up period, although naltrexone-treated subjects were, on average, still doing better than control subjects, the effectiveness of naltrexone was no longer statistically significant. O'Malley *et al*.[84] also found that some, but not all, of the benefits resulting from short-term naltrexone treatment persist after discontinuation of treatment. Naltrexone resulted in higher abstinence rates during treatment but this effect was no longer apparent by the second month of follow-up. The effect of naltrexone on relapse rates was more durable and persisted in a diminished fashion through month 4 of follow-up.[86] In the Combine Study, there was a decline in the percent days abstinence across the follow-up points post-treatment regardless of treatment condition. Previous treatment with medical management and either cognitive behavioural therapy or naltrexone or both, but not acamprosate, was associated with sustained efficacy beyond the discontinuation.

Rohsenow *et al*.[67], from a secondary analysis of Monti 2001, reported that compliance was not predicted by demographic or pretreatment alcohol use variables. The number and severity of side effects in the first week, particularly nausea and fatigue, predicted early termination. Compliance was not predicted by commitment to abstinence or self-efficacy about abstinence, but was greater among patients who believed more strongly that

the medication would help them stay sober. Compliance was not predicted by general level of urge to drink during the first week on medication but compliance was greater among those with a higher urge to drink in response to alcohol stimuli in the laboratory.

Kranzler *et al*.[143] used a database for an employee health care program in the USA to identify patients who had at least one medication claim for oral naltrexone, no claims for disulfiram or acamprosate in the three months prior to the earliest naltrexone claim, and at least one claim for an alcohol-related diagnosis in the 6 months before or 6 months after the earliest naltrexone claim. Of 1138 oral naltrexone patients identified, 85.8% failed to fill prescriptions for 80% or more of the 6-month treatment period. The majority (51.8%) filled only a single prescription.

Participants in a study by Davidson *et al*.[141] received naltrexone for six months or three months, followed by three months of placebo, with comparison of adjunct psychological therapy (see section 8). Medication compliance decreased from about 65% in the first three months to 30% in the second three months.

Interest in extended-release (depot) naltrexone relates to the potential to promote adherence to medication[9]. The use of extended release preparation decouples medication from compliance and motivation – medication is administered at a time of motivation and lasts over periods when compliance and motivation might not be maintained, such as holiday periods.[144]

Linking medication intake with drinking may improve compliance over daily dosing, providing the subject with a more active role in the treatment. It may also be easier for the subject to remember to take a tablet when he or she feels an urge to drink rather than to take a tablet every morning. In comparison with injectable depot formulations, simple administration and faster discontinuation of treatment, eg if opioid analgesia is needed, are potential advantages of the oral formulation. The duration of action of nalmefene after a single dose appears to be sufficiently long for targeted use.[57]

In Kranzler 2009, participants in the targeted naltrexone group drank 16.5% less per day and on 19% less days than other groups.

In Kranzler 2003, subjects in the targeted placebo group drank on average of 21.6% less each day than those in the daily placebo group. Subjects in the targeted naltrexone group drank 25.8% less on average each day than those in the daily placebo group.[120] The overall probability of drinking on a given day was 0.62 (compared with 0.86 during the pretreatment period). On days when individuals took a tablet (naltrexone or placebo), they were less likely to drink. Individuals with fewer pretreatment drinking days, a treatment goal of abstinence, or greater lifetime alcohol dependence symptoms had fewer drinking days. Patients in the targeted condition reported fewer drinking days with a 13.6% lower likelihood of drinking in comparison with the daily condition overall. The greatest beneficial effect of targeted administration occurred early in treatment, with a decline in effect over time.

1.3.3 Treatment goal

	Naltrexone may be effective in supporting reduced alcohol consumption in controlled drinking programs as well as in treatment with a goal of total abstinence but there are insufficient studies to form a view on the effectivess of opioid antagonist treatment in the context of controlled drinking compared to a goal of total abstinence.

Supporting evidence

The effect of naltrexone in modifying the response to alcohol consumption (O'Malley 1992, Volpicelli 1992, Volpicelli 1997) has led to suggestions that naltrexone may be of value in treatment with a goal of controlled drinking as well as treatment with a goal of total abstinence.

The concept of controlled drinking has at times been controversial.[145] Controlled drinking is now widely accepted as a goal of treatment[146;147] but often as an intermediate rather than a final goal, and generally only for people with lower severity of dependence and without significant risk factors. An abstinence goal is still preferred for those with more severe problems, higher levels and longer histories of alcohol consumption.[147;148]

A review of the effectiveness of controlled drinking programs is outside the scope of this review. The majority of studies included in this review were oriented towards total abstinence.

Participants in Kranzler 2003 were selected on the basis of heavy drinking, with people with moderate or severe alcohol dependence excluded from the study. Sensible drinking was selected as the treatment goal for 83.3% of participants in this study. The study also compared targeted (ie. use of medication in anticipation of

high-risk drinking situations) and daily medication, and naltrexone compared with placebo. Participants in the targeted condition, irrespective of whether they received naltrexone or placebo, reported 14% fewer drinking days than those in the daily condition. The effect was most evident during the first half of the study when participants in the targeted condition had more tablets per week to use. There was also a 24% reduction in the likelihood of heavy drinking among participants in the targeted condition.

Heinala 2001 compared two different counselling approaches, cognitive behavioural therapy that accepted some alcohol consumption (the coping groups, or "coping with drinking"), or supportive therapy that supported complete abstinence. Comparison of adjunct therapies is discussed further in section 9, but it is relevant to note here that at the end of 12 weeks, naltrexone was not better than placebo in the supportive groups, but it had a significant effect in the coping groups.

1.3.4 Abstinence at commencement of treatment

	A period of abstinence prior to treatment with naltrexone is predictive of a better response to treatment. Psychological aspects of preparedness for treatment, motivation, and support are likely to be factors underlying this outcome.

Supporting evidence

In Garbutt 2005, participants with several days of abstinence prior to treatment exhibited a greater treatment effect of depot naltrexone compared to placebo. In the subgroup of participants with 4 or more days of voluntary abstinence before treatment, the median time to first drink was 41 days for 380mg naltrexone, compared to 12 days for placebo, and the rate of continuous abstinence at the end of the study was 32% vs 11%. Outcomes for 190mg naltrexone were generally intermediate demonstrating a dose-response effect.

In Killeen 2004 there was a trend for dropouts to be actively drinking at the time of study entry (56% for dropouts compared to 38% for those who completed 12-week follow-up). The authors reanalysed data for participants who did or did not drink during the 2-week period between signing consent and commencing medication. Participants who were taking naltrexone and reported drinking just before the initiation of study medications did as well on drinking outcomes as participants who were abstinent immediately before initiation of study medications. In the treatment as usual and placebo groups, the entry drinkers had substantially poorer outcomes as compared with entry abstainers. The authors suggest that naltrexone may have preferential efficacy on the subgroup of alcohol-dependent individuals who are actively drinking while in treatment. However, the authors note that entry abstainers were at an advantage at study entry in that they were significantly more likely to have an inpatient hospitalisation immediately before entry into inpatient treatment.

In Hersh 1998 naltrexone was no more effective in subjects who had an initial period of abstinence but this was in a subpopulation with dual cocaine and alcohol dependence.

Monterosso 2001 identified drinking during the placebo lead-in week and familial loading of alcohol problems as covariates positively associated with clinical deterioration (ie. relapse to heavy drinking).

1.3.5 Comorbid mental health condition

	There is no clear evidence to indicate that the presence or degree of depression, or prescription of antidepressants, is predictive of response to naltrexone.
	One study has reported a greater response to naltrexone in people with more antisocial traits.
	Naltrexone is well tolerated by people with schizophrenia or schizoaffective disorder or bipolar disorder.

Supporting evidence

Jaffe *et al*.[83], from a secondary analysis of O'Malley 1992, found no relationship between naltrexone and pretreatment levels of alcohol dependence severity or psychopathology.

Morley 2006 found no significant benefit of naltrexone compared to placebo overall, but a significant beneficial treatment effect on time to first relapse was revealed for subjects with 'no depression' and for subjects with 'low dependence' allocated to naltrexone. The authors suggest this finding supports the efficacy of naltrexone in relapse prevention of alcoholism amongst those with low levels of clinical depression and alcohol dependence severity. However, a secondary analysis of Kiefer 2003 found that in alcohol addicts with high

depression scores, treatment with naltrexone was associated with significantly better outcome, compared to those with low depression scores.[24]

A secondary analysis of Krystal 2001 compared study participants on the basis of prescription of antidepressants in addition to naltrexone (or placebo). In patients randomised to placebo, prescription of antidepressants was associated with a significantly higher percentage of drinking days. For patients receiving naltrexone, there were no significant differences in drinking-related outcomes in the groups who did or did not receive antidepressants. Among the group of patients receiving antidepressants, naltrexone prescription was associated with a reduction in the percent drinking days compared to placebo.[128]

All participants in Oslin 2005 met criteria for alcohol dependence and depressive disorder (substance induced or primary major depression). A 12 month follow-up study[97] of participants found that initial full responders (defined by remission of depression and no relapse to heavy drinking) to treatment with naltrexone and sertraline had better overall treatment outcomes at six and 12 months, compared with partial responders and non-responders. The authors point to a need for maintenance strategies for full responders and treatment adaptations for those who do not respond fully.

A study by Petrakis *et al*.[103] is significant in that all the participants were all diagnosed with concomitant alcohol dependence and schizophrenia or schizoaffective disorder (stable on medication). A secondary analysis of data from this study found that naltrexone had no effect on cognitive functioning for patients with alcohol dependence and schizophrenia, and there was no relationship between change in alcohol consumption and change in cognitive functioning in patients with alcohol dependence and schizophrenia. While not detecting an improvement in cognitive functioning, the authors consider that the absence of a negative effect emphasises the safety of naltrexone in comorbid alcohol dependence and schizophrenia.[104] The study demonstrates the effectiveness of naltrexone for the treatment of alcohol dependence in this population group. Petrakis *et al.* note that the anti-emetic effect of antipsychotic medication may have reduced nausea associated with naltrexone, thereby helping with acceptability of medication.

Similarly, Brown 2009 found that naltrexone has potential value and acceptable tolerability for the treatment of alcohol dependence in patients with bipolar disorder.

1.3.6 Age at entry to treatment

	Naltrexone is suitable for a wide range of age groups.

Supporting evidence

Oslin *et al*.[149] looked at age as a factor predictive of outcome from naltrexone treatment. They compared subgroups of participants in a randomised controlled trial aged up to 55 years (n=143), or aged 55 years and older (n=40). They found that older participants were significantly more likely to complete the course of medication (85% vs 64.1%, p=0.004). Tolerance of naltrexone by older participants was reported as good with 45% of older and 52.1% of younger participants reporting nausea.

All participants in Niederhofer 2003a were adolescents (aged 15 to 19). This was a relatively small study (20 participants treated with naltrexone) but suggests that naltrexone is effective and well-tolerated in adolescents.

1.3.7 Gender

	There may be gender differences in the response to naltrexone but more information is needed to confirm the significance of the difference and the implications for treatment decisions.

Supporting evidence

Participants in a number of studies included in this review were all male, but only one study (O'Malley 2007) involved all female participants. This prevented any analysis to investigate the effect of gender.

In the Combine Study gender did not significantly affect response to any of the treatments.[59;150] A secondary analysis of Morley 2006 also found no significant gender effects.[74]

Garbutt 2005 reported greater treatment response in men for depot naltrexone compared to naltrexone. In a study comparing naltrexone and placebo in a group of non-treatment-seeking heavy drinkers,[136] naltrexone reduced the stimulating effects of alcohol in women but not men, without moderating any other measures.

Patients' experience of naltrexone-associated nausea may limit its effectiveness, via poor medication adherence, and this finding may be seen more frequently in women than in men. In Pettinati 2008A, men in

naltrexone treatment reduced their cocaine and alcohol use to a greater extent than those receiving placebo, whereas women taking naltrexone had poorer outcomes than the women taking placebo (but differences were not statistically significant). A secondary analysis[116] found that women were more likely to discontinue treatment when reporting severe pretreatment psychiatric problems or nausea while in treatment, whereas no significant predictors were associated with treatment discontinuation in men. This study used a higher than normal dose of naltrexone (150mg/day) and the authors suggest this high dose may be problematic for women.

Baros *et al*.[151] undertook a secondary analysis of data from Anton 1999 and Anton 2005 comparing outcomes for men and women receiving either naltrexone or placebo with CBT. The only baseline variable with a significant gender difference and an interaction of gender by treatment was drinks per drinking day which was lower for women. The effect size for naltrexone compared to placebo was similar for most outcomes in women and men. The authors suggest that the findings of gender differences in naltrexone response might have to do with sample size and/or endpoint drinking variables rather than any inherent pharmacological or biological differences in response.

1.3.8 Genetics, family history and typology of alcohol-related disorder

	The underlying mechanism of addiction, as indicated by genetics, family history and typology of alcohol-related disorder, appears to be an important factor determining response to naltrexone treatment. However practical implications of this remain to be determined.

Supporting evidence

Rohsenow *et al*.,[68] for a subset of participants in Monti 2001, found that the percentage of relatives with problem drinking moderated the effects of naltrexone on drinking such that naltrexone resulted in lower drinking rate only for patients with a higher percentage (20% or more) of relatives with problem drinking. Jaffe *et al*.,[83] in a secondary analysis of data from O'Malley 1992, also found that patients with a higher familial loading of alcohol problems benefited most from naltrexone therapy in terms of reduced heavy drinking during treatment. Tidey *et al*.[136] reported that, compared to placebo, naltrexone increased the time between drinks in non-treatment-seeking heavy drinkers with at least 20% of relatives with problem drinking. Compared to placebo, naltrexone also decreased urge levels in participants with younger age of alcoholism onset. Family history and age of onset did not significantly moderate the effects of naltrexone on any other measures.

In Rubio 2005 predictors of a positive response to naltrexone treatment were family history of alcoholism, early age at onset of drinking problems, and comorbid use of other drugs of abuse. Among the subjects not treated with naltrexone, the greater the number of predictor variables, the lower the rates of abstinence in the final 28 days of treatment, but this was not the case in patients treated with naltrexone. In other words, patients with onset of alcohol abuse before age 25, family history of alcoholism and history of abuse of other substances show poorer outcome, which can be attenuated by naltrexone treatment.

Krishnan-Sarin *et al*.[152] investigated alcohol consumption by alcohol dependent participants in a laboratory setting in response to a priming dose of alcohol after pretreatment with naltrexone (0, 50 or 100mg/day). In male drinkers 100mg naltrexone significantly decreased alcohol consumption in those with a family history of alcoholism, but increased drinking in those without a family history.

The various typologies of alcohol dependence incorporate age of onset and family history as distinguishing features and several studies have related response to opioid antagonist treatment to typology.

Kiefer *et al*.[24] used data from Kiefer 2003 to look at factors predictive of outcome. Pharmacological treatment was efficacious in type II (early-onset) alcoholics according to Cloninger. Applying Lesch's typological differentiation, acamprosate was shown to be mainly effective in type I (characterised by early withdrawal symptoms), whereas naltrexone revealed best treatment effects in type III (often associated with a family history of alcohol dependence) and type IV (characterised by cerebral damage during brain development).

In a secondary analysis of data from the Combine Study, among those receiving medical management without cognitive behavioural intervention (CBI), Type A alcoholics had better drinking outcomes with naltrexone than placebo, whereas medication condition did not influence outcomes significantly in the Type Bs. Age of onset was not significantly related to outcome. For those receiving CBI, no significant effects were found for either typology. These findings suggest that less severe alcoholics are more likely to benefit from naltrexone in the context of low-intensity psychosocial treatment. The findings are consistent with negative results of naltrexone trials such as Krystal 2001 which recruited primarily high-severity alcoholics but contrasts with other studies finding stronger naltrexone effects in early-onset alcoholics and among individuals with greater severity on a

number of univariate markers of severity or risk.

A secondary analysis of data from Kiefer 2003 and Rubio 2005 looked at outcomes by alcoholism type. Naltrexone associated with significantly longer time to first drink and time to relapse for Cloninger Type II but not Type I. Cloninger Type II associated with positive family history of alcoholism, early-onset of drinking problems, higher comorbidity with antisocial behaviours and a higher prevalence of other substance abuse. Differences in proportion of Type I & Type II subjects may be one explanation for variability between studies in response to naltrexone.

The relationship between family history of alcohol problems and a greater response to naltrexone has been the basis of considerable recent effort to relate variation in the opioid receptor genes to response to opioid antagonists. As naltrexone is an antagonist at the mu opioid receptor, most attention has been focused on OPRM1, the gene that encodes that receptor. In particular, there has been strong interest in a single nucleotide polymorphism in OPRM1 that changes the amino acid sequence of the 40th residue from asparagine to aspartate (denoted Asn40Asp), affecting the affinity of β-endorphin for the mu opioid receptor.[153]

Results have been mixed with some studies finding an association, while other studies found no support for an association between opioid receptor gene polymorphism and treatment response (Karhuvaara 2007[58], Krystal 2001[126], O'Malley 2008, Tidey 2008[136]). However, based on data from three randomised controlled trials, Oslin *et al*.[154] found that among alcoholics prescribed naltrexone, those carrying the Asp40 allele had significantly lower rates of relapse and took longer to resume heavy drinking than Asn40/Asn40 homozygotes. Kim *et al*.[155] similarly found a higher therapeutic effect of naltrexone in Korean alcohol-dependent individuals with the Asp40 compared to the Asn40 genotype.

Anton *et al*.[60] in an analysis of data from the Combine Study found that those with the Asp40 allele who were receiving medical monitoring only (no cognitive behavioural treatment) had a better response to naltrexone compared to placebo than did those with the Asn40/Asn40 genotype. There were no gene by medication interactions for those treated with both medical monitoring and cognitive behavioural intervention. This suggests that the significance of genetic factors may depend on the type of treatment.

Another secondary analysis of data from the Combine Study[156] found that naltrexone may not be effective in the treatment of alcohol dependence in African Americans. This may be due to the low prevalence of the Asn40Asp polymorphism in this population, but more data are needed on ethnic difference.

Mitchell *et al*.[157] reported that naltrexone significantly reduced alcohol consumption compared to placebo, in non-treatment-seeking heavy drinkers who were not receiving any treatment in addition to medication. The study found no interaction between naltrexone and Asp40 allele status. In another study[158] involving non-treatment seeking heavy drinkers, OPRM1 gene was found to moderate naltrexone's impact on alcohol cue reactivity. The authors suggested that naltrexone, under certain circumstances, may increase rather than decrease the urge to drink alcohol and variation in the OPRM1 gene may be a moderator of naltrexone's effects on cue-elicited urge to drink. However, relapse may be determined by factors other than, or in addition to urge, such as self-efficacy, coping skills etc. Hence the effect of naltrexone on cue reactivity in non-treatment seeking individuals needs to be distinguished from effect on relapse in treatment-seeking population.

Garbutt *et al*.[135] have taken the approach of looking at indicators of functional activity of the endogenous opioid system, one of which is the hedonic response to sweet taste. Sweet-liking subjects (SL) note increasing pleasantness of sucrose concentrations up to 2.0M, whereas sweet-disliking people (SDL) do not like sucrose concentrations about the 0.4M range. In a study, a group of alcohol dependent men and women were treated with naltrexone and motivational enhancement therapy. Treatment outcomes were related to SL/SDL phenotype, determined (blind) before treatment. There were no differences in retention rates, but SL patients took longer (14.1±6.0 compared to 10.1±4.3 days for SDL) to achieve three days of abstinence required before commencing medication. All patients demonstrated a sharp reduction in the percent of heavy drinking days during treatment but SL and SDL individuals differed significantly in their ability to abstain from alcohol. The median time to achieve two consecutive abstinent days was 10 times longer for SL compared to SDL patients. There was also an interaction between the SL/SDL phenotype and craving for alcohol such that SL patients with high levels of craving were more likely to achieve abstinence whereas SDL patients with high levels of craving were less likely to achieve abstinence.

SECTION 2: ACAMPROSATE

Overview

Rationale

By normalising hyperexcitability of the glutamate system, acamprosate should dampen negative affect and craving following cessation of alcohol consumption.

Comparisons

Acamprosate has been compared with placebo, no medication and naltrexone in randomised controlled trials.

Retention in treatment

Treatment with acamprosate is associated with significantly greater retention in treatment relative to placebo when participants are abstinent for four days or more prior to commencement of medication****. The difference translates to an NNT of 20, which is a relatively small benefit.

Acamprosate has no significant effect on completion of treatment, compared to placebo, when active drinking is possible at commencement of treatment*.

Acamprosate has no significant effect on completion of treatment compared to naltrexone**.

Abstinence

Treatment with acamprosate significantly increases the probability of total abstinence from alcohol during treatment relative to placebo (NNT=5)***.

Acamprosate had no significant effect on rates of continuous abstinence, compared to placebo, when active drinking was possible at the commencement of medication*.

There is no significant difference between acamprosate and naltrexone in rates of total abstinence from alcohol*.

Relapse to heavy drinking

Treatment with acamprosate significantly decreases the risk of relapse to heavy drinking compared with placebo***. The difference translates to an NNT of 11, meaning that for every 11 people treated with acamprosate, one less person can be expected to relapse during treatment than would be the case with placebo. The effect of acamprosate on relapse appears to be lost when active drinking is possible at commencement of medication*.

There is no significant difference between acamprosate and naltrexone in the risk of relapse to heavy drinking**.

The NNT values for abstinence (NNT=5) and prevention of relapse (NNT=11) suggest that the effect of acamprosate on relapse is largely through promotion of abstinence.

Amount of alcohol consumed

Based on limited data, it appears that acamprosate has little effect, compared to placebo, on the amount of alcohol consumed during treatment*.

One study found that acamprosate is associated with less alcohol consumption than treatment without medication.

Alcohol consumption during treatment may be greater with acamprosate than oral naltrexone, at least in terms of drinks per drinking day*.

Periods of abstinence or heavy drinking during treatment

Treatment with acamprosate is associated with significantly more days of abstinence compared to placebo, particularly when medication is commenced after four or more days of abstinence – for this subset of studies acamprosate is associated with 14% more treatment days of abstinence compared to placebo***.

There is no significant difference between acamprosate and placebo in terms of days of abstinence during treatment if active drinking is possible when medication is commenced*.

Compared to placebo, acamprosate appears to have little effect on heavy drinking days during treatment*.

Acamprosate and naltrexone appear to be associated with similar extents of abstinence during treatment.

Time to first drink and time to relapse

Treatment with acamprosate significantly prolongs the period of abstinence prior to recommencement of drinking. The additional time without alcohol consumption, relative to placebo, is around 21 days*.

There is no significant difference between acamprosate and naltrexone in terms of time to first drink*.

Compared to placebo, treatment with acamprosate does not prolong the interval between recommencement of drinking and relapse to heavy drinking*.

Naltrexone is more effective than acamprosate in delaying relapse to heavy drinking**. The additional time without relapse for naltrexone relative to acamprosate is around 9 days.

Objective indicators of alcohol consumption

Levels of GGT, or change in GGT, are not sufficiently sensitive measures to distinguish between acamprosate and placebo or naltrexone.

Data on the number of participants with GGT levels outside the normal range may be a more practical objective outcome indicator.

Craving

Treatment with acamprosate does not significantly reduce average craving levels relative to placebo, treatment without medication, or naltrexone.

Acamprosate may reduce craving for alcohol in a subgroup of alcohol dependent people, as indicated by greater proportions of study participants reporting no desire for alcohol with acamprosate compared to placebo.

Adverse effects

Compared with placebo, treatment with acamprosate is associated with an increased risk of adverse effects, particularly gastrointestinal symptoms (diarrhoea)***.

The increased risk of adverse effects is associated with a greater likelihood of dose reductions to manage adverse effects, and an increased risk of withdrawal from treatment due to adverse effects for acamprosate compared to placebo**. However, the difference translates to an NNT of 100 which is not clinically significant.

Compared to naltrexone, acamprosate is associated with significantly lower risk of adverse effects but there is no difference in the likelihood of a dose reduction to manage adverse effects or in the risk of withdrawal from treatment because of adverse effects**.

Very few studies reported data on liver function enzymes. Acamprosate appears to have little effect on liver function, other than through the effect on alcohol consumption.

Factors affecting treatment response

(a) Compliance

Poor compliance with acamprosate appears to be associated with a reduced treatment response. Factors related to compliance are unclear but may include the need for three daily doses of medication.

(b) Treatment goal

Acamprosate may be most effective if used to support a goal of total abstinence.

(c) Abstinence at commencement of treatment

It is possible to commence acamprosate prior to cessation of alcohol consumption but the effect of acamprosate on alcohol consumption is reduced when acamprosate is commenced without a prior period of abstinence (four days or more)***.

(d) Comorbid mental health disorder

Insufficient data are available to determine the significance of comorbid disorders as predictors of response to acamprosate treatment, or the effectiveness of acamprosate for treatment of alcohol dependence in populations with significant comorbid mental health disorders.

(e) Age and gender

Gender probably is not a factor influencing the response to acamprosate.

Insufficient data are available to determine the acceptability of acamprosate to different age groups.

(f) Family history and typology of alcohol dependence

Family history of alcoholism does not predict response to acamprosate.

Acamprosate may be more effective in people with Lesch Type I alcoholism, characterised by strong withdrawal symptoms.

2.1 Rationale for effect

Acamprosate (Campral®) is a synthetic derivative of homotaurine which is a structural analogue of GABA.[159] Acamprosate is thought to reduce glutamate transmission[160] by acting at the N-methyl-D-aspartate (NMDA) receptor complex,[4] possibly through interference with the binding of calcium channel blockers[8;161].

Chronic alcohol exposure is associated with decreased levels of gamma-amino butyric acid (GABA) transmission and increased glutamate activity.[160] When alcohol consumption is stopped, the glutamate system remains hyperexcitable, resulting in withdrawal symptoms.[35] Acamprosate appears to modulate glutamate hyperactivity,[8;161;162] which suggests that it could reduce a hyperglutaminergic state that may characterise some alcohol-dependent individuals.[9;163] Acamprosate may also modulate the endogenous opioid system.[164]

By reducing central nervous system hyperexcitability acamprosate diminishes the negative reinforcement of conditioned craving that follows cessation of drinking. In this way acamprosate may attenuate the physiological mechanisms that can prompt relapse.[8;36] Acamprosate is hypothesised to be effective in 'relief craving' where patients consume to avoid the negative feelings and mood states associated with withdrawal from alcohol or triggered by cues.[162] As such acamprosate is seen as useful in helping patients avoid initial alcohol consumption and enhancing treatment retention by attenuating protracted alcohol withdrawal.[37]

Based on a review of European studies of acamprosate, Mason *et al*.[36] concluded that acamprosate has a slow onset of action, requiring around a week to reach steady-state levels in the nervous system, but its effects on drinking behaviour persist after the treatment is completed.

Most studies of acamprosate use a dose of 2g/day, delivered in three divided doses. The COMBINE Study Research Group chose a higher dose (3g/day, in three divided doses) citing evidence that the effectiveness of acamprosate is dose-dependent.[52]

2.2 Evidence of effectiveness

Acamprosate has been compared with placebo in 26 studies, with no medication in four studies, and with naltrexone in seven studies (see Table 2.1). Brief information on the design of these studies is included in Appendix 1.

Table 2.1: Studies involving the use of acamprosate for relapse prevention treatment of alcohol dependence

Placebo comparison		No medication comparison	Naltrexone comparison
Baltieri 2004[165;166] Barrias 1997 [167] (Cited by [168, 169]) Besson 1998 [171] Borg 1994 (Cited by [168, 169]) Chick 2000A[176] Combine Pilot[52] Combine Study[15;22;37;59-63] Geerlings 1997 [181] Gual 2001 [183] Hammarberg 2009 [185;186] Kiefer 2003[24;111-113] Ladewig 1993 [190] Lhuintre 1985 [192]	Lhuintre 1990 [159] Mason 2006 [163;170] Morley 2006[72-74] Namkoong 2003 [173] Niederhofer 2003 [177] Paille 1995 [178] Pelc 1992 (Cited by [168, 169]) Pelc 1997 [182] Poldrugo 1997 [184] Roussaux 1996 [187] (Cited by [168, 169]) Sass 1996 [188;189] Tempesta 2000 [191] Whitworth 1996 [193]	Combine Pilot[52] Combine Study[15;22;37;59-63] Kiritze-Topor 2004 [172] Tolliver 2009[174]	Combine Pilot[52] Combine Study[15;22;37;59-63] Kiefer 2003[24;111-113] Laaksonen 2008 [175] Morley 2006[72;73] Narayana 2008 [179] Rubio 2001 [180]

There is some evidence that the response to acamprosate may be different when administered after several days of abstinence, compared to commencement while active drinking is occurring.[194] To assess the significance of a period of abstinence as a factor predictive of treatment response, the studies included in this review have been grouped according to whether participants were abstinent for four days or more, whether active drinking was possible, or whether drinking status was unclear when medication was commenced. Where sufficient data are available, meta-analyses are presented with these subgroups. The significance of prior abstinence as a factor predictive of treatment response is discussed in more detail in section 2.3.3.

2.2.1 Retention in treatment

****	Treatment with acamprosate is associated with significantly greater retention in treatment relative to placebo when participants are abstinent for four days or more prior to commencement of medication. The difference translates to an NNT of 20, which is a relatively small benefit.
*	Acamprosate has no significant effect on completion of treatment, compared to placebo, when active drinking is possible at commencement of treatment.
**	Acamprosate has no significant effect on completion of treatment compared to naltrexone.

Supporting evidence

Compared to placebo, acamprosate is associated with a significantly higher rate of completion of treatment (Figure 2.1: RR 1.06, 95% CI 1.00, 1.13; P=0.05)****; this difference translates to an NNT of 25 (95% CI 100, 12.5) which is a relatively small benefit. The effect of acamprosate on retention is somewhat more marked (NNT=20) in those studies where participants were abstinent for four days or more prior to commencement of medication (Figure 2.1: RR 1.08, 95% CI 1.01, 1.16; P=0.02)****, whereas there is no significant difference in rates of completion of treatment where active drinking is possible at commencement of treatment (Figure 2.1: RR 0.97, 95% CI 0.59, 1.60; P=0.91)*.

There is no significant difference in the rates of completion of treatment for patients receiving acamprosate compared to those receiving:

> no medication (Figure 2.2: RR 0.99, 95% CI 0.87, 1.13; P=0.90)*; or

> oral naltrexone (Figure 2.3: RR 0.96, 95% CI 0.90, 1.02; P=0.17)**.

Based on three studies, there is no significant difference in the average weeks in treatment for acamprosate compared to placebo (Figure 2.4: mean difference -0.06, 95% CI -1.95, 1.83; P=0.95).

Two studies reported the average weeks in treatment for acamprosate compared to naltrexone, with no significant difference overall (Figure 2.5: mean difference -4.20, -13.58, 5.18; P=0.38). Rubio 2001 reported a significantly longer time in treatment for naltrexone compared to acamprosate, but participants in this study were abstinent for an average of 16 days when medication was commenced, compared to an average of five days.

Figure 2.1: Acamprosate compared with placebo, number of participants completing treatment

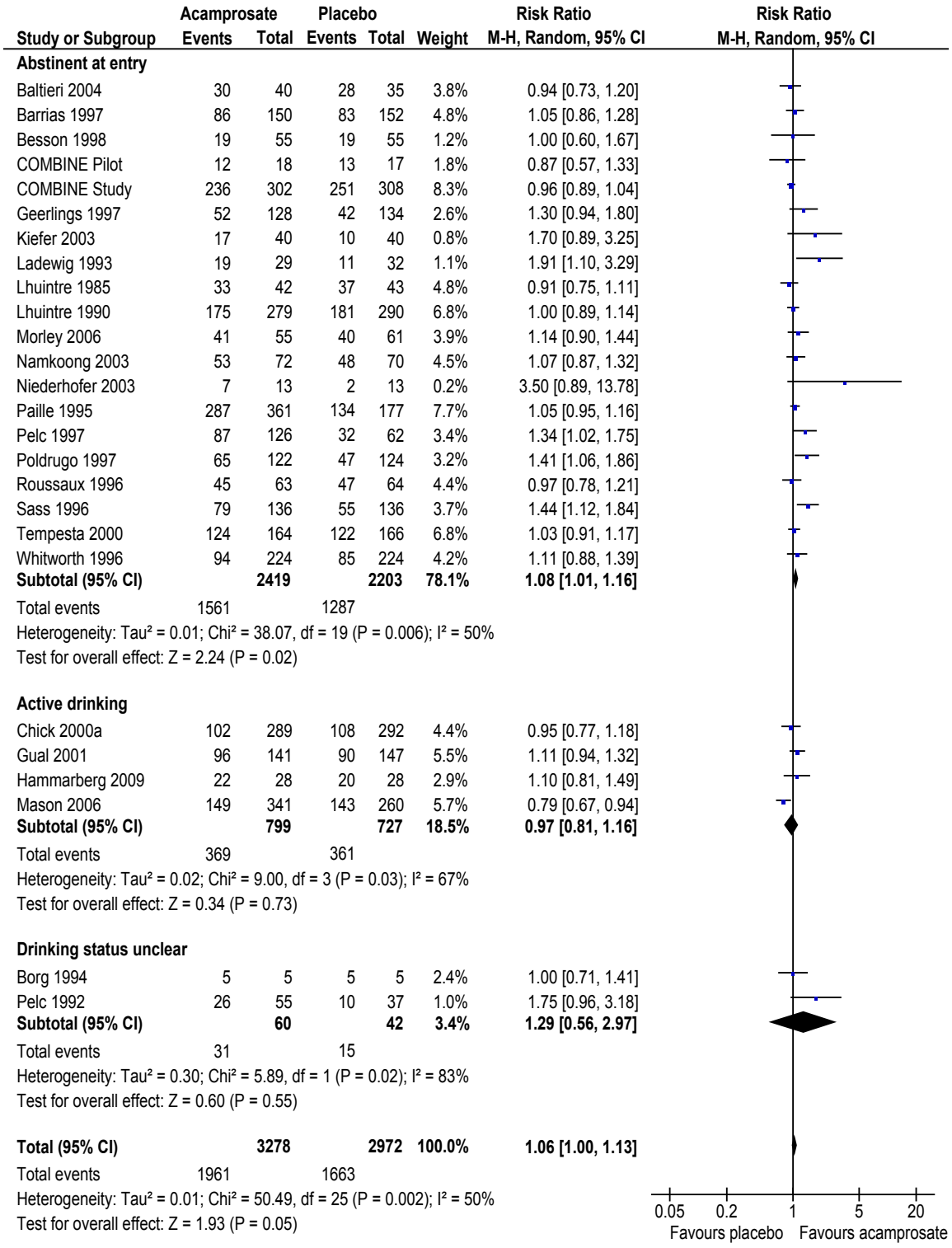


Figure 2.2: Acamprosate compared with no medication, number of participants completing treatment

Study or Subgroup	Acamprosate Events	Acamprosate Total	No medication Events	No medication Total	Weight	Risk Ratio M-H, Random, 95% CI
COMBINE Pilot	12	18	15	19	9.2%	0.84 [0.57, 1.26]
COMBINE Study	236	302	111	157	41.3%	1.11 [0.98, 1.24]
Kiritze-Topor 2004	169	211	179	211	48.0%	0.94 [0.86, 1.03]
Tolliver 2009	2	4	4	5	1.5%	0.63 [0.21, 1.83]
Total (95% CI)		**535**		**392**	**100.0%**	**0.99 [0.87, 1.13]**
Total events	419		309			

Heterogeneity: Tau² = 0.01; Chi² = 5.95, df = 3 (P = 0.11); I² = 50%
Test for overall effect: Z = 0.13 (P = 0.90)

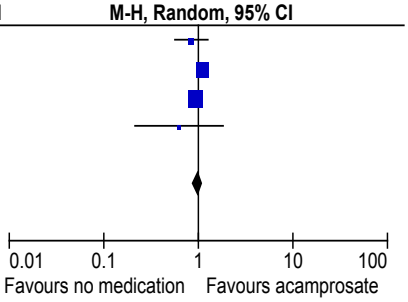


Figure 2.3: Acamprosate compared with naltrexone, number of participants completing treatment

Study or Subgroup	Acamprosate Events	Acamprosate Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
COMBINE Pilot	12	18	10	18	2.1%	1.20 [0.71, 2.03]
COMBINE Study	236	302	246	308	51.4%	0.98 [0.90, 1.06]
Kiefer 2003	17	40	22	40	4.6%	0.77 [0.49, 1.22]
Laaksonen 2008	58	81	64	81	13.5%	0.91 [0.76, 1.08]
Morley 2006	41	55	36	53	7.7%	1.10 [0.86, 1.40]
Narayana 2008	28	40	26	37	5.7%	1.00 [0.74, 1.33]
Rubio 2001	62	80	69	77	14.8%	0.86 [0.75, 1.00]
Total (95% CI)		**616**		**614**	**100.0%**	**0.96 [0.90, 1.02]**
Total events	454		473			

Heterogeneity: Chi² = 5.51, df = 6 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)

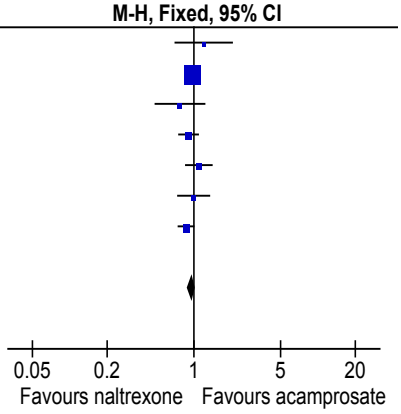


Figure 2.4: Acamprosate compared with placebo, average weeks in treatment

Study or Subgroup	Acamprosate Mean	Acamprosate SD	Acamprosate Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Geerlings 1997	14.57	10.14	128	12.57	10.43	134	26.1%	2.00 [-0.49, 4.49]
Mason 2006	16.24	9.51	341	18	9.67	260	36.0%	-1.76 [-3.31, -0.21]
Morley 2006	8.71	3.71	55	8.57	3.86	61	37.9%	0.14 [-1.24, 1.52]
Total (95% CI)			**524**			**455**	**100.0%**	**-0.06 [-1.95, 1.83]**

Heterogeneity: Tau² = 1.97; Chi² = 7.08, df = 2 (P = 0.03); I² = 72%
Test for overall effect: Z = 0.06 (P = 0.95)

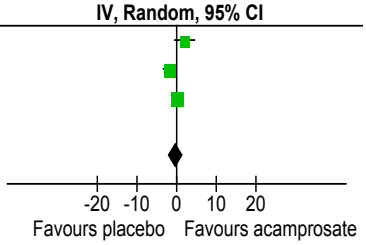
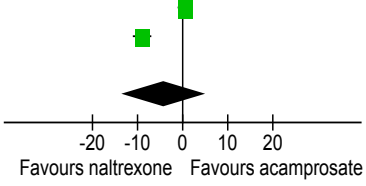


Figure 2.5: Acamprosate compared with naltrexone, average weeks in treatment

Study or Subgroup	Acamprosate Mean	Acamprosate SD	Acamprosate Total	Naltrexone Mean	Naltrexone SD	Naltrexone Total	Weight	Mean Difference IV, Random, 95% CI
Morley 2006	8.71	3.71	55	8.14	4.29	53	50.2%	0.57 [-0.95, 2.09]
Rubio 2001	35	6	80	44	6	77	49.8%	-9.00 [-10.88, -7.12]
Total (95% CI)			**135**			**130**	**100.0%**	**-4.20 [-13.58, 5.18]**

Heterogeneity: Tau² = 45.03; Chi² = 60.45, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.88 (P = 0.38)



2.2.2 Effect on alcohol consumption

	Total abstinence
***	Treatment with acamprosate significantly increases the probability of total abstinence from alcohol during treatment relative to placebo (NNT=5).
*	Acamprosate had no significant effect on rates of continuous abstinence, compared to placebo, when active drinking was possible at the commencement of medication.
*	There is no significant difference between acamprosate and naltrexone in rates of total abstinence from alcohol.

Supporting evidence

For all studies combined, significantly more people treated with acamprosate, compared to placebo, were continuously abstinent from alcohol during treatment (Figure 2.6: RR 1.52, 95% CI 1.30, 1.78; P<0.001)***. This translates to an NNT of 5 (95% CI 17, 3), indicating that for every five people treated with acamprosate, one additional person will be abstinent throughout the treatment period.
For the three studies where active drinking was possible at commencement of medication, there was no significant difference between acamprosate and placebo in the likelihood of continuous abstinence during treatment (Figure 2.6: RR 0.97, 95% CI 0.59, 1.60; P=0.91)*.

Based on three studies, there is no significant difference between acamprosate and naltrexone in the number of participants continuously abstinent during treatment (Figure 2.7: RR 0.95, 95% CI 0.73, 1.22; P=0.67)*.

Significantly more people treated with acamprosate were abstinent after three months of treatment, or at the completion of treatment, compared to those receiving placebo (Figure 2.8: RR 1.43, 95% CI 1.28, 1.60; P<0.001)***. This translates to an NNT of 7 (95% CI 10, 5). No data were reported for studies where participants may have been actively drinking when medication was commenced.

No data were reported on this outcome for acamprosate compared with no medication and only one study (Rubio 2001) reported data for acamprosate compared with naltrexone. In this study significantly more people treated with naltrexone were abstinent at the end of treatment, compared to acamprosate (RR 0.52, 95% CI 0.34, 0.78; P=0.002)*.

	Relapse to heavy drinking
***	Treatment with acamprosate significantly decreases the risk of relapse to heavy drinking compared with placebo. The difference translates to an NNT of 11, meaning that for every 11 people treated with acamprosate, one less person can be expected to relapse during treatment than would be the case with placebo.
*	The effect of acamprosate on relapse appears to be lost when active drinking is possible at commencement of medication.
**	There is no significant difference between acamprosate and naltrexone in the risk of relapse to heavy drinking.
	The NNT values for abstinence (NNT=5) and prevention of relapse (NNT=11) suggest that the effect of acamprosate on relapse is largely through promotion of abstinence.

Supporting evidence

For all studies combined, participants treated with acamprosate were significantly less likely to relapse during treatment compared to those receiving placebo (Figure 2.9: RR 0.83, 95% CI 0.75, 0.93; P=0.001)***. This is equivalent to an NNT of 11 (95% CI 7, 25).

For the three studies where active drinking was possible at commencement of medication, there was no significant difference between acamprosate and placebo in the likelihood of relapse (Figure 2.9: RR 0.98, 95% CI 0.86, 1.12; P=0.76).*

Only one study (Combine Study) reported data for acamprosate compared to no medication, with those treated with acamprosate being significantly less likely to relapse during treatment (RR 0.88, 95% CI 0.79, 0.99; P=0.03)*.

Figure 2.6: Acamprosate compared with placebo, number of participants continuously abstinent during treatment

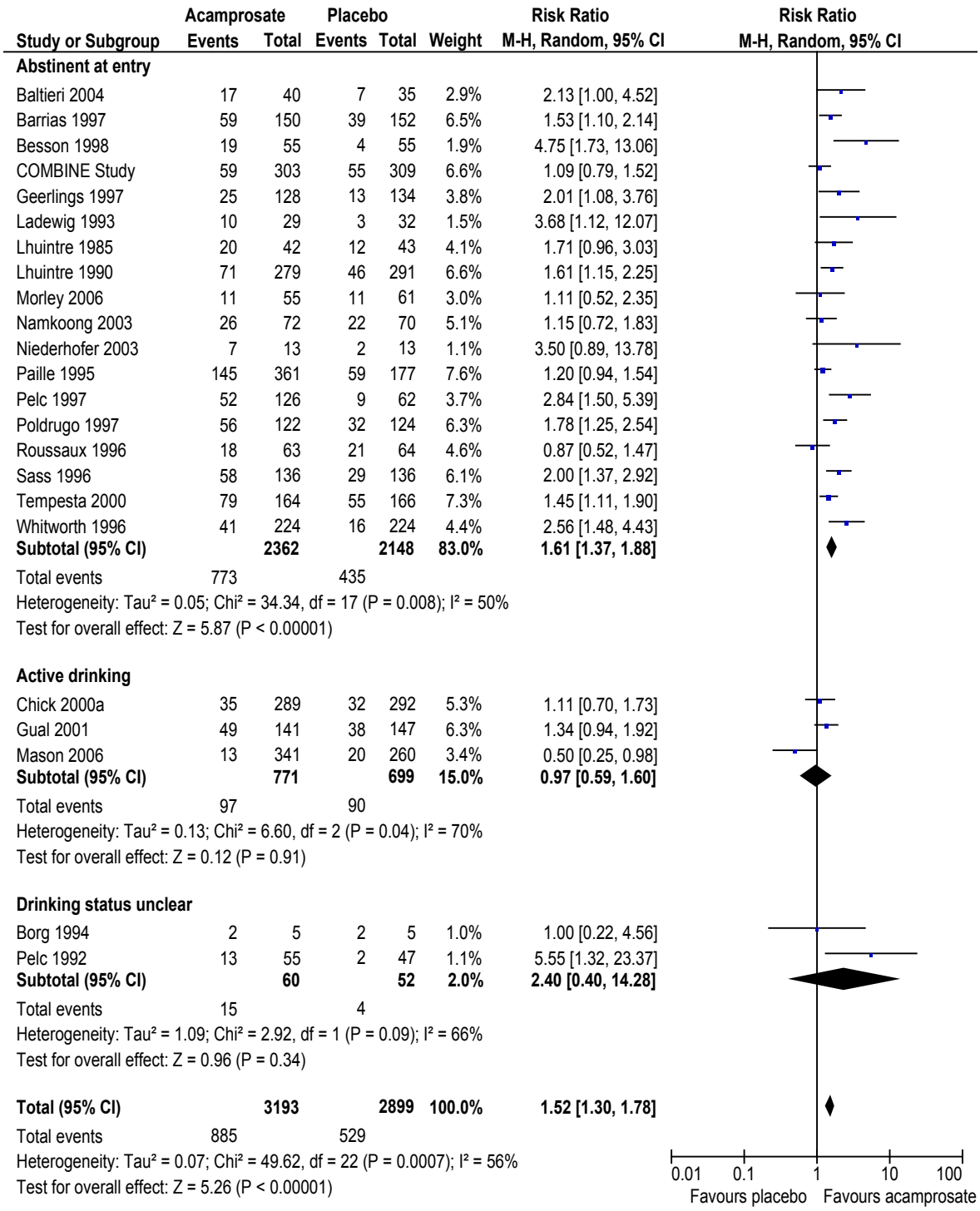


Figure 2.7: Acamprosate compared with naltrexone, number of participants continuously abstinent during treatment

Study or Subgroup	Acamprosate Events	Acamprosate Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Random, 95% CI
COMBINE Study	59	303	68	309	66.9%	0.88 [0.65, 1.21]
Morley 2006	11	55	9	53	10.2%	1.18 [0.53, 2.61]
Narayana 2008	17	40	15	37	22.9%	1.05 [0.62, 1.78]
Total (95% CI)		**398**		**399**	**100.0%**	**0.95 [0.73, 1.22]**
Total events	87		92			

Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.67)

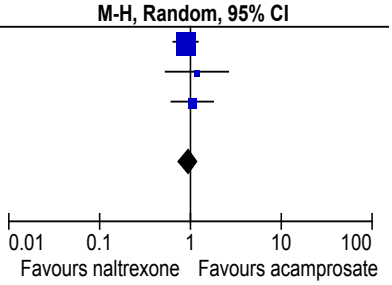


Figure 2.8: Acamprosate compared with placebo, number of participants abstinent after 3 months of treatment or at end of the study

Study or Subgroup	Acamprosate Events	Acamprosate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Besson 1998	29	55	18	55	5.5%	1.61 [1.02, 2.54]
Geerlings 1997	43	128	30	134	8.9%	1.50 [1.01, 2.23]
Lhuintre 1985	20	42	12	43	3.6%	1.71 [0.96, 3.03]
Niederhofer 2003	7	13	2	13	0.6%	3.50 [0.89, 13.78]
Paille 1995	174	361	70	177	28.6%	1.22 [0.99, 1.51]
Pelc 1997	60	126	16	62	6.5%	1.85 [1.16, 2.92]
Poldrugo 1997	59	122	40	124	12.1%	1.50 [1.10, 2.05]
Sass 1996	61	136	34	136	10.3%	1.79 [1.27, 2.53]
Tempesta 2000	96	164	79	166	23.9%	1.23 [1.00, 1.51]
Total (95% CI)		**1147**		**910**	**100.0%**	**1.43 [1.28, 1.60]**
Total events	549		301			

Heterogeneity: Chi² = 9.55, df = 8 (P = 0.30); I² = 16%
Test for overall effect: Z = 6.42 (P < 0.00001)

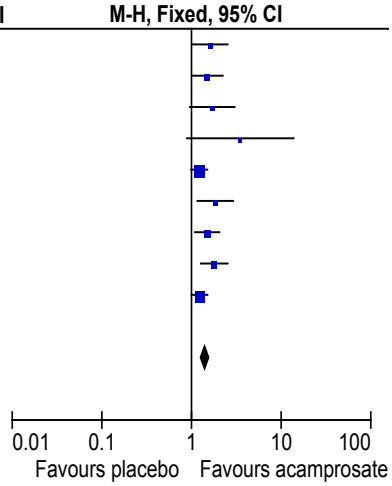


Figure 2.9: Acamprosate compared with placebo, number of participants relapsing during treatment

Study or Subgroup	Acamprosate Events	Acamprosate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Abstinent at entry						
Besson 1998	11	55	19	55	2.4%	0.58 [0.30, 1.10]
COMBINE Study	211	302	226	308	12.7%	0.95 [0.86, 1.05]
Geerlings 1997	84	128	104	134	11.0%	0.85 [0.72, 0.99]
Kiefer 2003	17	40	30	40	4.8%	0.57 [0.38, 0.85]
Lhuintre 1985	13	33	25	37	3.8%	0.58 [0.36, 0.94]
Morley 2006	40	55	43	61	8.7%	1.03 [0.82, 1.30]
Namkoong 2003	43	72	42	70	7.6%	1.00 [0.76, 1.30]
Niederhofer 2003	1	13	6	13	0.3%	0.17 [0.02, 1.20]
Pelc 1997	15	126	10	62	1.9%	0.74 [0.35, 1.55]
Poldrugo 1997	20	122	29	124	3.4%	0.70 [0.42, 1.17]
Sass 1996	75	136	102	136	10.2%	0.74 [0.61, 0.88]
Subtotal (95% CI)		**1082**		**1040**	**66.6%**	**0.81 [0.71, 0.93]**
Total events	530		636			
Heterogeneity: Tau² = 0.02; Chi² = 23.04, df = 10 (P = 0.01); I² = 57%						
Test for overall effect: Z = 3.06 (P = 0.002)						
Active drinking						
Chick 2000a	245	289	242	292	13.4%	1.02 [0.95, 1.10]
Gual 2001	4	96	7	90	0.8%	0.54 [0.16, 1.77]
Mason 2006	143	341	119	260	10.1%	0.92 [0.76, 1.10]
Subtotal (95% CI)		**726**		**642**	**24.3%**	**0.98 [0.86, 1.12]**
Total events	392		368			
Heterogeneity: Tau² = 0.01; Chi² = 3.08, df = 2 (P = 0.21); I² = 35%						
Test for overall effect: Z = 0.30 (P = 0.76)						
Drinking status unclear						
Pelc 1992	35	55	43	47	9.0%	0.70 [0.56, 0.86]
Subtotal (95% CI)		**55**		**47**	**9.0%**	**0.70 [0.56, 0.86]**
Total events	35		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.26 (P = 0.001)						
Total (95% CI)		**1863**		**1729**	**100.0%**	**0.83 [0.75, 0.93]**
Total events	957		1047			
Heterogeneity: Tau² = 0.02; Chi² = 43.56, df = 14 (P < 0.0001); I² = 68%						
Test for overall effect: Z = 3.27 (P = 0.001)						

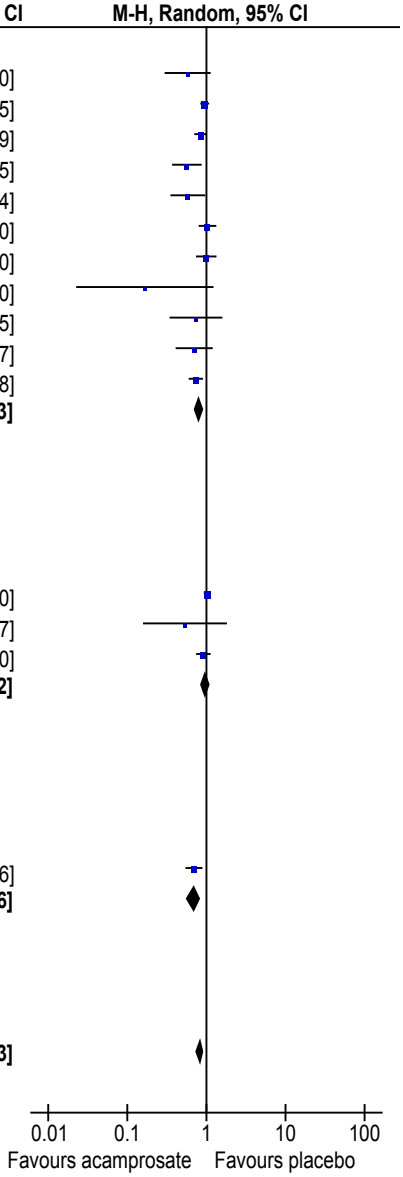
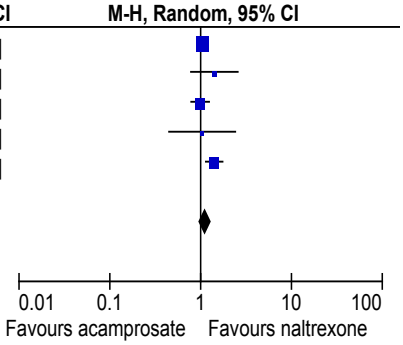


Figure 2.10: Acamprosate compared with naltrexone, number of participants relapsing during treatment

Study or Subgroup	Acamprosate Events	Acamprosate Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Random, 95% CI
COMBINE Study	211	302	207	308	39.3%	1.04 [0.93, 1.16]
Kiefer 2003	17	40	12	40	6.5%	1.42 [0.78, 2.57]
Morley 2006	40	55	39	53	24.6%	0.99 [0.79, 1.24]
Narayana 2008	9	40	8	37	3.5%	1.04 [0.45, 2.41]
Rubio 2001	66	80	45	77	26.2%	1.41 [1.14, 1.75]
Total (95% CI)		**517**		**515**	**100.0%**	**1.13 [0.96, 1.34]**
Total events	343		311			
Heterogeneity: Tau² = 0.01; Chi² = 7.87, df = 4 (P = 0.10); I² = 49%						
Test for overall effect: Z = 1.52 (P = 0.13)						



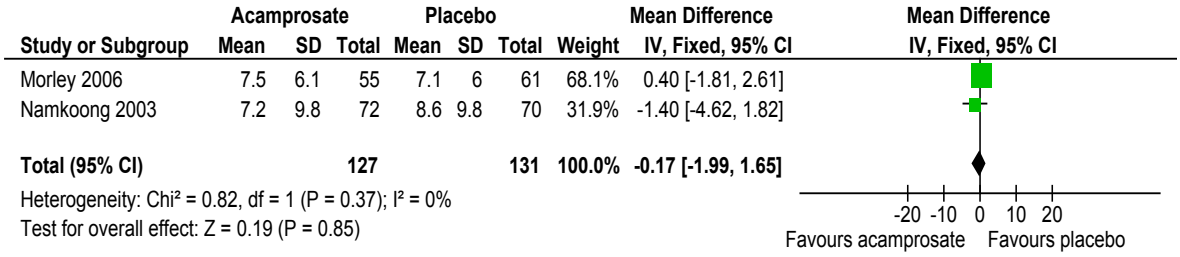
Five studies reported data on the rate of relapse during treatment for acamprosate compared with naltrexone. In one study (Rubio 2001) the rate of relapse was significantly higher with acamprosate, but there was no significant difference in the combined effect (Figure 2.10, RR 1.13, 95% CI 0.96, 1.34; P=0.13)**. Participants in all five studies had been abstinent for at least four days when medication was commenced.

	Amount of alcohol consumed
*	Based on limited data, it appears that acamprosate has little effect, compared to placebo, on the amount of alcohol consumed during treatment.
	One study found that acamprosate is associated with less alcohol consumption than treatment with no medication.
*	Alcohol consumption during treatment may be greater with acamprosate than naltrexone, at least in terms of drinks per drinking day.

Supporting evidence

Two studies comparing acamprosate and placebo reported data on the average drinks per drinking day during treatment, with no significant difference (Figure 2.11: mean difference -0.17 drinks, 95% CI -1.99, 1.65; P=0.85)*. Data reported by Mason 2006 was unable to be included in this meta-analysis. They reported that all treatment groups (two doses of acamprosate and one placebo) showed significant within group reductions from baseline in the number of drinks per week, drinking days per week, and rate of on-study drinking as a percent of baseline drinking, with no significant differences between groups.

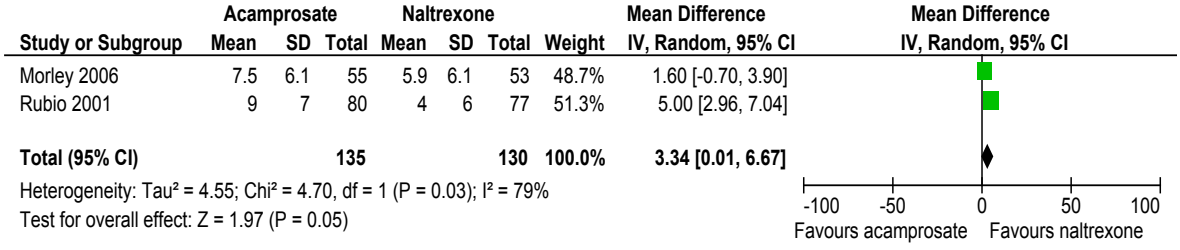
Figure 2.11: Acamprosate compared with placebo, average drinks per drinking day



For acamprosate compared to no medication, one study (Tolliver 2009) reported significantly less alcohol consumption in the acamprosate group both in terms of drinks per drinking day (mean difference -4.70 drinks, 95% CI -8.39, -1.01, P=0.01)* and average drinks per week (mean difference -15.3 drinks, 95% CI -27.05, -3.55, P=0.01)*.

For acamprosate compared to naltrexone, two studies reported significantly less drinks per drinking day associated with naltrexone treatment (Figure 2.12: mean difference 3.34 drinks, 95% CI 0.01, 6.67; P=0.05)* and one study (Laaksonen 2008) reported the average drinks per week, with no significant difference between the two treatments (mean difference 1.95, 95% CI -4.35, 8.25; P=0.54).

Figure 2.12: Acamprosate compared with naltrexone, average drinks per drinking day



	Periods of abstinence or heavy drinking during treatment
***	Treatment with acamprosate is associated with significantly more days of abstinence compared to placebo, particularly when medication is commenced after four or more days of abstinence – for this subset of studies acamprosate is associated with 14% more treatment days of abstinence compared to placebo.
*	There is no significant difference between acamprosate and placebo in terms of days of abstinence during treatment if active drinking is possible when medication is commenced.
*	Compared to placebo, acamprosate appears to have little effect on heavy drinking days during treatment.
	Acamprosate and naltrexone appear to be associated with similar extents of abstinence during treatment.

Supporting evidence

A majority of studies reported the percent of treatment days with abstinence (cumulative abstinence duration). Significantly more days of abstinence were reported for:

> acamprosate compared to placebo (Figure 2.13: mean difference 10.99 % days, 95% CI 5.52, 16.46; P<0.001)***; and

> acamprosate compared to no medication (Figure 2.14: mean difference 12.2 % days, 95% CI 8.21, 16.19; P<0.001)*.

The difference between acamprosate and placebo was most marked for studies where participants were abstinent at treatment entry (Figure 2.13: mean difference 13.64%, 95% CI 8.07, 19.21; P<0.001)***. For the three studies where active drinking was possible when medication was commenced, there was no significant difference between acamprosate and placebo in the cumulative abstinence duration (Figure 2.13: mean difference -0.13%, 95% CI -6.83, 6.56; P=0.97)*.

Based on two studies, there is no significant difference between acamprosate and placebo in the percent of treatment days with heavy drinking (Figure 2.15: mean difference -2.26% days, 95% CI -5.35, 0.83; P=0.15)*.

There was no significant difference between acamprosate and naltrexone in terms of cumulative abstinence duration (Figure 2.16: mean difference -3.07 % days, 95% CI -14.82, 8.68; P=0.61)*. The heterogeneity in the findings of the three studies included in this analysis makes the combined result very uncertain. Participants in all three studies had been abstinent for at least four days when medication was commenced.

Figure 2.13: Acamprosate compared with placebo, % treatment days abstinent (cumulative abstinence duration)

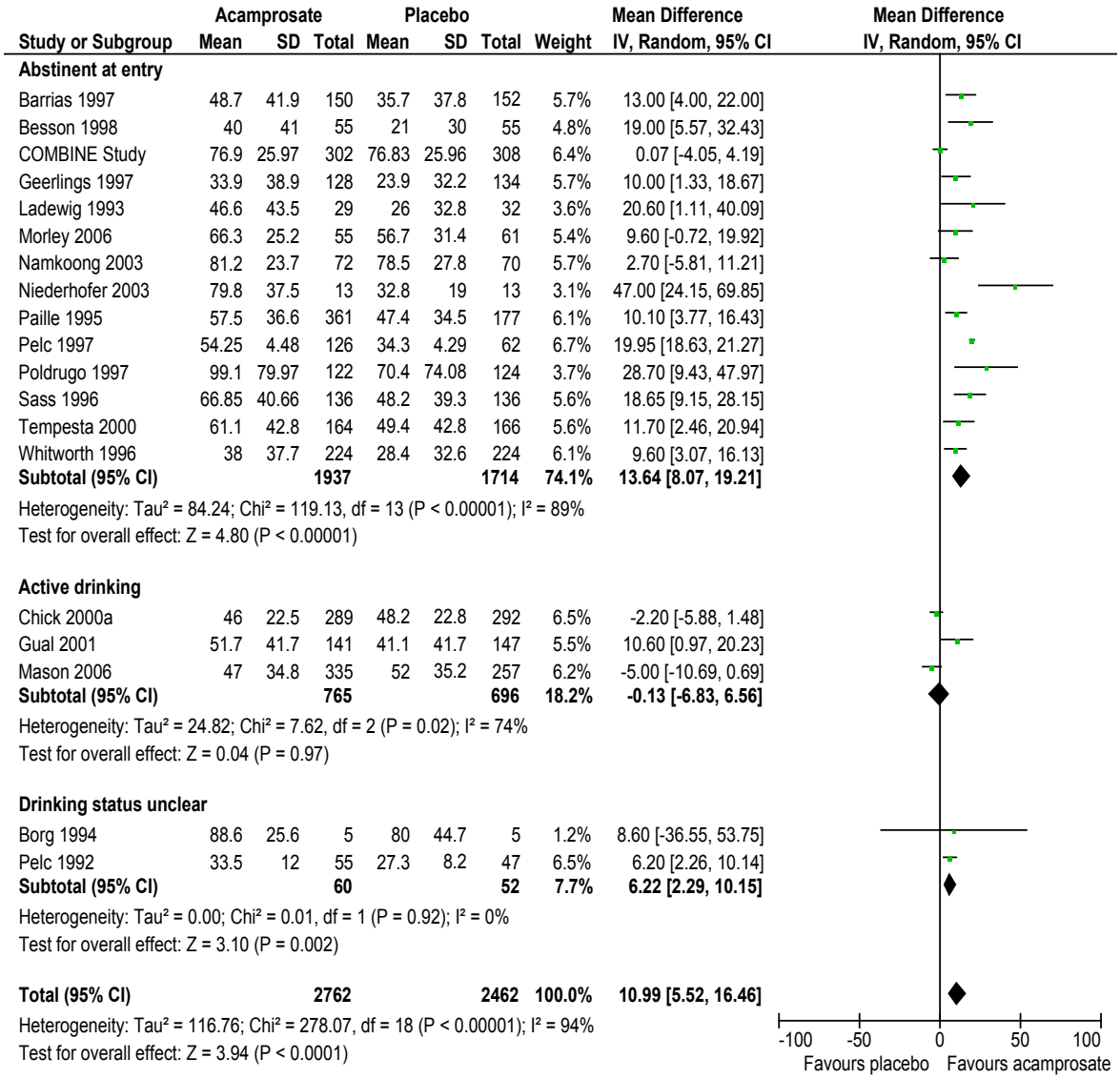


Figure 2.14: Acamprosate compared with no medication, % treatment days abstinent (cumulative abstinence duration)

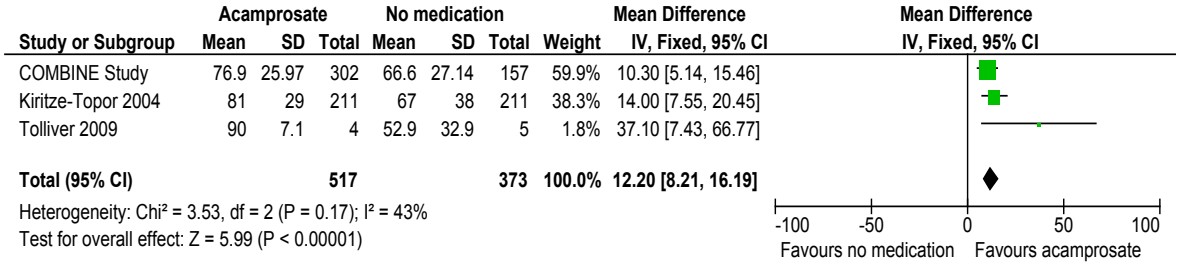


Figure 2.15: Acamprosate compared with placebo, % treatment days with heavy drinking

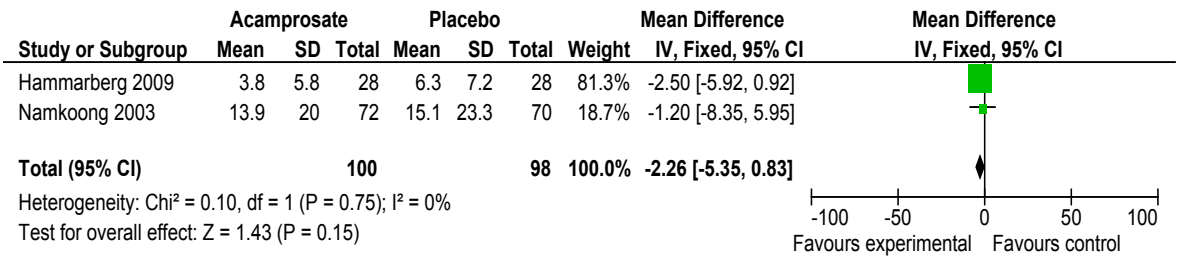
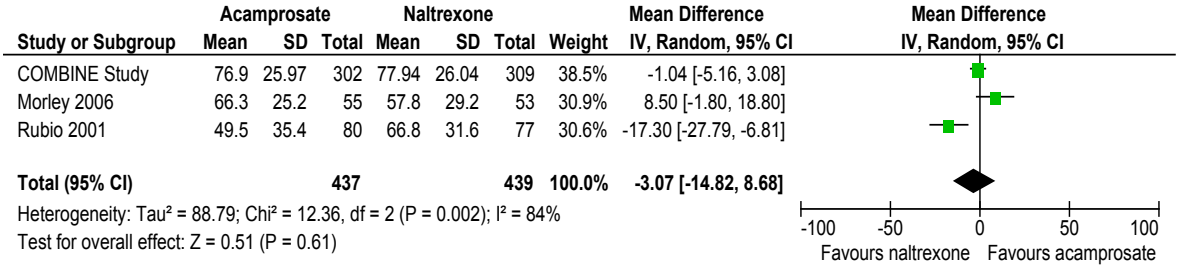


Figure 2.16: Acamprosate compared with naltrexone, % treatment days abstinent (cumulative abstinence duration)



	Time to first drink and time to relapse
*	Treatment with acamprosate significantly prolongs the period of abstinence prior to first drink. The additional time without alcohol consumption is around 21 days.
*	There is no significant difference between acamprosate and naltrexone in terms of time to first drink.
*	Compared to placebo, treatment with acamprosate does not prolong the interval between recommencement of drinking and relapse to heavy drinking.
**	Naltrexone is more effective than acamprosate in delaying relapse to heavy drinking. The additional time without relapse for naltrexone relative to acamprosate is around 9 days.

Supporting evidence

Based on four studies, the average time to first drink is significantly longer with acamprosate compared to placebo (Figure 2.17: mean difference 21.41 days, 95% CI 0.78, 42.04; P=0.04)*.

Data from four studies were unable to be incorporated into this meta-analysis. All four studies reported that acamprosate was associated with a longer time to first drink compared to placebo:

> Poldrugo 1997 (median 150.5 days acamprosate compared with 60.9 days for placebo)

> Geerlings 1997 (median 45 days acamprosate, 15 days placebo)

> Namkoong 2003 (median 14 days acamprosate, 8 days placebo)

> Pelc 1997 (55.5 days for 1332g/day acamprosate, 56.3 days for 1998g/day acamprosate and 15 days for placebo)

Four studies reported the average time to first drink for acamprosate compared to naltrexone, with a trend favouring naltrexone, but with no significant difference in the combined result (Figure 2.18: mean difference -4.67 days, 95% CI -9.71, 0.36; P=0.07)**.

Two studies reported the average time to relapse to heavy drinking, with no significant difference between acamprosate and placebo (Figure 2.19: mean difference 3.48 days, 95% CI -6.20, 13.16; P=0.48)*.

One study (Namkoong 2003) was unable to be incorporated into this meta-analysis, and reported the median time to relapse as 21 days for acamprosate and 22 days for placebo.

Figure 2.17: Acamprosate compared with placebo, average days to first drink

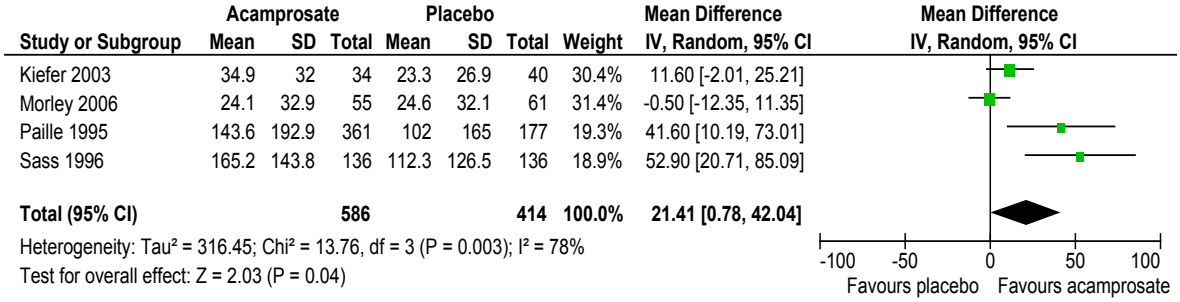


Figure 2.18: Acamprosate compared with naltrexone, average days to first drink

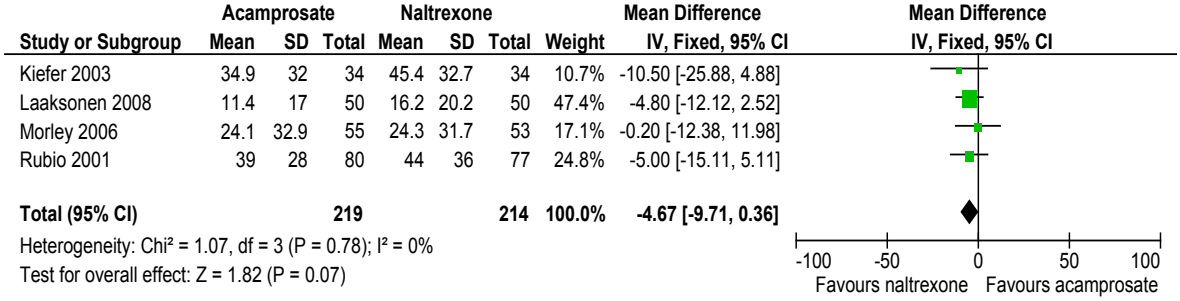
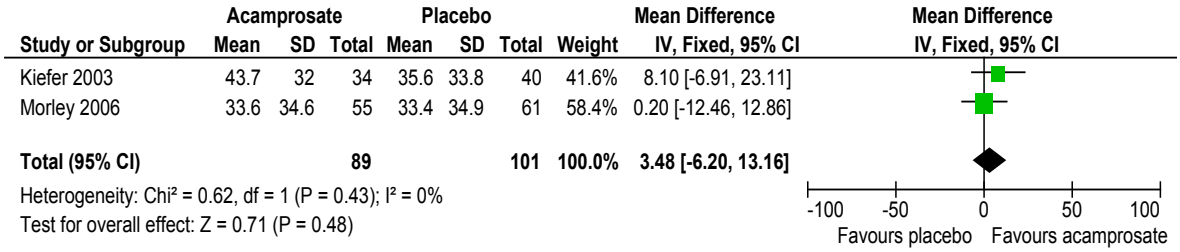
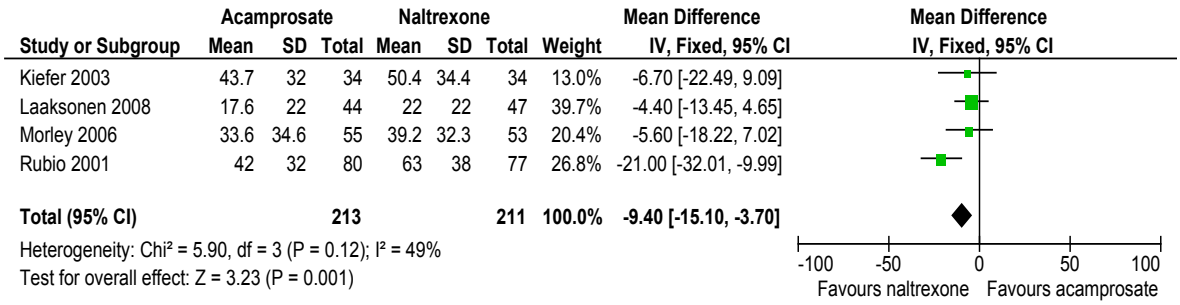


Figure 2.19: Acamprosate compared with placebo, average days to relapse to heavy drinking



Based on four studies, the average time to relapse was significantly shorter for acamprosate relative to naltrexone treatment (Figure 2.20: mean difference -9.40 days, 95% CI -15.10, -3.7; P=0.001)**.

Figure 2.20: Acamprosate compared with naltexone, average days to relapse to heavy drinking



	Objective indicators of alcohol consumption
	Levels of GGT, or change in GGT, are not sufficiently sensitive measures to distinguish between acamprosate and placebo or naltrexone.
	Data on the number of participants with GGT levels outside the normal range may be a more practical outcome indicator.

Supporting evidence

Six studies (Besson 1998, Poldrugo 1997, Gual 2001, Mason 2006, Paille 1995, Pelc 1997) reported a trend or a significant difference in objective indicators, favouring acamprosate compared to placebo. In Paille 1995 there was no significant difference for any biological marker of drinking even after log transformation, but at 6 months, 42.8% high-dose acamprosate compared to 29.4% placebo had GGT level within normal range (difference significant with P=0.011). Similarly, Poldrugo 1997 reported that 26 of 124 placebo (21%) and 48 of 122 acamprosate (39%) had GGT <1.3 times upper limit of normal at 6 months (difference significant).

Five studies (Chick 2000A, Combine Study, Geerlings 1997, Hammarberg 2009, Namkoong 2003) reported declines in GGT or CDT during treatment with no significant differences between acamprosate and placebo.

Kiritze-Topor 2004 used the score on the Alcohol-Related Problems Questionnaire (11 items marked present/absent) as the primary outcome measure. On average patients treated with acamprosate had one less alcohol-related problem than controls (standard care without medication). Based on ARPQ score, 106 of 211 (50.2%) in standard care and 135 of 211 (64%) in acamprosate group were treatment successes.

Two studies (Rubio 2001, Laaksonen 2008) reported greater decreases in GGT levels with naltrexone compared to acamprosate but the differences were not statistically significant.

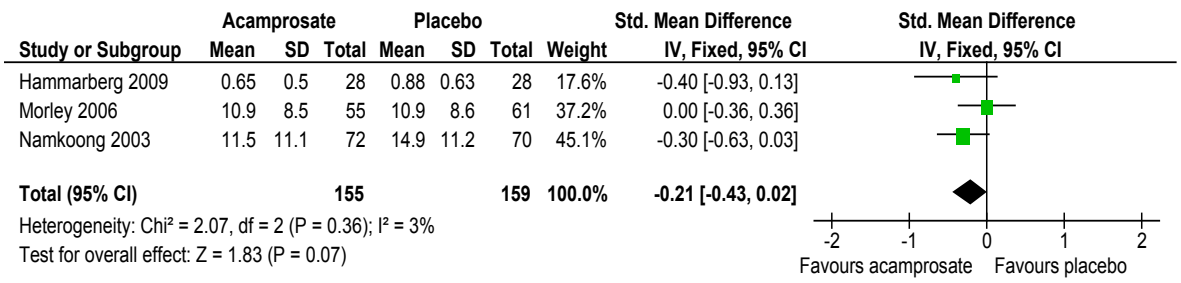
Kiefer 2003, in comparison of acamprosate, naltrexone, acamprosate plus naltrexone, and placebo, reported that final GGT values at week 12 were significantly decreased compared with baseline, with no significant differences across treatment groups.

	Craving
*	Treatment with acamprosate does not significantly reduce average craving levels relative to placebo, no medication or naltrexone.
	Acamprosate may reduce craving for alcohol in a subgroup of alcohol dependent people, as indicated by greater proportions of study participants reporting no desire for alcohol with acamprosate compared to placebo.

Supporting evidence

Three studies reported average craving scores for acamprosate compared to placebo, with a trend towards lower craving associated with acamprosate, but overall the difference was not statistically significant (Figure 2.21: SMD -0.21, 95% CI -0.43, 0.02; P=0.07)*.

Figure 2.21: Acamprosate compared with placebo, average craving scores



A number of studies reported on craving without providing data suitable for inclusion in the above meta-analysis. Five studies (Poldrugo 1997, Tempesta 2000, Kiefer 2003, Mason 2006, Namkoong 2003) reported

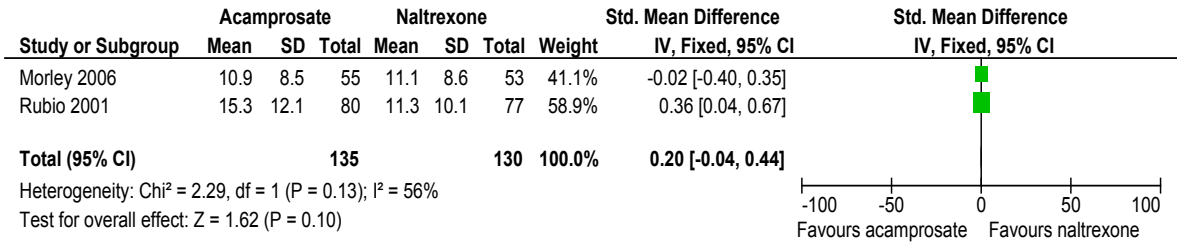
no significant difference in craving, or a decline in craving during treatment with no significant differences between acamprosate and placebo.

In addition, Gual 2001 reported no significant difference in mean craving score at any timepoint but 26% of participants receiving acamprosate compared to 16% receiving placebo reported no craving for alcohol. In Paille 1995, 40% receiving placebo and 59.4% receiving high dose acamprosate reported no craving at 3 months. There were no differences at other time points. In Pelc 1997, 31% receiving placebo compared with 57% receiving low dose and 58% high dose acamprosate reported no desire at all for alcohol, while 22% receiving placebo compared with 13% low dose and 11% high dose acamprosate reported overwhelming desire for alcohol.

In Chick 2000A the mean decrease in craving was significantly greater in acamprosate compared to the placebo group after 2 and 4 weeks of treatment and at one month after the end of the medication phase.

One study (Tolliver 2009) reported lower average craving scores with acamprosate compared with no medication, but the difference did not achieve statistical significance (SMD -1.24, 95% CI -2.75, 0.28, P=0.11). Two studies reported average craving scores for acamprosate compared to naltrexone, with no significant difference (Figure 2.22, SMD 0.20, 95% CI -0.04, 0.44; P=0.10)*.

Figure 2.22: Acamprosate compared with naltrexone, average craving scores



Hammarberg 2009 examined the effect of acamprosate on cue reactivity and alcohol priming in alcohol-dependent patients seeking treatment. Study participants were randomly allocated to 21 days of either acamprosate or placebo treatment and then participated in a series of cue- and alcohol-priming sessions. Placebo-treated participants showed an increase in subjectively experienced alcohol craving and a corresponding increase in blood cortisol levels following an alcohol priming drink, whereas craving and cortisol levels among acamprosate-treated subjects did not increase following alcohol administration. There was also no change in HPA-axis hormones or beta-endorphin.[186]

Average craving scores across a treatment period may not be sufficiently sensitive to detect the effect of acamprosate on craving, but it suggests a mechanism by which acamprosate prolongs the time to relapse.

2.2.3 Adverse effects

***	Compared with placebo, treatment with acamprosate is associated with an increased risk of adverse effects, particularly gastrointestinal symptoms (diarrhoea).
**	The increased risk of adverse effects is associated with a greater likelihood of dose reductions to manage adverse effects, and an increased risk of withdrawal from treatment due to adverse effects for acamprosate compared to placebo. However, the difference translates to an NNT of 100 which is not clinically significant.
**	Compared to naltrexone, acamprosate is associated with significantly lower risk of adverse effects but there is no difference in the likelihood of a dose reduction to manage adverse effects or in the risk of withdrawal from treatment because of adverse effects.
	Very few studies reported data on liver function enzymes. Acamprosate appears to have little effect on liver function, other than through the effect on alcohol consumption.

Supporting evidence

The risk of experiencing any adverse effects is significantly higher for acamprosate compared to placebo (Figure 2.23, RR 1.13, 95% CI 1.01, 1.27; P=0.04)**, but (based on two studies) significantly lower for

acamprosate compared to naltrexone (Figure 2.24: RR 0.78, 95% CI 0.60, 1.00, P=0.05)*. In a large longitudinal study of acamprosate in standard health care settings, 57.6% of patients experienced an adverse event, most commonly gastrointestinal disorders.[195]

Figure 2.23: Acamprosate compared with placebo, number of participants experiencing any adverse effects

	Acamprosate		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Chick 2000a	93	289	83	292	28.9%	1.13 [0.88, 1.45]	
Gual 2001	99	141	94	147	32.2%	1.10 [0.93, 1.29]	
Lhuintre 1985	7	42	2	43	0.7%	3.58 [0.79, 16.27]	
Morley 2006	31	55	29	61	9.6%	1.19 [0.83, 1.68]	
Paille 1995	136	361	61	177	28.6%	1.09 [0.86, 1.39]	
Total (95% CI)		**888**		**720**	**100.0%**	**1.13 [1.01, 1.27]**	
Total events	366		269				

Heterogeneity: Chi² = 2.51, df = 4 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)

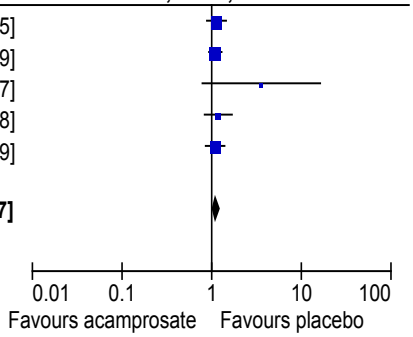
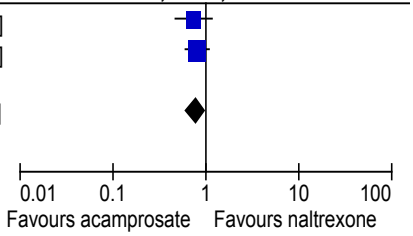


Figure 2.24: Acamprosate compared with naltrexone, number of participants experiencing any adverse effects

	Acamprosate		Naltrexone			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Laaksonen 2008	21	71	30	75	43.6%	0.74 [0.47, 1.16]	
Morley 2006	31	55	37	53	56.4%	0.81 [0.60, 1.08]	
Total (95% CI)		**126**		**128**	**100.0%**	**0.78 [0.60, 1.00]**	
Total events	52		67				

Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.93 (P = 0.05)



Based on three studies, people treated with acamprosate are significantly more likely to require a dose reduction to manage adverse effects than those treated with placebo (Figure 2.25: RR 1.40, 95% CI 1.01, 1.95; P=0.04)*. However, based on two studies, there is no significant difference between acamprosate and naltrexone (Figure 2.26: RR 1.02, 95% CI 0.68, 1.51; P=0.93)*. One retrospective study of acamprosate in routine care identified the need for a dose decrease in 18.9% of patients.[196]

In terms of specific adverse effects, people treated with acamprosate are significantly more likely to experience gastrointestinal symptoms (diarrhoea) than those treated with placebo (Figure 2.27: RR 1.64, 95% CI 1.33, 2.02; P<0.001)*** but there is no significant difference for acamprosate compared with placebo in the likelihood of nausea or vomiting (Figure 2.28: RR 1.15, 95% CI 0.90, 1.46; P=0.26)** or neuropsychiatric symptoms (Figure 2.29: RR 0.99, 95% CI 0.74, 1.32; P=0.94)**. From their analysis, Rosner *et al*.[169] also concluded that the only side effect reported more frequently with acamprosate was diarrhoea.

Figure 2.25: Acamprosate compared with placebo, number of participants requiring a dose reduction to manage adverse effects

	Acamprosate		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Chick 2000a	33	289	27	292	50.0%	1.23 [0.76, 2.00]	
COMBINE Pilot	6	18	3	17	5.7%	1.89 [0.56, 6.38]	
COMBINE Study	36	302	24	308	44.2%	1.53 [0.94, 2.50]	
Total (95% CI)		**609**		**617**	**100.0%**	**1.40 [1.01, 1.95]**	
Total events	75		54				

Heterogeneity: Chi² = 0.62, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.04)

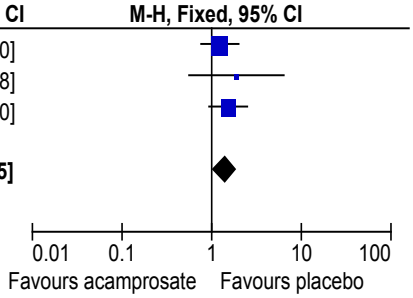


Figure 2.26: Acamprosate compared with naltrexone, number of participants requiring a dose reduction to manage adverse effects

Study or Subgroup	Acamprosate Events	Acamprosate Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
COMBINE Pilot	6	18	5	18	12.0%	1.20 [0.45, 3.23]
COMBINE Study	36	302	37	308	88.0%	0.99 [0.65, 1.53]
Total (95% CI)		**320**		**326**	**100.0%**	**1.02 [0.68, 1.51]**
Total events	42		42			

Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%

Test for overall effect: Z = 0.08 (P = 0.93)

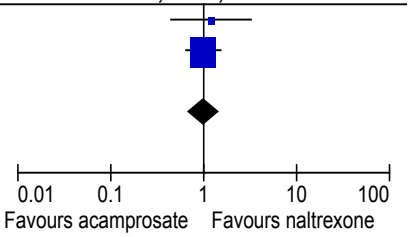


Figure 2.27: Acamprosate compared with placebo, participants experiencing gastrointestinal symptoms

Study or Subgroup	Acamprosate Events	Acamprosate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Abstinent at entry						
Baltieri 2004	5	40	4	35	2.3%	1.09 [0.32, 3.76]
Barrias 1997	14	150	4	152	2.9%	3.55 [1.19, 10.53]
Besson 1998	17	55	4	55	3.1%	4.25 [1.53, 11.82]
COMBINE Pilot	11	18	10	17	7.0%	1.04 [0.60, 1.79]
COMBINE Study	193	302	108	308	12.4%	1.82 [1.53, 2.17]
Geerlings 1997	25	128	15	128	6.4%	1.67 [0.92, 3.01]
Kiefer 2003	3	40	3	40	1.6%	1.00 [0.21, 4.66]
Ladewig 1993	7	29	4	32	2.7%	1.93 [0.63, 5.92]
Lhuintre 1985	4	42	1	43	0.9%	4.10 [0.48, 35.14]
Lhuintre 1990	31	279	20	290	7.1%	1.61 [0.94, 2.76]
Morley 2006	19	55	1	61	1.0%	21.07 [2.92, 152.26]
Namkoong 2003	8	72	2	70	1.6%	3.89 [0.86, 17.68]
Paille 1995	35	361	6	177	4.1%	2.86 [1.23, 6.67]
Pelc 1997	52	126	30	62	10.1%	0.85 [0.61, 1.19]
Sass 1996	10	136	11	136	4.3%	0.91 [0.40, 2.07]
Tempesta 2000	5	164	4	166	2.1%	1.27 [0.35, 4.63]
Whitworth 1996	45	224	27	224	8.4%	1.67 [1.07, 2.59]
Subtotal (95% CI)		**2221**		**1996**	**78.0%**	**1.67 [1.28, 2.18]**
Total events	484		254			

Heterogeneity: Tau² = 0.13; Chi² = 38.79, df = 16 (P = 0.001); I² = 59%

Test for overall effect: Z = 3.80 (P = 0.0001)

Active drinking						
Gual 2001	61	141	46	147	10.5%	1.38 [1.02, 1.88]
Mason 2006	119	341	48	260	10.6%	1.89 [1.41, 2.54]
Subtotal (95% CI)		**482**		**407**	**21.1%**	**1.62 [1.19, 2.21]**
Total events	180		94			

Heterogeneity: Tau² = 0.03; Chi² = 2.13, df = 1 (P = 0.14); I² = 53%

Test for overall effect: Z = 3.06 (P = 0.002)

Drinking status unclear						
Pelc 1992	5	48	1	34	0.9%	3.54 [0.43, 28.97]
Subtotal (95% CI)		**48**		**34**	**0.9%**	**3.54 [0.43, 28.97]**
Total events	5		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.18 (P = 0.24)

Total (95% CI)		**2751**		**2437**	**100.0%**	**1.64 [1.33, 2.02]**
Total events	669		349			

Heterogeneity: Tau² = 0.08; Chi² = 41.31, df = 19 (P = 0.002); I² = 54%

Test for overall effect: Z = 4.69 (P < 0.00001)

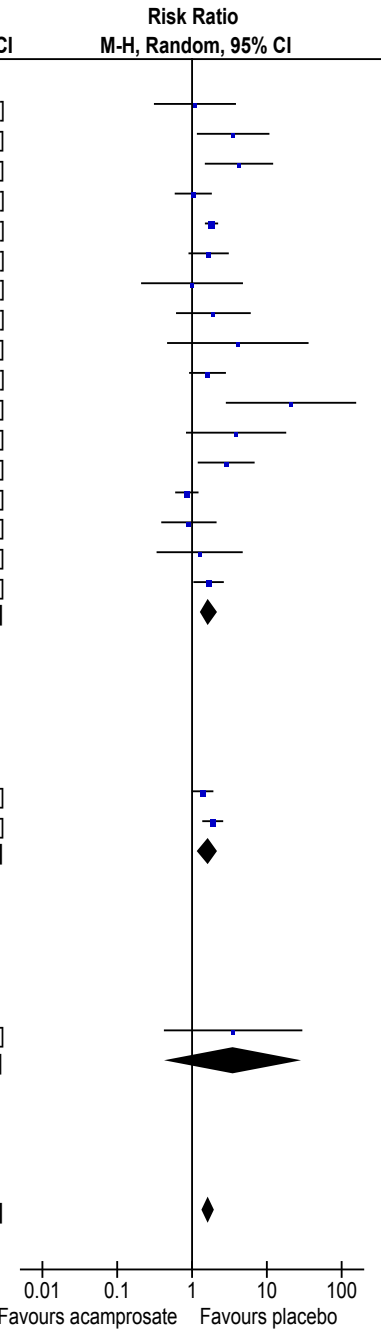


Figure 2.28: Acamprosate compared with placebo, participants experiencing nausea or vomiting

Study or Subgroup	Acamprosate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
COMBINE Pilot	3	18	8	17	8.0%	0.35 [0.11, 1.12]
COMBINE Study	72	302	65	308	62.4%	1.13 [0.84, 1.52]
Kiefer 2003	1	40	1	40	1.0%	1.00 [0.06, 15.44]
Lhuintre 1990	24	279	25	290	23.8%	1.00 [0.58, 1.70]
Mason 2006	14	341	2	260	2.2%	5.34 [1.22, 23.28]
Morley 2006	5	55	3	61	2.8%	1.85 [0.46, 7.38]
Total (95% CI)		**1035**		**976**	**100.0%**	**1.15 [0.90, 1.46]**
Total events	119		104			

Heterogeneity: Chi² = 8.94, df = 5 (P = 0.11); I² = 44%
Test for overall effect: Z = 1.12 (P = 0.26)

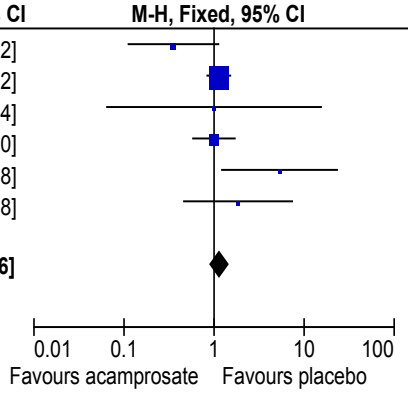


Figure 2.29: Acamprosate compared with placebo, participants experiencing neuropsychiatric symptoms

Study or Subgroup	Acamprosate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Baltieri 2004	4	40	1	35	1.3%	3.50 [0.41, 29.86]
COMBINE Pilot	8	18	6	17	7.6%	1.26 [0.55, 2.87]
Lhuintre 1990	38	279	39	290	46.9%	1.01 [0.67, 1.53]
Morley 2006	2	55	12	61	14.0%	0.18 [0.04, 0.79]
Pelc 1992	11	48	4	34	5.7%	1.95 [0.68, 5.60]
Sass 1996	7	136	9	136	11.0%	0.78 [0.30, 2.03]
Tempesta 2000	12	164	11	166	13.4%	1.10 [0.50, 2.43]
Total (95% CI)		**740**		**739**	**100.0%**	**0.99 [0.74, 1.32]**
Total events	82		82			

Heterogeneity: Chi² = 8.70, df = 6 (P = 0.19); I² = 31%
Test for overall effect: Z = 0.08 (P = 0.94)

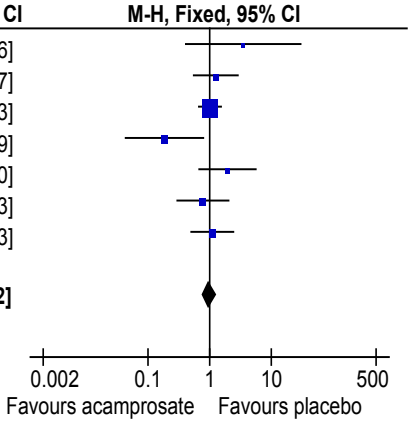


Figure 2.30: Acamprosate compared with naltrexone, participants experiencing gastrointestinal symptoms

Study or Subgroup	Acamprosate Events	Total	Naltrexone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
COMBINE Pilot	11	18	10	18	19.5%	1.10 [0.63, 1.91]
COMBINE Study	193	302	92	308	22.5%	2.14 [1.77, 2.59]
Kiefer 2003	3	40	1	40	5.9%	3.00 [0.33, 27.63]
Laaksonen 2008	14	71	17	75	18.6%	0.87 [0.46, 1.63]
Morley 2006	19	55	7	53	16.9%	2.62 [1.20, 5.71]
Narayana 2008	6	40	0	37	4.0%	12.05 [0.70, 206.72]
Rubio 2001	3	80	18	77	12.6%	0.16 [0.05, 0.52]
Total (95% CI)		**606**		**608**	**100.0%**	**1.30 [0.69, 2.42]**
Total events	249		145			

Heterogeneity: Tau² = 0.44; Chi² = 30.53, df = 6 (P < 0.0001); I² = 80%
Test for overall effect: Z = 0.81 (P = 0.42)

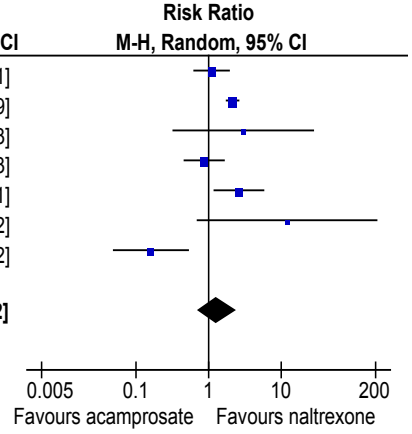


Figure 2.31: Acamprosate compared with naltrexone, participants experiencing nausea or vomiting

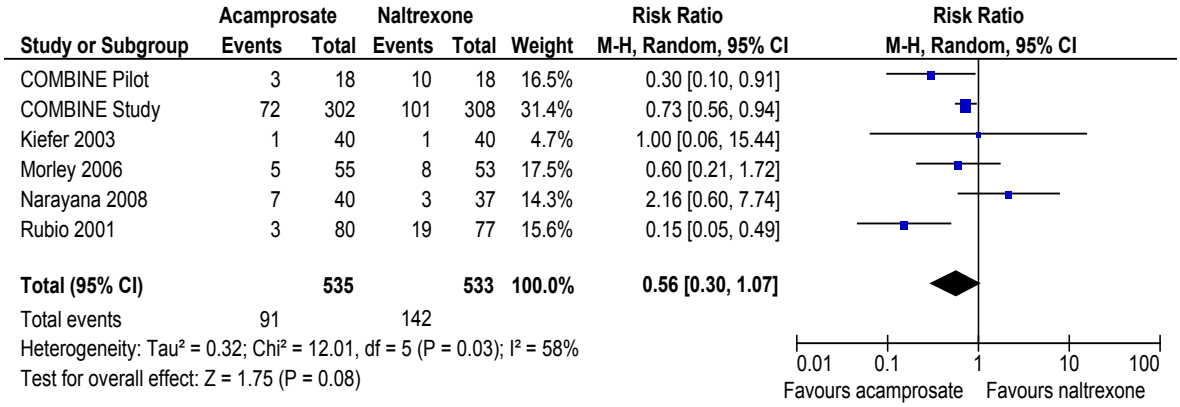
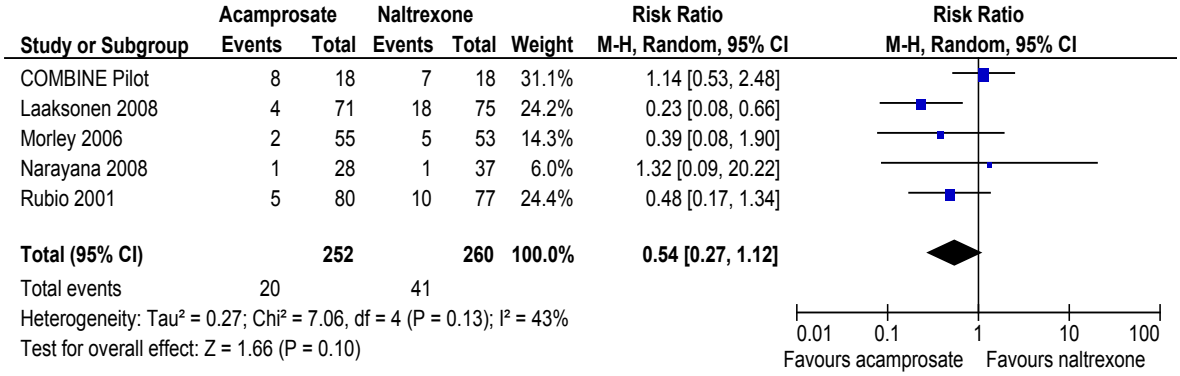


Figure 2.32: Acamprosate compared with naltrexone, participants experiencing neuropsychiatric symptoms



There is considerable variability in the specific adverse effects reported for people treated with acamprosate compared to those treated with naltrexone. Overall there is no significant difference between acamprosate and naltrexone in the likelihood of gastrointestinal symptoms (Figure 2.30: RR 1.30, 95% CI 0.69, 2.42; P=0.42)*, nausea or vomiting (Figure 2.31: RR 0.56, 95% CI 0.30, 1.07; P=0.08)*, or neuropsychiatric symptoms (Figure 2.32: RR 0.54, 95% CI 0.27, 1.12; P=0.10)* but there is a trend towards greater likelihood of the latter two groups of symptoms with naltrexone treatment and substantial variability between studies.

Significantly more people treated with acamprosate withdrew from treatment because of adverse effects, compared to those who received placebo (Figure 2.33: RR 1.39, 95% CI 1.06, 1.83; P = 0.02)***. Based on two studies, there was no difference between acamprosate and no medication in terms of the likelihood of withdrawing from treatment because of adverse effects (Figure 2.34: RR 1.97, 95% CI 0.53, 7.35; P=0.31)*.

There was no significant difference between acamprosate and naltrexone in the likelihood of people withdrawing from treatment because of adverse effects (Figure 2.35: RR 0.82, 95% CI 0.45, 1.48; P=0.50)**.

In a large longitudinal study of acamprosate in Europe, 2.5% of patients withdrew from treatment because of adverse effects.[195] A retrospective study of acamprosate in routine care put the rate much higher, with 23.6% of patients withdrawing from treatment due to adverse effects.[196]

Very few studies reported data on liver function:

> In Geerlings 1997, acamprosate and placebo groups had comparable decreases in AST and ALT.

> In Pelc 1997, AST was significantly lower in the acamprosate group at 90 days.

> In Laaksonen 2008, ALT decreased in the naltrexone group during the study. In the acamprosate group a significant reduction in ALT was observed but only at follow-up, not during treatment.

Figure 2.33: Acamprosate compared with placebo, participants withdrawn due to adverse effects

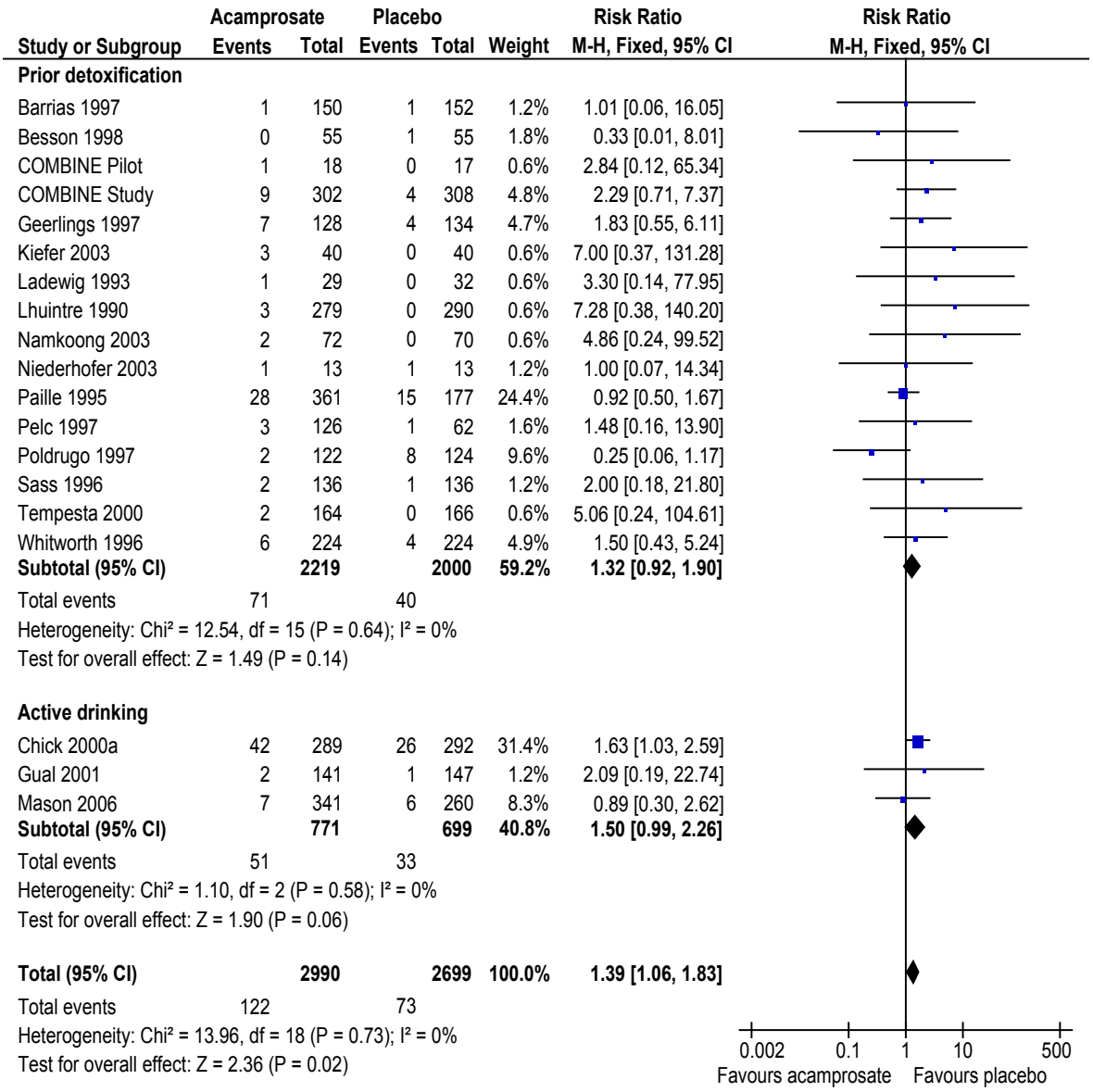


Figure 2.34: Acamprosate compared with no medication, participants withdrawn due to adverse effects

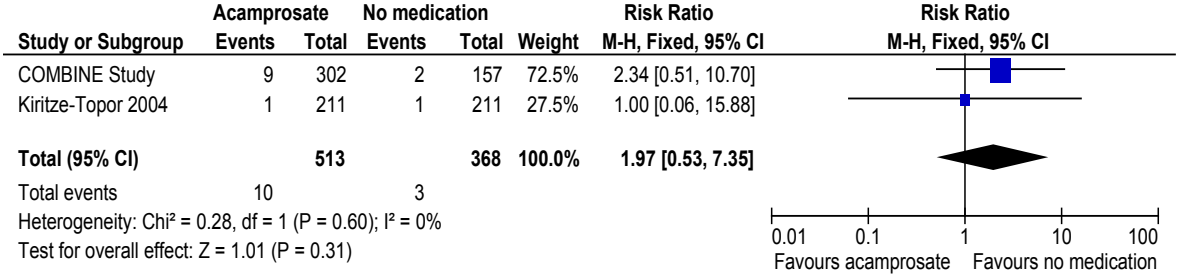
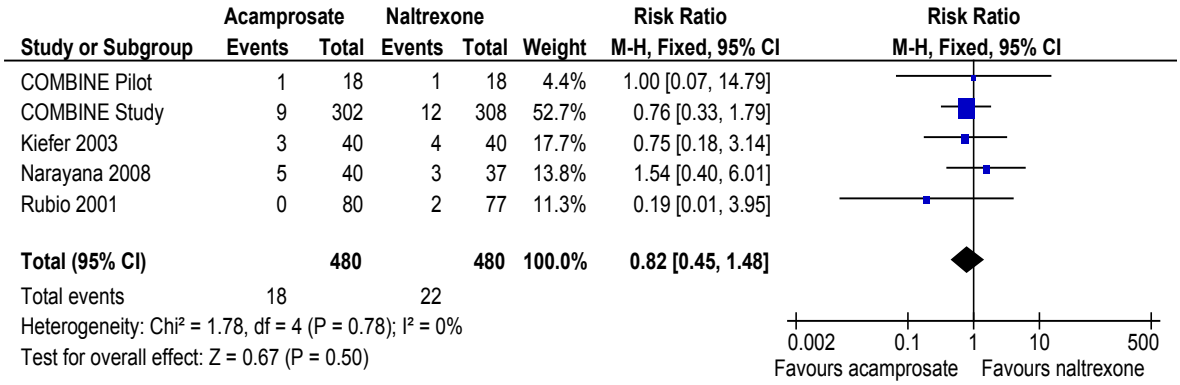


Figure 2.35: Acamprosate compared with naltrexone, participants withdrawn due to adverse effects



2.3 Factors influencing treatment outcomes

Factors considered in research literature include:

> type of adjunct psychosocial treatment (considered further in section 9)

> compliance

> abstinence, or active drinking at commencement of treatment

> typology of alcohol dependence.

2.3.1 Compliance

	Poor compliance with acamprosate appears to be associated with a reduced treatment response. Factors related to compliance are unclear but may include the need for three daily doses of medication.

Supporting evidence

The level of medication compliance reported by studies included in this review was variable.

Chick 2000A reported that compliance with acamprosate was poor – by the end of the second week only 57% of patients were judged to be taking 90% of their tablets. At the end of the 6-month medication phase, 27% of acamprosate and 28% of placebo groups were compliant. In this study 32% of participants drank in the week prior to commencement of acamprosate.

In contrast, Pelc 1997 reported 95% patient compliance by pill count, while Geerlings 1997 reported mean compliance of 86% for acamprosate and 88% for placebo. Namkoong 2003 reported medication compliance of 80.5±30.8% for acamprosate and 74.4±32.3% for placebo.

During the initial 12-week study period of Laaksonen 2008, 82.5% naltrexone and 79.3% acamprosate took medication daily. During the targeted medication period, 81.4% naltrexone and 87.5% acamprosate took medication at least once a week. There were no significant differences between acamprosate and naltrexone in the targeted medication period. Detoxification was not required prior to this study.

Variability in compliance may explain some heterogeneity between studies. Chick 2000A, the study with lowest compliance, found no difference between acamprosate and placebo in most outcomes.

The factors influencing compliance are unclear, although the need to take tablets three times a day may contribute to low compliance.[197;198] If alternative formulations of acamprosate requiring less frequent dosing become available it will be of interest to see if it is associated with higher levels of compliance.

2.3.2 Treatment goal

	Acamprosate may be most effective if used to support a goal of total abstinence.

Supporting evidence

Mason 2006 found no significant group differences overall in cumulative abstinence duration (54.3% placebo, 56.1% 2g acamprosate, 60.7% 3g acamprosate). However, for the subgroup with a goal of total abstinence,

cumulative abstinence duration showed a significant difference favouring acamprosate (58.1% placebo, 70% 2g acamprosate, 72.5% 3g acamprosate).

Poldrugo 1997 provided treatment in the context of a rehabilitation program that included the "Club of treated alcoholics" described as reality-orientated group sessions supervised by former alcoholics and health professionals trained in alcoholism. The degree of intervention varied from approximately 44 hours/ week during the first month to weekly club meetings for up to 5 years. This approach would be expected to have strongly supported a goal of total abstinence. This study found that significantly more participants in the acamprosate group were continuously abstinent, or abstinent after at least three months of treatment, and cumulative abstinence duration was significantly higher in the acamprosate group.

2.3.3 Abstinence at commencement of treatment

***	It is possible to commence acamprosate prior to cessation of alcohol consumption, but the effect of acamprosate is reduced when acamprosate is commenced without a prior period of abstinence (four days or more).

Supporting evidence

The rationale for use of acamprosate in treating alcohol dependence is through reduction of glutamatergic hyperactivity associated with chronic alcohol consumption. By reducing glutamatergic activity, acamprosate may also reduce symptoms of alcohol withdrawal. This has led to suggestions that there may be some benefit arising from commencement of acamprosate during detoxification. Indeed a randomised controlled trial[199] comparing the effects of acamprosate and placebo initiated eight days prior to alcohol withdrawal and continued during 15 days of withdrawal treatment showed that acamprosate ameliorated both sleep continuity and sleep architecture parameters that are typically disturbed in alcohol withdrawal, with no significant adverse effects. However, this study focused on sleep parameters and did not report effects on subsequent alcohol consumption.

Participants in a recent randomised controlled trial[194] were allocated to receive either acamprosate or placebo from the beginning of detoxification. After detoxification all participants received acamprosate. There were no significant group differences during detoxification, but in the post-detoxification phase, those who had received acamprosate during detoxification drank significantly more alcohol during the post-detoxification phase compared to those who had received placebo during detoxification.

To explore the effect of timing of commencement of acamprosate, the meta-analyses in this review included subgroup analyses where possible to compare studies where medication was commenced after four or more days of abstinence, with studies where there was the possibility of active drinking when medication was commenced. For the subgroup of studies with four or more days of abstinence prior to medication, but not the subgroup of studies with active drinking:

> completion of treatment is more likely with acamprosate compared to placebo (Figure 2.1);
> continuous abstinence during treatment is more likely with acamprosate compared to placebo (Figure 2.6);
> relapse to heavy drinking is significantly less likely with acamprosate compared to placebo (Figure 2.9); and
> cumulative abstinence duration during treatment is significantly greater with acamprosate compared to placebo (Figure 2.13).

There is no difference between the subgroups in the likelihood of adverse effects (Figures 2.27 and 2.33).

The requirement for several days of abstinence prior to acamprosate treatment may select participants who are more motivated and better supported for abstinence and this selection bias could be the basis of the differences detected through the subgroup analyses. Koeter *et al*.[198] analysed data from 11 randomised controlled trials and concluded that motivation to become fully abstinent and abstinence at the start of treatment are important for early compliance with medication, which in turn may influence outcomes. When taken together with the findings of Kampman *et al*.,[194] the subgroup differences support the view that commencement of acamprosate during detoxification may worsen drinking outcomes.

2.3.4 Comorbid mental health disorder

	Insufficient data are available to determine the significance of comorbid disorders as predictors of response to acamprosate treatment, or the effectiveness of acamprosate for treatment of alcohol dependence in populations with significant comorbid mental health disorders.

Supporting evidence

In a comparison of acamprosate with placebo, Tempesta et al.[191] found no differential effects for anxiety, depression or craving.

Kiefer *et al*. found that acamprosate treatment was especially effective in people with low scores on somatic distress whereas naltrexone showed a tendency to be more effective in patients with high somatic symptoms. There was no predictive value of baseline craving.[24]

A secondary analysis of data from Mason 2006[170] looked at the effect of psychiatric symptoms or history of severe psychopathology on treatment outcomes (people with current major psychiatric disorders were excluded from this study). Subsyndromal anxiety and the presence of at least one psychiatric antecedent were significant negative predictors of good response. The authors also note that acamprosate does not interact with psychiatric medications, including antidepressants, antipsychotics and sedative-hypnotics.

2.3.5 Age and gender

	Gender probably is not a factor influencing the response to acamprosate.
	Insufficient data are available to determine the acceptability of acamprosate to different age groups.

Supporting evidence

Acamprosate has been used in the treatment of adolescents (Niederhofer 2003) but for the majority of studies included in this review, the average age of participants was around 40 years.

Chick 2000A reported no significant difference in response to acamprosate and placebo by gender.[176] Verheul *et al*.[200] pooled data from seven randomised controlled trials of acamprosate compared to placebo. In this secondary analysis they found no effect of gender on the effectiveness of acamprosate. Secondary analyses of the Combine Study[150] and Morley 2006[74] also found no significant gender differences in response to acamprosate.

2.3.6 Family history and typology of alcohol dependence

	Family history of alcoholism does not predict response to acamprosate.
	Acamprosate may be more effective in people with Lesch Type I alcoholism, characterised by strong withdrawal symptoms.

Supporting evidence

Most studies included in this review do not clearly report the proportion of participants with familial, or non-familial alcohol dependence. Hence a sub-group analysis exploring the effect of this factor on treatment outcome is not possible.

In a crossover study, Gerra et al.[201] compared ethanol intake during treatment with fluoxetine, acamprosate (Ca-acetyl-homotaurinate) or placebo, for participants with familial or non-familial alcohol dependence. Alcohol consumption decreased significantly during treatment with acamprosate in participants with non-familial alcohol dependence, but not in those with familial dependence.

Kiefer *et al*. reported that acamprosate was mainly effective in Lesch Type I[24] which is characterised by early withdrawal symptoms. Verheul *et al*.[200], using data from seven European randomised controlled trials, found that family history of alcoholism did not predict acamprosate effectiveness.

In Morley 2006, participants with high baseline severity of dependence who were allocated to acamprosate were less likely to lapse and relapse.[74] This is consistent with the finding of greater efficacy in Lesch Type I.

Section 3: Aversive Agents

Overview

Rationale

Disulfiram inhibits the action of acetaldehyde dehydrogenase. The resultant accumulation of acetaldehyde produces an unpleasant reaction that is aversive.

Comparisons

Disulfiram has been compared with placebo, no medication, and other active medications (naltrexone and acamprosate). One study used cyanamide and four studies used implant preparations of disulfiram.

Retention in treatment

Treatment with disulfiram has no significant effect on retention in treatment**.

Abstinence

Treatment with disulfiram is not associated with increased rates of abstinence relative to placebo or no medication**.

Abstinence from alcohol may be more likely with disulfiram compared to oral naltrexone*, but studies were somewhat varied in their findings.

Relapse to heavy drinking

Disulfiram may be more effective than placebo, naltrexone and acamprosate in preventing relapse to heavy drinking. However, data are limited and additional studies are required to confirm this finding.

Amount of alcohol consumed

Insufficient data are available to form a view on the effectiveness of aversive agents in reducing alcohol consumption.

It appears that oral disulfiram may be at least as effective as oral naltrexone and acamprosate in reducing average drinks per week*.

Periods of abstinence or heavy drinking during treatment

Some individual studies reported longer cumulative abstinence duration with aversive agent compared to placebo or oral naltrexone, but combined results suggest no significant difference. Studies are limited by small size and focus on specific populations. More studies are needed to confirm the finding.

Insufficient data are available to form a view on the effect of disulfiram on the proportion of treatment days with heavy drinking.

Time to first drink and time to relapse

Treatment with oral disulfiram appears to significantly prolong the time to first drink and the time to relapse relative to oral naltrexone and acamprosate*.

Implant disulfiram is no more effective than placebo in delaying recommencement of drinking but there is a strong placebo effect*.

There are limitations to all data, with further studies needed to confirm findings.

Objective indicators of alcohol consumption

Data on GGT levels are consistent with self-report data suggesting that oral disulfiram is at least as effective as oral naltrexone in reducing alcohol consumption.

Insufficient data are available to form a view on the effectiveness of disulfiram relative to placebo or acamprosate based on objective indicators of alcohol consumption.

Craving

Data are limited but it appears that disulfiram has little effect on craving for alcohol*.

Adverse effects

For the studies included in this review, disulfiram was associated with increased risk of nausea or vomiting* and neuropsychiatric symptoms relative to placebo*. Withdrawal from treatment is more likely with disulfiram compared to placebo*.

The implantation of disulfiram tablets as performed by the studies included in this review appears to be associated with significantly greater risk of wound complications*.

Disulfiram may be associated with more neuropsychiatric symptoms than acamprosate*, but otherwise there appear to be no significant differences between disulfiram and naltrexone or disulfiram and acamprosate in terms of the incidence of adverse effects*.

Factors affecting treatment response

(a) Compliance

Treatment compliance is critical to outcome and compliance is more likely with supervised administration, and stable relationships.

Available evidence does not support significantly improved outcomes with implanted compared to oral disulfiram.

(b) Adverse effects

Accumulated clinical experience with disulfiram indicates an adverse drug reaction rate of one per 200-2000 patients per year, and a risk of disulfiram-induced fatal hepatitis of 1 case in 30,000 patients treated per year.

Most serious adverse reactions, and the possibility of fatal disulfiram-alcohol reaction, are more likely with higher doses of disulfiram (≥500mg/day).

(c) Comorbid mental health disorders

The presence of different mental health disorders may influence response to treatment.

Data are limited, but there is no evidence to suggest that treatment with disulfiram has any negative impact on comorbid mental health disorders.

3.1 Rationale for effect

The most common aversive agent is Disulfiram (Antabuse®) which acts by inhibiting the enzyme acetaldehyde dehydrogenase that metabolises acetaldehyde to acetate. The resulting accumulation of acetaldehyde produces an unpleasant reaction including flushing, rapid or irregular heartbeat, dizziness, nausea and vomiting, difficulty breathing, and headache. The medication is used as a form of contingency management, in that patients are deterred by the potential for unpleasant side effects.[35;202]

The severity of the disulfiram-ethanol reaction is dependent upon the dose of each compound.[203] Treatment efficacy is also dependent on compliance [9;202]

Cyanamide has been used in the past as an aversive agent but appears to have lost popularity because of a greater risk of adverse effects and the need for multiple daily doses. Tamai *et al*.[204] reviewed the laboratory data of alcoholics treated with cyanamide or disulfiram. Cyanamide was more frequently associated with elevations of alanine aminotransferase (ALT) that persisted after abstinence from alcohol. Only one study included in this review used cyanamide.

Another aversive agent, Calcium carbimide (Temposil), also inhibits aldehyde dehydrogenase[205;206] but has a shorter duration of action than disulfiram with dosing required every 12 hours. Calcium carbimide has been used in Canada, Great Britain and Europe but is not approved for use in the USA in view of reported hypothyroid activity in experimental animals.[207] Poldrugo[208] also notes that calcium carbimide is no longer recommended because of adverse effects.

3.2 Evidence of effectiveness

Disulfiram has been compared with placebo in 10 studies (six involving oral naltrexone, four using depot or implant preparations), with no medication in seven studies (six with oral naltrexone, one using an implant preparation), and with other active medication in eight studies (six with naltrexone and two with acamprosate). One compared cyanamide with placebo (see Table 3.1). Brief information on the design of these studies is included in Appendix 1.

Table 3.1: Studies involving the use of aversive agents for relapse prevention treatment of alcohol dependence.

Compared with placebo			Compared with no medication		Disulfiram compared with other active medication	
Oral disulfiram	Implant disulfiram	Cyanamide	Oral disulfiram	Implant disulfiram	Opioid antagonist (naltrexone)	Acamprosate
Chick 1992 [209] Fuller 1979[217-219] Fuller 1986 [222] Niederhofer 2003B [226] Petrakis 2005[106-110] Pettinati 2008 [114]	Johnsen 1987 [210] Johnsen 1991 [220] Wilson 1976 [223;224] Wilson 1980 [214]	Niederhofer 2003C [211]	Carroll 1998[212;213] Fuller 1979[217-219] Fuller 1986[222] Gerrein 1973 [227] Powell 1985 [228] Ulrichsen 2010 [230]	Wilson 1980 [214]	Carroll 1993 [215] De Sousa 2004 [221] De Sousa 2008A[225] Laaksonen 2008 [175] Nava 2006 [229] Petrakis 2005 [107] Pettinati 2008[114]	De Sousa 2005 [216] Laaksonen 2008 [175]

In most studies oral disulfiram was administered as a single daily dose and most studies used doses of 200 or 250mg/day. Disulfiram or cyanamide were administered in three daily doses in Niederhofer 2003B and 2003C, respectively. Laaksonen 2008 administered higher doses (400mg) twice a week if daily supervised dosing (100-200mg/day) was not possible. Ulrichsen 2010 used doses of 800mg twice a week, supervised at an outpatient clinic. Carroll 1998 used doses of 250-500mg/day in a population with dual cocaine and alcohol abuse or dependence.

The implants used in four studies comprised eight or ten 100mg tablets of disulfiram.

3.2.1 Retention in treatment

**	Treatment with disulfiram has no significant effect on retention in treatment.

Supporting evidence

There is no significant difference in the proportion of participants completing treatment for disulfiram compared to:

> placebo (Figure 3.1: RR 1.03, 95% CI 0.94, 1.13; P=0.50)*;

> no medication (Figure 3.2: RR 1.05, 95% CI 0.89, 1.23; P=0.59)*;

> naltrexone (Figure 3.3: RR 0.98, 95% CI 0.91, 1.06; P=0.66)**; or

> acamprosate (Figure 3.3: RR 1.01, 95% CI 0.90, 1.13; P=0.87)*.

Petrakis 2005 reported the average weeks in treatment for oral disulfiram compared with placebo, with no significant difference (mean difference 0.26 weeks, 95% CI -0.97, 1.49; P=0.68). However, in Carroll 1998, participants assigned to disulfiram were retained significantly longer than those assigned to no medication (8.4 vs 5.8 weeks, P<0.05).

Based on two studies, there is no significant difference in the average time in treatment for disulfiram compared with naltrexone (Figure 3.4: mean difference -0.24, 95% CI -1.37, 0.88; P=0.67)*.

Figure 3.1: Aversive agent compared with placebo, participants completing the study

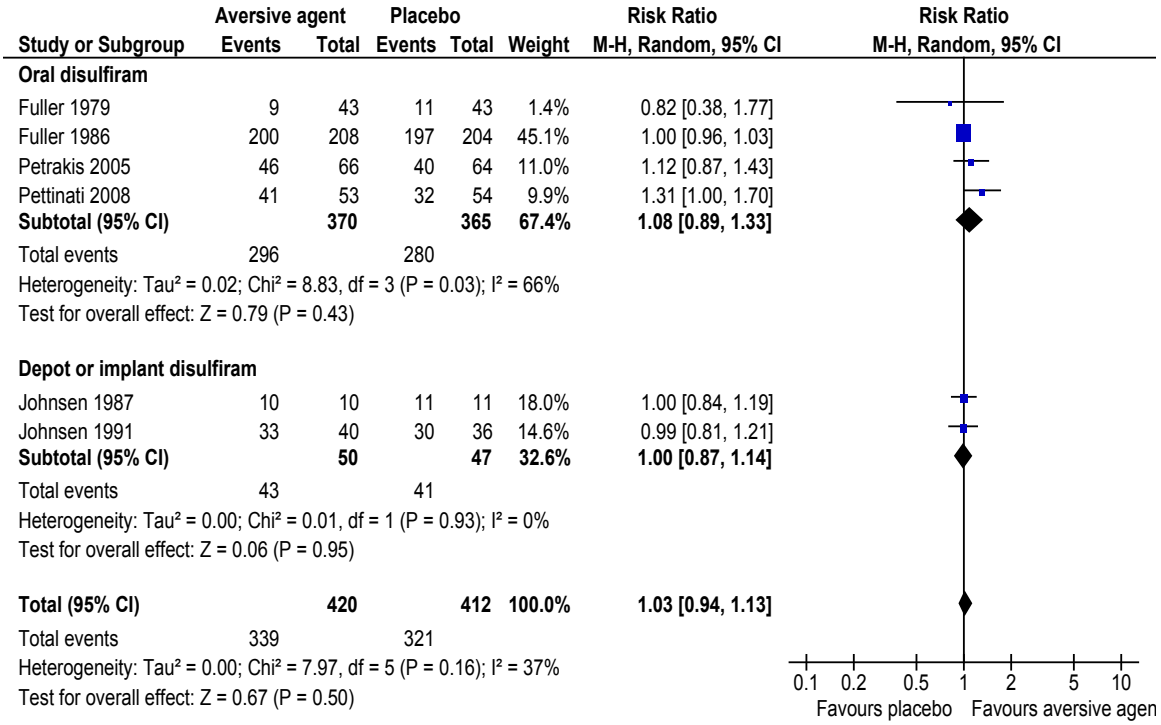


Figure 3.2: Aversive agent compared with no medication, participants completing the study

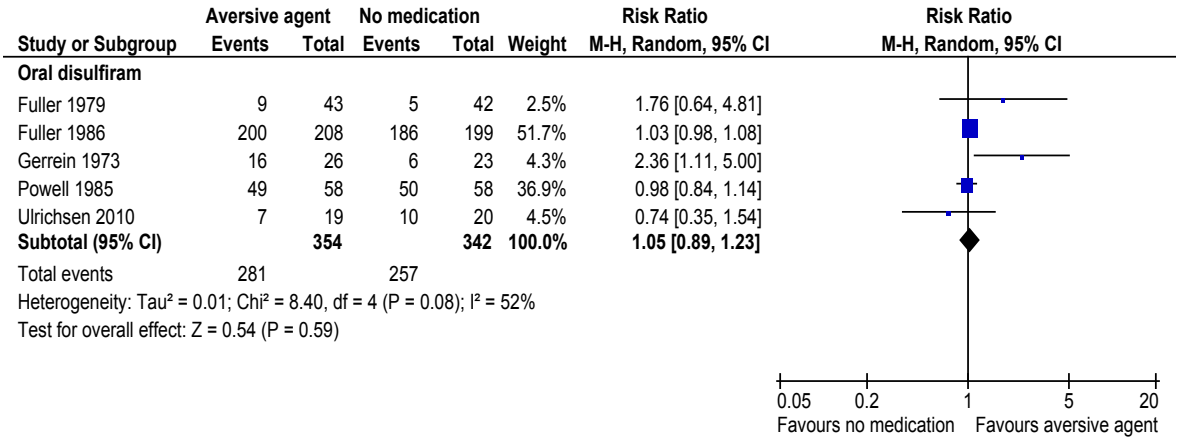


Figure 3.3: Disulfiram compared with other active medication, participants completing the study

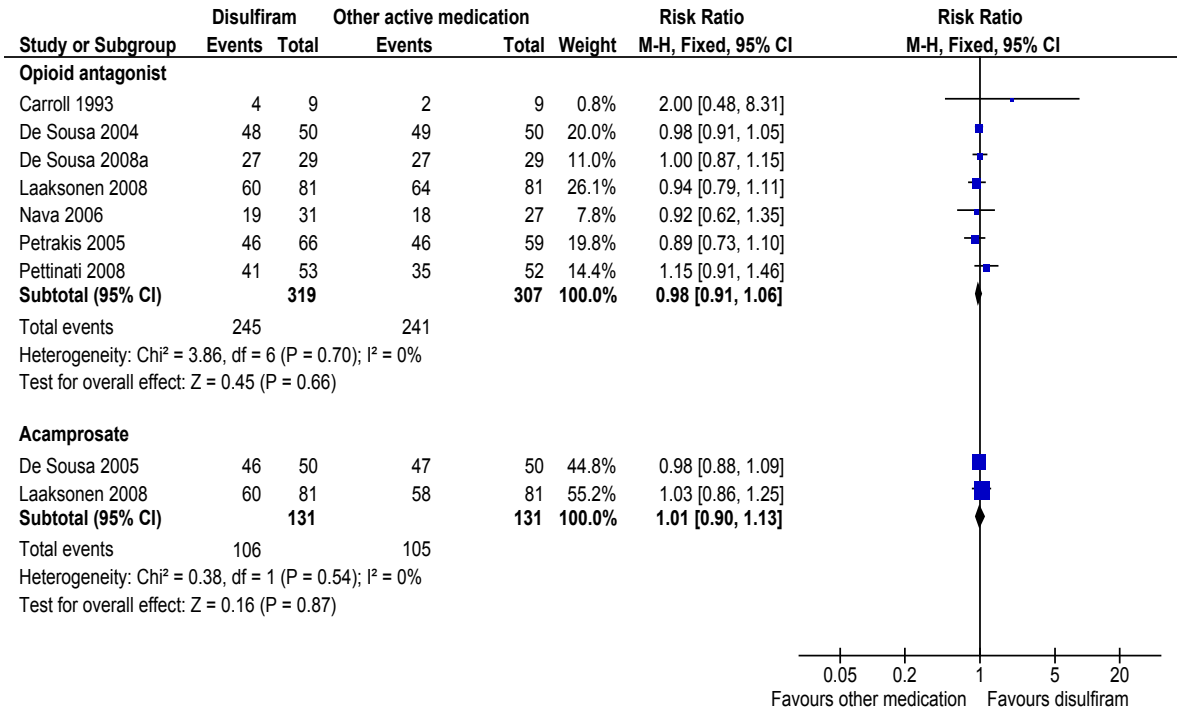
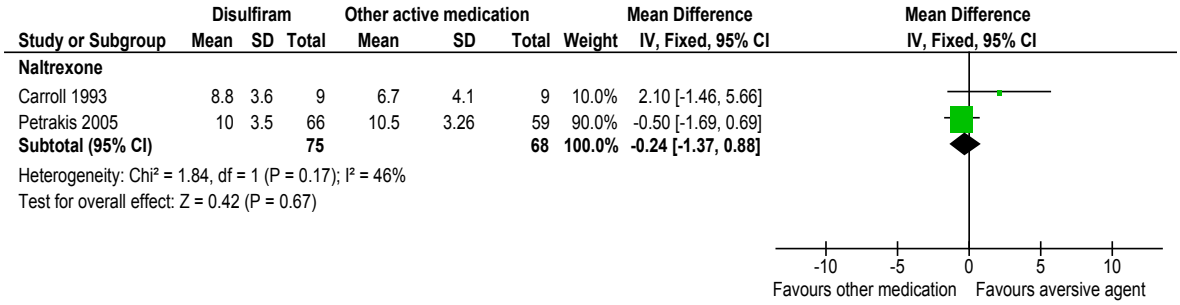


Figure 3.4: Disulfiram compared with other active medication, average weeks in treatment



3.2.2 Effect on alcohol consumption

	Total abstinence
**	Treatment with disulfiram is not associated with increased rates of abstinence relative to placebo or no medication.
*	Abstinence from alcohol may be more likely with disulfiram compared to oral naltrexone, but studies were somewhat varied in their findings.

Supporting evidence

There is no significant difference in the proportion of participants abstinent at the end of treatment, or continuously abstinent during treatment with:

> oral disulfiram compared to placebo (Figure 3.5: RR 1.08, 95% CI 0.88, 1.31; P=0.47)*;

> implant disulfiram compared to placebo (Figure 3.5: RR 1.39, 95% CI 0.79, 2.44; P=0.25)* or

> oral disulfiram compared to no medication (Figure 3.6: RR 1.29, 95% CI 0.97, 1.70; P=0.08)*.

Figure 3.5: Aversive agent compared with placebo, participants abstinent at end of treatment or continuously abstinent during treatment

Study or Subgroup	Aversive agent Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Oral disulfiram						
Fuller 1979	18	43	15	43	12.1%	1.20 [0.70, 2.06]
Fuller 1986	38	202	46	204	37.0%	0.83 [0.57, 1.22]
Niederhofer 2003b	7	13	2	13	1.6%	3.50 [0.89, 13.78]
Petrakis 2005	51	66	42	64	34.5%	1.18 [0.94, 1.47]
Subtotal (95% CI)		**324**		**324**	**85.2%**	**1.08 [0.88, 1.31]**
Total events	114		105			
Heterogeneity: Chi² = 5.34, df = 3 (P = 0.15); I² = 44%						
Test for overall effect: Z = 0.73 (P = 0.47)						
Other aversive agents						
Niederhofer 2003c	7	13	2	13	1.6%	3.50 [0.89, 13.78]
Subtotal (95% CI)		**13**		**13**	**1.6%**	**3.50 [0.89, 13.78]**
Total events	7		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.79 (P = 0.07)						
Depot or implant disulfiram						
Johnsen 1991	6	40	6	36	5.1%	0.90 [0.32, 2.54]
Wilson 1976	5	10	1	10	0.8%	5.00 [0.70, 35.50]
Wilson 1980	12	40	9	40	7.3%	1.33 [0.63, 2.81]
Subtotal (95% CI)		**90**		**86**	**13.2%**	**1.39 [0.79, 2.44]**
Total events	23		16			
Heterogeneity: Chi² = 2.32, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 1.14 (P = 0.25)						
Total (95% CI)		**427**		**423**	**100.0%**	**1.16 [0.96, 1.39]**
Total events	144		123			
Heterogeneity: Chi² = 10.36, df = 7 (P = 0.17); I² = 32%						
Test for overall effect: Z = 1.53 (P = 0.12)						

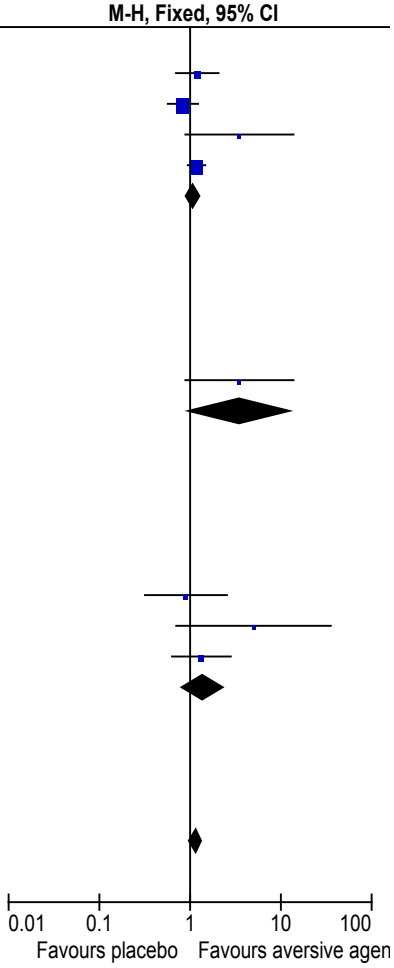
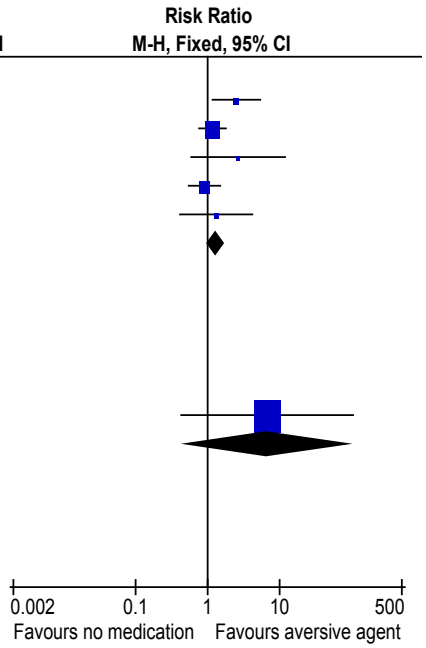


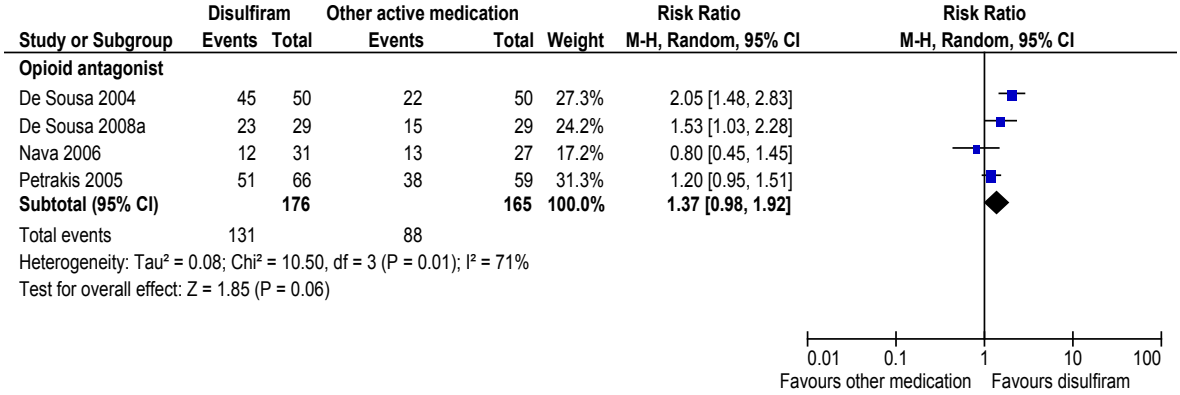
Figure 3.6: Aversive agent compared with no medication, participants abstinent at end of treatment or continuously abstinent during treatment

Study or Subgroup	Aversive agent Events	Total	No medication Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Oral disulfiram						
Fuller 1979	18	43	7	42	10.7%	2.51 [1.17, 5.38]
Fuller 1986	38	202	32	199	48.6%	1.17 [0.76, 1.79]
Gerrein 1973	6	26	2	23	3.2%	2.65 [0.59, 11.88]
Powell 1985	19	58	21	58	31.7%	0.90 [0.55, 1.50]
Ulrichsen 2010	5	19	4	20	5.9%	1.32 [0.41, 4.18]
Subtotal (95% CI)		**348**		**342**	**100.0%**	**1.29 [0.97, 1.70]**
Total events	86		66			
Heterogeneity: Chi² = 5.93, df = 4 (P = 0.20); I² = 33%						
Test for overall effect: Z = 1.74 (P = 0.08)						
Depot or implant disulfiram						
Wilson 1980	12	40	0	10	100.0%	6.71 [0.43, 104.63]
Subtotal (95% CI)		**40**		**10**	**100.0%**	**6.71 [0.43, 104.63]**
Total events	12		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.36 (P = 0.17)						



Based on four studies, more participants were abstinent at the end of treatment or were continuously abstinent during treatment with oral disulfiram compared to oral naltrexone (Figure 3.7: RR 1.37, 95% CI 0.98, 1.92; P=0.06)*. The difference was not statistically significant and the meta-analysis was influenced by two studies (De Sousa 2004 and De Sousa 2008A) reporting outcomes strongly favouring disulfiram. Both these studies were undertaken in India; one (De Sousa 2008A) involved adolescents, and participants in both studies had stable family environments to provide support. These factors have the potential to influence the response to treatment and limit the extent to which this finding can be extrapolated to the general alcohol dependent population.

Figure 3.7: Disulfiram compared with other active medication, participants abstinent at end of treatment or continuously abstinent during treatment



	Relapse to heavy drinking
	Disulfiram may be more effective than placebo, naltrexone and acamprosate in preventing relapse to heavy drinking. However, data are limited and additional studies are required to confirm this finding.

Supporting evidence

One study (Niederhofer 2004B) reported less relapse to heavy drinking with oral disulfiram compared to placebo. The difference was not statistically significant (RR 0.17, 95% CI 0.02, 1.20; P=0.08), the study was small (13 participants in each group) and involved adolescents, limiting the interpretation of this finding.

One study (Niederhofer 2004C) reported similar rates of relapse for cyanamide compared to placebo (RR 0.82, 95% CI 0.53, 1.26; P=0.36). Again the study was small (13 participants in each group) and involved adolescents.

Ulrichsen 2010 also reported similar rates of relapse for oral disulfiram compared to no medication (RR 0.75, 95% CI 0.29, 1.96; P=0.56) but this study was subject to selection bias – of 242 people who were eligible for the study, only 39 entered the study; 62 refused participation because they wanted disulfiram.

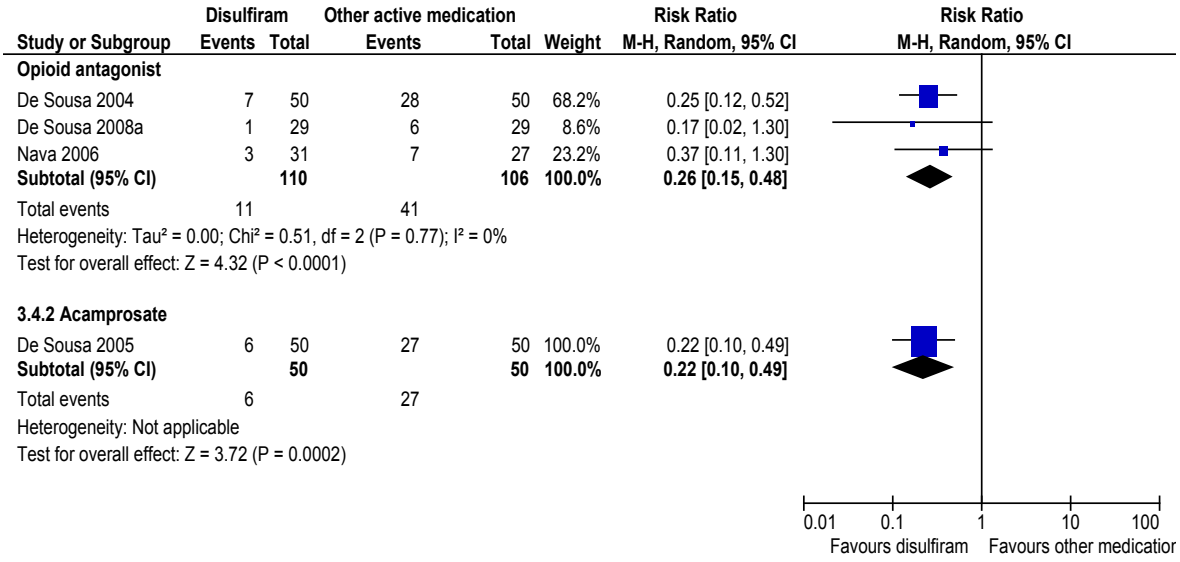
Significantly less people treated with disulfiram relapsed to heavy drinking during treatment compared with:

> oral naltrexone (Figure 3.8: RR 0.26, 95% CI 0.15, 0.48; P<0.001)*; and

> acamprosate (Figure 3.8: RR 0.22, 95% CI 0.10, 0.49; P<0.001)*.

As with data on abstinence, these analyses are influenced by two studies (De Sousa 2004, De Sousa 2008A) undertaken in India where participants had stable family environments to provide support. Additional data are required to confirm the finding.

Figure 3.8: Disulfiram compared with other active medication, participants relapsing during treatment



	Amount of alcohol consumed
	Insufficient data are available to form a view on the effectiveness of aversive agents in reducing alcohol consumption.
*	It appears that oral disulfiram may be at least as effective as oral naltrexone and acamprosate in reducing average drinks per week.

Supporting evidence

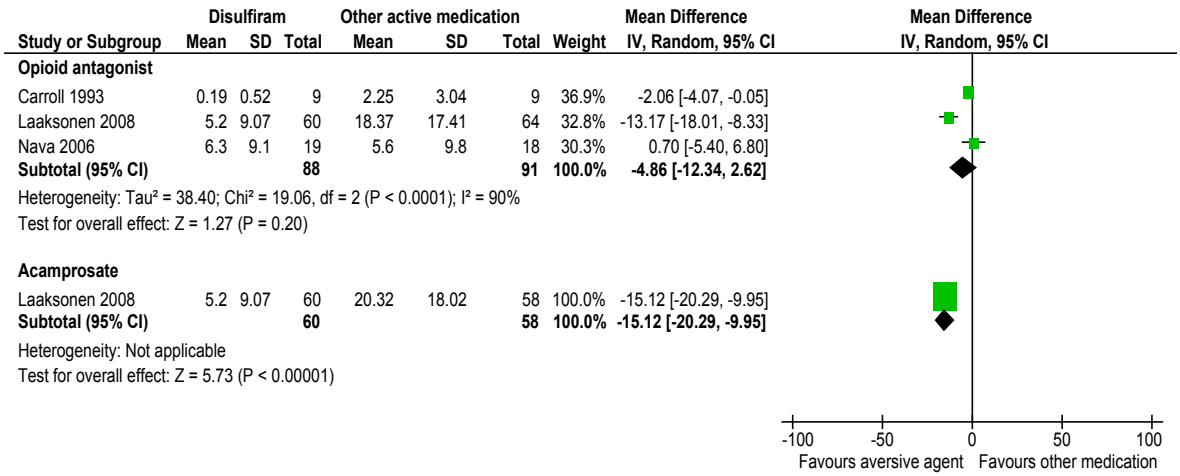
Data reported on alcohol consumption for oral disulfiram compared to placebo or no medication were not suitable for inclusion in meta-analyses. Chick 1992 reported no significant difference in the change from baseline to six months in drinks per week, but significantly greater reduction in the number of drinks consumed in the whole six month period for disulfiram compared to placebo. Carroll 1998 reported that the effect of disulfiram, relative to no medication, was significant for both quantity and frequency of alcohol use.

Johnsen 1987 reported average drinks per week, with no significant difference between implant naltrexone and placebo (mean difference 18.48 drinks/week, 95% CI -23.00, 59.96, P=0.38). Johnson 1991 reported a mean 22.2 drinks per week in the disulfiram and placebo groups (data not suitable for meta-analysis).

One study (De Sousa 2004) reported average drinks per drinking day, with no significant difference between disulfiram and oral naltrexone (mean difference -1.0 drinks, 95% CI -4.6, 2.6; P=0.59).

Three studies reported average drinks per week during treatment for oral disulfiram compared with naltrexone. In one study alcohol consumption by this measure was significantly less with disulfiram, but there was no significant difference in the other two studies, and, while the combined result favours disulfiram, it is not statistically significant (Figure 3.9: mean difference -4.86 drinks per week, 95% CI -12.34, 2.62; P=0.20)*. The study reporting a significant difference, also reported significantly less average drinks per week for people treated with disulfiram compared to those treated with acamprosate (Figure 3.9: mean difference -15.12, 95% CI -20.29, -9.95; P<0.001).

Figure 3.9: Disulfiram compared with other active medication, average drinks per week



	Periods of abstinence or heavy drinking during treatment
	Some individual studies reported longer cumulative abstinence duration with aversive agent compared to placebo or oral naltrexone, but combined results suggest no significant difference.
	Studies are limited by small size and focus on specific populations. More studies are needed to confirm the finding.
	Insufficient data are available to form a view on the effect of disulfiram on the proportion of days with heavy drinking during treatment.

Supporting evidence

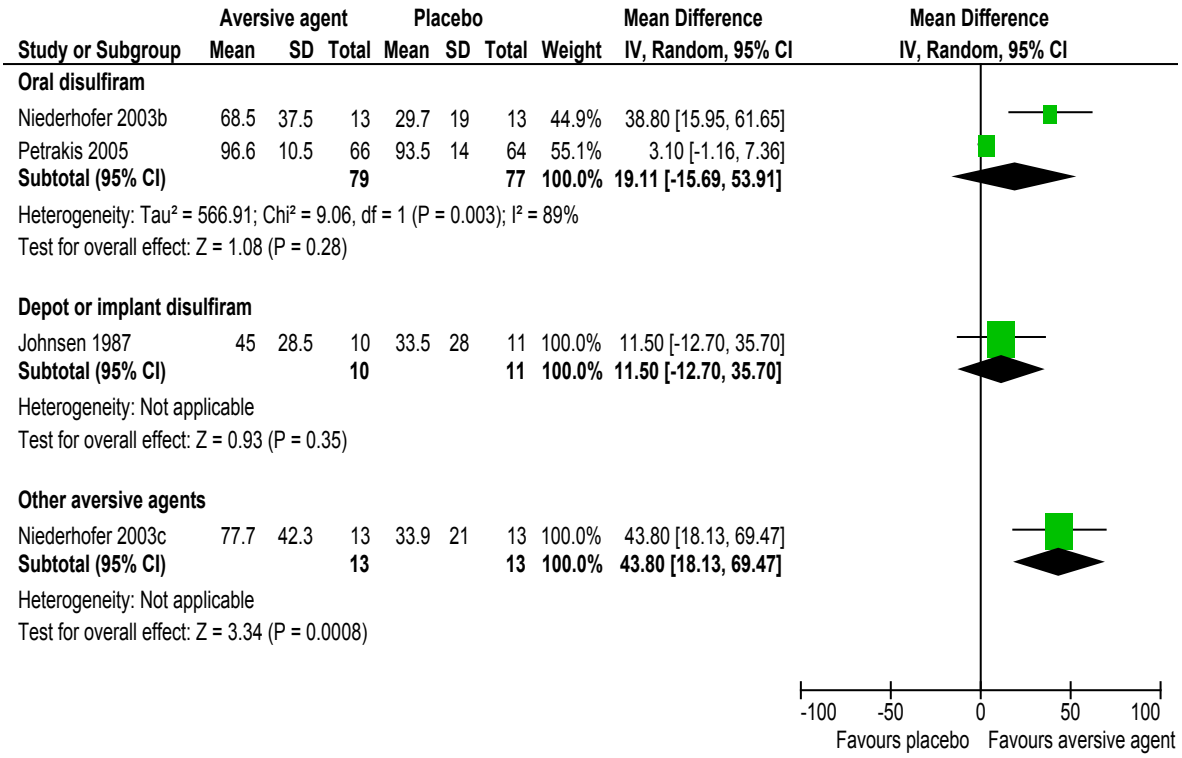
Two studies reported data on the percent of treatment days abstinent (cumulative abstinence duration) for oral disulfiram compared with placebo. One study (Niederhofer 2003B) reported significantly more abstinence with disulfiram but the combined result was not statistically significant (Figure 3.10: mean difference 19.11% days, 95% CI -15.69, 53.91, P=0.28). A further two studies reported data that was not suitable for inclusion in the meta-analysis. Chick 1992 reported significantly greater increase in the number of abstinent days in six months of treatment with disulfiram compared to placebo, while Pettinati 2008 reported that 9 of 52 (17%) participants treated with oral disulfiram, compared to 8 of 54 (15%) receiving placebo, achieved at least three weeks abstinence from cocaine and alcohol. In the latter study there was also no significant difference in the proportion of treatment days with alcohol use or with heavy drinking.

Johnsen 1987 reported no difference between implant naltrexone and placebo in cumulative abstinence duration (Figure 3.10: mean difference 11.5% days, 95% CI -12.90, 35.70, P=0.35). Johnsen 1991 also reported no significant difference in the percent of treatment days with abstinence (data not suitable for entry in meta-analyses).

Niederhofer 2003C reported significantly greater cumulative abstinence duration for cyanamide compared to placebo (Figure 3.10: mean difference 43.80% days, 95% CI 18.13, 69.47, P<0.001). This study was small (13 in each group) and involved adolescents and it is uncertain whether the findings can be extrapolated to the general alcohol dependent population.

Carroll 1998 reported a significant effect for disulfiram on consecutive weeks of alcohol abstinence – 54% receiving disulfiram compared to 17% not receiving medication achieved at least three weeks of abstinence during the study.

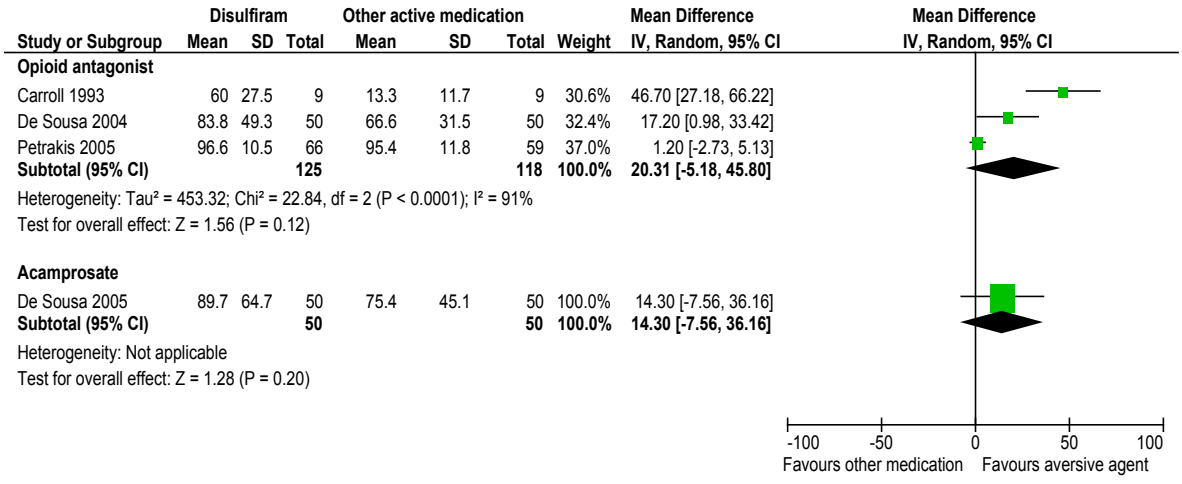
Figure 3.10: Aversive agent compared with placebo, % treatment days abstinent (cumulative abstinence duration)



Three studies reported data on cumulative abstinence duration for disulfiram compared with oral naltrexone. Two studies reported greater abstinence with disulfiram but the combined result is not statistically significant (Figure 3.11: mean difference 20.31%, 95% CI -5.18, 45.80; P=0.12). The studies were diverse with Carroll 1993 involving participants with dual cocaine dependence and alcohol abuse or dependence, De Sousa 2004 being one of the studies undertaken in India involving men from stable family backgrounds, and Petrakis 2005 involving participants with comorbid Axis I psychiatric disorders. In addition, Petrakis 2008 reported that 9 of 53 (17%) treated with disulfiram, 9 of 52 (17.3%) treated with naltrexone and 8 of 54 (14.8%) receiving placebo achieved three weeks of abstinence from cocaine and alcohol. There was also no significant difference between the groups in the proportion of treatment days with alcohol use or with heavy drinking. The variability in outcomes reported by these studies suggests the potential influence of several factors which can only be explored with more data.

One study (De Sousa 2005) reported no significant difference between disulfiram and acamprosate in cumulative abstinence duration (Figure 3.11: mean difference 14.30, 95% CI -7.65, 36.16; P=0.20).

Figure 3.11: Disulfiram compared with other active medication, % treatment days abstinent (cumulative abstinence duration)

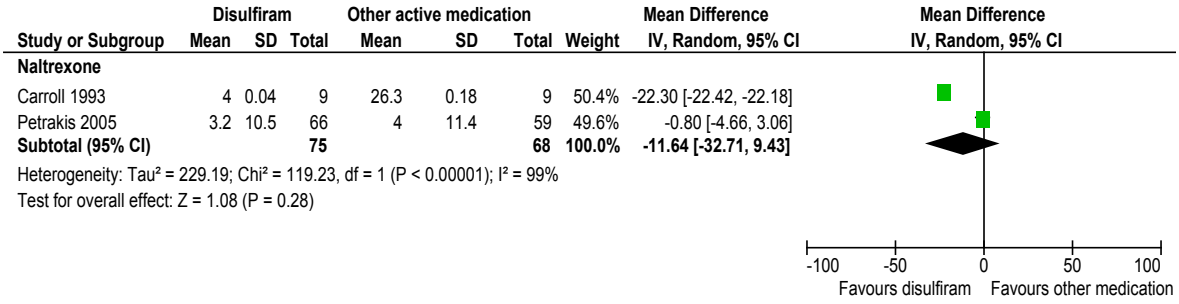


Petrakis 2005 reported no significant difference between oral disulfiram and placebo in the proportion of treatment days with heavy drinking (Mean difference -2.70% days, 95% CI -6.75, 1.35; P=0.19). Johnsen 1987 reported no significant difference between implant disulfiram and placebo (mean difference 11.50 days, 95% CI -7.87, 30.87; P=0.24). Johnsen 1991 also reported no significant difference in the proportion of treatment days with heavy drinking.

Ulrichsen 2010 reported similar numbers of days of heavy drinking during treatment for oral disulfiram compared to no medication.

Two studies reported the proportion of treatment days with heavy drinking for oral disulfiram compared to naltrexone. One study reported less heavy drinking with disulfiram but the combined result was not statistically significant and the diverse nature of the studies limits conclusions (Figure 3.12: mean difference -11.64% days, 95% CI -32.71, 9.43; P=0.28).

Figure 3.12: Disulfiram compared with other active medication, % treatment days with heavy drinking



	Time to first drink and time to relapse
*	Treatment with oral disulfiram appears to significantly prolong the time to first drink and the time to relapse relative to oral naltrexone and acamprosate.
*	Implant disulfiram is no more effective than placebo in delaying recommencement of drinking, but there is a strong placebo effect.
	There are limitations to all data, with further studies needed to confirm findings.

Supporting evidence

No studies reported data on time to first drink or time to relapse for oral disulfiram compared to placebo.

Johnsen 1987 reported the average days to first drink, with no significant difference between implant disulfiram and placebo (mean difference 12.5 days, 95% CI -19.8, 44.8; P=0.45). Johnsen 1991 also reported that the time to first drink was almost the same for the disulfiram and placebo implant groups. However, the authors questioned the adequacy of dose release by the implants used. Wilson 1976 reported that, subsequent to an ethanol challenge, six patients with sham operations and five with disulfiram implants began to drink, at a mean post-operation time of 81 and 109 days, respectively (data not suitable for inclusion in meta-analyses). In Wilson 1980, the disulfiram patients were abstinent for a mean of 361 days, placebo patients 307 days and no-operation controls 24 days. The latter finding shows the presence of a strong placebo effect.

Ulrichsen 2010 reported somewhat less days to first drink for oral disulfiram compared to no medication, but the difference was not statistically significant (mean difference: -20 days, 95% CI -62.88, 22.68; P=0.36) and, as discussed previously, this study is at some risk of selection bias due to low participation rates.

The average time to first drink is significantly longer for disulfiram compared to oral naltrexone (Figure 3.13: mean difference 38.59 days, 95% CI 13.80, 63.38; P=0.002)*, and there is a trend towards a longer time to first drink for oral disulfiram compared with acamprosate (Figure 3.13: mean difference 41.48 days, 95% CI -2.62, 85.58; P=0.07)*. Consistent with these data, the average time to relapse is significantly longer for disulfiram compared with naltrexone (Figure 3.14: mean difference 37.80 days, 95% CI 20.95, 54.66; P<0.001)* and acamprosate (Figure 3.14: mean difference 40.76 days, 95% CI 18.23, 63.30; P<0.001)*.

Figure 3.13: Disulfiram compared with other active medication, Average days to first drink

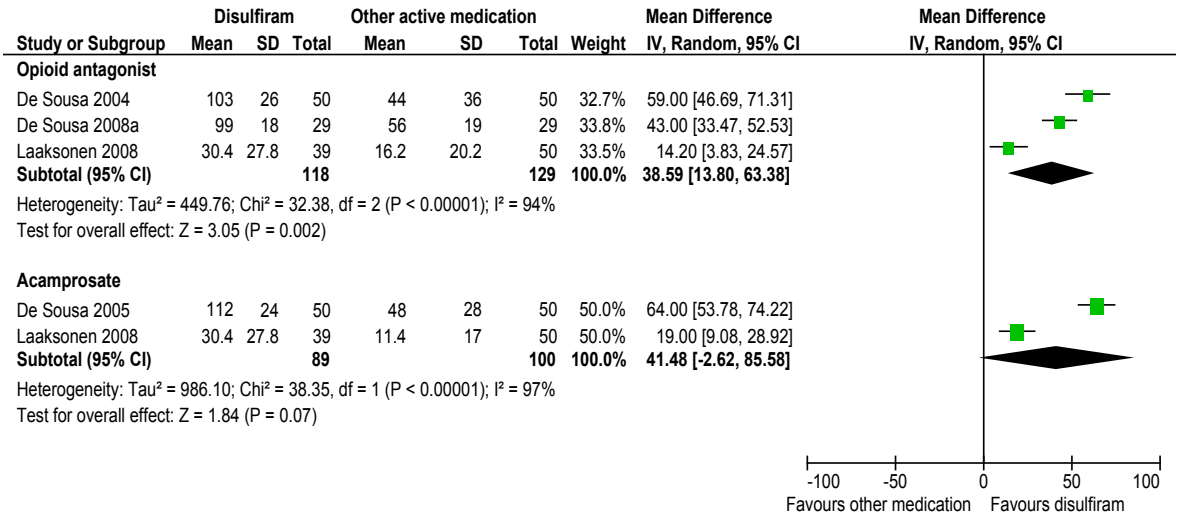
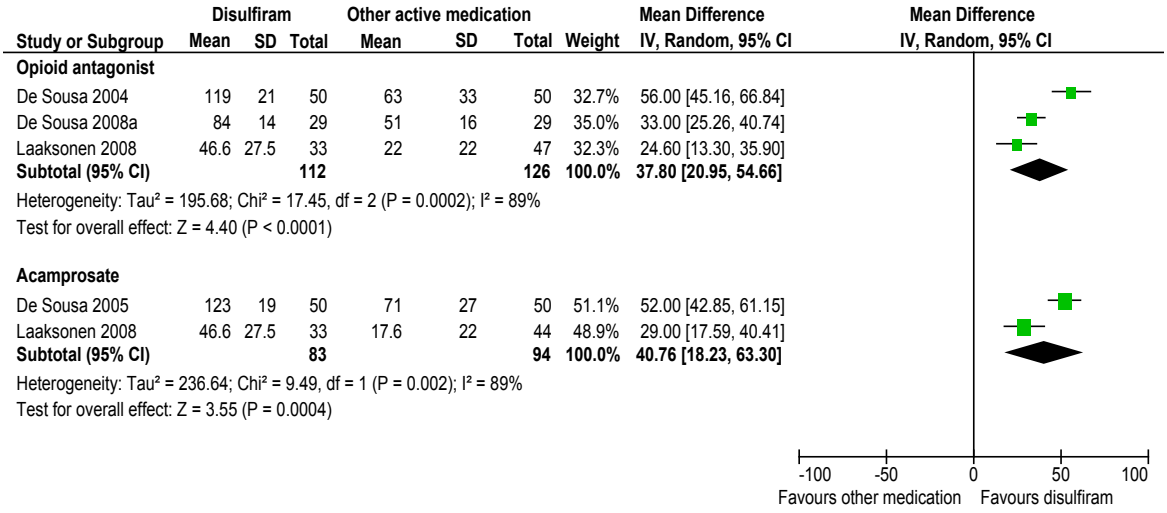


Figure 3.14: Disulfiram compared with other active medication, Average days to relapse to heavy drinking



As discussed previously, these analyses are substantially influenced by two studies (De Sousa 2004, De Sousa 2008A) undertaken in India where participants had stable family environments to provide support. Additional data are required to confirm the findings.

	Objective indicators of alcohol consumption
	Data on GGT levels are consistent with self-report data suggesting that oral disulfiram is at least as effective as oral naltrexone in reducing alcohol consumption.
	Insufficient data are available to form a view on the effectiveness of disulfiram relative to placebo or acamprosate based on objective indicators of alcohol consumption.

Supporting evidence

Only one study (Chick 1992) reported serum GGT levels for disulfiram compared with placebo, with levels decreasing from baseline to 6 months in the disulfiram group and increasing in the placebo group (the group difference was significant).

For disulfiram compared with naltrexone, De Sousa 2004 and Petrakis 2005 reported greater reductions in GGT for disulfiram compared with naltrexone. In Nava 2006, there were significant reductions in GGT during treatment with no significant difference between disulfiram and naltrexone.

Laaksonen 2008 also reported that GGT decreased significantly in the disulfiram group in weeks one to six, with no significant differences between groups.

In De Sousa 2005, serum GGT was significantly lower in the acamprosate group after eight months. This was not consistent with the alcohol consumption data. The authors do not discuss the GGT levels.

	Craving
*	Data are limited, but it appears that disulfiram has little effect on craving for alcohol.

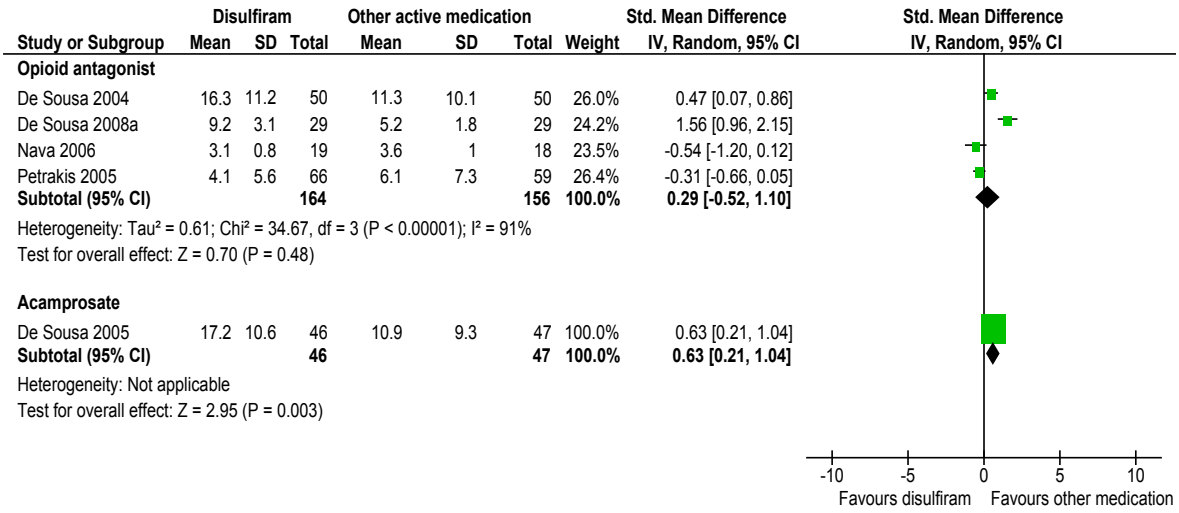
Supporting evidence

Only one study (Petrakis 2005) reported average craving scores with no significant difference between disulfiram and placebo (mean difference -0.8, 95% CI -3.12, 1.52; P=0.50).

Based on four studies, there is no significant difference for average craving scores with disulfiram compared to naltrexone (Figure 3.15: SMD 0.29, 95% CI -0.52, 1.10; P=0.48)*, but in Petrakis 2005 disulfiram-treated subjects reported a significantly greater change in craving over time compared to those treated with naltrexone.

One study reported significantly less craving with acamprosate compared with disulfiram (Figure 3.15: SMD 0.63, 95% CI 0.21, 1.04; P=0.003).

Figure 3.15: Disulfiram compared with other active medication, Average craving scores



3.2.3 Adverse effects

*	For the studies included in this review, disulfiram was associated with increased risk of nausea or vomiting and neuropsychiatric symptoms relative to placebo. Withdrawal from treatment is more likely with disulfiram compared to placebo.
*	The implantation of disulfiram tablets as performed by the studies included in this review appears to be associated with significantly greater risk of wound complications.
*	Disulfiram may be associated with more neuropsychiatric symptoms than acamprosate, but otherwise there appear to be no significant differences between disulfiram and naltrexone or disulfiram and acamprosate in terms of the incidence of adverse effects.

Supporting evidence

Data are limited, but indicate that for oral disulfiram compared to placebo:

> there is no significant difference in the likelihood of any adverse effects (Figure 3.16: RR 1.00, 95% CI 0.07, 14.34; P=1.0)* or gastrointestinal symptoms (Figure 3.17: RR 1.07, 95% CI 0.73, 1.57; P=0.73)*; but

> there is a significantly greater risk of nausea or vomiting (Figure 3.18: RR 1.44, 95% CI 1.07, 1.94; P=0.01)* and neuropsychiatric symptoms (Figure 3.19: RR 1.39, 95% CI 1.02, 1.90; P=0.04)*.

De Sousa 2005 reported that side effects abated in the first week of the study. One study (Chick 1992) reported that 7 of 64 people treated with disulfiram required a dose reduction to manage adverse effects, compared to none of 62 receiving placebo. The difference was not statistically significant (RR 14.54, 95% CI 0.85, 249.25; P=0.06)*. Ulrichsen 2010 reported that the disulfiram dose was reduced in 7 of 19 people allocated to disulfiram. In this study there were no serious adverse effects, but 11 of 19 (58%) receiving disulfiram complained of gastrointestinal disturbances.

Based on three studies, significantly more people treated with oral disulfiram were withdrawn from treatment due to adverse effects compared to placebo (Figure 3.20: RR 4.86, 95% CI 1.08, 21.93; P=0.04)*.

Figure 3.16: Aversive agent compared with placebo, participants experiencing any adverse effects

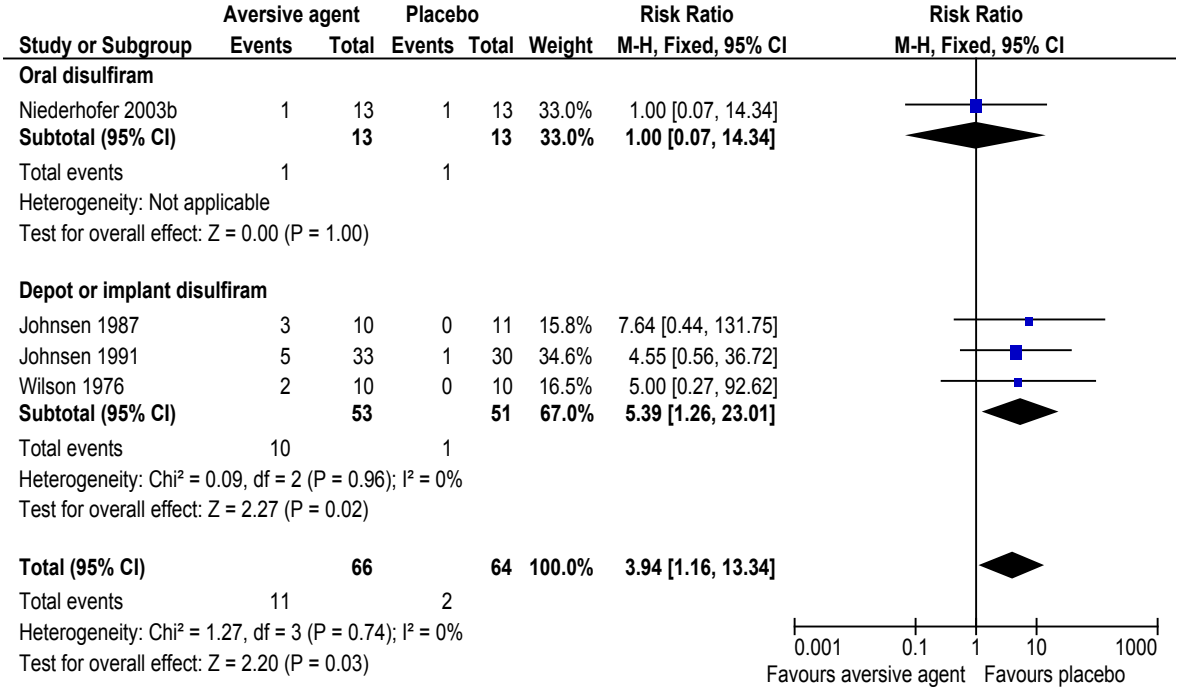


Figure 3.17: Aversive agent compared with placebo, participants experiencing gastrointestinal symptoms

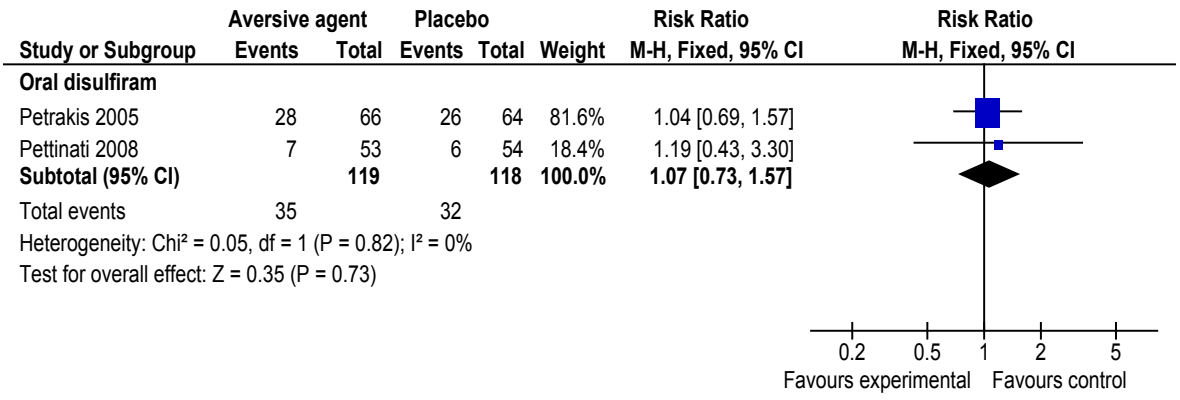


Figure 3.18: Aversive agent compared with placebo, participants experiencing nausea or vomiting

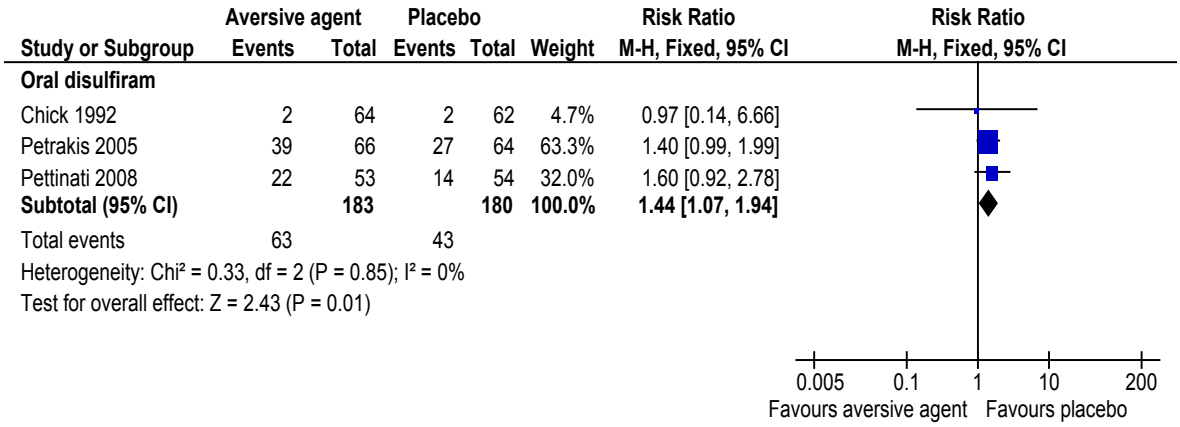
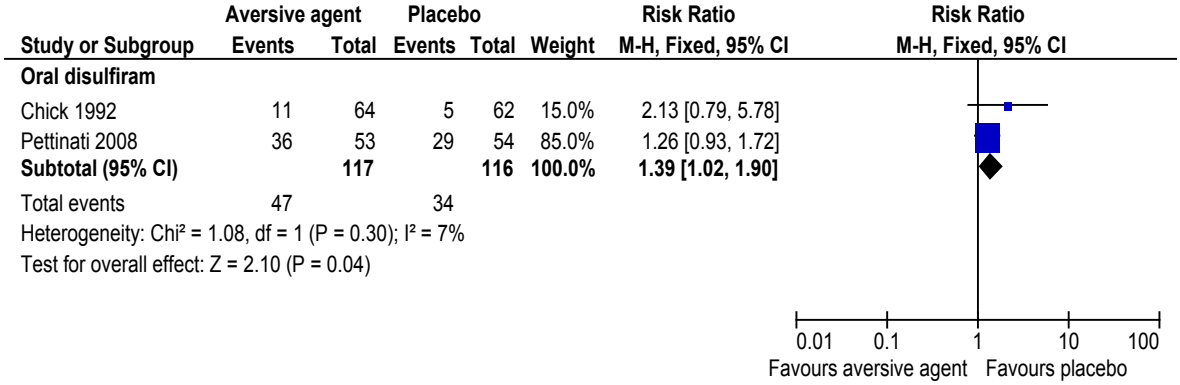


Figure 3.19: Aversive agent compared with placebo, participants experiencing neuropsychiatric symptoms



Based on three studies, implant preparations of disulfiram are associated with significantly more adverse effects than placebo (Figure 3.16: RR 5.39, 95% CI 1.26, 23.01; P=0.02)*. Adverse effects of implants are largely due to a greater risk of wound complications. Allen and Litten 231 commented that implants are frequently problematic due to inadequate release of the drug as well as infections and other adverse physiological consequences of the surgical procedure.

In Wilson 1976, five patients with disulfiram implants resumed drinking after an ethanol challenge. Two of the five required emergency treatment for disulfiram-ethanol reactions, and the others experienced mild reactions. In Wilson 1980, on resumption of drinking, seven patients with disulfiram implants did not experience a disulfiram-ethanol reaction, six experienced mild reactions, and four experienced severe reactions requiring hospitalisation for up to three days.

The studies included in this review indicate no significant differences between disulfiram and naltrexone in:

> the likelihood of any adverse events (Laaksonen 2008: RR 0.76, 95% CI 0.48, 1.20; P=0.24)*;

> gastrointestinal symptoms (Figure 3.21: RR 0.78, 95% CI 0.56, 1.08; P=0.14)*;

> nausea or vomiting (Figure 3.22: RR 0.74, 95% CI 0.37, 1.46; P=0.39)*;

> neuropsychiatric symptoms (Figure 3.23: RR 1.12, 95% CI 0.86, 1.45; P=0.41)*; or

> the number of people withdrawn from treatment due to adverse effects (Figure 3.24: RR 1.50, 95% CI 0.48, 4.64; P=0.48)*.

Figure 3.20: Aversive agent compared with placebo, participants withdrawn due to adverse effects

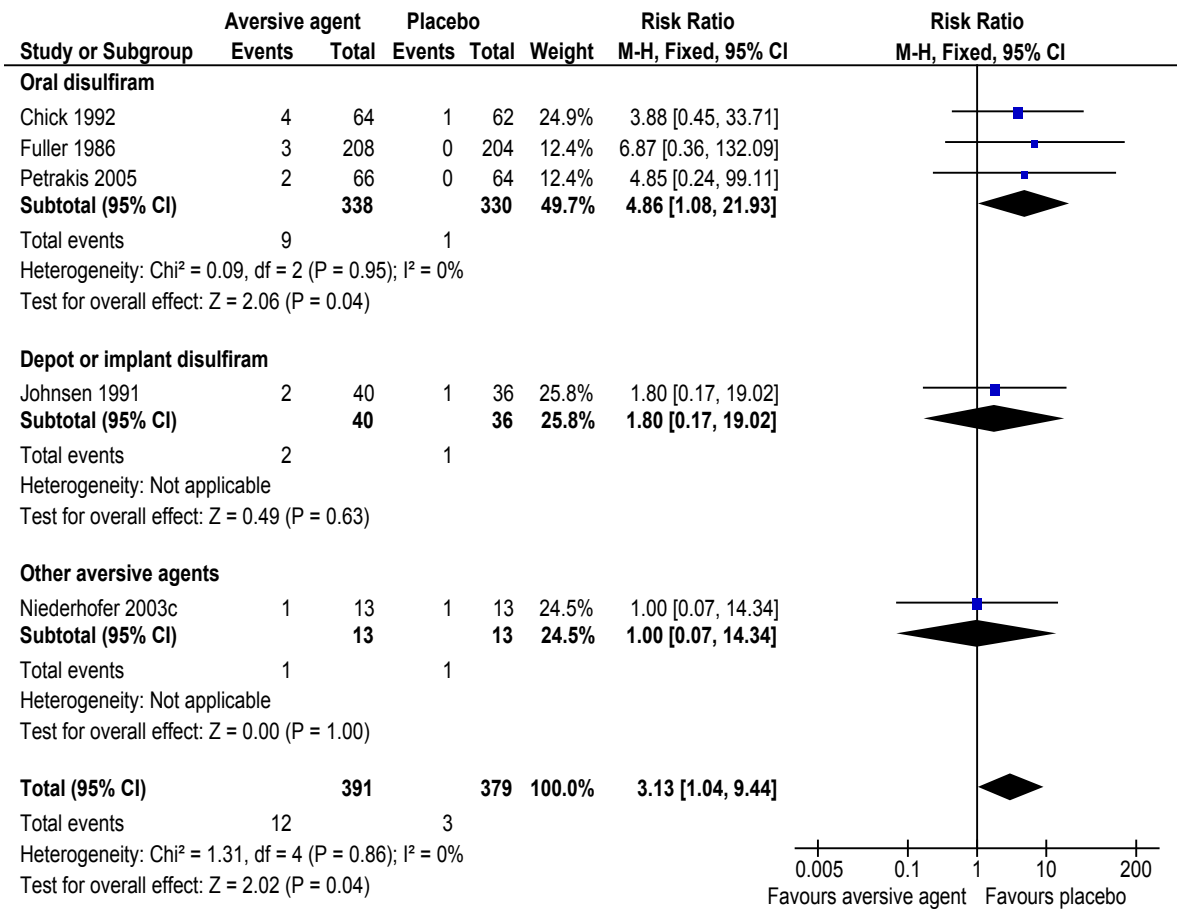


Figure 3.21: Disulfiram compared with other active medication, participants experiencing gastrointestinal symptoms

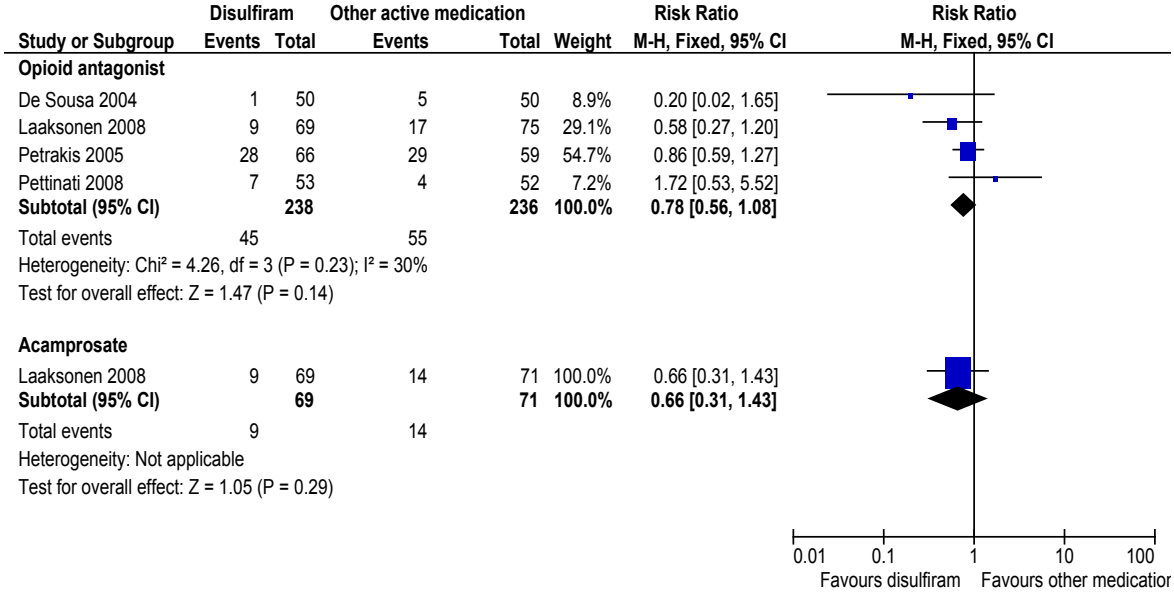


Figure 3.22: Disulfiram compared with other active medication, participants experiencing nausea or vomiting

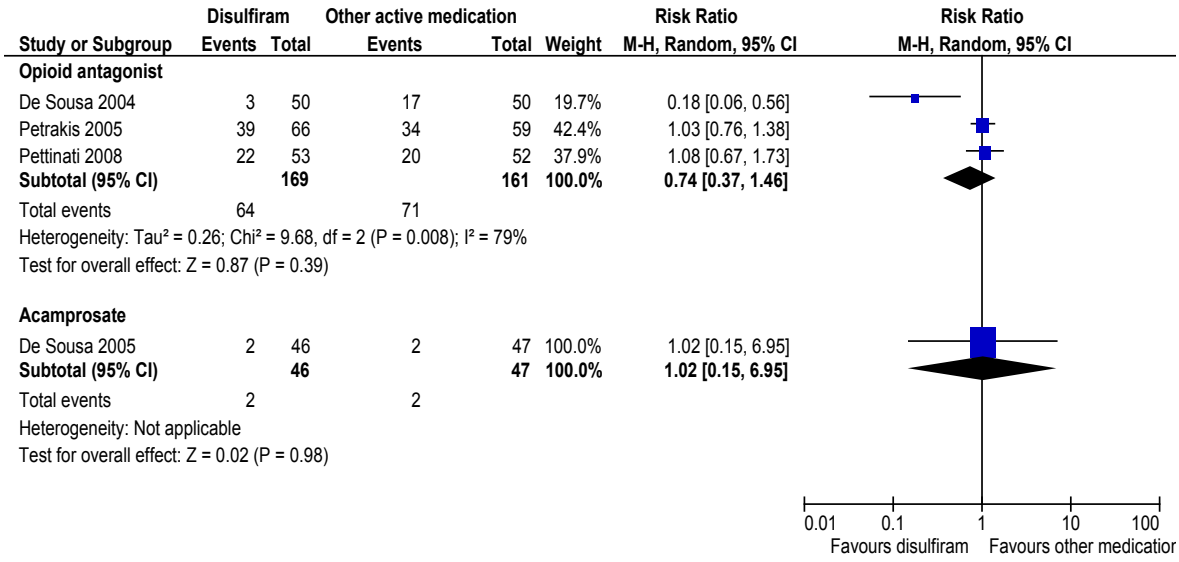
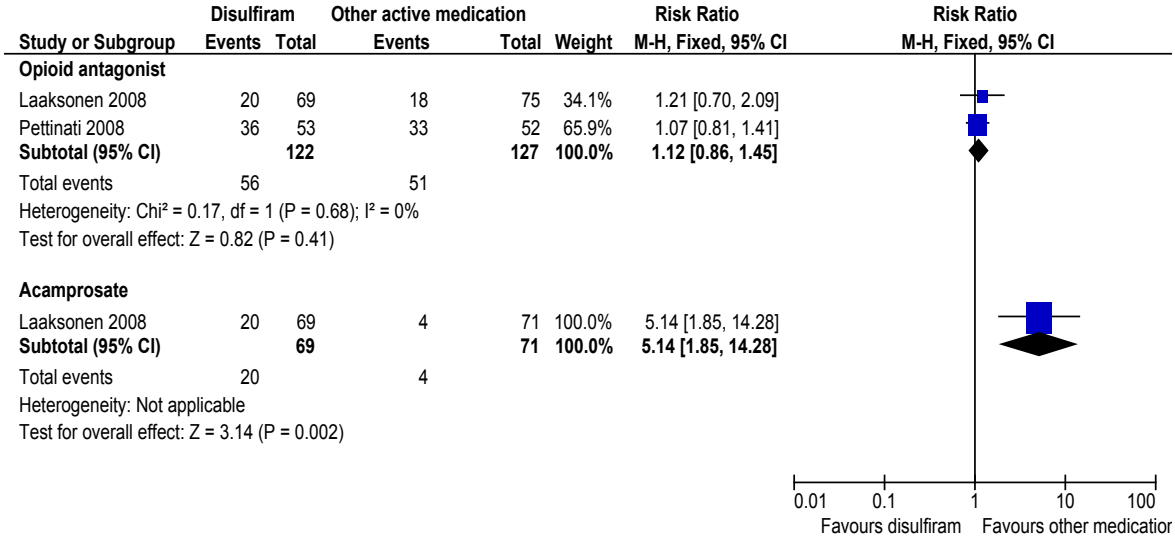


Figure 3.23: Disulfiram compared with other active medication, participants experiencing neuropsychiatric symptoms



One study reported significantly more neuropsychiatric symptoms with disulfiram compared to acamprosate (Figure 3.23: RR 5.14, 95% CI 1.85, 14.28; P=0.002)*. Apart from this there were no significant differences between disulfiram and acamprosate in:

> the number of participants experiencing any adverse effects (Laaksonen 2008: RR 1.03, 95% CI 0.62, 1.71; P=0.91)*;

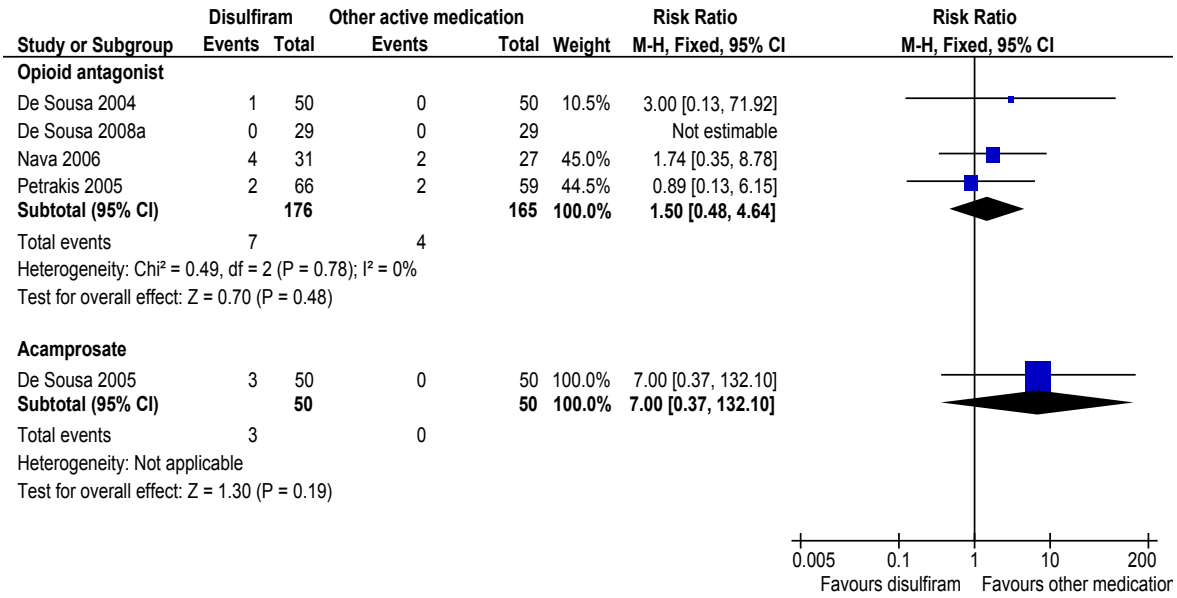
> gastrointestinal symptoms (Figure 3.21: RR 0.66, 95% CI 0.31, 1.43; P=0.29)*;

> nausea or vomiting (Figure 3.22: RR 1.02; 95% CI 0.15, 6.95; P=0.98)*; or

> the number of people withdrawn from treatment due to adverse effects (Figure 3.23: RR 7.0, 95% CI 0.37, 132.1; P=0.19)*.

A retrospective analysis of the outcomes of disulfiram or acamprosate treatment involving 353 alcohol-dependent patients in a naturalistic outpatient treatment setting, found there were significantly more adverse events in the disulfiram group (62%) compared with the acamprosate group (48%, P=0.02). Tiredness during the day (which would be included in neuropsychiatric symptoms) in combination with sleep disturbnances was the most prominent adverse effect with disulfiram (experienced by 50% of people receiving disulfiram compared to 15.9% of those receiving acamprosate). Gastrointestinal complaints were most prominent in the acamprosate group (31.8% acamprosate compared to 14.8% disulfiram). However, dropout rates due to adverse events were less than 5% in both groups.

Figure 3.24: Disulfiram compared with other active medication, participants withdrawn due to adverse effects



3.3 Factors influencing treatment outcome

Despite the long history of use of disulfiram for treatment of alcohol dependence, data on effectiveness remain sparse. There has been some rekindling of interest in disulfiram for use in combination with other medications (see section 5), in comparison with the newer medications (naltrexone, acamprosate) and as a treatment for cocaine dependence, with or without concomitant alcohol abuse,[232] but as yet research evidence is insufficient to form a clear view on the relative effectiveness of disulfiram and factors that might influence treatment response, such as ethnicity, gender, typology and genetics of alcohol dependence. However, it is clear that compliance is a key factor in treatment outcome, and the risk of adverse effects is a central consideration in choosing to use disulfiram.

3.3.1 Compliance

	Treatment compliance is critical to outcome and compliance is more likely with supervised administration, and stable relationships.
	Available evidence does not support significantly improved outcomes with implanted compared to oral disulfiram.

Supporting evidence

Fuller *et al*.[222], in a randomised controlled trial, found that disulfiram did not result in more total abstinence, but there were fewer drinking days among a subset of men who received disulfiram, were slightly older and had more residential stability. Fuller *et al*. concluded that disulfiram prescribed for patients to take at their discretion has limited effectiveness.[233] Mattick and Jarvis[203] concluded from a review of research that unsupervised use of oral disulfiram has a limited impact on abstinence from alcohol, due to low compliance. However, they concluded that if compliance is improved, the results can be promising. Overall, a small positive effect for disulfiram was found immediately after treatment (effect size +0.15), at 6–11 months post-treatment (effect size +0.30) and at 12–23 months post-treatment (effect size +0.10).

In Fuller 1979, attendance at scheduled appointments was a good indication of abstinence, no matter which medication group participants were in. Of the 24 participants with greater than 85% scheduled appointments kept, 14 (58%) were totally abstinent, while only 11 of 100 (11%) with 85% or less attendance were abstinent. In Fuller 1986 there was a highly significant relationship between compliance to a drug regimen and abstinence, regardless of which drug the patient received. Overall, 20% of those who finished the study were judged compliant, and of these 43% were abstinent, whereas only 8% of the noncompliant group were abstinent ($p<0.001$).

In Gerrein 1973 the disulfiram groups had significantly higher attendance than the non-disulfiram groups. The difference was largely attributable to the disulfiram maintenance group (ie. those given disulfiram twice a

week under supervision). The disulfiram groups attended 50% of all possible visits during the 8-week follow-up period, compared to 32% for the no-medication groups.

Supervision and stable relationships both appear to improve compliance and treatment efficacy.[35;234;235] Hence, where it is prescribed, disulfiram use should be supervised and it should be employed as one part of a comprehensive treatment program.

Allen and Litten [231] identify several possible strategies for improving compliance with disulfiram, including the use of implant preparations (problematic to date), incentives, contracts with the client and a significant other, and modification of patient instructions and expectations for the medication. Limited evidence exists in relation to any of these strategies. The significance of compliance is in the effective exposure to medication. Implants were seen as a way of ensuring this but data suggests that inadequate release from implanted disulfiram was problematic.[210;220] In Johnsen 1987, there was no difference between the disulfiram and placebo groups in response to ethanol challenge (no change in blood acetone levels) and no disulfiram-alcohol interactions. The authors questioned the efficacy of the implants.

3.3.2 Adverse effects

	Accumulated clinical experience with disulfiram indicates an adverse drug reaction rate of one per 200-2000 patients per year, and a risk of disulfiram-induced fatal hepatitis of 1 case in 30,000 patients treated per year.
	Most serious adverse reactions, and the possibility of fatal disulfiram-alcohol reaction, are more likely with higher doses of disulfiram (≥500mg/day).

Supporting evidence

Although there is little data from controlled trials, there is considerable knowledge of the adverse effects of disulfiram derived from many years of experience with this medication.

At disulfiram doses between 200 and 250 mg/day, the severity of the disulfiram-alcohol interaction varies from a slight flush to a distressing state of nausea, headache, dizziness and tightness in the chest. Very rarely, when larger amounts of disulfiram have been taken, the reaction has been fatal. Because of this risk, disulfiram should normally not be offered to patients with heart disease or taking hypotensive medication. Deaths from the disulfiram-alcohol reaction have not been reported in recent years, possibly because the doses used are now lower and patient with cardiac disease are excluded.[236]

In addition to cardiovascular disease, idiopathic seizure disorder, and any condition impairing ability to understand the risks associated with disulfiram, pregnancy has been identified as a contraindication to the prescription of disulfiram because disulfiram has been reported to cause fetal abnormalities.[233]

Of the less serious adverse effects, tiredness, headaches and sleepiness are most common. Skin complaints are rare but rashes, pruritis and exfoliative dermatitis have been described.[236] Drowsiness is usually of short duration. If it persists, it usually can be managed by having the patient take the dose in the evening.[233]

There are interactions between disulfiram and compounds that utilise the cytochrome P450 enzyme system – demonstrated with amitryptiline, imipramine, warfarin and phenytoin, but interactions are also likely with the benzodiazepines chlordiazepoxine and diazepam, but not lorazepam and oxazepam. There is no hazardous interaction with paracetamol.[236] Animal and human data indicate that the concomitant use of MAO inhibitors and disulfiram is not safe.[233]

An analysis of reports of adverse drug reactions in Denmark produced an estimate of one adverse drug reaction per 200-2000 patients per year for disulfiram. This is considered to be an intermediate rate of adverse reactions for a medication.[233]

Disulfiram is known to cause hepatitis, which is sometimes fatal. The best estimate of the frequency of disulfiram-induced fatal hepatitis is one case in 30,000 patients treated per year. It appears to be more common in patients given disulfiram for the treatment of nickel sensitivity. There is no evidence that a pre-existing liver disorder increases the risk of disulfiram hepatotoxicity – in most reported cases patients had normal liver function at the start of treatment. Fatal outcome was more likely when the drug was continued for some days after jaundice had been noticed. Onset of hepatitis is usually very rapid, so even frequent liver function testing may not detect it.[236] Fuller and Gordis[233] recommend informing the patient of the symptoms and signs of hepatotoxicity and also doing frequent testing of liver function in the early months of treatment. Because of the seriousness of the disulfiram hepatotoxicity, they recommend not prescribing disulfiram to

those with abnormal liver tests.

Kulig and Beresford[237] discuss the use of disulfiram in patients with hepatitis C. Based on a literature review they conclude that continued drinking appears much more toxic to the liver than does disulfiram in this group.

There have been occasional reports of disulfiram-linked psychosis or a confusional state – more common when higher doses were routinely prescribed (≥500mg/day). Symptoms usually completely resolved after withdrawal of disulfiram and sometimes after a short course of treatment with an antipsychotic drug. Rates of unwanted psychiatric effects are extremely low at recommended disulfiram doses of 200-250mg/day.[236]

Peripheral neuropathy and optic neuritis have been reported in conjunction with disulfiram treatment. The rate of disulfiram-induced neuropathy is around one in 15,000 patient years. Neuropathy is more likely with higher doses and possibly drug interactions. It is reversible if detected early.[236] In De Sousa 2005, three of 50 in the disulfiram group dropped out of treatment because of neuropathy.

3.3.3 Comorbid mental health disorders

	The presence of different mental health disorders may influence response to treatment.
	Data are limited, but there is no evidence to suggest that treatment with disulfiram has any negative impact on comorbid mental health disorders.

Supporting evidence

A number of secondary analyses of data from Petrakis 2005 considered treatment outcomes for groups of participants with different comorbid mental health disorders. The findings of these analyses included the following:

> subjects with post-traumatic stress disorder had better outcomes with any active medication over placebo;

> subjects with psychotic spectrum disorder similarly had better outcomes with any active medication;

> subjects with depression receiving disulfiram reported lower craving over time than subjects with depression who were receiving naltrexone; and

> for subjects with comorbid personality disorder, medications were not more effective in reducing craving over placebo.

A retrospective study of disulfiram in 33 patients with alcohol use disorder and severe mental illness (schizophrenia or schizoaffective disorder) found that 64% saw a remission of alcoholism for at least one year during a three-year follow-up. Side effects from disulfiram were reported by 21% but significant psychiatric complications were not reported.[238]

Mutschler *et al*.[239] note that due to the intended adverse reaction with alcohol, there is a view that the use of disulfiram is dangerous for people with personality disorders or psychiatric comorbidities because of their increased risk of impulsivity or suicidal behaviour. They reported the use of disulfiram (1.5-2.5g/week) in eight patients with borderline personality disorder with no serious adverse events or ethanol-disulfiram interactions (2 of 8 were completely abstinent for an average 9.25 months of treatment).

SECTION 4: ANTIDEPRESSANTS

Overview

Rationale

The co-occurrence of alcohol dependence and depression is common and depressive symptoms may be a factor triggering relapse to heavy drinking. In addition serotonergic dysfunction has been implicated in alcohol dependence and the regulation of alcohol intake. Hence, the use of antidepressants in people who are alcohol dependent may support relapse prevention treatment.

Type of antidepressant

Most data on the effectiveness of antidepressants comes from studies comparing selective serotonin reuptake inhibitors (SSRIs) with placebo, with some studies of tricyclic antidepressants or nefazodone compared to placebo. A few studies compared antidepressants with other active medication (another antidepressant, naltrexone, or memantine).

Retention in treatment

Treatment with an antidepressant has no effect on retention in treatment relative to placebo, in terms of either completion of treatment or time in treatment ***.

Treatment with a tricyclic antidepressant may be associated with reduced retention in treatment relative to placebo*.

Rates of retention in treatment are somewhat lower with antidepressants relative to placebo when used in the treatment of people without concurrent depression*.

Abstinence

Treatment with an antidepressant has no effect on the likelihood of abstinence during treatment relative to placebo or no medication ***.

Abstinence during treatment with antidepressants may be significantly more likely when concurrent depression is present*.

Relapse to heavy drinking

Treatment with an antidepressant has no effect on the probability of relapse to heavy drinking during treatment relative to placebo**.

Insufficient data are available to determine whether the presence of concurrent depression influences the effect of antidepressants on the risk of relapse.

Amount of alcohol consumed

Compared with placebo, antidepressants have no significant effect on drinks per drinking day or average drinks per week**.

Insufficient data are available to assess the effect of antidepressants on alcohol consumption relative to no medication or other active medication.

Antidepressants may be more effective in reducing alcohol consumption, at least in terms of drinks per drinking day, in people with concurrent depression, compared to those without depression*.

Periods of abstinence or heavy drinking during treatment

There is no significant difference between antidepressants and placebo in terms of cumulative abstinence duration*.

Nefazodone may be associated with significantly more heavy drinking days, but overall there is no significant difference between antidepressants and placebo in terms of the proportion of treatment days on which heavy drinking occurred*.

The presence or absence of concurrent depression did not affect these outcomes*.

Time to first drink and time to relapse

Antidepressants have no effect on time to first drink or time to relapse, relative to placebo*.

Objective indicators of alcohol consumption

Available information indicates no significant difference between antidepressants and placebo in objective indicators of alcohol consumption.

Craving

The limited data available suggest that antidepressants have no effect on craving for alcohol, relative to placebo.

Adverse effects

People treated with antidepressants are more likely to experience any adverse effects, compared to those receiving placebo*.

Significantly more gastrointestinal symptoms, nausea and vomiting, and neuropsychiatric symptoms are experienced with antidepressants, compared to placebo*.

Withdrawal from treatment due to adverse effects is significantly more likely with antidepressants compared to placebo**.

Factors affecting treatment response

(a) Concurrent depression

Antidepressants are not effective in relapse prevention treatment of alcohol dependence in people without concurrent depression*.

Antidepressants are beneficial in people with concurrent alcohol dependence and depression, particularly for alleviation of depressive symptoms*.

Antidepressants may have a beneficial effect on alcohol consumption through the alleviation of depression in people with alcohol dependence and concurrent depression.

(b) Type of alcohol dependence

Antidepressants appear more likely to be beneficial in low risk/severity, late onset alcoholism.

There is no clear evidence on the role of family history or genetic factors, but are less likely to be significant in low risk/severity, late onset alcoholism.

(c) Gender

There is no clear evidence on the effect of gender on response to antidepressants.

(d) Other factors

Treatment compliance and level of social support are likely to affect treatment outcome.

4.1 Rationale for effect

The co-occurrence of alcohol dependence and mental health disorders is common. As many as 80% of patients seeking treatment for an alcohol disorder report distress from psychiatric symptoms, most commonly depressive symptoms.[240]

Alcohol dependence prolongs the course of depression, and depression that persists with abstinence from alcohol is a risk factor for relapse to drinking.[240]

In primary depression, depressive symptoms will often persist, even after treatment of alcohol dependence. In these cases treatment with antidepressant medication seems warranted. In cases where alcohol is self-medicating the primary depression, then alleviating depression should positively impact on the alcohol disorder and reduce drinking.[240]

If the depression is a clear result of alcohol use, it might be questioned whether an antidepressant would have any therapeutic impact beyond what abstinence would achieve. However, distinguishing between primary and secondary depression is not straightforward and the persistence of depressive symptoms during abstinence

is still a possibility. Not treating depression (whether primary or secondary) is predictive of worse drinking outcomes.[240]

In addition to the frequent co-occurrence of alcohol dependence and depressive symptoms, there is evidence implicating serotonergic dysfunction in alcohol dependence and the regulation of alcohol intake.[23;241] Acute administration of alcohol causes 5-HT release, while chronic administration causes a decrease in 5-HT in the nucleus accumbens in rats. Animal studies have consistently demonstrated reductions in alcohol consumption, with the administration of a variety of 5-HT agents.[242] There is some evidence of a relationship between variations of the serotonin transporter gene and alcohol dependence but the significance of this remains unclear.[243]

Preclinical trials with humans initially provided encouraging results for the use of SSRIs (fluoxetine, citalopram, fluvoxamine, sertraline) in treating alcohol use disorders. One major advantage of SSRIs is their safety profile. They have a low potential for abuse and do not potentiate alcohol effects on motor skills or cognition (although they may alter ability to drive or operate heavy machinery) and are relatively safe in overdose.[23;35]

This section considers the evidence for the effectiveness of tricyclic antidepressants and nefazodone, as well as SSRIs, in relapse prevention treatment of alcohol dependence.

4.2 Evidence for effectiveness

The trials included in this group of studies used a variety of antidepressants, including:

> fluvoxamine, citalopram, fluoxetine, sertraline (all SSRIs);

> desipramine, tianeptine, imipramine (tricyclic antidepressants); and

> nefazodone, an antidepressant related to trazodone that has a moderate inhibitory effect on reuptake of serotonin, norepinephrine, and dopamine, and selectively blocks the postsynaptic 5-HT_2 receptor which has been implicated in alcohol drinking behaviour[117].

The majority of studies compared an antidepressant with placebo (see Table 4.1) but two studies (Angelone 1998, Habrat 2006) compared different antidepressants, two studies (Kranzler 2000, Pettinati 2010) included comparison with naltrexone, and one study (Muhonen 2008) compared the SSRI escitalopram with memantine (an NMDA glutamate receptor blocking agent). One study (Angelone 1998) also included a comparison with no medication.

Table 4.1: Studies involving the use of antidepressants for relapse prevention treatment of alcohol dependence

Antidepressant compared with placebo				Antidepressant compared with other active medication		
SSRI		Tricyclic	Nefazodone	Other antidepressant	Opioid antagonist	Other (Memantine)
Brady 2005[244;245] Chick 2004 [252] Cornelius 1997[258-260] Cornelius 2009 [263] Coskunol 2002 [266] Deas 2000 [268] Eriksson 2001 [271] Gual 2003 [276] Janiri 1996 [277] Kabel 1996 [279] Kranzler 1993 [246]	Kranzler 1995[253;254] Kranzler 2006 [261] Moak 2003 [264] Naranjo 1990 [267] Naranjo 1995[269;270] Pettinati 2000[272-275] Pettinati 2010 [118] Tiihonen 1996 [278]	Favre 1997[247;248] Mason 1996 [255] McGrath 1996 [262]	Hautzinger 2005 [249] Hernandez-Avila 2004 [256] Kranzler 2000 [117] Roy-Byrne 2000 [265]	Angelone 1998 [241] Habrat 2006[257]	Kranzler 2000 [117] Pettinati 2010 [118]	Muhonen 2008 [250;251]

The SSRIs themselves are not a homogeneous class of drugs and may differ in their efficacy.[241] Hence, while these studies have been grouped for an initial analysis of effectiveness relative to placebo or no medication, diversity in the antidepressants may explain any heterogeneity of findings. This is considered in the sections below presenting the analyses. Consideration is also given to the effect of the presence of concurrent depression at the time of antidepressant treatment.

4.2.1 Retention in treatment

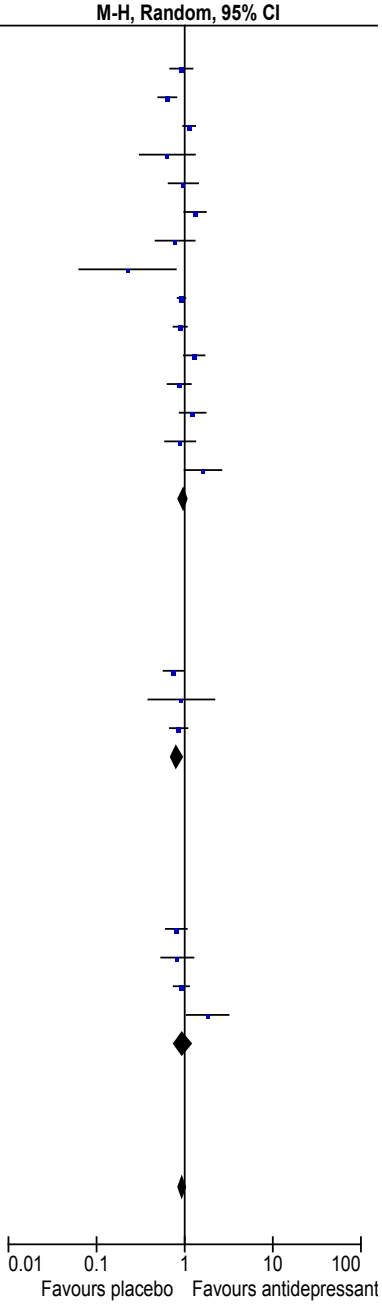
***	Treatment with an antidepressant has no effect on retention in treatment relative to placebo, in terms of either completion of treatment or time in treatment.
*	Treatment with a tricyclic antidepressant may be associated with reduced retention in treatment relative to placebo.
*	Rates of retention in treatment are somewhat lower with antidepressants relative to placebo when used in the treatment of people without concurrent depression.

Supporting evidence

There is no significant difference between SSRIs (Figure 4.1: RR 0.97, 95% CI 0.85, 1.10; p=0.61)*** or nefazodone (Figure 4.1: RR 0.95, 95% CI 0.74, 1.23; P=0.72)* and placebo in the number of participants completing the study treatment, but rates of completion of treatment are significantly lower for tricyclic antidepressants compared with placebo (Figure 4.1: RR 0.81, 95% CI 0.69, 0.96; P=0.02)*.

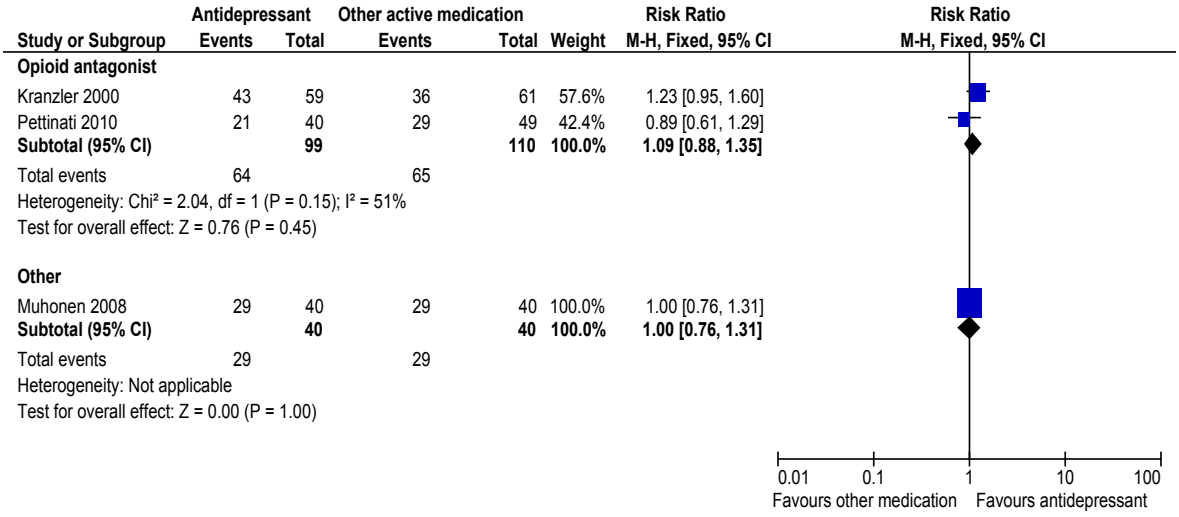
Figure 4.1: Antidepressant compared with placebo, participants completing the study

Study or Subgroup	Antidepressant Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SSRI						
Brady 2005	31	49	31	45	5.1%	0.92 [0.69, 1.23]
Chick 2004	72	243	116	249	6.0%	0.64 [0.50, 0.80]
Cornelius 2009	24	24	23	26	7.4%	1.13 [0.96, 1.32]
Deas 2000	3	5	5	5	1.6%	0.64 [0.31, 1.30]
Gual 2003	24	44	22	39	3.8%	0.97 [0.66, 1.42]
Janiri 1996	19	21	20	29	5.3%	1.31 [0.99, 1.74]
Kabel 1996	9	15	10	13	2.7%	0.78 [0.47, 1.30]
Kranzler 1993	2	10	8	9	0.6%	0.23 [0.06, 0.79]
Kranzler 1995	46	51	49	50	8.3%	0.92 [0.83, 1.02]
Kranzler 2006	92	159	110	169	7.1%	0.89 [0.75, 1.06]
Moak 2003	31	38	28	44	5.4%	1.28 [0.98, 1.68]
Naranjo 1995	31	53	31	46	4.9%	0.87 [0.64, 1.18]
Pettinati 2000	32	50	26	50	4.4%	1.23 [0.88, 1.73]
Pettinati 2010	21	40	23	39	3.7%	0.89 [0.60, 1.32]
Tiihonen 1996	21	31	13	31	2.9%	1.62 [1.00, 2.61]
Subtotal (95% CI)		**833**		**844**	**69.3%**	**0.97 [0.85, 1.10]**
Total events	458		515			
Heterogeneity: Tau² = 0.04; Chi² = 44.56, df = 14 (P < 0.0001); I² = 69%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Tricyclic antidepressants						
Favre 1997	58	170	78	172	5.5%	0.75 [0.58, 0.98]
Mason 1996	8	37	8	34	1.2%	0.92 [0.39, 2.18]
McGrath 1996	27	36	29	33	6.1%	0.85 [0.68, 1.07]
Subtotal (95% CI)		**243**		**239**	**12.8%**	**0.81 [0.69, 0.96]**
Total events	93		115			
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 2 (P = 0.71); I² = 0%						
Test for overall effect: Z = 2.39 (P = 0.02)						
Nefazodone						
Hautzinger 2005	47	103	55	97	5.4%	0.80 [0.61, 1.06]
Hernandez-Avila 2004	13	21	15	20	3.5%	0.83 [0.54, 1.26]
Kranzler 2000	43	59	50	63	6.6%	0.92 [0.75, 1.12]
Roy-Byrne 2000	20	32	11	32	2.4%	1.82 [1.05, 3.15]
Subtotal (95% CI)		**215**		**212**	**17.9%**	**0.95 [0.74, 1.23]**
Total events	123		131			
Heterogeneity: Tau² = 0.04; Chi² = 7.16, df = 3 (P = 0.07); I² = 58%						
Test for overall effect: Z = 0.36 (P = 0.72)						
Total (95% CI)		**1291**		**1295**	**100.0%**	**0.94 [0.85, 1.04]**
Total events	674		761			
Heterogeneity: Tau² = 0.03; Chi² = 55.43, df = 21 (P < 0.0001); I² = 62%						
Test for overall effect: Z = 1.15 (P = 0.25)						



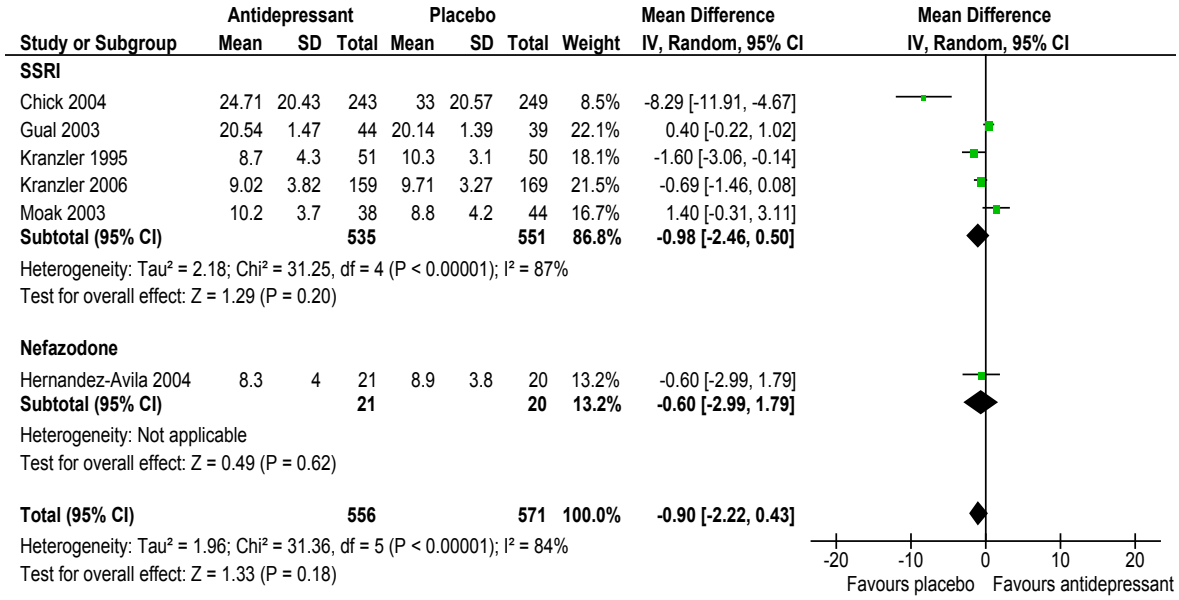
Based on two studies, there was no significant difference in the rate of completion of treatment for an antidepressant compared with naltrexone (Figure 4.2: RR 1.09, 95% CI 0.88, 1.35; P=0.45)* while one study found no significant difference compared with memantine (Muhonen 2008, RR 1.0, 95% CI 0.76, 1.31; P=1.0). No data were reported for antidepressants compared with no medication.

Figure 4.2: Antidepressant compared with other active medication, participants completing the study



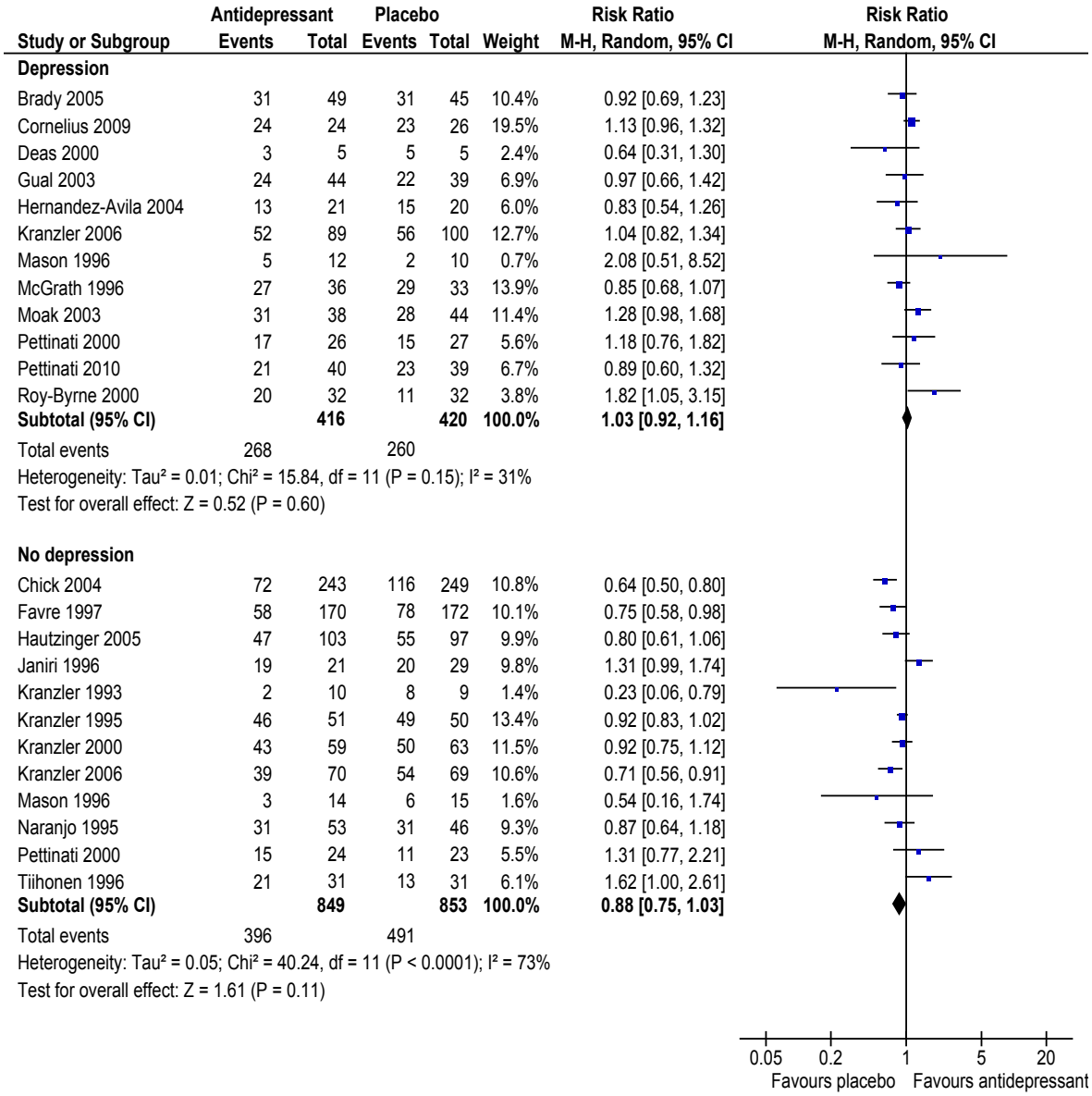
One study reported significantly shorter time in treatment for SSRIs compared with placebo, but overall, from five studies, there is no significant difference in average weeks in treatment (Figure 4.3: mean difference -0.98 weeks, 95% CI -2.46, 0.50; P=0.20)*. In one study there was no significant difference in the average time in treatment for nefazodone compared with placebo (Figure 4.3: mean difference -0.60 weeks, 95% CI -2.99, -0.43; P=0.62).Data from Mason 1996 were unable to be incorporated into the analysis, but indicated the median time in treatment was longer for participants treated with desipramine (tricyclic antidepressant) compared to those treated with placebo.

Figure 4.3: Antidepressant compared with placebo, average weeks in treatment



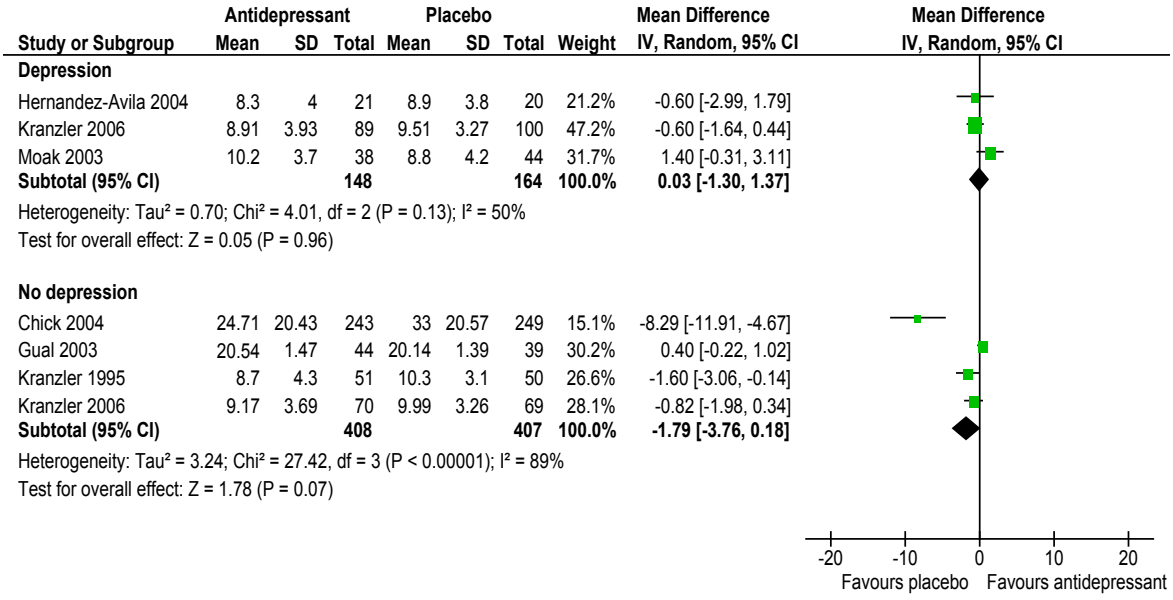
The analyses were repeated with studies grouped on the basis of whether or not the majority of participants had a current diagnosis of depression. These data suggest that in terms of rates of completion of treatment, antidepressants may be somewhat less effective than placebo where there is no concurrent depression (Figure 4.4: RR 0.88, 95% CI 0.75, 1.03; P=0.11)* whereas there is no difference between antidepressants and placebo when the majority of study participants have concurrent depression (Figure 4.4: RR 1.03, 95% CI 0.92, 1.16; P=0.60)*. However, there is significant heterogeneity between studies preventing any firm conclusions.

Figure 4.4: Antidepressant compared with placebo, participants completing the study, by presence or absence of concurrent depression



There is a similar situation with data on the average time in treatment, with no difference between antidepressants and placebo in the presence of concurrent depression (Figure 4.5: mean difference 0.03, 95% CI -1.30, 1.37; P=0.96) and somewhat less (but not statistically significant) retention with antidepressants compared to placebo in the absence of concurrent depression (Figure 4.5: mean difference -1.79, 95% CI -3.76, 0.18; P=0.07). In Mason 1996, the median time in treatment was greater for those treated with desipramine, compared to those treated with placebo, regardless of the presence of concurrent depression.

Figure 4.5: Antidepressant compared with placebo, average weeks in treatment by presence or absence of concurrent depression



4.2.2 Effect on alcohol consumption

	Abstinence
***	Treatment with an antidepressant has no effect on the likelihood of abstinence during treatment relative to placebo, no medication or naltrexone.
*	Abstinence during treatment with antidepressants may be significantly more likely when concurrent depression is present.

Supporting evidence

There is no significant difference between antidepressants and placebo in terms of the number of participants continuously abstinent during treatment or abstinent at the end of treatment (Figure 4.6 RR 1.10, 95% CI 0.92, 1.31; P=0.31). There appears to be little variability by type of antidepressant.

One study (Angelone 1998) reported that significantly more people treated with an SSRI were continuously abstinent compared to no medication (RR 2.04, 95% CI 1.06, 3.92; P=0.03). The same study found no significant difference between fluvoxamine and citalopram (both SSRIs) in the likelihood of continuous abstinence during treatment (Figure 4.7: RR 1.05, 95% CI 0.68, 1.62; P=0.83).

Based on two studies, there is no significant difference between an antidepressant and naltrexone in terms of the number of people continuously abstinent during treatment (Figure 4.7: RR 1.18, 95% CI 0.76, 1.82; P=0.46).*

However, the presence of concurrent depression may be a factor in the capacity of antidepressants to promote abstinence. For studies where the majority of participants had concurrent depression, treatment with an antidepressant is associated with significantly greater probability of continuous abstinence during treatment or abstinence at the end of treatment (Figure 4.8: RR 1.57, 95% CI 1.08, 2.29; P=0.02)*.

For studies where the majority of participants did not have depression, there was no significant difference between antidepressants and placebo in terms of the likelihood of abstinence during treatment (Figure 4.8: RR 1.03, 95% CI 0.84, 1.26; P=0.79)*.

Figure 4.6: Antidepressant compared with placebo, participants continuously abstinent during treatment or abstinent at the end of treatment

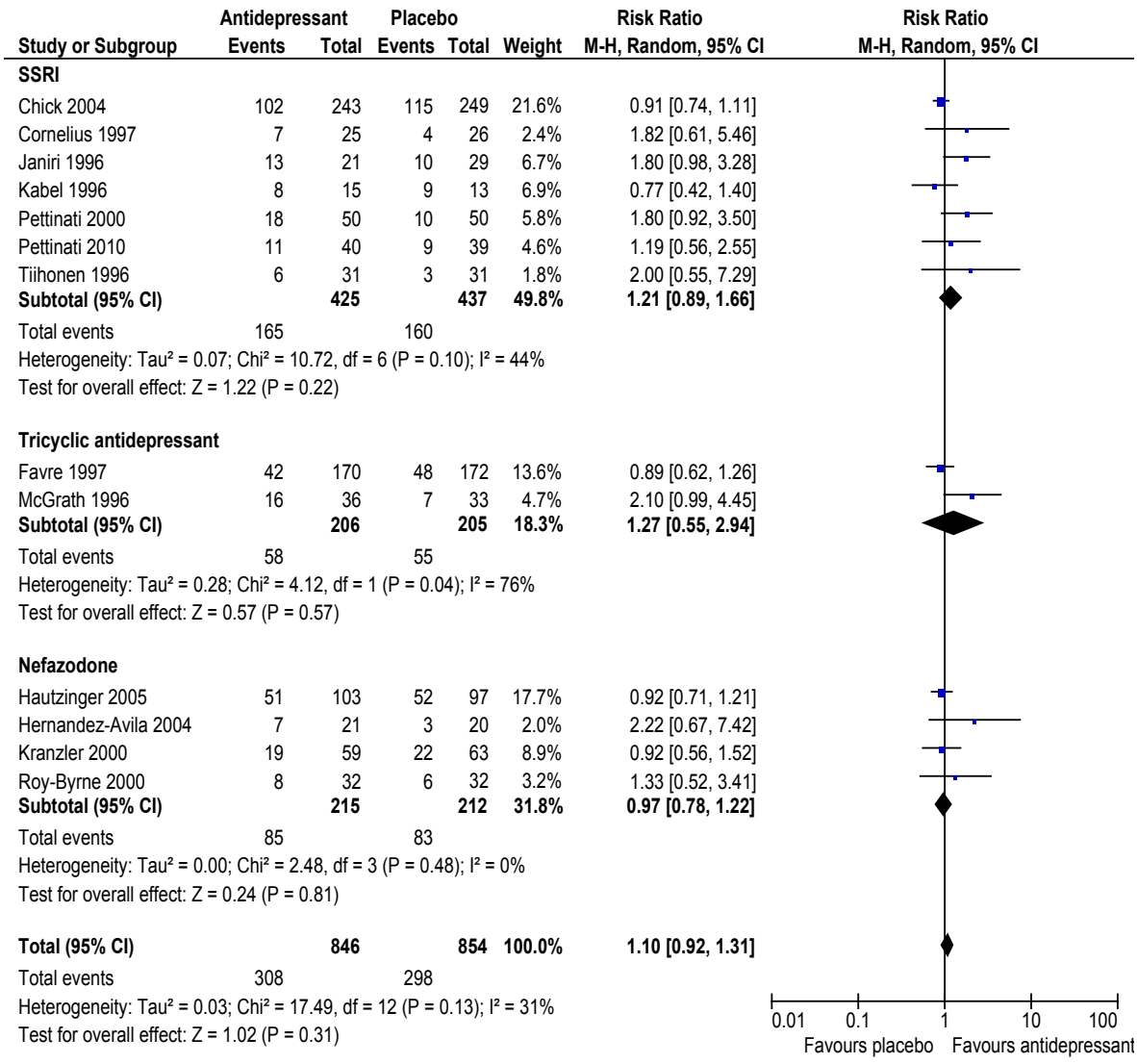


Figure 4.7: Antidepressant compared other active medication, participants continuously abstinent during treatment or abstinent at the end of treatment

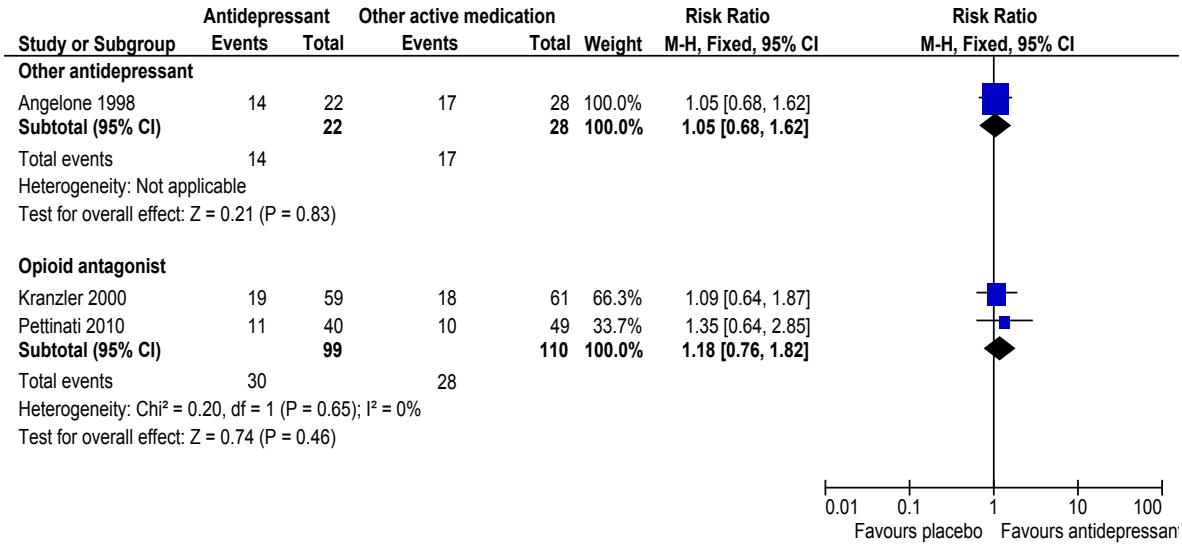
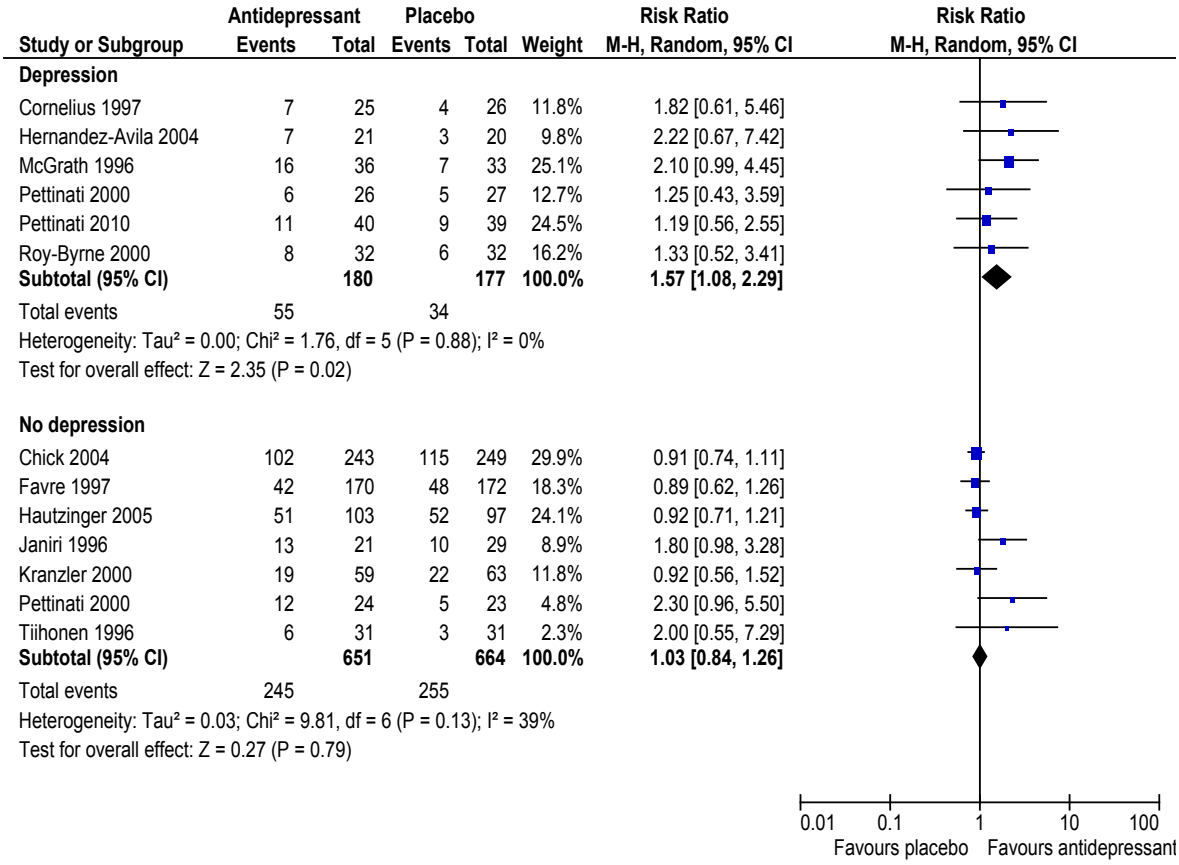


Figure 4.8: Antidepressant compared with placebo, participants continuously abstinent during treatment or abstinent at end of treatment by presence or absence of concurrent depression



	Relapse to heavy drinking
**	Treatment with an antidepressant has no effect on the probability of relapse to heavy drinking during treatment relative to placebo.
	Insufficient data are available to determine whether the presence of concurrent depression influences the effect of antidepressants on the risk of relapse.

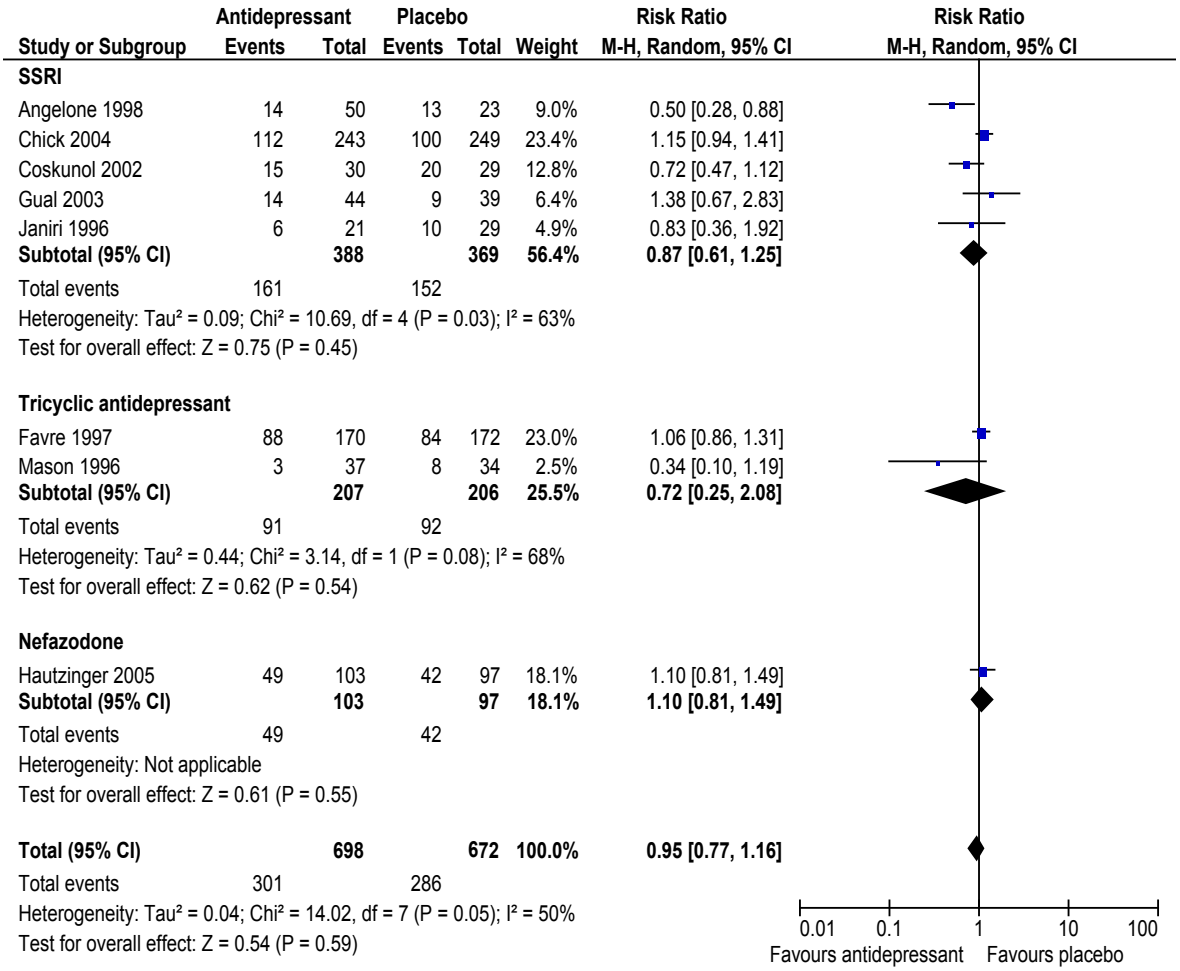
Supporting evidence

There is no significant difference between antidepressants and placebo in terms of the number of people relapsing during treatment (Figure 4.9: RR 0.95, 95% CI 0.77, 1.16; P=0.59)**. There appears to be little variability by type of antidepressant.

One study (Angelone 1998) reported significantly less people relapsed to heavy drinking (RR 0.50, 95% CI 0.28, 0.88; P=0.02) during treatment compared to those not receiving medication. The same study (Angelone 1998) found no significant difference between two different antidepressants in the number of people relapsing to heavy drinking (RR 1.27, 95% CI 0.52, 3.09) during treatment.

Only one study (Gual 2003) reported data on rates of relapse to heavy drinking during antidepressant treatment in people with concurrent depression and alcohol dependence. The lack of data prevented a comparison of outcomes on the basis of the presence and absence of concurrent depression.

Figure 4.9: Antidepressant compared with placebo, participants relapsing during treatment



	Amount of alcohol consumed
**	Compared with placebo, antidepressants have no significant effect on drinks per drinking day or average drinks per week.
	Insufficient data are available to assess the effect of antidepressants on alcohol consumption relative to no medication or other active medication.
*	Antidepressants may be more effective in reducing alcohol consumption, at least in terms of drinks per drinking day, in people with concurrent depression, compared to those without depression.

Supporting evidence

There is no significant difference in the average drinks per drinking day (Figure 4.10: mean difference -0.61 drinks per drinking day, 95% CI -1.36, 0.15; P=0.12)**, or the average drinks per week (Figure 4.11: mean difference -0.01 drinks per week, 95% CI -2.04, 2.02; P=0.99)* for any type of antidepressant compared to placebo. Data from Roy-Byrne 2000 was unable to be incorporated into the analyses, but it was reported that the average drinks per day decreased significantly over the course of the study in both the nefazodone and placebo groups with no significant difference between the groups. Kranzler 2006 also reported that both depressive symptoms and alcohol consumption decreased substantially over time with SSRI and placebo, with no significant medication differences.

Figure 4.10: Antidepressant compared with placebo, average drinks per drinking day

Study or Subgroup	Antidepressant Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
SSRI								
Brady 2005	6.8	6.5	49	6.3	7.8	45	5.1%	0.50 [-2.42, 3.42]
Cornelius 1997	2.4	2.9	25	5.4	5.5	26	6.8%	-3.00 [-5.40, -0.60]
Cornelius 2009	5.12	3.54	24	4.9	3.36	26	9.0%	0.22 [-1.70, 2.14]
Deas 2000	4.99	4.48	5	2.81	4.81	5	1.6%	2.18 [-3.58, 7.94]
Kranzler 1995	3.2	5.2	46	2.7	5.3	49	8.0%	0.50 [-1.61, 2.61]
Moak 2003	2.3	0.5	38	3.5	0.5	44	21.3%	-1.20 [-1.42, -0.98]
Naranjo 1990	7.52	2.11	19	8.1	2.21	10	10.5%	-0.58 [-2.25, 1.09]
Naranjo 1995	5.4	2.22	31	4.7	2.22	31	14.8%	0.70 [-0.41, 1.81]
Subtotal (95% CI)			**237**			**236**	**77.2%**	**-0.36 [-1.30, 0.58]**
Heterogeneity: Tau² = 0.91; Chi² = 20.21, df = 7 (P = 0.005); I² = 65%								
Test for overall effect: Z = 0.76 (P = 0.45)								
Tricyclic antidepressants								
McGrath 1996	3.7	4.8	27	4.1	4.1	29	7.0%	-0.40 [-2.75, 1.95]
Subtotal (95% CI)			**27**			**29**	**7.0%**	**-0.40 [-2.75, 1.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.33 (P = 0.74)								
Nefazodone								
Hautzinger 2005	13.79	9.64	103	17.8	14.26	97	4.0%	-4.01 [-7.40, -0.62]
Hernandez-Avila 2004	3.45	2.45	21	4.47	2.39	20	11.8%	-1.02 [-2.50, 0.46]
Subtotal (95% CI)			**124**			**117**	**15.8%**	**-2.11 [-4.93, 0.71]**
Heterogeneity: Tau² = 2.69; Chi² = 2.50, df = 1 (P = 0.11); I² = 60%								
Test for overall effect: Z = 1.47 (P = 0.14)								
Total (95% CI)			**388**			**382**	**100.0%**	**-0.61 [-1.36, 0.15]**
Heterogeneity: Tau² = 0.69; Chi² = 23.39, df = 10 (P = 0.009); I² = 57%								
Test for overall effect: Z = 1.57 (P = 0.12)								

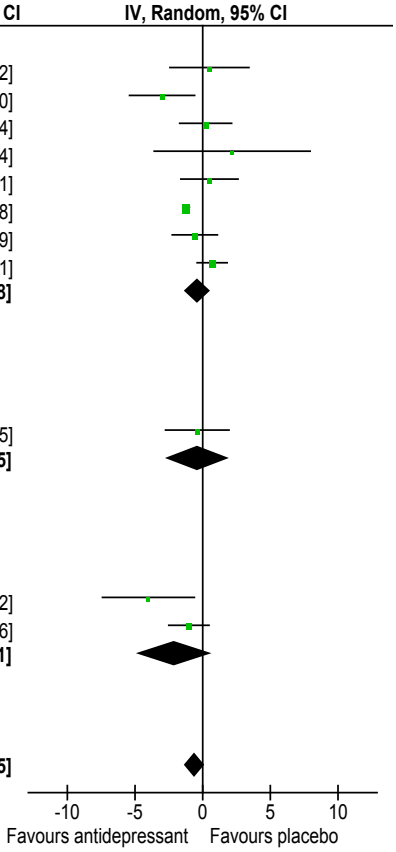
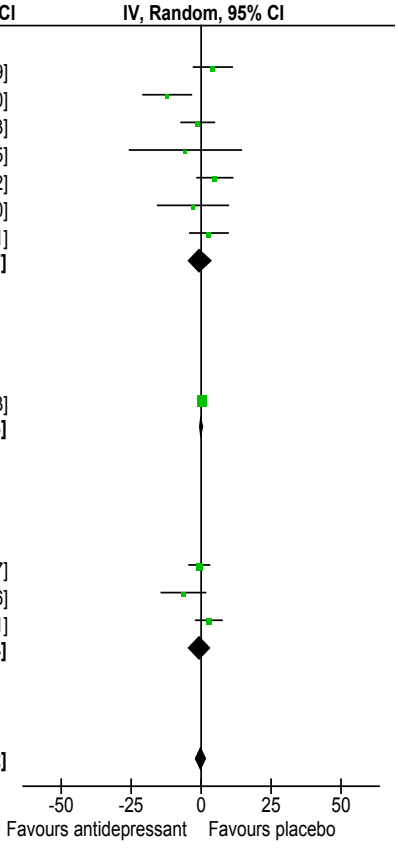


Figure 4.11: Antidepressant compared with placebo, average drinks per week

Study or Subgroup	Antidepressant Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
SSRI								
Brady 2005	14	20.3	49	9.8	13.3	45	6.8%	4.20 [-2.69, 11.09]
Cornelius 1997	5.85	8.39	25	17.96	20.71	26	4.7%	-12.11 [-20.72, -3.50]
Cornelius 2009	10.92	10.08	24	12.11	11.27	26	8.5%	-1.19 [-7.11, 4.73]
Eriksson 2001	54.6	31.5	16	60.2	26.6	17	1.0%	-5.60 [-25.55, 14.35]
Kranzler 1995	8.4	20.3	46	3.5	8.4	49	7.7%	4.90 [-1.42, 11.22]
Naranjo 1990	49.81	16.45	19	52.7	16.44	10	2.4%	-2.89 [-15.48, 9.70]
Naranjo 1995	28.7	15.4	31	25.9	11.69	31	6.9%	2.80 [-4.01, 9.61]
Subtotal (95% CI)			**210**			**204**	**37.9%**	**-0.30 [-4.78, 4.17]**
Heterogeneity: Tau² = 17.71; Chi² = 12.58, df = 6 (P = 0.05); I² = 52%								
Test for overall effect: Z = 0.13 (P = 0.89)								
Tricyclic antidepressant								
Favre 1997	2.47	2.58	170	2.27	3.33	172	29.6%	0.20 [-0.43, 0.83]
Subtotal (95% CI)			**170**			**172**	**29.6%**	**0.20 [-0.43, 0.83]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.62 (P = 0.53)								
Nefazodone								
Hautzinger 2005	4.65	15.34	103	5.31	10.58	97	15.4%	-0.66 [-4.29, 2.97]
Hernandez-Avila 2004	6.52	7.33	21	12.83	16.48	20	5.5%	-6.31 [-14.18, 1.56]
Kranzler 2000	8.4	16.1	59	5.67	9.1	63	11.6%	2.73 [-1.95, 7.41]
Subtotal (95% CI)			**183**			**180**	**32.5%**	**-0.52 [-4.59, 3.54]**
Heterogeneity: Tau² = 6.21; Chi² = 3.88, df = 2 (P = 0.14); I² = 48%								
Test for overall effect: Z = 0.25 (P = 0.80)								
Total (95% CI)			**563**			**556**	**100.0%**	**-0.01 [-2.04, 2.02]**
Heterogeneity: Tau² = 3.52; Chi² = 16.56, df = 10 (P = 0.08); I² = 40%								
Test for overall effect: Z = 0.01 (P = 0.99)								

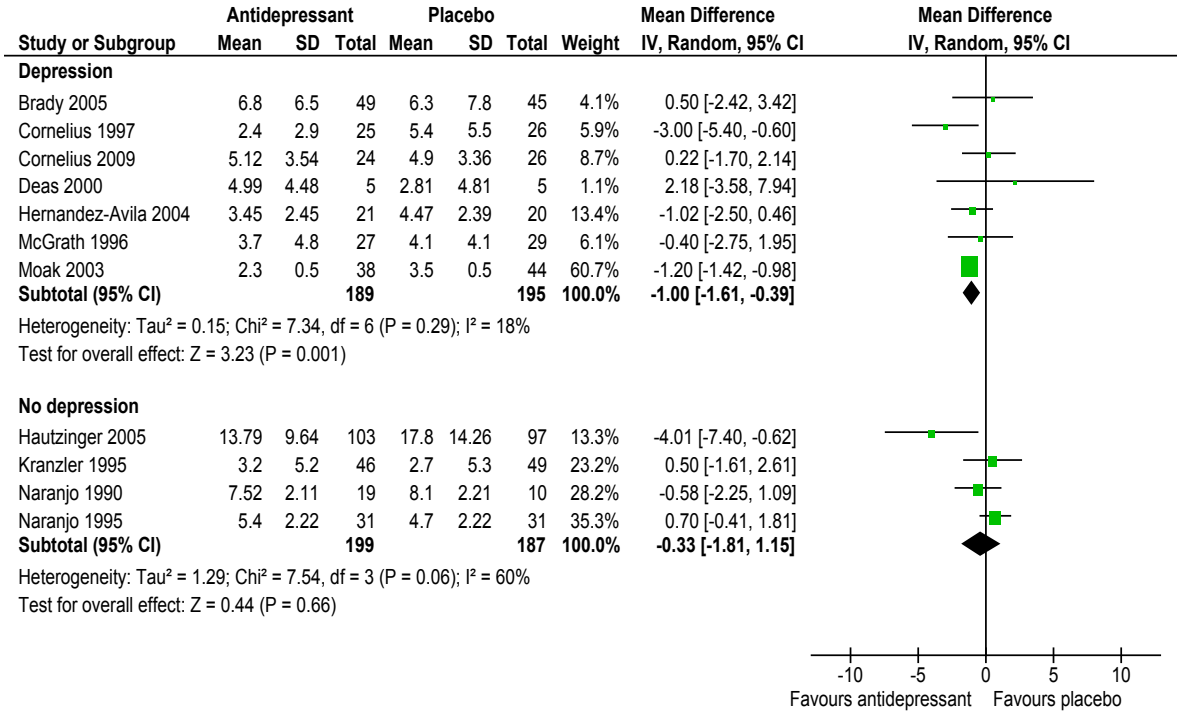


One study (Kranzler 2000) reported no significant difference in the average drinks per week (mean difference -1.40 drinks, 95% CI -6.94, 4.14; P=0.62) for antidepressant compared with naltrexone.

One study (Muhonen 2008) reported significantly less average drinks per week by people treated with memantine compared to those treated with an antidepressant (mean difference 4.27 drinks, 95% CI 3.31, 5.23; P<0.001). As memantine is not typically used for the treatment of alcohol dependence, the implication of this finding is unclear.

Antidepressants may have a greater effect on alcohol consumption, relative to placebo, in people with concurrent depression. For studies with a majority of participants with concurrent depression, antidepressant treatment is associated with significantly less drinks per drinking day, relative to placebo (Figure 4.12: mean difference -1.00 drinks, 95% CI -1.61, -0.39; P=0.001)*. In contrast there is no significant difference in drinks per drinking day during antidepressant treatment, relative to placebo, in studies where the majority of participants do not have concurrent depression (Figure 4.12: mean difference -0.33 drinks, 95% CI -1.81, 1.15; P=0.66)*.

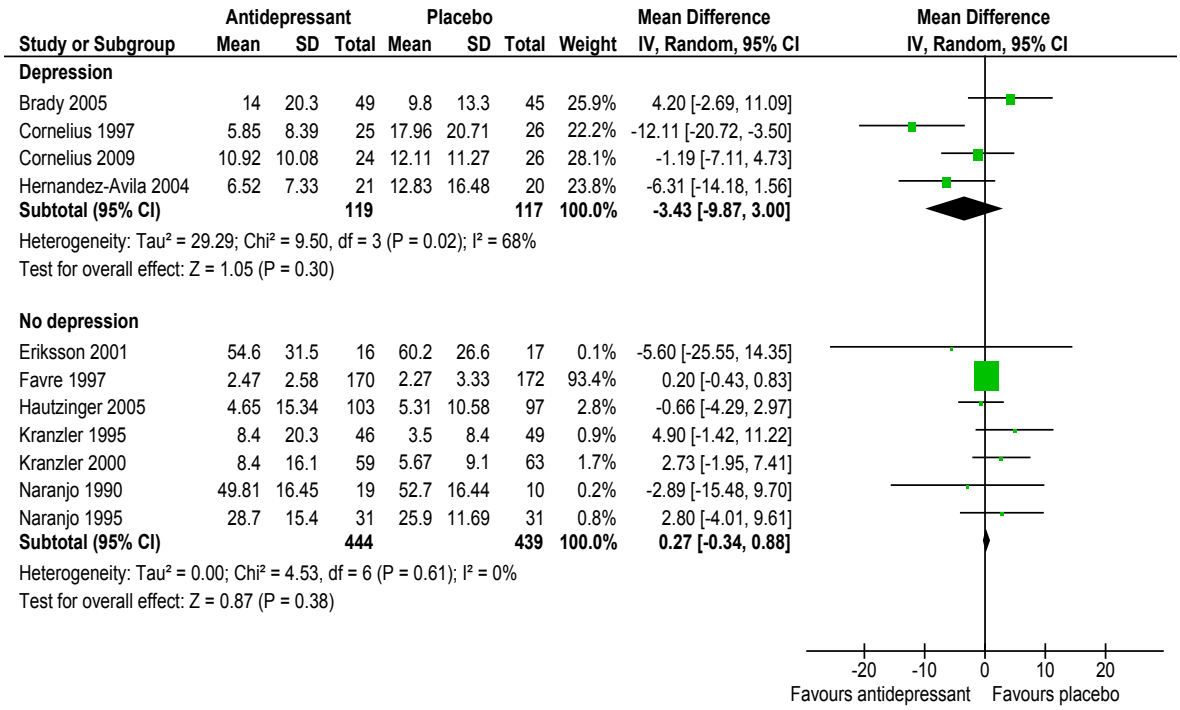
Figure 4.12: Antidepressant compared with placebo, drinks per drinking day by presence or absence of concurrent depression



Similarly, in people with concurrent depression, alcohol consumption expressed as average drinks per week is lower with antidepressant treatment relative to placebo, although the difference is not statistically significant (Figure 4.13: mean difference -3.43 drinks, 95% CI -9.87, 3.00; P=0.30)*. There is no difference in average drinks per week for antidepressant compared with placebo in people without concurrent depression (Figure 4.13: 0.27, 95% CI -0.34, 0.88; P=0.38)*.

These data support the conclusion that antidepressants may have a greater effect on alcohol consumption in people who have concurrent depression. However, it should be noted that there is significant heterogeneity in study findings. This reduces the strength of this finding.

Figure 4.13: Antidepressant compared with placebo, average drinks per week by presence or absence of concurrent depression



	Periods of abstinence or heavy drinking during treatment
*	There is no significant difference between antidepressants and placebo in terms of cumulative abstinence duration.
*	Nefazodone may be associated with significantly more heavy drinking days, but overall there is no significant difference between antidepressants and placebo in terms of the proportion of treatment days on which heavy drinking occurred.
*	The presence or absence of concurrent depression did not affect these outcomes.

Supporting evidence

There is no significant difference in the percent of treatment days of abstinence for any type of antidepressant compared with placebo, with no variability between the different types of antidepressant (Figure 4.14: mean difference -0.84 % days, 95% CI -2.10, 0.43; P=0.19).*

Based on two studies, nefazodone may be associated with more heavy drinking days relative to placebo (Figure 4.15: mean difference 3.11% treatment days, 95% CI 1.80, 4.41; P<0.01)* but overall there is no significant difference for any antidepressant compared to placebo (Figure 4.15: mean difference 1.14, 95% CI -1.36, 3.65; P=0.37)**.

One study (Kranzler 2000) reported significantly more treatment days of abstinence (mean difference 4.40% days, 95% CI -4.95, 13.75; P=0.36), and significantly less treatment days with heavy drinking (mean difference -1.3% days, 95% CI -9.29, 6.69; P=0.75) for an antidepressant compared with naltrexone.

There is no significant difference between antidepressants and placebo in the percent of treatment days with abstinence either for studies where the majority of participants have concurrent depression, or for studies where the majority of participants do not have concurrent depression (Figure 4.16)*. Data from Kranzler 2006 was not able to be included in this analysis, but it was reported that in patients with depression, those treated with placebo had 3.5% more days of abstinence than those treated with sertraline, while for patients without depression, those treated with placebo had 3.2% more abstinent days. These differences were not statistically significant. Insufficient data are available on the percent of treatment days with heavy drinking to compare outcomes on the basis of the presence or absence of depression.

Figure 4.14: Antidepressant compared with placebo, % treatment days abstinent (cumulative abstinence duration)

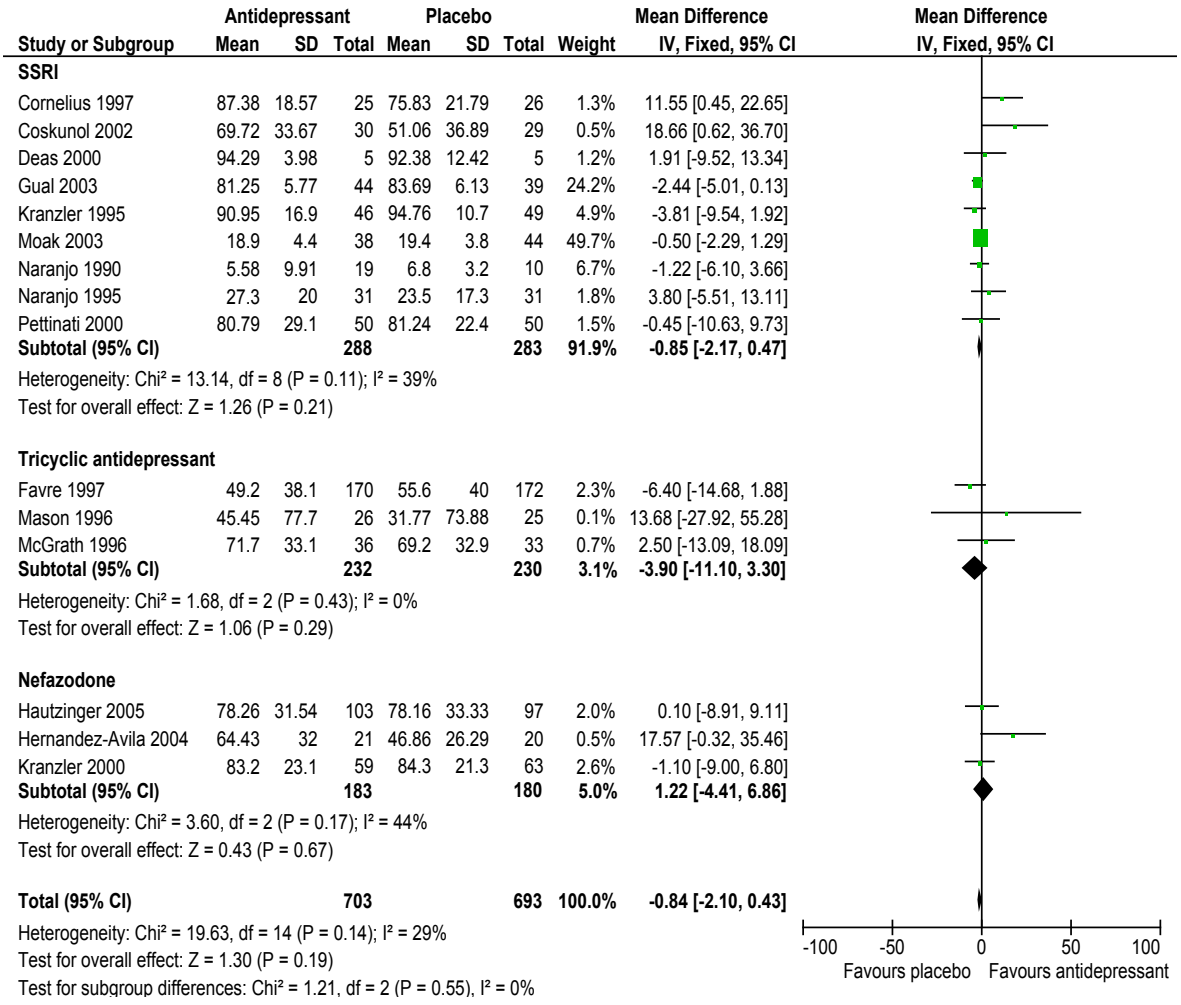


Figure 4.15: Antidepressant compared with placebo, % treatment days with heavy drinking

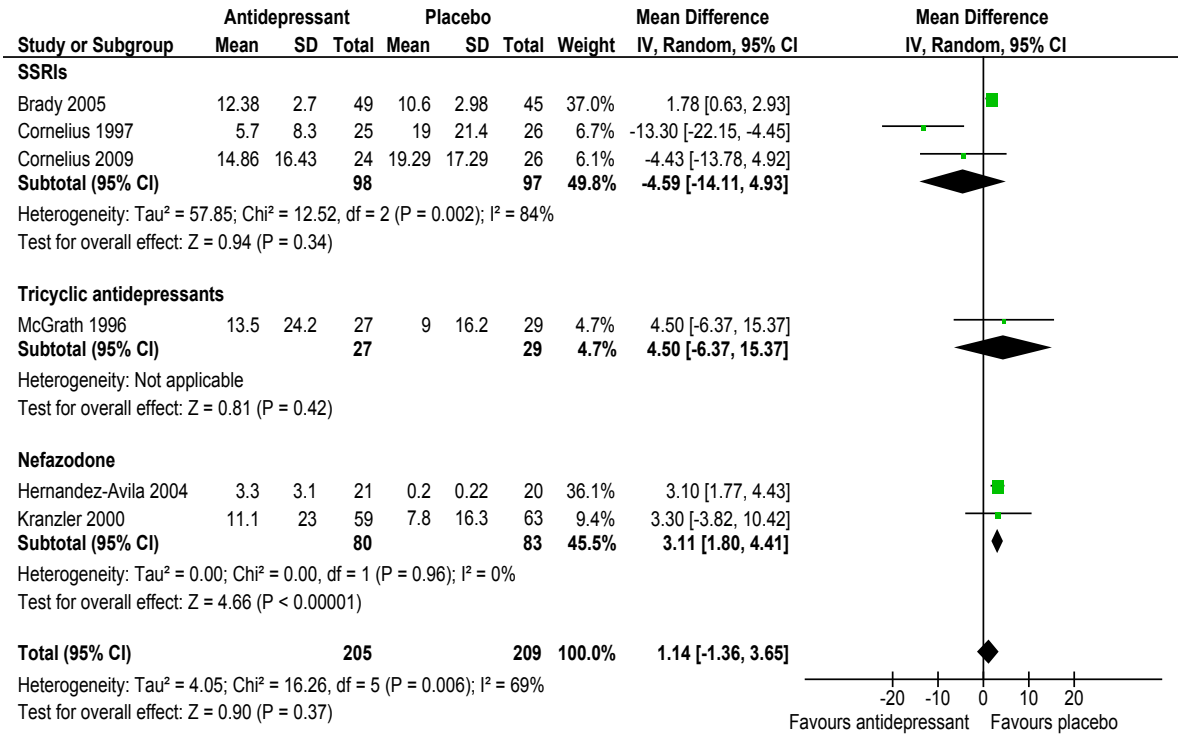
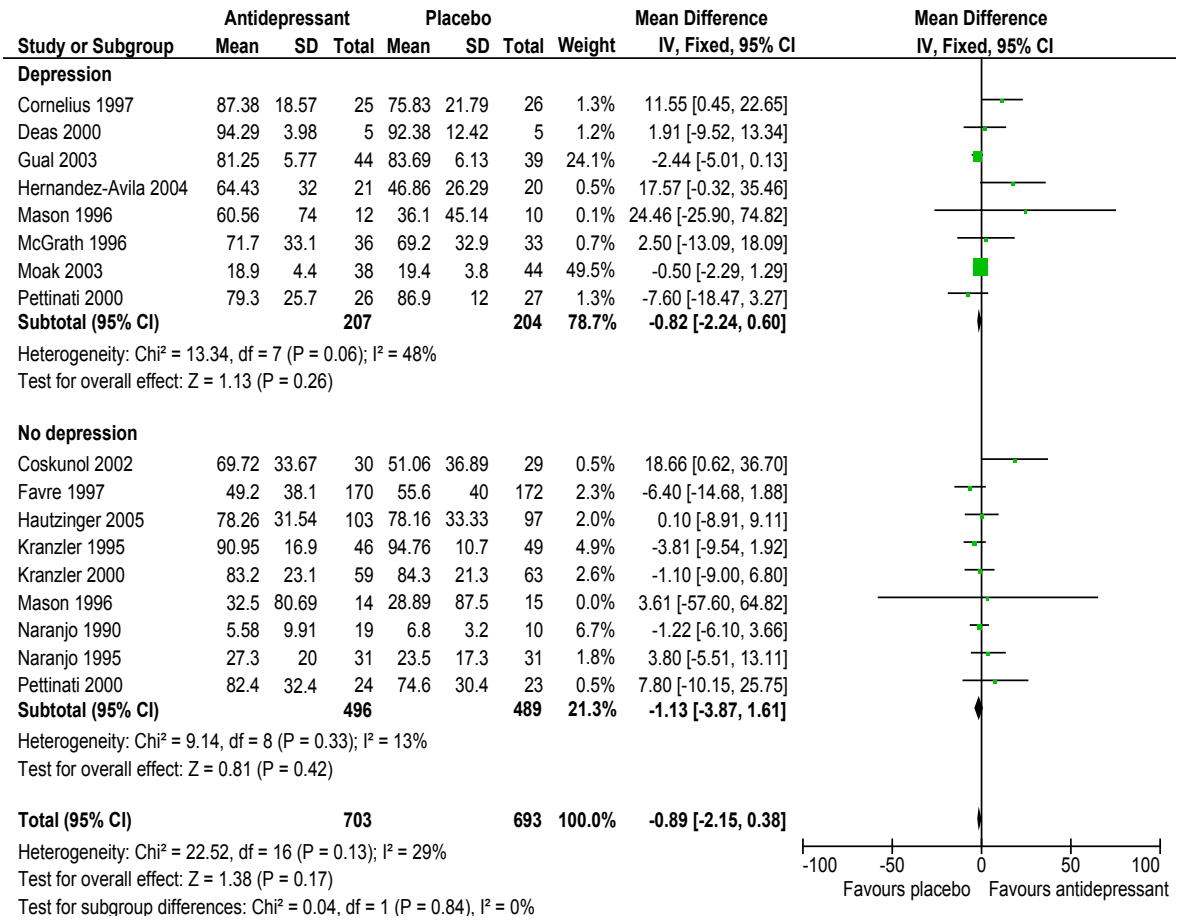


Figure 4.16: Antidepressant compared with placebo, % treatment days abstinent (cumulative abstinence duration) by presence or absence of concurrent depression



	Time to first drink and time to relapse
*	Antidepressants have no effect on time to first drink or time to relapse, relative to placebo.

Supporting evidence

Based on two studies, there is no significant difference between antidepressants and placebo in the average days to first drink (Figure 4.17: mean difference 1.65 days, 95% CI -7.58, 10.89; P=0.73)*. Based on six studies, there is no significant difference between antidepressants and placebo in the average days to relapse to heavy drinking (Figure 4.18: mean difference 1.16 days, 95% CI -6.54, 8.86; P=0.77)*.

One study (Angelone 1998) reported no significant difference in the average time to first drink for antidepressant compared with no medication (mean difference 5.60 days, 95% CI -2.32, 13.52; P=0.17), or for fluvoxamine compared with citalopram (mean difference 0 days, 95% CI -11.48, 11.48; P=1).

One study (Kranzler 2000) reported no significant difference between nefazodone and naltrexone in the average time to first drink (mean difference -4.90 days, 95% CI -16.42, 6.62; P=0.40) and, based on two studies, there is no significant difference between an antidepressant and naltrexone in the average time to relapse to heavy drinking (Figure 4.19: mean difference -1.80 days, 95% CI -11.20, 7.59; P=0.71).*

Kranzler 1995 reported that the groups (SSRI and placebo) did not differ on weeks to first alcohol consumption or weeks to first heavy drinking data, but data were not suitable for inclusion in analyses. Moak 2003 also reported no difference between groups in time to first drink or time to first heavy drinking day, but Mason 1996 reported that patients were abstinent significantly longer when receiving desipramine (tricyclic antidepressant) compared to placebo.

Insufficient data are available for analysis based on the presence or absence of concurrent depression.

Figure 4.17: Antidepressant compared with placebo, average days to first drink

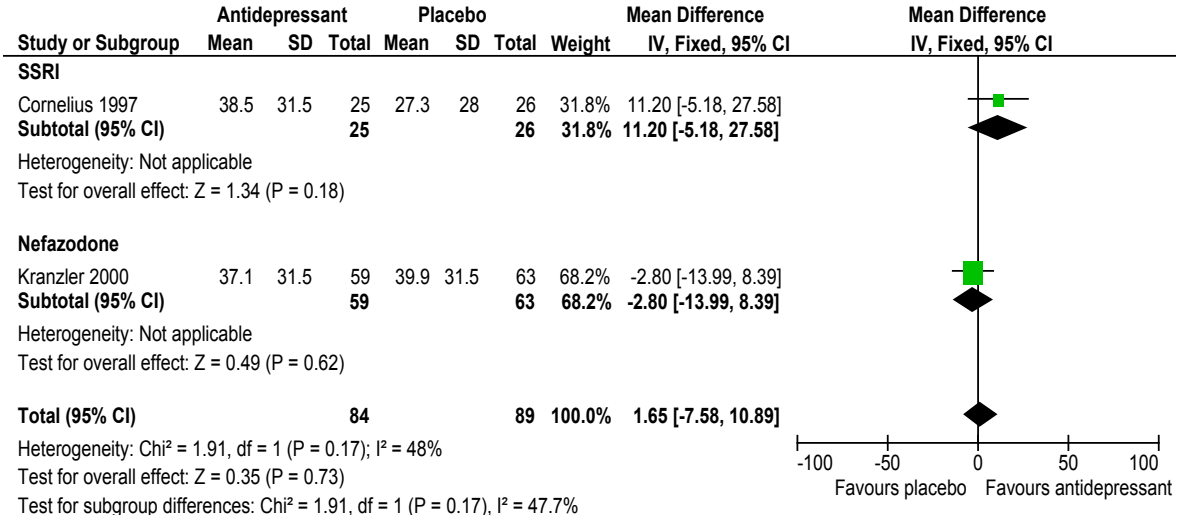


Figure 4.18: Antidepressant compared with placebo, average days to relapse to heavy drinking

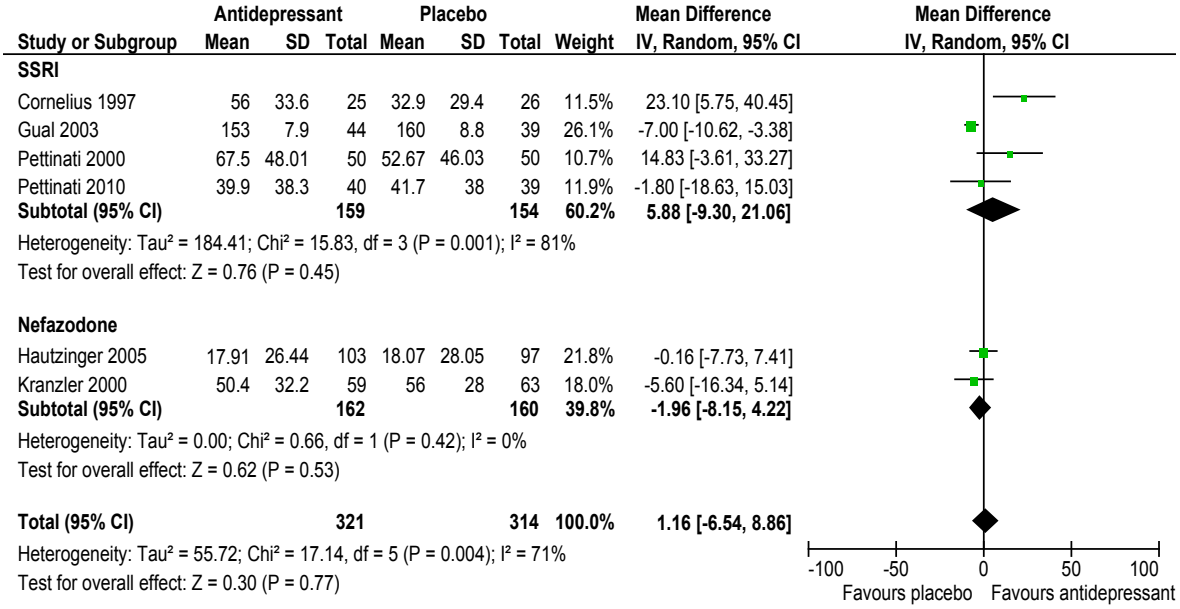
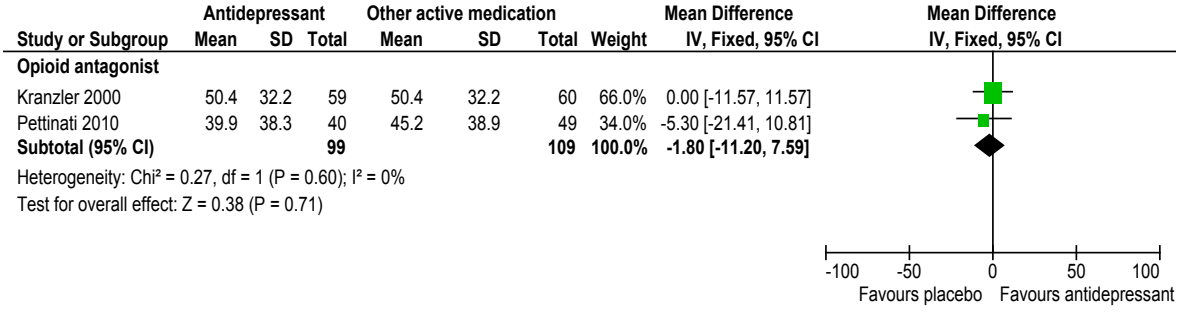


Figure 4.19: Antidepressant compared with other active medication, average days to relapse to heavy drinking



	Objective indicators of alcohol consumption
	Available information indicates no significant difference between antidepressants and placebo in objective indicators of alcohol consumption.

Supporting evidence

Eight studies (Chick 2004, Coskunol 2002, Eriksson 2001, Hernandez-Avila 2004, Kranzler 2000, Moak 2003, Tiihonen 1996) provided some information on GGT or CDT levels, or liver function enzyme levels. Seven of these studies reported no significant differences between antidepressants and placebo. Tiihonen 1996 reported that 11 of 31 in the citalopram group, and 5 of 31 in the placebo group had at least a 20% decrease in serum GGT after three months. These data parallel the data from this study on the number of participants abstinent during treatment (see Figure 4.6).

	Craving
	The limited data available suggest that antidepressants have no effect on craving for alcohol, relative to placebo.

Supporting evidence

Based on two studies (Naranjo 1995, Kranzler 2000) there is no significant difference in average craving score for antidepressants compared with placebo (SMD -0.07, 95% CI -0.36, 0.22; P=0.65)*. Two studies (Moak 2003, Roy-Byrne 2000) reported that craving decreased in both groups with no significant difference between groups. Chick 2004 reported no treatment-related effect on craving. In Angelone 1998, patients treated with citalopram (but not those treated with placebo or fluoxetine) reported a significant reduction in craving. In Kabel 1996 craving decreased in the fluoxetine group over 12 weeks, but not in the placebo group. Although Hautzinger reported a significantly greater decrease in mean craving score for nefazodone compared to placebo, overall these data suggest that antidepressants do not significantly affect craving, relative to placebo.

There is also no significant difference in average craving scores for antidepressant compared with naltrexone (Kranzler 2000; SMD -0.33, 95% CI -0.70, 0.03; P=0.07)* or for antidepressant compared with memantine (Muhonen 2008; SMD 0.27, 95% CI -0.24, 0.79; P=0.30)*.

4.2.3 Adverse effects

*	People treated with antidepressants are more likely to experience any adverse effects, compared to those receiving placebo.
*	Significantly more gastrointestinal symptoms, nausea and vomiting, and neuropsychiatric symptoms are experienced with antidepressants, compared to placebo.
**	Withdrawal from treatment due to adverse effects is significantly more likely with antidepressants compared to placebo.

Supporting evidence

Based on five studies, there is no significant difference between SSRIs and placebo in the number of people experiencing any adverse effects (Figure 4.20: RR 1.50, 95% CI 0.93, 2.43; P=0.10)*. Kranzler 2000 reported no significant difference between nefazodone and placebo in total adverse effects (Figure 4.20: RR 1.09, 95% CI 0.94, 1.27; P=0.27), but when combined with studies using SSRIs, antidepressants overall are associated with a greater likelihood of any adverse effects (Figure 4.20: RR 1.26, 95% CI 1.00, 1.59; P=0.05)*. Mason 1996 reported that total adverse effects did not differ between desipramine and placebo, but did not report data. Roy-Byrne 2000 reported that adverse effects were significantly greater for the nefazodone group, but these effects were not severe.

Significantly more people treated with an antidepressant experience gastrointestinal symptoms (Figure 4:21: RR 1.53, 95% CI 1.19, 1.98; P=0.001)*, nausea or vomiting (Figure 4.22: RR 1.95, 95% CI 1.11, 3.44; P=0.02)* and neuropsychiatric symptoms (Figure 4.23: RR 1.38, 95% CI 1.14, 1.67; P<0.001)* compared to people receiving placebo.

Figure 4.20: Antidepressant compared with placebo, participants experiencing any adverse effects

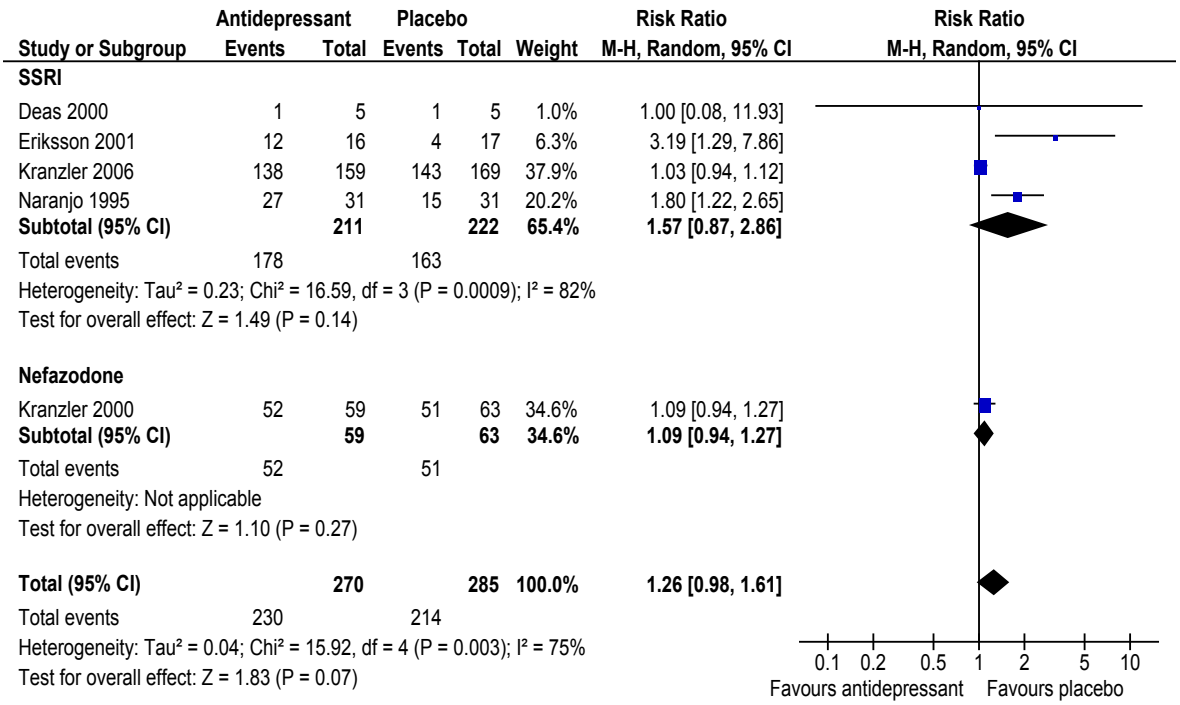


Figure 4.21: Antidepressant compared with placebo, participants experiencing gastrointestinal symptoms

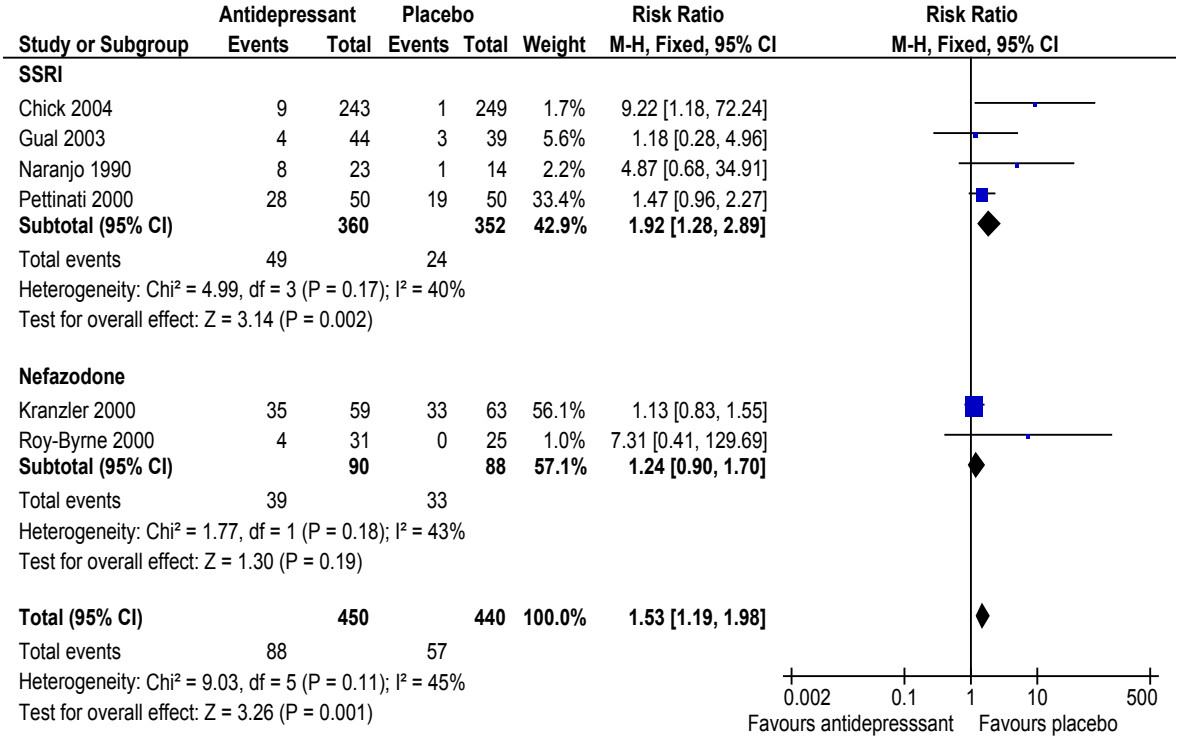


Figure 4.22: Antidepressant compared with placebo, participants experiencing nausea or vomiting

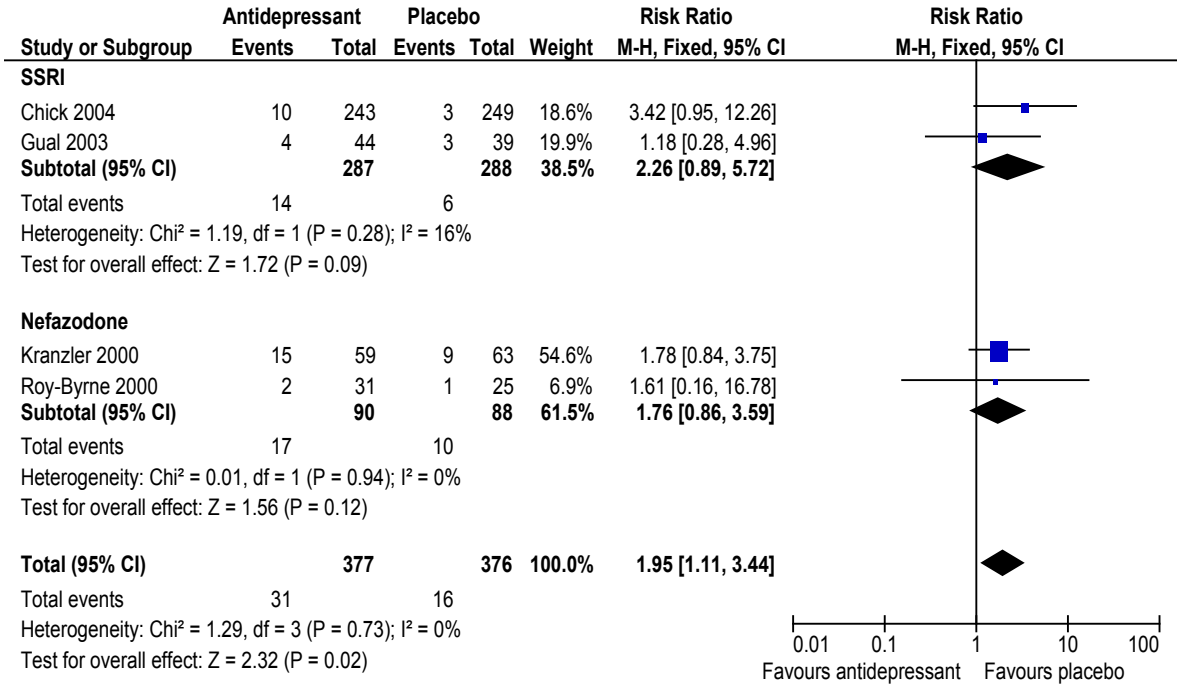
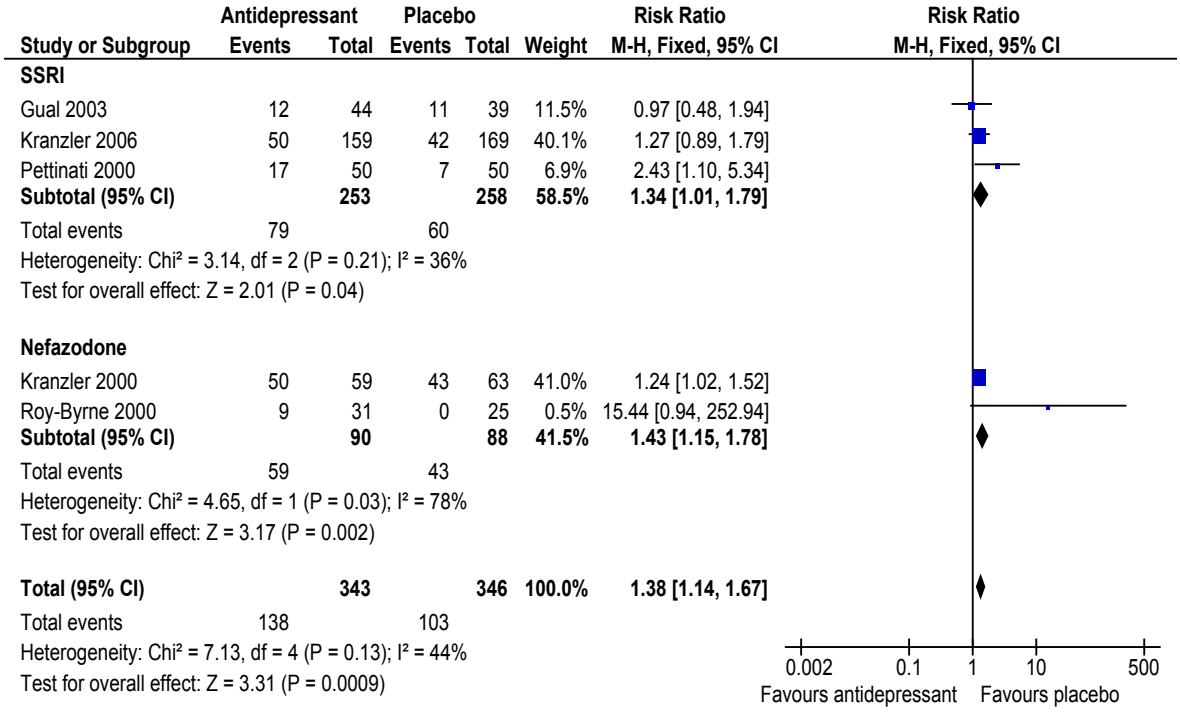


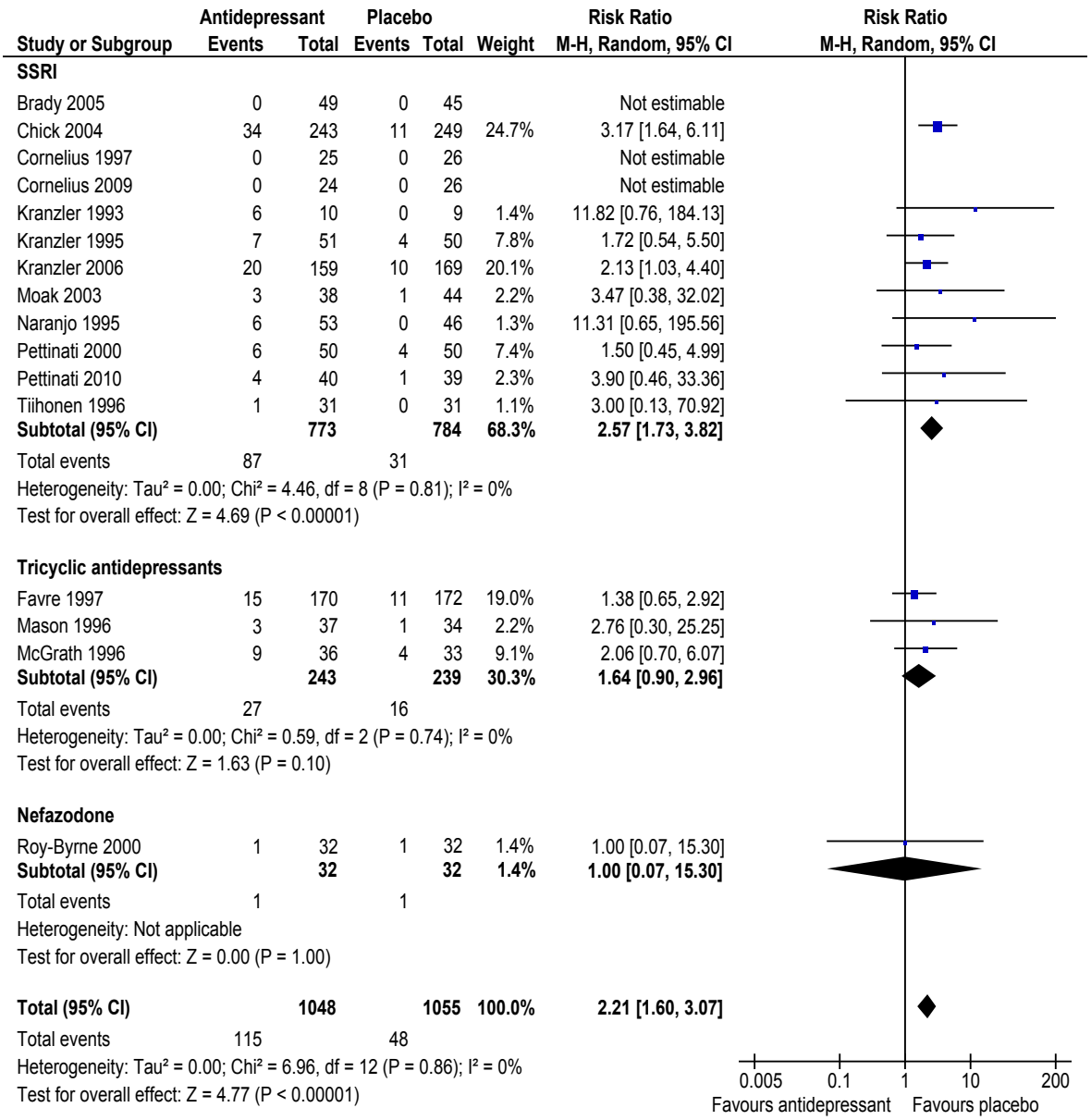
Figure 4.23: Antidepressant compared with placebo, participants experiencing neuropsychiatric symptoms



Based on two studies, there is no significant difference between antidepressants and naltrexone in the likelihood of any adverse effects (RR 1.05, 95% CI 0.90, 1.24; P=0.51). Kranzler 2000 reported significant less gastrointestinal symptoms with naltrexone, but no significant difference between antidepressant and naltrexone in nausea or vomiting, or neuropsychiatric symptoms.

Significantly more people treated with an SSRI were withdrawn from treatment due to adverse effects (Figure 4.24: RR 2.57, 95% CI 1.73, 3.82; P<0.001)** compared to those receiving placebo. There was no significant difference between tricyclic antidepressants or nefazodone and placebo, but the overall result for any antidepressant was significant (Figure 4.24: RR 2.21, 95% CI 1.60, 3.07; P<0.001)**.

Figure 4.24: Antidepressant compared with placebo, participants withdrawn due to adverse effects



Kranzler 1993 commented that those who completed the study had consistently low side effect scores. Those who did not complete had peak side effects at week two, most commonly gastrointestinal symptoms (eg. nausea) and CNS effects (eg. headache and sedation). A relatively high rate of early dropout from Kranzler 2006 was also attributed, at least in part, to adverse effects of study medication.

Eriksson 2001 reported that at the end of the medication period the citalopram group had lower ALT levels compared with the placebo group. Within group comparisons in the citalopram group showed significant increases in AST and ALT.

Insufficient data were available for any other comparisons.

4.3 Factors affecting outcomes

Factors considered in the research literature include:

> concurrent depression;

> type of alcohol dependence

> gender.

4.3.1 Concurrent depression

*	Antidepressants are not effective in relapse prevention treatment of alcohol dependence in people without concurrent depression.
	Antidepressants are beneficial in people with concurrent alcohol dependence and depression, particularly for alleviation of depressive symptoms.
	Antidepressants may have a beneficial effect on alcohol consumption through the alleviation of depression in people with alcohol dependence and concurrent depression.

Supporting evidence

To explore the effect of concurrent depression, the meta-analyses in this review included subgroup analyses where possible to compare outcomes for studies where the majority of participants had concurrent depression with studies where the majority of participants did not have concurrent depression. Table 4.2 summarises the findings.

Table 4.2: Summary of findings of analyses of any antidepressant compared with placebo, for subgroups of studies where concurrent depression was present or absent in the majority of participants.

Outcome	Concurrent depression	No concurrent depression	Figure
Completion of treatment	No effect	Completion of treatment less likely with antidepressants	4.4
Abstinence during treatment	More likely with antidepressants	No effect	4.8
Relapse to heavy drinking	Insufficient data		
Drinks per drinking day	Less	No effect	4.12
Average drinks per week	Reduced but not statistically significant	No effect	4.13

These analyses suggest that in people without concurrent depression, antidepressants are not effective in relapse prevention treatment of alcohol dependence.

Not all of the studies reviewed reached the same conclusion. Pettinati *et al*.[274] commented that sertraline treatment seemed to provide an advantage in reducing drinking in alcohol-dependent patients without lifetime depression, but sertraline was no better than placebo in patients with a diagnosis of lifetime comorbid depression, and current depression did not change the results. However, a systematic review by Torrens *et al*.[280] came to a conclusion similar to this review, that the use of antidepressants was not justified in people with alcohol dependence without comorbid depression.

Antidepressants may have some beneficial effects on alcohol-related outcomes as well as depression in people with concurrent alcohol dependence and depression. (Note that the analyses in this review do not distinguish between primary and secondary depression.) However, the primary benefit is likely to be in the alleviation of depression. For example, Roy-Byrne 2000 concluded that nefazodone was superior to placebo in alleviating depression but did not add any advantage over the psychoeducational group in terms of drinking outcomes. McGrath 1996 found no overall effect on drinking outcomes, but patients whose mood improved showed decreased alcohol consumption that was more marked in those treated with imipramine. Mason 1996 reported that the depression scores of desipramine-treated depressed alcoholics decreased significantly, and desipramine-treated depressed patients were more satisfied and were rated as more improved.

In Moak 2003, all subjects had decreases in both depression and alcohol use during the study compared with baseline. Less drinking during the study was associated with improved depression outcome.

Gual 2003 found no significant effect of sertraline overall, but when patients were stratified into severe or moderate depression at baseline, a significant treatment benefit with sertraline was observed in those with severe depression.

4.3.2 Type of alcohol dependence

	Antidepressants appear more likely to be beneficial in low risk/severity, late onset alcoholism.
	There is no clear evidence on the role of family history or genetic factors, but are less likely to be significant in low risk/severity, late onset alcoholism.

Supporting evidence

In a review of pharmacological treatments for alcoholism, Johnson concluded that SSRIs can improve the drinking outcomes of Type A-like or late-onset alcoholics, but not the heterogeneous population of alcohol-dependent people.[8]

Consistent with this, in Pettinati 2000, lower risk/severity (Type A) subjects had more favourable outcomes when treated with sertraline compared to placebo. Kranzler *et al*.[254] also compared low risk/severity drinkers (Type A) with high risk/severity drinkers and found that among Type B subjects, fluoxetine treatment resulted in poorer drinking-related outcomes than placebo. Among Type A subjects, there was no effect of medication group.

In Chick 2004, Types I and II (by Cloninger typology) had similar rates of survival over 52 weeks without relapse on placebo (Type I: 19.3%, Type II: 18.2%) but on fluvoxamine Type II (early-onset) did worse than Type I (Type I: 13.7%, Type II: 6.1%).

In Eriksson 2001 subjects were grouped according to the presence or absence of the DRD2 A1 allele. Those with the genotype DRD2 A2/A2 transiently reduced their alcohol consumption during citalopram treatment. It was noted that in some people citalopram may result in increased alcohol consumption.

On the other hand Kranzler 2006 found no effect of family history.

4.3.3 Gender

	No clear evidence on the effect of gender on response to antidepressants.

Supporting evidence

Some gender differences were reported by the studies included in this review. Naranjo 2000 reported that men receiving citalopram reduced their average drinks per day by 44%, whereas women exhibited a 27% decrease ($P<.05$). Kranzler 1995 also found that men showed greater reductions in drinks per drinking day (7.1 fewer drinks) than women (4.8 fewer drinks).

On the other hand Chick 2004 reported that males responded better to placebo than fluoxetine, and Kranzler 2006 found no effect of gender.

A secondary analysis of Pettinati 2000 looked at gender and alcoholism typology as factors in response to sertraline treatment.[275] Babor Type A “lower risk/severity” alcoholic men, but not Type A alcoholic women, had consistently better outcomes with sertraline compared to placebo on several measures of alcohol consumption. There were no significant differences in drinking with sertraline compared to placebo in Type B alcoholic men or women.

4.3.4 Other factors

	Treatment compliance and level of social support are likely to affect treatment outcome.

Supporting evidence

Kranzler 2006 found that treatment-adherent patients had marginally more abstinent days during treatment (mean 77.3±1.8%) compared with non-adherent patients (mean 67.4±4.9%) but adherence was not related to treatment condition.

In Kabel 1996, 36% of participants were homeless at entry. Supportive living arrangements after hospital discharge reduced relapse rates: 8 of 9 subjects (89%) discharged to a Veterans Affairs domiciliary were sober at 12 weeks, compared with 9 of 19 (47%) subjects discharged back to the community.

Section 5: Combination Drug Therapy

Overview

Rationale

The use of medications, with different mechanisms of effect, in combination may augment the treatment effects of the individual medications on their own.

Comparisons

This section reviews combination drug therapies that have been investigated in controlled trials, with one or more of the medications on their own as comparison(s). All combinations included naltrexone as one of the medications.

Naltrexone plus acamprosate

The available data suggests that the combination of naltrexone plus acamprosate is no more effective than naltrexone or acamprosate alone.

Naltrexone plus antidepressant

The combination of naltrexone and an antidepressant is no more effective than naltrexone alone, other than for amelioration of depression.

Insufficient data were available to assess the effectiveness of naltrexone combined with an antidepressant relative to an antidepressant alone.

Naltrexone plus disulfiram

It appears that combining naltrexone with disulfiram offers few, if any benefits, over either medication alone, and is associated with somewhat increased risk of adverse effects, and lower rates of retention in treatment.

Naltrexone plus GHB

There may be benefits from the combination of GHB and naltrexone over individual medications but data on GHB itself is still limited.

GHB is subject to abuse and it remains unclear whether the benefits of GHB are sufficient to outweigh the risks of abuse.

5.1 Rationale for effect

The combination of medications with distinctly different mechanisms may augment the effects of single medications for the treatment of alcohol dependence. For example, naltrexone reduces craving for alcohol that is driven by positive reinforcement by modifying the sense of intoxication from alcohol. Acamprosate diminishes the negative reinforcement of conditioned craving that follows cessation of drinking. These differences make it likely that they can act in an additive or even synergistic fashion[37;242].

With combined medications there is also the potential for reduced compliance (due to the need to take additional tablets) or heightened or new treatment emergent adverse effects, and inefficacy (if the medications counteract one another).[8] In the case of naltrexone and acamprosate, there are no specific toxic interactions between these agents, suggesting they can be safely co-administered.[37;242]

Furthermore, co-administration of acamprosate with naltrexone significantly increases the rate and extent of absorption of acamprosate.[36;281;282] Thus combination treatment may make acamprosate more available systemically, with no decrease in tolerability, which may have clinical advantages.[36]

This section reviews clinical trials that have compared a combination of medications with any of the individual medications administered separately.

5.2 Evidence of effectiveness

The key question in relation to combination therapies is whether the combination is more effective than either of the individual pharmacotherapies alone. Four types of combinations have been investigated in controlled studies; all include naltrexone, combined with acamprosate, an antidepressant, disulfiram or GHB (see Table 5.1). Brief information on the individual studies is provided by Appendix 1.

Table 5.1: Studies involving combination of pharmacotherapies for relapse prevention treatment of alcohol dependence

Naltrexone + acamprosate compared with single medications	Naltrexone + antidepressant compared with single medications	Naltrexone + disulfiram compared with single medications	Naltrexone + GHB compared with single medications
Combine Pilot[52]	Farren 2009 [283]	Petrakis 2005[107-110]	Caputo 2007 [284]
Combine Study[15;37;59-62]	O'Malley 2008[91]	Pettinati 2008 [114]	Stella 2008 [285]
Kiefer 2003[24;111-113]	Stella 2008 [285]		

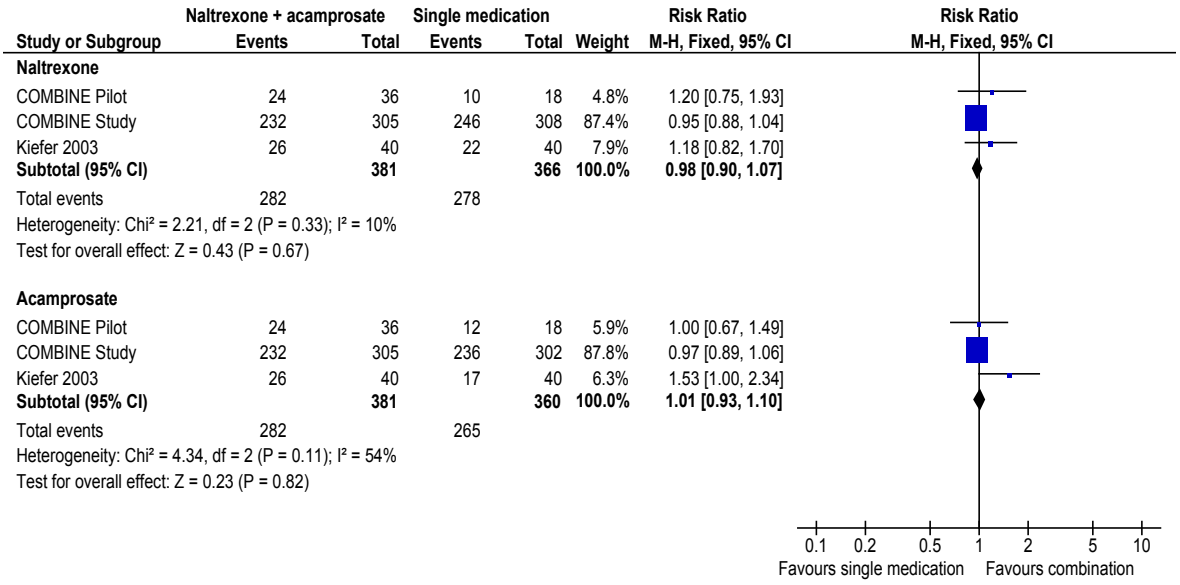
5.2.1 Naltrexone combined with acamprosate

	Retention in treatment
	Naltrexone combined with acamprosate has no effect on retention in treatment compared with either naltrexone or acamprosate alone.

Supporting evidence

There is no significant difference in the number of participants completing the study treatment for naltrexone plus acamprosate compared with either naltrexone (Figure 5.1: RR 0.98, 95% CI 0.90, 1.07; P=0.67)* or acamprosate (Figure 5.1: RR 1.01, 95% CI 0.93, 1.10)* alone.

Figure 5.1: Naltrexone plus acamprosate compared with single medications, participants completing the study treatment

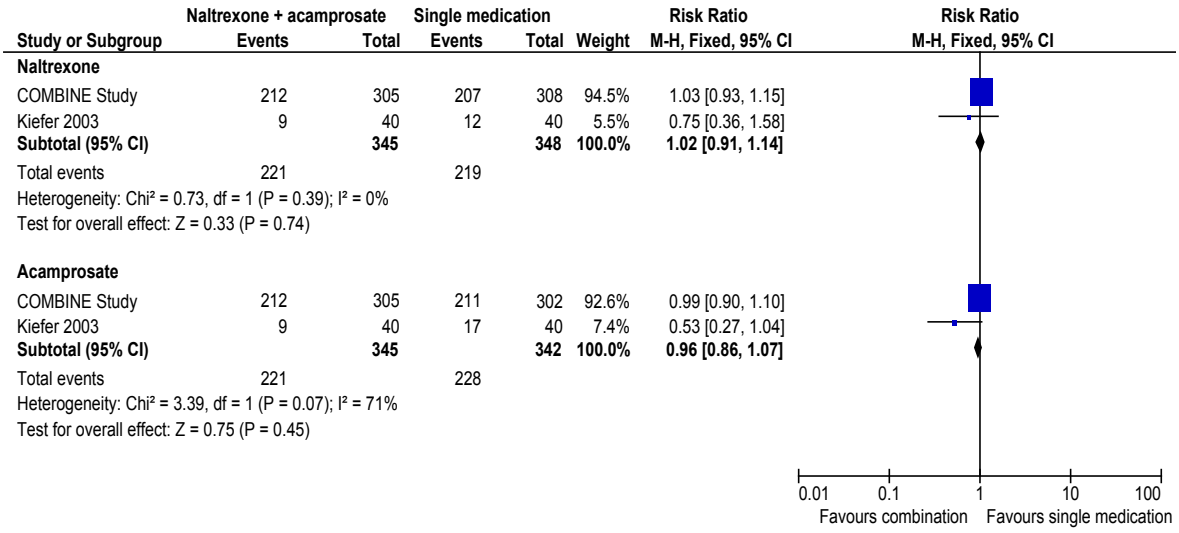


	Relapse to heavy drinking
	Naltrexone combined with acamprosate has no effect on the probability of relapse.

Supporting evidence

There is no significant difference in the number of participants relapsing to heavy drinking during treatment for naltrexone plus acamprosate compared with either naltrexone (Figure 5.2: RR 1.02, 95% CI 0.91, 1.14; P=0.74)* or acamprosate (Figure 5.2: RR 0.96, 95% CI 0.86, 1.07; P=0.45)* alone.

Figure 5.2: Naltrexone plus acamprosate compared with single medications, participants relapsing during treatment



	Abstinence during treatment
	Naltrexone combined with acamprosate has no effect on cumulative abstinence duration.
	Naltrexone combined with acamprosate may prolong the time to first drink and time to relapse to a greater extent than acamprosate, but has no significant effect compared to naltrexone alone.

Supporting evidence

Based on one study (Combine Study) there is no significant difference in the percent of treatment days with abstinence (cumulative abstinence duration) for naltrexone plus acamprosate compared with naltrexone (mean difference 1.07 % days, 95% CI -3.04, 5.18; P=0.61) or acamprosate (mean difference 2.11 % days, 95% CI -2.02, 6.24; P=0.32) alone. Similarly, the Combine Study reported no significant difference in the number of participants continuously abstinent during treatment with naltrexone plus acamprosate, compared with naltrexone (RR 0.95, 95% CI 0.70, 1.29; P=0.76) or acamprosate (RR 1.08, 95% CI 0.79, 1.48; P=0.64) alone.

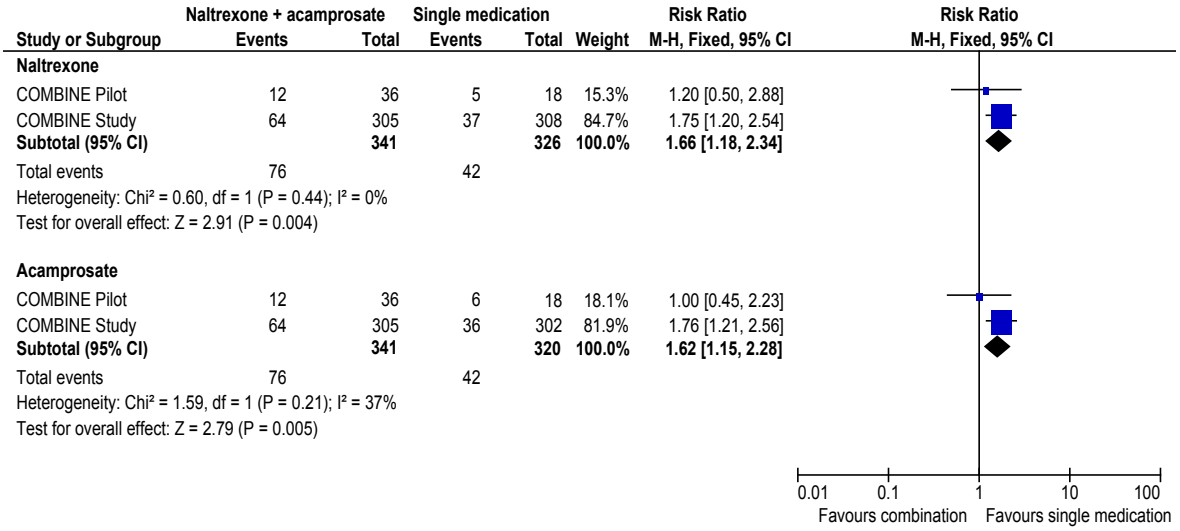
One study (Kiefer 2003) found significantly longer time to first drink for naltrexone plus acamprosate compared to acamprosate alone (mean difference 19.90 days, 95% CI 4.23, 35.57, P=0.01), but not compared to naltrexone alone (mean difference 9.4 days, 95% CI -6.43, 25.33; P=0.24). In the same study the time to relapse to heavy drinking was somewhat longer but not statistically significant for naltrexone plus acamprosate compared to acamprosate alone (mean difference 14.80 days, 95% CI -0.73, 30.33; P=0.06), and there was no significant difference for naltrexone plus acamprosate compared to naltrexone alone (mean difference 8.10 days, 95% CI -8.0, 24.20; P=0.32). In Kiefer 2003, final GGT values were significantly decreased compared with baseline, with no significant differences across treatment groups. Craving also decreased from baseline with no significant differences between groups.

	Adverse effects
	Naltrexone combined with acamprosate is associated with significantly more adverse effects but there is no significant difference in the probability of withdrawal from treatment due to adverse effects relative to naltrexone or acamprosate alone.

Supporting evidence

Significantly more people treated with naltrexone plus acamprosate required a dose reduction to manage adverse effects than those treated with naltrexone alone (Figure 5.3: RR 1.66, 95% 1.18, 2.34; P=0.004)* or acamprosate alone (Figure 5.3: RR 1.62, 95% CI 1.15, 2.28; P=0.005)*.

Figure 5.3: Naltrexone plus acamprosate compared with single medications, participants requiring a dose reduction to manage adverse effects



Gastrointestinal symptoms were more likely to be experienced by those people treated with naltrexone plus acamprosate compared to those treated with naltrexone only (Figure 5.4: RR 1.79, 95% CI 1.49, 2.16; P<0.001)*, but there was no significant difference for the combination compared to acamprosate only (Figure 5.4: RR 0.89, 95% CI 0.78, 1.01; P=0.07)*.

Nausea or vomiting is more likely to be experienced by those people treated with naltrexone plus acamprosate compared to those treated with acamprosate only (Figure 5.5: RR 1.74, 95% CI 1.37, 2.20; P<0.001)*, but there was no significant difference for the combination compared to naltrexone only (Figure 5.5: RR 1.18, 95% CI 0.97, 1.44; P=0.10)*.

Based on one study (Combine Pilot) there was no significant difference in the number of participants experiencing neuropsychiatric symptoms for naltrexone plus acamprosate compared to naltrexone (RR 1.43, 95% CI 0.75, 2.73; P=0.28) or acamprosate (RR 1.25, 95% CI 0.69, 2.26; P=0.46) only.

There was no significant difference in the number of participants withdrawn due to adverse effects for naltrexone plus acamprosate compared to naltrexone only (Figure 5.6: RR 0.97, 95% CI 0.51, 1.84; P=0.93)* or acamprosate only (Figure 5.6: RR 1.23, 95% CI 0.62, 2.44; P=0.55)*.

Figure 5.4: Naltrexone plus acamprosate compared with single medications, participants experiencing gastrointestinal symptoms

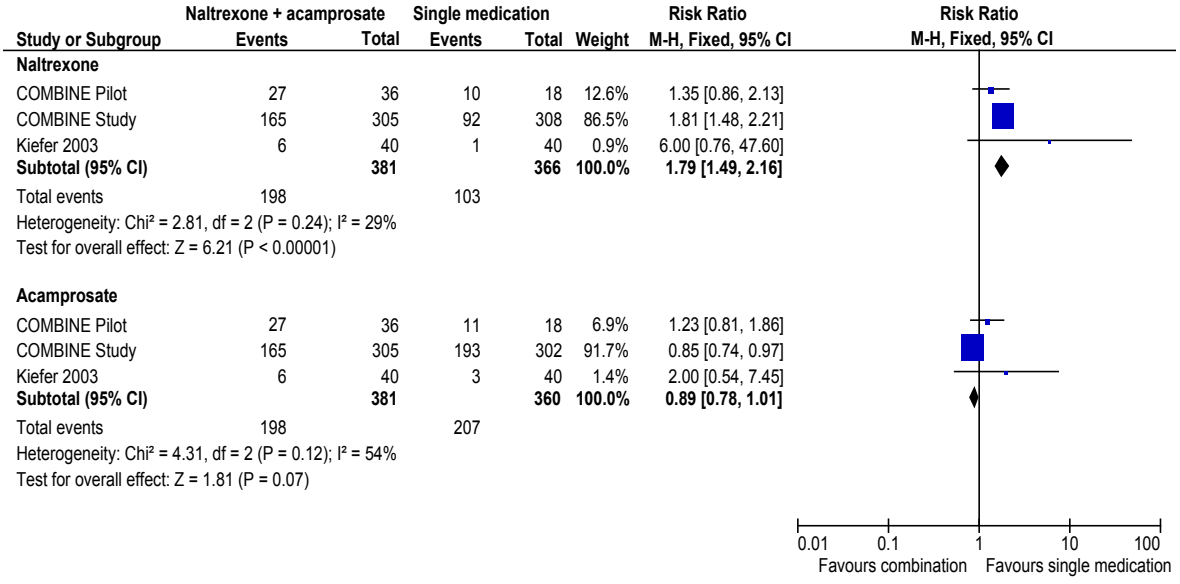


Figure 5.5: Naltrexone plus acamprosate compared with single medications, participants experiencing nausea or vomiting

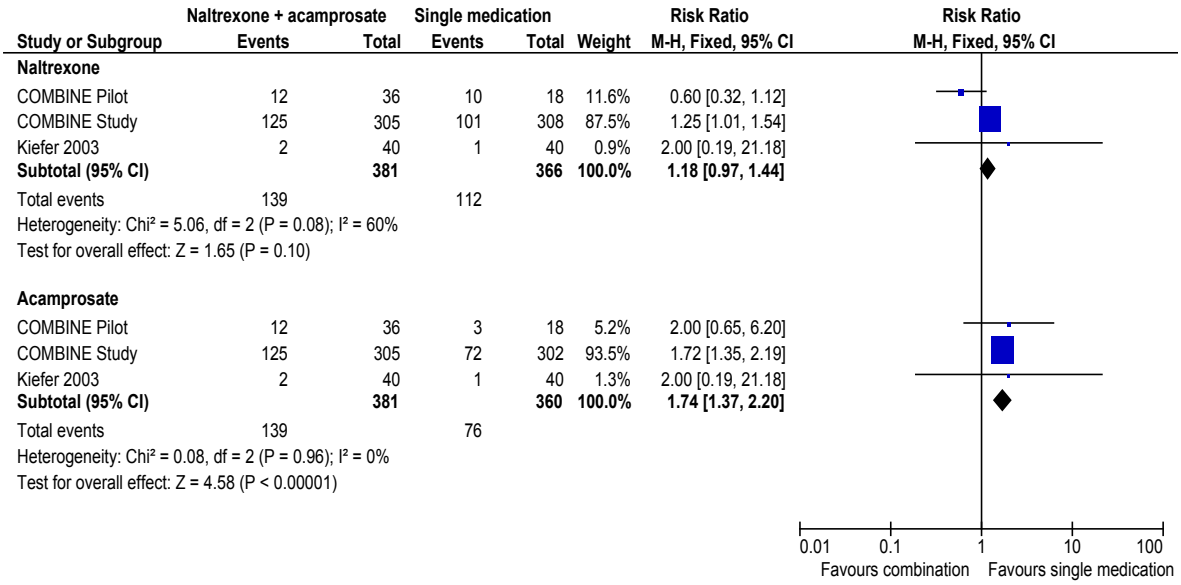
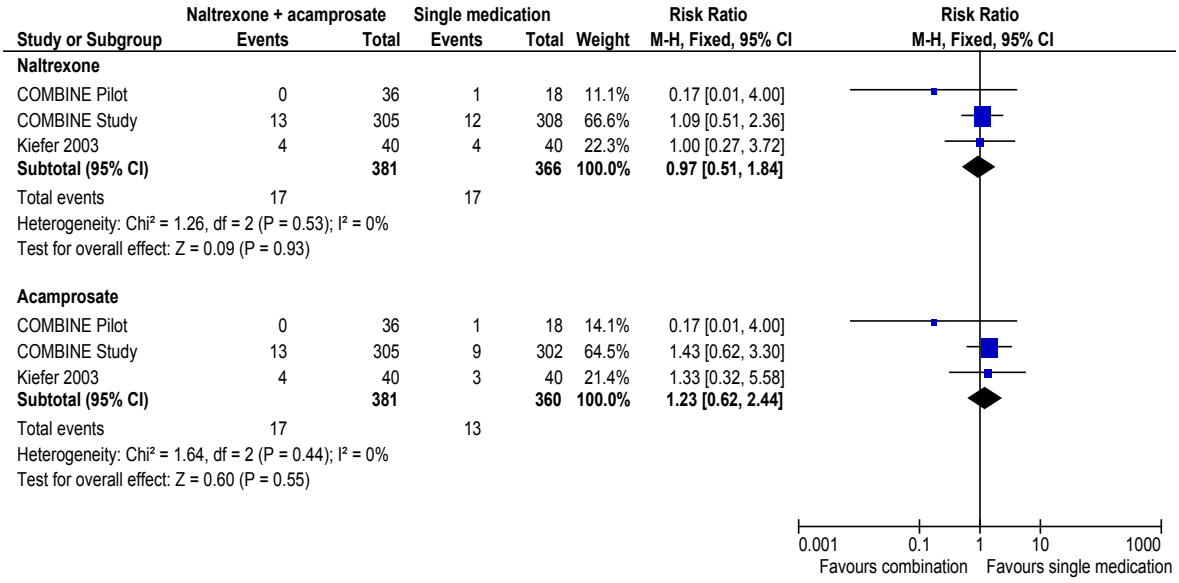


Figure 5.6: Naltrexone plus acamprosate compared with single medications, participants withdrawn due to adverse effects



	Conclusion
	The available data suggests that the combination of naltrexone plus acamprosate is no more effective than naltrexone or acamprosate alone.

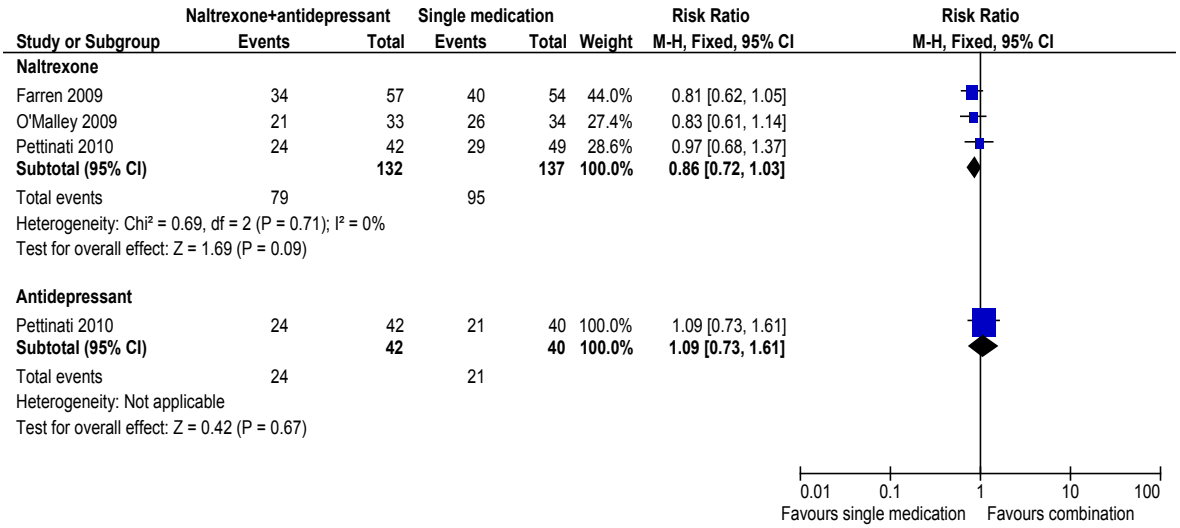
5.2.2 Naltrexone combined with antidepressant

	Retention in treatment
*	Naltrexone combined with antidepressant may result in less retention in treatment compared with naltrexone alone.

Supporting evidence

Based on three studies, completion of treatment is somewhat less likely with naltrexone plus antidepressant compared with naltrexone alone but the difference is not statistically significant (Figure 5.7: RR 0.86, 95% CI 0.72, 1.03; P=0.09)*. Pettinati 2010 reported no significant difference in rates of completion of treatment for naltrexone plus antidepressant compared with antidepressant alone (RR 1.09, 95% CI 0.73, 1.61; P=0.67).

Figure 5.7: Naltrexone plus antidepressant compared with single medications, participants completing the study treatment



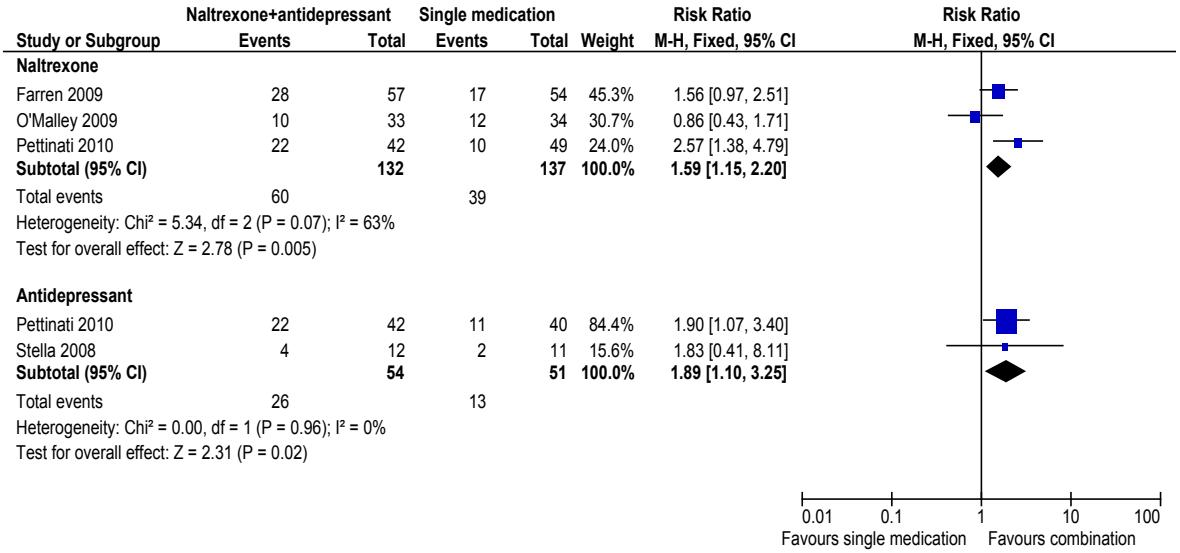
	Abstinence during treatment
*	Naltrexone combined with antidepressant is associated with greater probability of abstinence compared to antidepressant alone, but not naltrexone.

Supporting evidence

Based on three studies, there is no significant difference in the number of participants continuously abstinent during treatment, or abstinent at the end of treatment, with naltrexone plus antidepressant compared to naltrexone alone (Figure 5.8: RR 1.54, 95% CI 0.88, 2.68; P=0.13)*. Based on two studies, significantly more participants are likely to be continuously abstinent during treatment with naltrexone plus antidepressant compared with antidepressant alone (Figure 5.8: RR 1.90, 95% CI 1.10, 3.25; P=0.02)*.

In Farren 2009, the time to first drinking day was 29 days for naltrexone plus sertraline, compared to 18 days for naltrexone plus placebo. The difference was not statistically significant (P=0.10).

Figure 5.8: Naltrexone plus antidepressant compared with single medications, participants abstinent during treatment or abstinent at the end of the study



	Relapse to heavy drinking
	Naltrexone combined with antidepressant has no effect on relapse to heavy drinking compared with either naltrexone or antidepressant alone.
	Naltrexone combined with antidepressant may be more effective in prolonging the time to relapse, but data are limited.

Supporting evidence

One study (O'Malley 2008) reported no significant difference in the number of participants relapsing during treatment (RR 1.03, 95% CI 0.73, 1.46; P=0.87) for naltrexone plus antidepressant compared with naltrexone alone. Another study (Stella 2008) reported no significant difference in the number of participants relapsing during treatment (RR 0.81, 95% CI 0.50, 1.33; P=0.41) for naltrexone plus antidepressant compared with antidepressant alone.

Farren 2009 reported that there was no significant difference in the time to relapse to heavy drinking for those treated with naltrexone plus sertraline, compared to those receiving naltrexone plus placebo, without reporting data. However, in Pettinati 2010 the time to relapse was significantly longer for those treated with naltrexone plus sertraline, compared to those receiving sertraline alone (mean difference 23.70 days, 95% CI 6.58, 40.82; P=0.007) or naltrexone alone (mean difference 18.40 days, 95% CI 1.94, 34.86; P=0.03).

	Alcohol consumption during treatment
	Naltrexone combined with acamprosate has no significant effect on alcohol consumption during treatment compared with naltrexone alone.

Supporting evidence

One study reported significantly less drinks per drinking day for naltrexone plus antidepressant compared with naltrexone alone, while a second study found no significant difference. The combined result is not statistically significant (Figure 5.9: mean difference -1.13 drinks per drinking day, 95% CI -2.56, 0.30; P=0.12)*. There was also no significant difference in the percent of treatment days with abstinence for naltrexone plus acamprosate compared with naltrexone alone (Figure 5.10: mean difference -0.33 % days, 95% CI -6.24, 5.58; P=0.91)*.

Figure 5.9: Naltrexone plus antidepressant compared with single medications, average drinks per drinking day

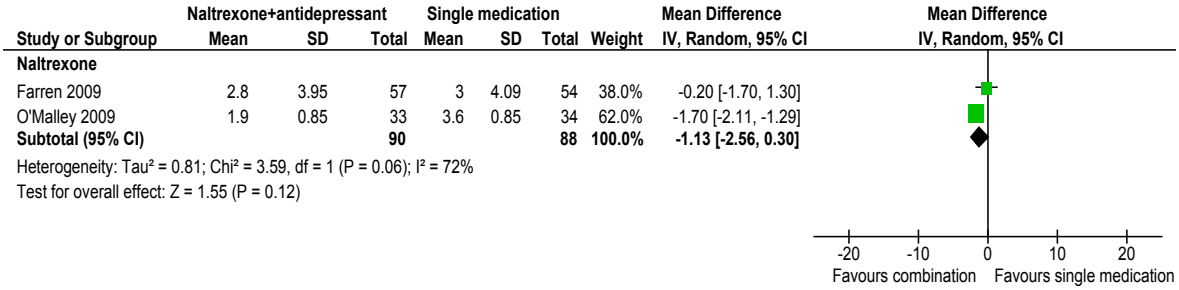
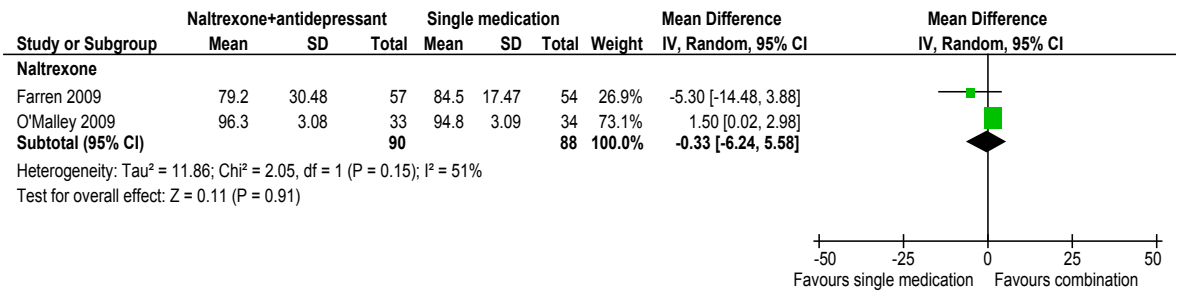


Figure 5.10: Naltrexone plus antidepressant compared with single medications, % treatment days abstinent (cumulative abstinence duration)



One study (O'Malley 2008) reported no significant difference in the percent of treatment days with heavy drinking for naltrexone plus antidepressant compared with naltrexone alone (mean difference -0.70 % days, 95% CI -2.15, 0.75; P=0.34)*. Farren 2009 reported no significant change in GGT or ALT levels, which is consistent with no significant difference in alcohol consumption for naltrexone plus sertraline compared to naltrexone plus placebo.

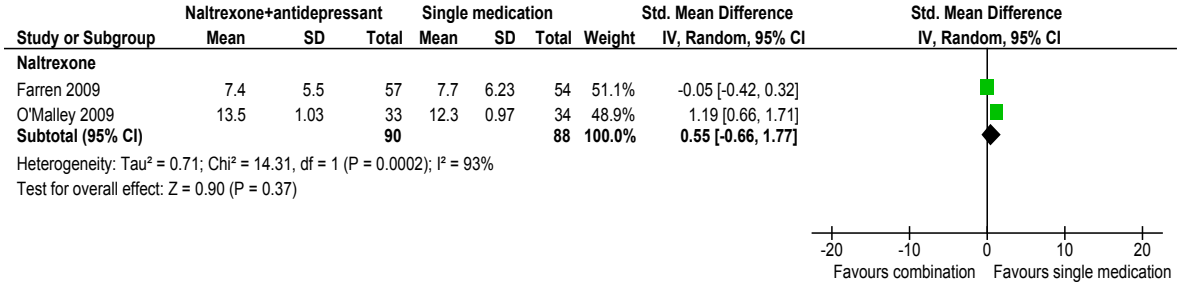
No data on alcohol consumption were reported for naltrexone plus antidepressant compared with antidepressant alone.

	Craving
	Naltrexone combined with acamprosate has no significant effect on craving compared with naltrexone alone.

Supporting evidence

One study reported significantly lower average craving scores for naltrexone alone compared with naltrexone plus antidepressant, while a second study reported no significant difference. The combined result is not statistically significant (Figure 5.11: SMD 0.55, -0.66, 1.77; P=0.37)*.

Figure 5.11: Naltrexone plus antidepressant compared with single medications, average craving scores



	Adverse effects
	Naltrexone combined with acamprosate has no significant effect on adverse effects compared with naltrexone alone.

Supporting evidence

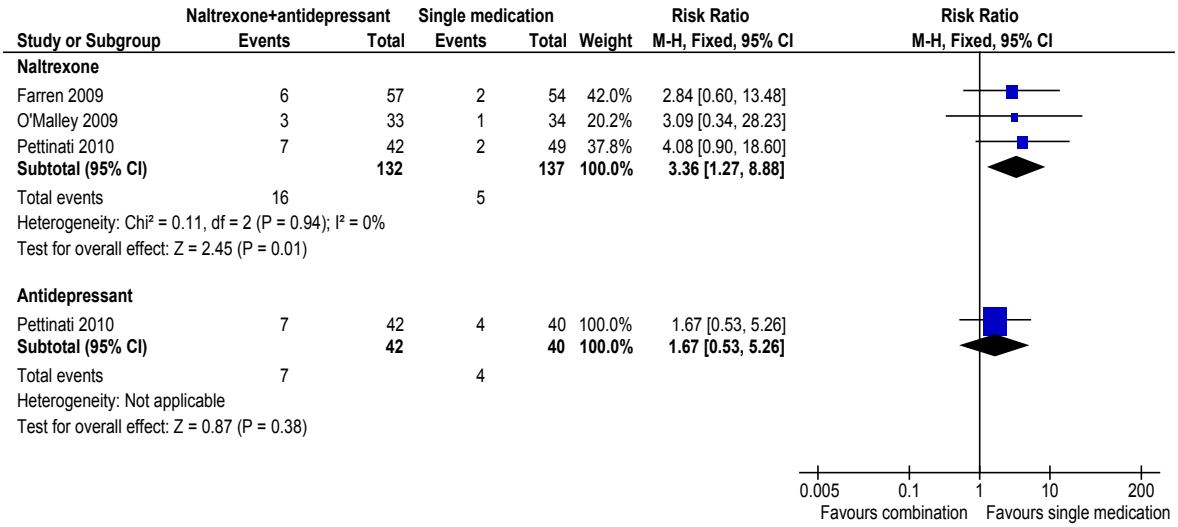
Pettinati 2010 reported less adverse effects with the combination of sertraline and naltrexone compared to naltrexone alone, but the difference was not statistically significant (RR 0.45, 95% CI 0.17, 1.16; p=0.10). Adverse effects were significantly less likely with the sertraline-naltrexone combination compared to sertraline alone (RR 0.32, 95% CI 0.13, 0.79; P=0.01).

O'Malley 2008 reported no significant difference in the number of participants experiencing neuropsychiatric symptoms for naltrexone plus antidepressant compared with naltrexone alone (RR 1.29, 95% CI 0.92, 1.81; P=0.15).

Based on three studies, significantly more participants were withdrawn due to adverse effects for naltrexone plus antidepressant compared to naltrexone alone (Figure 5.12: RR 3.36, 95% CI 1.27, 8.88; P=0.01)*. Pettinati 2010 reported no significant difference in the number of participants withdrawn due to adverse effects for the sertraline-naltrexone combination compared to sertraline alone (Figure 5.12: RR 1.67, 95% CI 0.53, 5.26; P=0.38).

	Conclusion
	The combination of naltrexone and an antidepressant is no more effective than naltrexone alone, other than for amelioration of depression.
	Naltrexone combined with an antidepressant may be more effective relative to an antidepressant alone for the treatment of alcohol dependence, but data are limited.

Figure 5.12: Naltrexone plus antidepressant compared with single medications, participants withdrawn due to adverse effects



5.2.3 Naltrexone combined with disulfiram

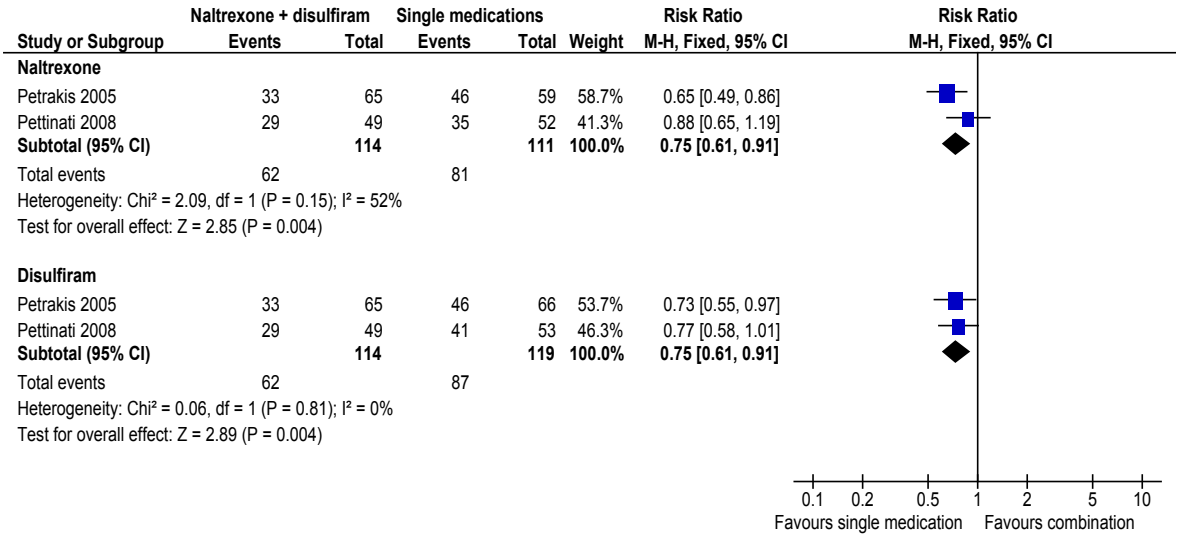
	Retention in treatment
*	Naltrexone combined with disulfiram is associated with reduced retention in treatment relative to either naltrexone or disulfiram alone.

Supporting evidence

Based on two studies, completion of treatment is significantly less likely with naltrexone-disulfiram combination compared with either naltrexone (Figure 5.13: RR 0.75, 95% CI 0.61, 0.91; P=0.004)* or disulfiram (Figure 5.13: RR 0.75, 95% CI 0.61, 0.91; P=0.004)* alone.

One study (Petrakis 2005) also reported the average weeks in treatment, with treatment duration significantly shorter with naltrexone-disulfiram combination compared with either naltrexone (mean difference -1.77 weeks, 95% CI -3.05, -0.49; P=0.007) or disulfiram (mean difference -1.27 weeks, 95% CI -2.56, 0.02; P=0.05) alone.

Figure 5.13: Naltrexone plus disulfiram compared with single medications, participants completing the study



	Abstinence, relapse and craving
	Based on one study, the combination of naltrexone and disulfiram is no more effective than naltrexone or disulfiram alone, in terms of abstinence, relapse to heavy drinking, or craving for alcohol during treatment.

Supporting evidence

One study (Petrakis 2005) reported no significant difference for the naltrexone-disulfiram combination compared with either naltrexone or disulfiram alone in the number of participants continuously abstinent during treatment, the percent of treatment days abstinent (cumulative abstinence duration), the percent of treatment days with heavy drinking, or the average craving score (See Table 5.2).

Table 5.2: Summary of alcohol consumption findings from Petrakis 2005 for naltrexone-disulfiram combination compared with naltrexone or disulfiram alone.

Outcome	Naltrexone-disulfiram combination compared with	
	Naltrexone alone	Disulfiram alone
Participants continuously abstinent during treatment	RR 1.10, 95% CI 0.86, 1.40; P=0.45	RR 0.92, 95% CI 0.75, 1.12; P=0.40
Percent of treatment days abstinent	Mean difference 1.20 % days, 95% CI -2.48, 4.88; P=0.52	Mean difference 0.00 % days, 95% CI -3.30, 3.30; P=1.0
Percent of treatment days with heavy drinking	Mean difference -0.90 % days, 95% CI -4.41, 2.61; P=0.62	Mean difference -0.10 % days, 95% CI -3.31, 3.11; P=0.95
Average craving scores	Mean difference -0.30, 95% CI -2.96, 2.36; P=0.82	Mean difference 1.70, 95% CI -0.63, 4.03; P=0.15

It was also reported that participants assigned to the naltrexone-disulfiram combination tended to have greater reduction of GGT over time compared with those treated with either medication alone, but the difference was not statistically significant.

	Adverse effects
*	Adverse effects are somewhat more likely with the combination of naltrexone and disulfiram, but this does not appear to result in increased withdrawal from treatment due to adverse effects.

Supporting evidence

Based on two studies, gastrointestinal symptoms were somewhat more likely with the naltrexone-disulfiram combination compared with naltrexone alone, but the difference was not statistically significant (Figure 5.14: RR 1.31, 95% CI 0.96, 1.79; P=0.09)*. Gastrointestinal symptoms were significantly more likely with the naltrexone-disulfiram combination compared with disulfiram alone (Figure 5.14: RR 1.38, 95% CI 1.00, 1.90; P=0.05)*. These two studies also reported significantly more participants experienced nausea or vomiting with naltrexone-disulfiram combination compared with either naltrexone (Figure 5.15: RR 1.39, 95% CI 1.11, 1.74; P=0.004)* or disulfiram (Figure 5.15; RR 1.33, 95% CI 1.08, 1.64; P=0.008)* alone.

One study (Pettinati 2008) reported no significant difference in the likelihood of neuropsychiatric symptoms with the naltrexone-disulfiram combination compared with either naltrexone (RR 1.16; 95% CI 0.89, 1.51; P=0.28) or disulfiram (RR 1.08, 95% CI 0.84, 1.39; P=0.54) alone.

One study (Petrakis 2005) reported no significant difference in the number of participants withdrawn due to adverse effects for the naltrexone-disulfiram combination compared to either naltrexone (RR 1.36, 95% CI 0.24, 7.87; P=0.73) or disulfiram (RR 1.52, 95% CI 0.26, 8.82; P=0.64) alone.

	Conclusion
	It appears that combining naltrexone with disulfiram offers few, if any benefits, over either medication alone, and is associated with somewhat increased risk of adverse effects, and lower rates of retention in treatment.

Figure 5.14: Naltrexone plus disulfiram compared with single medications, participants experiencing gastrointestinal symptoms

Study or Subgroup	Naltrexone + disulfiram Events	Total	Single medications Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Naltrexone						
Petrakis 2005	43	65	29	59	88.7%	1.35 [0.98, 1.84]
Pettinati 2008	4	49	4	52	11.3%	1.06 [0.28, 4.01]
Subtotal (95% CI)		**114**		**111**	**100.0%**	**1.31 [0.96, 1.79]**
Total events	47		33			
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.72 (P = 0.09)						
Disulfiram						
Petrakis 2005	43	65	28	66	80.5%	1.56 [1.12, 2.17]
Pettinati 2008	4	49	7	53	19.5%	0.62 [0.19, 1.98]
Subtotal (95% CI)		**114**		**119**	**100.0%**	**1.38 [1.00, 1.90]**
Total events	47		35			
Heterogeneity: Chi² = 2.36, df = 1 (P = 0.12); I² = 58%						
Test for overall effect: Z = 1.94 (P = 0.05)						

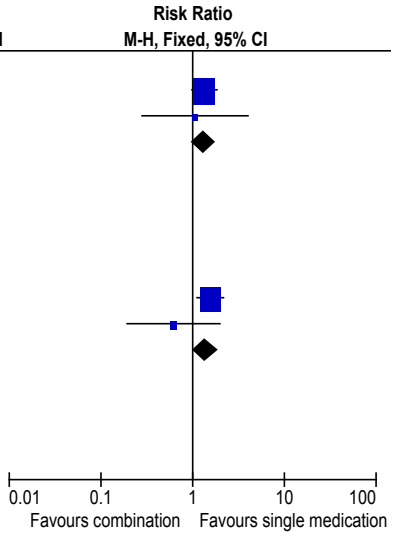
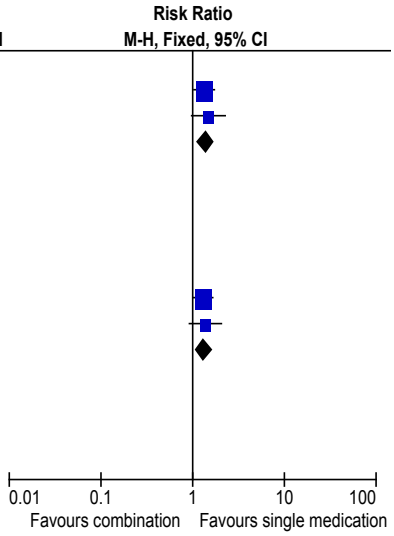


Figure 5.15: Naltrexone plus disulfiram compared with single medications, participants experiencing nausea or vomiting

Study or Subgroup	Naltrexone + disulfiram Events	Total	Single medications Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Naltrexone						
Petrakis 2005	50	65	34	59	64.7%	1.33 [1.03, 1.72]
Pettinati 2008	28	49	20	52	35.3%	1.49 [0.98, 2.26]
Subtotal (95% CI)		**114**		**111**	**100.0%**	**1.39 [1.11, 1.74]**
Total events	78		54			
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 2.87 (P = 0.004)						
Disulfiram						
Petrakis 2005	50	65	39	66	64.7%	1.30 [1.02, 1.66]
Pettinati 2008	28	49	22	53	35.3%	1.38 [0.92, 2.06]
Subtotal (95% CI)		**114**		**119**	**100.0%**	**1.33 [1.08, 1.64]**
Total events	78		61			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 2.63 (P = 0.008)						



5.2.4 Naltrexone combined with GHB

	Retention in treatment
	Based on one study, the combination of naltrexone and GHB has no significant effect on treatment retention compared with naltrexone or GHB alone.

Supporting evidence

One study (Caputo 2007) reported no significant difference in the number of participants completing the study treatment for naltrexone combined with GHB compared with naltrexone (RR 1.09, 95% CI 0.78, 1.52) or GHB (RR 0.93, 0.72, 1.19; P=0.55) alone.

	Abstinence and relapse
*	Available data suggests that the combination of naltrexone and GHB is associated with significantly more abstinence and significantly less relapse to heavy drinking compared with either naltrexone or GHB alone.

Supporting evidence

Based on two studies, significantly more participants were continuously abstinent during treatment with naltrexone combined with GHB, compared with naltrexone (Figure 5.16: RR 4.5, 95% CI 1.99, 10.20; P<0.001)* or GHB (Figure 5.16: RR 1.74, 95% CI 1.13, 2.70; P=0.01)* alone. The number of participants relapsing during treatment is also significantly less for naltrexone combined with GHB compared with either naltrexone (Figure 5.17: RR 0.26, 95% CI 0.08, 0.89; P=0.03)* or GHB (Figure 5.17: RR 0.27, 95% CI 0.08, 0.96; P=0.04)* alone.

Figure 5.16: Naltrexone plus GHB compared with single medications, participants continuously abstinent during treatment

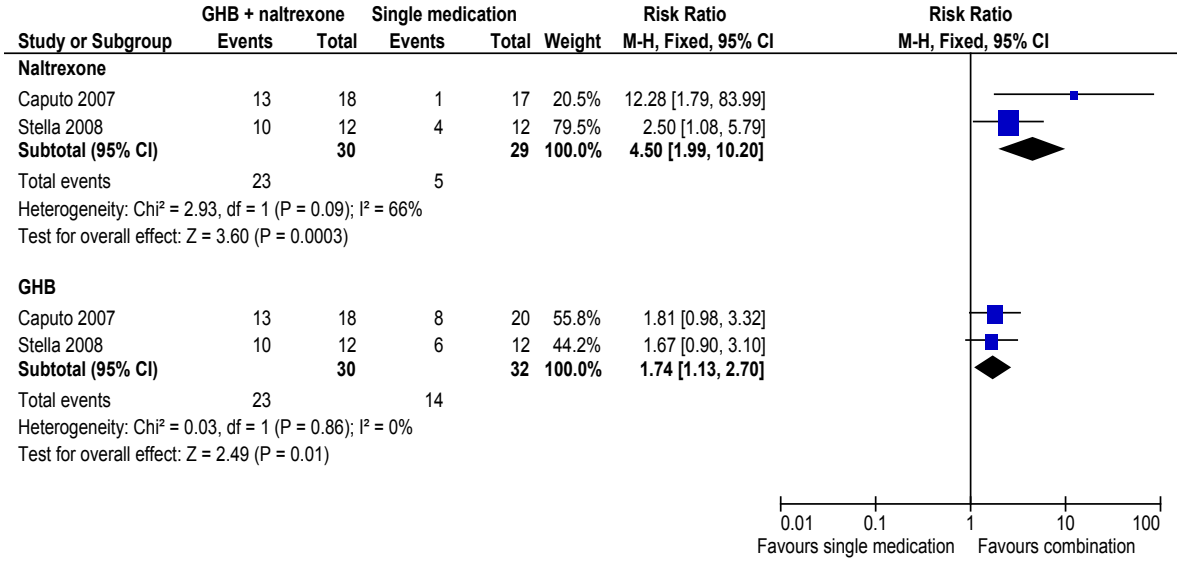
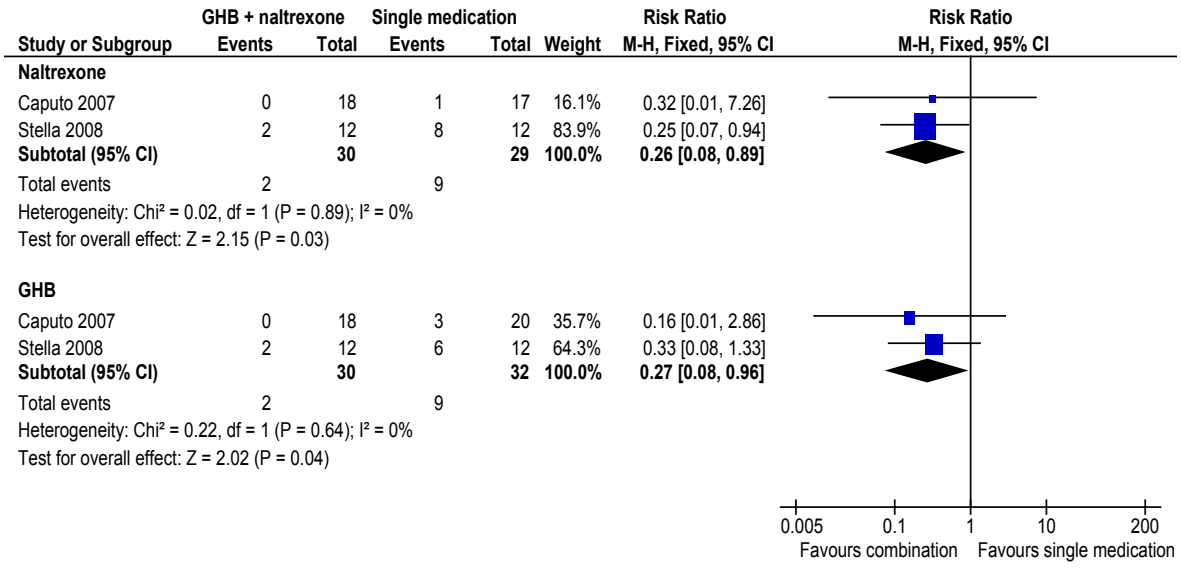


Figure 5.17: Naltrexone plus GHB compared with single medications, participants relapsing during treatment



	Alcohol consumption during treatment
	The combination of naltrexone and GHB may result in less alcohol consumption compared to either naltrexone or GHB alone, but insufficient data are available for firm conclusions.

Supporting evidence

One study (Caputo 2007) reported significantly less average drinks per drinking day for people treated with naltrexone combined with GHB compared to those treated with naltrexone alone (mean difference -1.50, 95% CI -2.45, -0.55; P=0.002)*. In the same study the average drinks per drinking day was less for people treated with naltrexone combined with GHB compared to those treated with GHB alone but the difference was not statistically significant (mean difference -1.50, 95% CI -3.16, 0.16; P=0.08)*. However, Stella 2008 reported that alcohol consumption was significantly lower in the group receiving both naltrexone and GHB compared to other groups. Self-reported craving was also significantly lower in the group receiving naltrexone and GHB, compared to baseline and compared to other treatment groups.

	Adverse effects
	Based on one study, participants treated with naltrexone combined with GHB are significantly more likely to experience adverse effects, compared to those treated with GHB alone.
	All other comparisons show more adverse effects, and withdrawal from treatment due to adverse effects, associated with naltrexone combined with GHB, compared with naltrexone or GHB alone, but the differences are not statistically significant.

Supporting evidence

One study (Caputo 2007) reported data on adverse effects for participants treated with naltrexone plus GHB, compared with those treated with naltrexone alone or GHB alone. The findings are summarised in Table 5.3.

Table 5.3: Number of participants experiencing specific adverse effects during treatment with naltrexone plus GHB compared to naltrexone or GHB alone.

Outcome	Naltrexone-GHB combination compared to	
	Naltrexone	GHB
Any adverse effects	RR 2.13, 95% CI 0.80, 5.63; P=0.13	RR 5.0, 95% CI 1.24, 20.15, 95% CI 0.02
Nausea or vomiting	RR 1.89, 95% CI 0.40, 9.01; P=0.43	RR 9.95, 95% CI 0.57, 172.84; P=0.11
Neuropsychiatric symptoms	RR 10.42, 95% CI 0.62, 175.25; P=0.10	RR 2.78, 95% CI 0.61, 12.59; P=0.19
Withdrawn due to adverse effects	RR 2.83, 95% CI 0.33, 24.66; P=0.35	RR 3.33, 95% CI 0.38, 29.25, P=0.28

These data show significantly greater likelihood of any adverse effects associated with the combination of naltrexone and GHB compared to GHB alone. All other comparisons show somewhat greater risk of adverse effects associated with the combination of naltrexone and GHB, but the differences are not statistically significant.

	Conclusion
	There may be benefits from the combination of GHB and naltrexone over individual medications but data on GHB itself is still limited.
	GHB is subject to abuse and it remains unclear whether the benefits of GHB are sufficient to outweigh the risks of abuse (see section 8.3).

SECTION 6: ANTICONVULSANTS

Overview

Rationale

Anticonvulsants have the capacity to dampen the hyperglutaminergic state associated with chronic alcohol consumption through their effect on GABA or glutaminergic function.

Type of anticonvulsant

Most data on the effectiveness of anticonvulsants for relapse prevention treatment comes from studies comparing topiramate with placebo, with some studies comparing an anticonvulsant to naltrexone, acamprosate or disulfiram.

Retention in treatment

Relative to placebo, anticonvulsants appear to have no effect on rates of completion of treatment**, but may prolong time in treatment*.

Retention in treatment may be better with anticonvulsants relative to naltrexone**.

Insufficient data are available to form a view on anticonvulsants compared with acamprosate or disulfiram in terms of retention in treatment.

Abstinence

In terms of continuous abstinence during treatment, anticonvulsants are significantly more effective than placebo, naltrexone and acamprosate.

No data are available on continuous abstinence during treatment with anticonvulsants compared with disulfiram.

Relapse to heavy drinking

Relapse to heavy drinking is significantly less likely with anticonvulsant treatment compared to placebo**.

There is no significant difference between anticonvulsants and naltrexone in terms of relapse to heavy drinking*.

Insufficient data are available to form a view on the likelihood of relapse to heavy drinking during treatment with an anticonvulsant compared to acamprosate or disulfiram.

Amount of alcohol consumed

On all indicators of alcohol consumption, anticonvulsant treatment appears to be more effective than placebo*.

Data are limited, but suggest that anticonvulsants are at least of equivalent efficacy to naltrexone, acamprosate and disulfiram in terms of the effect on the amount of alcohol consumed during treatment*.

Time to first drink and time to relapse

Limited data suggest that, compared with placebo, anticonvulsant treatment may prolong the time to first drink and time to relapse to heavy drinking.

Limited data suggest that anticonvulsant treatment is associated with a longer time to relapse compared to naltrexone.

Insufficient data are available to form a view on the effectiveness of anticonvulsants compared to acamprosate or disulfiram in terms of time to first drink and time to relapse.

Objective indicators of alcohol consumption

GGT levels support a finding that anticonvulsants are more effective than placebo, and have similar effectiveness to naltrexone in terms of reducing alcohol consumption.

Insufficient data are available to form a conclusion on the effectiveness of anticonvulsants relative to acamprosate or disulfiram.

Craving

Treatment with anticonvulsants is associated with less craving during treatment relative to placebo.

There is no significant difference between anticonvulsants and naltrexone in terms of total craving during treatment.

Insufficient data are available to form a view on the effect of anticonvulsants on craving relative to acamprosate or disulfiram.

Adverse effects

There are no statistically significant differences between anticonvulsants and placebo, naltrexone, acamprosate or disulfiram in terms of adverse effects experienced, but there are indications that adverse effects associated with topiramate, particularly paresthesia, could be an issue.

Withdrawal from treatment due to adverse effects is significantly less likely with anticonvulsants compared to naltrexone suggesting that the adverse effects associated with anticonvulsants are more readily managed or more tolerable than those associated with naltrexone.

Factors affecting outcomes

The severity of alcohol withdrawal symptoms at the commencement of treatment, dose of anticonvulsant, commitment to abstinence, and tobacco smoking are factors that have been identified as potentially affecting the outcomes of anticonvulsant treatment of alcohol dependence. Insufficient data are available to determine if, and to what extent, these factors do affect the outcomes of treatment.

6.1 Rationale for effect

Anticonvulsants exhibit a range of neuropharmacologic effects, with their capacity to facilitate GABA or impede glutaminergic function predicted to dampen the hyperglutaminergic state seen following chronic alcohol consumption.[8;76] Most of the research on the use of anticonvulsants to treat alcohol dependence relates to the management of alcohol withdrawal.[286] However, some studies of anticonvulsants for relapse prevention treatment have been undertaken. These studies are the focus of this section.

6.2 Evidence of effectiveness

Anticonvulsants have been compared with placebo for the treatment of alcohol dependence in 10 studies, while seven studies have compared anticonvulsants with other active medication (see Table 6.1). Brief information on the design of these studies is included in Appendix 1.

Table 6.1: Studies involving the use of anticonvulsants for relapse prevention treatment of alcohol dependence

Comparison with placebo	Comparison with other active medication		
	Opioid antagonist	Acamprosate	Disulfiram
Anton 2009[287]	Baltieri 2008 [76]	Croissant 2006 [288]	De Sousa 2008 [289]
Arias 2010 [290]	Florez 2008 [291]	Narayana 2008 [179]	
Baltieri 2008 [76]	Martinotti 2007 [292]		
Brady 2002 [293]	Martinotti 2010 [294]		
Brower 2008 [295]			
Furieri 2007 [296]			
Johnson 2003[297-299]			
Johnson 2007[300;301]			
Mueller 1997 [302]			
Rubio 2009[303]			
Salloum 2005[304-306]			

The anticonvulsants investigated in these studies are topiramate (Baltieri 2008, De Sousa 2008, Florez 2008, Johnson 2003, Johnson 2007, Narayana 2008, Rubio 2009), zonisamide (Arias 2010), divalproex (Brady 2002), oxcarbazepine (Croissant 2006, Martinotti 2007), carbamazepine (Mueller 1997), gabapentin (Anton 2009, Brower 2008, Furieri 2007), pregabalin (Martinotti 2010) and valproate (Salloum 2005).

6.2.1 Retention in treatment

**	Relative to placebo, anticonvulsants appear to have no effect on rates of completion of treatment, but may prolong time in treatment.
**	Retention in treatment may be better with anticonvulsants relative to naltrexone.
	Insufficient data are available to form a view on anticonvulsants compared with acamprosate or disulfiram in terms of retention in treatment.

Supporting evidence

There is no significant difference between anticonvulsants and placebo in the number of participants completing the study (Figure 6.1: RR 1.06, 95% CI 0.90, 1.25; P=0.51)**. However, based on two studies, the average time in treatment is significantly longer for anticonvulsants compared to placebo (Figure 6.2: mean difference 0.90 weeks, 95% CI 0.63, 1.17; P<0.001)*. Brower 2008 also reported a somewhat longer duration of medication for participants treated with gabapentin (median 42 days) compared with those receiving placebo (median 39 days).

Figure 6.1: Anticonvulsant compared with placebo, participants completing the study

	Anticonvulsant		Placebo			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Arias 2010	17	20	19	20	14.2%	0.89 [0.73, 1.10]
Baltieri 2008	33	52	23	54	9.6%	1.49 [1.03, 2.16]
Brady 2002	14	19	15	20	9.6%	0.98 [0.68, 1.42]
Brower 2008	8	10	6	11	5.1%	1.47 [0.79, 2.73]
Furieri 2007	27	30	21	30	12.6%	1.29 [0.99, 1.67]
Johnson 2003	55	75	48	75	14.0%	1.15 [0.92, 1.42]
Johnson 2007	112	183	144	180	16.3%	0.77 [0.67, 0.88]
Rubio 2009	31	38	32	38	14.4%	0.97 [0.79, 1.19]
Salloum 2005	12	27	8	25	4.2%	1.39 [0.68, 2.83]
Total (95% CI)		**454**		**453**	**100.0%**	**1.06 [0.90, 1.25]**
Total events	309		316			

Heterogeneity: Tau² = 0.04; Chi² = 26.77, df = 8 (P = 0.0008); I² = 70%
Test for overall effect: Z = 0.67 (P = 0.51)

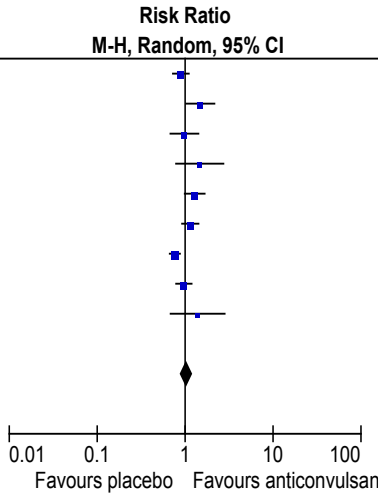
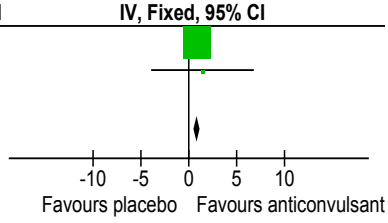


Figure 6.2: Anticonvulsant compared with placebo, average weeks in treatment

	Anticonvulsant			Placebo			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Johnson 2003	10.1	0.8	75	9.2	0.9	75	99.7%	0.90 [0.63, 1.17]
Salloum 2005	16	9.86	27	14.57	9.57	25	0.3%	1.43 [-3.85, 6.71]
Total (95% CI)			**102**			**100**	**100.0%**	**0.90 [0.63, 1.17]**

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 6.49 (P < 0.00001)

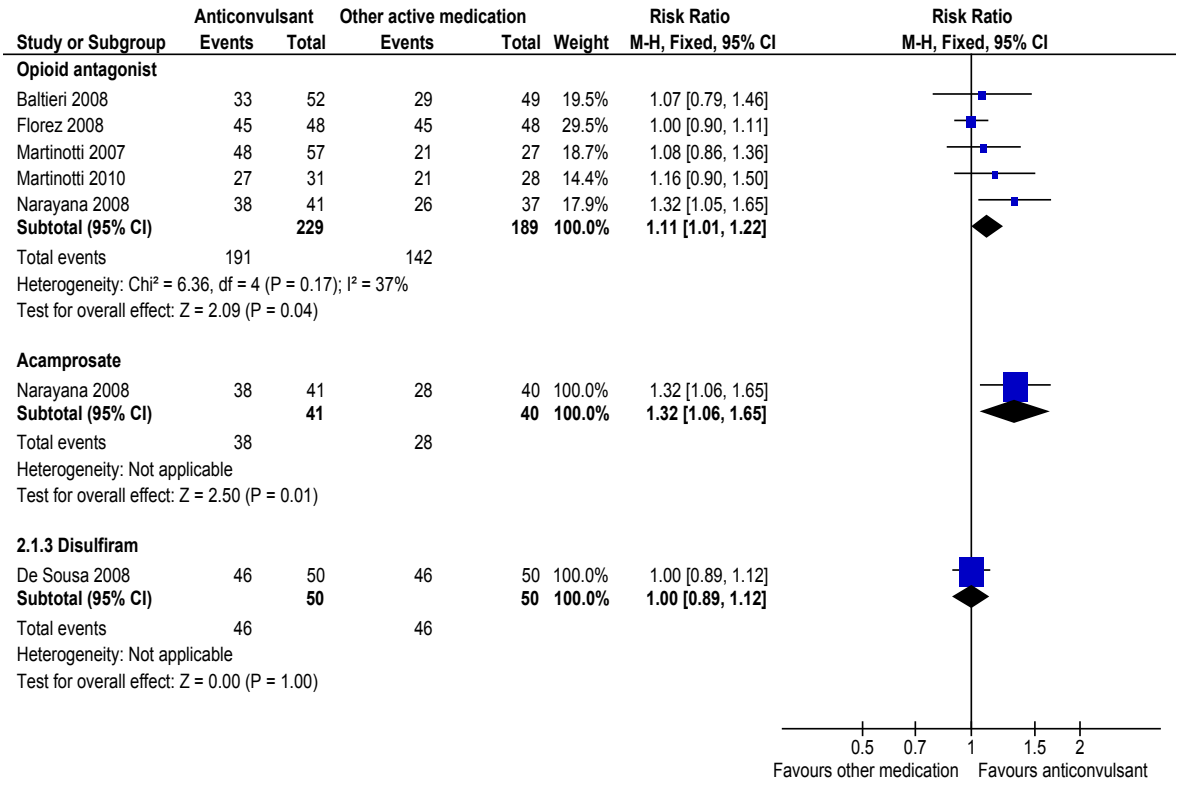


Based on five studies, significantly more people treated with anticonvulsants completed treatment compared with those treated naltrexone (Figure 6.3: RR 1.11, 95% CI 1.01, 1.22; P=0.04)**.

One study reported significantly more people treated with anticonvulsants completed treatment compared to those treated with acamprosate (Figure 6.3: RR 1.32, 95% CI 1.06, 1.65; P=0.01), and one study (Croissant 2006) reported no significant difference in the average time in treatment for anticonvulsant compared with acamprosate (mean difference 5.92 weeks, 95% CI -1.80, 13.64, P=0.13).

One study reported no significant difference in completion of treatment for anticonvulsants compared with disulfiram (Figure 6.3: RR 1.00, 95% CI 0.89, 1.12; P=1.0)*.

Figure 6.3: Anticonvulsant compared with other active medication, participants completing the study



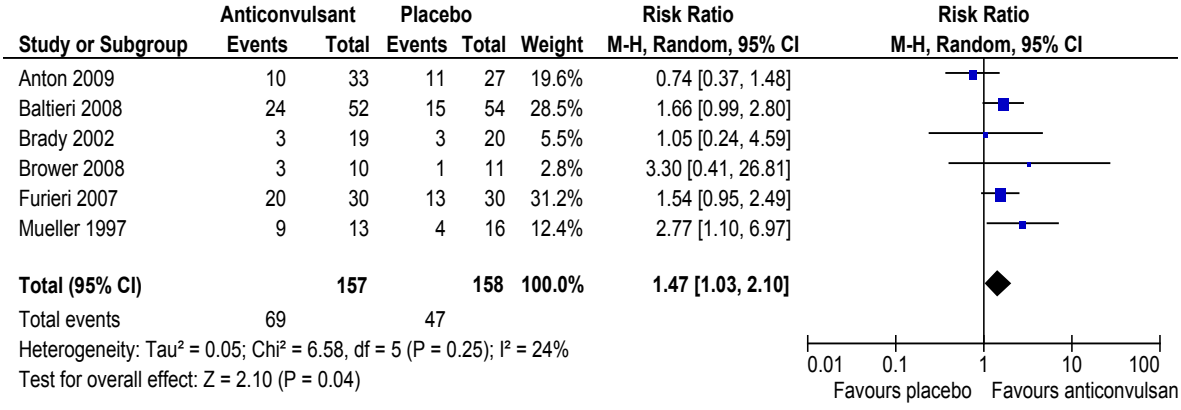
6.2.2 Effect on alcohol consumption

	Abstinence
	In terms of continuous abstinence during treatment, anticonvulsants are significantly more effective than placebo, naltrexone and acamprosate.
	No data are available on continuous abstinence during treatment with anticonvulsants compared with disulfiram.

Supporting evidence

Based on six studies, people treated with an anticonvulsant are significantly more likely to be continuously abstinent during treatment compared to people receiving placebo (Figure 6.4, RR 1.47, 95% CI 1.03, 2.10; P=0.04)*. However, the studies are small making the quantitative estimate of effect unreliable.

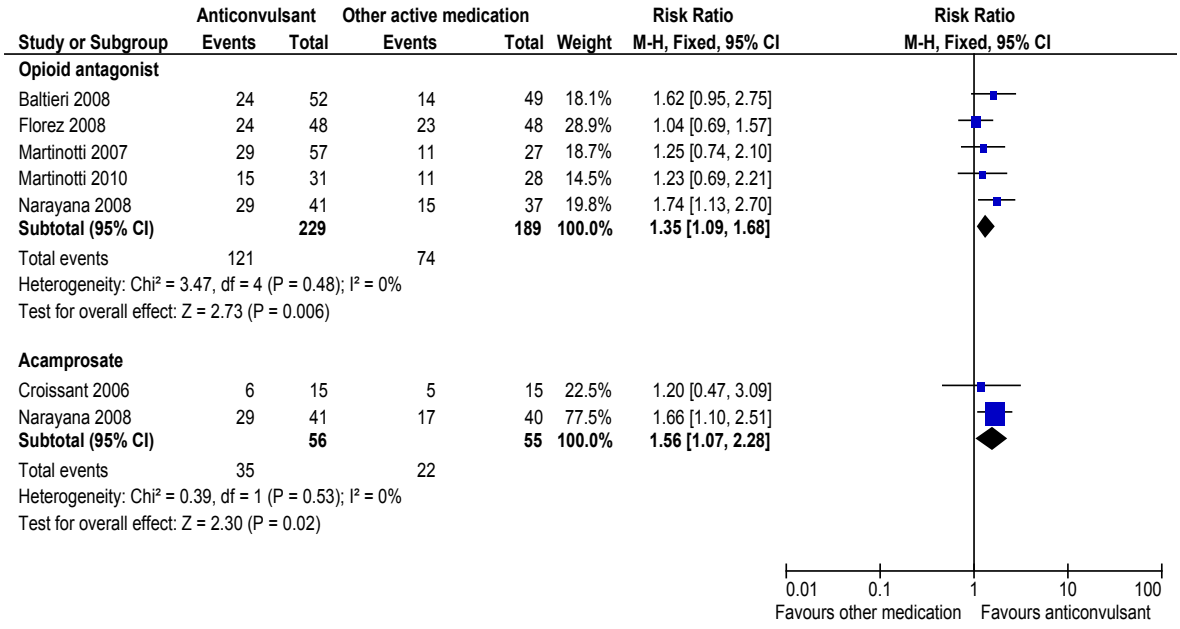
Figure 6.4: Anticonvulsant compared with placebo, participants continuously abstinent during treatment



Arias 2010 did not report data on abstinence, and in this study the outcome of abstinence was confounded in that two-thirds of participants had a goal of controlled drinking rather than total abstinence.

Based on five studies, people treated with an anticonvulsant are significantly more likely to be continuously abstinent during treatment than people treated with naltrexone (Figure 6.5: RR 1.35, 95% CI 1.09, 1.68; P=0.006).** Based on two studies, continuous abstinence is significantly more likely during treatment with an anticonvulsant compared to acamprosate (Figure 6.5: RR 1.56, 95% CI 1.07, 2.28; P=0.02)*.

Figure 6.5: Anticonvulsant compared with other active medication, participants continuously abstinent during treatment

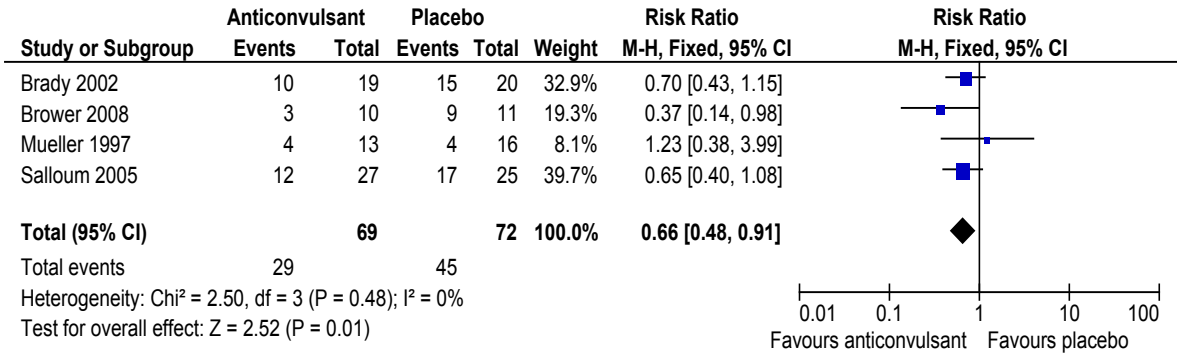


	Relapse to heavy drinking
**	Relapse to heavy drinking is significantly less likely with anticonvulsant treatment compared to placebo.
*	There is no significant difference between anticonvulsants and naltrexone in terms of relapse to heavy drinking.
	Insufficient data are available to form a view on the likelihood of relapse to heavy drinking during treatment with an anticonvulsant compared to acamprosate or disulfiram.

Supporting evidence

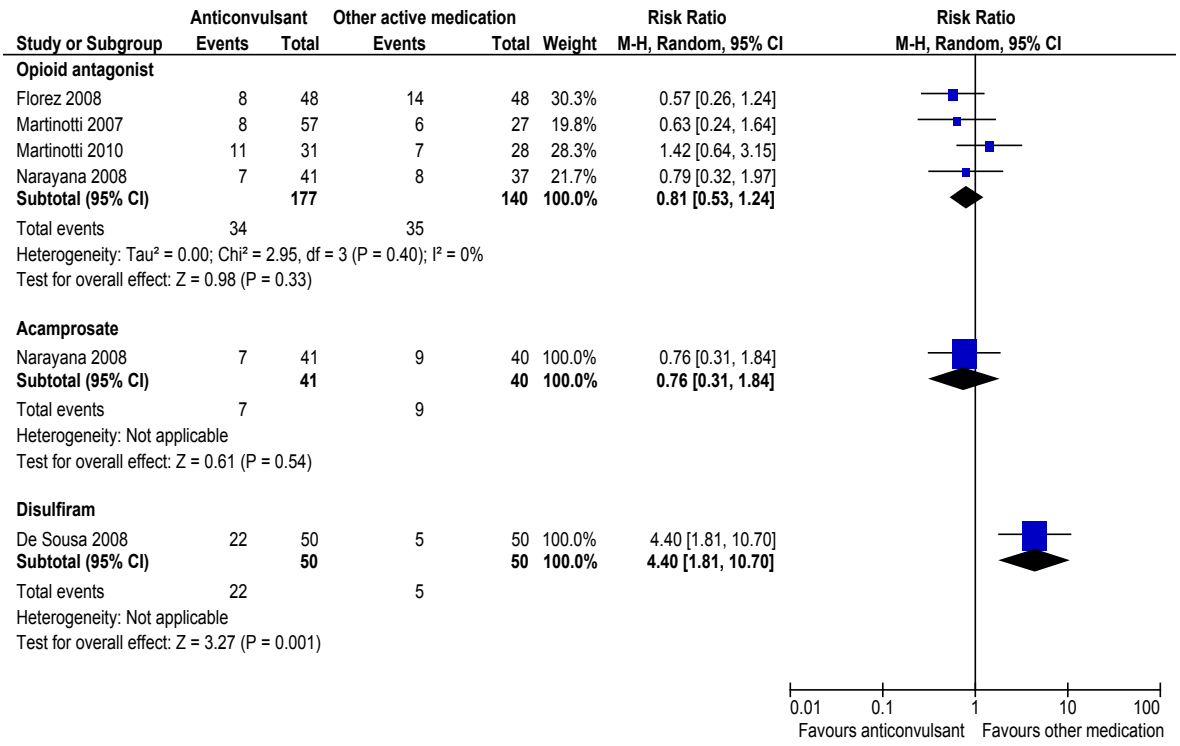
People treated with an anticonvulsant are significantly less likely to relapse during treatment compared to people treated with placebo (Figure 6.6: RR 0.66, 95% CI 0.48, 0.91; P=0.01)*.

Figure 6.6: Anticonvulsant compared with placebo, participants relapsing during treatment



Based on four studies, there is no significant difference between anticonvulsants and naltrexone in the likelihood of relapse to heavy drinking (Figure 6.7: RR 0.81, 95% CI 0.53, 1.24; P=0.33)*. One study (Narayana 2008) reported no significant difference in the number of people relapsing during treatment with topiramate compared to acamprosate (Figure 6.7: RR 0.76, 95% CI 0.31, 1.84; P=0.54), while another study (De Sousa 2008) reported significantly more relapse to heavy drinking during treatment with topiramate compared with oral disulfiram (Figure 6.7: RR 4.40, 95% CI 1.81, 10.70; P=0.001).

Figure 6.7: Anticonvulsant compared with other active medication, participants relapsing during treatment



	Amount of alcohol consumed
*	On all indicators of alcohol consumption, anticonvulsant treatment appears to be more effective than placebo.
*	Data are limited, but suggest that anticonvulsants are at least of equivalent efficacy to naltrexone, acamprosate and disulfiram in terms of the effect on the amount of alcohol consumed during treatment.

Supporting evidence

Combined data from four studies indicates that treatment with an anticonvulsant is associated with significantly less average drinks per drinking day compared to placebo (Figure 6.8: mean difference -1.35 drinks, 95% CI -2.24, -0.45; P=0.003).** Data suitable for inclusion in meta-analyses was not able to be extracted from three studies (Furieri 2007, Johnson 2003, Mueller 1997) all of which reported less drinks per drinking day with anticonvulsant compared to placebo. In addition, Arias 2010 reported a decrease of 2.2 drinks/week in the zonisamide group compared to 1.4 drinks/week in the placebo group (P=0.004). Laboratory studies with heavy drinkers also indicate significant reductions in the frequency of drinking with anticonvulsant (topiramate) compared with placebo.[307]

Data from three studies indicates that treatment with an anticonvulsant is associated with significantly more treatment days abstinent compared to placebo (Figure 6.9: mean difference 11.74 % days, 95% CI 5.66, 17.76; P<0.001).* Five studies did not report data in a form suitable for meta-analysis: Anton 2009 and Arias 2010 found no main effect of medication on per cent days abstinent; Brady found no significant differences in percent of days with drinking; however Johnson 2003 and Furieri 2007 reported significantly more days abstinent with topiramate compared with placebo. Overall it seems likely that anticonvulsant treatment is associated with more abstinent days during treatment relative to placebo.

Figure 6.8: Anticonvulsant compared with placebo, average drinks per drinking day

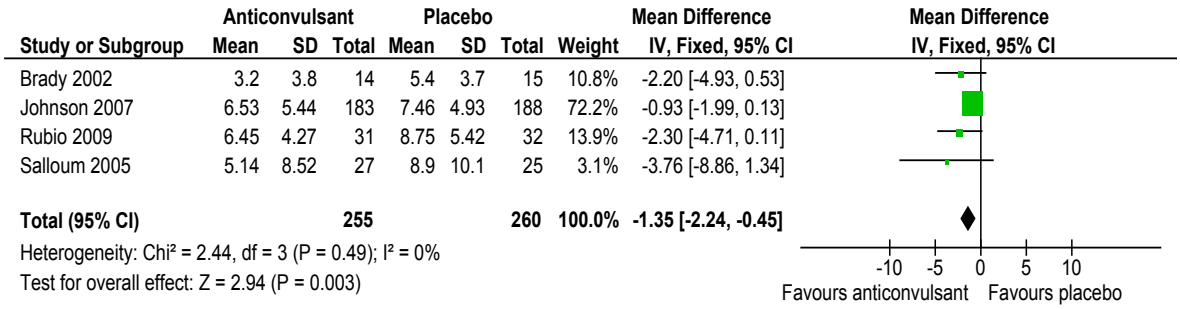
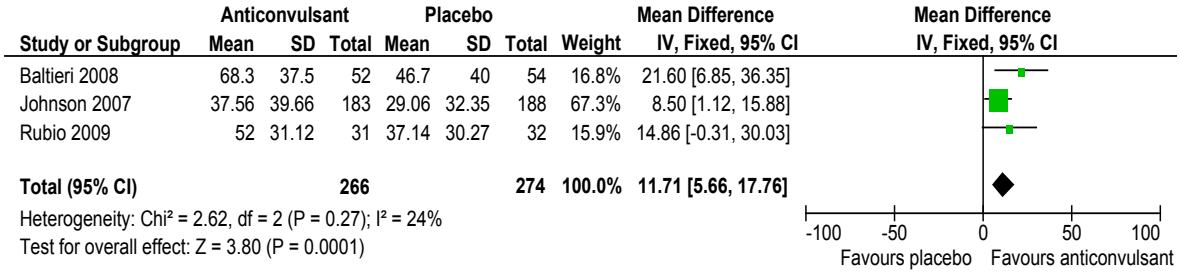
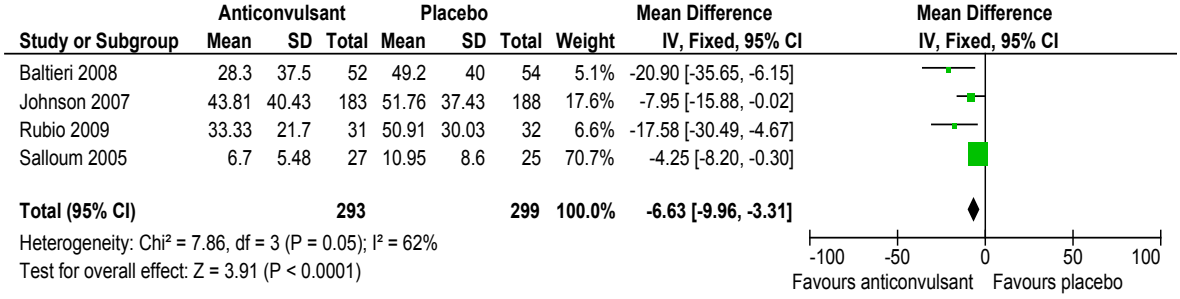


Figure 6.9: Anticonvulsant compared with placebo, % treatment days abstinent (cumulative abstinence duration)



Based on four studies, treatment with an anticonvulsant, relative to placebo, is associated with significantly less treatment days with heavy drinking (Figure 6.10: mean difference -6.63 % days, 95% CI -9.96, -3.31; P<0.001)*. Two studies (Furieri 2007, Johnson 2003) reported significantly less heavy drinking days during treatment with anticonvulsant relative to placebo, while Brady 2002 reported a trend towards less heavy drinking days in the divalproex group. Arias 2010 reported a significant (P=0.012) reduction of 0.3 heavy drinking days per week in the zonisamide group compared to 0.2 heavy drinking days per week in the placebo group. Data from these studies were not able to be included in the meta-analysis.

Figure 6.10: Anticonvulsant compared with placebo, % treatment days with heavy drinking



One study (Croissant 2006) reported no significant difference in the average drinks per drinking day for an anticonvulsant compared with acamprosate (mean difference -2.70 drinks per drinking day, 95% CI -8.43, 3.03; P=0.36)*.

There is no significant difference in the percent of treatment days abstinent (cumulative abstinence duration) for people treated with an anticonvulsant compared with people treated with:

> naltrexone (Figure 6.11: mean difference 10.76% days, 95% CI -1.25, 22.76; P=0.08)*;

> acamprosate (mean difference -3.60 % days, 95% CI -14.27, 7.07; P=0.51); or

> disulfiram (mean difference -13.0 % days, 95% CI -29.73, 3.73; P=0.13).

Based on three studies, treatment with an anticonvulsant is associated with significant less days of heavy drinking compared to treatment with naltrexone (Figure 6.12: mean difference -5.62, 95% CI -10.42, -0.82; P=0.02)*.

Figure 6.11: Anticonvulsant compared with other active medication, % treatment days abstinent (cumulative abstinence duration)

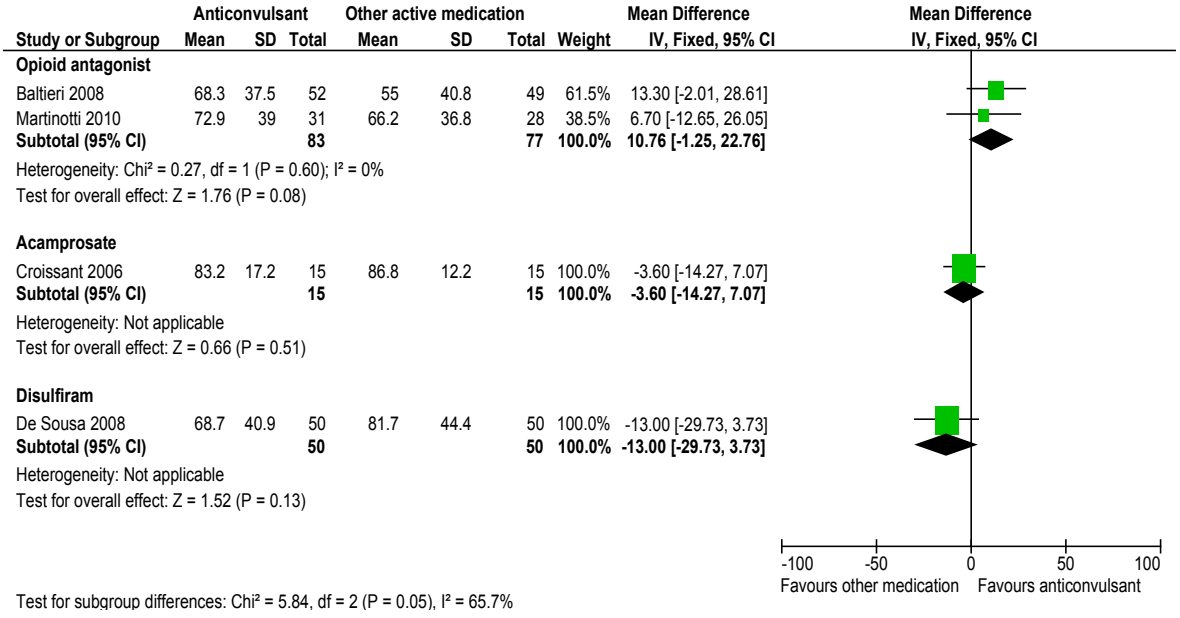
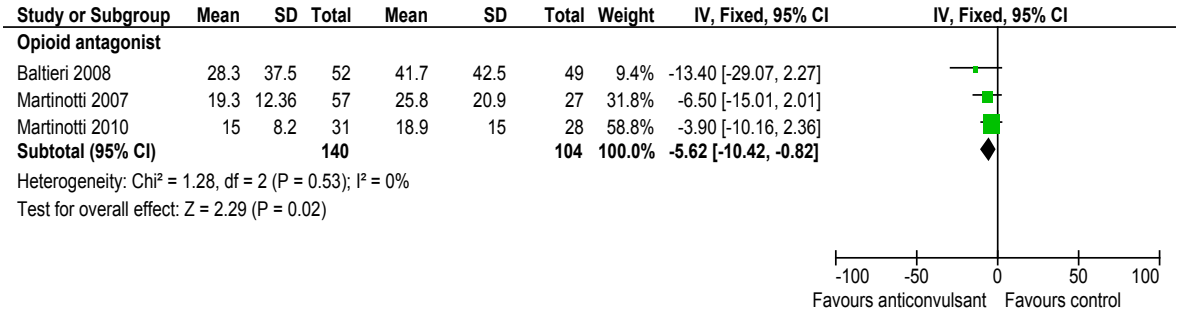


Figure 6.12: Anticonvulsant compared with naltrexone, % treatment days with heavy drinking



	Time to first drink and time to relapse
	Limited data suggest that, compared with placebo, anticonvulsant treatment may prolong the time to first drink and time to relapse to heavy drinking.
	Limited data suggest that anticonvulsant treatment is associated with a longer time to relapse compared to naltrexone.
	Insufficient data are available to form a view on the effectiveness of anticonvulsants compared to acamprosate or disulfiram in terms of time to first drink and time to relapse.

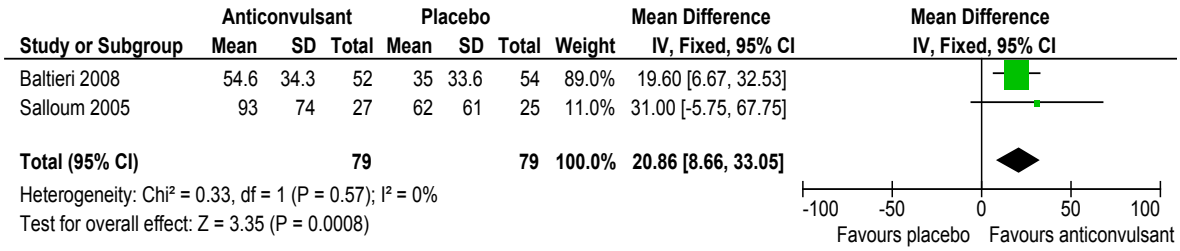
Supporting evidence

Martinotti 2010 reported a longer period of abstinence from any alcohol for anticonvulsant compared to placebo, but did not report data.

Two studies reported the average time to relapse to heavy drinking, with a significantly longer time for people treated with anticonvulsant compared to those treated with placebo (Figure 6.13: mean difference 20.86 days, 95% CI 8.66, 33.05; P<0.001)*. Brower 2008 also reported a significant difference in time to heavy drinking favouring gabapentin over placebo (P=0.03) based on a survival analysis.

One study (Croissant 2006) reported the average days to first drink with no significant difference between people treated with anticonvulsant and those treated with acamprosate (mean difference 29.60 days, 95% CI -22.30, 81.50; P=0.26).

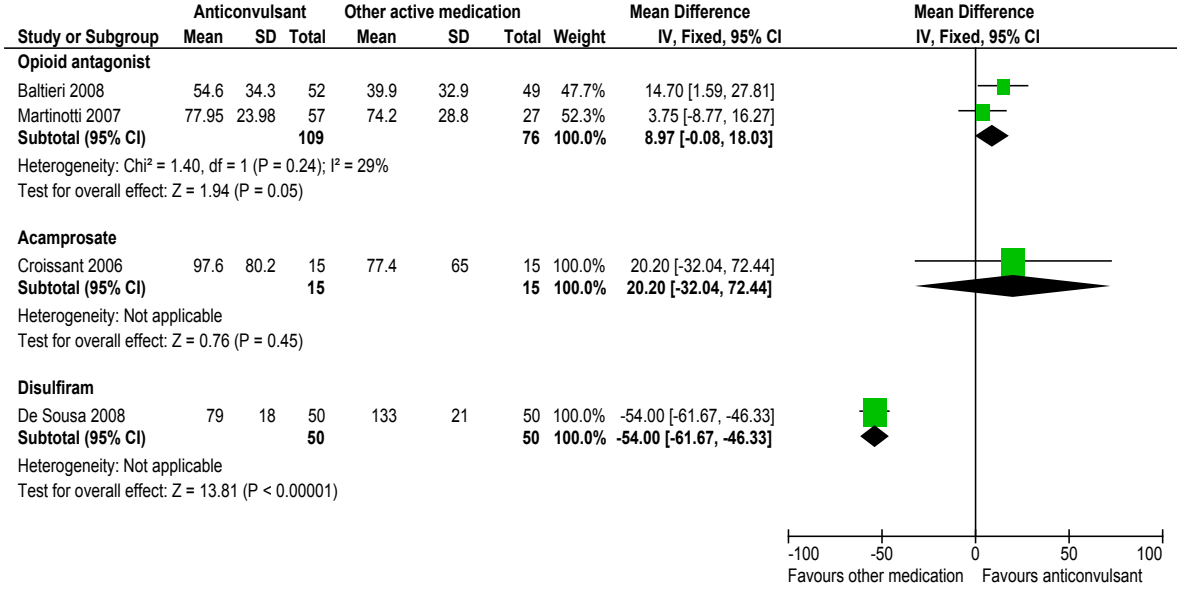
Figure 6.13: Anticonvulsant compared with placebo, average days to relapse to heavy drinking



One study (De Sousa 2008) reported significantly less average days to first drink for anticonvulsant compared with disulfiram (mean difference -70.0 days, 95% CI -78.62, -61.38; P<0.001).

Based on two studies, the average time to relapse is significantly more for people treated with an anticonvulsant compared to those treated with naltrexone (Figure 6.14: mean difference 8.97 days, 95% CI -0.08, 18.03; P=0.05)*. One study reported no significant difference in the average time to relapse for anticonvulsant compared with acamprosate (Figure 6.14: mean difference 20.20 days, 95% CI -32.04, 72.44; P=0.45), and one study reported significantly less average time to relapse for anticonvulsant compared with disulfiram (Figure 6.14: mean difference -54 days, 95% CI -61.67, -46.33; P<0.001).

Figure 6.14: Anticonvulsant compared with other active medication, average days to relapse to heavy drinking



	Objective indicators of alcohol consumption
	GGT levels support a finding that anticonvulsants are more effective than placebo, and have similar effectiveness to naltrexone in terms of reducing alcohol consumption.
	Insufficient data are available to form a conclusion on the effectiveness of anticonvulsants relative to acamprosate or disulfiram.

Supporting evidence

Six studies reported decreases in GGT or CDT over time:

> in Arias 2010, Brady 2002 and Baltieri 2008 there were no significant differences between anticonvulsant and placebo groups;

> in Furieri 2007 the decrease in GGT levels was statistically significant only in the gabapentin group;

> in Johnson 2007 and Johnson 2003 GGT was reduced significantly more for topiramate relative to placebo; and

> in Rubio 2009 CDT was significantly lower for topiramate relative to placebo after 12 weeks of treatment.

In Salloum 2005, GGT levels were significantly higher in the placebo group, and correlated with weekly alcohol use. Anton 2009 reported only that %CDT levels were consistent with total abstinence data. Similarly Brower 2008 reported that GGT levels were consistent with levels of self-reported drinking.

Four studies (Baltieri 2008, Florez 2008, Martinotti 2007, Martinotti 2010) reported declines in GGT levels during treatment with no significant differences between anticonvulsants and naltrexone.

For oxcarbazepine compared with acamprosate, Croissant 2006 reported that abstinent patients in both groups showed somewhat lower GGT than the relapsed patients.

In De Sousa 2008, serum GGT levels were significantly lower in the disulfiram group at the end of the study.

	Craving
**	Treatment with anticonvulsants is associated with less craving during treatment relative to placebo.
*	There is no significant difference between anticonvulsants and naltrexone in terms of total craving during treatment.
	Insufficient data are available to form a view on the effect of anticonvulsants on craving relative to acamprosate or disulfiram.

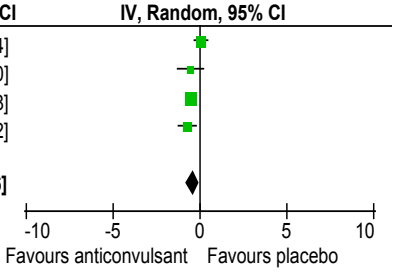
Supporting evidence

Based on four studies, treatment with an anticonvulsant is associated with significantly lower average craving scores compared to placebo (Figure 6.15: SMD -0.41, 95% CI -0.77, 0.06; P=0.02)*.

Figure 6.15: Anticonvulsant compared with placebo, average craving scores

	Anticonvulsant			Placebo				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Baltieri 2008	22.4	9.4	52	21.9	8.6	54	28.2%	0.06 [-0.33, 0.44]
Brady 2002	3.6	4.5	14	7.5	8.6	15	14.8%	-0.55 [-1.29, 0.20]
Johnson 2007	7.67	6.79	112	10.86	5.31	144	34.5%	-0.53 [-0.78, -0.28]
Rubio 2009	3.11	2	31	5.06	3.1	32	22.4%	-0.74 [-1.25, -0.22]
Total (95% CI)			**209**			**245**	**100.0%**	**-0.41 [-0.77, -0.06]**

Heterogeneity: Tau² = 0.08; Chi² = 8.29, df = 3 (P = 0.04); I² = 64%
Test for overall effect: Z = 2.27 (P = 0.02)



Furieri 2007 reported lower mean scores on OCDS in the gabapentin group, but these were statistically significant only for automaticity of drinking. Johnson 2003 did not report the total OCDS score, but reported that patients on topiramate had significantly reduced drinking obsessions, automaticity of drinking and interference of drinking. In Arias 2010, alcohol urge scores decreased by 1.4 points per week in the zonisamide group compared to 0.6 points per week for placebo (P=0.006).

In a laboratory study involving heavy drinkers, Miranda *et al*.[307] compared two doses of topiramate (200 and 300 mg/day) with placebo. Topiramate did not affect self-reported craving for alcohol while topiramate was being titrated to maximal dose (over 32 days), during cue reactivity tests, or in response to alcohol challenge. The authors concluded that reduction in craving is not the behavioural mechanism underlying the effect of topiramate on alcohol consumption.

Rubio 2009 focused on the effect of topiramate treatment on impulsivity. They reported that at the end of the 12-week study, topiramate subjects performed significantly better on most behavioural impulsivity tests. The scores of the topiramate group on self-reported impulsivity and anxiety were significantly lower. The difference in the number of drinks correlated with the difference in behavioural impulsivity. The authors suggested that the negative findings of Miranda et al. in relation to craving may reflect the use of a non-treatment-seeking group.

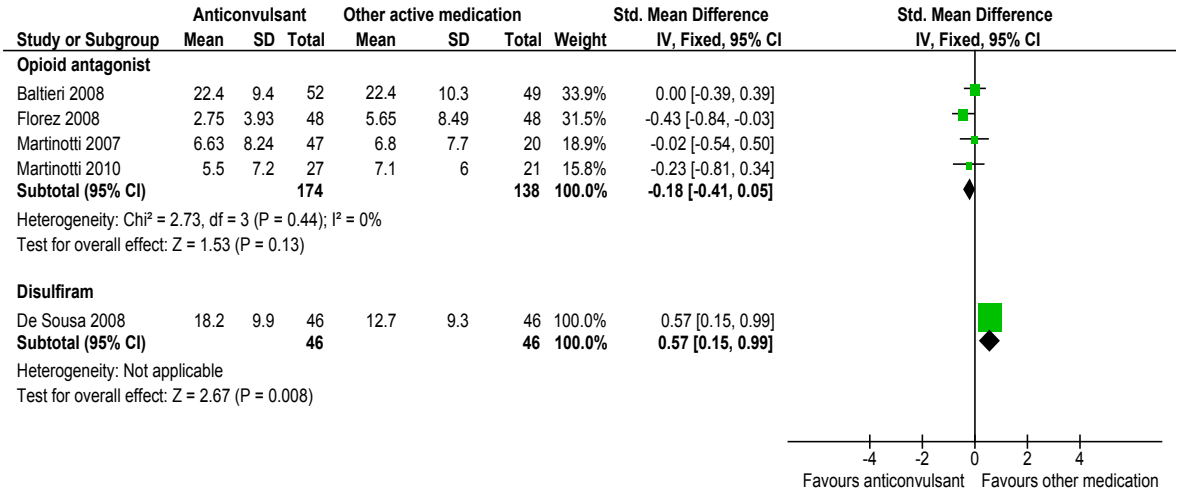
Based on four studies, there is no significant difference in the average craving scores for people treated with anticonvulsant, compared to those receiving naltrexone (Figure 6.16: SMD -0.18, 95% CI -0.41, 0.05;

P=0.13)*. Martinotti 2010 also reported no significant difference between groups in the mean change in craving from baseline.

Croissant 2006 did not report data suitable for inclusion in analyses, but stated that craving was reduced in anticonvulsant and acamprosate groups with no significant group differences.

One study (De Sousa 2008) reported significantly higher average craving scores for people treated with topiramate compared to those treated with disulfiram (Figure 6.16: SMD 0.57, 95% CI 0.15, 0.99; P=0.003).

Figure 6.16: Anticonvulsant compared with other active medication, average craving scores



6.2.3 Adverse effects

	There are no statistically significant differences between anticonvulsants and placebo, naltrexone, acamprosate or disulfiram in terms of adverse effects experienced, but there are indications that adverse effects associated with topiramate, particularly paresthesia, could be an issue.
	Withdrawal from treatment due to adverse effects is significantly less likely with anticonvulsants compared to naltrexone suggesting that the adverse effects associated with anticonvulsants are more readily managed or more tolerable than those associated with naltrexone.

Supporting evidence

There was considerable variability between studies in the nature of adverse effects reported:

> Anton 2009 reported that adverse events were rare with no significant group differences;

> in Brower 2008, 6 of 38 adverse events were rated as moderate or severe, others were rated as mild;

> in Brady 2002, the only side effects reported by 5% or more of participants were nausea, sedation and headache, with no differences between groups;

> 56.6% of participants in Furieri 2007 did not report undesirable effects, with sleep disturbance the most common problem reported in both groups;

> Arias 2010 and Johnson 2003 reported there were no serious adverse events;

> Johnson 2007 reported parasthesia (abnormal sensation), taste perversion, anorexia and difficulty with concentration as the adverse effects that were more common with topiramate compared to placebo; and

> Salloum 2005 reported no serious drug-related adverse events, with only nausea and vomiting being more common in the valproate group.

For oxcarbazepine compared with naltrexone, Martinotti 2007 reported that common adverse events (whether or not considered treatment related) occurred in 10% of participants.

There is considerable heterogeneity between (which may reflect variability in anticonvulsants) studies reporting data on adverse effects, but overall there is no significant difference between anticonvulsants and placebo in the number of participants:

> experiencing any adverse effects (Figure 6.17: RR 1.10, 95% CI 0.88, 1.36; P=0.40)*;

> experiencing gastrointestinal symptoms (Figure 6.18: RR 1.31, 95% CI 0.97, 1.76; P=0.08)* - although in Arias 2010 gastrointestinal symptoms were significantly more likely with zonisamide compared to placebo;

> experiencing nausea or vomiting (Figure 6.19: RR 1.19, 95% CI 0.43, 3.32; P=0.74)*; or

> experiencing neuropsychiatric symptoms (Figure 6.20; RR 1.41, 95% CI 0.72, 2.75; P=0.31)*.

Overall treatment with an anticonvulsant was associated with significantly higher risk of withdrawal from treatment due to adverse effects compared to placebo (Figure 6.21: RR 2.90, 95% CI 1.11, 7.57; P=0.03)*. However, studies are small and it should be noted that in two studies (Baltieri 2008, Brower 2008) no participants were withdrawn due to adverse effects.

Figure 6.17: Anticonvulsant compared with placebo, participants experiencing any adverse effects

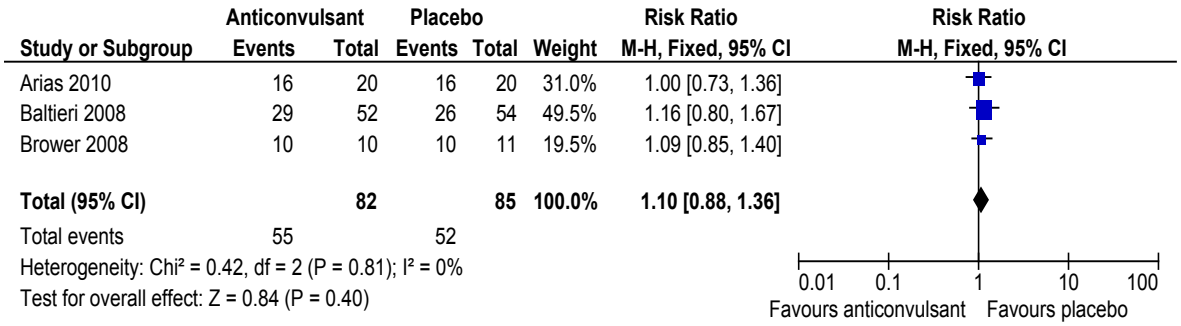


Figure 6.18: Anticonvulsant compared with placebo, participants experiencing gastrointestinal symptoms

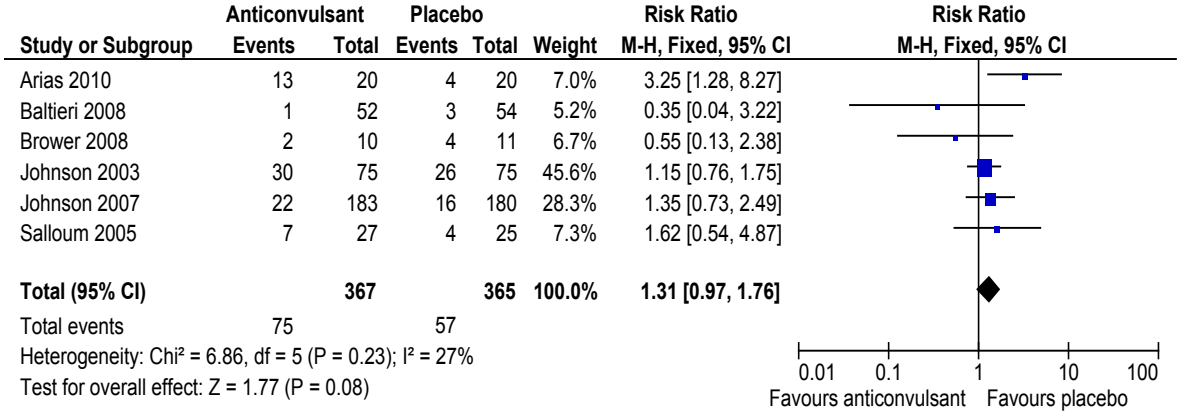


Figure 6.19: Anticonvulsant compared with placebo, participants experiencing nausea or vomiting

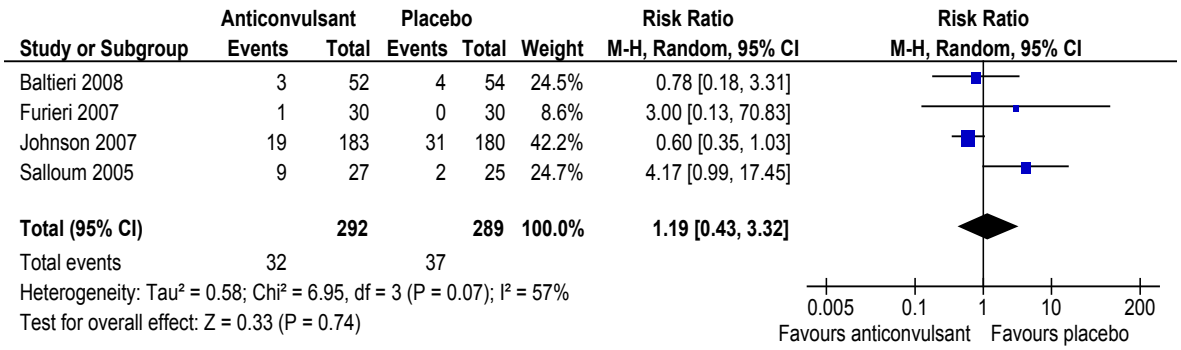


Figure 6.20: Anticonvulsant compared with placebo, participants experiencing neuropsychiatric symptoms

Study or Subgroup	Anticonvulsant Events	Anticonvulsant Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Baltieri 2008	3	52	1	54	7.1%	3.12 [0.33, 29.00]
Brower 2008	3	10	1	11	7.9%	3.30 [0.41, 26.81]
Furieri 2007	1	30	1	30	5.1%	1.00 [0.07, 15.26]
Johnson 2003	21	75	8	75	24.4%	2.63 [1.24, 5.55]
Johnson 2007	44	183	60	180	32.5%	0.72 [0.52, 1.00]
Salloum 2005	9	27	7	25	22.9%	1.19 [0.52, 2.71]
Total (95% CI)		**377**		**375**	**100.0%**	**1.41 [0.72, 2.75]**
Total events	81		78			

Heterogeneity: Tau² = 0.33; Chi² = 12.67, df = 5 (P = 0.03); I² = 61%
Test for overall effect: Z = 1.01 (P = 0.31)

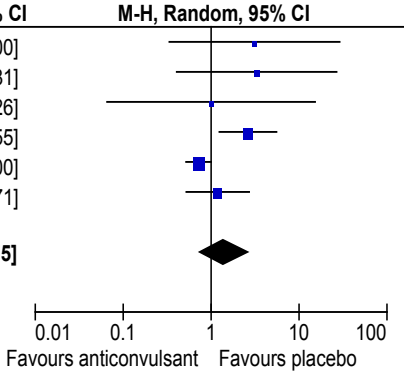
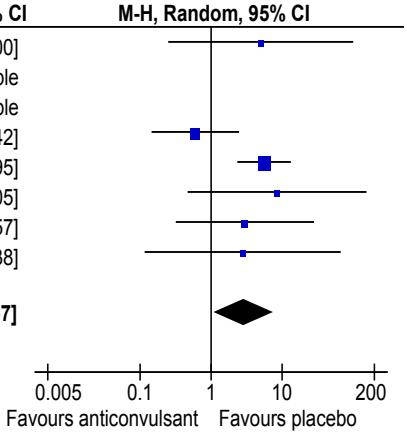


Figure 6.21: Anticonvulsant compared with placebo, participants withdrawn due to adverse effects

Study or Subgroup	Anticonvulsant Events	Anticonvulsant Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Arias 2010	2	20	0	20	8.6%	5.00 [0.26, 98.00]
Baltieri 2008	0	52	0	54		Not estimable
Brower 2008	0	10	0	11		Not estimable
Johnson 2003	3	75	5	75	24.4%	0.60 [0.15, 2.42]
Johnson 2007	34	183	6	180	36.3%	5.57 [2.40, 12.95]
Mueller 1997	3	13	0	16	9.1%	8.50 [0.48, 151.05]
Rubio 2009	3	38	1	38	13.7%	3.00 [0.33, 27.57]
Salloum 2005	1	27	0	25	7.8%	2.79 [0.12, 65.38]
Total (95% CI)		**418**		**419**	**100.0%**	**2.90 [1.11, 7.57]**
Total events	46		12			

Heterogeneity: Tau² = 0.48; Chi² = 7.77, df = 5 (P = 0.17); I² = 36%
Test for overall effect: Z = 2.17 (P = 0.03)



Paresthesias and cognitive dulling are reported as the most common and problematic side effects associated with topiramate.[308] In Johnson 2007 (but not other studies of topiramate) significantly more people withdrew from treatment due to adverse effects than was the case with placebo. Shinn *et al*.[308] consider that more research is needed on dose regimes to reduce the impact of adverse effects to avoid the use of topiramate being limited by its side effect profile.

There is no significant difference between anticonvulsants and naltrexone in the number of people experiencing:

> any adverse effects (Figure 6.22: RR 1.01, 95% CI 0.17, 5.87; P=0.27)*, although there was substantial heterogeneity between studies;

> gastrointestinal symptoms (Figure 6.23: note that for one study, no participants in either treatment group reported gastrointestinal symptoms preventing estimation of a relative risk for this study);

> nausea or vomiting (Figure 6.24: RR 0.59, 95% CI 0.16, 2.19; P=0.43)*; or

> neuropsychiatric symptoms (Figure 6.25: RR 1.85, 95% CI 0.48, 7.19; P=0.37)*.

However, significantly less people treated with anticonvulsant were withdrawn from treatment due to adverse effects compared to those treated with naltrexone (Figure 6.26: RR 0.17, 95% CI 0.05, 0.56; P=0.003)*.

Figure 6.22: Anticonvulsant compared with other active medication, participants experiencing any adverse effects

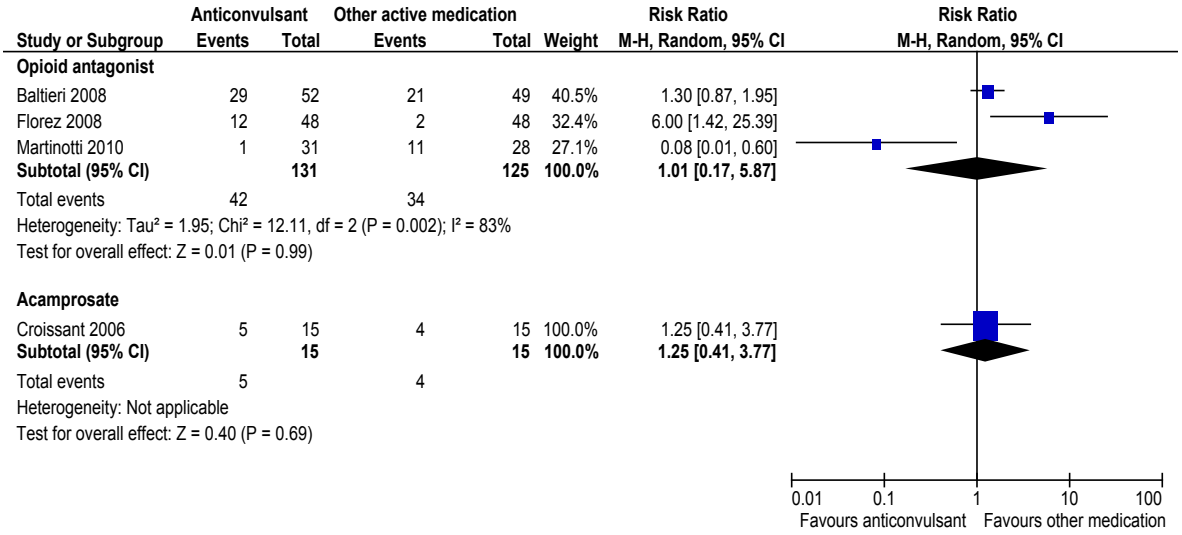


Figure 6.23: Anticonvulsant compared with other active medication, participants experiencing gastrointestinal symptoms

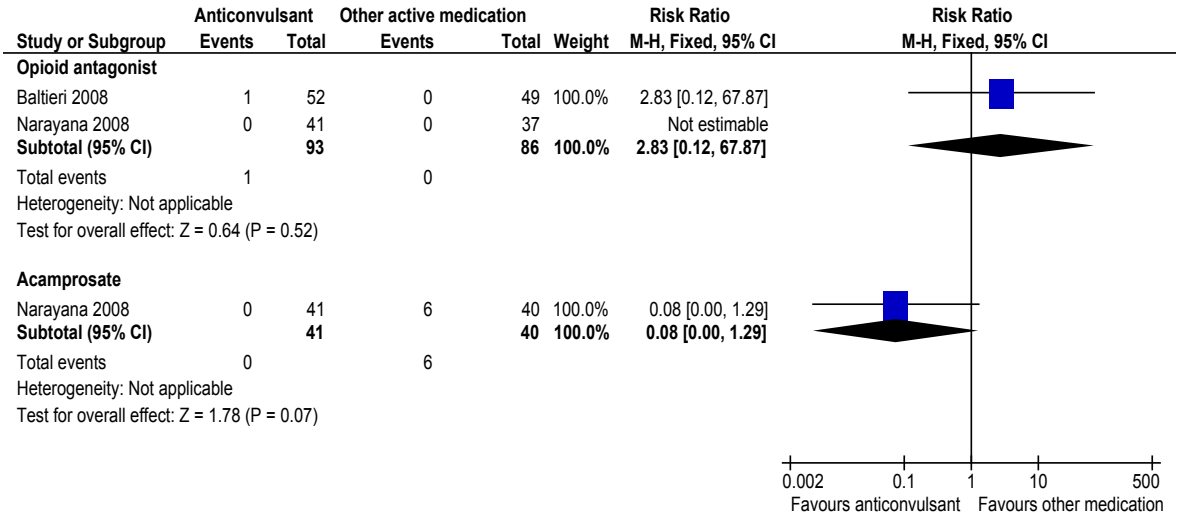


Figure 6.24: Anticonvulsant compared with other active medication, participants experiencing nausea or vomiting

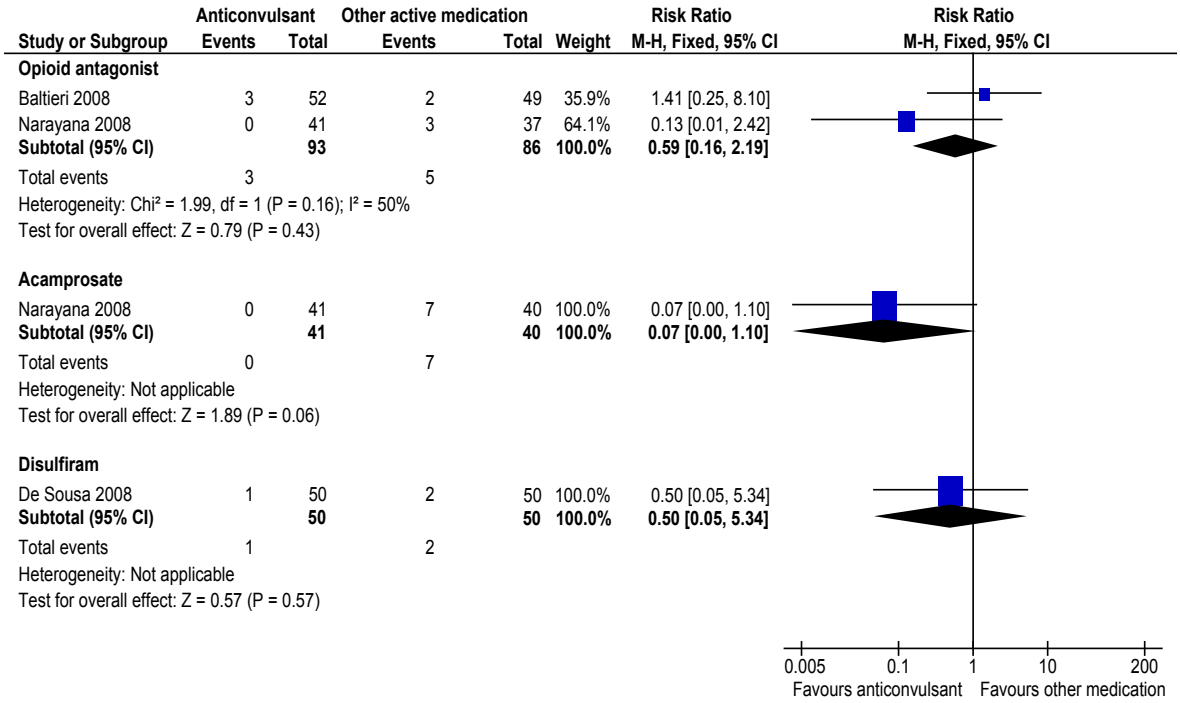


Figure 6.25: Anticonvulsant compared with other active medication, participants experiencing neuropsychiatric symptoms

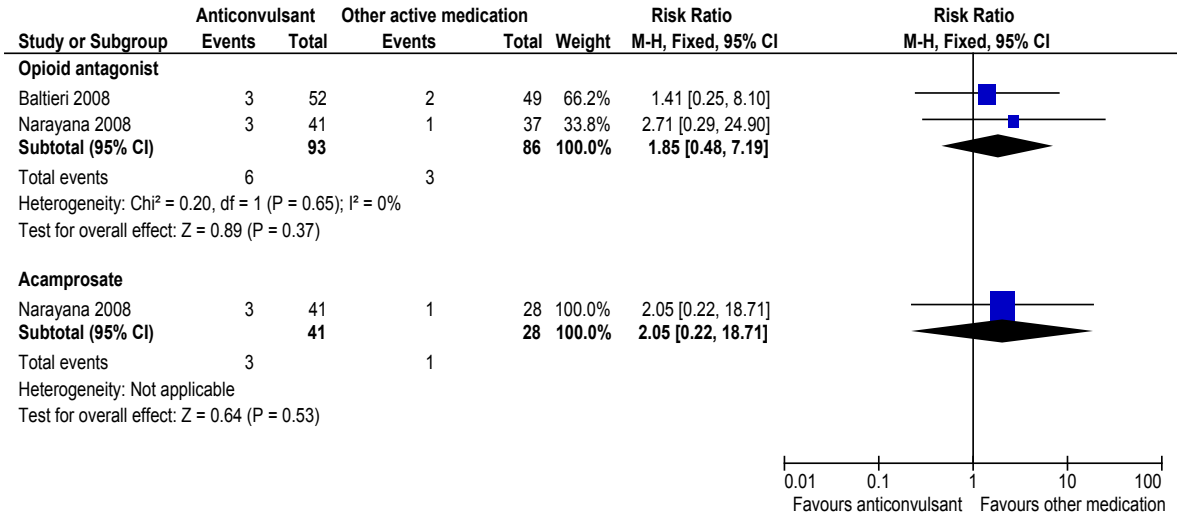
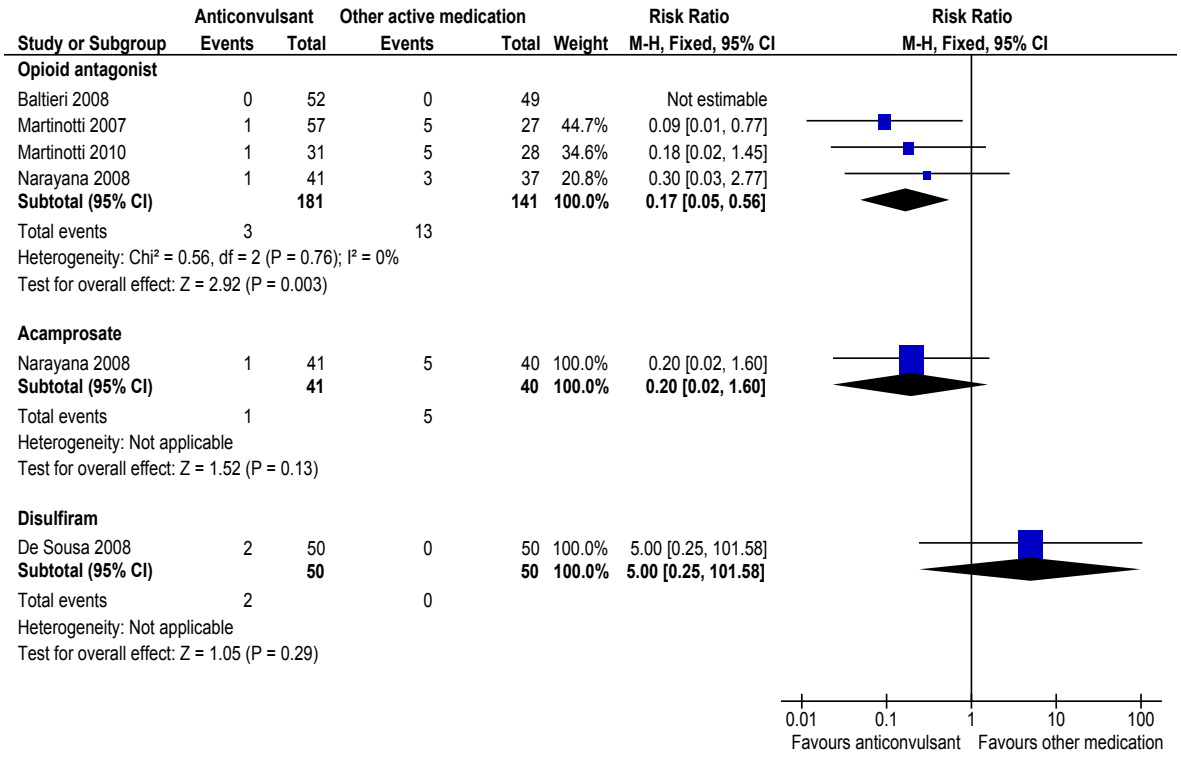


Figure 6.26: Anticonvulsant compared with other active medication, participants withdrawn due to adverse effects



For anticonvulsants compared with acamprosate:

> Croissant 2006 reported no significant difference in the number of people experiencing any adverse effects (Figure 6.22: RR 1.25, 95% CI 0.41, 3.77; P=0.69);

> in Narayana 2008 there were no significant differences in the number of people experiencing gastrointestinal symptoms (Figure 6.23: RR 0.08, 95% CI 0.00, 1.29; P=0.07), nausea or vomiting (Figure 6.24: RR 0.07, 95% CI 0.00, 1.10; P=0.06), or neuropsychiatric symptoms (Figure 6.25: RR 2.05, 95% CI 0.22, 18.71; P=0.53); and

> in Narayana 2008 there is no significant in the number of people withdrawn from treatment due to adverse effects (Figure 6.26: RR 0.20, 95% CI 0.02, 1.60; P=0.13).

One study (De Sousa 2008) reported no significant difference between anticonvulsants and disulfiram in:

> the number of people experiencing nausea or vomiting (Figure 6.24: RR 0.50, 95% CI 0.05, 5.34; P=0.57); or

> the number of participants withdrawn due to adverse effects (Figure 6.26: RR 5.00, 95% CI 0.25, 101.58; P=0.29)*.

Liver enzyme levels are affected by both alcohol consumption and toxicity of medications. Five studies reported on liver enzyme levels:

> Brady 2002 and Martinotti 2007 reported significant decreases in AST and ALT over time with no significant group differences;

> Salloum 2005 reported no group differences in ALT and AST levels;

> Johnson 2007 reported reduced AST and ALT levels in the topiramate group compared to the placebo group at the end of the study;

> Florez 2008 and Martinotti 2010 reported no group differences in AST or ALT for anticonvulsant compared with naltrexone; and

> Croissant reported no group differences in AST, and a tendency toward lower ALT in abstinent patients and those treated with acamprosate.

6.3 Factors affecting outcomes

The relatively small number of studies of anticonvulsants for relapse prevention treatment of alcohol dependence prevents any meaningful analysis of factors influencing treatment outcomes. However, various factors that have been identified as possibly affecting outcome are identified here.

6.3.1 Typology of dependence

Johnson 2003 found no difference in response to topiramate treatment between participants with early-onset versus late-onset alcoholism. However, there may be an effect of severity of withdrawal symptoms at the commencement of treatment. Anton 2009 analysed outcomes of treatment with flumazenil (3 days) plus gabapentin, compared to placebo flumazenil plus placebo gabapentin, based on groups with high or low alcohol withdrawal symptoms at baseline. They reported some interaction between medication adherence rates and withdrawal symptoms, with those with low withdrawal symptoms having lower levels of adherence to active medication. In participants with high alcohol withdrawal, those treated with active drug had significantly more days abstinent compared to those receiving placebo. In participants with low alcohol withdrawal at baseline, the placebo group had more days abstinent than the group receiving active drug. The time to first heavy drinking day followed a similar pattern but the differences were not statistically significant. It is not possible to separate the effects of flumazenil and gabapentin in this study, but it identifies a factor that could be explored in future studies of anticonvulsants.

It has also been suggested that polymorphism in the genes underlying glutamatergic neurotransmission may help predict heterogeneity in topiramate-induced side effects.[309]

6.3.2 Dose of anticonvulsant

Shah and Basu,[310] in commenting on Baltieri 2008, note that in that study topiramate was associated with a significantly higher rate of abstinence compared to placebo at the 4th and 8th weeks, but not the 12th week of the study. The dose of topiramate was 100mg/day at 4 weeks, and 300mg/day at 12 weeks. The authors therefore raise the possibility that a small dose of topiramate may be as good as, or even better than, a dose of 300mg/day. Again, this is a factor that could be explored in future studies.

In Brower 2008, gabapentin was administered as a single dose at bedtime. The authors postulate that the effectiveness of gabapentin may have been due to a nocturnal effect. This was a small study investigating the efficacy of gabapentin in alcohol dependence with insomnia that had persisted beyond the period of acute alcohol withdrawal. Given that somnolence is a side effect of gabapentin, it is of interest that gabapentin had no significant effect on sleep relative to placebo. However, the positive outcomes do suggest that it may be important to pay attention to dosing patterns when using anticonvulsants for treatment of alcohol dependence.

6.3.3 Compliance and commitment to abstinence

Compliance was relatively high in the studies that reported data. Anton 2009 stated that groups with more abstinence were also more compliant. As with other medications, compliance is itself likely to be affected by several factors, including commitment to abstinence. Johnson 2007 reported that participants with a greater pretreatment commitment to abstinence had more abstinent days during the study. It is also worth noting that the inclusion criteria for this study were highly restrictive – people with current Axis I psychiatric diagnosis, clinically significant alcohol withdrawal symptoms, who had made more than four unsuccessful inpatient treatment attempts, had clinically significant depression, were receiving treatment for alcohol dependence, or had been compelled to receive treatment for alcohol dependence to avoid imprisonment, parole, probation or loss of employment, were all excluded, as were people using other drugs. Of 707 individuals screening for the study, 336 were excluded. Hence the participants were a highly selected group which has implications for application of the findings of the study to the general population of alcohol dependent people.

6.3.4 Tobacco smoking

A secondary analysis of data from Baltieri 2008[311] found that tobacco smoking increased the odds of relapse into drinking by 65%, independent of the medications prescribed. However, topiramate (but not naltrexone or placebo) was associated with a significant decrease in the number of cigarettes smoked per day.

Alcohol and tobacco dependence are highly comorbid disorders and animal models suggest a role for nicotinic acetylcholine receptors in alcohol consumption. A preliminary investigation found that varenicline, a partial nicotinic agonist, significantly reduced the number of drinks consumed compared to placebo in human

laboratory trials of alcohol consumption and craving. Following a priming drink, varenicline attenuated alcohol craving and reduced subjective reinforcing alcohol effects.[312] Hence, tobacco smoking as a factor predicting treatment outcome may apply much more broadly than to anticonvulsant treatment. There may also be significant cue response activity with smoking and drinking frequently going together and acting as a cue for each other.

Section 7: Antipsychotic Medications

Overview

Rationale

Antipsychotic medications affect the dopaminergic system and thence potentially influence reward and craving. Atypical antipsychotics target both the dopaminergic and serotonergic systems offering potential advantages in efficacy with fewer adverse effects.

Type of antipsychotics

The majority of clinical trials have compared atypical antipsychotics with placebo. One study used a typical antipsychotic (flupenthixol). One recent study compared an atypical antipsychotic with naltrexone.

Retention in treatment

Completion of treatment is significantly less likely with antipsychotic medication compared with placebo***.

Abstinence

Study findings were varied, but overall it appears that treatment with antipsychotics does not increase the likelihood of abstinence relative to placebo*.

Relapse to heavy drinking

Study findings were again variable, but it appears that overall antipsychotic medications do not reduce the risk of relapse to heavy drinking relative to placebo*.

Amount of alcohol consumed

Available data suggests that antipsychotic medications have no effect on alcohol consumption during treatment relative to placebo*.

Time to first drink and time to relapse

Treatment with antipsychotic medication appears to have no effect on the time to first drink or time to relapse to heavy drinking compared to placebo*.

Objective indicators of alcohol consumption

Treatment with antipsychotic medication has no significant effect on objective indicators of alcohol consumption, consistent with the apparent lack of effect on reported alcohol drinking during treatment with antipsychotics relative to placebo.

Craving

Antipsychotic medications appear to have no significant effect on craving relative to placebo, but in some instances antipsychotics may be associated with higher levels of craving.

Adverse effects

The risk of adverse effects is similar for antipsychotic medication and placebo*.

The likelihood of withdrawal from treatment due to adverse effects is greater with antipsychotics relative to placebo**.

Factors affecting outcomes

(a) Dose may be important as the pharmacology of some antipsychotics results in different effects at high and low doses.

(b) Data from two studies indicate possible gender differences, but the extent and direction of any effect is unclear.

(c) One study found an effect of typology of alcohol dependence, another found no significant effect of age of onset of heavy drinking, leaving the effect of typology and family history uncertain.

7.1 Rationale for effect

There is strong evidence for the importance of the dopaminergic system in mediating reward and craving. There is evidence from animal studies that dopamine agonists as well as antagonists reduce the response to alcohol. This provides the rationale for investigations of whether medication which manipulates the dopaminergic system is effective in maintaining alcohol abstinence[313;314].

Dopamine antagonists that block dopamine actions in the nucleus accumbens have been shown to reduce craving and alcohol consumption in a research setting. However, clinical trials have been limited, perhaps because of concern over the acute and long-term side effects of traditional dopamine antagonists.[313] Atypical antipsychotics target both the dopamine and serotonin systems and offer potential advantages in reduction of alcohol craving and consumption[315] with acceptable side effect profiles (particularly less sedative effect to reduce the risk potential for interactions with alcohol[313]).

7.2 Evidence of effectiveness

Antipsychotic medications have been compared with placebo for relapse prevention treatment of alcohol dependence in 11 studies (see Table 7.1). One study (Wiesbeck 2001) used a typical antipsychotic (flupenthixol) while the other studies used various atypical antipsychotics. One study (Martinotti 2009) compared an antipsychotic (aripiprazole) with naltrexone. Brief information on the design of these studies is included in Appendix 1.

Table 7.1: Studies involving the use of antipsychotic medications for relapse prevention treatment of alcohol dependence

Antipsychotic compared with placebo		Antipsychotic compared with naltrexone
Anton 2008[314]	Bender 2007 [313]	Martinotti 2009 [316]
Brown 2008 [317]	Guardia 2004 [318]	
Johnson 1996 [319]	Kampman 2007 [315]	
Marra 2002 [320]	Shaw 1987 [321]	
Shaw 1994 [322]	Wiesbeck 1999[323;324]	
Wiesbeck 2001[325;326]		

The antipsychotic medications that have been investigated are aripiprazole (Anton 2008, Martinotti 2009), tiapride (Bender 2007, Shaw 1987, Shaw 1994), quetiapine (Brown 2008, Kampman 2007), olanzapine (Guardia 2004), ritanserin (Johnson 1996, Wiesbeck 1999), amisulpride (Marra 2002), and flupenthixol (Wiesbeck 2001).

7.2.1 Retention in treatment

***	Completion of treatment is significantly less likely with antipsychotic medication compared with placebo.

Supporting evidence

Based on 10 studies, significantly less people treated with an antipsychotic completed the study treatment compared with people receiving placebo (Figure 7.1: RR 0.88, 95% CI 0.79, 0.98; P=0.03)***.

Two studies reported the average weeks in treatment, with no significant difference between people treated with an antipsychotic and those receiving placebo (Figure 7.2: mean difference 0.79 weeks, 95% CI -3.71, 5.29; P=0.73)*.

In Martinotti 2009, there was no significant difference between aripiprazole and naltrexone in terms of the number of participants completing treatment (RR 1.01, 95% CI 0.75, 1.36; P=0.94).

Figure 7.1: Antipsychotic compared with placebo, participants completing the study

Study or Subgroup	Antipsychotic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Anton 2008	87	146	104	142	15.2%	0.81 [0.69, 0.96]
Bender 2007	118	149	115	150	18.4%	1.03 [0.92, 1.17]
Guardia 2004	17	29	24	31	6.6%	0.76 [0.53, 1.09]
Johnson 1996	171	283	90	140	16.0%	0.94 [0.80, 1.10]
Kampman 2007	23	29	24	32	9.5%	1.06 [0.80, 1.39]
Marra 2002	14	37	17	34	3.5%	0.76 [0.44, 1.29]
Shaw 1987	8	13	12	19	3.3%	0.97 [0.56, 1.69]
Shaw 1994	24	50	30	50	6.4%	0.80 [0.55, 1.15]
Wiesbeck 1999	199	371	71	122	14.5%	0.92 [0.77, 1.10]
Wiesbeck 2001	33	142	58	139	6.6%	0.56 [0.39, 0.80]
Total (95% CI)		**1249**		**859**	**100.0%**	**0.88 [0.79, 0.98]**
Total events	694		545			

Heterogeneity: Tau² = 0.01; Chi² = 17.86, df = 9 (P = 0.04); I² = 50%
Test for overall effect: Z = 2.24 (P = 0.03)

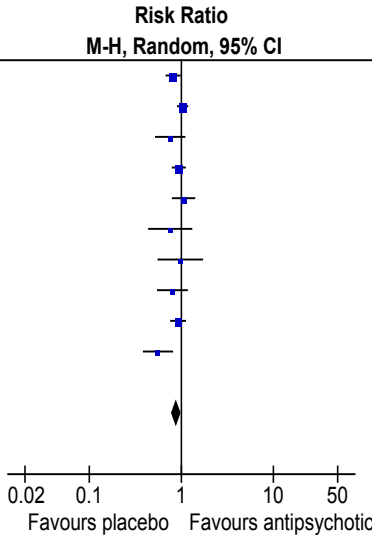
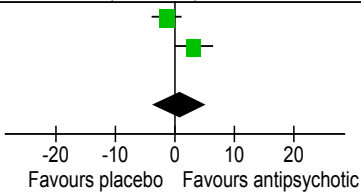


Figure 7.2: Antipsychotic compared with placebo, average weeks in treatment

Study or Subgroup	Antipsychotic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Guardia 2004	12.5	5.05	29	13.9	4.35	31	52.4%	-1.40 [-3.79, 0.99]
Marra 2002	12.2	6.5	37	9	6.8	34	47.6%	3.20 [0.10, 6.30]
Total (95% CI)			**66**			**65**	**100.0%**	**0.79 [-3.71, 5.29]**

Heterogeneity: Tau² = 8.58; Chi² = 5.30, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 0.34 (P = 0.73)



7.2.2 Effect on alcohol consumption

	Abstinence
*	Study findings were varied, but overall it appears that treatment with antipsychotics does not increase the likelihood of abstinence relative to placebo.

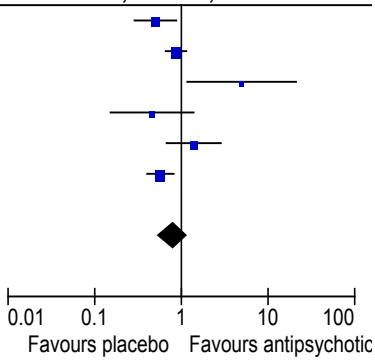
Supporting evidence

Based on six studies, there is no significant difference between treatment with an antipsychotic and placebo in terms of the number of participants continuously abstinent during treatment or abstinent at the end of treatment (Figure 7.3: RR 0.80, 95% CI 0.53, 1.20; P=0.28)*.

Figure 7.3: Antipsychotic compared with placebo, participants continuously abstinent during treatment or abstinent at the end of the study

Study or Subgroup	Antipsychotic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Anton 2008	16	146	31	142	19.0%	0.50 [0.29, 0.88]
Bender 2007	56	149	65	150	26.0%	0.87 [0.66, 1.14]
Kampman 2007	9	29	2	32	6.2%	4.97 [1.17, 21.11]
Marra 2002	4	37	8	34	9.3%	0.46 [0.15, 1.39]
Shaw 1994	10	24	9	30	15.3%	1.39 [0.67, 2.86]
Wiesbeck 2001	34	142	58	139	24.2%	0.57 [0.40, 0.82]
Total (95% CI)		**527**		**527**	**100.0%**	**0.80 [0.53, 1.20]**
Total events	129		173			

Heterogeneity: Tau² = 0.15; Chi² = 15.36, df = 5 (P = 0.009); I² = 67%
Test for overall effect: Z = 1.08 (P = 0.28)



However, there is significant heterogeneity in these six studies. The factors contributing to this heterogeneity are unclear, but may include the type of antipsychotic medication, and dose (see also section 7.3).

In Martinotti 2009 there is no significant difference between aripiprazole and naltrexone in the proportion of participants abstinent during treatment (RR 1.05, 95% CI 0.56, 1.98; P=0.87).

	Relapse to heavy drinking
*	Study findings were again variable, but it appears that overall antipsychotic medications do not reduce the risk of relapse to heavy drinking relative to placebo.

Supporting evidence

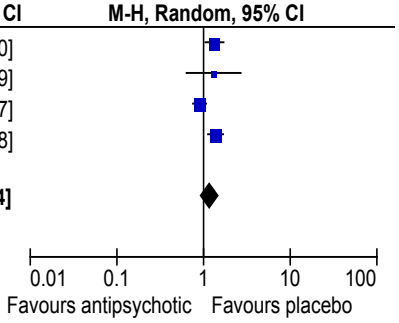
Based on four studies, there is no significant difference between treatment with an antipsychotic and placebo in the number of participants relapsing during treatment (Figure 7.4: RR 1.19, 95% CI 0.91, 1.54; P=0.20)*. Again there is significant heterogeneity in these studies, but the small number of studies reporting data prevents any exploration of the factors contributing to this heterogeneity.

Martinotti 2009 reported somewhat lower rates of relapse with aripiprazole compared to naltrexone but the difference was not statistically significant (RR 0.55, 95% CI 0.18, 1.68; P=0.30).

Figure 7.4: Antipsychotic compared with placebo, participants relapsing during treatment

	Antipsychotic		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Bender 2007	81	149	61	150	28.1%	1.34 [1.05, 1.70]	
Guardia 2004	11	29	9	31	9.7%	1.31 [0.64, 2.69]	
Wiesbeck 1999	197	371	72	122	31.8%	0.90 [0.75, 1.07]	
Wiesbeck 2001	97	142	69	139	30.4%	1.38 [1.13, 1.68]	
Total (95% CI)		**691**		**442**	**100.0%**	**1.19 [0.91, 1.54]**	
Total events	386		211				

Heterogeneity: Tau² = 0.05; Chi² = 12.14, df = 3 (P = 0.007); I² = 75%
Test for overall effect: Z = 1.29 (P = 0.20)



	Amount of alcohol consumed
*	Available data suggests that antipsychotic medications have no effect on alcohol consumption during treatment relative to placebo.

Supporting evidence

There is no significant difference between antipsychotic medications and placebo in:

> average drinks per drinking day (Figure 7.5: mean difference -1.85 drinks, 95% CI -4.26, 0.57; P=0.13)*;

> average drinks per week (Guardia 2004; mean difference 0.43, 95% CI -0.54, 1.40; P=0.39)*;

> the percent of treatment days abstinent (Figure 7.6: mean difference 2.03% days, 95% CI -4.26, 0.57; P=0.13)*; or

> the percent of treatment days with heavy drinking (Figure 7.7: mean difference -6.53% days, 95% CI -13.33, 0.26; P=0.06)*.

In a group of people with comorbid alcohol abuse or dependence and bipolar disorder (Brown 2008), quetiapine therapy was associated with a statistically significant decrease in depressive symptoms, but not alcohol use. Number of drinking days per week, and number of heavy drinking days per week showed no significant differences between groups at baseline or subsequently.

Wiesbeck 1999 reported no significant difference between ritanserin and placebo in the quantity or frequency of drinking after relapse. In Johnson 1996, drinks per day, drinking days per week and drinks per drinking day all decreased during treatment with no group differences.

In Martinotti 2009, there was no significant difference between aripiprazole and naltrexone in percent of treatment days abstinent (mean difference 4.28, 95% CI -15.77, 24.33; P=0.68) or percent of treatment days with heavy drinking (mean difference -3.03, 95% CI -9.92, 3.86; P=0.39).

Figure 7.5: Antipsychotic compared with placebo, average drinks per drinking day

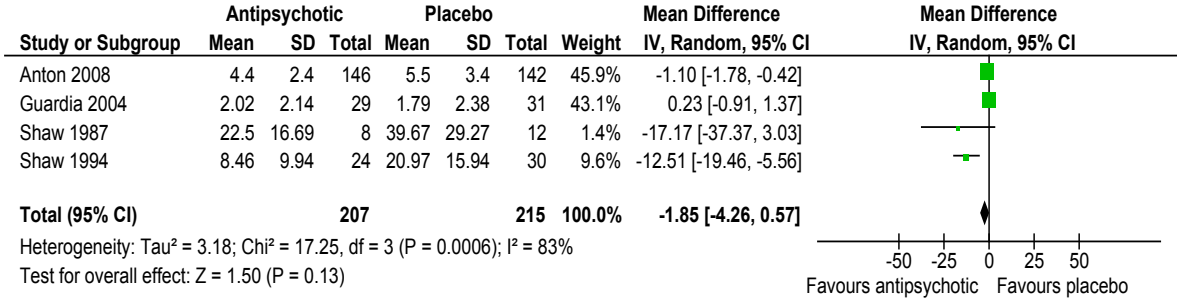


Figure 7.6: Antipsychotic compared with placebo, % treatment days abstinent (cumulative abstinence duration)

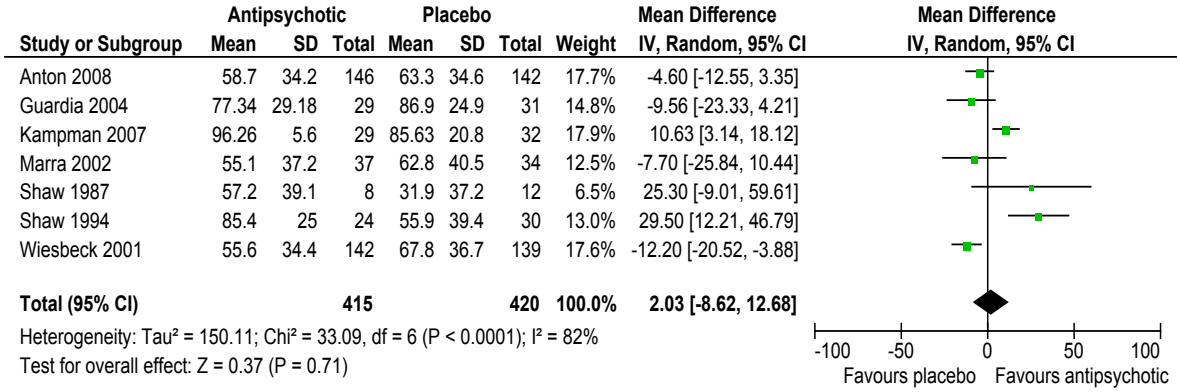
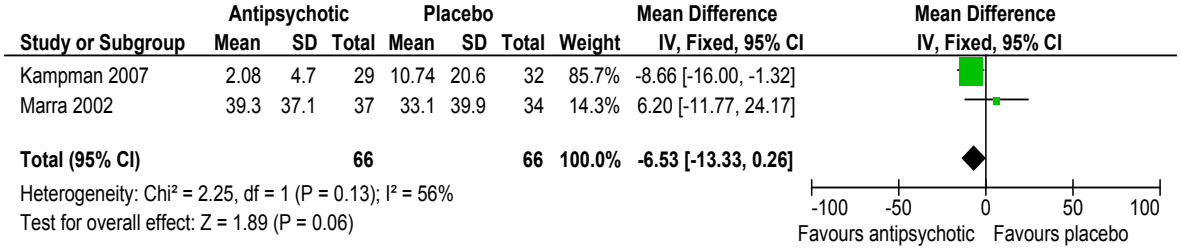


Figure 7.7: Antipsychotic compared with placebo, % treatment days with heavy drinking



	Time to first drink and time to relapse
*	Treatment with antipsychotic medication appears to have no effect on the time to first drink or time to relapse to heavy drinking compared to placebo.

Supporting evidence

There is no significant difference between antipsychotic medication and placebo in:

> average days to first drink (Figure 7.8: mean difference 4.20 days, 95% CI -4.17, 12.58; P=0.33)*; or

> average days to relapse to heavy drinking (Figure 7.9: mean difference 2.19, 95% CI -4.97, 9.35; P=0.55)*.

Data suitable for inclusion in meta-analyses were not able to be extracted from three studies. Two studies (Anton 2008, Bender 2007) found no significant difference between antipsychotic treatment and placebo in the time to first drink, and one (Wiesbeck 1999) found no significant difference in the time to relapse.

Based on survival curve analysis, Martinotti 2009 reported that the aripiprazole group remained abstinent from any alcohol for a longer time than those treated with naltrexone.

Figure 7.8: Antipsychotic compared with placebo, average days to first drink

	Antipsychotic			Placebo				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Guardia 2004	27.89	23.3	29	29.82	21.18	31	55.0%	-1.93 [-13.22, 9.36]	
Kampman 2007	45.25	35.8	29	28.3	29.8	32	25.4%	16.95 [0.33, 33.57]	
Marra 2002	41.4	43.2	37	36.5	38.1	34	19.6%	4.90 [-14.01, 23.81]	
Total (95% CI)			**95**			**97**	**100.0%**	**4.20 [-4.17, 12.58]**	

Heterogeneity: Chi² = 3.40, df = 2 (P = 0.18); I² = 41%
Test for overall effect: Z = 0.98 (P = 0.33)

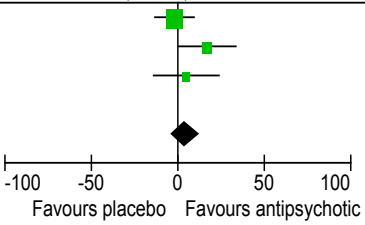
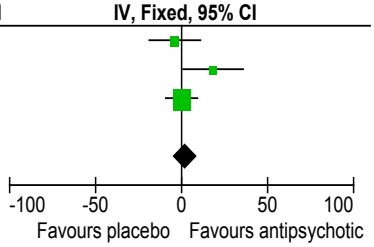


Figure 7.9: Antipsychotic compared with placebo, average days to relapse to heavy drinking

	Antipsychotic			Placebo				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Guardia 2004	63.37	30.1	29	67.28	28.62	31	23.1%	-3.91 [-18.79, 10.97]	
Kampman 2007	58.6	34.4	29	40.23	35.07	32	16.8%	18.37 [0.92, 35.82]	
Wiesbeck 2001	48	39	142	48	40	139	60.0%	0.00 [-9.24, 9.24]	
Total (95% CI)			**200**			**202**	**100.0%**	**2.19 [-4.97, 9.35]**	

Heterogeneity: Chi² = 4.16, df = 2 (P = 0.12); I² = 52%
Test for overall effect: Z = 0.60 (P = 0.55)



	Objective indicators of alcohol consumption
	Treatment with antipsychotic medication has no significant effect on objective indicators of alcohol consumption, consistent with the apparent lack of effect on reported alcohol drinking during treatment with antipsychotics relative to placebo.

Supporting evidence

In Anton 2008, the aripiprazole group showed a larger decrease in percent CDT at weeks 4 and 8, but not at week 12. A further four studies (Bender 2007, Guardia 2004, Johnson 1996, Shaw 1994) found decreases in biological indicators with no significant group differences for antipsychotic treatment compared to placebo.

In Marra 2002, biological measures (GGT, AST, ALT) were somewhat higher in the amisulpride group compared with placebo during treatment, but it is unclear whether the differences were statistically significant.

In Martinotti 2009, there were significant decreases in the values of GGT, AST and ALT with no group differences between antipsychotic and naltrexone treatment.

	Craving
*	Antipsychotic medications appear to have no significant effect on craving relative to placebo, but in some instances antipsychotics may be associated with higher levels of craving.

Supporting evidence

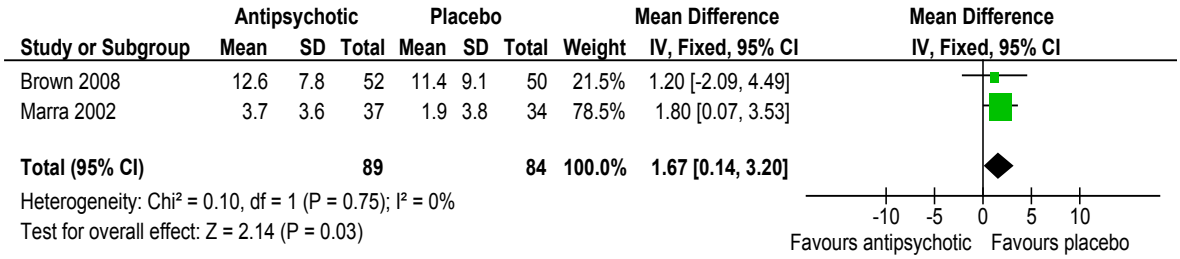
Based on two studies, treatment with antipsychotic medications appears to be associated with significantly more craving than placebo (Figure 7.10: mean difference 1.67, 95% CI 0.14, 3.20; P=0.03)*.

However, five studies (Anton 2008, Brown 2008, Guardia 2004, Johnson 1996, Wiesbeck 1999) reported no significant difference between antipsychotics and placebo in craving for alcohol, without reporting data suitable for inclusion in meta-analysis.

In Wiesbeck 2001, craving scores (by visual analogue scale) decreased in the placebo group independent of relapse, but craving scores increased in participants treated with flupenthixol who relapsed.

In Martinotti 2009, the aripiprazole group showed a significant reduction in craving assessed by visual analogue scale, whereas the naltrexone group showed a significant reduction in craving score by both OCDS and visual analogue scale. Reduction in the OCDS score was reported to be the most relevant factor in maintenance of abstinence.

Figure 7.10: Antipsychotic compared with placebo, average craving scores



7.2.3 Adverse effects

*	The risk of adverse effects is similar for antipsychotic medication and placebo.
**	The likelihood of withdrawal from treatment due to adverse effects is greater with antipsychotics relative to placebo.

Supporting evidence

There is no significant difference between antipsychotic and placebo in participants experiencing:

> any adverse effects (Figure 7.11: RR 1.04, 955 CI 0.92, 1.17; P=0.56)**;

> gastrointestinal symptoms (Figure 7.12: RR 1.29, 95% CI 0.77, 2.16; P=0.33)*;

> nausea or vomiting (Anton 2008: RR 0.97, 95% CI 0.42, 2.27; P=0.95)*; or

> neuropsychiatric symptoms (Figure 7.13: RR 0.90, 95% CI 0.69, 1.18; P=0.45)*.

Figure 7.11: Antipsychotic compared with placebo, participants experiencing any adverse effects

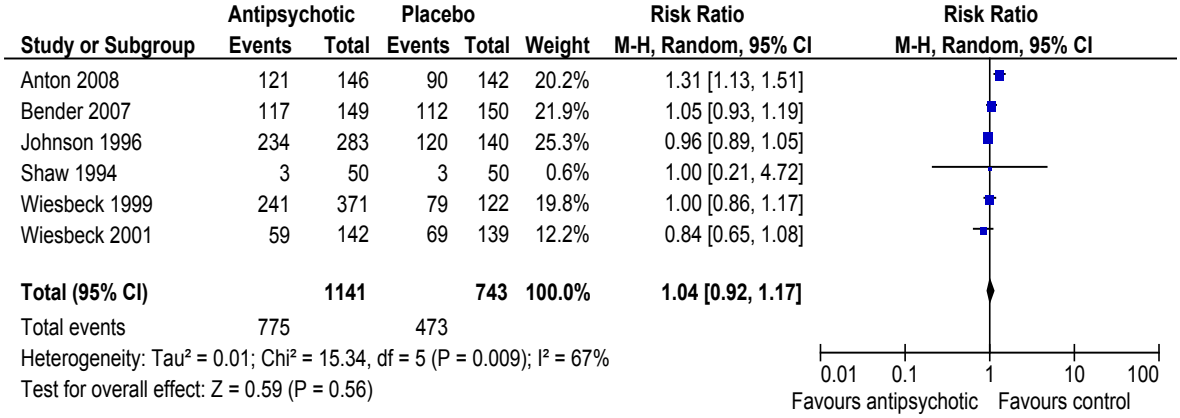


Figure 7.12: Antipsychotic compared with placebo, participants experiencing gastrointestinal symptoms

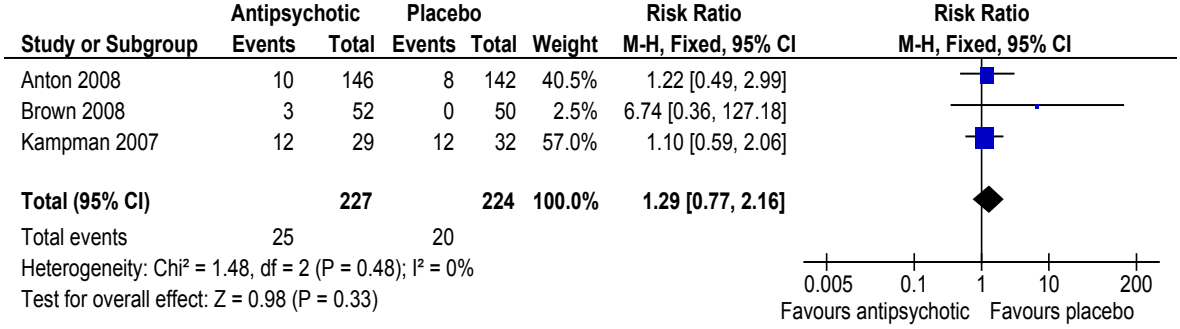


Figure 7.13: Antipsychotic compared with placebo, participants experiencing neuropsychiatric symptoms

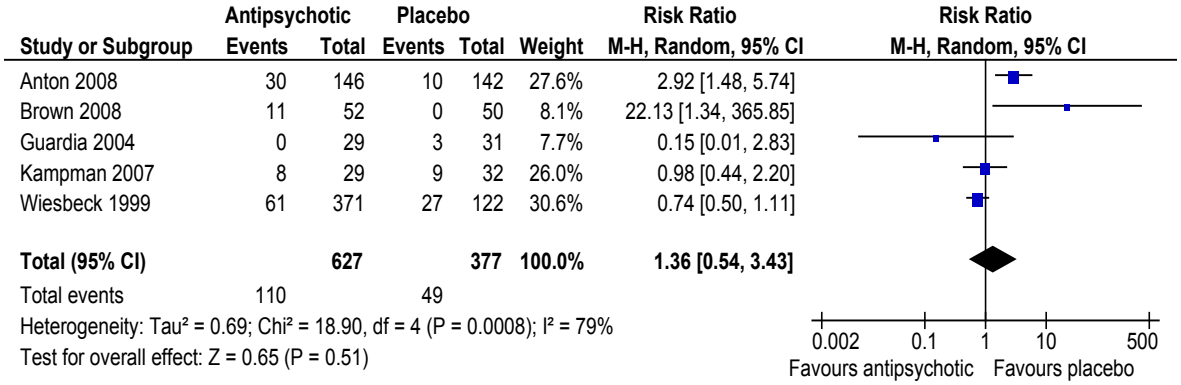
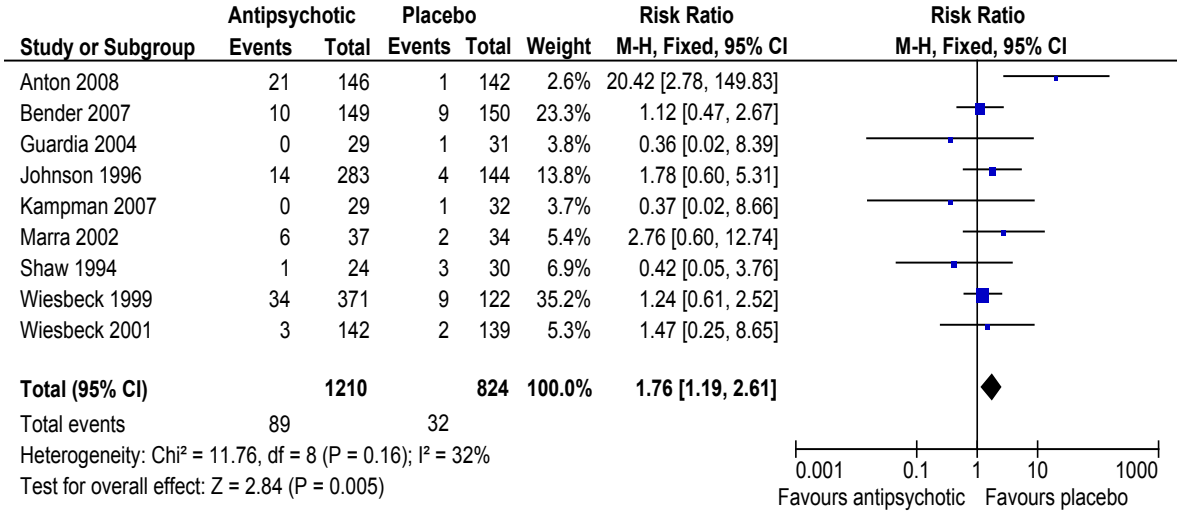


Figure 7.14: Antipsychotic compared with placebo, participants withdrawn due to adverse effects



However, significantly more people treated with antipsychotic were withdrawn from treatment due to adverse effects compared to those receiving placebo (Figure 7.14: RR 1.76, 95% CI 1.19, 2.61; P=0.005)**.

Anton 2008 identified the most common adverse effects as fatigue, insomnia, headache, restlessness and somnolence, while the adverse effects that most frequently caused discontinuation among aripiprazole-treated patients were insomnia, anxiety and restlessness.

In Brown 2008, side effects that occurred in 5% or more of participants included sedation, dizziness, dry mouth, fatigue and indigestion.

Guardia 2004 reported that some adverse effects (weight gain, increased appetite, drowsiness, constipation, and dry mouth) were more frequent in the olanzapine group but differences were not statistically significant.

In Johnson 1996 there were no significant differences in reported adverse events. Ritanserin treatment was associated with a dose-related prolongation of QTc interval recording but this was not associated with clinical deterioration in any study participants.

In Kampman 2007, adverse effects were mainly mild and evenly distributed between groups. Quetiapine-treated participants were more likely to report sedation and dry mouth. Liver function tests declined over time with no significant group differences.

In Marra 2002, the most frequently reported adverse effects were headache, pruritis and rash, and weight gain and occurred with similar frequency in the two groups.

In Anton 2008, the mean ALT and AST levels decreased in both groups with somewhat (but not significant) greater decrease in the aripiprazole group.

In Martinotti 2009, adverse effects were somewhat less likely with aripiprazole compared to naltrexone (RR 0.44, 95% CI 0.17, 1.10; P=0.08) but the difference was not statistically significant. There was also no

significant difference between aripiprazole and naltrexone in the likelihood of nausea and vomiting (RR 0.48, 95% CI 0.13, 1.74; P=0.27) or the likelihood of withdrawal from treatment due to adverse effects (RR 0.39, 95% CI 0.08, 1.83; P=0.23).

7.3 Factors affecting outcomes

The diversity of antipsychotics investigated and the small number of studies prevent any meaningful analysis of factors that might influence the outcome of treatment. However, various factors that have been identified as possibly having an affect are briefly discussed here.

7.3.1 Dose and type of antipsychotic

	Dose may be important as the pharmacology of some antipsychotics results in different effects at high and low doses.

Supporting evidence

In Anton 2008, aripiprazole-treated subjects discontinued from study medication significantly sooner than placebo-treated subjects (mean 64 vs 71 days). The difference was most evident when the dose of aripiprazole exceeded 15 mg/day. The authors suggest further study of the medication at lower doses.

Amisulpride is an example of an antipsychotic that has different effects at high and low doses. In standard doses used for treatment of psychosis (400-1200mg/day), amisulpride inhibits dopaminergic neurotransmission, but low doses (50-200mg/day) preferentially block inhibitory pre-synaptic autoreceptors. This results in a facilitation of dopamine activity. Hence, for antipsychotics to be useful for the treatment of alcohol dependence, it may be important to investigate different dose levels, based on the pharmacology of the different antipsychotics.

First-generation (conventional) antipsychotics are considered to be unhelpful in the treatment of comorbid schizophrenia and substance use disorder. Indeed it has been suggested that conventional antipsychotics may precipitate or worsen substance abuse in patients with schizophrenia.[327]

7.3.2 Gender

	Data from two studies indicate possible gender differences, but the extent and direction of any effect is unclear.

Supporting evidence

In Guardia 2004, among males the relapse rate was 26.1% in both groups, while in females the relapse rate was 83.3% in the olanzapine group and 37.5% in the placebo group. Due to small numbers the difference was not statistically significant, but the finding is suggestive of a possible gender difference in response to antipsychotic medications.

A secondary analysis[326] of data from Wiesbeck 2001 identified that the risk of relapse in male patients was almost four-fold higher with flupenthixol compared to placebo, but was barely elevated for females.

7.3.3 Typology of alcohol dependence

	One study found an effect of typology of alcohol dependence, another found no significant effect of age of onset of heavy drinking, leaving the effect of typology and family history uncertain.

Supporting evidence

In Kampman 2007, Type A and Type B alcoholics were separately randomised to receive either quetiapine or placebo, following detoxification. (Type B alcoholics are characterised by an early age of onset of problem drinking, high severity of alcohol dependence, increased psychopathology, and treatment resistance.) There was a significant interaction between quetiapine and alcoholic subtype. Quetiapine-treated Type B alcoholics had significantly fewer drays of drinking, relative to placebo-treated Type B alcoholics, and fewer days of heavy drinking. Among Type A alcoholics, quetiapine provided no advantage over placebo in improving drinking outcomes. Type B alcoholics were less likely to complete treatment, but there were no differences in completion rate by medication. Craving among Type B alcoholics declined significantly more in quetiapine-

treated patients compared to those receiving placebo, but there was no significant difference in Type A alcoholics. There were no significant differences in adherence by medication or alcoholism type.

However, Wiesbeck 1999 found no significant difference between ritanserin and placebo in relapse rate based on age of onset of heavy drinking.

Studies by Hutchison *et al*.[328] on the effect of olanzapine on cue-elicited craving and alcohol consumption suggest that polymorphisms in the dopamine D4 receptor may be a factor in responses to antipsychotics, but the clinical implications of this work remain unclear.

Section 8: Other Medications

Overview

A diverse range of medications that did not fit under any of the other groupings are reviewed in this section (see Table 8.1).

Table 8.1: Studies involving relapse prevention treatment of alcohol dependence with medications other than those included in previous sections

Medication	Studies
Ondansetron or ondansetron combined with naltrexone	Johnson 2000[329-332]; Johnson 2000A[333-335]
Buspirone	Bruno 1989 [336]; Fawcett 2000 [337]; Kranzler 1994 [338]; Malcolm 1992 [339]; Malec 1996[340]; Tollefson 1992 [341]
GHB	Caputo 2003 [342]; Caputo 2007 [284]; Gallimberti 1992 [343]; Nava 2006 [229]; Stella 2008 [285]
Baclofen	Addolorato 2002[344]; Addolorato 2007[345]; Garbutt 2010 [346]
Lithium	de la Fuente 1989 [347]; Dorus 1989[348]; Fawcett 1987 [349;350]; Fawcett 2000 [337]; Merry 1976 [351]
Alpha-adrenergic agonists (prazocin)	Simpson 2009 [352]
Rimonabant	Soyka 2008 [353]

Brief information on the design of these studies is included in Appendix 1.

Ondansetron or ondansetron plus naltrexone

Ondansetron alone or in combination with naltrexone, may be associated with reduced alcohol consumption, and reduced craving relative to placebo. Ondansetron appears to be more effective in early-onset alcoholism compared to late-onset alcoholism. However, insufficient data are available to assess the extent of benefit likely to be gained from the use of ondansetron for relapse prevention treatment of alcohol dependence.

Buspirone

Buspirone appears to have no significant effect on retention in treatment or alcohol drinking outcomes relative to placebo*, despite some apparent effect in reduction of anxiety. Adverse effects are more likely with buspirone* compared to placebo. Insufficient data are available to determine whether concomitant depression or degree of anxiety at baseline, or change in these conditions during treatment, have an effect on treatment outcome.

GHB

GHB has no significant effect on retention in treatment relative to naltrexone, disulfiram or placebo*.

GHB appears to be associated with significantly higher rates of abstinence than naltrexone or placebo and possibly disulfiram, but the likelihood of relapse to heavy drinking during treatment is similar with GHB and naltrexone* or disulfiram.

It appears that GHB has similar effectiveness as naltrexone and disulfiram, but may be more effective than placebo, in terms of alcohol consumption during treatment.

GHB appears to be associated with less craving for alcohol than disulfiram and placebo, but probably has no more effect on craving than naltrexone*.

GHB is associated with more adverse effects than placebo, but the incidence of adverse effects is similar with GHB and naltrexone. There is no significant difference between GHB and naltrexone*, disulfiram or placebo in the number of participants withdrawn from treatment due to adverse effects.

GHB is subject to abuse, and some people receiving GHB for treatment of alcohol dependence may develop craving for GHB. This limits the therapeutic value of GHB.

Better control of craving for alcohol may be achieved by administering GHB in five or more daily doses, but this has practical implications for supervision of treatment.

Baclofen

Baclofen has no significant effect on retention in treatment and appears to have no significant effect on rates

of abstinence during treatment compared to placebo. Data on the effect of baclofen on relapse to heavy drinking are limited and conflicting, and insufficient data are available to form a view on its effect on craving. Adverse effects, particularly drowsiness, may be somewhat more likely with baclofen, but baclofen is not associated with significantly greater withdrawal from treatment due to adverse effects, relative to placebo.

Gender appears to have no significant effect, but dose of baclofen and the goal of treatment may be important – further evidence is needed.

Lithium

Available studies indicate that lithium has no significant effect on retention in treatment, alcohol consumption or adverse effects, relative to placebo. Compliance appears to be a significant factor influencing treatment outcome; the presence of depression may also influence outcomes.

Alpha-adrenergic antagonists (prazocin)

Relative to placebo, Prazocin appears to have no significant effect on retention in treatment, abstinence or craving, but may be associated with less alcohol consumption during treatment. In the single study undertaken assessing the use of Prazocin for treatment of alcohol dependence there was no significant difference between Prazocin and placebo in the occurrence of adverse effects, or withdrawal from treatment due to adverse effects.

Rimonabant

In the one study that has been undertaken comparing the cannabinoid CB1 receptor antagonist, rimonabant, with placebo in people who are alcohol dependent, there was no significant difference between group in retention in treatment, abstinence or relapse to heavy drinking, alcohol consumption during treatment, or the incidence of adverse effects or withdrawal from treatment due to adverse effects.

8.1 Ondansetron or ondansetron plus naltrexone

Ondansetron is a 5-HT_3 antagonist that has been shown to reduce alcohol-induced positive subjective effects and craving in healthy social drinkers, and to diminish drinking and increase abstinence among alcoholics with a biological disease predisposition.

Johnson and colleagues explored the effectiveness of ondansetron in the treatment of alcohol dependence in two studies. In the first study (Johnson 2000) three different doses of ondansetron were compared with placebo. Outcomes were also compared for early-onset and late-onset alcoholism, and for Type A and Type B alcoholism.

In the second study (Johnson 2000A) the combination of ondansetron and naltrexone was compared with placebo in a sample of early-onset alcoholics. The ability of naltrexone to diminish alcohol consumption may be greater in biologically predisposed alcoholics (see section 1.3.8). The rationale for this is that early-onset alcoholics may have abnormalities in both opioid and serotonergic systems. In addition, compliance with naltrexone treatment is reduced in the early stages when nausea may occur. Ondansetron has both anti-nausea and antiemetic properties and hence has the potential to counter this side effect of naltrexone.[354] Through these interactions, ondansetron and naltrexone in combination may act synergistically at reducing alcohol consumption among biologically predisposed alcoholics.[334]

	Retention in treatment
	Ondansetron alone or in combination with naltrexone has no significant effect on retention rates relative to placebo.

Supporting evidence

Johnson 2000 reported no significant difference between ondansetron and placebo in the number of participants completing the study treatment (RR 0.88, 95% CI 0.70, 1.11; P=0.28). Johnson 2000A reported no significant difference between ondansetron plus naltrexone and placebo in the average weeks in treatment (mean difference -0.03 weeks, 95% CI -1.63, 1.57; P=0.97).

	Amount of alcohol consumed
	In early-onset alcoholics, ondansetron alone or in combination with naltrexone appears to be associated with reduced alcohol consumption relative to placebo.

Supporting evidence

Johnson 2000 found that ondansetron significantly reduced alcohol consumption and increased abstinence among patients with early-onset, but not late-onset alcoholism.

All participants in Johnson 2000A were early-onset alcoholics, and those treated with ondansetron plus naltrexone compared to those receiving placebo reported:

> significantly less average drinks per drinking day (mean difference -3.62 drinks, 95% CI -5.82, -1.42; P=0.001);

> significantly less average drinks per week (mean difference -18.83 drinks, 95% CI -30.77, -6.89; P=0.002); and

> greater (but not statistically significant) cumulative abstinence duration (mean difference 23.82 % treatment days abstinent, 95% CI -0.80, 48.44; P=0.06).

Serum CDT levels were significantly lower in those treated with ondansetron plus naltrexone compared to those receiving placebo, supporting the reported decreases in alcohol consumption.

	Craving
	One study found that the combination of ondansetron and naltrexone is associated with significantly less craving compared with placebo in early-onset but not late-onset alcoholism.

Supporting evidence

In Johnson 2000A, participants treated with ondansetron plus naltrexone compared to those receiving placebo reported significantly lower average craving scores (mean difference -1.83, 95% CI -2.86, -0.80; P<0.001). An analysis of a subset of participants in Johnson 2000[332] found that ondansetron (4μg/kg bid) significantly reduced overall craving among early-onset alcoholics, but ondanstetron (1μg/kg bid) significantly increased craving in late-onset alcoholics.

	Adverse effects
	There appears to be no significant difference between ondansetron or ondansetron plus naltrexone and placebo in adverse effects.

Supporting evidence

In Johnson 2000, adverse event rates were similar for the ondansetron and placebo groups.

In Johnson 2000A, the ondansetron-naltrexone combination was reported to be well tolerated with few side effects, and no significant differences from placebo. No adverse effects persisted between weekly visits or required medical intervention. No participants withdrew from treatment due to adverse effects.

	Factors affecting treatment
	People with early-onset alcoholism are more likely to receive benefit from treatment with ondansetron.

Supporting evidence

In Johnson 2000, there was a significant effect for Type B alcoholics (72% of whom were early-onset alcoholics) to respond to ondansetron (4μg/kg), while Type A alcoholics (67% of whom were late-onset alcoholics) receiving ondansetron showed no beneficial effect. However, early-onset versus late-onset classification predicted ondansetron response substantially better than the Type A/B classification.[330]

8.2 Buspirone

Anxious patients may use alcohol to obtain an anxiolytic effect.[341] Hence control of anxiety may reduce relapse. For example, in a study comparing ondansetron and placebo, participants who experienced decreases in anxiety during treatment, regardless of which medication they received, reported fewer drinks per day at their last visit compared with those who reported increases in anxiety.[331]

Buspirone is a non-benzodiazepine anxiolytic (a 5-HT_{1A} partial agonist). The net effect of repeated administration of buspirone is to enhance 5-HT function via facilitation of the post-synaptic receptor[8].

	Retention in treatment
**	Buspirone has no significant effect on retention in treatment relative to placebo.

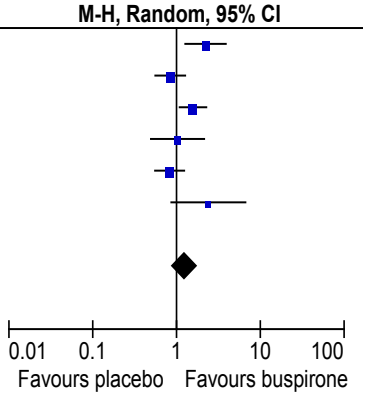
Supporting evidence

Based on six studies, there is no significant difference between buspirone and placebo in the number of people completing the study treatment (Figure 8.2.1: RR 1.27, 95% CI 0.88, 1.83; P=0.21)**.

Figure 8.2.1: Buspirone compared with placebo, participants completing the study

	Buspirone		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Bruno 1989	20	25	9	25	16.6%	2.22 [1.27, 3.88]	
Fawcett 2000	21	48	27	52	20.1%	0.84 [0.56, 1.27]	
Kranzler 1994	26	31	16	30	21.2%	1.57 [1.09, 2.27]	
Malcolm 1992	10	33	10	34	12.9%	1.03 [0.49, 2.15]	
Malec 1996	16	28	20	29	20.4%	0.83 [0.55, 1.24]	
Tollefson 1992	10	26	4	25	8.7%	2.40 [0.87, 6.68]	
Total (95% CI)		**191**		**195**	**100.0%**	**1.27 [0.88, 1.83]**	
Total events	103		86				

Heterogeneity: Tau² = 0.13; Chi² = 14.77, df = 5 (P = 0.01); I² = 66%
Test for overall effect: Z = 1.27 (P = 0.21)



In Kranzler 1994, participants treated with buspirone remained in treatment significantly longer than those receiving placebo (mean difference 2.77 weeks, 95% CI 0.90, 4.64; P=0.004)*. However, in Malcolm 1992 participants treated with buspirone remained in treatment for a median 9.1 weeks compared to 12.8 weeks for those receiving placebo (difference not statistically significant).

In Bruno 1989, 12 of 25 (48%) receiving placebo, compared to 2 of 25 (8%) receiving buspirone, discontinued treatment due to a lack of improvement or worsening of their condition. Similarly in Tollefson 1992, 12 of 25 placebo (48%) and 3 of 26 (11.5%) buspirone withdrew from treatment because their condition was worse or not improved.

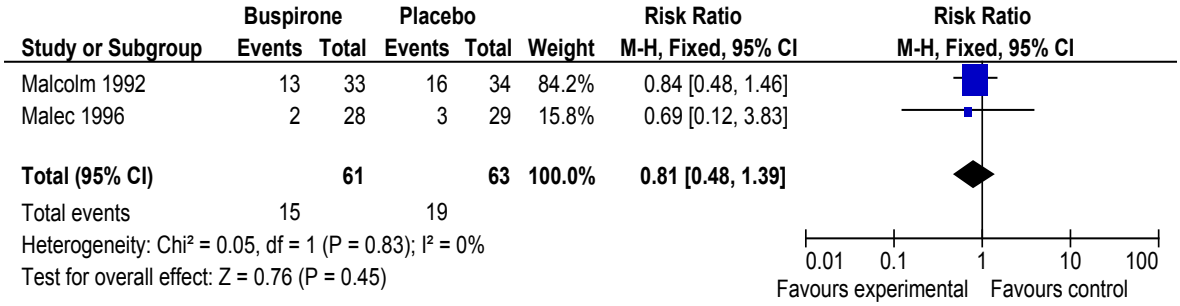
	Abstinence
*	Buspirone has no significant effect on rates of abstinence during treatment relative to placebo.

Supporting evidence

Based on two studies, there is no significant difference between buspirone and placebo in the number of participants abstinent at the end of treatment (Figure 8.2.2: RR 0.81, 95% CI 0.48, 1.39; P=0.45)*.

In addition Fawcett 2000 reported that 28% of study participants were abstinent through threee months with no significant difference between buspirone, lithium and placebo groups.

Figure 8.2.2: Buspirone compared with placebo, participants abstinent at end of the study



	Amount of alcohol consumed
*	Buspirone has no significant effect on alcohol consumption during treatment relative to placebo.

Supporting evidence

One study (Kranzler 1994) reported somewhat less drinks per drinking day in the group treated with buspirone, compared to those receiving placebo, but the difference was not statistically significant (mean difference -3.30 drinks, 95% CI -6.92, 0.32; P=0.07). Malcolm 1992 also reported no significant difference between buspirone and placebo in average drinks per drinking day.

Based on two studies, there is also no significant difference between buspirone and placebo in the average drinks per week (Figure 8.2.3: mean difference 0.07 drinks, 95% CI -4.12, 4.27; P=0.97)* or the cumulative abstinence duration (Figure 8.2.4: mean difference 2.83 % treatment days, 95% CI -1.15, 6.80; P=0.16)*.

In Fawcett 2000 the decrease with time in quantity of alcohol consumed was greater with buspirone compared to placebo, although the difference was not statistically significant. In Malec 1996 an index of ethanol consumption decreased during treatment in both buspirone and placebo groups, but the difference between the groups was not statistically significant.

Kranzler 1994 reported that at the end of treatment, the number of drinking days and drinks per day correlated with levels of GGT and AST. In Malec 1996 the reported reduction in alcohol consumption was also positively correlated with a decrease in GGT from baseline to endpoint.

Figure 8.2.3: Buspirone compared with placebo, average drinks per week

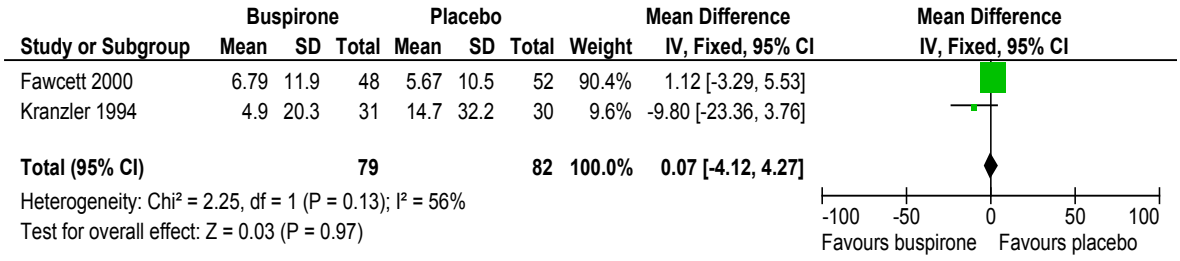
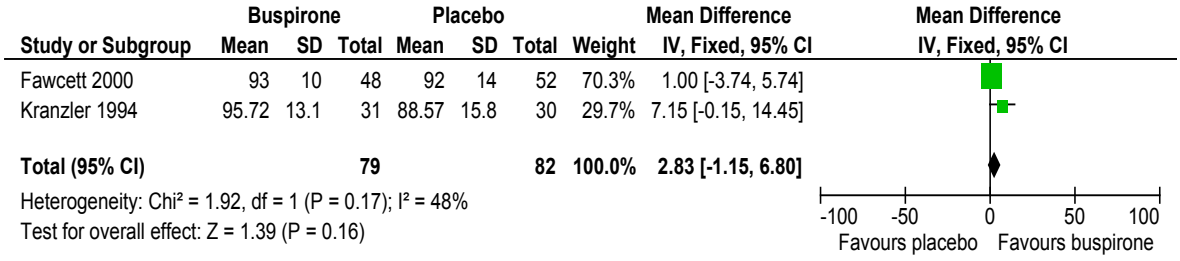


Figure 8.2.4: Buspirone compared with placebo, % treatment days abstinent (cumulative abstinence duration)



	Time to first drink and time to relapse
	Data are limited, but it appears that buspirone does not significantly delay the recommencement of drinking or relapse to heavy drinking, relative to placebo.

Supporting evidence

In Kranzler 1994, there was a significant difference favouring buspirone in the interval to first heavy drinking day, but the groups did not differ on the number of weeks to first alcohol consumption.

In Malcolm 1992, the median time to first drink was 2.1 months for buspirone and 4.2 months for placebo, but the difference was not statistically significant. There was also no significant difference in the time to five consecutive drinking days.

	Craving
	Buspirone may have some effect on craving but insufficient data are available to confirm the extent of any effect.

Supporting evidence

In Bruno 1989, buspirone reduced alcohol craving by 40% and craving scores were significantly lower with buspirone compared to placebo (P=0.001).

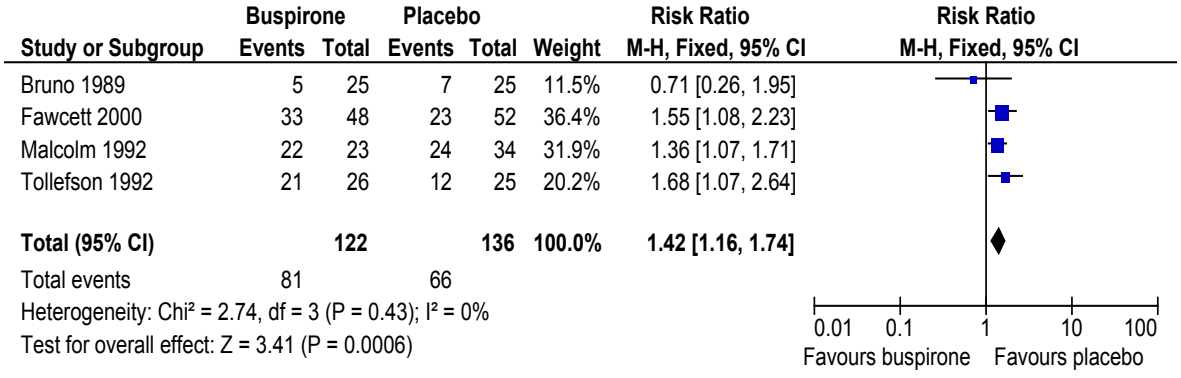
In Malec 1996, craving improved in both groups with no significant difference.

	Adverse effects
*	Buspirone is associated with significantly more adverse effects relative to placebo.
	Adverse effects are usually of low intensity, and there is no significant difference between buspirone and placebo in terms of withdrawal from treatment due to adverse effects.

Supporting evidence

Based on four studies, significantly more people treated with buspirone experienced any adverse effects compared to placebo (Figure 8.2.5: RR 1.42, 95% CI 1.16, 1.74; P<0.001)*. However Kranzler 1994 reported that there were no significant group differences in the frequency of adverse effects. Malec 1996 reported that side effects occurred more often with buspirone, but only 2 of 28 participants required a dose reduction.

Figure 8.2.5: Buspirone compared with placebo, participants experiencing any adverse effects



Malec 1996 reported that 7 of 28 treated with buspirone, compared to 1 of 29 receiving placebo, experienced nausea or vomiting (P=0.06).

Based on five studies, significantly more people treated with buspirone experienced neuropsychiatric symptoms (Figure 8.2.6: RR 3.14, 95% CI 1.58, 6.23; P=0.001)**.

However, there was no significant difference in the number of people withdrawn from treatment due to adverse effects (Figure 8.2.7: RR 2.18, 95% CI 0.63, 7.59; P=0.22)*. Bruno 1989 reported that all adverse effects were of mild intensity, except in one participant receiving placebo.

Figure 8.2.6: Buspirone compared with placebo, participants experiencing neuropsychiatric symptoms

	Buspirone		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Fawcett 2000	25	48	5	52	23.2%	5.42 [2.25, 13.01]	
Kranzler 1994	15	31	9	30	27.9%	1.61 [0.84, 3.11]	
Malcolm 1992	15	33	0	34	5.2%	31.91 [1.99, 512.50]	
Malec 1996	16	28	5	29	23.6%	3.31 [1.40, 7.83]	
Tollefson 1992	9	26	4	25	20.1%	2.16 [0.76, 6.13]	
Total (95% CI)		**166**		**170**	**100.0%**	**3.14 [1.58, 6.23]**	
Total events	80		23				

Heterogeneity: Tau² = 0.33; Chi² = 9.52, df = 4 (P = 0.05); I² = 58%

Test for overall effect: Z = 3.27 (P = 0.001)

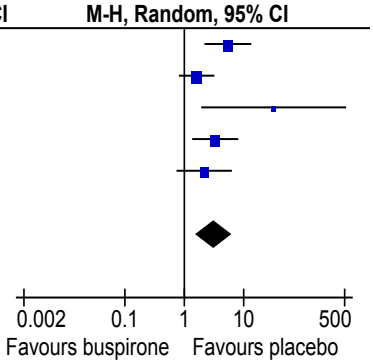
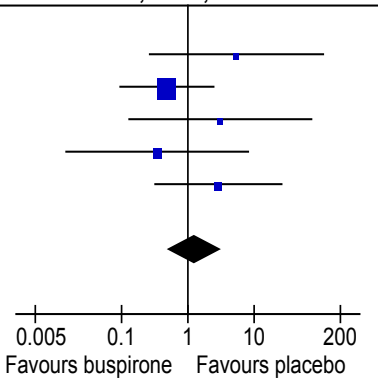


Figure 8.2.7: Buspirone compared with placebo, participants withdrawn due to adverse effects

	Buspirone		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Bruno 1989	0	25	0	25		Not estimable	
Fawcett 2000	2	48	0	52	6.4%	5.41 [0.27, 109.87]	
Kranzler 1994	2	31	4	30	54.0%	0.48 [0.10, 2.45]	
Malcolm 1992	1	33	0	34	6.5%	3.09 [0.13, 73.20]	
Malec 1996	0	28	1	29	19.6%	0.34 [0.01, 8.12]	
Tollefson 1992	3	26	1	25	13.5%	2.88 [0.32, 25.92]	
Total (95% CI)		**191**		**195**	**100.0%**	**1.27 [0.50, 3.20]**	
Total events	8		6				

Heterogeneity: Chi² = 3.74, df = 4 (P = 0.44); I² = 0%

Test for overall effect: Z = 0.50 (P = 0.62)



	Factors affecting treatment
	The presence of depression and anxiety may affect the response to buspirone. Insufficient data are available to determine the extent of any effect.

Supporting evidence

(1) Depression

In Fawcett 2000, regression analysis for time to first drink showed significant group-by-depression interaction indicating that a depressive disorder at the beginning of treatment may be a moderator of treatment effect. Among nondepressed participants, the hazard ratio for drinking again was two times higher in the buspirone group compared with the placebo group.

(2) Anxiety

In Kranzler 1994, buspirone was significantly more effective as an anxiolytic among subjects with high pretreatment levels of anxiety. However, all participants in Malcolm 1992 were highly anxious and those receiving buspirone spent less time in treatment than those receiving placebo. The authors concluded that anxious alcoholics taking buspirone did not receive any benefit over placebo on a number of anxiety and alcohol use measures.

(3) Alcoholic subtype

Tollefson 1992 found no significant response differences relative to Cloninger subtype.

8.3 GHB

GHB occurs naturally in the brain and arises from metabolism of GABA.[343] It modulates the activity of neurotransmitters including dopamine and serotonin, and is thought to have an ethanol-mimicking effect on the central nervous system.[342]

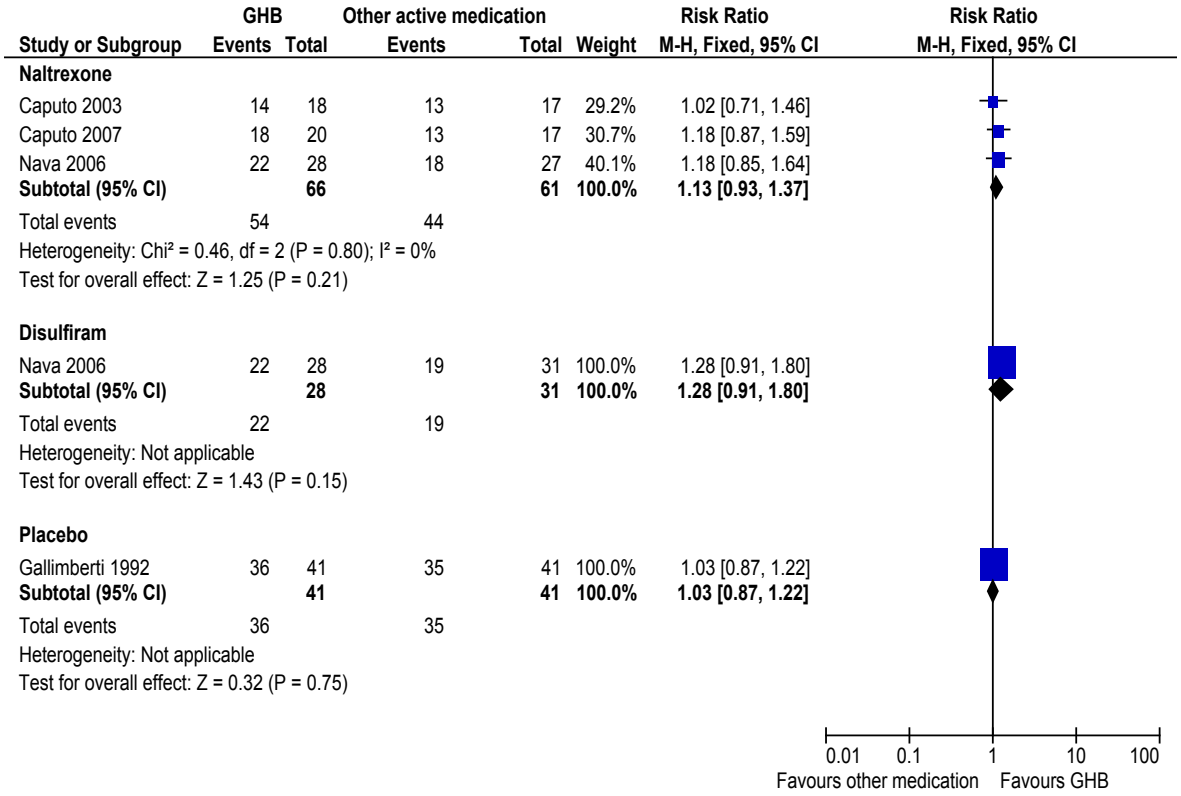
Of the five studies involving the use of GHB for relapse prevention treatment of alcohol dependence, four compared GHB with naltrexone (Caputo 2003, Caputo 2007, Nava 2006, Stella 2008). Nava 2006 also included a comparison with disulfiram, while Gallimberti 1992 is the only study that compared GHB with placebo.

	Retention in treatment
*	GHB has no significant effect on retention in treatment relative to naltrexone, disulfiram or placebo.

Supporting evidence

There is no significant difference in the number of participants completing treatment with GHB compared to naltrexone (Figure 8.3.1: RR 1.13, 95% CI 0.93, 1.37; P=0.21)*, disulfiram (Figure 8.3.1: RR 1.28, 95% CI 0.91, 1.80; P=0.15), or placebo (Figure 8.3.1: RR 1.03, 95% CI 0.87, 1.22; P=0.75).

Figure 8.3.1: GHB compared with other active medication, participants completing the study



	Abstinence
*	GHB appears to be associated with higher rates of abstinence than naltrexone or placebo, and possibly disulfiram.

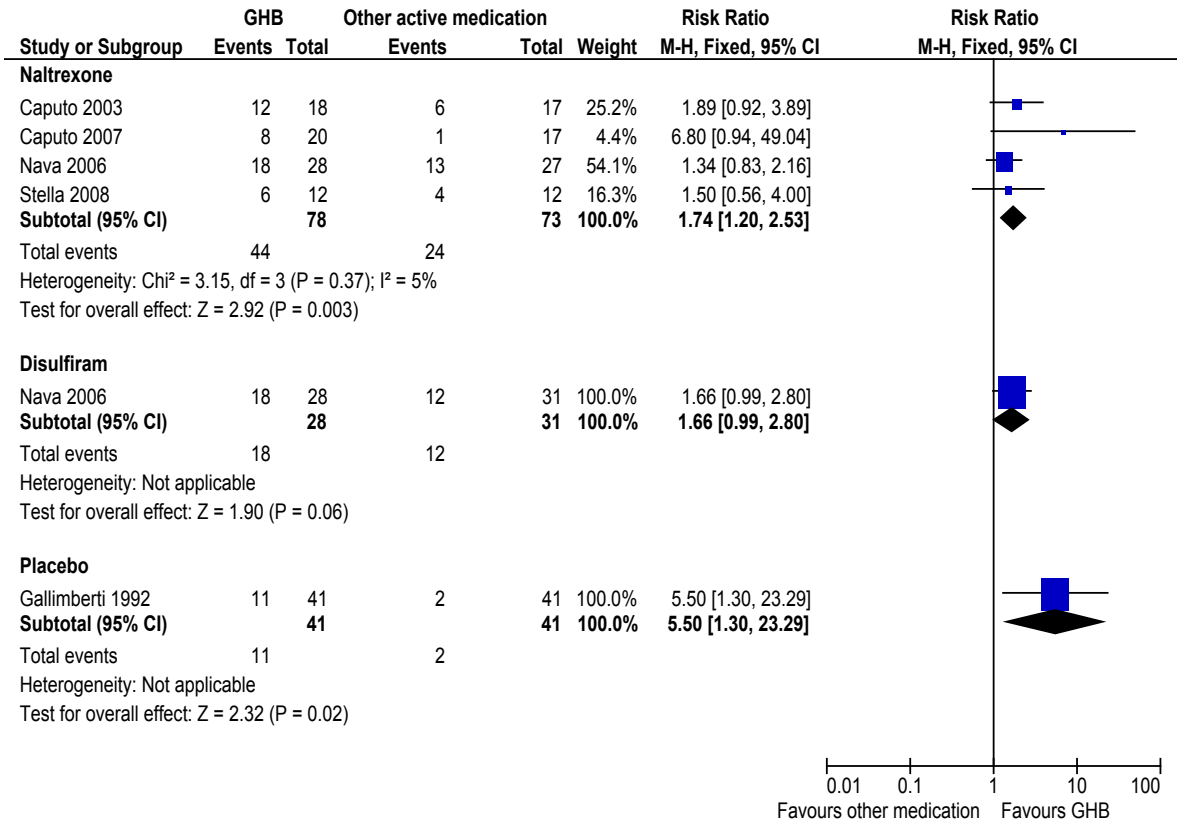
Supporting evidence

Based on four studies, significantly more people treated with GHB were continuously abstinent during treatment or abstinent at the end of treatment compared to those treated with naltrexone (Figure 8.3.2: RR 1.74, 95% CI 1.20, 2.53; P=0.003)*.

In Nava 2006, more people treated with GHB were continuously abstinent compared to those treated with disulfiram, but the difference was not statistically significant (Figure 8.3.2: RR 1.66, 95% CI 0.99, 2.80; P=0.06).

In Gallimberti 1992, abstinence was significantly more likely with GHB compared to placebo (Figure 8.3.2: RR 5.50, 95% CI 1.30, 23.39; P=0.02).

Figure 8.3.2: GHB compared with other active medication, participants continuously abstinent during treatment

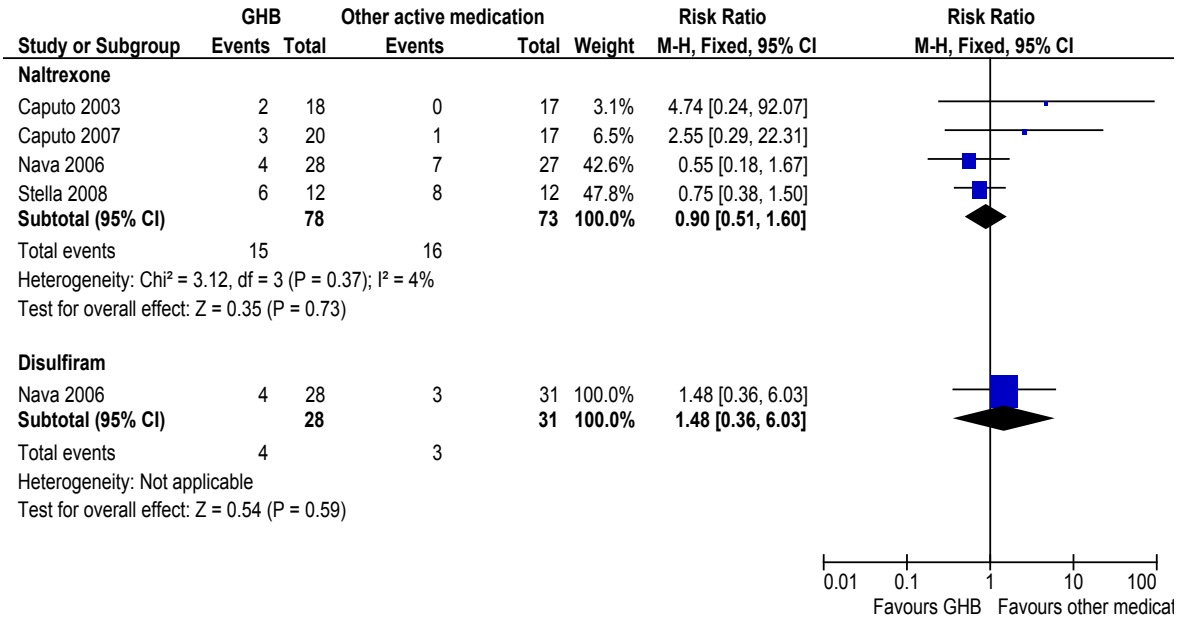


	Relapse to heavy drinking
*	The likelihood of relapse to heavy drinking during treatment is similar with GHB and naltrexone or disulfiram.

Supporting evidence

There is no significant difference in the number of participants relapsing during treatment with GHB compared to naltrexone (Figure 8.3.3: RR 0.90, 95% CI 0.51, 1.60; P=0.73)* or compared to disulfiram (Figure 8.3.3: RR 1.48, 95% CI 0.36, 6.03; P=0.59).

Figure 8.3.3: GHB compared with other active medication, participants relapsing during treatment



	Amount of alcohol consumed
	It appears that GHB has similar effectiveness as naltrexone and disulfiram, but may be more effective than placebo, in terms of alcohol consumption during treatment.

Supporting evidence

One study (Nava 2006) reported no significant difference between GHB and naltrexone (mean difference -1.40, 95% CI -7.31, 4.51; P=0.64) or between GHB and disulfiram (mean difference -2.10, 95% CI -7.69, 3.49; P=0.46) in average drinks per week during treatment.

One study (Caputo 2007) reported no significant difference between GHB and naltrexone in average drinks per drinking day (mean difference 0.00, 95% CI -1.72, 1.72; P=1.0).

One study (Gallimberti 1992) found that, compared to placebo, GHB was associated with significantly less drinks per week (mean difference -32.20, 95% CI -37.92, -26.48; P<0.001) and significantly more cumulative days abstinent (mean difference 17.50, 95% CI 11.40, 23.60; P<0.001).

	Objective measures of alcohol consumption
	GGT levels were consistent with reported changes in alcohol consumption.

Supporting evidence

Nava 2006 reported that patients in the GHB group had greater decreases in laboratory markers of alcohol abuse than did patients in the naltrexone and disulfiram groups.

In Caputo 2003, GGT, AST and ALT decreased in both groups with no significant group differences.

Gallimberti 1992 reported that serum GGT activity correlated with estimated alcohol consumption.

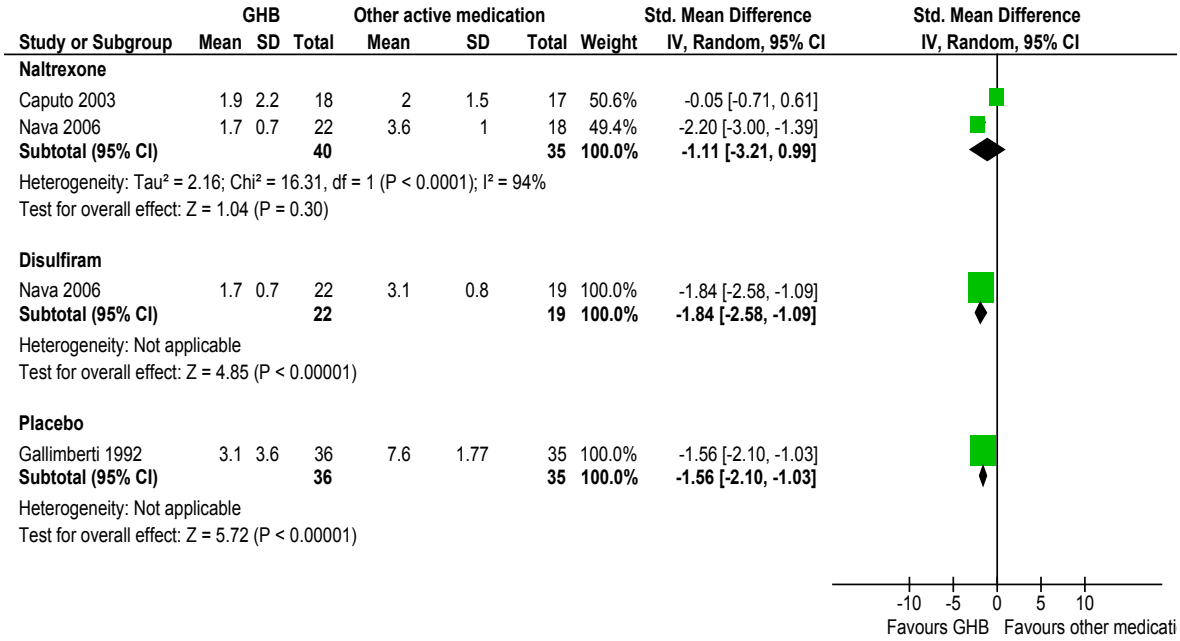
	Craving
*	GHB appears to be associated with less craving for alcohol than disulfiram and placebo, but probably has no more effect on craving than naltrexone.

Supporting evidence

Based on two studies, there is no significant difference in average craving scores for people treated with GHB compared to those treated with naltrexone (Figure 8.3.4: SMD -1.11, 95% CI -3.21, 0.99; P=0.30)*, but

one study (Nava 2006) reported significantly lower average craving scores with GHB compared to disulfiram (Figure 8.3.4: SMD -1.84, 95% CI -2.58, -1.09; P<0.001) and Gallimberti 1992 reported significantly lower craving in those who completed treatment with GHB compared to placebo (Figure 8.3.4: SMD -1.56, 95% CI -2.10, -1.03; P<0.001).

Figure 8.3.4: GHB compared with other active medication, average craving score



	Adverse effects
	GHB is associated with more adverse effects than placebo, but the incidence of adverse effects is similar with GHB and naltrexone.
	There is no significant difference between GHB and naltrexone, disulfiram or placebo in the number of participants withdrawn from treatment due to adverse effects.

Supporting evidence

In Gallimberti 1992, more participants treated with GHB reported experiencing adverse effects (6 of 36) than those receiving placebo (2 of 35) but the difference was not statistically significant (P=0.17). Those treated with GHB experienced somewhat more neuropsychiatric symptoms, largely dizziness (4 of 36 GHB compared to 1 of 35 placebo, P=0.21).

Caputo 2007 reported no significant difference between GHB and naltrexone in:

> participants experiencing any adverse effects (2 of 20 GHB compared to 4 of 17 naltrexone, P=0.29);

> participants experiencing nausea and vomiting (0 of 20 GHB compared to 2 of 17 naltrexone, P=0.24);

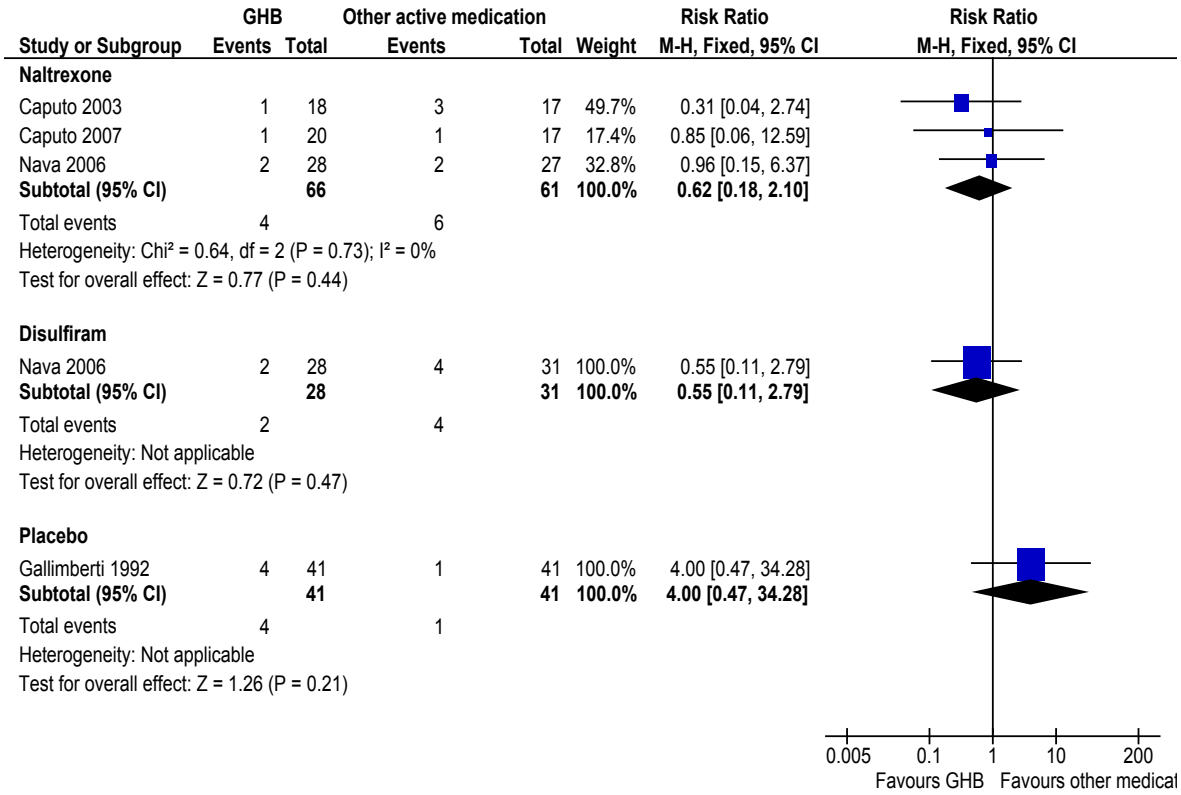
> participants experiencing neuropsychiatric symptoms (2 of 20 GHB, 0 of 17 naltrexone, P=0.34).

Caputo 2003 did not report data but noted that the incidence of side effects did not differ between GHB and naltrexone.

Despite the higher incidence of adverse effects with GHB, Gallimberti 1992 reported no significant difference between GHB and placebo in withdrawal from treatment due to adverse effects (Figure 8.3.5: RR 4.00, 95% CI 0.47, 34.28; P=0.21). Adverse effects were described as transient which may have helped participants to tolerate the effects.

There were no significant differences between GHB and naltrexone (Figure 8.3.5: RR 0.62, 95% CI 0.18, 2.10; P=0.44)* or GHB and disulfiram (Figure 8.3.5: RR 0.55, 95% CI 0.11, 2.79; P=0.47) in the number of participants withdrawn due to adverse effects.

Figure 8.3.5: GHB compared with other active medication, participants withdrawn due to adverse effects



	Factors affecting treatment outcome
	GHB is subject to abuse, and some people receiving GHB for treatment of alcohol dependence may develop craving for GHB. This limits the therapeutic value of GHB.
	Better control of craving for alcohol may be achieved by administering GHB in five or more daily doses, but this has practical implications for supervision of treatment.

(1) Craving for GHB

Analyses have found that 10-15% of patients treated with GHB developed a craving for, and abuse of the drug. Caputo *et al*.[355] assessed craving in cohorts of people treated with GHB for alcohol dependence. Cohorts were identified as those who were only alcohol dependent, those with a history of cocaine or heroin dependence, and those currently receiving methadone maintenance treatment. All were treated with oral GHB, 50mg/kg by body weight three times a day, for three months. In this study 34% of participants developed craving for GHB, and 23% abused GHB by taking amounts above those prescribed (abuse was to a large extent avoided by entrusting the medication to a family member). Craving for GHB was significantly higher in those with previous cocaine dependence compared to all other groups. Abuse of GHB was significantly higher in those with previous cocaine or heroin dependence. Caputo *et al*. concluded that administration of GHB in alcoholics with a history of cocaine or heroin dependence is not recommended. The administration of naltrexone in combination with GHB (see section 5.2.4) may help to counter craving for GHB.[356]

(2) Dose regime

Addolorato et al.[357] observed that patients treated with GHB (50mg/day in three doses) experienced temporary reduction in alcohol craving, but this did not last a whole day. Given the short half-life of GHB, they concluded that benefits may arise, particularly through improved control of craving, from splitting the dose of GHB further. They found that administration of GHB (50mg/day) in six daily doses promoted abstinence in a greater proportion of subjects than had been the case with three daily doses.

All the studies included in this review administered GHB in three daily doses, except Stella 2008, where five daily doses were used. This does not provide enough data to explore the effect of dose regime on treatment outcome, leaving this as an unanswered question.

Increasing the number of daily doses of a medication increases the inconvenience of treatment. Addolorato and colleagues typically entrust medication to a family member – increasing dosing frequency would risk a reduction in the level of supervision which may be undesirable in a medication that itself has abuse potential.

8.4 Baclofen

Baclofen is a γ-aminobutyric acid ($GABA_B$) receptor agonist.[8] It is usually used as a muscle relaxant, particularly in the management of spasticity.

Studies in animal models have demonstrated baclofen can suppress alcohol withdrawal signs and voluntary alcohol intake. Preliminary studies in humans showed baclofen can reduce alcohol craving and intake, and alcohol withdrawal symptoms in alcohol-dependent patients.[344]

	Retention in treatment
*	Baclofen has no significant effect on retention in treatment compared to placebo.

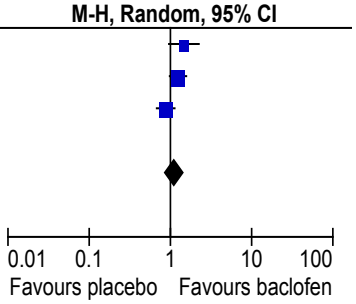
Supporting evidence

Based on three studies, there is no significant difference between baclofen and placebo in rates of completion of treatment (Figure 8.4.1: RR 1.14, 95% CI 0.85, 1.52; P=0.39)*.

Figure 8.4.1: Baclofen compared with placebo, participants completing the study

	Baclofen		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Addolorato 2002	17	20	11	19	24.5%	1.47 [0.96, 2.25]	
Addolorato 2007	36	42	29	42	38.5%	1.24 [0.98, 1.57]	
Garbutt 2010	28	40	32	40	37.0%	0.88 [0.68, 1.13]	
Total (95% CI)		**102**		**101**	**100.0%**	**1.14 [0.85, 1.52]**	
Total events	81		72				

Heterogeneity: Tau² = 0.04; Chi² = 5.86, df = 2 (P = 0.05); I² = 66%
Test for overall effect: Z = 0.86 (P = 0.39)



	Abstinence
	Baclofen appears to have no significant affect on abstinence during treatment compared with placebo.

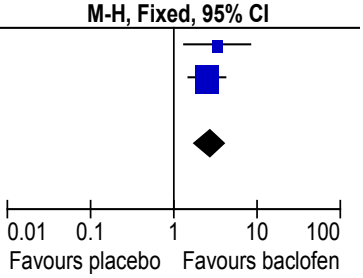
Supporting evidence

Based on two studies (Addolorato 2002, Addolorato 2007), significantly more people were continuously abstinent during treatment with baclofen compared with placebo (Figure 8.4.2: RR 2.71, 95% CI 1.73, 4.25; P<0.001)*.

Figure 8.4.2: Baclofen compared with placebo, participants continuously abstinent during treatment

	Baclofen		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Addolorato 2002	14	20	4	19	25.5%	3.33 [1.33, 8.32]	
Addolorato 2007	30	42	12	42	74.5%	2.50 [1.49, 4.18]	
Total (95% CI)		**62**		**61**	**100.0%**	**2.71 [1.73, 4.25]**	
Total events	44		16				

Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 4.34 (P < 0.0001)

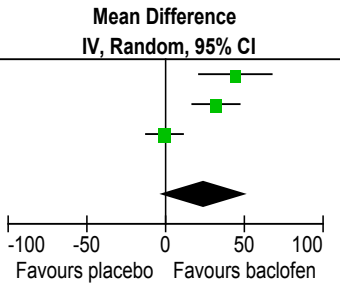


The two studies by Addolorato *et al*. also found significantly greater cumulative abstinence duration during treatment with baclofen compared to placebo but in a third study (Garbutt 2010) the cumulative abstinence duration was similar for baclofen and placebo. Overall there was no significant difference between baclofen and placebo in cumulative abstinence duration (Figure 8.4.3: mean difference 24.04% days, 95% CI -3.54, 51.61; P=0.09)*.

Figure 8.4.3: Baclofen compared with placebo, % treatment days abstinent (cumulative abstinence duration)

Study or Subgroup	Baclofen Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Addolorato 2002	65.3	38.7	20	21	35	19	30.1%	44.30 [21.16, 67.44]
Addolorato 2007	62.8	35	42	30.8	35.64	42	34.2%	32.00 [16.89, 47.11]
Garbutt 2010	49.9	27.9	40	50.6	25.9	40	35.7%	-0.70 [-12.50, 11.10]
Total (95% CI)			**102**			**101**	**100.0%**	**24.04 [-3.54, 51.61]**

Heterogeneity: Tau² = 518.81; Chi² = 17.75, df = 2 (P = 0.0001); I² = 89%
Test for overall effect: Z = 1.71 (P = 0.09)



	Relapse to heavy drinking
	Data on the effect of baclofen on relapse to heavy drinking are limited and conflicting.

Supporting evidence

One study (Addolorato 2007) found that significantly less people relapsed to heavy drinking during treatment with baclofen compared to placebo (RR 0.43, 95% CI 0.22, 0.82; P=0.01).

On the other hand, Garbutt 2010 found no significant difference between baclofen and placebo in the percent of days during treatment with heavy drinking (mean difference 0.40, 95% CI -9.86, 10.66; P=0.94).

	Objective measures of alcohol consumption
	Baclofen appears to have no significant effect on GGT and indicators of liver function, relative to placebo.

Supporting evidence

In Addolorato 2002 and 2007, GGT and liver function tests declined during treatment in baclofen and placebo groups. Garbutt 2010 did not report data.

	Craving
	Insufficient data available to form a view.

Supporting evidence

In Garbutt 2010, the average craving score was lower in the baclofen group compared to the placebo group, but the difference was not statistically significant.

Addolorato 2002 and 2007 both reported a significant reduction in craving score with baclofen compared with placebo, but data were not able to be incorporated into meta-analyses.

	Adverse effects
	Adverse effects, particularly drowsiness, may be somewhat more likely with baclofen, but baclofen is not associated with significantly greater withdrawal from treatment due to adverse effects, relative to placebo.

Supporting evidence

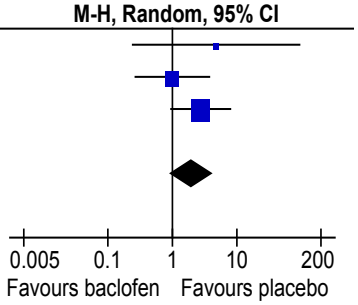
Based on three studies, neuropsychiatric effects such as sleepiness, tiredness, dizziness appear to be somewhat more common with baclofen compared to placebo but the difference is not statistically significant (Figure 8.4.4: RR 1.98, 95% CI 0.89, 4.38; P=0.09).

No participants in Addolorato 2002 or 2007 withdrew from treatment due to adverse effects. However, three of 40 participants receiving baclofen in Garbutt 2010 withdrawal from treatment due to adverse effects, compared to none receiving placebo. The difference was not statistically significant (RR 7.00; 95% CI 0.37, 131.28; P=0.19).

Figure 8.4.4: Baclofen compared with placebo, participants experiencing neuropsychiatric symptoms

Study or Subgroup	Baclofen Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Addolorato 2002	2	20	0	19	7.1%	4.76 [0.24, 93.19]
Addolorato 2007	4	42	4	42	36.3%	1.00 [0.27, 3.74]
Garbutt 2010	11	40	4	40	56.5%	2.75 [0.96, 7.91]
Total (95% CI)		**102**		**101**	**100.0%**	**1.98 [0.89, 4.38]**
Total events	17		8			

Heterogeneity: Tau² = 0.00; Chi² = 1.74, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.68 (P = 0.09)



	Factors affecting treatment outcome
	Gender appears to have no significant effect but dose of baclofen and the goal of treatment may be important – further evidence is needed.

Supporting evidence

A recent open trial of baclofen[358] used doses ranging from 15 mg/day to 300 mg/day. The authors noted that two-thirds of participants needed a dose higher than the approved 80 mg/day dose. The absence of a comparison group limits the value of the study, but the findings suggest the possibility that dose (and compliance) may be important to treatment response.

The dose of baclofen does not explain the differences between Addolorato 2002 and 2007 and Garbutt 2010 as all three studies used a dose of 30 mg/day.

Addolorator 2007 involved a higher proportion of male participants (72%) compared to Garbutt 2010. However, Garbutt 2010 reported there were no significant gender differences in heavy drinking days or the percent of days abstinent.

Addolorato 2007 involved people with liver cirrhosis – while not specifically stated, it is likely with this population that the goal of treatment was total abstinence. In contrast, in Garbutt 2010, only 24% of participants had abstinence as their treatment goal.

In Addolorato 2002 and 2007, medication was entrusted to a family member. This may have helped to encourage compliance, and maintain commitment to a goal of abstinence.

8.5 Lithium

The choice of lithium for treatment of alcohol dependence was based on its effectiveness in treating affective disorders which, in turm, might affect the course of alcohol dependence.[337]

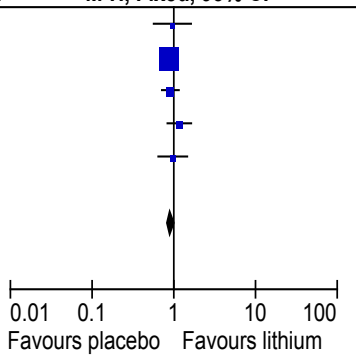
	Retention in treatment
*	Lithium has no significant effect on rates of completion of treatment compared to placebo.

Supporting evidence

Based on five studies there is no significant difference between lithium and placebo in the number of participants completing the study (Figure 8.5.1: RR 0.92, 95% CI 0.83, 1.03; P=0.16)*.

Figure 8.5.1: Lithium compared with placebo, participants completing the study

	Lithium		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
de la Fuente 1989	14	28	13	25	5.5%	0.96 [0.57, 1.63]	
Dorus 1989	130	228	150	229	59.6%	0.87 [0.75, 1.01]	
Fawcett 1987	35	51	40	53	15.6%	0.91 [0.71, 1.16]	
Fawcett 2000	34	56	27	52	11.2%	1.17 [0.84, 1.64]	
Merry 1976	20	36	20	35	8.1%	0.97 [0.65, 1.46]	
Total (95% CI)		**399**		**394**	**100.0%**	**0.92 [0.83, 1.03]**	
Total events	233		250				
Heterogeneity: Chi² = 2.62, df = 4 (P = 0.62); I² = 0%							
Test for overall effect: Z = 1.41 (P = 0.16)							



	Abstinence and alcohol consumption
	Lithium has no significant effect on abstinence or alcohol consumption during treatment relative to placebo.

Supporting evidence

There was no significant difference between lithium and placebo in:

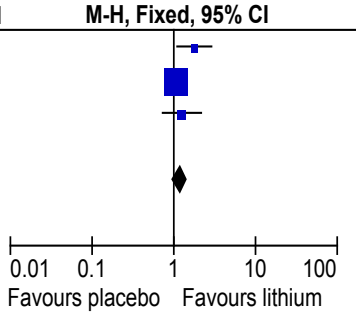
> the number of participants continuously abstinent during treatment (Figure 8.5.2: RR 1.19, 95% CI 0.96, 1.48; P=0.11)*;

> average drinks per week (Fawcett 2000: mean difference -0.84 drinks/week, 95% CI -4.24, 2.56; P=0.63); or

> cumulative abstinence duration (Fawcett 2000: mean difference -2.0 % days, 95% CI -7.49, 3.49; P=0.48).

Figure 8.5.2: Lithium compared with placebo, participants continuously abstinent during treatment

	Lithium		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
de la Fuente 1989	22	28	11	25	12.0%	1.79 [1.10, 2.89]	
Dorus 1989	74	228	69	229	71.0%	1.08 [0.82, 1.41]	
Fawcett 1987	23	67	15	55	17.0%	1.26 [0.73, 2.17]	
Total (95% CI)		**323**		**309**	**100.0%**	**1.19 [0.96, 1.48]**	
Total events	119		95				
Heterogeneity: Chi² = 3.26, df = 2 (P = 0.20); I² = 39%							
Test for overall effect: Z = 1.58 (P = 0.11)							



Dorus 1989 did not report data, but stated there was no significant difference between lithium and placebo in:

> the number of days of drinking;

> alcohol-related hospitalisations;

> changes in rating of severity of alcoholism;

> time to first drink; or

> craving.

	Adverse effects
	Data are limited but suggest no significant difference between lithium and placebo in adverse effects.

Supporting evidence

In Fawcett 2000, 34 of 56 treated with lithium experienced adverse effects, compared to 23 of 52 receiving placebo, but the difference was not statistically significant (P=0.09). In the same study 1 of 56 treated with lithium and none receiving placebo were withdrawn from treatment due to adverse effects.

In Dorus 1989, significantly more participants receiving lithium experienced gastrointestinal effects (diarrhoea) compared to those receiving placebo (RR 1.41, 95% CI 1.11, 1.80; p=0.005).

	Factors affecting treatment outcome
	Compliance with medication and the presence of depression may affect treatment outcomes.

Supporting evidence

In Fawcett 1987 continuous abstinence was more likely in participants considered to be compliant in both lithium and placebo groups. In the lithium group, those who achieved higher blood levels of lithium were also more likely to be continuously abstinent than those participants who were considered compliant, but had lower blood levels of lithium. However, Dorus 1989 found no significant difference in outcomes even when analyses were limited to compliant patients.

In Merry 1976, lithium had no significant effect on alcohol consumption in non-depressed participants, but amongst participants with depression, lithium was associated with less days of alcohol consumption. However, this study was small and data was largely reported only for those who completed treatment. Fawcett 2000, a larger study, found the reverse – in this study lithium was less effective than placebo in reducing alcohol consumption among depressed participants. Dorus 1989 found no significant differences in the effectiveness of lithium in subgroups of participants with or without depression.

8.6 Alpha-adrenergic antagonists

Blockade of noradrenaline binding to postsynaptic α_1 receptors with alpha-adrenergic antagonists such as Prazocin, should reduce central adrenergic activity associated with alcohol dependence. This may reduce alcohol-induced reward and stress-induced relapse.[352]

	Retention in treatment
	Prazocin has no significant effect on retention in treatment relative to placebo.

Supporting evidence

In Simpson 2009 there was no significant difference between Prazocin and placebo in the number of participants completing the study (RR 0.82, 95% CI 0.57, 1.18; P=0.29).

	Abstinence during treatment
	Prazocin has no significant effect on abstinence during treatment relative to placebo.

Supporting evidence

In Simpson 2009, there was no significant difference between Prazocin and placebo in:

> the number of participants continuously abstinent during treatment (RR 0.48, 95% CI 0.06, 3.69);

> the number of participants abstinent at the end of the study (RR 2.14, 95% CI 0.95, 4.85; P=0.07); or

> cumulative abstinence duration (mean difference -11.50% days, 95% CI -36.56, 13.56; P=0.37).

	Alcohol consumption and craving
	Prazocin may be associated with significantly less alcohol consumption during treatment relative to placebo.
	Prazocin has no significant effect on craving relative to placebo.

Supporting evidence

In Simpson 2009, there was no significant difference in average drinks per week or average drinking days per week over the full six weeks of the study. However, a difference in alcohol consumption became apparent after week three, with the full dose of medication achieved at the end of week two. Over the last three weeks of the study there was significantly less alcohol consumption during treatment in the group treated with Prazocin compared to those receiving placebo (mean difference -6.06 drinks per week, 95% CI -10.39, -1.73; P=0.006). Craving decreased in both groups during treatment with no significant group differences.

In Simpson 2009 levels of AST and ALT were monitored, but not GGT. There was no consistent significant relationship between liver enzymes and alcohol consumption during the study.

	Adverse effects
	Based on limited data there appears to be no significant difference between prazocin and placebo in adverse effects.

Supporting evidence

In Simpson 2009, one of 12 treated with prazocin, and none of 12 receiving placebo, required a dose reduction to manage adverse effects. None in either group were withdrawn due to adverse effects.

8.7 Rimonabant

Animal studies suggest that cannabinoids and alcohol activate similar reward pathways. The cannabinoid CB1 receptors also seem to regulate the reinforcing properties of alcohol.[4] Alcohol increases the synthesis or impairs the degradation of endocannabinoids leading to a locally elevated endocannabinoid tone within the brain.[359] Moderating this excitability may moderate the effects of alcohol.[8]

The effectiveness of the CB1 receptor antagonist, rimonabant, in relapse prevention treatment of alcohol dependence has been explored in one study (Soyka 2008). The primary indication for which rimonabant has been developed is for appetite suppression in the treatment of obesity. Concerns that the benefits of rimonabant do not outweigh potential psychiatric risks[8] have led to approval processes for rimonabant in Europe and the USA being suspended.

	Retention in treatment
	Rimonabant has no significant effect on retention in treatment relative to placebo.

Supporting evidence

In Soyka 2008, there was no significant difference between rimonabant and placebo in the number of participants completing the study (RR 1.15, 95% CI 0.97, 1.37; P=0.11).

	Abstinence and relapse during treatment
	Rimonabant has no significant effect on abstinence during treatment or relapse to heavy drinking compared to placebo.

Supporting evidence

In Soyka 2008, there was no significant difference between rimonabant and placebo in:

> the number of participants continuously abstinent during treatment (RR 1.15, 95% CI 0.87, 1.53; P=0.32);

> cumulative abstinence duration (mean difference 2.60% treatment days, 95% CI -4.51, 9.71; P=0.47); or

> the number of participants relapsing to heavy drinking during treatment (RR 0.89, 95% CI 0.67, 1.18; P=0.43).

	Alcohol consumption during treatment
	Rimonabant has no significant effect on alcohol consumption during treatment, compared to placebo.

Supporting evidence

In Soyka 2008, there was no significant difference between rimonabant and placebo in average drinks per drinking day (mean difference -0.40 drinks, 95% CI -1.95, 1.15; P=0.61). There were also no statistically significant differences between rimonabant and placebo in time to first drink or time to heavy drinking.

No significant differences were observed for CDT or GGT values.

Craving reduced in both groups, with no significant group differences.

In a recent study[360], non-treatment-seeking heavy alcohol drinkers received either 20mg/day rimonabant or placebo. Rimonabant did not change alcohol consumption during two weeks with daily phone calls to report drinking, nor did it change alcohol self-administration or endocrine measures during a laboratory session during which alcohol was offered after a priming dose.

	Adverse effects
	Based on limited data, there appears to be no difference between rimonabant and placebo in terms of adverse effects during relapse prevention treatment of alcohol dependence.

Supporting evidence

In Soyka 2008, there was no significant difference between rimonabant and placebo in:

> the number of participants experiencing any adverse effects (RR 1.09. 95% CI 0.86, 1.39; P=0.46); or

> the number of participants withdrawn due to adverse effects (RR 0.58, 955 CI 0.22, 1.55; P=0.28).

Section 9: Adjunct Psychosocial Support and Therapy

Overview

Rationale

Different types of psychosocial support or psychological therapy may interact with different types of pharmacological treatment to enhance the effectiveness of treatment.

Types of therapy

This section reviews the effectiveness of psychosocial support and therapy as adjuncts to pharmacological treatment. It considers cognitive-behavioural therapy compared to other types of psychological therapy, psychological therapy compared with medical monitoring, and different intensities of therapy or support. In most of the studies the pharmacotherapy was naltrexone, but small numbers of studies involved acamprosate, disulfiram, and antidepressants.

Retention in treatment

There is no significant difference between CBT and other psychological therapies as adjuncts to pharmacological treatment in terms of retention in treatment*.

Psychological therapy may increase retention in treatment compared to basic medical monitoring as adjuncts to disulfiram treatment.

More frequent follow-up contact appears to be associated with greater retention in acamprosate or disulfiram treatment.

Abstinence

There is no significant difference between CBT and other forms of psychological therapy as adjuncts to pharmacological treatment in terms of continuous abstinence*.

Abstinence is more likely with psychological therapy compared to medical monitoring as adjuncts to opioid antagonist treatment* but it appears this difference does not extend to acamprosate or disulfiram treatment.

Abstinence appears to be more likely with more frequent follow-up of people receiving disulfiram or acamprosate treatment.

Relapse to heavy drinking

There is no significant difference between CBT and other psychological therapies* or between any psychological therapy and medical monitoring* in terms of relapse to heavy drinking during treatment.

Amount of alcohol consumed

CBT is associated with somewhat less alcohol consumption during treatment compared to other types of psychological therapy as adjuncts to opioid antagonist*, and possibly also disulfiram treatment.

Psychological therapy is probably more effective than medical monitoring in terms of alcohol consumption during treatment with disulfiram, but probably not naltrexone.

Periods of abstinence or heavy drinking during treatment

CBT is associated with longer cumulative abstinence and less heavy drinking compared to other forms of psychological therapy as adjuncts to naltrexone* but possibly not other pharmacological treatments. The difference may become more marked with time in treatment.

There is no significant difference between any psychological therapy and medical monitoring in terms of periods of abstinence* or heavy drinking during pharmacological treatment.

Time to first drink and time to relapse

It is unclear whether CBT affects the time to first drink, but it appears to delay the time to relapse to heavy drinking compared to other psychological therapies as adjuncts to opioid antagonist treatment but not other pharmacological therapies.

Based on limited data it appears that any psychological therapy is more effective than medical monitoring in terms of the time to first drink and time to relapse.

Craving

Psychological therapy has no significant effect on craving*.

Factors affecting treatment response

Psychological therapies and supportive approaches may enhance treatment outcome by promoting compliance with pharmacotherapies.

Greater participation in psychological therapies is likely to be associated with improved outcomes.

People with less severe alcohol dependence may be more likely to benefit from naltrexone with less intensive adjunct therapies.

People with lower levels of verbal learning may have poorer outcomes with relapse prevention therapy compared to supportive therapy.

9.1 Rationale

Different types of psychosocial support or psychological therapy may interact with different types of pharmacological treatment to enhance the effectiveness of treatment. For example, cognitive behavioural therapy and naltrexone share common mechanisms of action (craving reduction and relapse prevention) potentially making these therapies more effective in combination.[64]

9.2 Evidence for effectiveness

The studies included in this section include comparisons of different forms of psychosocial support and therapy as adjuncts to pharmacological treatment. The studies have been grouped according to the type of comparison: cognitive-behavioural therapy compared with another form of psychological therapy; any form of psychological therapy compared with medical monitoring, and differing levels of support or intensities of psychosocial support and therapy. The medical monitoring procedures include formal manualised approaches, as used in the Combine Study,[361] as well as less formal approaches entailing a series of medical appointments.

Table 9.1 lists the studies included in these groupings, and indicates the nature of the pharmacological treatment.

Table 9.1: Studies involving comparison of psychosocial support and therapy in conjunction with pharmacological treatment

Cognitive-behavioural compared with other psychological therapy			Psychological therapy compared with medical monitoring			Differing levels of support
Opioid antagonist	Acamprosate	Other	Opioid antagonist	Acamprosate	Disulfiram	
Anton 2005[64;65] Balldin 2003[71] Davidson 2007 [141;364;365] Heinala 2001[98] Monti 2001[66-68] O'Malley 1992[83-86] Oslin 2008[99;100]	De Wildt 2002 [362]	Azrin 1982 [234] (disulfiram) Carroll 1998 [212;213] (disulfiram) Hautzinger 2005 [249] (SSRI)	Combine Study [15;52;59-62] O'Malley 2003-1[88] Oslin 2008[99;100] Pettinati 2008A[115]	Combine Study [15;52;59-62] De Wildt 2002[362] Reid 2005 [197]	Azrin 1982 [234] Carroll 1998 [212;213] Powell 1985 [228]	Gerrein 1973 [227] (disulfiram) Hammarberg 2004 [363] (acamprosate) Pelc 2005 [366] (acamprosate) Schmitz 2009 [122]

Summary information about the study designs is given in Appendix 1.

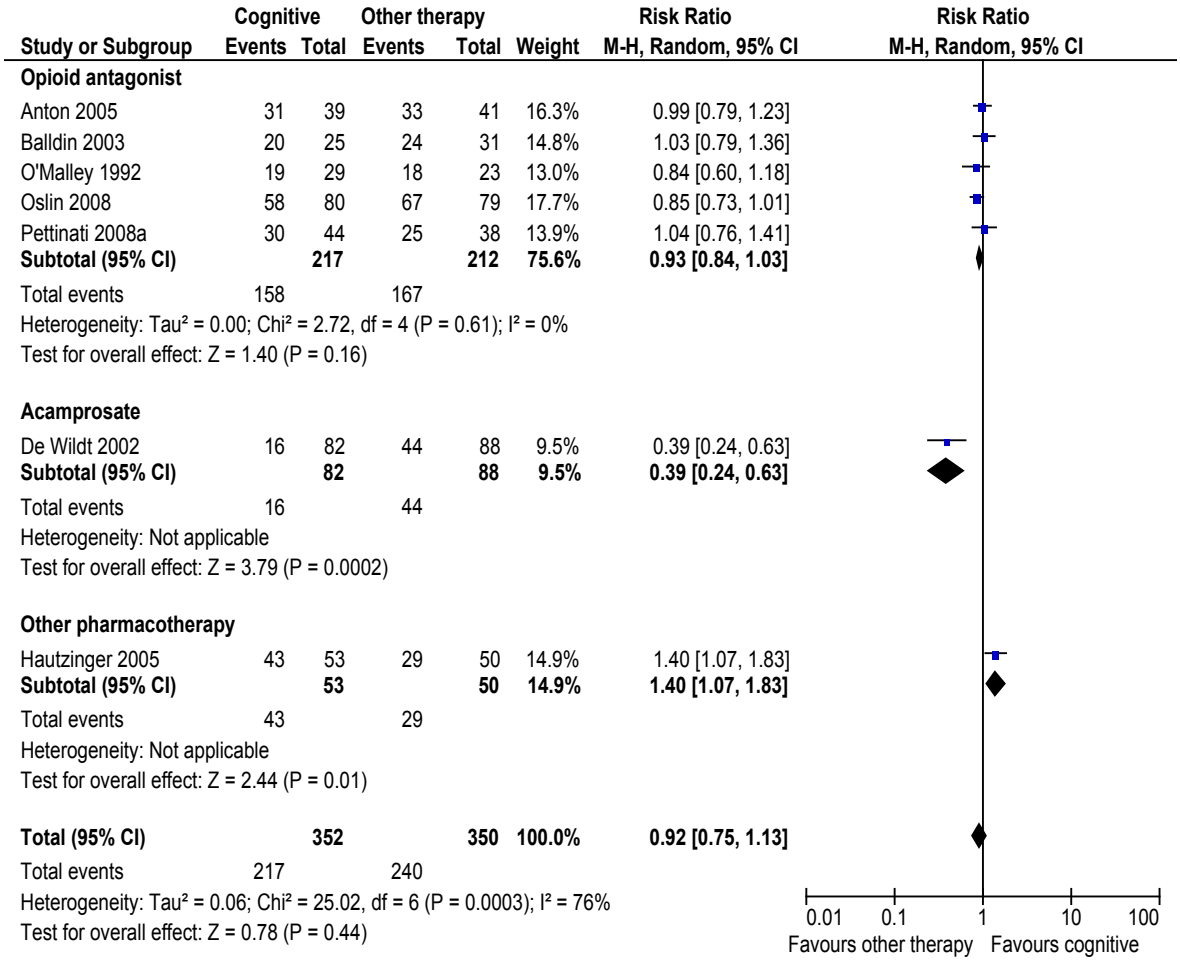
9.2.1 Retention in treatment

*	There is no significant difference between CBT and other psychological therapies as adjuncts to pharmacological treatment in terms of retention in treatment.
	Psychological therapy may increase retention in treatment compared to basic medical monitoring as adjuncts to disulfiram treatment.
	More frequent follow-up contact appears to be associated with greater retention in acamprosate or disulfiram treatment.

Supporting evidence

Based on five studies, there is no significant difference between CBT and other types of psychotherapy in the number of participants completing the study when the pharmacotherapy is an opioid antagonist (Figure 9.1: RR 0.93, 95% CI 0.84, 1.03; P=0.16)*. One study found that CBT is associated with a lower rate of completion of treatment compared to motivational interviewing in conjunction with acamprosate (Figure 9.1: RR 0.39, 95% CI 0.24, 0.63; P<0.001). One study reported higher rates of completion of treatment with CBT compared with non-directional group counselling in conjunction with antidepressants (Figure 9.1: RR 1.40, 95% CI 1.07, 1.83; P=0.01).

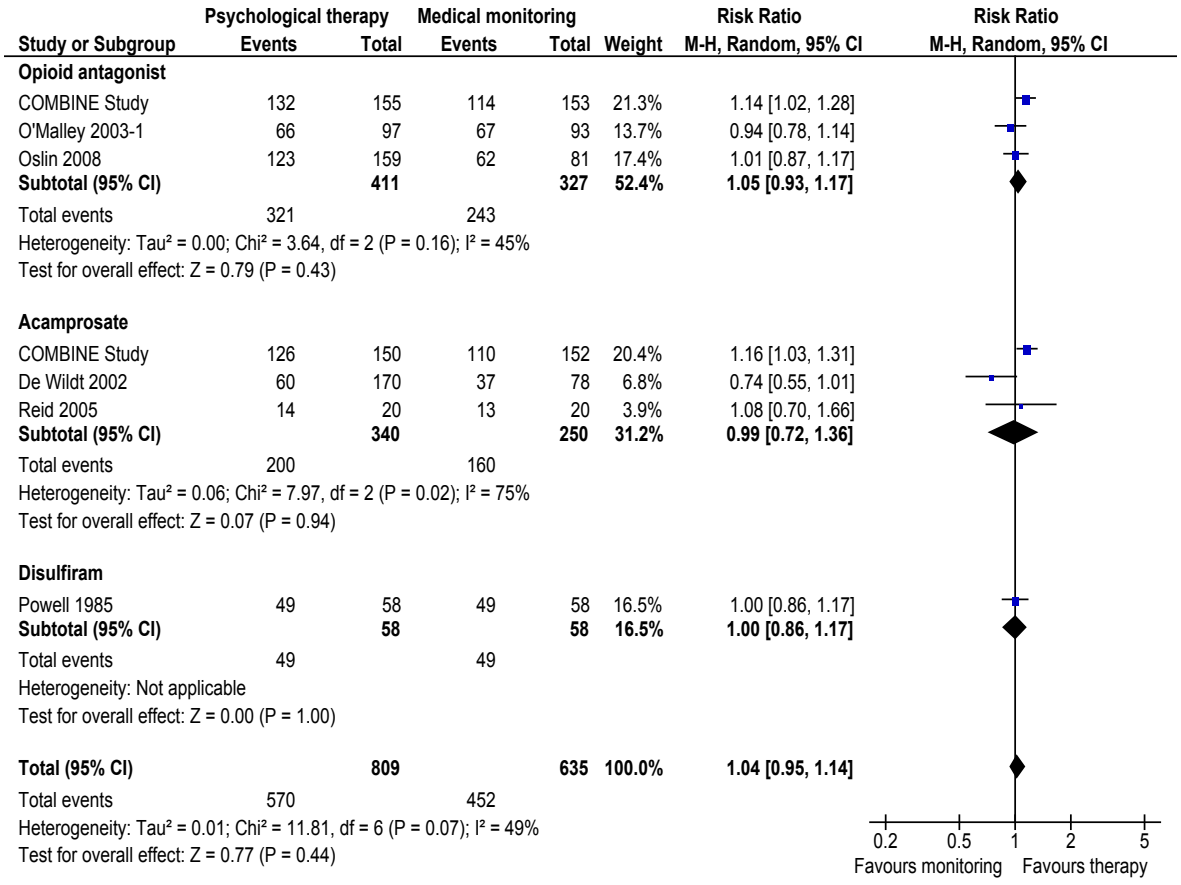
Figure 9.1: Cognitive-behavioural compared with another form of psychological therapy as adjunct to pharmacological treatment, participants completing the study



There is no significant difference between psychological therapy and medical monitoring as an adjunct to any form of pharmacological therapy in terms of the number of participants completing treatment (Figure 9.2: RR 1.04: 95% CI 0.95, 1.14; P=0.44)**. In O'Malley 2003-1 there was no significant difference between psychological therapy and medical monitoring as adjuncts to naltrexone treatment in terms of average time in treatment (mean difference -0.30 weeks, 95% CI -1.17, 0.57; P=0.50) but Reid 2005 reported significantly

longer time in treatment for people receiving psychological therapy, compared with medical monitoring, as an adjunct to acamprosate treatment (mean difference 4.70 weeks, 95% CI 3.83, 5.57; P<0.001).

Figure 9.2: Any psychological therapy compared to medical monitoring, as adjunct to pharmacological treatment, participants completing the study



In Azrin 1982, during the sixth month of follow-up, 24.8% (3 of 14) in the behaviour therapy group, 19.3% (3 of 15) in the assurance group, and none of the traditional medical monitoring group were still taking disulfiram. This supports a conclusion of no significant difference between behavioural therapy and other psychological therapy as adjuncts to disulfiram, and suggests that, at least in the case of disulfiram, therapy may be associated with increased retention in treatment compared to traditional medical monitoring.

Carroll 1998 reported that there were no significant differences in retention by psychotherapy (CBT, Twelve-Step Facilitation or medical management) as adjuncts to disulfiram treatment of dual cocaine and alcohol dependence.

In Gerrein 1973, retention in treatment was greater in the group receiving more frequent clinic contact. In the group visiting the clinic twice weekly (with one tablet of disulfiram administered under supervision at each visit) 85% (11 of 13) remained in treatment for eight weeks or longer, compared to 39% (5 of 13) in the group visiting the clinic once a week and not receiving any doses of disulfiram under supervision.

In Pelc 2005, participants received acamprosate with medical management only, or with medical management plus phone follow-up by a community nurse. Those receiving nurse follow-up were more likely to be retained in treatment (46% compared to 24%, P<0.05).

Schmitz 2009 compared naltrexone or placebo with CBT alone or in combination with contingency management for dual cocaine and alcohol dependence. The addition of contingency management had no effect on retention in treatment (median 30.0 days for naltrexone with CBT and contingency management, and 31.5 days for naltrexone with CBT alone).

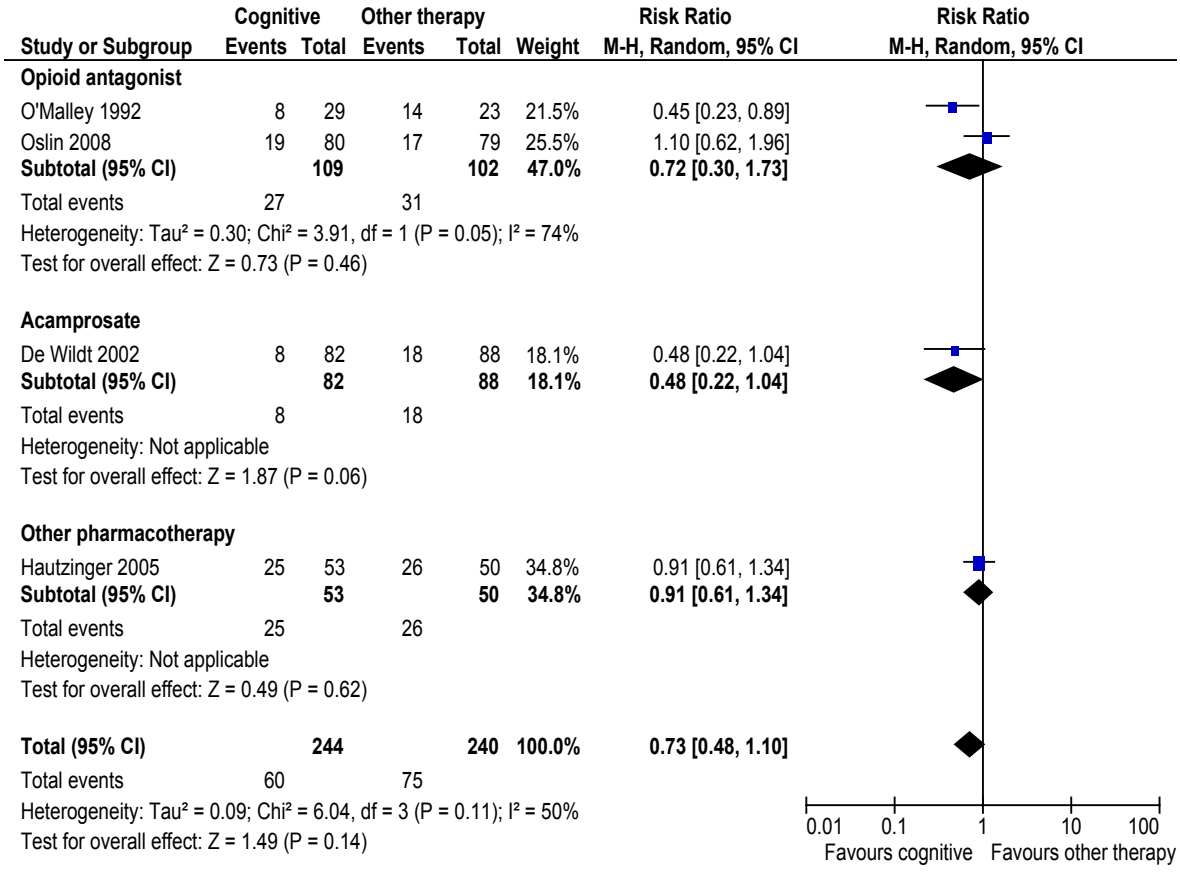
9.2.2 Effect on alcohol consumption

	Abstinence
*	There is no significant difference between CBT and other forms of psychological therapy as adjuncts to pharmacological treatment in terms of continuous abstinence.
*	Abstinence is more likely with psychological therapy compared to medical monitoring as adjuncts to opioid antagonist treatment but it appears this difference does not extend to acamprosate or disulfiram treatment.
	Abstinence appears to be more likely with more frequent follow-up of people receiving disulfiram or acamprosate treatment.

Supporting evidence

Based on two studies, there is no significant difference between cognitive-behavioural therapy and another form of psychological therapy as an adjunct to opioid antagonist treatment in terms of the number of participants continuously abstinent during treatment (Figure 9.3: RR 0.72, 95% CI 0.3, 1.73; P=0.46)*.
De Wildt 2002 found somewhat more people receiving cognitive-behavioural therapy were continuously abstinent during treatment with acamprosate, compared to those receiving another form of psychological therapy, but the difference was not statistically significant (Figure 9.3: RR 0.48, 95% CI 0.22, 1.04; P=0.06).
Hautzinger 2005 reported no significant difference between cognitive-behavioural therapy and another form of psychological therapy as an adjunct to treatment with an SSRI in terms of the number of participants continuously abstinent during treatment (Figure 9.3: RR 0.91, 95% CI 0.61, 1.34; P=0.62).

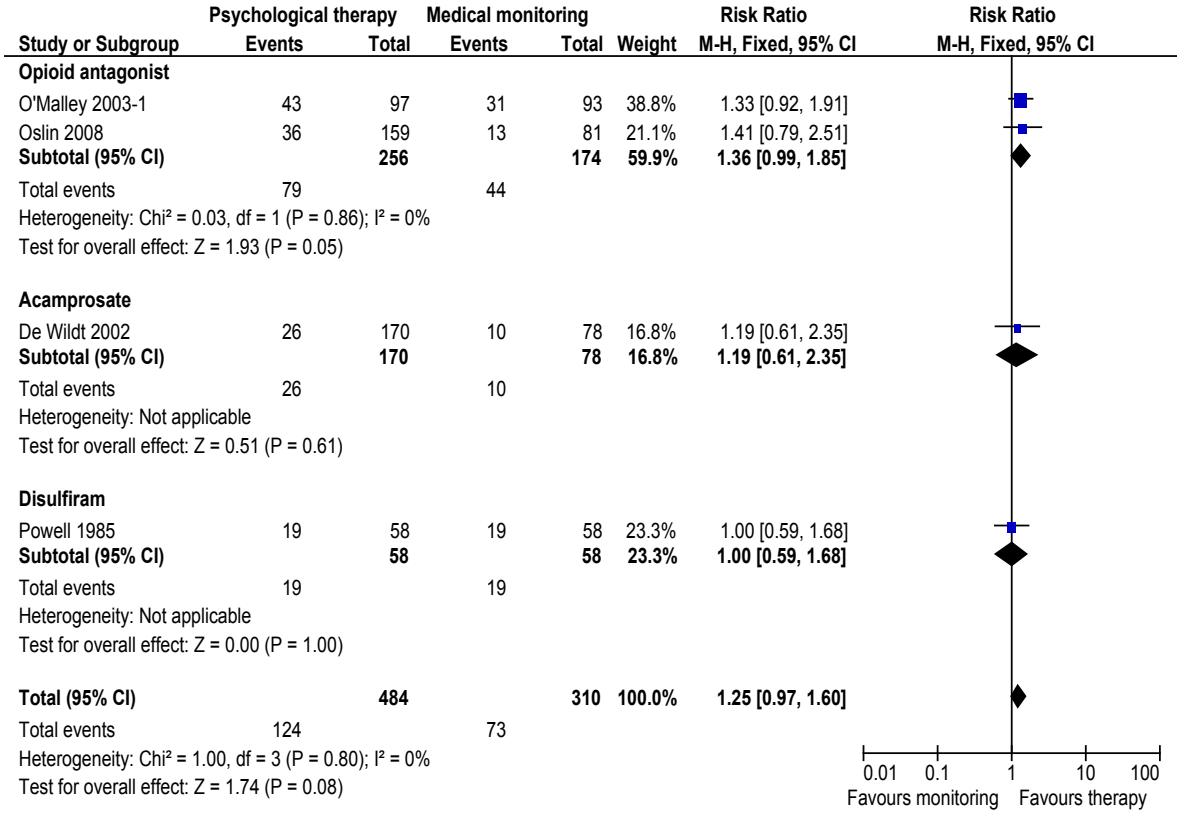
Figure 9.3: Cognitive-behavioural compared with another form of psychological therapy as adjunct to pharmacological treatment, participants continuously abstinent during treatment



Based on two studies, abstinence during treatment is more likely with psychological therapy compared with medical monitoring as an adjunct to opioid antagonist treatment (Figure 9.4: RR 1.36, 95% CI 0.99, 1.85; P=0.05)*. There is no significant difference in the likelihood of abstinence during treatment with psychological

therapy compared with medical monitoring as an adjunct to acamprosate (Figure 9.4: RR 1.19, 95% CI 0.61, 2.35; P=0.61) or disulfiram treatment (Figure 9.4: RR 1.00, 95% CI 0.59, 1.68; P=1).

Figure 9.4: Any psychological therapy compared to medical monitoring, as adjunct to pharmacological treatment, participants continuously abstinent during treatment



In Gerrein 1973, in the group visiting the clinic twice weekly and who were administered disulfiram under supervision at each visit, 40% (5 of 13) were abstinent for eight weeks, compared to 7% (1 of 13) of the group visiting the clinic once a week and with no supervised doses of disulfiram.

In Pelc 2005, those receiving nurse follow-up as an adjunct to acamprosate and medical monitoring were more likely to be continuously abstinent during treatment (32% compared to 16%, P<0.05).

Schmitz 2009 compared naltrexone or placebo with CBT alone or in combination with contingency management for dual cocaine and alcohol dependence. The probability of any drinking decreased during treatment with no significant group differences.

	Relapse to heavy drinking during treatment
*	There is no significant difference between CBT and other psychological therapies or between any psychological therapy and medical monitoring in terms of relapse to heavy drinking during treatment.

Supporting evidence

There is no significant difference in the likelihood of relapse to heavy drinking for cognitive-behavioural therapy compared to another form of psychological therapy as an adjunct to any form of pharmacological treatment (Figure 9.5: RR 1.04, 95% CI 0.87, 1.25; P=0.64)*.

There is no significant difference in the likelihood of relapse to heavy drinking for any form of psychological therapy compared to medical monitoring as an adjunct to opioid antagonist or acamprosate treatment (Figure 9.6: RR 1.05, 95% CI 0.94, 1.17; P=0.36)*.

Figure 9.5: Cognitive-behavioural compared with another form of psychological therapy as adjunct to pharmacological treatment, participants relapsing to heavy drinking during treatment

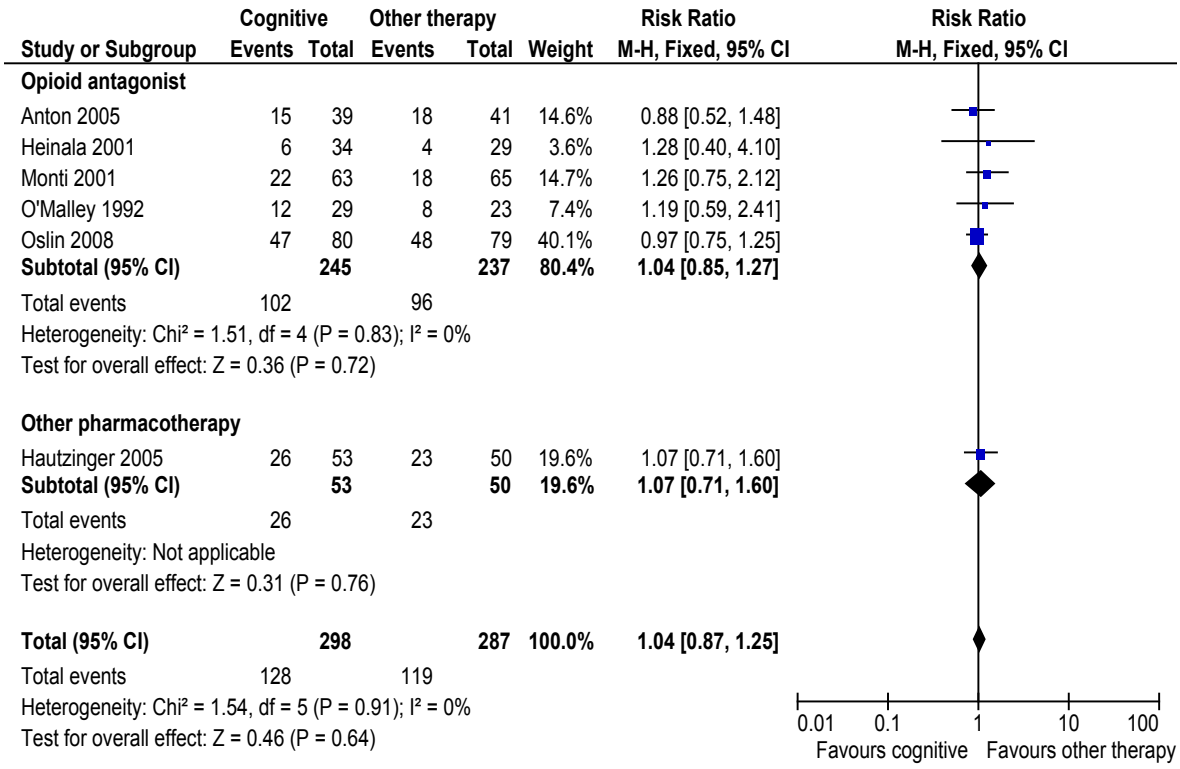
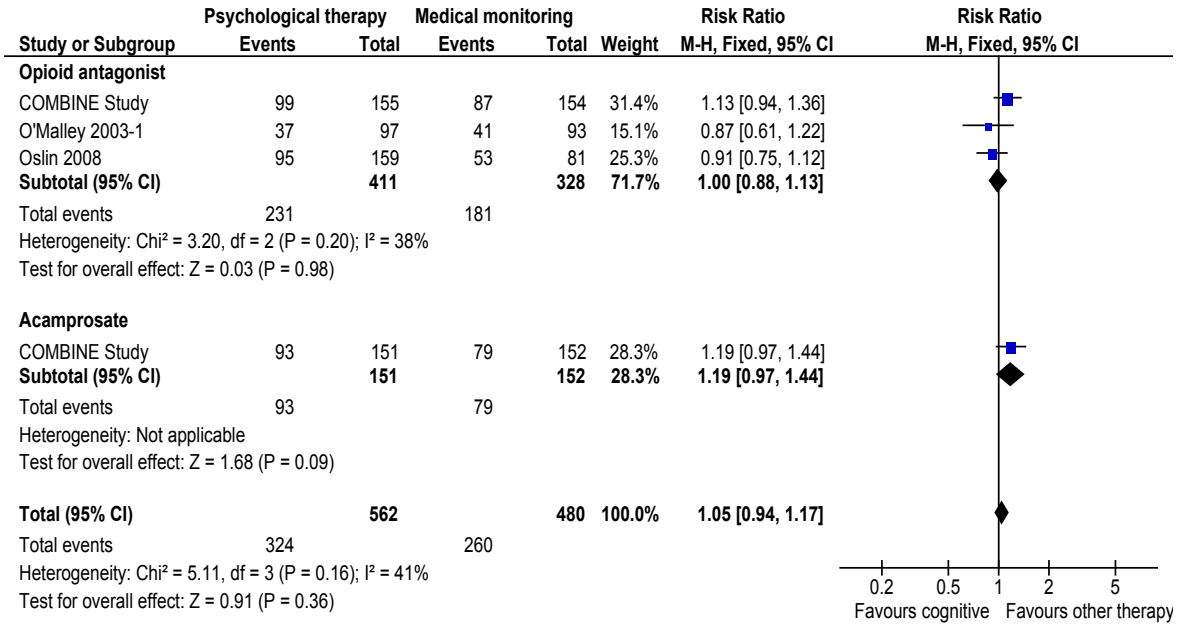


Figure 9.6: Any psychological therapy compared to medical monitoring, as adjunct to pharmacological treatment, participants relapsing to heavy drinking during treatment



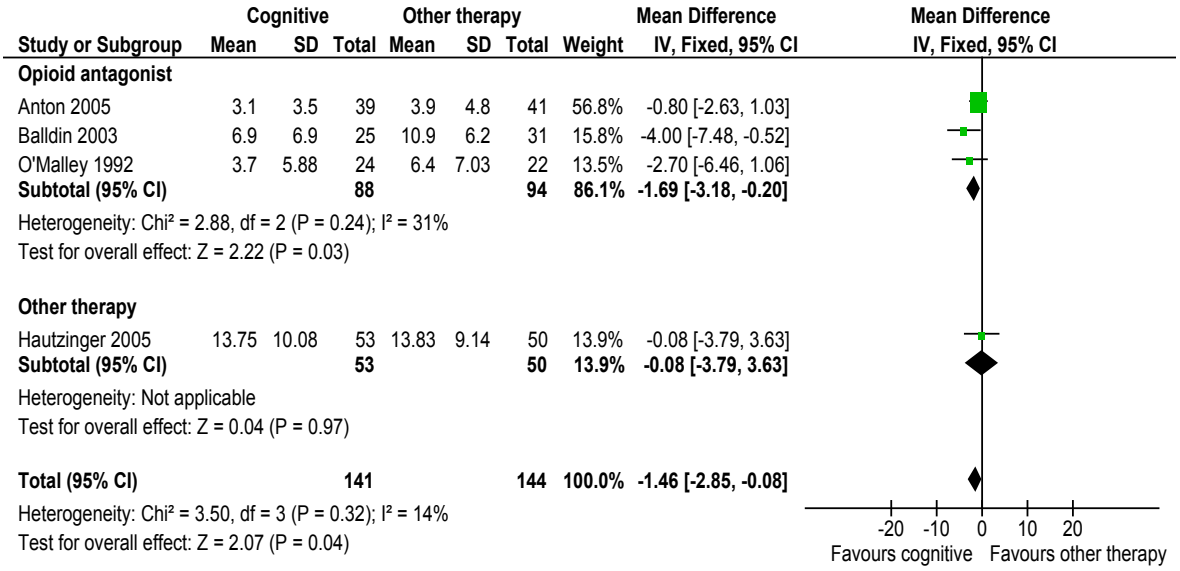
	Amount of alcohol consumed during treatment
*	CBT is associated with somewhat less alcohol consumption during treatment compared to other types of psychological therapy as adjuncts to opioid antagonist, and possibly also disulfiram treatment.
	Psychological therapy is probably more effective than medical monitoring in terms of alcohol consumption during treatment with disulfiram, but probably not naltrexone.

Supporting evidence

Based on three studies, cognitive behavioural therapy is associated with significantly less average drinks per drinking day compared to other types of psychological therapy as adjuncts to opioid antagonist treatment (Figure 9.7: mean difference -1.69 drinks, 95% CI -3.18, -0.20; P=0.03)*. Anton 2005 reported that CDT levels decreased over time and CBT-treated participants had lower levels than MET-treatment at weeks 6 and 12 providing objective evidence supporting a conclusion that CBT is associated with lower alcohol consumption.

One study (Hautzinger 2005) found no significant difference between CBT and nondirective group counselling as adjuncts to nefazodone in average drinks per drinking day (Figure 9.7: mean difference -0.08, 95% CI -3.79, 3.63; P=0.97).

Figure 9.7: Cognitive-behavioural compared with another form of psychological therapy as adjunct to pharmacological treatment, average drinks per drinking day

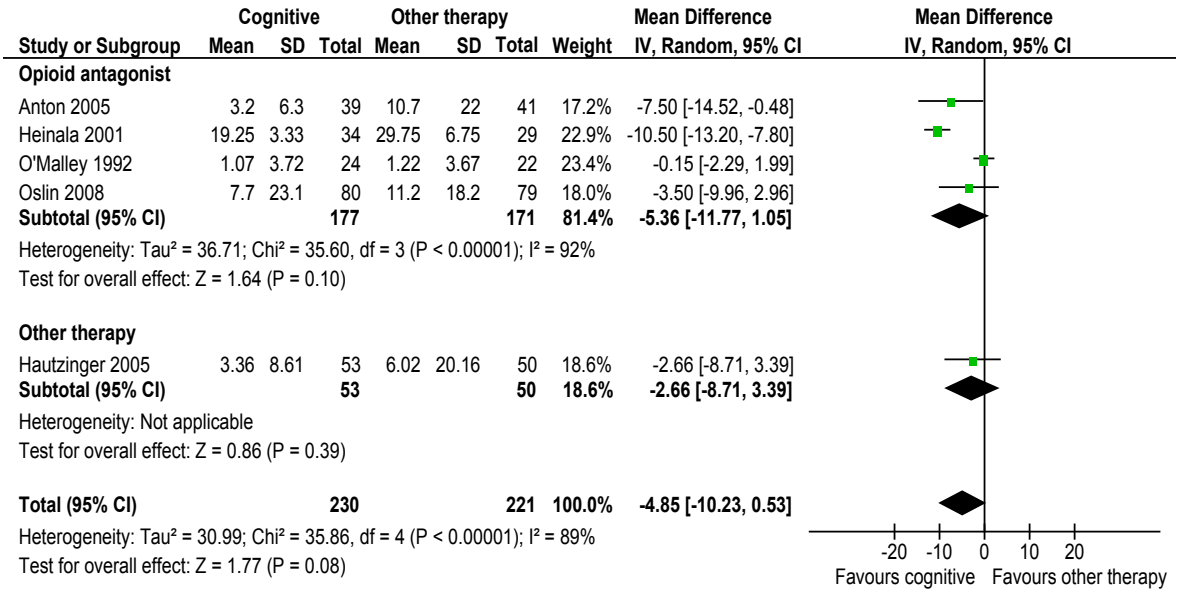


Based on five studies, CBT is associated with somewhat less average drinks per week compared with other types of psychological therapy, but the difference is not statistically significant (Figure 9.8: mean difference -5.36, 95% CI -11.77, 1.05; P=0.10)*.

Monti 2001 compared cue exposure with coping skills plus communication skills (considered CBT) and education plus relaxation as adjuncts to naltrexone or placebo. They reported there were no significant interactions of medication with behavioural treatments.

In O'Malley 2003-1 there was no significant difference between psychological therapy and medical monitoring as adjuncts to naltrexone treatment in average drinks per drinking day (mean difference 0.2, 95% CI -1.28, 1.68; P=0.79). In Oslin 2008 there was no significant difference between psychological therapy and medical monitoring as adjuncts to naltrexone treatment in average drinks per week (mean difference -0.36, 95% CI -4.81, 4.09; P=0.87).

Figure 9.8: Cognitive-behavioural compared with another form of psychological therapy as adjunct to pharmacological treatment, average drinks per week



Azrin 1982 compared assurance training plus behavioural treatment and assurance training only with traditional treatment (effectively basic medical monitoring) as adjuncts to disulfiram. The following data on alcohol consumption were reported but not able to be incorporated into meta-analyses:

Outcome	Behaviour therapy	Assurance	Medical monitoring
Drinking days/30 days	0.9	7.9	16.4
Ounces alcohol/episode	0.7	1.7	4.1
Days with intoxication/30 days	0.4	5	10

These data support a finding that behaviour therapy is more effective than assurance alone and both are more effective than medical monitoring in reducing alcohol consumption during treatment with disulfiram.

	Periods of abstinence or heavy drinking during treatment
*	CBT is associated with longer cumulative abstinence and less heavy drinking compared to other forms of psychological therapy as adjuncts to naltrexone but possibly not other pharmacological treatments. The difference may become more marked with time in treatment.
*	There is no significant difference between any psychological therapy and medical monitoring in terms of periods of abstinence or heavy drinking during pharmacological treatment.

Supporting evidence

The cumulative abstinence duration was significantly greater for participants receiving cognitive-behavioural therapy, in comparison with another form of psychological therapy, as an adjunct to treatment with an opioid antagonist (Figure 9.9: mean difference 5.47 % treatment days, 95% CI 1.84, 9.09; P=0.003)*. However, single studies reported no significant difference when the pharmacological treatment was acamprosate (Figure 9.9: mean difference -5.60 % treatment days, 95% CI -23.77, 12.57; P=0.55) or an SSRI (Figure 9.9: mean difference 3.99 % treatment days, 95% CI -8.22, 16.20; P=0.52).

Cognitive-behavioural therapy, compared to another form of psychological therapy, as an adjunct to opioid antagonist treatment was associated with significantly less treatment days with heavy drinking (Figure 9.10: mean difference -4.11 % treatment days, 95% CI -6.90, -1.32; P=0.004)**. No data were reported for other types of pharmacological treatment.

Oslin 2008 reported that CBT was associated with lower rates of heavy drinking and higher rates of abstinence compared to BRENDA (motivational enhancement counselling) or medical monitoring as adjuncts to naltrexone, but the effect was only evident over time, not when collapsed over the entire 24 weeks of the study. Pettinati 2008A found no significant differences in the presence of any drinking or the presence of heavy drinking across therapy groups (CBT or BRENDA) in conjunction with naltrexone or placebo.

Figure 9.9: Cognitive-behavioural compared with another form of psychological therapy as adjunct to pharmacological treatment, % treatment days abstinent (cumulative abstinence duration)

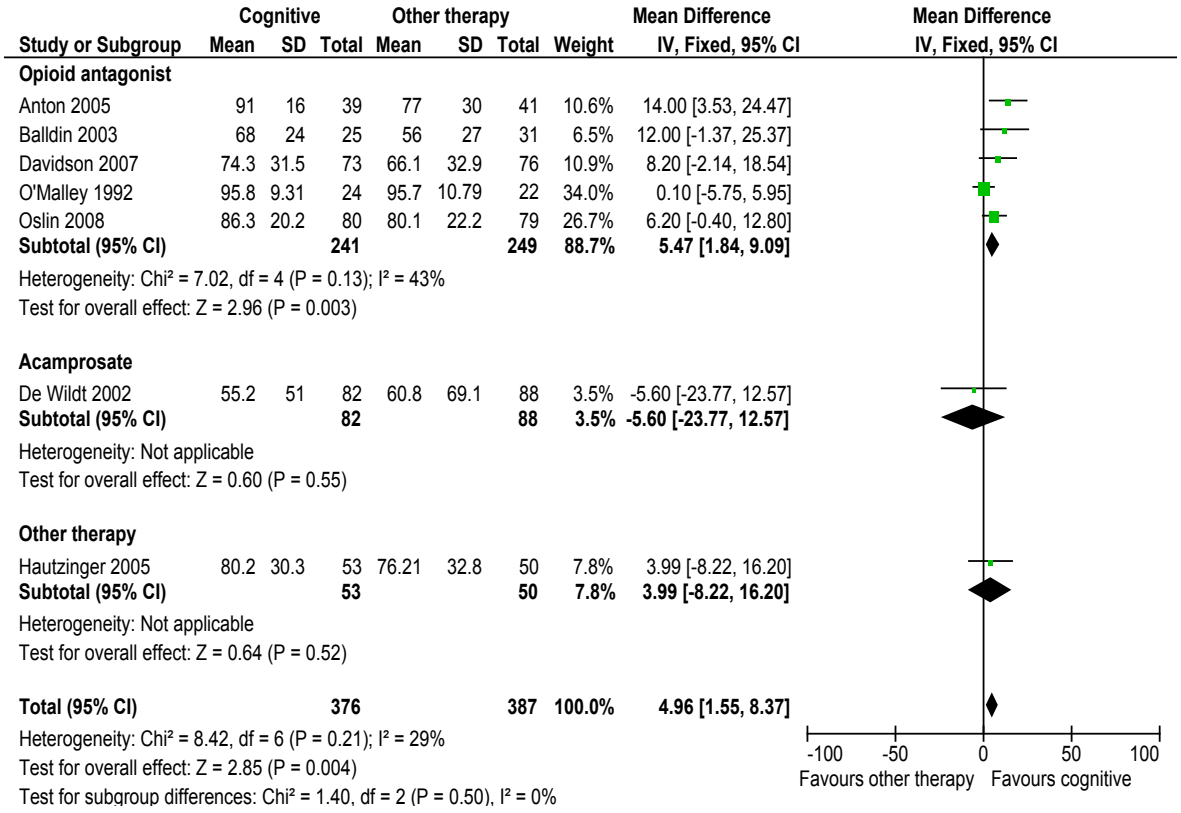
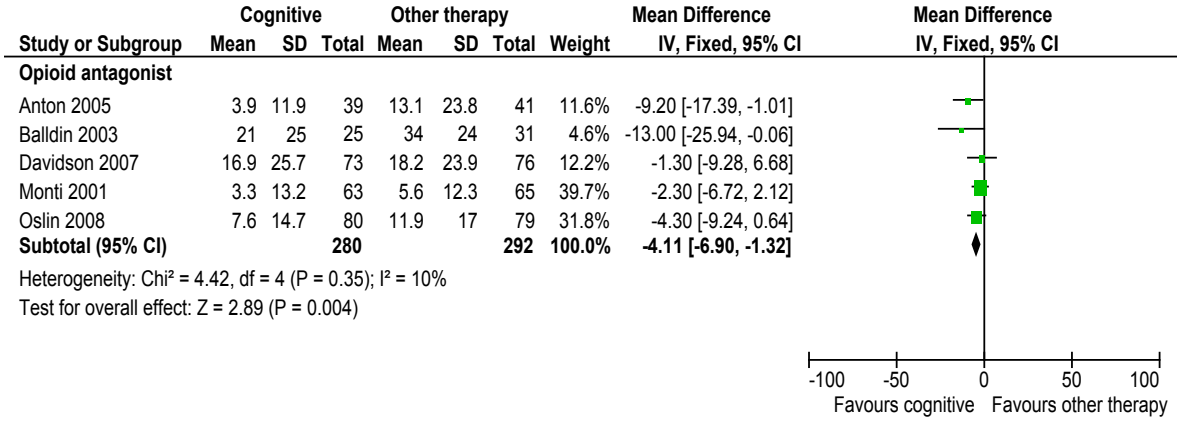


Figure 9.10: Cognitive-behavioural compared with another form of psychological therapy as adjunct to pharmacological treatment, % treatment days with heavy drinking



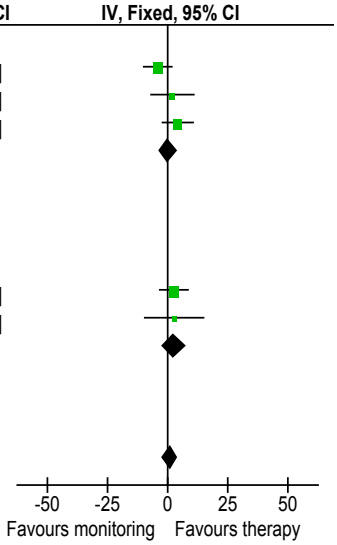
There is no significant difference between any psychological therapy and medical monitoring as adjuncts to opioid antagonist or acamprosate treatment, in terms of cumulative abstinence duration (Figure 9.11: mean difference 1.00 % treatment days, 95% CI -2.12, 4.11; P=0.53)*. In one study (Oslin 2008) there was also no significant difference between any psychological therapy and medical monitoring in percent treatment days with heavy drinking.

Hammarberg 2004 compared minimal and extended psychosocial support as adjuncts to acamprosate treatment. Participants on average reported a decline in days with heavy drinking and in cumulative number of drinking days with no significant differences between groups. There were also no significant differences in biomarkers (AST, GGT, CDT) of alcohol consumption.

In Schmitz 2009 the probability of heavy drinking decreased with time in the group receiving CBT only as an adjunct to naltrexone, but remained stable with CBT plus contingency management. Overall the group receiving naltrexone with CBT reported drinking on 40% of treatment days, compared with 33% for those receiving naltrexone with CBT and contingency management.

Figure 9.11: Any psychological therapy compared to medical monitoring, as adjunct to pharmacological treatment, % treatment days abstinent (cumulative abstinence duration)

Study or Subgroup	Psychological therapy Mean	SD	Total	Medical monitoring Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Opioid antagonist								
COMBINE Study	75.9	26.02	155	80	26.06	154	28.7%	-4.10 [-9.91, 1.71]
O'Malley 2003-1	79.9	31.4	97	77.9	30.9	93	12.4%	2.00 [-6.86, 10.86]
Oslin 2008	83.22	21.22	159	79	24.9	81	24.1%	4.22 [-2.13, 10.57]
Subtotal (95% CI)			**411**			**328**	**65.2%**	**0.13 [-3.73, 3.99]**
Heterogeneity: Chi² = 3.80, df = 2 (P = 0.15); I² = 47%								
Test for overall effect: Z = 0.07 (P = 0.95)								
Acamprosate								
COMBINE Study	78.2	25.93	151	75.6	26.01	152	28.3%	2.60 [-3.25, 8.45]
De Wildt 2002	58.1	61.05	170	55.4	36.3	78	6.5%	2.70 [-9.51, 14.91]
Subtotal (95% CI)			**321**			**230**	**34.8%**	**2.62 [-2.66, 7.89]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%								
Test for overall effect: Z = 0.97 (P = 0.33)								
Total (95% CI)			**732**			**558**	**100.0%**	**1.00 [-2.12, 4.11]**
Heterogeneity: Chi² = 4.36, df = 4 (P = 0.36); I² = 8%								
Test for overall effect: Z = 0.63 (P = 0.53)								
Test for subgroup differences: Chi² = 0.56, df = 1 (P = 0.46), I² = 0%								



	Time to first drink and time to relapse to heavy drinking
	It is unclear whether CBT affects the time to first drink, but it appears to delay the time to relapse to heavy drinking compared to other psychological therapies as adjuncts to opioid antagonist treatment but not other pharmacological therapies.
	Based on limited data it appears that any psychological therapy is more effective than medical monitoring in terms of the time to first drink and time to relapse.

Supporting evidence

In Balldin 2003, cognitive behavioural therapy, compared to supportive therapy, as an adjunct to opioid antagonist treatment was associated with significantly longer time to relapse to heavy drinking (mean difference 37.0 days, 95% CI 31.69, 42.31; P<0.001). In contrast, De Wildt 2002 reported significantly less time to relapse to heavy drinking with cognitive behavioural therapy, compared to motivational interviewing, as an adjunct to acamprosate treatment (mean difference -10.10 days, 95% CI -12.13, -8.07; P<0.001). Hautzinger 2005 reported no significant difference for cognitive behavioural therapy compared to nondirective group therapy as an adjunct to treatment with an SSRI (mean difference -2.70 days, 95% CI -12.94, 7.54; P=0.61).

In Davidson 2007, median time to first drink and time to first heavy drinking day were significantly longer for participants who received broad spectrum therapy (based on CBT) and extended naltrexone than for other treatment groups.

In Anton 2005, naltrexone delayed the time to first relapse compared to placebo, independent of therapy type (CBT or motivational enhancement therapy). However, the time to successive relapses was significantly prolonged only in those receiving both naltrexone and CBT.

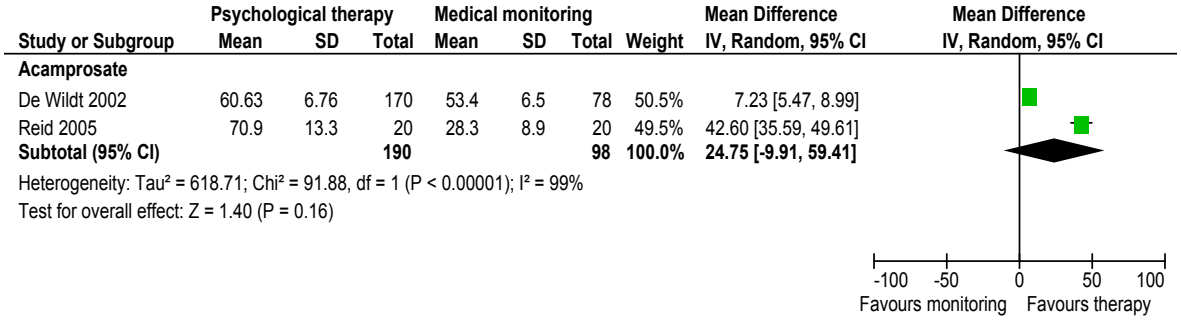
In Reid 2005, compliance therapy, compared to usual care (medical monitoring), as an adjunct to acamprosate treatment was associated with significantly longer time to first drink (mean difference 32 days, 95% CI 24.33, 39.67; P<0.001). Based on two studies, any psychological therapy, compared to medical monitoring as an adjunct to opioid antagonist treatment, is associated with somewhat longer (but not statistically significant) time to relapse to heavy drinking (Figure 9.12: mean difference 24.75, 95% CI -9.91, 59.41; P=0.16)*.

In Carroll 1998, the two active psychotherapies (CBT and Twelve-Step Facilitation) were associated with significantly longer periods of abstinence from cocaine and simultaneous abstinence from both cocaine and alcohol, compared with medical monitoring.

In Hammarberg 2004, there was no significant difference in days to first drink for acamprosate plus minimal or extended psychological support.

In Pelc 2005, those receiving nurse follow-up as an adjunct to acamprosate and medical monitoring remained abstinent for longer (time to first drink 81 days compared with 67 days, P<0.05).

Figure 9.12: Any psychological therapy compared to medical monitoring, as adjunct to pharmacological treatment, average days to relapse to heavy drinking



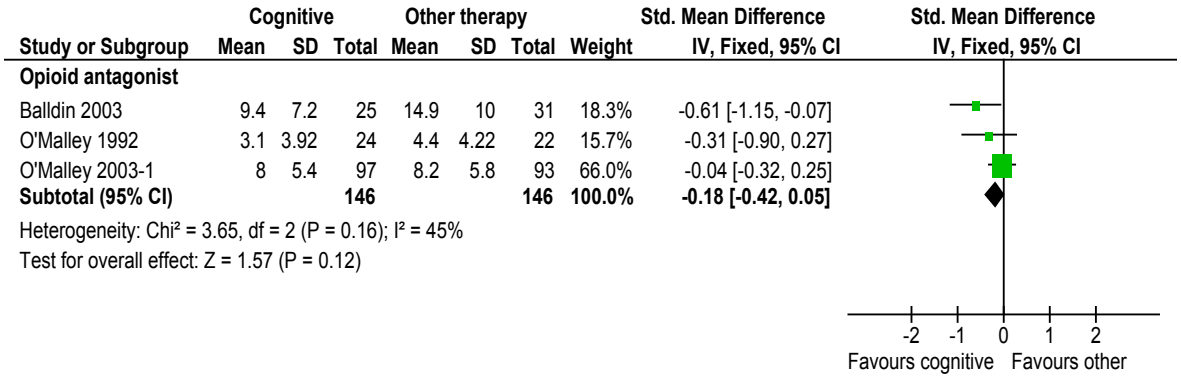
	Craving
*	Psychological therapy has no significant effect on craving.

Supporting evidence

Based on three studies, there is no significant difference in average craving scores for people receiving cognitive-behavioural therapy or another form of psychological therapy as an adjunct to opioid antagonist treatment (Figure 9.13: SMD -0.18, 95% CI -0.42, 0.05; P=0.12)*. Anton 2005 reported no effect of therapy group (CBT or motivational enhancement therapy) on craving score during treatment with naltrexone or placebo.

One study (O'Malley 2003-1) found no significant difference in average craving scores for people receiving any psychological therapy compared to medical monitoring as adjuncts to naltrexone treatment (SMD -0.04, 95% CI -0.32, 0.25; P=0.81).

Figure 9.13: Cognitive-behavioural compared with another form of psychological therapy as adjunct to pharmacological treatment, average craving scores



9.2.3 Factors affecting treatment response

	Psychological therapies and supportive approaches may enhance treatment outcome by promoting compliance with pharmacotherapies.
	Greater participation in psychological therapies is likely to be associated with improved outcomes.
	People with less severe alcohol dependence may be more likely to benefit from naltrexone with less intensive adjunct therapies.
	People with lower levels of verbal learning may have poorer outcomes with relapse prevention therapy compared to supportive therapy.

Supporting evidence

(1) Compliance

Beneficial effects of some therapies may be mediated by compliance with medication regime. For example, Azrin 1982 found reduced alcohol consumption with behaviour therapy and assurance training compared with traditional medical monitoring. Clients receiving traditional treatment took disulfiram about two-thirds of the time during the first month, decreasing rapidly thereafter with no disulfiram taken after three months. The assurance and behaviour therapy groups were taking about 90% of disulfiram doses initially and showed less of a decrease in time.

In Anton 2005, the most compliant participants showed a significant medication by therapy interaction.[65] All of the positive effects of naltrexone occurred in the CBT group, with this group having more abstinent days, less heavy drinking days, and less total drinks than other groups. The effect size of this interaction increased from about 0.2 in the intent-to-treat analysis to about 0.4 to 0.5 in the compliant group analysis.

Motivation and support may also have been factors influencing treatment response in Azrin 1982 as an interaction was seen between marital status and treatment group. For married clients the assurance procedure was sufficient to produce nearly complete abstinence; the addition of behaviour therapy was unnecessary. For single clients, however, the assurance procedure had little effect whereas the addition of the behaviour therapy program produced nearly complete abstinence.

Reid 2005 looked at the effect of compliance therapy (based on CBT principles) added to acamprosate and medical monitoring. Intention-to-treat analyses showed little difference between the two groups in the drinking outcome measures, but per protocol analyses revealed that participation in three or more sessions of compliance therapy significantly increased adherence to acamprosate and improved overall treatment outcomes.

(2) Severity of dependence

In a secondary analysis of data from the COMBINE Study,[22] among those receiving medical management without CBI, Type A alcoholics had better drinking outcomes with naltrexone than placebo, whereas medication condition did not influence outcomes significantly in Type B alcoholics. Age of onset was not significantly related to outcome. For those receiving CBI, no significant effects were found for either typology. Relative to Type A alcoholics, Type B alcoholics are characterised by greater severity, earlier onset, stronger family history, more childhood risk factors (eg. conduct disorder), and greater frequency of comorbid psychiatric disorders. The findings of this secondary analysis suggest that less severe alcoholics are more likely to benefit from naltrexone in the context of low-intensity psychosocial treatment.

(3) Cognitive function

Jaffe *et al*.[83] concluded from analysis of O'Malley 1992, that patients experiencing the higher levels of craving and poorer cognitive functioning may derive the greatest benefit from naltrexone versus placebo. For psychotherapy, lower levels of verbal learning were associated with poorer drinking outcomes for relapse prevention therapy but not for supportive therapy. Conversely, higher levels of verbal learning were associated with better outcomes for relapse prevention therapy but not for supportive therapy.

Medications supported by the evidence

The data presented in this review indicate that naltrexone, acamprosate and disulfiram are moderately effective for relapse prevention treatment.

Naltrexone has a significant effect on the maintenance of abstinence as well as the prevention of heavy drinking. Acamprosate is more effective at promoting total abstinence from alcohol, but does not influence alcohol consumption after the first drink. Acamprosate is more effective in preventing a lapse, whereas naltrexone is better at preventing a lapse from becoming a relapse.[367]

The evidence for disulfiram is limited, but indicates that disulfiram is more effective at preventing relapse to heavy drinking. It appears to have little effect on total abstinence, but significantly prolongs the time to first drink and time for relapse to heavy drinking.

These findings are consistent with the mechanisms of action of these medications: acamprosate diminishes withdrawal symptoms, while opioid antagonists block positive reinforcement and modify the sense of intoxication from acamprosate, and disulfiram causes an aversive reaction to alcohol.

Treatment with naltrexone, acamprosate or disulfiram is associated with adverse effects. Naltrexone increases the risk of nausea or vomiting, acamprosate increases the risk of diarrhoea, and disulfiram is associated with nausea or vomiting and neuropsychiatric symptoms. These adverse effects are associated with increased risk of premature withdrawal from treatment, but not to a clinically significant extent.

Other systematic reviews have come to similar conclusions. Carmen *et al*.[161] found that acamprosate was associated with a significant improvement in abstinence rates and days of cumulative abstinence, while short-term administration of naltrexone significantly reduces the relapse rate but not the abstinence rate. They considered acamprosate to have a good safety pattern; naltrexone was noted to have more numerous side effects but was nonetheless tolerated acceptably without a lower adherence to treatment. Kranzler and Van Kirk[368] found that there is no statistical difference in the efficacy of acamprosate and naltrexone. Mason[36] also concluded that acamprosate and naltrexone are both useful in the treatment of alcohol dependence. As has been noted by other reviews,[369] the use of disulfiram is widespread, but is less clearly supported by research evidence.

Factors affecting treatment effectiveness

(1) Adherence to medication

Adherence to medication (compliance) is a key to the effectiveness of all the pharmacotherapies and appears to be particularly important with disulfiram.

A retrospective study of a database of organisations providing health care plans to five million employees and their dependents in the USA found that only 14.2% of those with alcohol-related claims who were prescribed naltrexone persisted with treatment, meaning they filled prescriptions for at least 80% of a 6-month period. Carmen *et al*.[161] noted that overall compliance was relatively low with both acamprosate and naltrexone.

Data on depot preparations of naltrexone are still limited such that it is unclear whether these preparations are achieving the aim of increasing the period of exposure to medications and consequently improving outcomes relative to oral naltrexone.

Studies of disulfiram implants did not support increased effectiveness from this route of administration, with complications around the point of implant insertion comprising a significant source of adverse effects.

All pharmacotherapies for relapse prevention treatment of alcohol dependence need to be delivered with adjunct therapies and support to maintain commitment to treatment and promote adherence to medication.

Diehl *et al*.[370] undertook a retrospective analysis of outcomes of disulfiram or acamprosate treatment within a naturalistic outpatient treatment setting. There were differences at baseline – those receiving disulfiram tended to have a longer duration of alcohol dependence, higher amounts of daily alcohol consumption and more previous detoxification treatments than those receiving acamprosate. This reflects the fact that disulfiram is usually not a first choice treatment. A more significant difference was that administration of disulfiram was supervised with patients visiting the clinic three times a week, while acamprosate was unsupervised and clinic visits were weekly. The authors note that the close monitoring and high frequency contact may have enhanced

outcomes in the disulfiram group. In this context, time elapsed to first alcohol consumption, attendance to outpatient treatment and cumulative abstinence were longer in the disulfiram group.

Colagiuri *et al*.[371], in a secondary analysis of Morley 2006, found expectation to be a factor influencing treatment outcome. Participants who believed they had been taking active medication consumed fewer alcoholic drinks and reported less alcohol dependence and craving irrespective of actual treatment (acamprosate, naltrexone or placebo).

Targeted use of naltrexone (ie. the use of naltrexone when there is a perceived risk of drinking, rather than on a daily basis) may increase compliance by linking administration of medication to awareness of a high risk of alcohol consumption occurring.

(2) Abstinence prior to medication commencement

A period of abstinence prior to treatment with naltrexone or acamprosate is predictive of a better response to treatment. In the case of naltrexone, this probably largely reflects psychological aspects of preparedness for treatment, motivation, and support, but in the case of acamprosate effectiveness appears to be reduced if acamprosate is commenced without a prior period of abstinence (4 days or more).

(3) Adjunct psychosocial support and therapy

The findings of this review suggest that:

> CBT and other psychological therapies are generally equally effective as adjuncts to pharmacological treatment;

> Psychological therapy appears to be more effective than basic medical monitoring as adjuncts to disulfiram treatment;

> More frequent follow-up contact is associated with better outcomes from acamprosate or disulfiram treatment;

> Psychological therapy has no significant effect on craving, but assists with strategies to manage craving;

> Greater participation in psychological therapies and supportive approaches is likely to be associated with improved outcomes;

> People with less severe alcohol dependence may be more likely to benefit from naltrexone with less intensive adjunct therapies; and

> People with lower levels of verbal learning may have poorer outcomes with relapse prevention therapy compared to supportive therapy.

Factors influencing treatment selection

(1) Treatment goal

Acamprosate appears to be most effective if used to support a goal of total abstinence. Naltrexone may be effective in supporting reduced alcohol consumption in controlled drinking programs as well as in treatment with a goal of total abstinence, but data on this application of naltrexone are limited. It should be noted that naltrexone is not currently approved for this purpose in Australia.

(2) Typology of alcohol dependence

The interaction of genetics, family history and typology of alcohol dependence is an area of active research. There are indications that people with a strong family history of alcoholism (at least 20% of relatives with problem drinking) is predictive of a good response to naltrexone treatment. Early age of onset of alcoholism (which is typically associated with a family history of alcohol problems) also appears to predict a good response to naltrexone.

In contrast, it appears that family history of alcoholism does not predict response to acamprosate. Rather, acamprosate may be more effective in alcoholism that is characterised by the rapid development of strong withdrawal symptoms (Lesch Type I)

Some consideration has also been given by researchers to different types of craving as indicators of underlying differences in the mechanism of alcohol dependence. Thus patients characterised with indicators of postive reinforcement or reward drinking (mediated by opioidergic pathways) will benefit most from naltrexone, whereas patients characterised with indicators of negative reinforcement or relief drinking will benefit most from acamprosate.[372]

Antidepressants may have a beneficial effect on alcohol consumption through the alleviation of depression in people with alcohol dependence and concomitant depression, but it appears that such benefits are most likely to be seen in low risk/severity, late onset alcoholism.

(3) Gender

There may be gender differences in the response to naltrexone and antidepressants but more information is needed to confirm the significance of any difference and the implications for treatment decisions, particularly as men have constituted the majority of participants in treatment trials to date. Psychological and social factors are also relevant. Women are often passive in seeking help and are less likely to enter treatment groups due to the associated social stigma. Women are also less likely to be encouraged by a partner to seek assistance. Middle-aged alcoholic women are more likely to be depressed, use psychoactive drugs and express more family-related problems than alcoholic men.[14] These differences point to the need for adjustment of psychosocial therapies provided as adjuncts to whatever pharmacological treatment is considered appropriate.

(4) Cost

There are differences in the cost of medications. Disulfiram is cheaper than either naltrexone or acamprosate. The need for psychological therapies and support may also add expense for patients, many of whom are likely to have financial constraints and limited social supports.

Medications not supported by evidence

The evidence suggests that the following approaches are not effective in relapse prevention treatment of alcohol dependence:

> Antidepressants (particularly in the absence of concomitant depression);
> Antipsychotics;
> Lithium;
> Buspirone;
> Rimonabant (cannabinoid CB1 receptor antagonist).

The combination of naltrexone with acamprosate, antidepressants or disulfiram do not appear to add additional benefits beyond what can be achieved with naltrexone alone.

While the use of antidepressants or lithium for patients with primary alcohol dependence is not supported by the data, these medications may still have a positive effect in patients with co-existing psychiatric disorders. Antidepressants do have value for the management of depression associated with alcohol dependence, particularly depression that remains present after cessation of alcohol use.[373] Buspirone also may have value in the treatment of people with concomitant anxiety disorders and alcohol dependence.

Medications for which evidence is currently insufficient

The use of anticonvulsants for relapse prevention treatment of alcohol dependence is an area of development. Topiramate has promise if adverse effects can be controlled, and initial results with gabapentin have also been good.

Studies of acamprosate in which disulfiram was also offered suggest that disulfiram may have value as an adjunct medication. However, further data are needed to confirm this.

Ondansetron may have promise, particularly in combination with naltrexone, but more evidence is needed.

GHB may have some efficacy, including in combination with naltrexone, but the need for it to be administered in multiple daily doses and the potential for abuse would appear to limit its application in the relapse prevention treatment of alcohol dependence. In a systematic review of GHB for treatment of alcohol withdrawal and prevention of relapse Leone *et al*.[374] concluded that GHB is as effective as naltrexone and disulfiram in maintaining abstinence in previously detoxified alcoholics. However, they also noted that potential abuse must be considered and that GHB must be administered only in the context of medical surveillance. Since abuse and toxicity are more frequent in polydrug abusers or previous abusers, they recommended avoiding GHB for these people.

There is insufficient information to determine the effectiveness of baclofen or alpha-adrenergic agonists.

Comorbid mental health disorders

The misuse of alcohol and other drugs is more common among people with mental illness compared with the general population, and mental health disorders are more common in people who abuse alcohol and other drugs. It appears that genetic as well as environmental factors underlie the link between alcohol use disorders and psychiatric disorders.[373] The Australian National Survey of Mental Health and Well Being found that respondents with an alcohol use disorder (abuse or dependence), compared to those without an alcohol use disorder, were four times more likely to have an affective disorder and three times more likely to have an anxiety disorder.[375] Drugs of abuse may have direct impact on mental disorders, or may impact on the effects of medication for the treatment of mental disorders. Substance misuse can precipitate psychotic illness in those biologically predisposed and it is also associated with earlier onset of illness. It may modify the clinical presentation of mental illness, exacerbate existing psychotic symptoms and interfere with treatment compliance.[376;377] Mentally ill patients who are substance misusers (compared to non-users) have higher readmission rates and increased use of inpatient services. Substance use and dependence in the context of severe psychiatric disorder, results in poorer social functioning, greater psychiatric service utilisation and overall poorer prognosis.[375;378-380] Relapses in people with comorbid alcohol and mental disorders have significantly different precipitants – negative affect, social isolation and intrapersonal contexts are important in this population.[373] This complex interaction between mental health disorders and substance abuse, including alcohol abuse, make it important to consider the effectiveness of relapse prevention treatment of alcohol dependence in the presence of concomitant mental health disorders.

Single studies have found that naltrexone is well tolerated by people with schizophrenia or schizoaffective disorder, or bipolar disorder. Disulfiram has been used with a wide range of comorbid mental conditions (see section 3.3.3) with no indications that disulfiram has any negative impact on comorbid mental health. There is no evidence on the effectiveness of acamprosate.

People with co-occurring psychiatric disorders may respond better to higher service intensity.

Given the significance of alcohol dependence in people with comorbid mental conditions, this is an area of research worthy of more attention.

Tobacco smoking

Alcohol and tobacco (nicotine) dependence are highly comorbid disorders. Dependence on both nicotine and alcohol rather than on just one of them has a more severe and unfavourable course and dependence on one facilitates dependence on the other.[381] Animal models suggest a role for nicotinic acetylcholine receptors in alcohol consumption and there may be significant cue response activity with smoking and drinking frequently occurring together. This review identified only one study that had considered the impact of tobacco smoking on relapse prevention treatment of alcohol dependence (see section 6.3.4). This study found that tobacco smoking increased the odds of relapse into drinking by 65%, independent of the medications prescribed. However, topiramate (but not naltrexone or placebo) was associated with a significant decrease in the number of cigarettes smoked per day. Tobacco smoking as a factor predicting treatment outcome is likely to apply much more broadly than to anticonvulsant treatment. This is another area where further research is desirable.

Appendix 1: Summary of Studies Included in Analyses

Study	Country	Participant characteristics	Intervention
Addolorato 2002 [344]	Italy	Alcohol dependent by DSM-IV, 12-24 hours abstinence at entry. Mean age 47	Baclofen 15-30mg/day or placebo. Medication entrusted to referred family member. Routine psychological support counselling weekly. 30 day study.
Addolorato 2007 [345]	Italy	Alcohol dependent by DSM-IV, with diagnosis of liver cirrhosis; heavy drinking in month prior to study entry; 3-4 day hospital admission for assessment and detoxification at beginning of study. Mean age 49, 72% male, 60% married, 77% employed.	Baclofen 15mg/day increasing to 30mg/day or placebo. Medication entrusted to family member. Assessments weekly for 1 month then fortnightly. Individual psychological support counselling at every visit. Attendance at support groups (AA) encouraged.
Ahmadi 2002 [43;44]	Iran	Alcohol dependent by DSM-IV, 3-30 days abstinence at entry. Mean age 43, all male, 87% married, 16% unemployed.	Naltrexone, 50mg/day, or placebo. Weekly individual relapse prevention counselling. 12 weeks treatment.
Angelone 1998 [241]	Italy	Alcohol dependent by DSM-IV, 3 weeks inpatient detoxification prior to study. Mean age 48.8, 68% male.	Fluvoxamine 150mg/day, citalopram 20mg/day or no medication, commenced while inpatient. Cognitive behavioural group therapy daily for 8 weeks, then weekly. 12 week study.
Anton 1999 [53;54]	USA	Alcohol dependent by DSM-III-R, ≥5 days abstinence at entry. Mean age 44, 71% male, 68% married, 81% employed full-time.	Naltrexone 50mg/day, or placebo. Individual cognitive behavioural therapy weekly. 12 week treatment
Anton 2004 [51]	USA	Alcohol dependent by DSM-IV, abstinent ≥3 days at entry. Mean age 45, 72% male, 49% married.	Nalmefene, 5, 20 or 40 mg/day (groups combined for this review), or placebo. Motivational enhancement therapy (4 sessions) individualised to goal of total abstinence or drinking reduction. 12 week treatment.
Anton 2005 [64;65]	USA	Alcohol dependent by DSM-IV, ≥5 days abstinence at study entry. Mean age 44, 75% male, 39% married, 87% employed full-time.	Naltrexone 50mg/day or placebo. Weekly cognitive behavioural therapy or motivational enhancement therapy (4 sessions). 12 week study.
Anton 2008 [314]	USA	Alcohol dependent by DSM-IV, abstinent mean 6.6 days at study entry. Mean age 47, 68% male.	Aripiprazole (atypical antipsychotic) 2mg/day in single daily dose titrated to max 30mg/day by day 28, or placebo. Weekly cognitive behavioural therapy. 12 week treatment.
Anton 2009 [287]	USA	Alcohol dependent by DSM-IV. No other major psychiatric conditions, no other substance abuse or dependence except marijuana or nicotine. Last drink ≤72 hours before randomisation. Mean age 47, 77% male, 52% married.	Flumazenil (2mg in 9 bolus doses iv) on days 1-3, plus gabapentin to 1200mg on days 4-30 before tapering, or placebos (infusion and oral). Weekly manualised behavioural counselling. 40 days treatment.
Arias 2010 [290]	USA	Alcohol dependent by DSM-IV, at least 2 heavy drinking days per week between screening and baseline. Mean age 49, 57.5% male, 65% married, 80% working, average 54 drinking days in 60 days prior to baseline. Two-thirds had a goal of controlled drinking.	Zonisamide (anticonvulsant) or placebo, 100mg/day increasing over 8 weeks to 500mg/day, continued for 4 weeks then tapered and discontinued. Cognitive behavioural counselling (6 biweekly sessions of 20 minutes) and psychoeducation as adjunct. 12 week treatment.
Azrin 1982 [234]	USA	Clients of outpatient alcoholism clinic, willing to take disulfiram. Mean age 33.9, 83% male, 67% married or cohabiting, 46% employed.	Disulfiram 250mg. Adjunct therapy 5 weekly sessions of about 1 hour of traditional (no special assurance procedures for taking disulfiram, total abstinence encouraged), traditional plus disulfiram assurance (specific training in adhering to the disulfiram regime), or traditional plus disulfiram assurance plus behavioural training.

Study	Country	Participant characteristics	Intervention
Balldin 2003 [71]	Sweden	Alcohol dependent by DSM-IV, <14 days abstinence at screening, 1 week placebo before randomisation. Mean age 50, 71% male, 68% married, 81% employed.	Naltrexone 50mg/day, or placebo. Cognitive behavioural therapy (9 sessions) or supportive therapy (treatment as usual). 6 month study.
Baltieri 2004 [165;166]	Brazil	Alcohol dependent by ICD-10, 1 week detoxification before study. Mean age 44.2, all male.	Acamprosate 1998 mg/day or placebo. Encouraged to attend AA. 12 week treatment.
Baltieri 2008 [76;311;382]	Brazil	Alcohol dependent by ICD-10, 1 week detoxification prior to study. Mean age 44.3, all male, 51.6% married.	Topiramate 25mg/day increasing to 300mg/day by week 8, naltrexone 50mg/day, or placebo. Brief cognitive behavioural intervention by treating doctor (8 appointments). Encouraged to attend AA. 12 week treatment.
Barrias 1997 (cited by Mann 2004 [168] and Rosner 2010 [169])	Portugal	Alcohol dependent (97.7%) by DSM III. Abstinent ≥5 days at baseline. Mean age 40.3, 92% male, 73% married.	Acamprosate 1332 or 1998mg/day or placebo. Encouraged to participate in AA. 12 month treatment.
Bender 2007 [313]	Germany	Alcohol dependent by ICD-10, abstinent ≥7 days before study. Mean age 42, 73% male, 75% in permanent relationship, 55% employed.	Tiapride up to 600mg/day for 1 month, then 300mg/day in 3 doses, or placebo. Usual psychosocial treatment program. 24 week treatment.
Besson 1998 [171]	Switzerland	Alcohol dependent by DSM-III, completed withdrawal with ≥5 days abstinence before study. Mean age 42.5, 80% male.	Acamprosate 1332 or 1998mg/day (by bodyweight) or placebo; 42% received concomitant disulfiram. Supportive psychosocial treatment twice a month. 12 month treatment.
Borg 1994 (cited by Mann 2004 [168] and Rosner 2010 [169])	Sweden	Mean age 45.7, all male, 70% married.	Acamprosate or placebo, 6 month treatment.
Brady 2002 [293]	USA	Alcohol dependent by DSM-IV, mean 74% days drinking in 90 days before study. Mean age 40, 39% male.	Divalproex (anticonvulsant) 1500mg/day or placebo. Weekly cognitive-behavioural therapy. 12 week treatment.
Brady 2005 [244;245]	USA	Alcohol dependent and (civilian) post-traumatic stress disorder by DSM-IV; 7 days abstinence prior to diagnostic assessment and 1 week placebo washout prior to medication (placebo responders excluded). Mean age 37, 54% male.	Sertraline 150mg/day or placebo. Weekly individual cognitive behavioural therapy (alcohol-focused). 12 week treatment.
Brower 2008 [295]	USA	Alcohol dependent by DSM-IV, insomnia persisting after acute alcohol withdrawal. Mean age 45, 52% male, 67% employed, 38% married, 19% living alone. 60% in gabapentin group and 27% in placebo group tobacco smokers.	Gabapentin, titrated to 1500mg (5 pills) in single dose at bedtime, or placebo. Up to six 30-minute sessions of behavioural therapy focused on enhancing adherence to study medication. 6 weeks medication.
Brown 2008 [317]	USA	Bipolar disorder and alcohol abuse or dependence (97%). Mean age 38, 63% male, 82% depressed.	Quetiapine (atypical antipsychotic) titrated to 600mg/day or placebo. Psychosocial treatment as usual. 12 week study.
Brown 2009[79]	USA	Alcohol dependence by DSM-IV and bipolar disorder with current mixed or depressed mood and ≥5 drinks in 7 days prior to intake. Mean age 41.4, 51.2% male.	Naltrexone 50mg/day or placebo. CBT designed for comorbid bipolar disorders and substance use, 16 sessions. 12 week study.
Bruno 1989 [336]	Italy	Mild to moderate alcohol abuse by DSM-III, none abstinent at entry. Mean age 40, 48% male, 32% married, 14% unemployed, 76% with mild to moderate anxiety.	Buspirone 15-30mg/day, or placebo. Adjunct treatment not reported. 8 week treatment.
Caputo 2003 [342]	Italy	Alcohol dependent by DSM-IV, abstinent mean 5.1 days at study entry. Mean age 49, 77% male, 50% married, 60% employed.	GHB, oral, 150mg/kg/day, or naltrexone 50mg/day. Medication entrusted to family member. Weekly counselling, self-help groups and AA offered. 3 month treatment.

Study	Country	Participant characteristics	Intervention
Caputo 2007 [284]	Italy	Alcohol dependent by DSM-IV-TR, abstinent ≥7 days at study entry. Mean age 48, 78% male, 50% employed, 34% married.	GHB 50mg/kg, naltrexone 50mg/day or GHB and naltrexone. Adjunct therapy unclear (probably medical management). 3 month treatment.
Carroll 1993 [215]	USA	Cocaine dependence and alcohol abuse or dependence by DSM-III-R, drinking 5.3 standard drinks/day at baseline. Mean age 32, 72% male.	Disulfiram 250mg/day or naltrexone 50mg/day. Weekly individual psychotherapy. 12 week study.
Carroll 1998 [212;213]	USA	Cocaine dependence and alcohol abuse or dependence (85%) by DSM-III-R, mean 17.2 days of alcohol consumption in 30 days prior to study. Mean age 30, 67% male, 50% married or cohabiting, 70% unemployed.	Disulfiram 250-500mg/day or no medication. Weekly individual counselling (cognitive behavioural therapy, Twelve Step Facilitation, or clinical management). 12 week study.
Castro 2009	Brazil	Alcohol dependence by DSM-IV, seeking outpatient treatment. Randomisation after 5 days abstinence. Demographics not reported but no significant differences between groups.	Naltrexone 50mg/day or placebo. Brief intervention as adjunct treatment. 12 week study.
Chick 1992 [209]	UK	Attending alcoholism treatment centres, had relapsed after previous therapy or other support. Mean age 43, 84% male, 65% unemployed, 46% cohabiting. Supported by nominated informant with whom they had contact at least once a week.	Disulfiram 200mg/day or vitamin C, 100 mg/day. Medication supervised by informant. Standard counselling and support. 6 month study.
Chick 2000 [87]	UK	Alcohol abuse or dependence (87%) by DSM-III-R, median 10-11 days abstinence before study. Mean age 43.5, 75% male, 40% cohabiting. 27% employed.	Naltrexone 50mg/day or placebo. Psychosocial treatment program as usual. 12 week study.
Chick 2000A [176]	UK	Alcohol dependence by DSM-III, detoxified within 5 weeks of study, one-third episodic drinkers, 32% drank in week between detoxification and study. Mean age 43, 84% male, 44% unmarried, 48% unemployed.	Acamprosate 1998mg/day or placebo. Psychosocial treatment as usual. 6 month study.
Chick 2004 [252]	UK, Eire, Austria, Switzerland	Alcohol dependent by DSM-III-R, abstinent 10-30 days at entry. Mean age 42, 74% male.	Fluvoxamine up to 300mg/day or placebo. Usual psychosocial treatment. 12 month study (week 12 data used to minimise bias due to dropout).
Combine Pilot[52]	USA	Alcohol dependence by DSM-IV, abstinent <21 days at entry. Mean age 42, 74% male, 42% married, 70% employed.	Naltrexone 100mg/day, Acamprosate 3g/day, Acamprosate and Naltrexone, placebo or no medication. Medical Management only, or Medical management and Combined Behavioural Intervention or Combined Behavioural Intervention only (no medication group). 16 week study.
Combine Study [15;22;37;59-63]	USA	Alcohol dependent by DSM-IV, mean 25 days abstinence in 30 days prior to study. Median age 44, 42% married, 69% male, 73% employed.	Acamprosate 3g/day, naltrexone 100mg/day, acamprosate plus naltrexone, placebo or no medication. Medical management (9 sessions), Combined Behavioural Intervention (up to 20 sessions) plus medical management, or Combined Behavioural Intervention only (no medication group). 16 week study.
Cornelius 1997 [258-260]	USA	Alcohol dependence and major depressive disorder by DSM-III-R, inpatient detoxification (2-3 days) and 1 week washout before study entry. Mean age 35, 51% male, 20% (fluoxetine) or 4% (placebo) currently married, 31% employed.	Fluoxetine 20-40mg/day or placebo, commenced in inpatient setting. Weekly supportive psychotherapy and attendance at AA encouraged. 12 week treatment.

Study	Country	Participant characteristics	Intervention
Cornelius 2009 [263]	USA	Alcohol abuse or dependence and major depressive disorder by DSM-IV. All adolescents (aged 15-20 at baseline); 44% male.	Fluoxetine, 10mg/day increasing to 20mg/day after 2 weeks, or placebo. Nine sessions manualised intensive therapy (CBT and Motivational Enhancement Therapy). 12 week study.
Coskunol 2002 [266]	Turkey	Alcohol dependent by DSM-III-R, withdrawn from alcohol 7-21 days before study. Mean age 43.8, all male, 76% married, 69% employed.	Sertraline 100mg/day or placebo, commenced as inpatient. Alcoholism information groups and AA meetings during inpatient treatment. Encouraged to continue attending AA. 6 month study.
Croissant 2006 [288]	Germany	Alcohol dependent by ICD-10 and DSM-IV, abstinent at least 1 week at study entry. Declared total commitment to abstinence. Mean age 46, 73% male, 50% employed, 50% married.	Oxcarbazepine (anticonvulsant) titrated to 1200mg/day by day 12, or acamprosate 1998mg/day. Adjunct treatment not reported. 12 week medication.
Davidson 2007 [141;364;365]	USA	Alcohol dependent by DSM-IV, abstinent 3-21 days at study entry. Mean age 44, 63% male, 44% married/common law, 64% employed full-time.	Naltrexone 50mg/day for 3 months (followed by 3 months placebo) or 6 months, plus broad spectrum treatment (CBT-based) or motivational enhancement therapy. 24 week study.
Deas 2000 [268]	USA	Alcohol use disorder and primary depressive disorder, mean 29% drinking days at baseline. Average age 16.6 years (all adolescents), 80% male.	Sertraline 25-100mg/day or placebo. Weekly cognitive behavioural group therapy. 12 week treatment.
de Goes e Castro 2004 (Cited by Rosner 2010A [383])	Brazil	Alcohol dependent, 5-30 days abstinence at baseline. Mean age 46, 82% male, 58% married, 44% employed.	Oral naltrexone, 50mg/day or placebo. Psychosocial treatment based on CBT and motivational enhancement therapy, plus 12-step approach. 12 week study.
de la Fuente 1989 [347]	USA	Alcoholism by National Council on Alcoholism major criteria, 4 weeks inpatient treatment prior to study. Mean age 44, 74% male, 47% with probable depression.	Lithium carbonate (mean 814±65mg/day) or placebo. No specific psychosocial treatment reported. Study duration 6 months.
De Sousa 2004 [221]	India	Alcohol dependent by DSM-IV, mean 15 days abstinence at study start. Stable family environment to ensure compliance and follow-up. Mean age 45, all male, 95% married, 77% employed.	Naltrexone 50mg/day or disulfiram 250mg/day. Weekly supportive group psychotherapy. 12 month treatment.
De Sousa 2005 [216]	India	Alcohol dependent by DSM-IV, mean 20 days abstinence at baseline. Stable family environment to encourage medication compliance and follow-up. Mean age 42 years, all male, 95% married, 69% employed.	Disulfiram 250mg/day or acamprosate 1998mg/day. Weekly supportive group therapy offered. 8 month treatment.
De Sousa 2008 [289]	India	Alcohol dependent by DSM-IV, mean 20 days abstinence at baseline. Stable family environment to encourage medication compliance and follow-up. Mean age 43, all male, 98% married, 72% employed.	Topiramate (anticonvulsant) 50mg three times a day or disulfiram 250mg as single daily dose. Weekly supportive group therapy available. 9 month treatment.
De Sousa 2008A[225]	India	Alcohol dependent by DSM-IV; stable family environment to encourage medication compliance and follow-up. Mean 17 days abstinence at baseline. Mean age 17 (all adolescents).	Oral disulfiram, 250mg as single daily dose, or naltrexone, 50mg in 2 daily doses. Twice weekly supportive group psychotherapy available. Six month treatment, follow-up at 9 months.
De Wildt 2002 [362]	The Netherlands	Alcohol dependence or abuse by DSM-IV, 3-17 days abstinence at entry. Mean age 44.5, 83% male, 53.1% married or cohabiting, 58.1% employed.	Acamprosate 1332 or 1998mg/day by body weight, with (1) medical monitoring only (2) medical monitoring plus motivational interviewing by physician, 3x20 minute sessions, (3) monitoring plus brief cognitive behavioural therapy by social worker or psychologist, 5-7x60 minute sessions per week in weeks 2-8. 28 weeks treatment.

Study	Country	Participant characteristics	Intervention
Dorus 1989[348]	USA	Male veterans hospitalised for alcoholism, with or without depression (defined as a history of major depression, current depression or dysthymic disorders). Drug-free 25-30 days before medication commenced. Mean age 41, 31% married, 73.5% employed full-time.	Lithium 600-1200 mg/day or placebo. Encouraged to participat in AA. Weekly clinic visits for 13 weeks then biweekly. 1 year treatment.
Eriksson 2001 [271]	Sweden	Consuming 300-800g pure alcohol per week (73% dependent by DSM-IV). Mean age 51, all male, 73% cohabiting, 94% employed.	2 week premedication period, then citalopram 40mg/day or placebo. 4 weeks medication, 2 weeks post-medication, 8-12 months follow-up. Data for medication period used for this review.
Farren 2009 [283]	USA	Alcohol dependent by DSM-IV, mean 28 days abstinent at baseline (no depression). Mean age 43, 82% male, 40% married or living with partner.	Naltrexone 50mg/day, plus sertraline 50-100mg/day or placebo. Weekly group relapse prevention psychotherapy and encouraged to attend AA. 12 week treatment.
Favre 1997 [247;248]	France	Alcohol dependence by DSM-III-R. withdrawal period of 1-4 weeks prior to study, no significant depression. Mean age 42, 86% male.	Tianeptine (tricyclic antidepressant) 12.5mg three times a day or placebo. Multicentre study – adjunct psychosocial treatment not reported. 9 month treatment.
Fawcett 1987 [349;350]	USA	Alcohol dependent by DSM-III, assessed between 7th and 21st day of inpatient treatment at private medical centres. Mean age 40, 88% male, 45% married, 79% working full-time, 89% with history of major depression.	Lithium 900mg/day or placebo, commenced during inpatient stay. Dose adjusted to plasma lithium of 0.7-1.2 meq/litre. No specific adjunct therapy but strongly encouraged to participate in AA. 18 month treatment.
Fawcett 2000 [337]	USA	Alcohol dependent by DSM-III-R, treatment commenced after 5 days abstinence. Mean age 40, all male, 49% married or cohabiting, 80% employed.	Lithium to max 1200mg/day, Buspirone to max 40mg/day, or placebo. Supportive interventions to maintain abstinence at time of follow-up visits. Encouraged to attend AA. 6 month treatment (3 month data used for this review).
Florez 2008 [291]	Spain	Alcohol dependent by ICD-10, medication commenced after detoxification completed. Mean age 47, 85% male, 70% married, 485 employed.	Naltrexone 50mg/day, or Topiramate 50mg, increasing to 200mg/day with further increases to 300-400mg/day if craving not controlled. Disulfiram added if naltrexone or topiramate not effective. Individualised psychological therapy (relapse prevention model). Outcome assessed at 3 and 6 months – 3 month data used in this review.
Fuller 1979 [217-219]	USA	Hospitalised for alcohol-related illness or requesting treatment for alcoholism. Mean age 42.6, all male; 65% married; 44% employed.	Disulfiram 250mg/day, placebo (1mg/day disulfiram) or no medication. Medical care and counselling. 1 year study.
Fuller 1986 [222]	USA	Alcoholism by National Council of Alcoholism criteria. <1 month abstinence at entry. Mean age 42, all male, 54% employed, 72% married.	Disulfiram 250mg/day, placebo (1mg/day disulfiram) or riboflavin 50 mg/day (this group aware they were receiving vitamin not disulfiram). Counselling every 1-2 weeks. 1 year study.
Furieri 2007 [296]	Brazil	Alcohol dependent by DSM-IV, abstinent 7-14 days at study entry. Mean age 44, all male, 37% married, 37% unemployed.	Gabapentin 300mg twice daily or placebo. Weekly brief behavioural compliance enhancement treatment. 4 week treatment.
Galarza 1997 [90] (Cited by Rosner 2010A[383])	Puerto Rico	Alcohol dependence by DSM-IV. All male veterans, mean age 55.	Naltrexone or placebo (dose not reported). Standard psychosocial treatment. 4 week study.
Gallimberti 1992 [343]	Italy	Alcoholism by DSM-III-R. Actively drinking (abstinence not required). Mean age 40.5, 66% male. Data only on 71 of 82 who completed the study.	GHB 50mg/kg in 3 daily doses as oral syrup or placebo (syrup only). Adjunct psychological treatment not reported. First 3 days as day care, then outpatient with weekly clinic visits. 3 month treatment.

Study	Country	Participant characteristics	Intervention
Garbutt 2005 [46-48;50]	USA	Alcohol dependent by DSM-IV, 8.8% abstinent in 7 days before first injection, 43% had treatment goal of total abstinence. Mean age 45, 68% male, 71% employed at least 20 hours/week.	Depot naltrexone 380mg or 190mg or placebo by intramuscular injection. Standardised supportive therapy (low intensity), 12 sessions. Naltrexone groups combined for this review.
Garbutt 2010 [346]	USA	Alcohol dependent by DSM-IV, at least 2 heavy drinking days per week in 4 weeks prior to screening, 3 days abstinence prior to randomisation. Average age 49, 55% male, 57% married, average age of onset of alcohol dependence 34 years; 24% had abstinence as treatment goal.	Baclofen 30mg/day or placebo with medical monitoring and 8 sessions of low intensity psychological intervention (BRENDA). Participants encouraged to attend AA. 12 week treatment.
Gastpar 2002 [92]	Germany	Alcohol abuse or dependence (97.7%) by DSM-III-R, abstinent for mean 19.5 days before study. Mean age 43, 73% male.	Naltrexone 50mg/day or placebo. Outpatient and inpatient (up to 28 days) treatment. Psychosocial program (treatment as usual). 12 week study.
Geerlings 1997 [181]	Netherlands, Belgium, Luxembourg	Alcohol dependent by DSM-III, ≥5 days abstinence before study. Mean age 40, 76% male, 51% married.	Acamprosate, 1998 or 1332 mg/day (by bodyweight) or placebo. Psychosocial support (treatment as usual). 6 month treatment.
Gerrein 1973 [227]	USA	New admissions to alcoholism clinic. Mean age 43, 88% male, 10% with spouse, 21% living alone, 16% in a hospital, 35% in halfway house. 51% unemployed.	Disulfiram 250mg/day or no medication. Clinic visits once or twice weekly (with supervised administration). 6 month study.
Gual 2001 [183]	Spain	Alcohol dependent by DSM-III-R, 13% episodic drinkers. Medication from start of withdrawal. Mean age 41, 80% male, 68% married.	Acamprosate 1998mg/day or placebo. Adjunct psychosocial support not reported. 6 month treatment.
Gual 2003 [276]	Spain	Major depression (98%) or dysthymia and alcohol dependence by DSM-IV and ICD-10. Abstinent 2 weeks at entry. Mean age 47, 53% male.	Sertraline 50mg/day to max 150mg/day or placebo. Adjunct psychosocial treatment not reported. 24 week study.
Guardia 2002 [95]	Spain	Alcohol dependent by DSM-IV, 5-30 days abstinence at entry. Mean age 42, 75% male, 59% married, 45% employed.	Naltrexone 50mg/day or placebo. Weekly supportive group therapy (relapse prevention) and individual supportive counselling. 12 week study.
Guardia 2004 [318]	Spain	Alcohol dependent by DSM-IV, 5-30 days since last drink. Mean age 43, 77% male, 48% married, 67% employed.	Olanzapine (antipsychotic, dopamine antagonist) 5mg/day up to max 15mg/day or placebo. Intensive outpatient rehabilitation treatment. 12 week treatment.
Habrat 2006 [257]	Poland	Depression and alcohol dependence or harmful use by ICD-10. Participant characteristics not available (article in Polish – data from abstract only).	Tianeptine 37.5mg/day or fluvoxamine 100mg/day. Adjunct treatment unclear. 6 week study.
Hammarberg 2004 [363]	Sweden	Alcohol dependent by DSM-IV, 1 week abstinence at study entry. Mean age 47, 73% male, 31% married.	Acamprosate 1998mg/day plus minimal psychosocial intervention (4 sessions with psychiatrist) or extended psychosocial intervention (4 sessions with psychiatrist plus 10-15 sessions with psychiatric nurse). 24 week treatment.
Hammarberg 2009 [185;186]	Sweden	Alcohol dependent by DSM-IV, treatment seeking with a goal of controlled drinking (excluded if goal total abstinence) but asked to refrain from alcohol during treatment. Average age 50, 54% male, 41% married or with partner, 75% employed full- or part-time.	Acamprosate (1998mg/day) or placebo. Weekly clinic attendance with laboratory sessions of cue reactivity and alcohol priming on day 21. 21-day treatment.
Hautzinger 2005 [249]	Germany	Alcohol dependent by DSM-IV and ICD-10, detoxification prior to study entry. Mean age 42.8, all male, 58.9% living with partner. No depression in previous 2 years. Article in German. Assessed using Google Translator.	Nefazodone 600mg/day or placebo. Cognitive behavioural therapy or nondirective group counselling. 12 weeks therapy, outcomes assessed at 3 and 12 months (3 month data used for this review).

Study	Country	Participant characteristics	Intervention
Heinala 2001 [98]	Finland	Dependent by DSM-IV, not detoxified prior to study. Mean age 46, 71% male, 73% married, 75% employed.	Naltrexone 50mg/day or placebo, 12 weeks daily medication, 20 weeks targeted (when drinking likely). Cognitive coping skills (allowed some drinking) or supportive therapy (supported total abstinence) as 4 sessions group therapy.
Hernandez-Avila 2004 [256]	USA	Major depression (at least 1 week after cessation of heavy drinking) and alcohol dependence by DSM-IV. Mean age 43, 48% male, 71% employed, 35% married.	Nefazodone to max 300mg twice daily or placebo. Supportive psychotherapy (8 sessions). 10 week treatment.
Hersh 1998 [101]	USA	Alcohol abuse or dependence (92%) and cocaine abuse or dependence (96%) by DSM-III-R. Mean age 35.5, 92% male, 81% employed.	Naltrexone 50mg/day or placebo. Individual relapse prevention psychotherapy (12 sessions). 8 week treatment.
Huang 2005 [105]	Taiwan	Alcohol dependent by DSM-III-R, medication commenced at end of 2-week detoxification. Mean age 40.5, 65% married, all male.	Naltrexone 50mg/day or placebo. Weekly supportive psychotherapy. 4 week study.
Janiri 1996 [277]	Italy	Alcohol dependent by DSM-III-R,. abstinent ≥7 days at entry. Mean age 45, 80% male. Patients living alone or of no fixed abode excluded.	Fluoxetine 20mg/day or placebo. Weekly psychological interviews, AA attendance. 2 month treatment.
Johnsen 1987 [210]	Norway	Alcoholism by Short Michigan Screening Test. Mean age 40, all male.	Disulfiram or calcium phosphate (placebo) implant (10x100mg tablet). No adjunct treatment reported – participants not told some would receive placebo. 20 week study.
Johnsen 1991 [220]	Norway	Alcohol dependent by DSM-III, requested disulfiram implant. Mean age 42, male and female (proportions not reported).	Disulfiram (10x100mg) or placebo (9x100mg calcium phosphate, 1x100mg disulfiram) tablet implant. No adjunct treatment reported. Participants not told some would receive placebo. 10 month study.
Johnson 1996 [319]	USA	Alcohol dependence by DSM-III-R. Mean age 41, 77% male.	1 week placebo, then ritanserin 2.5 or 5mg/day, or placebo. Weekly individual cognitive behavioural therapy. 12 week study. Ritanserin groups combined for this review.
Johnson 2000 [329-331]	USA	Early (59%) or late onset alcoholism by DSM-III-R. Abstinence not required at entry. Mean age 40, 70% male.	1 week placebo, then ondansetron, 1, 4 or 16ug/kg or placebo. Weekly cognitive behavioural therapy. 11 week treatment. Ondansetron groups combined for this review.
Johnson 2000A[333-335]	USA	Early-onset alcoholism by DSM-IV. Abstinence not required at entry. Mean age 38, 75% male.	Naltrexone 50mg/day plus ondansetron 8ug/kg or placebo. Weekly group cognitive behavioural therapy. 8 week study.
Johnson 2003 [297-299]	USA	Alcohol dependence by DSM-IV. Abstinence at study entry not required. Mean age 42, 52% male, 46% early-onset alcoholism.	Topiramate 25mg/day to max 300mg/day or placebo, Weekly medication compliance management. 12 week treatment.
Johnson 2004 [56]	USA, France, Netherlands	Alcohol dependence by DSM-IV. Abstinent 5 days before study. Mean age 42.6, 68% male in naltrexone group, all male in placebo group. 57% identified total abstinence as their treatment goal.	Naltrexone 400mg depot preparation, or placebo, by intramuscular injection every 28 days. Psychosocial support at each monthly visit. 4 month study.
Johnson 2007 [300;301]	USA	Alcohol dependent by DSM-IV, currently drinking but with desire to stop or reduce intake. Mean age 47, 73% male.	Topiramate up to 300mg/day or placebo. Weekly compliance enhancement intervention. Medication tapered weeks 14 to 16.

Study	Country	Participant characteristics	Intervention
Kabel 1996 [279]	USA	Severe alcohol dependence, mean 20.4 drinking days in 30 days prior to study. Mean age 46.8, all male; 36% homeless at entry, average 4 personality disorder diagnoses;.	Fluoxetine 60mg/day or placebo. Nature of psychosocial support unclear – AA mentioned. 3 weeks inpatient, then outpatient, 12 week study.
Kampman 2007 [315]	USA	Alcohol dependent by DSM-IV (grouped as Type A or Type B), at least 3 days abstinence before study. Mean age 47, 77% male, 31% married, 90.2% employed.	Quetiapine (antipsychotic) to maximum 400mg/day at bedtime, or placebo. Weekly psychosocial treatment. Scheduled duration 12 weeks.
Karhuvaara 2007 [57;58]	Finland	Heavy drinking (93% dependent by DSM-IV). Mean age 49, 82% male, 27% living alone, 64% employed.	Nalmefene 20mg/day or placebo, taken 1-2 hours before any event when drinking seemed imminent. No formal psychosocial treatment. 28 weeks treatment. (2nd phase involving those who responded to nalmefene excluded from this review due to high risk of selection bias.)
Kiefer 2003 [24;111-113]	Germany	Alcohol dependent by DSM-IV. Abstinent 12-15 days before study. Mean age 46.2, 74% male, 28% married, 39% unemployed.	Naltrexone 50mg/day, Acamprosate 1998 mg/day, naltrexone plus acamprosate or placebo. Medication commenced 5 days before discharge from inpatient treatment. Weekly group therapy abstinence-oriented – coping skills and cognitive behavioural relapse prevention. 12 week study.
Killeen 2004 [70]	USA	Entered rural community treatment centre for alcohol use disorder, with drinking in 30 days before study entry. Mean age 37.3, 63% male, 28% married, 55% employed, 58% court ordered, 51% comorbid psychiatric disorder, 35% other substance use disorder.	Naltrexone 50mg/day, placebo or no medication. Usual treatment program (group and/or individual therapy); 88% in intensive program. Encouraged to attend AA. 12 week treatment.
Kiritze-Topor 2004 [172]	France	Alcohol dependent by DSM-IV, study entry from 3 days to 2 weeks from start of acute alcohol detoxification. Mean age 47.1, 73% male, 50% in stable employment, 72% living with a partner.	Standard care by general practitioner with or without acamprosate. 12 month study.
Kranzler 1993 [246]	USA	Alcohol dependent by DSM-III-R. Mean 11.5 days abstinence in 30 days prior to treatment. Mean age 44, 95% male.	Fluvoxamine 50mg/day at bed-time to max 200mg/day or placebo. Weekly medication monitoring and relapse prevention psychotherapy. 12 week study.
Kranzler 1994 [338]	USA	Alcohol dependent by DSM-III-R, all with anxiety and mood disorders, 14% with current major depression. Abstinent ≥7 days before entry to study. Mean age 39, 77% male, 57% married or cohabiting, 82% employed.	Buspirone, max 20mg three times a day, or placebo. Weekly individual cognitive behavioural psychotherapy. 12 week study.
Kranzler 1995 [253;254]	USA	Alcohol dependence by DSM-III-R. Mean age 40.1, 80% male; 97% employed, 14% current diagnosis of major depression.	Fluoxetine max 60mg/day or placebo. Weekly individual or group cognitive behavioural psychotherapy. 12 week study.
Kranzler 1998 [38]	USA	Alcohol dependence by DSM-IV. Abstinent ≥3 days at entry. Mean age 48, 75% male, 70% employed full-time, 70% married.	Oral naltrexone 50mg/day 2 weeks, no medication for 2 weeks, then depot naltrexone (206mg) or placebo, expected to last 4 weeks. Weekly individual coping skills psychotherapy 8 weeks. This review used data for 4 weeks of depot naltrexone.
Kranzler 2000 [117]	USA	Dependence by DSM-III-R. Abstinent 3-28 days before study. Mean age 41, 78% male, 45% married, 72% employed full-time.	Naltrexone, 50mg/day, Nefazodone (anti-depressant) 400-600mg/day or placebo. Coping skills training weekly. 11 weeks treatment.

Study	Country	Participant characteristics	Intervention
Kranzler 2003 [119;120]	USA	Heavy drinking (78.7% mild alcohol dependence by DSM-IV – moderate or severe dependence excluded). Mean age 47.3, 58% male, 83.3% chose sensible drinking as treatment goal. Drinking reported for 85.7% of days in 90-day period prior to treatment.	Naltrexone 50mg/day or placebo as daily or targeted medication (ie. one tablet taken in anticipation of a high-risk drinking situation). Brief coping skills therapy every other week. Scheduled duration 8 weeks.
Kranzler 2004 [39]	USA	Alcohol dependence by DSM-IV, at least 3 consecutive days sobriety prior to medication. Mean age 44, 65% male.	Naltrexone, 300mg first injection, then 150 mg/month, or placebo, intramuscular depot injection. Motivational enhancement therapy, 5 sessions. Self-help groups encouraged. 12 week study.
Kranzler 2006 [261]	USA	Major depressive disorder and alcohol dependence by DSM-IV, 7-14 day placebo lead-in with ≥4 days with no heavy drinking and ≤16 days abstinence prior to randomisation. Mean age 42.7, 63.8% male, 39.2% married.	Sertraline to max 200mg/day or placebo. Supportive therapy. 10 week study.
Kranzler 2009[123]	USA	Weekly alcohol consumption ≥24 standard drinks for men or ≥18 for women. Clinically severe alcohol dependence excluded, but 95.1% were alcohol dependent. Mean age 49.1, 58.3% male.	Naltrexone 50mg/day or placebo, targeted or daily administration. Brief coping skills therapy every 2 weeks. 12 week study.
Krystal 2001 [126-128]	USA	Severe alcohol dependence by DSM-IV, 67% drinking days in previous 90 days. Mean age 49, 98% male, 35% married or living with partner.	Naltrexone, 50mg/day for 3 or 12 months, or placebo. (3 month data used for this review, naltrexone groups combined.) Weekly individual 12-step facilitation counselling, encouraged to attend AA.
Laaksonen 2008 [175]	Finland	Alcohol dependence by ICD-10. Alcohol consumption at baseline 57 drinks/ week (detoxification not required prior to study). Mean age 43.1, 70.8% male, 56.2% married, 66.1% employed.	Naltrexone 50mg/day, Acamprosate 1998 or 1333mg/day, or Disulfiram 100-200 mg/day or 400mg twice a week. Supervised daily administration 12 weeks, 'targeted' (taken when propensity to drink high) 9 months. Data extracted for first 12 weeks only. Manualised cognitive behavioural therapy (4 sessions).
Ladewig 1993 [190]	Switzerland	Dependence by DSM-III-R, ≥5 days abstinence before study. Mean age 47.3, 77% male.	Acamprosate 1998 or 1332mg/day (by bodyweight) or placebo, 6 months.
Landabaso 1999 [75]	Spain	Alcohol dependence or abuse by DSM-IV. Mean age 30, 73% male, 53% married, 77% employed.	Aversion agent (disulfiram or calcium cyanamide) with or without naltrexone 25mg/day. Supportive psychotherapy 1 year study.
Latt 2002 [130]	Australia	Alcohol dependence by DSM-IV. Abstinent mean 12 days before study. Mean age 44.8, 69% male.	Naltrexone 50mg/day or placebo. Standardised medical advice, counselling and AA encouraged but not obligatory. 12 week study.
Lee 2001 [45]	Singapore	Alcohol dependence by DSM-IV. Entered study 1 week after detoxification. Mean age 45, all male, 72% married, 40% employed.	Naltrexone 50mg/day or placebo. 12-step oriented program. 1 month inpatient, then outpatient. 12 week study.
Lhuintre 1985 [192]	France	Daily alcohol consumption >20 drinks, dependence by clinical assessment within 48h of hospitalisation for alcohol withdrawal. Study entry at end of 5-day inpatient detoxification. Mean age 42, 89% male.	Acamprosate 25mg/kg/day or placebo. Meprobomate (sedative hypnotic) 1 month. No specific psychosocial therapy identified. 3 month study.
Lhuintre 1990 [159]	France	Alcohol dependence by clinical assessment within 48 hours after hospitalisation for withdrawal, 5-30 days abstinence before study. Mean age 42, 82% male, 64% married, 62% employed.	Acamprosate 1.3g/day or placebo. Psychotherapy "allowed". 12 week study.

Study	Country	Participant characteristics	Intervention
Malcolm 1992 [339]	USA	Alcohol dependence and anxiety disorder by DSM-III-R, enrolled in 3rd week of 28-day hospital treatment. Mean age 43, all male (veterans).	Buspirone, 45-60mg/day or placebo. Standard support, encouraged to attend AA. 1 week inpatient then outpatient. 26 week treatment.
Malec 1996 [340]	Canada	Alcohol dependence by DSM-III-R, abstinent <15 days at entry (abstinence not a required goal). Mean age 41, 80% male, 47% married or cohabiting. Social stability required; no antisocial and borderline personality disorders.	2 weeks placebo, then buspirone 20mg/day to max 40mg/day, or placebo. Psychological or psychosocial treatment, including AA, permitted but not standardised. 12 week treatment.
Marra 2002 [320]	France	Alcohol dependence by DSM-IV, 10-18 days inpatient detoxification before study. Mean age 45, 69% male, 59% employed, 35% living alone.	Amisulpride (benzamide neuroleptic) 50mg/day or placebo. Individual counselling by physician and continued participation in activities commenced during inpatient treatment. 6 month study.
Martinotti 2007 [292]	Italy	Alcohol dependent by DSM-IV, 5-10 days detoxification prior to study, committed to goal of total abstinence. Mean age 40.3, 81% male, 32% married.	Oxcarbazepine (anticonvulsant) 1500-1800mg or 600-900mg/day or naltrexone 50mg/day. Supportive self-help group twice a week. 90 day treatment.
Martinotti 2009 [316]	Italy	Alcohol dependent by DSM-IV. 5-10 days detoxification prior to study. Declared commitment to total abstinence. Mean age 40.3, 80% male.	Aripiprazole 5-15mg/day or naltrexone 50mg/day, single daily dose. Compliance monitored by family member. Supportive self-help group offered. 16 week study.
Martinotti 2010 [294]	Italy	Alcohol dependent by DSM-IV, declared commitment to goal of total abstinence. Regular use of anticonvulsants, antidepressants or antipsychotics an exclusion criterion. Detoxification prior to randomisation. Average age 40, 80% male, average 8.5 drinks/day, 14.8 years of addiction. Family member selected to support compliance.	Naltrexone (10mg/day increased after 1 week to 50mg/day) or pregalbin (anticonvulsant) increased over 1 week to flexible dose of 150-450mg/day (average 275.8mg/day). Supportive self-help group available 2 days per week. 16 week study.
Mason 1994 [69]	USA	Alcohol dependent by DSM-III-R, drinking mean 8.8 drinks per day at entry. Mean age 42, 71% male.	Nalmefene 10 or 40mg/day, or placebo. (Nalmefene groups combined for this review). No psychosocial treatment. 12 week study.
Mason 1996 [255]	USA	Alcohol dependence by DSM-III-R, median 8 days abstinence at entry. Mean age 39.5, 83% male.	Desipramine, median 200mg/day, or placebo. Encouraged to attend AA and other psychosocial treatments. 6 month treatment.
Mason 1999 [41]	USA	Alcohol dependence by DSM-III-R, abstinent for mean 14 days prior to randomisation. Stated goal of complete abstinence. Mean age 42, 67% male, 38% married, 70% employed.	Nalmefene 20 or 80mg/day, or placebo (nalmefene groups combined). Individual cognitive behavioural therapy. 12 week study.
Mason 2006 [163;170]	USA	Alcohol dependent by DSM-IV, <10 days abstinence prior to randomisation, 41% had total abstinence as treatment goal. Mean age 44, 68% male, 19% living alone, 57% employed full-time.	Acamprosate (3 tablets, twice a day), 2g or 3g/day, or placebo (acamprosate groups combined for this review). Brief abstinence-oriented protocol-specific counselling and self-help materials (8 sessions). 24 week study.
McGrath 1996 [262]	USA	Alcohol dependence and current depressive disorder by DSM-III-R. Actively drinking (excluded if >2 weeks abstinence at baseline). Mean age 35, 51% male, 30.6% (imipramine) and 9.1% (placebo) currently married, 51% employed.	Imipramine 50mg/day to max 300mg/day, or placebo at bedtime. Weekly individual relapse prevention counselling and attendance at AA strongly encouraged. 12 week treatment.
Merry 1976 [351]	UK	Alcoholic by WHO definition. Study commenced after detoxification, during 6 week inpatient treatment. Mean age 45, 71% male, 40% depressed. Most data for 40 of 71 who completed the study.	Lithium, sustained release, at night – dose adjusted to plasma concentration of 0.8-1.2mmol/l. Group psychotherapy during inpatient treatment. Participants seen every 6 weeks at special lithium clinic. 12 month study.

Study	Country	Participant characteristics	Intervention
Moak 2003 [264]	USA	Mild to moderate alcohol dependence and depressive disorder by DSM-III-R. Mean 22 days abstinence in 90 days before study. Mean age 42, 61% male.	Sertraline 50mg/day to max 200mg/ day or placebo. Individual cognitive behavioural therapy. 12 weeks treatment.
Monterosso 2001 [55]	USA	Alcohol dependence by DSM-III-R, abstinent 3 days before study and completed 1-week placebo lead-in period. Mean age 46.2, 72.8% male.	Naltrexone 100mg/day or placebo. Weekly manualised counselling ("BRENDA"). 12 weeks treatment.
Monti 2001 [66-68]	USA	Alcohol dependent by DSM-IV. Mean age 39.2, 76% male, 84% employed, 46% married or cohabiting.	Psychosocial treatment (cue exposure with coping skills and communication skills treatment or education and relaxation) commenced during inpatient phase (mean 14.1 days). At discharge randomised to naltrexone 50mg/day, or placebo. 12 week treatment program.
Morley 2006 [72-74]	Australia	Alcohol dependence by DSM-IV, abstinent for mean 5 days before enrolment. Mean age 45, 70% male, 35% married, 33% unemployed.	Naltrexone 50mg/day, Acamprosate 1998mg/day or placebo. Four medical reviews and 4-6 sessions compliance therapy during treatment. Scheduled treatment duration 12 weeks.
Morris 2001 [77]	Australia	Alcohol dependence by DSM-III-R, mean 8 days sobriety prior to study. Mean age 47.5, all male, 48% married, 58% with psychiatric comorbidity.	Naltrexone 50mg/day or placebo. Group psychoeducation and social support (12 weekly 1.5-hour sessions). 12 week treatment.
Mueller 1997 [302]	USA	Alcohol dependence by DSM-III-R, treatment group allocated on mean day 5.3 of hospitalisation. Mean age 39, 62% male, 52% married.	Carbamazepine 300-600mg/day or placebo. Nature of psychosocial intervention not reported. 12 month study (data from 2 month follow-up used for this review – substantial loss to follow-up increases risk of bias for later data).
Muhonen 2008 [250;251]	Finland	Alcohol dependence and current major depressive disorder by DSM-IV. Abstinence not required bur encouraged – current alcohol use by 43% at baseline. Mean age 48, 56% male.	Memantine (NMDA-receptor blocker) 20mg/day or escitalopram (SSRI) 20mg/ day. Routine treatment. 26 week study.
Namkoong 2003 [173]	South Korea	Alcohol dependence by DSM-IV, mean 4 days between last drink and first medication. Mean age 44, 96% male, 76% married, 60% employed.	Acamprosate 1998 or 1332mg/day (by bodyweight) or placebo. Usual psychosocial care (medical counselling, brief psychotherapy, encouraged to attend AA or cognitive behavioural therapy). 8 week treatment.
Naranjo 1990 [267]	Canada	Alcohol dependence (69% low level by Alcohol Dependence Scale). Mean 7.9 drinks per day during 2-week baseline period. Mean age 40, all male.	Fluoxetine 40 or 60mg/day, or placebo. (Fluoxetine groups combined for this review.) Adjunct psychosocial treatment not reported. 28 days medication. Data analysis based on 29/41 who completed the study.
Naranjo 1995 [269;270]	Canada	Mild or moderate alcohol dependence, drinking reduced by less than 20% in 2-week placebo phase prior to study. Mean age 46, 56% male.	Citalopram 40mg/day or placebo. Brief psychosocial intervention (5 sessions, total 1.25 hours) emphasising moderate drinking as a goal. 12 week treatment. Data analysis based on 62/99 who completed the study.
Narayana 2008 [179]	India	Alcohol dependent by ICD-10; medication started after detoxification and return of liver function to near normalisation (3-4 weeks). Mean age 38.4, all male (serving military personnel), 82.6% married.	Topiramate 100-125mg/day, naltrexone 50mg/day or acamprosate 1332 or 1998mg/day (by bodyweight). Counseling, AA meetings, individual psychotherapy, cognitive behavioural therapy and occupational-recreational therapy offered. 1 year study.
Nava 2006 [229]	Italy	Alcohol dependent by DSM-IV-TR, abstinent ≥14 days before study entry. Mean age 41, 85% male, 28% married, 7% no stable living arrangements.	GHB 50mg/kg bodyweight tid, naltrexone 500mg/day, disulfiram 200mg/day. Cognitive behavioural therapy. 12 month treatment.
Niederhofer 2003 [177]	Austria	Chronic or episodic dependence by DSM-IV, ≥5 days abstinence before study. Mean age 17, 65% male.	Acamprosate 1332mg/day or placebo. Details of adjunct psychosocial treatment not reported. 90 day study.

Study	Country	Participant characteristics	Intervention
Niederhofer 2003A [80]	Austria	Chronic or episodic dependence by DSM-III, abstinent ≥5 days at entry. All adolescents (16-19).	Naltrexone 50mg/day or placebo. Psychosocial and behavioural treatment as adjunct – details not reported. 90 day treatment.
Niederhofer 2003B[226]	Austria	Chronic or episodic alcohol dependence by DSM-IV, abstinent at least 5 days at entry. Mean age 17 (all adolescents), 65% male.	Disulfiram 200mg/day or placebo. Psychosocial and behavioural treatment as adjunct – details not reported. 90 day treatment.
Niederhofer 2003C[211]	Austria	Chronic or episodic alcohol dependence by DSM-IV, abstinent at least 5 days at entry. Mean age 17.5 (all adolescents), 58% male.	Cyanamide 200mg/day (3 doses), or placebo. Psychosocial and behavioural treatment – details not reported. 90 day study.
O'Malley 1992 [83-86]	USA	Alcohol dependence by DSM-III-R, abstinent mean 9.4 days before study. Mean age 40.5 years, 74% male, 73% employed full-time, 34% married.	Naltrexone 50mg/day or placebo. Coping skills/relapse prevention or supportive therapy. 12 week treatment.
O'Malley 2003-1 [88]	USA	Alcohol dependence by DSM-III-R, mean 12 days abstinence before study. Mean age 44, 71% male, 45% married, 78% employed.	First of 3 linked studies. Primary care management or cognitive behavioural therapy as adjunct to naltrexone 50mg/day. 10 week treatment.
O'Malley 2003-2 [88]	USA	Recruited from O'Malley 2003-1, <2 heavy drinking days in last 28 days of naltrexone treatment. Mean age 46.5, 68% male, 74% employed, 49% married.	Naltrexone 50mg/day or placebo as adjuncts to primary care management. 24 week treatment.
O'Malley 2003-3 [88]	USA	Recruited from O'Malley 2003-1, <2 heavy drinking days in last 28 days of naltrexone treatment. Mean age 45.4, 72% male, 78% employed, 48% married.	Naltrexone 50mg/day or placebo as adjuncts to cognitive behavioural therapy. 24 week treatment.
O'Malley 2007 [89]	USA	Alcohol dependent by DSM-IV, <30 days abstinence at baseline (mean 34.4% abstinent days prior to study entry). Mean age 40, all female, 28% with eating disorder, 51% married, 73% employed.	Naltrexone 50mg/day or placebo. Weekly group cognitive behavioural coping skills therapy, and referred to AA. 12 week treatment.
O'Malley 2008 [91]	USA	Alcohol dependent by DSM-IV, abstinent 4-30 days prior to study entry. Mean age 40, 66% male, 67% American-Indian or Alaskan Native, 37% married or common law, 59% full-time employment.	Naltrexone 50mg/day, Sertraline to 100mg/day plus naltrexone, or placebo. Nine sessions medical management and supportive advice. 16 weeks treatment.
Oslin 1997 [93;94]	USA	Alcohol dependence by DSM-III-R. Mean age 57.8 years, 15.9% married, all veterans (probably male).	Naltrexone 100mg Mon & Wed, 150mg Fri, or placebo. Weekly group therapy and 2 meetings per month with case manager. 12 weeks treatment.
Oslin 2005 [96;97]	USA	Current depressive disorder and alcohol dependence by DSM-IV, at least 3 consecutive days abstinent prior to study entry. Mean age 63.4 (all >55), 79.7% male, 44.6% currently married.	Naltrexone 50mg/day or placebo. All received sertraline 100mg/day. Individual compliance enhancement therapy weekly for 8 weeks, then bi-weekly. 12 week study.
Oslin 2008 [99;100]	USA	Alcohol dependent by DSM-IV, at least 3 consecutive days abstinence prior to medication. Mean age 41, 72.9% male, 85% employed, 32.8% married.	Naltrexone 100mg/day or placebo. Cognitive behavioural therapy (CBT) plus medication clinic, BRENDA plus medication clinic, or medication clinic only. Up to 18 sessions CBT or BRENDA, 9 sessions medication clinic. 24 week treatment.
Paille 1995 [178]	France	Alcohol dependence by DSM-III-R, mean 18 days abstinence at entry. Mean age 43.2, 80% male, 76% living with family, 68% employed.	Acamprosate 1.3 or 2g/day or placebo. (Acamprosate groups combined for this review.) Supportive psychotherapy as required. 12 month treatment.
Pelc 1992 (cited by Mann 2004 [168] and Rosner 2010 [169])	Belgium	Alcohol dependence by DSM-III, ≤23 days abstinence at baseline. Mean age 42.6, 68.6% male, 79% married.	Acamprosate (1332 or 1998mg/day by body weight) or placebo. Supportive psychotherapy. 6 month treatment.

Study	Country	Participant characteristics	Intervention
Pelc 1997 [182]	Belgium	Alcohol dependence by DSM-III-R, abstinent 14 days at baseline. Age 18-65, 85% male, 49.5% married.	Acamprosate 1332 or 1998mg/day or placebo. (Acamprosate groups combined for this review.) Supportive counselling and social support. 3 month treatment.
Pelc 2005 [366]	Belgium	Alcohol dependent by DSM-IV, 1 week abstinence at study entry. Mean age 43, 78% male, 18% married.	Acamprosate 1998 or 1332 mg/day by bodyweight. Medical management only or medical management plus community nurse follow-up. 26 week treatment.
Petrakis 2004 [103;104]	USA	Alcohol abuse or dependence (97%) by DSM-IV, drank on average 11.7 days of 30 prior to study. Mean age 46, all male, 16% employed. All with schizophrenia or schizoaffective disorder.	Naltrexone 50mg/day or placebo. Weekly cognitive-behavioural relapse prevention plus skills training and usual psychiatric treatment. 12 week treatment.
Petrakis 2005 [106-110]	USA	Alcohol dependence and comorbid Axis I psychiatric disorder by DSM-IV (70% major depression, 43% PTSD). Abstinent ≥3 days before randomisation; goal total abstinence. Mean age 47, 97% male.	Naltrexone alone, placebo alone, disulfiram and naltrexone or disulfiram and placebo. Weekly clinical management/compliance enhancement therapy. 12 week study.
Pettinati 2000 [272-275]	USA	Alcohol dependence by DSM-III-R, with or without lifetime depression. Abstinent ≥3 days at entry. Mean age 44.6, 52% male, “most” working, 42% married.	Sertraline 200mg/day or placebo. 12-step facilitation therapy and encouraged to attend community-based support groups. 14 weeks treatment.
Pettinati 2008 [114]	USA	Alcohol and cocaine dependent by DSM-IV, ≥3 days abstinence before medication. Mean age 41, 70% male.	Disulfiram 250mg/day, naltrexone 100mg/day, disulfiram and naltrexone, or double placebo. Twice weekly individual cognitive behavioural therapy. 11 week treatment.
Pettinati 2008A[115;116]	USA	Cocaine and alcohol dependent by DSM-IV, 71.7% smoked crack cocaine; abstinent from alcohol for ≥3 consecutive days at study entry. Mean age 39.1, 70.7% male, 17.3% married, 70.9% employed.	Naltrexone 150mg/day or placebo. Weekly individual cognitive behavioural therapy or medical management (BRENDA) designed to enhance treatment adherence and motivation. 12 week treatment.
Pettinati 2010	USA	Alcohol dependence and major depression by DSM-IV; 3 consecutive days abstinence before treatment. Other substance abuse (except nicotine), other mental disorders or regular medication exclusion criteria. Average age 43.4, 62.4% male, 78.8% not currently married, 75.3% family history of alcohol or drug problems, 49.4% family history of depression.	(1) Sertraline 200mg/day plus naltrexone 100mg/day (2) naltrexone 100mg/day (3) sertraline 200mg/day (4) double placebo. Weekly individual cognitive behavioural therapy adapted to treat alcohol dependence and depression. Support groups. 14 week study.
Poldrugo 1997 [184]	Italy	Alcohol dependence by DSM-III, ≥5 days abstinence before study (medication commenced at end of inpatient withdrawal treatment). Mean age 44, 73% male, 58% married.	Acamprosate, 1332 or 1998mg/day (by bodyweight) or placebo. Alcohol rehabilitation program (psychological support, group sessions, activities. Disulfiram allowed. 6 month treatment.
Powell 1985 [228]	USA	Alcohol abuse or dependence by DSM-III, 2-4 weeks inpatient treatment before study. Mean age 45, all male, 40% married and living with spouse.	Disulfiram plus monthly prescription renewal, disulfiram with tailored counselling and support, or no medication with monthly monitoring only. 12 month study.
Reid 2005 [197]	Australia	Moderate alcohol dependence by DSM-IV, abstinent 3-21 days prior to study. Mean age 44, 65% male, 25% (compliance therapy) and 60% (usual care) married or de facto, 47% employed.	Acamprosate 1998mg/day plus usual care (7 medical reviews) only, or usual care plus compliance therapy (4-6 individual sessions). Treatment duration 4 months.
Roussaux 1996 (cited by Mann 2004 [168] and Rosner 2010 [169])	Belgium	Alcohol dependence (65%) or abuse by DSM-III, ≥14 days abstinence before study. Mean age 42.2, 70% male, 32% married, 64% employed.	Acamprosate 1998mg/day vs placebo, 3 months. Group, individual and family counselling as adjunct.

Study	Country	Participant characteristics	Intervention
Roy-Byrne 2000 [265]	USA	Alcohol dependence and major depression by DSM-III-R; 9.5% stopped drinking prior to entry. Mean age 40.2, 45.3% male, 26.6% married, 70.3% employed.	Nefazodone, 200mg/day to max 500mg/day, or placebo. Cognitive behavioural skills training and psycho-educational group therapy (1 hour per week). Treatment duration 12 weeks.
Rubio 2001 [180]	Spain	Alcohol dependence by DSM-III-R, mean 16 days abstinence before study. Mean age 44, all male, 93% married, 75% employed full-time, stable family environment.	Acamprosate 1665-1998mg/day (by bodyweight in 3 doses) or naltrexone 50 mg/day (single daily dose). Supportive group therapy weekly. Accompanied by family member to appointments. 12 month study.
Rubio 2002 [78]	Spain	Mild alcohol dependence by DSM-III-R and Severity of Alcohol Dependence Scale. Mean age 30, all male.	Naltrexone 50mg/day or no medication as adjunct to controlled drinking program. 12 week study.
Rubio 2005 [81]	Spain	Alcohol dependent by DSM-IV, abstinent mean 14.5 days before medication. Mean age 41.5, all male, 24% using disulfiram, 24% using sertraline.	Naltrexone 50mg/day or no medication. Weekly supportive group therapy. 3 month study.
Rubio 2009[303]	Spain	Alcohol dependent by DSM-IV, abstinent mean 15 days before medication. All male, mean age 42, 16% married or living with partner, 84% employed.	Topiramate 250mg/day or placebo, 2 daily doses. Weekly visits to psychiatrist. Support group therapy offered weekly. 12 week study.
Salloum 2005 [304-306]	USA	Acute episode of bipolar I disorder and alcohol dependence by DSM-IV. Mean age 38, 71% male, 15% married, 58% employed.	Valproate 750mg/day increased as tolerated, or placebo. Treatment as usual including lithium, weekly individual dual diagnosis recovery counselling. Group therapy and self-help groups supported. 24 week study.
Sass 1996 [188;189]	Germany	Alcohol dependence by DSM-III-R. 14-28 days abstinence before study. Mean age 41, 78% male, 46% married, 26% unemployed.	Acamprosate 1332 or 1998mg/day (by bodyweight) or placebo. Adjunct counselling or psychotherapy as usual (mean 1 hour/week plus contact group every 2 weeks). 48 week study.
Schmitz 2009[122]	USA	Alcohol and cocaine dependence by DSM-IV. Used cocaine and alcohol in approximately 20 of the 30 days prior to treatment. Mean age 34.4, 87.3% male, 63.2% unemployed.	Naltrexone (100 mg/day) or placebo, and cognitive behavioural therapy (weekly, one-hour sessions) with or without contingency management. 12 week study.
Shaw 1987 [321]	UK	Assessed clinically as chemically dependent on alcohol and with current evidence of high levels of anxiety or depression. Detoxified prior to study. Aged 25-65, all male.	Tiapride (atypical neuroleptic) 300 mg/day or placebo. “Supportive follow-up interviews” as adjunct. 6 month treatment.
Shaw 1994 [322]	UK	Chemically dependent alcoholics admitted for detoxification. Mean age 41, 54% married or cohabiting, 57% employed. Gender not reported.	Tiapride 300mg/day or placebo, commenced in latter stages of detoxification. Routine counselling and support. 3 months medication, 3 months (drug-free) follow-up.
Simpson 2009 [352]	USA	Alcohol dependent by DSM-IV, last use of alcohol in month prior to study. Mean age 45.5, 79% male, 25% currently married. Most data on males who completed the study.	Prazosin, titrated to 16mg/day or placebo. Medical management (5 sessions, 1st 30-45 minutes then 10 minutes each). Text messaging system used to prompt reporting of data and administration of medication. 6 week treatment.
Soyka 2008 [353]	Germany	Alcohol dependent by DSM-IV, detoxified from alcohol 7-28 days before study entry. Mean age 44.8, 80.6% male.	Rimonabant 20mg/day or placebo. Participants seen 8 times over 12 weeks – nature of adjunct treatment not reported. 12 week study.
Stella 2008 [285]	Italy	Alcohol dependent by DSM-IV, detoxified prior to study. Mean age 42, 71% male, 74% employed, 58% married.	Escitalopram (SSRI) 20mg/day, escitalopram and naltrexone 50mg/day, escitalopram and GHB 75mg/kg/day, or escitalopram, naltrexone and GHB. Counselling and supportive behavioural therapy. 6 month treatment.

Study	Country	Participant characteristics	Intervention
Tempesta 2000 [191]	Italy	Alcohol dependent by DSM-III-R, ≥5 days abstinence before study. Mean age 46, 84% male, 68% married.	Acamprosate 1998mg/day or placebo. Weekly medical counselling, plus individual supportive counselling and AA available. 6 months treatment.
Tiihonen 1996 [278]	Finland	Alcohol dependence by DSM-III-R, abstinent ≥1 week before study. No major depressive disorder. Mean age 46, all male.	Citalopram 20 to 40mg/day, or placebo. Supportive psychotherapy. 3 month study.
Tollefson 1992 [341]	USA	Alcohol abuse or dependence and generalised anxiety disorder by DSM-III. 30-90 days abstinence at entry. Mean age 38.4, 73% male.	Buspirone to max 60mg/day (mean final dose 42.25mg) or placebo. Controlled participation in AA. 24 week study.
Tolliver 2009[174]	USA	Alcohol dependence and bipolar disorder by DSM-IV, abstinent 3 consecutive days before baseline. Mean age 47, 78% male.	Acamprosate 1998mg/day plus mood-stabilising medication, or mood-stabilising medication alone. Encouraged to attend substance use support/therapy groups. 8 week study.
Ulrichsen 2010	Denmark	Alcohol dependence by ICD-10, recruited from psychiatric emergency ward following alcohol withdrawal treatment. Study entry 10-25 days after discharge – drinking status at this time unclear. Average age 52, 69% male, 38% married or cohabiting, 44% employed.	Disulfiram 800mg twice a week (supervised at outpatient clinic) or no medication. Both groups had similar contact time including 16 group sessions cognitive behavioural therapy. 16 week treatment.
Volpicelli 1992 [124;125]	USA	Alcohol dependence by DSM-III-R, drank in 21 days prior to study entry. 1 week placebo treatment before randomisation. Mean age 43, all male, 42% employed, 44% married.	Naltrexone 50mg/day or placebo. Partial day treatment program in first month (6 hours/day of therapy and activities) then group therapy twice a week. 12 week study.
Volpicelli 1997 [129]	USA	Alcohol dependence by DSM-III-R, drank on mean 14 days of 30 prior to study entry. Mean age 38.5, 77% male, 68% employed, 44% married.	Naltrexone 50mg/day or placebo. Individual relapse prevention psychotherapy twice a week for 1 month, then weekly. 12 week study.
Whitworth 1996 [193]	Austria	Chronic (83%) or episodic dependence by DSM-III, ≥5 days abstinence at entry. Mean age 42, 78% male, 52% married.	Acamprosate 1332 or 1998mg/kg (by bodyweight) or placebo. Psychosocial behavioural treatment program (details not reported). 12 month study.
Wiesbeck 1999 [323;324]	International	Moderate or severe alcohol dependence by DSM-III-R. 2-6 weeks abstinence at entry. Median age 43, 80% male.	Ritanserin 2.5, 5 or 10mg/day or placebo (ritanserin groups combined for this review). Supportive individual and/ or group psychotherapy (treatment as usual). 6 month study.
Wiesbeck 2001 [325;326]	Germany, Austria	Moderate or severe alcohol dependence by DSM-III-R, abstinent 14-42 days at entry. Mean age 42, 72.6% male.	Flupenthixol (antipsychotic) 10mg or placebo as intramuscular injection every second week. Individual and/ or group supportive psychotherapy as needed. Participation in self-help groups recommended. 6 months medication, 6 months follow-up.
Wilson 1976 [223;224]	Canada	"Alcoholic", 17/20 from "Skid Row", mean age 34, 85% male.	Disulfiram 8 x 100mg tablets implanted, or sham operation. Alcohol challenge 120 hours after operation, monthly interviews.
Wilson 1980 [214]	Canada	"Alcoholic", weighted heavily towards "Skid Row". Mean age 36, 89% male	Disulfiram or placebo implant or no operation. No adjunct treatment reported. Follow-up interval mean 18 months.

Appendix 2: Definitions of Alcohol Dependence

DSM-IV Diagnostic Criteria for Alcohol Dependence

A maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three or more of the following seven criteria, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
   a) A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
   b) Markedly diminished effect with continued use of the same amount of alcohol.
2. Withdrawal, as defined by either of the following:
   a) The characteristic withdrawal syndrome for alcohol (refer to DSM-IV for further details).
   b) Alcohol is taken to relieve or avoid withdrawal symptoms.
3. Alcohol is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or there are unsuccessful efforts to cut down or control alcohol use.
5. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol or recover from its effects.
6. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
7. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the alcohol (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

DSM-IV Diagnostic Criteria for Alcohol Abuse

A maladaptive pattern of alcohol abuse leading to clinically significant impairment or distress, as manifested by one or more of the following, occurring within a 12-month period:

1. Recurrent alcohol use resulting in failure to fulfil major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions or expulsions from school; or neglect of children or household).
2. Recurrent alcohol use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine).
3. Recurrent alcohol-related legal problems (e.g., arrests for alcohol-related disorderly conduct).
4. Continued alcohol use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the alcohol (e.g., arguments with spouse about consequences of intoxication or physical fights).

These symptoms must never have met the criteria for alcohol dependence.

Proposed DSM-V Criteria for Alcohol-Use Disorder [1]

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by 2 (or more) of the following, occurring within a 12-month period:

1. recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)
2. recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
3. continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)
4. tolerance, as defined by either of the following:
   a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
   b) markedly diminished effect with continued use of the same amount of the substance

1 *From http://www.dsm5.org, accessed 6 August 2010*

5. withdrawal, as manifested by either of the following:
    a) the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for Withdrawal from the specific substances)
    b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
6. the substance is often taken in larger amounts or over a longer period than was intended
7. there is a persistent desire or unsuccessful efforts to cut down or control substance use
8. a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
9. important social, occupational, or recreational activities are given up or reduced because of substance use
10. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
11. Craving or a strong desire or urge to use a specific substance.

Moderate: 2-3 criteria positive

Severe: 4 or more criteria positive

ICD-10 Criteria for Alcohol Dependence Syndrome

A definite diagnosis of dependence should usually be made only if three or more of the following have been experienced or exhibited at some time during the previous year:

1. a strong desire or sense of compulsion to take alcohol;
2. difficulties in controlling alcohol-taking behaviour in terms of its onset, termination, or levels of use;
3. a physiological withdrawal state when alcohol use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for alcohol; or use of the alcohol with the intention of relieving or avoiding withdrawal symptoms;
4. evidence of tolerance, such that increased doses of alcohol are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol-dependent individuals who may take daily doses sufficient to incapacitate or kill non-tolerant users);
5. progressive neglect of alternative pleasures or interests because of alcohol use, increased amount of time necessary to obtain or take alcohol or to recover from its effects;
6. persisting with alcohol use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

Narrowing of the personal repertoire of patterns of alcohol use has also been described as a characteristic feature (e.g. a tendency to drink alcoholic drinks in the same way on weekdays and weekends, regardless of social constraints that determine appropriate drinking behaviour).

It is an essential characteristic of the dependence syndrome that either alcohol taking or a desire to take alcohol should be present; the subjective awareness of compulsion to use alcohol is most commonly seen during attempts to stop or control alcohol use.

Appendix 3: Glossary of Drugs and Therapies

Acamprosate	(*Campral*) Calcium acetylhomotaurinate, a synthetic derivative of homotaurine structurally similar to the neurotransmitter gamma-aminobutyric acid (GABA).
Alcoholics Anonymous	An international mutual aid movement claiming over 2 million members and declaring that its "primary purpose is to stay sober and help other alcoholics achieve sobriety". The philosophical foundation of AA is the 12 Steps. Only Step 1 mentions alcohol – the other steps focus more on personal growth. AA is not for everyone; some people object to perceived religious overtones, and many people simply do not like group approaches. Other people object because they believe AA to be opposed to the use of medication for people who are alcohol dependent.[384]
Amisulpride	Atypical antipsychotic. D_2 and D_3 antagonist. Standard doses for psychosis (400-1200mg/day) inhibit dopaminergic neurotransmission but low doses (50-200mg/day) preferentially block inhibitory pre-synaptic autoreceptors. This results in a facilitation of dopamine activity. Also 5-HT_7 antagonist.
Aripiprazole	Atypical antipsychotic and antidepressant. Distinct from other atypical antipsychotics (eg. olanzapine, quetiapine) in that it is a D_2 partial agonist, not D_2 antagonist. Also a partial agonist at 5-HT_{1A} and antagonist at 5-HT_{2A} receptors.
Baclofen	(*Kemstro*, *Lioresal*) A derivative of gamma-aminobutyric acid (GABA) primarily used to treat spasticity
Buspirone	(*Buspar*) Anxiolytic (non-benzodiazepine)
Calcium carbimide	(*Temposil*) An alcohol sensitising agent similar to disulfiram
Carbamazepine	An anticonvulsant and mood stabilizing drug used primarily in the treatment of epilepsy and bipolar disorder
Citalopram	(*Celexa*, *Cipramil*) An antidepressant drug of the selective serotonin reuptake inhibitor (SSRI) class
Cognitive Behavioural Therapy	Aims to teach patients how to identify high risk situations and develop skills to minimise the chances of relapse. Although the therapy encourages abstinence, coping with potential slips is explicitly discussed. The therapy is more highly structured than motivational enhancement therapy, although the empathic approach is encouraged in both forms of treatment.[384]
Cyanimide	An organic compound that is widely used in agriculture and the production of pharmaceuticals and other organic compounds. It is also used as an alcohol deterrent drug in Canada, Europe and Japan.
Desipramine	(*Norpramin*, *Pertofane*) A tricyclic antidepressant, it inhibits the reuptake of norepinephrine and to a lesser extent serotonin. It is used to treat depression, but not considered a first line treatment since the introduction of SSRI antidepressants. Desipramine is an active metabolite of imipramine.
Disulfiram	(*Antabuse*) Alcohol sensitising agent that inhibits the action of acetaldehyde dehydrogenase
Divalproex	Valproate semisodium or divalproex sodium consists of a compound of sodium valproate and valproic acid in a 1:1 molar relationship in an enteric coated form. It is used in the UK, Canada, and U.S. for the treatment of the manic episodes of bipolar disorder. Anticonvulsant
Fluoxetine	(*Prozac*, *Sarafem*) An antidepressant drug of the selective serotonin reuptake inhibitor (SSRI) class
Flupenthixol	(*Depixol*, *Fluanxol*) Typical antipsychotic; potent, relatively non-sedating. Antagonist at dopamine (D_1-D_5), serotonin (5-HT_2) adrenaline and histamine receptors.
Fluvoxamine	(*Luvox*) An antidepressant which functions as a selective serotonin reuptake inhibitor (SSRI).
Gabapentin	(*Neurontin*) A GABA analogue, anticonvulsant. It was originally developed for the treatment of epilepsy, but is also used for relief of pain, especially neuropathic pain.
Gamma Hydroxybutyrate (GHB)	Also known as 4-hydroxybutanoic acid and sodium oxybate, GHB occurs naturally in the central nervous system. It is categorized as an illegal drug in many countries and is currently regulated in Australia, Canada, most of Europe and in the US. Sodium oxybate (*Xyrem*) is sold for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy.
Imipramine	(*Antideprin*, *Deprimin*, *Deprinol*, *Depsonil*, *Dynaprin*, *Eupramin*, *Imipramil*, *Irmin*, *Janimine*, *Melipramin*, *Surplix*, *Tofranil*) Also known as melipramine, imipramine is a tricyclic antidepressant of the dibenzazepine group
Lithium carbonate	Lithium is a soft, silver-white metal; The lithium ion Li^+ administered as any of several lithium salts has proved to be useful as a mood stabilizing drug due to neurological effects of the ion in the human body.
Medical management	May be formal therapy as in the Combine Study where it was a manualised approach designed to approximate a primary care approach supporting sobriety and enhancing medication adherence through patient support, education and referral to support groups such as AA. Less formally, it may be a series of appointments with a clinical for the purpose of monitoring treatment and perhaps incorporating principles of motivational interviewing.
Motivational Enhancement Therapy	Based on motivational psychology and aims to mobilise the energy within the patient to change. The treatment is usually brief. During sessions the therapis maintains an empathic stance and works together with patients to develop and highlight the discrepancies between their current and desired level of functioning. The treatment assumes that highlighting these discrepancies will facilitate change particularly if the patients self-efficacy is affirmed. The therapist avoids confrontation and tries to evoke solutions from the patients instead of imposing them.[384]
Nalmefene	(*Revex*) An opioid receptor antagonist similar in structure and activity to naltrexone. Advantages of nalmefene relative to naltrexone include longer half-life, greater oral bioavailability and no observed dose-dependent liver toxicity.

Naltrexone	(*Revia*, *Depade*) An opioid antagonist that is also available as an extended-release formulation (*Vivitrol*).
Nefazodone	(*Serzone*, *Nefadar*) Weak serotonin-norepinephrine-dopamine reuptake inhibitor. Related to trazodone. Distinct from SSRIs, TCAs, MAOIs. Sale discontinued in some countries in 2003 (including USA) due to rare risk of hepatotoxicity.
Olanzapine	(*Zyprexa*, *Zalasta*, *Zolafren*, *Olzapin*, *Rexapin*, *Zypadhera*) An atypical antipsychotic; olanzapine has higher affinity for 5-HT_2 serotonin receptors than D_2 dopamine receptors
Ondansetron	(*Zofran*) A serotonin 5-HT_3 receptor antagonist used mainly as an antiemetic to treat nausea and vomiting
Oxcarbazepine	(*Trileptal*) An anticonvulsant and mood stabilizing drug. Oxcarbazepine is a structural derivative of carbamazepine with less impact on the liver from metabolism of the drug, and without the serious forms of anemia or agranulocytosis occasionally associated with carbamazepine
Prazocin	(*Minipress*, *Vasoflex*, *Pressin*, *Hypovase*) A sympatholytic drug used to treat high blood pressure. It is an alpha-adrenergic blockers, which lower blood pressure by relaxing blood vessels. Specifically, prazosin is selective for the alpha-1 receptors on vascular smooth muscle
Pregabalin	Anticonvulsant used for neuropathic pain and as an adjunct therapy for seizures. It has been found effective for generalised anxiety disorder. It is a structural analogue of GABA, with properties similar to gabapentin although it is more potent than gabapentin.[294]
Quetiapine	(*Seroquel*, *Ketipinor*) An atypical antipsychotic. D_1, D_2, D_3 and D_4 receptor antagonist; 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C} and 5-HT_7 antagonist plus anticholinergic and antihistamine properties
Rimonabant	(Also known as SR141716, trade names *Acomplia*, *Bethin*, *Monaslim*, *Remonabent*, *Riobant*, *Slimona*, *Rimoslim*, *Zimulti*, *Riomont*) Inverse agonist for the cannabinoid receptor CB1. Developed primarily as an anorectic anti-obesity drug.
Ritanserin	Atypical antipsychotic; 5-HT_{2A} and 5-HT_{2C} receptor antagonist
Sertraline	(*Zoloft*) Selective serotonin reuptake inhibitor; anti-depressant
Tianeptine	(*Stablon*, *Coaxil*, *Tatinol*) A selective serotonin reuptake enhancer used for treating major depressive episodes (mild, moderate, or severe). Unlike conventional tricyclic antidepressants, tianeptine enhances the reuptake of serotonin instead of inhibiting it, opposite to the action of SSRIs. Moreover, it enhances the extracellular concentration of dopamine in the nucleus accumbens and modulates the D_2 and D_3 dopamine receptors. It also has anticonvulsant and analgesic activity.
Tiapride	Dopamine antagonist; neuroleptic (non-sedative) similar to sulpride (selective antagonist at D_2 and D_3 receptors)
Topiramate	(*Topamax*) Anti-convulsant
Twelve-Step Facilitation Therapy	Shares the assumptions of Alcoholics Anonymous (ie. that alcohol dependence is a progressive emotional, physical and spiritual disease, which is characterised by loss of control over the use of alcohol). The therapy aims to encourage patients to join and maintain participation in the fellowship of AA. The therapy is flexible and allows for individualised treatment of those patients who have never been connected with AA and those who have participated in AA before.[384]
Valproate	Anticonvulsant

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