# Pharmacotherapies for Relapse Prevention in Alcohol Dependence Linda R. Gowing DASSA Monograph No. 17 Research Series

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#### SUMMARY VERSION

This topic review is a brief overview and analysis of research evidence of the effectiveness of different pharmacotherapies for relapse prevention in alcohol dependence.

The strength of evidence is rated as follows:

- \*\*\*\* strong evidence three or more RCTs with low risk of bias and consistent findings;
- \*\*\* good evidence three or more RCTs with low risk of bias but some variability of findings;
- \*\* moderate evidence two RCTs with low risk of bias, or 3 or more RCTs with risk of bias but consistent findings;
- some evidence 2 or more RCTs with risk of bias and variability of findings, or 1 RCT with low risk of bias.

If no rating is given, the statement is not supported by RCT evidence.

#### **Opioid antagonists**

#### Retention in treatment

Treatment with an opioid antagonist:

is not associated with increased retention in treatment;\*\*\*\*

#### Effect on alcohol consumption

Treatment with an opioid antagonist:

- increases the probability of total abstinence from alcohol\*\*\*\* for every 10 people treated with an opioid antagonist, one additional person will be continuously abstinent during treatment;
- decreases the risk of relapse to heavy drinking for every seven people treated with an opioid antagonist, one will be prevented from relapsing to heavy drinking;\*\*\*\*
- is associated with decreased alcohol consumption around one drink/drinking day, two drinks per week, and on 4% less treatment days;\*\*\*
- prolongs the interval between recommencement of drinking and relapse to heavy drinking

   the additional time without relapse associated with opioid antagonist treatment is around
   17 days.\*\*\*\*

#### Adverse effects

Treatment with an opioid antagonist:

- is not associated with an increased risk of experiencing any adverse effects, but is
  associated with an increased risk of specific adverse effects for every eight people
  treated, there will be one additional case of abdominal pain or other gastrointestinal
  symptoms, and one additional case of nausea or vomiting,\*\*\*\* and for every 14 people
  treated there will be one additional case of headache or neuropsychiatric symptoms.\*\*\*\*
- is associated with a significantly increased risk of premature withdrawal from treatment due to adverse effects – for every 17 people treated, one additional person will discontinue treatment because of adverse effects.\*\*\*\*

#### Other aspects

- People of Asian ethnicity may be more susceptible to adverse effects than those of Caucasian background.
- Naltrexone treatment may be associated with decreases in total cholesterol and triglycerides in plasma.
- 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.
- Better outcomes appear to be associated with higher levels of compliance with treatment.
- Outcomes appear to be independent of the nature and intensity of adjunct psychosocial treatment.
- People experiencing higher levels of craving may derive the greatest benefit from naltrexone.
- Naltrexone is effective for the treatment of alcohol dependence in people with concomitant schizophrenia or schizoaffective disorder.

## Acamprosate

# Retention in treatment

Compared with placebo or no medication, treatment with acamprosate:

 is associated with increased retention in treatment\*\*\*\* – for every 14 people treated with acamprosate, one additional person will complete treatment.

#### Compared with naltrexone:

• there is no significant difference in the rates of completion of treatment.\*\*\*

## Effect on alcohol consumption

Compared with placebo or no medication, treatment with acamprosate:

- increases the probability of continuous abstinence during treatment for every seven people treated, there will be one additional person continuously abstinent;\*\*\*\*
- increases the probability of abstinence on completion of treatment for every six people treated, there will be one additional person abstinent at follow-up;\*\*\*\*
- decreases the probability of relapse to heavy drinking during treatment for every 14
  people treated, there will be one person prevented from relapsing;\*\*\*\*
- increases the cumulative period of abstinence during treatment around 14% more days of abstinence;\*\*\*\*
- increases the time to first drink\*\*\*\* and may increase the time to first relapse.\*

It is unclear whether acamprosate has an effect on the number of drinks per drinking day, if a return to alcohol occurs.\*

When acamprosate is directly compared with naltrexone:

- naltrexone may be associated with significantly higher probability of abstinence on completion of treatment,\* longer cumulative period of abstinence during treatment,\* and longer time to first relapse;\*
- there is probably no significant difference in time to first drink\* and probably no significant difference in the likelihood of relapse during treatment.

However, the data is conflicting, and more information is required before conclusions can be drawn on the relative effectiveness of acamprosate and naltrexone in terms of alcohol consumption.

## Adverse effects

Compared with placebo or no medication, treatment with acamprosate:

- increases the risk of diarrhoea or other gastrointestinal effect for every 17 people treated, there will be one additional person who experiences diarrhoea;\*\*\*\*
- is not associated with an increase in risk of headache,\*\* overall adverse effects,\*\* or the number needing reductions of dose to manage adverse effects;\*\*
- marginally increases the number of people likely to withdraw from treatment due to adverse effects – for every 50 people treated there will be one additional premature withdrawal from treatment, a difference that is not clinically significant.

Compared with naltrexone, treatment with acamprosate is associated with:

- significantly less risk of nausea\* and abdominal pain\* but
- no difference in the risk of diarrhoea\* or headache,\* and
- no difference in the numbers discontinuing treatment prematurely because of adverse effects.\*\*

#### Other aspects

- The type of psychosocial therapy provided in conjunction with acamprosate does not appear to influence treatment outcomes\* and minimal adjunct treatment may be sufficient.\*
- Acamprosate may be more effective in people with non-familial alcohol dependence.

#### Combination drug therapy: naltrexone plus acamprosate

#### Retention in treatment

There appears to be no significant difference in rates of completion of treatment for combination therapy compared to either naltrexone or acamprosate alone, or placebo, but more data is required for a definitive conclusion.\*

#### Effect on alcohol consumption

On the basis of one study, combination therapy may be more effective than placebo or acamprosate in reducing relapse during treatment, and not significantly different to naltrexone alone.\* More data is needed to be conclusive. In particular, there is a need for combination therapy to be assessed on other indicators of alcohol consumption.

#### Adverse effects

Combination therapy is associated with increased incidence of adverse effects, particularly diarrhoea, abdominal pain and headache, but the increased incidence is not statistically significant.\* Combination therapy is not associated with increased need for reduction of dose to manage adverse effects, or increases in the number of participants discontinuing treatment because of adverse effects.\*\*

#### Disulfiram

Very few controlled studies of disulfiram are available. This limits the extent of conclusions that can be drawn about the relative effectiveness of disulfiram.

#### Retention in treatment

Disulfiram appears to have no significant effect on retention in treatment.\*

#### Alcohol consumption

Disulfiram appears not to significantly increase the number of people achieving and maintaining abstinence.\* Disulfiram may significantly increase the number of treatment days without drinking compared to placebo, no medication or naltrexone, particularly for people who are both alcohol and cocaine dependent.\*

#### Adverse effects

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. Overall, there is insufficient data available to form a view on the nature, relative incidence and severity of adverse effects associated with disulfiram treatment. However, accumulated clinical experience with disulfiram indicates:

an adverse drug reaction rate of one per 200–2000 patients per year;

- 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).

#### Other aspects

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.

Disulfiram may be effective in combination with acamprosate and other medications, but controlled trials have yet to be undertaken.

#### Antidepressants

#### Retention in treatment

Treatment with an antidepressant is not associated with increased retention in treatment.\*\*\*\*

#### Alcohol consumption

Treatment with an antidepressant:

- may increase the probability of total abstinence from alcohol;\*\*
- has no significant effect on rates of relapse, amount or frequency of alcohol consumption;\*\*\*
- does not prolong abstinence from alcohol.\*\*\*

#### Adverse effects

Treatment with an antidepressant is associated with increased risk of headache or neuropsychiatric symptoms and nausea – for every eight people treated with antidepressants, one additional person is likely to experience headache or neuropsychiatric symptoms,\*\* and for every 20 people treated with antidepressants, one additional person is likely to experience nausea or gastrointestinal symptoms.

Antidepressants, compared with placebo or no medication, are associated with increased risk of withdrawal from treatment due to adverse effects – for every 17 people treated with an antidepressant, one additional person is likely to withdraw from treatment due to adverse effects. The increased risk of dropout is more marked for SSRIs than for other antidepressants – for every 13 people treated with an SSRI, one additional person is likely to withdraw from treatment due to adverse effects.\*\*\*\*

#### Other aspects

The presence of comorbid depression, severity of dependence and gender may affect outcomes. However, data on these aspects is limited. Further information is required to be conclusive.

#### Other medication

#### Baclofen

Treatment with baclofen may increase the probability of abstinence during treatment without significant side effects.\* Further controlled studies are needed to confirm this finding.

#### Buspirone

Treatment with buspirone:

- significantly increases retention in treatment of alcohol-dependent people with an anxiety disorder;\*\*\*
- does not significantly reduce alcohol consumption;\*
- is associated with increased risk of adverse effects compared to placebo for every two
  people treated with buspirone, one additional person will experience adverse effects
  (dizziness is probably the symptom most frequently experienced);\*\*\*
- does not increase the risk of premature termination of treatment due to adverse effects.\*\*

#### Ondansetron

There is insufficient data to form a view of the effectiveness of ondansetron alone. The combination of ondansetron with naltrexone appears to reduce alcohol consumption to a greater extent than placebo. However, direct comparison with naltrexone is required to determine the extent of contribution of ondansetron.

#### Antipsychotics, neuroleptics and anticonvulsants

None of these medications are effective in relapse prevention treatment of alcohol dependence.\*\*

### GHB

GHB may have some efficacy in relapse prevention treatment of alcohol dependence, but further evidence is required. Given the potential for abuse of GHB, therapeutic use of this medication would need careful consideration.

#### Lithium

One study of lithium suggests this medication is not effective in treatment of alcohol dependence.

#### **Clinical implications**

Acamprosate and naltrexone are both effective for relapse prevention treatment of alcohol dependence. Acamprosate is more effective at promoting abstinence; naltrexone is more effective in preventing lapses to drinking becoming relapses to heavy drinking.

The effect of naltrexone in reducing alcohol consumption may make it effective in programs with controlled drinking as an alternative to total abstinence.

The evidence of the effectiveness of disulfiram is of poor quality, and suggests limited effectiveness of disulfiram on its own. However, disulfiram may have value as an adjunct to acamprosate.

Antidepressants are not effective for relapse prevention treatment of alcohol dependence, but have value in the management of depression associated with alcohol dependence.

There is insufficient information to determine the effectiveness of baclofen.

Buspirone has promise in the treatment of people with concomitant anxiety disorders and alcohol dependence.

Ondansetron may have promise, particularly in combination with naltrexone, but more evidence is needed.

Neuroleptic and antipsychotic medications are not effective for relapse prevention treatment of alcohol dependence.

# SCOPE

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

The pharmacotherapies considered are:

- opioid antagonists: naltrexone (ReVia®) and nalmefene;
- acamprosate (Campral®)
- disulfiram (Antabuse®)
- antidepressants: fluvoxamine, citalopram, fluoxetine, desipramine, sertraline, ritanserin;
- other medications: baclofen, buspirone, ondansetron, neuroleptics, anticonvulsants, GHB and lithium.

Treatment effectiveness is considered in terms of:

- retention in treatment
- alcohol consumption
- adverse effects.

#### METHOD

This topic review considers only randomised controlled trials comparing an active medication with placebo or no medication, with one exception – a study by Croop *et al.*<sup>1</sup> was included despite being non-randomised, as it included a large number of participants and focused on adverse effects, an aspect that needs large numbers.

Relevant randomised controlled trials were located by reference to recent reviews,<sup>2-9</sup> supplemented by searches of Medline, Embase and PsycINFO, using alcoholism, alcohol dependence, and medication names as search terms.

Studies were excluded from analyses where:

- there was a significant risk of attrition bias (>20% loss to follow-up and no assessment of differences in characteristics of those retained and those lost to follow-up);
- 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.

Included studies were grouped for analysis firstly on the basis of the medication being investigated, and secondly the comparison intervention. Statistical analyses of main outcomes were undertaken using Review Manager 4.2.7. For dichotomous outcomes (number completing treatment, number abstinent at follow-up), combined relative risk and number needed to treat was calculated. For continuous outcomes (days of abstinence, weeks in treatment) 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 evidence three or more RCTs with low risk of bias and consistent findings;
- \*\*\* good evidence three or more RCTs with low risk of bias but some variability of findings;
- \*\* moderate evidence two RCTs with low risk of bias, or 3 or more RCTs with risk of bias but consistent findings;
- some evidence two or more RCTs with risk of bias and variability of findings, or 1 RCT with low risk of bias.

In addition to the analyses of relative effectiveness, this topic 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 (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 relative risk 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 abstinent at follow-up), 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 relapsing to alcohol dependence), a relative risk less than 1 indicates that the active 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 relapsing, or to gain one additional person abstinent at the end of treatment, above the number for the comparison intervention.

The **Weighted Mean Difference (WMD)** is the sum of the differences in the individual studies, weighted by the individual variances for each study. Hence the weighted mean difference takes account of the precision of each study. The weighted 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 to relapse, a positive weighted mean difference indicates a longer time to relapse in the active group, indicating greater effectiveness than the comparison group. In the case of percent of treatment days with drinking, fewer days and hence a negative WMD indicates greater effectiveness in the active group relative to the comparison group.

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. 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 or WMD) 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 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  $l^2$  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.

#### STUDIES INCLUDED IN THIS TOPIC REVIEW

The studies contributing data to the analyses, grouped by type of medication and comparison, are listed below. (Note that some studies had multiple comparison groups and are included in more than one group.)

# 1. Opioid antagonist compared to placebo or no medication

(a) Oral naltrexone Ahmadi 2002<sup>10</sup> Anton 1999<sup>11; 12</sup> Balldin 200313 Chick 2000<sup>14</sup> Combine 200315; 16 Croop 1997<sup>1</sup> Galarza 1997<sup>17</sup> (cited by Srisurapanont *et al.*<sup>2</sup>) Gastpar 200218 Guardia 200219 Heinala 2001<sup>20</sup> Hersh 1998<sup>21; 22</sup> Kiefer 2003<sup>23</sup> Kranzler 2000B<sup>24</sup> Krystal 2001<sup>25</sup> Landabaso 1999<sup>26</sup> Latt 2002A27 Lee 2001<sup>28</sup> Monterosso 2001<sup>29</sup> Morris 2001<sup>30</sup> Niederhofer 2003A<sup>31</sup> O'Malley 199232-35 O'Malley 200336 Oslin 1997<sup>37; 38</sup> Petrakis 2004<sup>39</sup> Rohsenow 2000<sup>40; 41</sup>

Rubio 2002<sup>42</sup> Volpicelli 1992<sup>43; 44</sup> Volpicelli 1997<sup>45</sup>

(b) Depot or implant naltrexone
 Johnson 2004<sup>46</sup>
 Kranzler 1998<sup>47</sup>
 Kranzler 2004<sup>48</sup>

(c) Nalmefene Anton 2004<sup>49</sup> Mason 1994<sup>50</sup> Mason 1999<sup>51</sup>

# 2. Acamprosate

vs placebo or no medication (a) Baltieri 200452 Barrias 1997 (cited by Mann<sup>5</sup>) Besson 1998<sup>53</sup> Borg 1994 (cited by Mann<sup>5</sup>) Chick 2000A54 Combine 200315; 16 Geerlings 199755 Gual 2001<sup>56</sup> Kiefer 2003<sup>23</sup> Ladewig 1993<sup>57</sup> (cited by Mann *et al.*5 and Carmen *et al.*<sup>6</sup>) Lhuintre 1985<sup>58</sup> Lhuintre 1990<sup>59</sup> Namkoong 2003A<sup>60</sup> Niederhofer 2003<sup>61</sup> Paille 1995<sup>62</sup> Pelc 1992 (cited by Mann<sup>5</sup>)

Pelc 1997<sup>63</sup>

Poldrugo 1997<sup>64</sup> Roussaux 1996<sup>65</sup> (cited by Mann *et al.*<sup>5</sup>) Sass 1996<sup>66</sup> Tempesta 2000<sup>67</sup> Whitworth 1996<sup>68</sup>

(b) vs naltrexone
 Combine 2003<sup>15; 16</sup>
 Kiefer 2003<sup>23</sup>
 Rubio 2001<sup>69</sup>

# 3. Combination naltrexone and acamprosate

- (a) vs placebo or no medication
   Combine 2003<sup>15; 16</sup>
   Kiefer 2003<sup>23</sup>
- (b) vs acamprosate Combine 2003<sup>15; 16</sup> Kiefer 2003<sup>23</sup>
- (c) vs naltrexone Combine 2003<sup>15; 16</sup> Kiefer 2003<sup>23</sup>

# 4. Disulfiram

(a) oral vs placebo
 Chick 1992<sup>70</sup>
 Fuller 1979<sup>71-73</sup>
 Fuller 1986<sup>74</sup>
 Niederhofer 2003<sup>75</sup>

- (b) implant vs placebo
   Johnsen 1987<sup>76</sup>
   Johnsen 1991<sup>77</sup>
   Wilson 1976<sup>78; 79</sup>
   Wilson 1980<sup>80</sup>
- (c) oral vs no medication
   Carroll 1998<sup>81; 82</sup>
   Fuller 1979<sup>71-73</sup>
   Fuller 1986<sup>74</sup>
   Gerrein 1973<sup>83</sup>
   Powell 1985<sup>84</sup>
- (d) implant vs no medication Wilson 1980<sup>80</sup>
- (e) vs naltrexone Carroll 1993<sup>85</sup>

## 5. Antidepressants vs placebo or no medication

(a) Selective Serotonin Reuptake Inhibitors (SSRIs) Angelone  $1998^{86}$ Chick  $2004^{87}$ Cornelius  $1997^{88}$ Coskunol  $2002^{89}$ Deas  $2000^{90}$ Eriksson  $2001^{91}$ Gual  $2003^{92}$ Janiri  $1996^{93}$ Kabel  $1996^{94}$ Kranzler  $1993^{95}$ Kranzler  $1995^{96; 97}$ Moak  $2003^{98}$  Pettinati 2000<sup>99; 100</sup> Tiihonen 1996<sup>101</sup>

- (b) Tricyclic antidepressants
   Favre 1997<sup>102</sup>
   Mason 1996<sup>103</sup>
   McGrath 1996<sup>104</sup>
- (c) Ritanserin Johnson 1996A<sup>105</sup> Wiesbeck 1999<sup>106</sup>
- (d) Nefazodone Kranzler 2000B<sup>24</sup> Roy-Byrne 2000<sup>107</sup>

# 6. Other medications

- (a) baclofen vs placebo Addolorato 2002<sup>108</sup>
- (b) buspirone vs placebo
   Bruno 1989 <sup>109</sup>
   Fawcett 2000<sup>110</sup>
   Kranzler 1994<sup>111</sup>
   Malcolm 1992<sup>112</sup>
   Malec 1996<sup>113</sup>
   Tollefson 1992<sup>114</sup>
- (c) ondansetron vs placebo Johnson 2000<sup>115</sup>
- (d) combination naltrexone and ondansetron vs placebo Johnson 2000C<sup>116</sup>

- (e) antipsychotics (neuroleptics) vs placebo
   Marra 2002<sup>117</sup>
   Shaw 1987<sup>118</sup>
   Wiesbeck 2001<sup>119; 120</sup>
- (f) anticonvulsants
   Brady 2002<sup>121</sup>
   Johnson 2003G<sup>122</sup>
   Mueller 1997<sup>123</sup>
- (g) GHB vs naltrexone Caputo 2003<sup>124</sup>
- (h) lithium Fawcett 2000<sup>110</sup>

#### SECTION 1 OPIOID ANTAGONISTS

#### 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.<sup>3:9</sup>

Naltrexone (ReVia®) is the opioid antagonist that is approved in Australia for relapse prevention treatment of alcohol dependence. It has a rapid onset of action<sup>9</sup> and a single daily dose of 50mg (oral) is usually considered sufficient.

The COMBINE study Research Group<sup>15</sup> in presenting the rationale for a major randomised controlled trial of naltrexone and acamprosate (alone and combined) noted that very little work had been done to establish the optimal dose of naltrexone, with most studies testing the 50mg daily dose. On the basis of preclinical studies, clinical experience, preliminary results of a clinical trial, and a controlled laboratory study, this group suggest that the suppressive effects of naltrexone on alcohol self-administration are dose dependent. They also suggest 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. Full results from this study are not yet available.

A longer-acting opioid antagonist, nalmefene, is not available in Australia, but has been the subject of trials internationally. The claimed advantages of nalmefene over naltrexone include no dose-dependent association with toxic effects to the liver, greater oral bioavailability, longer duration of antagonist action, and more competitive binding with opioid receptor subtypes ( $\mu$ ,  $\delta$ , and  $\kappa$ ) that are thought to reinforce drinking,<sup>51</sup>

Depot and implant preparations of naltrexone have been the subject of trials but remain experimental. Data from these trials are included in analyses.

#### Evidence of effectiveness

Brief information about the trials included in this group of studies is given in

#### 1.2.1 Retention in treatment

There is no significant difference in the rates of completion of treatment for patients receiving an opioid antagonist compared to those receiving placebo or > no medication (Figure 1.1: RR 1.05, 95% CI 0.97, 1.13).

Eight studies reported retention in terms of time in treatment, rather than the proportion of participants completing treatment. These data also indicate no significant difference in retention for an opioid antagonist compared to placebo or no medication (Figure 1.2: WMD 0.35 weeks, 95% CI -0.26, 0.97).

# **CONCLUSION:** Treatment with an opioid antagonist is not associated with increased retention in treatment.\*\*\*\*

#### 1.2.2

1.2

Effect on alcohol consumption

Treatment with an opioid antagonist is associated with significantly more participants being abstinent from alcohol throughout the treatment period, compared to those receiving placebo or no medication (Figure 1.3: RR 1.39, 95% CI 1.18, 1.63). This difference translates to an NNT of 10, indicating that for every 10 people treated with an opioid antagonist, one additional person will be continuously abstinent during treatment than would be the case with placebo.

Only two studies reported data on the proportion of participants who were abstinent at the end of treatment. The data from these two studies indicate no significant difference on this outcome between opioid antagonist and placebo or no medication (Figure 1.4: RR 1.16, 95% CI 0.87, 1.54). However, given the small number of studies reporting this outcome, this finding is not reliable.

# **CONCLUSION:** Treatment with an opioid antagonist significantly increases the probability of total abstinence from alcohol.\*\*\*\*

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 naltrexone, compared to those receiving placebo or no medication (Figure 1.5: RR 0.73, 95% CI 0.64, 0.83). This difference in relapse rates translates to an NNT of 7, indicating that for every seven people treated with an opioid antagonist, one person will be prevented from relapsing to heavy drinking.

# **CONCLUSION:** Treatment with an opioid antagonist significantly decreases the risk of relapse to heavy drinking.\*\*\*\*

Consistent with this finding, treatment with an opioid antagonist is associated with significantly fewer drinks per drinking day (Figure 1.6: WMD -1.16 drinks/drinking day, 95% CI -2.11, -0.21), with some variability between studies.

Six studies reported consumption as drinks per week, rather than drinks per drinking day. By this measure, significantly lower alcohol consumption was associated with treatment with an opioid antagonist compared to placebo or no medication (Figure 1.7: WMD -2.97 drinks per week, 95% CI -4.71, -1.24).

A third way in which alcohol consumption was reported was in terms of the percent of days during treatment on which drinking occurred. Participants treated with an opioid antagonist drank on significantly fewer days than those receiving placebo or no medication (Figure 1.8: WMD -4.45% of treatment days, 95% CI -6.38, -2.52).

*CONCLUSION:* Treatment with an opioid antagonist is associated with decreased alcohol consumption – around one drink/drinking day, two drinks per week, and on 4% less treatment days.\*\*\*

Four studies reported the mean days to first drink. There was no significant difference in this outcome for people treated with an opioid antagonist
compared to those receiving placebo or no medication (Figure 1.9: WMD 1.06 days, 95% CI -3.28, 5.40).

Six studies reported the mean days to relapse (usually defined by heavy drinking – five or more standard drinks in a session for men, four or more for women). Treatment with an opioid antagonist was associated with a significantly longer time to relapse compared to placebo or no medication (Figure 1.10: WMD 17.20 days, 95% CI 8.16, 26.25).

*CONCLUSION:* Treatment with an opioid antagonist 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 opioid antagonist treatment is around 17 days.\*\*\*\*

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. This is supported by the findings in three studies<sup>11;43;45</sup> of significantly lower craving in participants treated with naltrexone, compared to those receiving placebo. In addition participants in three studies<sup>32;43;45</sup> reported a less-than-expected high when alcohol was consumed.

#### 1.2.3 Adverse effects

There is no significant difference in the proportion of participants treated with an opioid antagonist who experience adverse effects, compared to those receiving placebo or no medication (Figure 1.11: RR 1.19, 95% CI 0.97, 1.45). Only two studies reported data on reduction of doses of medication in response to adverse effects. These data indicated no significant difference in the proportion of those treated with an opioid antagonist having dose reductions, compared to those receiving placebo or no medication (Figure 1.12: RR 2.04, 95% CI 0.91, 4.58). This is consistent with the data indicating no significant difference in the probability of experiencing adverse effects.

However, when specific adverse effects are examined, there is a significant difference between opioid antagonists and placebo or no medication. Treatment with an opioid antagonist is associated with significantly higher
incidence of abdominal pain or other gastrointestinal symptoms (Figure 1.13:
RR 3.02, 95% Cl 1.44, 6.33) and nausea or vomiting (Figure 1.14: RR 2.45, 95% Cl 1.95, 3.07). The incidence of headache or neuropsychiatric symptoms
is also higher with opioid antagonist treatment (Figure 1.15: RR 1.37, 95% Cl 1.00, 1.87, P = 0.05). The risks of these specific adverse effects translate to NNTs of 8, 8, and 14, respectively.

*CONCLUSION:* Treatment with an opioid antagonist is not associated with an increased risk of experiencing any adverse effects, but is specifically associated with an increased risk of abdominal pain and other gastrointestinal symptoms, nausea or vomiting, or headache or neuropsychiatric symptoms – for every 8 people treated, there will be one additional case of abdominal pain or other gastrointestinal symptoms, and one additional case of nausea or vomiting, and for every 14 people treated there will be one additional case of headache or neuropsychiatric symptoms.\*\*\*\* Significantly more people treated with an opioid antagonist withdrew from treatment because of adverse effects, compared to those receiving placebo or no medication (Figure 1.16: RR 2.91, 95% Cl 2.01, 4.22). This difference translates to an NNT of 17, indicating that for every 17 people treated with an opioid antagonist, one person could be expected to discontinue treatment prematurely because of adverse effects than would be the case with placebo or no medication.

*CONCLUSION:* Adverse effects associated with opioid antagonist treatment significantly increase the risk of premature withdrawal from treatment. For every 17 people treated, one additional person will discontinue treatment because of adverse effects.\*\*\*\*

In addition to the adverse effects identified above, prescribing information warns of a potential risk of hepatotoxicity. Elevations of liver enzymes have been observed in studies involving doses of naltrexone up to 300 mg/day. At lower doses typically used for treatment of alcohol dependence, hepatotoxicity has not been identified as a concern.

It is possible that people of Asian ethnicity may be more susceptible to adverse effects than people of Caucasian background. Wilkin and Hazelrigg<sup>125</sup> 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.

# **CONCLUSION:** People of Asian ethnicity may be more susceptible to adverse effects than those of Caucasian background.

Budzynski *et al.*<sup>126</sup> 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.

# **CONCLUSION:** Naltrexone treatment may be associated with decreases in total cholesterol and triglycerides in plasma.

# 1.3 Factors influencing treatment outcome

Factors identified in the research literature include:

- nature of adverse effects experienced;
- compliance with medication;<sup>3</sup>
- type of adjunct psychosocial therapy.<sup>3; 9</sup>

# 1.3.1 Adverse effects

Oncken *et al.*<sup>127</sup> looked at adverse effects experienced by participants (n=89, 86.5% male, mean 38.6 years) in two randomised controlled trials who had been randomly allocated to naltrexone. They defined adverse effects as either neuropsychiatric (e.g. tiredness, sleepiness, drowsiness), experienced by 52.8%, or gastrointestinal (abdominal pain, nausea, dry mouth), experienced by 46.1%. They found that neuropsychiatric adverse effects 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.

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

Rohsenow *et al.*<sup>40</sup> also looked at adverse effects for participants in a randomised controlled trial. 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. The mean ( $\pm$ SD) duration of the four most common side effects was: nausea 17.9 $\pm$ 27.0 days; headache 10.1 $\pm$ 14.8 days; dizziness 8.7 $\pm$ 7.3 days; fatigue 17.7 $\pm$ 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.

*CONCLUSION*: 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.

#### 1.3.2 Compliance with medication

Volpicelli *et al.*<sup>45</sup> found that naltrexone showed only modest effects in reducing alcohol drinking when provided in a more naturalistic setting. However, treatment efficacy improved across a variety of outcome measures for subjects who completed treatment and were highly compliant in taking medication. Chick *et al.*<sup>14</sup> also 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). Cramer *et al.*<sup>128</sup> from an analysis of data from an RCT comparing naltrexone with placebo<sup>25</sup>, 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.

On the other hand the importance of the medication is indicated by follow-up data from one RCT<sup>12</sup>. 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.*<sup>33</sup> also found that some, but not all, of the benefits resulting from short-term naltrexone treatment persist after discontinuation of treatment.

Rohsenow *et al.*<sup>40</sup> concluded that compliance was greater among patients who believed more strongly that the medication would help them stay sober.

# *CONCLUSION*: Better outcomes appear to be associated with higher levels of compliance with treatment.

# 1.3.3 Adjunct psychosocial therapy

Balldin *et al.*<sup>13</sup> included a comparison of cognitive behavioural therapy (CBT) with supportive therapy (ST), in addition to naltrexone or placebo. They found a significant difference favouring CBT over ST, which they interpreted as indicating the importance of learning about coping with craving and relapse.

O'Malley *et al.*<sup>32</sup> also found that medication interacted with the type of psychotherapy received. The cumulative rate of abstinence was highest for patients treated with naltrexone and supportive therapy. For those patients who initiated drinking, however, patients who receiving naltrexone and coping skills therapy were the least likely to relapse.

Heinala 2001<sup>20</sup> included a comparison of cognitive coping skills with supportive therapy as adjuncts to either naltrexone or placebo. In the initial 12 weeks of this study, medication was administered daily and thereafter for 20 weeks only when craving alcohol (i.e. targeted medication). The data included in this review relates to the first 12 weeks for comparability with other studies. At the end of the continuous medication, the coping/naltrexone group had the best

outcome, and coping/placebo had the worst. This difference remained during the targeted medication period. Naltrexone was not better than placebo in the supportive groups.

On the other hand, a study by Latt *et al*,<sup>27</sup> showed that naltrexone with adjunctive medical advice is effective irrespective of whether it is accompanied by psychosocial interventions.

# **CONCLUSION**: Outcomes appear to be independent of the nature and intensity of adjunct psychosocial treatment.

# 1.3.4 Other factors

Oslin *et al.*<sup>129</sup> 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.

Jaffe *et al*,<sup>35</sup> analysed data from study by O'Malley *et al*,<sup>32</sup> to investigate treatment matching. They found that participants experiencing higher levels of craving and poorer cognitive functioning may derive the greatest benefit from naltrexone compared to placebo. Volpicelli *et al*.<sup>130</sup> also 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*,<sup>29</sup> found greater medication efficacy among patients with higher levels of craving. They 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.

Volpicelli *et al.*<sup>130</sup> pooled data from RCTs involving the Veterans Affairs population. They looked for baseline variables predictive of response to naltrexone. They found that the variables that predict whether an individual will drink during treatment are not independent, and cluster around symptoms of somatic distress, anxiety and alcohol craving.

# **CONCLUSION:** People experiencing higher levels of craving may derive the greatest benefit from naltrexone.

A recent study by Petrakis *et al.*<sup>39</sup> is significant in that all the participants were all diagnosed with concomitant alcohol dependence and schizophrenia or schizoaffective disorder (stable on medication). The positive finding from this 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.

*CONCLUSION*: Naltrexone is effective for the treatment of alcohol dependence in people with concomitant schizophrenia or schizoaffective disorder.

# SECTION 2 ACAMPROSATE

## 2.1 Rationale for effect

Acamprosate (Campral®) is a synthetic compound that is thought to reduce glutamate transmission by acting at the N-methyl-D-aspartate (NMDA) receptor complex, possibly through interference with the binding of calcium channel blockers.<sup>6</sup> Chronic alcohol exposure is associated with decreased levels of gamma-amino butyric acid (GABA) transmission and increased glutamate activity. When alcohol consumption is stopped, the glutamate system remains hyperexcitable, resulting in withdrawal symptoms.<sup>3</sup>

By normalising the dysregulation of NMDA-mediated glutamatergic neurotransmission, acamprosate is thought to reduce central nervous system hyperexcitability<sup>6</sup> and thus attenuate protracted withdrawal, which is one of the physiological mechanisms that may prompt relapse.<sup>9</sup>

Based on a review of European studies of acamprosate, Mason *et al.* 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.<sup>15</sup> Full results from this study are not yet available.

#### 2 Evidence of effectiveness

Table 2 provides brief information on the studies included in this review that compared acamprosate with placebo or no medication and studies comparing acamprosate and naltrexone. This section presents the evidence against the

major outcomes of interest, considering each of the above comparisons in turn.

2.2

# 2.2.1 Retention in treatment

(a) Acamprosate compared with placebo or no medication

Significantly more people treated with acamprosate, compared to placebo or no medication, completed treatment (Figure 2.1: RR 1.12, 95% CI 1.03, 1.22). This translates to an NNT of 14, indicating that for every 14 people treated with acamprosate, one additional person will complete treatment.

Geerlings *et al.*<sup>55</sup> also reported the mean ( $\pm$ SD) time in treatment: 102 $\pm$ 71 days for those treated with acamprosate, compared to 88 $\pm$ 73 days for those receiving placebo (P = 0.09).

# *CONCLUSION:* Compared with placebo or no medication, treatment with acamprosate is associated with increased retention in treatment.\*\*\*

#### (b) Acamprosate compared with naltrexone

Based on the limited data available, there is no significant difference in the proportion of people treated with acamprosate completing treatment, compared to those treated with naltrexone (Figure 2.2: RR 0.88, 95% CI 0.76, 1.02). However, there may be a trend in favour of naltrexone that could become more apparent as further studies report data.

# **CONCLUSION:** Compared with naltrexone, there is no significant difference in the rates of completion of treatment. \*\*\*

#### 2.2.2 Effect on alcohol consumption

(a) Acamprosate compared with placebo or no medication
 Significantly more people treated with acamprosate, compared to placebo or no medication, were continuously abstinent from alcohol during treatment
 (Figure 2.3: RR 1.58, 95% CI 1.36, 1.84). This translates to an NNT of 7, indicating that for every seven people treated with acamprosate, one additional person will be abstinent throughout the treatment period.

In addition, significantly more people treated with acamprosate were abstinent at follow-up (usually the completion of treatment), compared to those receiving placebo or no medication. (Figure 2.4: RR 1.52, 95% CI 1.35, 1.70). This translates to an NNT of 6, indicating that for every six people treated with acamprosate, one additional person will be abstinent at the end of scheduled treatment.

Participants treated with acamprosate were significantly less likely to relapse during treatment, compared to those receiving placebo or no medication
(Figure 2.5: RR 0.81, 95% CI 0.72, 0.91). This translates to an NNT of 14, indicating that for every 14 people treated with acamprosate, one less person will relapse during treatment.

Studies of acamprosate also typically report cumulative abstinence duration, in terms of the percent of the study days with no alcohol consumption. The cumulative abstinence duration is significantly longer for people treated with acamprosate, compared to those receiving placebo or no medication (Figure 2.6: WMD 14.41 % days, 95% CI 8.94, 19.88).

Only one study (Namkoong  $2003^{60}$ ) reported drinks/drinking day. In this study the mean drinks per drinking day were 7.2±9.8 for those treated with acamprosate, and 8.6±9.8 for those receiving placebo. The difference did not achieve statistical significance, but suggests the possibility of a magnitude of effect similar to that achieved with naltrexone. Further data is required to confirm whether acamprosate has an effect on the amount of alcohol consumed.

Most studies did not report the time to first drink or time to first relapse in a form suitable for meta-analysis. Five studies<sup>53;55;60;62;67</sup> reported a longer time to first drink for participants treated with acamprosate, compared to those receiving placebo. Two studies<sup>63;66</sup> reported a longer time to relapse, while one study<sup>60</sup> reported no difference in the time to first relapse. These data suggest that acamprosate does increase the time to first drink, a finding that is

consistent with data reported above showing that acamprosate increases cumulative abstinence duration.

*CONCLUSION:* Relative to placebo or no medication, treatment with acamprosate is associated with increased probability of continuous abstinence during treatment,\*\*\*\* increased probability of being abstinent on completion of treatment,\*\*\*\* significantly greater total abstinence during treatment,\*\*\*\* and decreased probability of relapse.\*\*\*\* It is unclear whether acamprosate has an effect on the number of drinks per drinking day, if a return to alcohol occurs.

## (b) Acamprosate compared with naltrexone

The COMBINE study has yet to report data on alcohol consumption, with the result that there are is currently very little information available on which to directly compare acamprosate and naltrexone.

There are no data on the proportion of participants continuously abstinent during treatment.

One study (Rubio 2001<sup>69</sup>) reported the number of participants abstinent at follow-up – 22 of 80 (27.5%) treated with acamprosate compared to 41 of 77 (53%) treated with naltrexone, giving an RR of 1.94 (95% CI 1.28, 2.93). This difference is statistically significant (P=0.002) in favour of naltrexone. The difference translates to an NNT of 4, indicating that for every four people treated with naltrexone, one additional person will be abstinent at the completion of treatment than would be the case if they had been treated with acamprosate.

The same study reported cumulative abstinence duration of  $49.3\pm35.3$  % days for acamprosate, compared to  $66.6\pm31.5$  % days for naltrexone, a mean difference of 17.3 (95% CI 6.84, 27.76), also statistically significant (P=0.001) in favour of naltrexone. The time to first relapse also significantly favoured the naltrexone group (mean  $63\pm38$  days compared to  $42\pm32$  days for the acamprosate group, P<0.001). However, there was no difference in the days to first drink ( $39\pm28$  days for acamprosate,  $44\pm36$  days for naltrexone, P=0.33).

Rubio *et al.*<sup>69</sup> reported numbers who had not relapsed at 1 year (41.5% naltrexone compared to 17.5% acamprosate). Kiefer *et al.*<sup>23</sup> reported the number who had relapsed. Assuming relapse for all other participants in Rubio 2001, these data were combined with the data from Kiefer 2003 as the numbers relapsing during treatment. Overall there was no significant difference between those treated with acamprosate and those treated with naltrexone (Figure 2.7: RR 0.95, 95% CI 0.47, 1.91).

It should be noted that a high proportion of participants in Rubio 2001 were married and employed, both factors likely to influence the response to treatment. Disulfiram was used in addition to naltrexone or acamprosate to manage relapse – 53% of the acamprosate group and 22% of the naltrexone group were prescribed disulfiram. This difference may have introduced a degree of bias.

*CONCLUSION:* Naltrexone, compared to acamprosate, may be associated with significantly higher probability of abstinence on completion of treatment,\* longer cumulative period of abstinence during treatment,\* and longer time to first relapse,\* but there is probably no significant difference in time to first drink\* and probably no significant difference in the likelihood of relapse during treatment. However, the data is conflicting, and further data are needed to make sense of the relative effectiveness of naltrexone and acamprosate.

#### 2.2.3 Adverse effects

(a) Acamprosate compared with placebo or no medication
 There is no significant difference in the proportion of people treated with acamprosate who experience adverse effects, compared to those receiving
 placebo or no medication (Figure 2.8: RR 1.13, 95% CI 0.99, 1.28).

Only two studies reported data on reduction of doses of medication in response to adverse effects. In both studies there was no significant difference in the proportion of those treated with acamprosate having dose reductions, compared to those receiving placebo or no medication (Figure 2.9: RR 1.3, 95% CI 0.83, 2.04).

When specific adverse effects are examined, there is no significant difference in the number of people treated with acamprosate, compared to placebo or no
medication, who experience headache (Figure 2.10: RR 1.13, 95% CI 0.70, 1.82). However, significantly more people treated with acamprosate experience
diarrhoea or other gastrointestinal effects (Figure 2.11: RR 1.57, 95% CI 1.34, 1.85). This translates to an NNT of 17 indicating that for every 17 people treated with acamprosate, one additional person will experience diarrhoea or gastrointestinal effects.

Marginally more people treated with acamprosate withdrew from treatment because of adverse effects, compared to those who received placebo or no medication (Figure 2.12: RR 1.35, 95% CI 1.00, 1.83, P=0.05). This translates to an NNT of 50.

*CONCLUSION:* Compared to placebo or no medication, treatment with acamprosate is associated with an increased risk of diarrhoea, or other gastrointestinal effects,\*\*\*\* but does not increase the risk of experiencing any adverse effect,\*\* or the number needing reductions in dose to manage adverse effects.\*\* The risk of early termination of treatment because of adverse effects is increased marginally by acamprosate, but the increase is not clinically significant.\*\*\*\*

Other studies have similarly reported that the only adverse event consistently reported across trials more frequently in acamprosate-treated patients with respect to placebo-treated patients is diarrhoea.<sup>6;9</sup> Compliance with acamprosate is typically greater than 85%, and not different from placebo.

Post-marketing monitoring has not identified any health risk associated with acamprosate in over 1.5 million patients.

Soyka *et al.*<sup>131</sup> assessed psychomotor performance before and after 6 weeks and 6 months of acamprosate treatment (1995mg/day). They recorded moderate improvement in two subscales and no change in the rest indicating no impairment of psychomotor performance by acamprosate.

#### (b) Acamprosate compared with naltrexone

There are no data currently available on the number of people treated with acamprosate experiencing any adverse effects, compared to those treated with naltrexone. However there are data on the number experiencing specific adverse effects.

Compared with people treated with naltrexone, those treated with acamprosate experience significantly less nausea (Figure 2.13: RR 0.20, 95% CI 0.09, 0.46, NNT 4), and significantly less abdominal pain (Figure 2.14: RR 0.18, 95% CI 0.06, 0.49, NNT 5). However, there is no significant difference in the numbers experiencing diarrhoea (Figure 2.15) or headache (Figure 2.16).

Only 1 study (COMBINE 2003<sup>15</sup>) reported the number of participants with doses reduced to manage adverse effects, finding no significant difference – 6 of 18 treated with acamprosate, compared to 5 of 18 treated with naltrexone.

On the basis of three studies, there is also no significant difference in the number of participants withdrawing from treatment with either naltrexone or acamprosate because of adverse effects (Figure 2.17: RR 0.61, 95% CI 0.19, 1.88).

*CONCLUSION*: Compared with naltrexone, treatment with acamprosate is associated with significantly less risk of nausea\* and abdominal pain\* but no difference in the risk of diarrhoea\* or headache,\* and no difference in

# the numbers discontinuing treatment prematurely because of adverse effects.\*\*

## 2.3 Factors influencing treatment outcome

Factors considered in research literature include:

- type of adjunct psychosocial treatment
- nature of alcohol dependence
- compliance.

# 2.3.1 Type of adjunct psychosocial treatment

Pelc *et al.*<sup>132</sup> report on a multi-country follow-up study of acamprosate and various types of psychosocial support in the setting of standard patient care. Higher scores on the alcohol health index (indicating a greater number of alcohol-related pathologies per patient), the presence of psychiatric antecedents and previous use of illicit drugs were identified as predictive of poor outcome. Outcomes were achieved irrespective of type of psychosocial support provided.

In a study by Soyka *et al.*<sup>133</sup>753 participants received acamprosate (1332–1998 mg/day according the bodyweight) and were assigned to one of four types of psychosocial therapy: individual psychotherapy, group psychotherapy, behavioural therapy, brief intervention or family therapy. The rates of abstinence were similar for all types of therapy.

De Wildt *et al.*<sup>134</sup> compared acamprosate alone with acamprosate plus motivational enhancement or brief cognitive behavioural therapy. No statistically significant differences were found between treatment groups for any of the drinking outcomes, medication compliance, drop-out rates or psychological distress. Hence the authors questioned the belief that pharmacotherapy for alcohol dependence should always be combined with psychological intervention. However, participants in this study had achieved 3–12 days of abstinence at entry and were clearly motivated to long-term abstinence. Hammarberg *et al.*<sup>135</sup> compared two levels of psychosocial intervention in combination with acamprosate in a randomised controlled trial. They found that adding more intensive individual treatments gave no extra improvement beyond that obtained by prescribing acamprosate and offering an infrequent consultation with a physician.

*CONCLUSION*: The type of psychosocial therapy provided in conjunction with acamprosate does not appear to influence treatment outcomes\* and minimal adjunct treatment may be sufficient.\*

# 2.3.2 Nature of alcohol dependence

In a crossover study, Gerra *et al.*<sup>136</sup> 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. 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.

# **CONCLUSION**: Acamprosate may be more effective in people with non-familial alcohol dependence.

## 2.3.3 Compliance

Chick *et al.*<sup>54</sup> 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.

In a comparison of acamprosate with placebo, Tempesta *et al*<sup>67</sup> found no differential effects for anxiety, depression or craving. Treatment remained positive, but not significant, three months after termination of study medication.

#### SECTION 3 COMBINATION DRUG THERAPY: NALTREXONE PLUS ACAMPROSATE

## 3.1 Rationale for effect

Naltrexone and acamprosate act by distinctly different mechanisms. 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. There are no specific toxic interactions between these agents, suggesting they can be safely co-administered.<sup>16:137</sup>

Furthermore, coadministration of acamprosate with naltrexone significantly increases the rate and extent of absorption of acamprosate.<sup>9; 138; 139</sup> Thus combination treatment may make acamprosate more available systemically, with no decrease in tolerability, which may have clinical advantages.<sup>9</sup>

## 3.2 Evidence of effectiveness

Brief information about the two trials included in this group of studies is given in Table 3.

# 3.2.1 Retention in treatment

(a) Combination treatment compared with placebo
 In Kiefer 2003,<sup>23</sup> significantly more participants treated with combination medications completed treatment. In Combine 2003,<sup>15:16</sup> the completion rate was higher in the placebo group, but did not reach statistical significance. The combined result is not significant (Figure 3.1: 1.48, 95% CI 0.44, 4.92).

# (b) Combination treatment compared with acamprosate

In Combine 2003,<sup>15</sup>; <sup>16</sup> there was no difference in completion rates for the combination therapy and acamprosate groups. In Kiefer 2003,<sup>23</sup> the difference in completion rates was in favour of the combination therapy group and just achieves significance. Overall there was no significant difference (Figure 3.2: RR 1.27, 95% CI 0.95, 0.71).

(c) Combination treatment compared with naltrexone

There was no significant difference in completion rates (Figure 3.3: RR 1.19, 95% CI 0.89, 1.58).

*CONCLUSION:* There appears to be no significant difference in rates of completion of treatment for combination therapy compared to either naltrexone or acamprosate alone, or placebo, but more data is required for a definitive conclusion.\*

# 3.2.2 Effect on alcohol consumption

Only Kiefer 2003 reported alcohol consumption data.

(a) Combination therapy compared with placebo
 The probability of relapse was significantly higher in the placebo group (23% vs 75%, RR 0.3, P < 0.0001).</li>

(b) Combination therapy compared with acamprosate
 The relapse rate was higher in the acamprosate group, but the difference was not statistically significant (23% vs 43%, RR 0.53, P = 0.07).

(c) Combination therapy compared with naltrexone
 There was no significant difference in the rates of relapse during treatment
 (23% vs 30%, RR 0.75, P = 0.45).

No other data on alcohol consumption were reported.

*CONCLUSION:* Combination therapy appears to be more effective than placebo, may be more effective than acamprosate alone in terms of relapse during treatment, but is not significantly different to naltrexone alone. More data are needed to be conclusive, particularly on other indicators of alcohol consumption.

# 3.2.3 Adverse effects

No data were reported on the number of people experiencing any adverse effect, but data are reported on the number experiencing specific adverse effects.

(a) Combination therapy compared with placebo

In Combine 2003, nausea was less frequent in the combination therapy group compared to the placebo group (33% vs 47%) but the difference was not statistically significant (RR 0.71, P = 0.32).

Diarrhoea, abdominal pain, and headache were more frequent in the combination therapy group than in the placebo group, but again the differences were not statistically significant. (RR for diarrhoea 1.28, P = 0.28; RR for abdominal pain 2.6, P = 0.18; RR for headache 1.57, P = 0.21).

The difference in the number of participants having their dose reduced due to adverse effects favoured placebo but was not statistically significant (RR 1.89, P = 0.27).

There was also no significant difference in the number who withdrew from > treatment due to adverse effects (Figure 3.4: RR 1.25, 95% CI 0.36, 4.31).

#### (b) Combination therapy compared with acamprosate

In Combine 2003, nausea, diarrhoea, abdominal pain, and headache were all somewhat more frequent in the combination therapy group, compared to the group receiving acamprosate only, but the differences were not statistically significant (RR for nausea 2.0, P = 0.23; RR for diarrhoea 1.23, P = 0.33; RR for abdominal pain 5.50, P = 0.09; RR for headache 1.25, P = 0.46).

There was no significant difference in the number having their dose reduced due to adverse effects (RR 1.0, P = 1.0).

There was also no significant difference in the number who discontinued treatment due to adverse effects (Figure 3.5: RR 0.87, 95% CI 0.26, 2.90).

#### (c) Combination therapy compared with naltrexone

In Combine 2003, nausea was somewhat less frequent in the combination therapy group than the naltrexone group (33% vs 56%), but the difference was not statistically significant (RR 0.60, P = 0.11). Diarrhoea, abdominal pain and headache were somewhat more frequent in the combination therapy group, but the differences were not statistically significant (RR for diarrhoea 1.35, P = 0.20; RR for abdominal pain 1.38, P = 0.53; RR for headache 1.43, P = 0.28).

There was no significant difference in the number having their dose reduced due to adverse effects (RR 1.20, P = 0.68). There was also no significant difference in the number who discontinued treatment due to adverse effects (Figure 3.6: RR 0.73, 95% CI 0.23, 2.29).

*CONCLUSION:* Combination therapy (naltrexone plus acamprosate) is associated with increased incidence of adverse effects, particularly diarrhoea, abdominal pain and headache, but the increased incidence is not statistically significant.\* Combination therapy is not associated with increased need for reduction of dose to manage adverse effects, or increases in the number of participants discontinuing treatment because of adverse effects.\*\*

#### SECTION 4 DISULFIRAM

#### 4.1 Rationale for effect

Disulfiram (Antabuse®) acts by inhibiting the action of enzymes that are required to metabolise acetaldehyde, thus resulting in its accumulation. The accumulated 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.<sup>3</sup>

The severity of the disulfiram-ethanol reaction is dependent upon the dose of each compound.<sup>140</sup>

#### Evidence of effectiveness

Table 4 provides brief information on the studies included in this review. The studies are grouped according to whether disulfiram is administered as an oral or a depot or implant preparation. Distinction is also made according to whether the comparison is placebo or no medication because of the potential psychological effect of expectation of a possible aversive reaction.

## 4.2.1 Retention in treatment

4.2

(a) Disulfiram compared with placebo

Only one study (Fuller 1986) reported data on retention in treatment. In that study, 93% treated with disulfiram compared to 97% treated with placebo completed treatment. This difference was not statistically significant (RR 0.97, P = 0.13).

#### (b) Disulfiram compared with no medication

There is also no significant difference in rates of completion of treatment for disulfiram compared to no medication (Figure 4.1: RR 1.02, 95% CI 0.88, 1.19). However, Carroll *et al.*<sup>81</sup> reported that participants dependent on

cocaine and alcohol who received disulfiram spent longer in treatment (8.4 weeks) compared to those not receiving medication (5.8 weeks, P < 0.05).

#### (c) Disulfiram compared with naltrexone

In Carroll 1993 (the only study making this comparison) 44% treated with disulfiram and 22% treated with naltrexone completed treatment. The sample size was small (9 in each group) and this difference was not statistically significant (RR 2.0, P = 0.34). There was also no significant difference in the number of weeks in treatment (WMD 2.10 in favour of disulfiram, P = 0.25). Participants in this study were all dependent on cocaine and alcohol. It is questionable whether this finding of similar retention in treatment for disulfiram and naltrexone would be applicable to the wider alcohol-dependent population.

# **CONCLUSION:** Disulfiram appears to have no significant effect on retention in treatment.\*

# 4.2.2 Effect on alcohol consumption

#### (a) Disulfiram compared with placebo

There is no significant difference in the proportion of participants treated with disulfiram, compared to those receiving placebo, continuously abstinent during
treatment (Figure 4.2: RR 0.92, 95% CI 0.66, 1.28). There is also no significant difference in the proportion of participants who were abstinent at follow-up
(Figure 4.3: RR 1.30, 95% CI 0.88, 1.92).

The number of days of abstinence during treatment were able to be calculated for three studies. (Fuller 1986 reported the percent of days during treatment with drinking. For inclusion in analyses, it was assumed that participants were abstinent for the rest of the time.) The data indicate no significant difference in cumulative abstinence duration for participants treated with disulfiram compared with placebo (Figure 4.4: WMD 18.47% days, 95% CI -2.31, 39.25).

Chick *et al.*<sup>70</sup> reported data that could not be combined with data from other studies. They reported that patients on disulfiram increased average total

abstinent days by 100 and patients on vitamin C by 69, thus enhancing by onethird this measure of treatment outcome. Mean weekly alcohol consumption was reduced by 162 units with disulfiram, compared with 105 units with vitamin C, and the disulfiram patients reduced their total 6-month alcohol consumption by 2572 units compared with an average reduction of 1448 units in the vitamin C group.

Besson *et al*<sup>53</sup> in a study of acamprosate compared to placebo, gave participants the option of also receiving disulfiram. They reported a cumulative abstinence duration that was significantly longer for those taking disulfiram in combination with acamprosate (55% compared to 28%) or placebo (31% compared to 14%). However, these data are subject to bias as those more motivated towards abstinence may have chosen to receive disulfiram.

Johnsen 1987 reported a mean 14.63 $\pm$ 8.41 drinks/week for participants receiving an active disulfiram implant, compared to 11.99 $\pm$ 4.77 drinks/week for those in the placebo group. This difference was not statistically significant (P = 0.38). In the same study the mean time to first drink was 49.9 $\pm$ 36.8 days for the disulfiram implant group, compared to 37.40 $\pm$ 38.70 days for the placebo group (P = 0.45). In a subsequent study by the same group<sup>77</sup>, the mean ethanol consumption during the study was 31.7g/day for those receiving an active implant, and 32.8g/day for those receiving placebo. The mean time to first drink was 148 compared with 149 days.

Niederhofer and Staffen<sup>75</sup> reported that one of 13 treated with disulfiram and six of 13 treated with placebo relapsed during treatment. This difference was not statistically significant (P = 0.08) probably due to the small sample sizes.

#### (b) Disulfiram compared with no medication

Compared to those receiving no medication, marginally more people treated with disulfiram were continuously abstinent during treatment, but the difference is not statistically significant (Figure 4.5: RR 1.33, 95% CI 0.91, 1.93). There was also no significant difference in the number of participants abstinent at >follow-up (Figure 4.6: RR 1.69, 95% CI 0.63, 4.57).

However, Carroll 1998<sup>81;82</sup> reported a significant difference in the maximum number of weeks of consecutive abstinence –  $4.45\pm4.27$  weeks in the disulfiram group, compared to  $1.75\pm2.64$  weeks in the group receiving no medication (P < 0.001). In addition 41 of 76 (54%) of the disulfiram group compared to 7 of 41 (17%) of the group receiving no medication achieved three or more consecutive weeks of abstinence from alcohol during treatment.

Powell *et al.*<sup>84</sup> reported the mean longest time abstinent in the six months prior to follow-up as 8.2 and 7.6 weeks for the two groups receiving disulfiram, compared to 7.2 weeks for the group receiving no medication.

Only Fuller 1986 reported the percent of treatment days with drinking, which was significantly lower in the disulfiram group (WMD -10.28 % days, 95% CI -10.89, -9.67).

## (c) Disulfiram compared with naltrexone

Only one study (Carroll 1993) makes this comparison. Participants were all cocaine dependent, but also met DSM-III criteria for alcohol abuse or dependence. Carroll 1993 reported significantly more weeks of alcohol abstinence (7.2 $\pm$ 3.3, compared to 1.6 $\pm$ 1.4, P < 0.001), less drinks per week (2.3 $\pm$ 6.2 compared with 27.0 $\pm$ 36.5, P = 0.06), and significantly less days with drinking during treatment (4.0 $\pm$ 0.04 compared to 26.3 $\pm$ 0.18%, P < 0.01) for the group treated with disulfiram compared to those treated with naltrexone.

*CONCLUSION:* Disulfiram appears not to significantly increase the number of people achieving and maintaining abstinence\* but may increase the number of days without drinking compared with placebo, no medication, or naltrexone, particularly for people who are both alcohol and cocaine dependent.\*

#### 4.2.3 Adverse effects

# (a) Disulfiram compared with placebo

In Niederhofer 2003<sup>75</sup> one participant in each of the oral disulfiram and placebo groups experienced adverse effects. In the three studies of depot or implant disulfiram, more participants in the disulfiram groups experienced adverse effects. While the differences in the individual studies did not achieve statistical significance, the calculated overall effect is statistically significant (Figure 4.7: RR 3.94, 95% CI 1.16, 13.34). The adverse effects related to the disulfiram implants were all wound complications around the insertion of the implant.

Chick 1992 reported 7 of 64 treated with disulfiram and none of 62 receiving placebo had dose reductions due to adverse effects. (The relative risk is inaccurate because of the zero incidence in the placebo group.) Two studies reported that more participants receiving disulfiram discontinued treatment due to adverse effects (Figure 4.8: RR 4.87, P = 0.07). The difference was not significant and the RR was again imprecise because of the low numbers.

## (b) Disulfiram compared with no medication

The only data reported comes from Fuller  $1986^{74}$ . In this study 3 of 208 (1.4%) receiving disulfiram and 1 of 199 (0.5%) receiving no medication discontinued treatment because of adverse effects. The difference was not statistically significant (P = 0.36)

(c) Disulfiram compared with naltrexoneNo data reported on adverse effects.

*CONCLUSION:* 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. Overall, there is insufficient data available to form a view on the nature, relative incidence and severity of adverse effects associated with disulfiram treatment.

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 250mg/day, the severity of the disulfiramalcohol 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 interaction have not been reported in recent years, possibly because the doses used are now lower and patients with cardiac disease are excluded.<sup>7</sup>

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.<sup>141</sup>

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.<sup>7</sup> Drowsiness is usually of short duration. If it persists, it usually can be managed by having the patient take the dose in the evening.<sup>141</sup>

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 chlordiazepoxide and diazepam, but not lorazepam and oxazepam. There is no hazardous interaction with paracetamol.<sup>7</sup> Animal and human data indicate that the concomitant use of MAO inhibitors and disulfiram is not safe.<sup>141</sup>

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.<sup>141</sup>

Disulfiram is known to cause hepatitis, which is sometimes fatal. The best estimate of the frequency of disulfiram-induced fatal hepatitis is 1 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.<sup>7</sup> Fuller and Gordis<sup>141</sup> recommend informing the patient of the symptoms and signs of hepatoxocity and also doing frequent testing of liver function in the early months of treatment. Because of the seriousness of the disulfiram hepatoxicity, they recommend not prescribing disulfiram to those with abnormal liver tests.

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. Rate of serious unwanted psychiatric effects are extremely low at recommended disulfiram dosages of 200–250mg/day.

Peripheral neuropathy and optic neuritis have been reported in conjunction with disulfiram treatment. The rate of disulfiram-induced neuropathy is around 1 in 15,000 patient years. Neuropathy is more likely with higher doses and possibly drug interactions. It is reversible if detected early.<sup>7</sup>

**CONCLUSION**: 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, ad the possibility of fatal disulfiram-alcohol reaction, are more likely with higher doses of disulfiram (≥500mg/day).

#### 4.3 Factors influencing treatment outcome

Factors considered in the research literature include treatment compliance and disulfiram as an adjunct medication.

## 4.3.1 Compliance

Other reviews of the effectiveness of disulfiram have made similar findings to those reported above, namely that few studies of disulfiram give a clear statement of efficacy.<sup>3</sup> Methodological rigour of studies of disulfiram is generally poor.<sup>141</sup> This field is hampered by the diversity of both the methods used and the subject populations studied. Support for the general use of oral disulfiram is equivocal, mostly being found in the form of reduced quantity of alcohol consumed and a reduced number of drinking days. Evidence for an effect in increasing the proportion of patients who achieve abstinence is lacking.<sup>142</sup>

However, a key factor appears to be compliance. Fuller *et al*,<sup>74</sup>, 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.<sup>141</sup> Mattick and Jarvis<sup>140</sup> 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). Fuller *et al.*<sup>73</sup> found that 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 11/100 (11%) with 85% or less attendance were abstinent.

Supervision and stable relationships both appear to improve compliance and hence treatment efficacy.<sup>3;143</sup> Hence, where it is prescribed, disulfiram use should be supervised and it should be employed as one part of a comprehensive treatment program.

CONCLUSION: 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.

# 4.3.2 Disulfiram as adjunct medication

Disulfiram has been used in combination with acamprosate. Poldrugo<sup>64</sup> found no evidence of any difference in outcome (but only 31 of 122 in the acamprosate group and 25 of 124 in the placebo group took disulfiram, and outcome data were not reported separately for these participants). However, Besson *et al*,<sup>53</sup> report a statistically significant greater cumulative abstinence duration for participants randomly allocated to acamprosate (24 of 55) who chose to also receive disulfiram (see also section 4.2.2(a)). The combination has not been tested in a controlled trial.

**CONCLUSION:** Disulfiram may be effective in combination with acamprosate and other medications, but controlled trials are yet to be undertaken.

# 4.3.3 Nature of adjunct treatment In a randomised controlled trial, Azrin *et al.*<sup>143</sup> compared disulfiram with three different types of adjunct support. Those in the traditional group received

standard counselling; those in the disulfiram assurance group received standard counselling plus training in adhering to the disulfiram regime, disulfiram administration was observed at the start of every session and a significant other was given training in how to support the client; the third group received all the support given to the second group, plus behavioural training. At 6-month follow-up, the traditional treatment clients were drinking on most days and no longer taking medication. The disulfiram assurance treatment resulted in almost total sobriety for married clients, but had little benefit for the single ones. The combined program produced near total sobriety for both single and married clients.

Similarly Annis and Peachey<sup>144</sup> compared two different types of support as adjuncts to the alcohol-sensitising drug, calcium carbamide. In the "Physician Advice" condition (n = 20), participants took the drug within a context designed to reinforce the medical management of their drinking problem. In the "Relapse Prevention" condition (n = 23), participants were instructed to link use of the drug with planned entry into high risk drinking situations and to gradually reduce reliance on the drug by developing alternative coping behaviour patterns. At 6, 12 and 18 months follow-up, there was some indication of superior treatment gains in the Relapse Prevention group but the effect did not achieve statistical significance.

Powell *et al.*<sup>84</sup> also found that the intensity of outpatient treatment experience was not related to outcome.

#### SECTION 5 ANTIDEPRESSANTS

#### 5.1 Rationale for effect

Serotonergic dysfunction has been implicated in alcohol dependence and the regulation of alcohol intake.<sup>86</sup> 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.<sup>137</sup>

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.<sup>3</sup>

#### 5.2 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);
- ritanserin (a 5-HT antagonist); and
- nefazodone, a serotonergic antidepressant that has a moderate inhibitory effect on reuptake of serotonin and norepinephrine, and selectively blocks the postsynaptic 5-HT<sub>2</sub> receptor which has been implicated in alcohol drinking behaviour,<sup>24</sup>

The SSRIs themselves are not a homogeneous class of drugs and hence may differ in their efficacy,<sup>86</sup> 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.

Further information about the trials included in this group of studies is given in **Table 5.** 

#### 5.2.1

#### Retention in treatment

There is no significant difference in the rates of completion of treatment for patients receiving an antidepressant compared to those receiving placebo or no medication (Figure 5.1: RR 0.98, 95% CI 0.85, 1.14). Indeed in two studies (Kranzler 1993<sup>95</sup> and Chick 2004<sup>87</sup>) rates of completion of treatment are significantly lower for those receiving an antidepressant. There is significant heterogeneity of results, but no obvious explanations for this variability of outcome.

For four studies the mean time in treatment was also reported (Figure 5.2).
 Again there is significant heterogeneity of outcomes, with time in treatment favouring antidepressants in two studies, and favouring placebo in two studies.
 Overall there is no significant difference (WMD -1.39 weeks, P = 0.24).

# **CONCLUSION:** Treatment with an antidepressant is not associated with increased retention in treatment.\*\*\*\*

#### 5.2.2 Effect on alcohol consumption

Three studies of SSRIs indicate significantly more participants treated with an SSRI were continuously abstinent during treatment, compared with those receiving placebo (Figure 5.3: RR 1.80, 95% Cl 1.18, 2.75). One study of nefazodone found no difference between nefazodone and placebo on this outcome (RR 0.92, 95% Cl 0.56, 1.52). The overall effect from all four studies is statistically significant, favouring antidepressant treatment (RR 1.37, 95% Cl 1.00, 1.89, P = 0.05).

However data from a further six studies on the number of participants abstinent at follow-up (usually completion of treatment) indicate no significant difference between antidepressant and placebo (Figure 5.4: RR 1.32, 95% CI 0.74, 2.38), except for one study<sup>104</sup> involving a tricyclic antidepressant (RR 2.10, 95% CI 0.99, 4.45, P = 0.05).

# **CONCLUSION:** Treatment with an antidepressant may increase the probability of total abstinence from alcohol.\*\*

Six studies reported the number of participants who relapsed during treatment. There was no significant difference on this outcome for those treated with an antidepressant (SSRI, tricyclic antidepressant or ritanserin) compared to those receiving placebo (Figure 5.5: RR 1.0, 95% CI 0.90, 1.12).

Five studies reported data on drinks per drinking day with variability in findings (Figure 5.6). In two studies (Cornelius 1997<sup>88</sup> and Moak 2003<sup>98</sup>) those treated with an SSRI consumed significantly less drinks per drinking day compared with those receiving placebo or no medication. Three studies found no significant difference, but the overall effect favoured antidepressant treatment (WMD -1.18 drinks, 95% CI -1.40, -0.97).

Two studies reported data on average drinks per week during treatment, with no significant difference between antidepressant and placebo (Figure 5.7: WMD 0.18, 95% CI -0.45, 0.81).

There is also no significant difference between antidepressant and placebo or no medication in terms of the percent of days during treatment with drinking (Figure 5.8: WMD -0.33% days, 95% CI -1.93, 1.28) or cumulative abstinence duration (Figure 5.9: WMD -0.73%, 95% CI -8.54, 7.08% days).

A number of studies considered the effect of antidepressants on alcohol consumption but did not report data in a form suitable for inclusion in the analyses presented above. Roy-Byrne *et al.*<sup>107</sup> found significant time effects, but no treatment group effects, for drinks consumed per day for nefazodone compared with placebo. Johnson *et al.*<sup>105</sup> and Kranzler *et al.*<sup>96</sup> also found that alcohol consumption measures reduced in all groups with no significant

differences between those treated with antidepressant, and those receiving placebo. Moak *et al.*<sup>98</sup> found no difference in time to first drink or time to first heavy drinking day in the full sample treated with sertraline or placebo, or for complier or complier and completer samples.

# *CONCLUSION:* Treatment with an antidepressant has no significant effect on rates of relapse, amount or frequency of alcohol consumption.\*\*\*

There was no significant difference in the time to first drink for people treated with an antidepressant (SSRI or nefazodone) compared to those receiving no medication or placebo (Figure 5.10: WMD 3.99 days, 95% CI -1.91, 9.89). There is also no significant difference in the time for relapse to heavy drinking for participants treated with an SSRI, compared to those receiving placebo or no medication (Figure 5.11: WMD 8.81 days, 95% CI -13.0, 30.61 days).

In the above analyses, data from Angelone 1998 is entered with the fluvoxamine and citalopram groups combined. While alcohol consumption data were similar for the two groups, Angelone *et al.*<sup>86</sup> reported that only citalopram showed a significant effect on craving throughout the study.

# *CONCLUSION:* Treatment with an antidepressant does not prolong abstinence from alcohol.\*\*\*

#### 5.2.3 Adverse effects

In Eriksson 2001 24% of participants treated with citalopram and 76% receiving placebo reported no side effects. These data have been converted to the proportion experiencing one or more side effects for comparison with other studies. Eriksson 2001 was the only study with a significant difference in the incidence of adverse effects associated with antidepressant compared to placebo or no medication. Overall there is no significant difference in the number of participants experiencing one or more side effects (Figure 5.12: RR 1.01, 95% CI 0.93, 1.10). Angelone 1998<sup>86</sup> stated there was no difference in overall adverse effects without reporting specific data. Mason 1996<sup>103</sup> reported

the most common adverse effects as dry mouth, insomnia, drowsiness, constipation, headache with no difference in the total number of adverse effects for desipramine and placebo groups.

On the basis of four studies, significantly more people treated with an antidepressant experience nausea or gastrointestinal symptoms (Figure 5.13: RR 1.37, 95% CI 1.06, 1.76; NNT= 20). Angelone 1998<sup>86</sup> also report more gastric symptoms with antidepressant (fluvoxamine or citalopram) compared to placebo. The incidence of headache or neuropsychiatric symptoms is also significantly higher with antidepressants compared to placebo or no medication (Figure 5.14: RR 1.33, 95% CI 1.07, 1.65; NNT = 8).

Significantly more participants treated with an antidepressant, compared to placebo or no medication, discontinued treatment because of adverse effects (Figure 5.15: RR 2.20, 95% CI 1.55, 3.11; NNT = 17). The increased risk of dropout is more marked for SSRIs than for other antidepressants (RR 2.79, 95% CI 1.73, 4.52; NNT = 13).

Johnson *et al.*<sup>105</sup> reported that ritanserin was associated with a dose-related prolongation of QTc interval, without clinical deterioration.

*CONCLUSION*: Treatment with an antidepressant is associated with increased risk of nausea or gastrointestinal symptoms, and headache or neuropsychiatric symptoms – for every eight people treated with an antidepressant, one additional person is likely to experience headache or neuropsychiatric symptoms,\*\* and for every 20 people treated with an antidepressant, one additional person is likely to experience nausea or gastrointestinal symptoms.\*\*\* Antidepressant treatment is also associated with a significant increase in withdrawal from treatment because of adverse effects (NNT = 17), particularly for SSRIs (NNT = 13).\*\*\*\*

## 5.3 Factors influencing treatment outcome

Outcomes appear to depend on the presence of comorbid depression,<sup>88;96</sup><sup>103</sup> the timeframe for follow-up and evaluation, severity of dependence and patient gender.<sup>3</sup>

It is possible that the inconsistencies (in trial outcomes) are related to the heterogeneity of the alcohol dependent population. SSRIs may be less effective in Type B (also called Type 2) population of alcohol dependence – late onset, males and females affected equally, low levels of sociopathy, polydrug use typically absent and alcohol dependence of low severity. For example, Kranzler *et al.*<sup>97</sup> found Type B alcoholics treated with fluoxetine drank more during treatment compared to placebo group. Pettinati *et al.*<sup>145</sup> found less alcohol use in Type A individuals treated with sertraline and no effect of sertraline in the type B group.<sup>137</sup>

Chick *et al.*<sup>87</sup> found no evidence that fluvoxamine helps prevent relapse in detoxified, abstinent, alcoholics. On the contrary, fluvoxamine was associated with worse outcomes than placebo for early-onset or Type II (by TPQ) drinkers. This result replicates that of Kranzler *et al.*<sup>97</sup> who found that random allocation to fluoxetine rather than placebo impaired drinking outcome of Type B alcoholics (in part defined by early onset). Also Pettinati *et al.*<sup>99</sup> who found that sertraline benefited Type A alcoholics but had no effect in Type B alcoholics.

In a crossover study, Gerra *et al.*<sup>136</sup> compared ethanol intake during treatment with fluoxetine, acamprosate or placebo, for participants with familial or nonfamilial alcohol dependence. Alcohol consumption decreased significantly during treatment with fluoxetine for participants with familial alcohol dependence, but not those with non-familial alcohol dependence.

Mason *et al.*,<sup>103</sup> in an RCT comparing desipramine with placebo, found that patients who relapsed had more severe alcohol dependence than those who did not.

All participants in Cornelius 1997 were diagnosed with comorbid major depression disorder and alcohol dependence. As indicated by figures 5.2, 5.5, 5.6, 5.7 and 5.8, fluoxetine did reduce alcohol consumption to a greater extent than did placebo (although not all differences were statistically significant). Cornelius *et al*,<sup>88</sup> reported that depressive symptoms were also reduced in the fluoxetine group, indicating possible vale for antidepressants in this population.

Kranzler *et al*,<sup>96</sup> found that fluoxetine had no effect on alcohol consumption but reduced depression scores more than placebo in subjects with current major depression. Kranzler *et al.* recommend that, in the absence of a comorbid mood or anxiety disorder, fluoxetine not be used to maintain abstinence or reduce drinking in high-risk/severity alcoholics.

Mason *et al.*<sup>103</sup> conclude that treating depression secondary to alcoholism may reduce risk for drinking relapse in some patients. They do not support use of desipramine to reduce relapse in non-depressed alcoholics. However, Pettinati *et al.*<sup>100</sup> found that sertraline was no better than placebo in patients with a diagnosis of lifetime comorbid depression, and current depression did not change the results.

*CONCLUSION*: Treatment with buspirone is associated with increased risk of adverse effects. \*\*\*

#### SECTION 6 OTHER MEDICATIONS

This group of studies includes a diverse range of medications that did not fit under any other of the groupings. Table 6 provides brief information on the studies. Each of the comparisons is considered in turn against the outcomes of interest.

#### 6.1 Baclofen compared with placebo

Baclofen is a potent and stereoselective  $\gamma$ -aminobutyric acid (GABAB) receptor agonist.

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.<sup>108</sup>

Baclofen has been compared with placebo in one randomised controlled trial (Addolorato 2002). In this study, 17 of 20 (85%) treated with baclofen and 11 of 19 (58%) receiving placebo completed treatment (RR 1.47, P = 0.08). Significantly more people treated with baclofen (14 of 20, 70%) compared to those receiving placebo (4 of 19, 21%) were continuously abstinent during treatment (RR 3.33, P = 0.01). The cumulative abstinence duration was also longer for those treated with baclofen (65.3±38.7 % days) compared to placebo (21±35% days) and this difference was significant (WMD 44.3% days, P <0.001). Addolorato *et al.*<sup>108</sup> also reported a decrease in the obsessive and compulsive components of craving, and a decrease in state anxiety for the baclofen compared to the placebo group.

Addolorato *et al.*<sup>108</sup> stated that the most common side effects were sleepiness (n=2), tiredness (n=1), and vertigo (n=1) in the baclofen group, and abdominal pain (n=1) in the placebo group. There were no serious adverse events requiring cessation of medication.

**CONCLUSION:** Treatment with baclofen may increase the probability of abstinence during treatment without significant side effects.\* Further controlled studies are needed to confirm this finding.

#### 6.2 Buspirone compared with placebo

Anxious patients may use alcohol to obtain an anxiolytic effect.<sup>114</sup> Hence control of anxiety may reduce relapse. Buspirone is a non-benzodiazepine anxiolytic (a 5-HT<sub>1A</sub> partial agonist) considered to have potential value in this regard.

Overall treatment with buspirone is not associated with a significant increase in the proportion of participants completing treatment (Figure 6.1: RR 1.27, 95% CI 0.88, 1.83). Two of the six studies (Fawcett 2000<sup>110</sup> and Malec 1996<sup>113</sup>) did not preferentially select participants with anxiety disorder. If these two studies are excluded from this analysis the outcome becomes significant, with more participants treated with buspirone completing treatment (RR 1.67, 95% CI 1.26, 2.22, P <0.001). This translates to an NNT of 4, indicating that for every four alcohol-dependent people with an anxiety disorder treated with buspirone, one additional person will complete treatment.

Kranzler 1994 reported the mean time in treatment:  $10.94\pm2.66$  weeks for those treated with buspirone, compared to  $8.17\pm4.53$  for those receiving placebo (WMD 2.77 weeks in favour of buspirone, P = 0.004). Malcolm 1992 reported median weeks in treatment: 9.1 for buspirone and 12.8 for placebo (not significant).

*CONCLUSION:* In alcohol-dependent people with an anxiety disorder, treatment with buspirone significantly increases the likelihood of completion of treatment.\*\*\*

Few of the studies reported data on alcohol consumption. In Malec 1996 two of 28 treated with buspirone and three of 29 receiving placebo were continuously abstinent during treatment (P = 0.67). Malcolm 1992 reported that 16 of 33 treated with buspirone and 21 of 34 receiving placebo were non-drinkers during study weeks 9 to 12 (P = 0.28). Kranzler 1994 and Fawcett 2000 reported the percent of treatment days with drinking, with no significant difference between those treated with buspirone and those receiving placebo (Figure 6.2: WMD -2.83%, 95% CI -6.80, 1.15%). Kranzler 1994 reported drinks per drinking day:  $3.3\pm6$  for the buspirone group, compared to  $6.6\pm8.2$  for the placebo group (P = 0.07). Bruno 1989 reported 3.9 drinks per drinking day for the buspirone group at 8 weeks, compared to 4.3 drinks per drinking day for the placebo group, with statistical comparison no possible due to a high rate of dropout from the placebo group. Fawcett 2000 reported average drinks per week:  $6.79\pm11.90$  for the buspirone group and  $5.67\pm10.50$  for the placebo group (P = 0.62).

# **CONCLUSION:** Treatment with buspirone does not significantly reduce alcohol consumption.\*

Buspirone treatment is associated with significantly more adverse effects, compared to placebo (Figure 6.3: RR 1.42, 95% CI 1.16, 1.74). This difference translates to an NNT of 5, indicating that for every five people treated with buspirone, one additional person will experience adverse effects.\*\*\*

Most of the studies did not report the detail of the adverse effects experienced, but two studies reported significantly more participants treated with buspirone experienced dizziness (Figure 6.4: RR 5.92, 95% CI 2.59, 13.56). This difference translates to an NNT of 2, indicating that one in every two people treated with buspirone will experience dizziness. Tollefson 1992<sup>114</sup> also identified dizziness as the most frequent adverse effect. Malec 1996<sup>113</sup> also reported that 7 of 28 treated with buspirone, compared to one of 29 receiving placebo, experienced nausea. The difference is not significant (P = 0.06). *CONCLUSION*: Treatment with buspirone is associated with increased risk of adverse effects. \*\*\*

Despite the adverse effects there is no significant difference in the number of participants discontinuing treatment due to adverse effects (Figure 6.5: RR 2.18, 95% CI 0.63, 7.59). Bruno 1989 reported that none in either group discontinued treatment due to adverse effects.

**CONCLUSION:** Treatment with buspirone does not increase the risk of premature termination of treatment due to adverse effects.\*\*

#### 6.3 Ondansetron

Johnson and colleagues have undertaken two trials involving ondansetron: one compared ondansetron with placebo,<sup>115</sup> and the other compared the combination of naltrexone and ondansetron with placebo.<sup>116</sup>

Ondansetron is a 5-HT<sub>3</sub> antagonist that has been shown to reduce alcoholinduced positive subjective effects and craving in healthy social drinkers, and to diminish drinking and increase abstinence among alcoholics with a biological disease predisposition. The ability of naltrexone to diminish alcohol consumption may be greater in biologically predisposed alcoholics. Hence it is postulated that ondansetron and naltrexone in combination may act synergistically at reducing alcohol consumption among biologically predisposed alcoholics.<sup>146</sup>

For ondansetron compared with placebo, there was no significant difference in the proportion of participants completing treatment (RR 0.88, 95% Cl 0.70, 1.11, P = 0.28). Ondansetron significantly reduced alcohol consumption and increased abstinence among early onset, but not late onset alcoholics.

No serious adverse events were reported and there were no significant differences in the incidence of specific adverse effects, apart from constipation which was experienced by 5% treated with ondansetron compared to 1.4% receiving placebo.

For the combination of ondansetron and naltrexone compared with placebo, alcohol consumption was significantly lower in the combination therapy group in terms of drinks per drinking day (WMD -3.62 drinks, 95% CI -4.32, -2.92, P < 0.001) and percent of treatment days with drinking (WMD -23.82 % days, 95% CI -31.61, -16.03, P < 0.001). No serious adverse effects were reported and none withdrew due to side effects. In a preliminary study, early onset alcoholics treated with ondansetron and naltrexone had lower scores, compared to those receiving placebo, on "automaticity of drinking" and "alcohol consumption" items of the obsessive compulsive drinking scale. Reduction in "automaticity of drinking" was correlated with self-reported drinking in the combination medication group.

In a subsequent cohort study, Johnson *et al.*<sup>147</sup> found that compared with placebo, ondansetron was associated with significant reductions in overall craving in early, but not late onset alcoholics.

In a secondary analysis of data from the RCT comparing ondansetron and placebo, Sloan *et al.*<sup>148</sup> found that change in anxiety level accounted for a significant proportion of the variance in end-state drinking. Those who experienced decreases in anxiety during the treatment reported fewer drinks per day at their last visit compared to those who reported increases in anxiety.

Ait-Daoud and Johnson<sup>149</sup> note that ondansetron has antiemetic and antinausea properties that help to counter the adverse effects of naltrexone, particularly in the early stages of treatment. This in turn may help to improve compliance with naltrexone.

*CONCLUSION:* There are insufficient data to form a view of the effectiveness of ondansetron alone in the treatment of alcohol dependence. The combination of ondansetron with naltrexone appears

to reduce alcohol consumption to a greater extent than placebo. However, direct comparison with naltrexone is required to determine the extent of contribution of ondansetron.

#### 6.4 Antipsychotics and neuroleptics

The potential for antipsychotic and neuroleptic medications in the treatment of alcohol dependence appears to relate to antidepressant and anxiolytic properties derived from effects on dopamine and serotonin receptors.<sup>117–119</sup>

Significantly fewer participants treated with an antipsychotic or neuroleptic completed treatment than did participants receiving placebo (Figure 6.6: RR 0.65, 95% CI 0.49, 0.84). Marra 2002 also reported days retained in the study, with no significant difference between amisulpride and placebo groups (125.10±61.6 compared with 124.7±71.5, P = 0.98).

Data from two studies indicates that significantly less participants treated with an antipsychotic or neuroleptic were abstinent at follow-up compared to those receiving placebo (Figure 6.7: RR 0.47, 95% CI 0.28, 0.77). Wiesbeck 2001 reported significantly lower cumulative abstinence duration for those treated with antipsychotic ( $55.56\pm34.44$  %days) compared to those receiving placebo ( $67.78\pm36.67$  %days, P = 0.007). In addition significantly more participants treated with antipsychotic relapsed to drinking during treatment (97/126compared to 69/118, P = 0.003) but there was no significant difference in the time to relapse ( $48\pm39$  days for those treated with antipsychotic and  $48\pm40$ days for those receiving placebo). The increased risk of relapse selectively affected men, not women, treated with flupenthixol.

Two studies reported the percent of days with drinking during treatment, with conflicting findings. Overall there was no significant difference in the percent of days with drinking during the study (Figure 6.8: WMD -2.53, 95% CI -17.59, 12.53). Only Marra 2002 reported days to first drink with no significant difference between those treated with amisulpride and those receiving placebo.  $(41.4\pm43.2 \text{ compared with } 36.5\pm38.1, P = 0.61).$ 

Wiesbeck 2001 reported that fewer participants treated with antipsychotic reported adverse effects than those receiving placebo (59 of 126 compared to 69 of 118) but the difference did not achieve statistical significance (P = 0.07). There was no significant difference in the number of participants discontinuing treatment due to adverse effects (Figure 6.9: RR 2.08, 95% CI 0.66, 6.54).

## **CONCLUSION:** Antipsychotic and neuroleptic medications are not effective in the treatment of alcohol dependence.\*

#### 6.5 Anticonvulsants

The rationale for the use of anticonvulsants in the treatment of alcohol and other drug dependence appears to be the association between mood disorders and substance use disorders. Hence, use of medication to modulate mood may impact on substance use.<sup>150</sup> Most of the research on the use of anticonvulsants to treat alcohol dependence relates to the management of alcohol withdrawal.<sup>151</sup> However, some studies of anticonvulsants for relapse prevention treatment have been undertaken. These studies are the focus of this section.

Treatment with anticonvulsants is not associated with increased rates of Completion of treatment (Figure 6.10: RR 1.05, 95% CI 0.88, 1.26).

Only one study<sup>121</sup> reported the number of participants abstinent throughout treatment, with no significant difference between those treated with an anticonvulsant and those receiving placebo (RR 1.05, 95% CI 0.36, 3.07, P = 0.93). A second study reported the number of participants abstinent at follow-up, again with no difference between those treated with an anticonvulsant and those receiving placebo (RR 1.38, 95% CI 0.75, 2.55, P = 0.30). There is also no significant difference in the number of participants who relapsed to heavy drinking during treatment (Figure 6.11: RR 0.81, 95% CI 0.55, 1.19). In Brady 2002, participants treated with anticonvulsant reported fewer drinks per drinking day ( $3.2\pm3.8$ ) compared to those receiving placebo ( $5.4\pm3.7$ ) but the difference did not achieve statistical significance (P = 0.11).

Johnson *et al.*<sup>122</sup> reported that over the study period, the group treated with topiramate had 1.06 less drinks per day, 1.20 less drinks per drinking day, 14.9% less heavy drinking days and 11.62% more days abstinent.

There is no significant difference in the number of participants who discontinued treatment due to adverse effects (Figure 6.12: RR 1.25, 95% CI 0.43, 3.70). Brady *et al.*<sup>121</sup> stated there were no group differences in side effects, but Johnson *et al.*<sup>122</sup> reported more dizziness, paraesthesia, psychomotor slowing, memory or concentration impairment, and weight loss in the group treated with topiramate, compared to those receiving placebo.

**CONCLUSION:** Anticonvulsants are not effective in relapse prevention treatment of alcohol dependence.

#### GHB compared with naltrexone

6.6

In the only study making this comparison<sup>124</sup> there was no significant difference in the number of participants completing treatment (74% GHB, 76% naltrexone, P = 0.93), the number abstinent during treatment (67% GHB, 35% naltrexone, P = 0.08), the number relapsing to heavy drinking (11% GHB, 0% naltrexone, P = 0.30) or the number discontinuing treatment due to adverse effects (6% GHB, 18% naltrexone, P = 0.30). This suggests that GHB may have some efficacy in relapse prevention treatment of alcohol dependence, but further evidence is required. Given the abuse of GHB in Australia, therapeutic use of this medication would need careful consideration.

## 6.7 Lithium compared with placebo

In only study making this comparison<sup>110</sup> there was no significant difference in the number of participants completing treatment (61% lithium, 52% placebo, P = 0.36), drinks per week during treatment (4.83±7.0 lithium, 5.67±10.5 placebo, P = 0.63), or percent of days with drinking during treatment (10±15 lithium, 8±14 placebo, P = 0.48). More participants treated with lithium experienced adverse effects (61% compared to 44%) but the difference was not statistically significant (P = 0.09). There was also no significant difference in the number of participants discontinuing treatment due to adverse effects (2% lithium, none placebo, P = 0.53).

#### SECTION 7 CLINICAL IMPLICATIONS

The data presented in this review indicate that acamprosate and naltrexone are both effective for relapse prevention treatment of alcohol dependence. However, retention in treatment is better with acamprosate, and acamprosate is more effective at promoting total abstinence from alcohol, but naltrexone appears to be more effective in preventing lapses to drinking becoming relapses to heavy drinking.

These findings are consistent with the mechanisms of action of these medications: acamprosate diminishes craving and withdrawal, while opioid antagonists have an effect on the sense of intoxication from alcohol, which acamprosate does not.

Treatment with naltrexone or acamprosate is associated with adverse effects. Naltrexone increases the risk of gastrointestinal symptoms, nausea or vomiting, and headache or other neuropsychiatric symptoms. Acamprosate increases the risk of diarrhoea or other gastrointestinal symptoms. Both medications increase the risk of premature withdrawal from treatment due to adverse effects, but in the case of acamprosate the increase is not clinically significant.

Other recent systematic reviews have come to similar conclusions. Carmen *et al*,<sup>6</sup> found that acamprosate was associated with a significant improvement in abstinence rates and days of cumulative abstinence, while short-term administration of naltrexone significantly reduced 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<sup>8</sup> found that there is no statistical difference in the efficacy of acamprosate and naltrexone. Mason<sup>9</sup> also concluded that acamprosate and naltrexone are both useful in the treatment of alcohol dependence. Carmen *et al.* noted that overall compliance was relatively low with both acamprosate and naltrexone. They suggest that issues of compliance need to be addressed adequately to assure the usefulness of naltrexone and acamprosate in clinical practice.

The effect of naltrexone in reducing alcohol consumption may make it effective in programs with controlled drinking as an alternative to total abstinence. This is supported by studies by Kranzler *et al.*<sup>152</sup> and Rubio *et al.*<sup>42</sup> involving early problem drinkers with lesser severity of dependence. Davidson *et al.*<sup>153</sup> assessed the effectiveness of naltrexone for decreasing alcohol drinking in hazardous (not dependent) drinkers. Participants received naltrexone (n = 19) or placebo (n = 19) plus two, 30-minute counselling sessions in the first two weeks. Both groups improved, but naltrexone-treated participants did not show the same degree of improvement on drinking outcomes as placebo-treated participants. However, the groups were not balanced on gender or family history of alcoholism which are potential confounding factors. It should be noted that naltrexone is not currently approved for this purpose in Australia.

As has been noted by other reviews,<sup>4</sup> the use of disulfiram is widespread, but is less clearly supported by research evidence. Available evidence is of poor quality, and suggests limited effectiveness of disulfiram on its own. 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. Changes in technology may offer means of improving implant or depot formulations, but no research of this nature has been reported.

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. Antidepressants are not effective for relapse prevention treatment of alcohol dependence, but the presence of comorbid depression, severity of dependence and gender may affect outcomes. Antidepressants do have value for the management of depression associated with alcohol dependence.

There is insufficient information to determine the effectiveness of baclofen.

Buspirone has promise in the treatment of people with concomitant anxiety disorders and alcohol dependence.

Ondansetron may have promise, particularly in combination with naltrexone, but more evidence is needed.

Neuroleptic, antipsychotic and anticonvulsant medications and lithium are not effective for relapse prevention treatment of alcohol dependence. GHB may have some efficacy, but potential abuse may limit its application in the treatment of alcohol dependence.

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## TABLES

## Table 1Studies involving an opioid antagonist

(a) Oral naltrexone compared with placebo or no medication

Study	Country	Participant characteristics	Intervention
Ahmadi 2002	Iran	Dependent, 3-30 days abstinence at entry. All male, 87% married, 16% unemployed.	(1) Naltrexone, 50mg/day, vs placebo, 12 weeks. Weekly counselling as adjunct.
Anton 1999	USA	Dependent by DSM-III-R, ≥5 days abstinence at entry. 71% male, 68% married, 81% employed.	Naltrexone 50mg/day, vs placebo, 12 weeks. Cognitive behavioural therapy as adjunct.
Balldin 2003	Sweden	Dependent by DSM-IV, 14-28 days abstinence at entry. 77-91% male, 48-63% married, 65-80% employed.	Naltrexone 50mg/day, vs placebo, 6 months. Cognitive behavioural therapy or supportive therapy as adjunct.
Chick 2000	UK	Abuse or dependence (87%) by DSM-III-R. Median 10-11 days abstinence before study. 75% male, 40% cohabiting. 27% employed.	Naltrexone 50mg/day, vs placebo, 12 weeks. Variable psychosocial treatment as adjunct.
Combine 2003	USA	Dependent y DSM-IV, abstinent <21 days at entry. 67-81% male, 35-47% married. 56-78% employed.	Acamprosate 3g/day vs naltrexone 100mg/day vs acamprosate plus naltrexone vs placebo, 16 weeks. Medical Management or Combined Behavioural Intervention as adjunct.
Croop 1997	USA	14 years heavy alcohol use. 74% male. 55% (naltrexone), 38% (no medication) employed	Naltrexone to max 200mg/day vs no medication, 12 weeks. Allocation by choice, open-label. Psychosocial program as adjunct.
Galarza 1997	Puerto Rico	All male.	Naltrexone vs placebo, 4 weeks. Psychosocial treatment as adjunct.
Gastpar 2002	Germany	Dependent by DSM-III-R. Abstinent for mean 20 days before study. 73% male.	Naltrexone 50mg/day vs placebo, 12 weeks. Outpatient and inpatient (up to 28 days) treatment. Adjunct psychosocial program.

Study	Country	Participant characteristics	Intervention
Guardia 2002	Spain	Dependent by DSM-III-R. 5-30 days abstinence at entry. 75% male, 58% married, 45% employed.	Naltrexone 50mg/day vs placebo, 12 weeks. Supportive group therapy, counselling and adjunct medications as required.
Heinala 2001	Finland	Dependent by DSM-IV. Not detoxified prior to study. 71% male, 73% married, 75% employed.	Naltrexone 50mg/day vs placebo, 12 weeks regular medication, 20 weeks targeted (when drinking likely). Cognitive behavioural therapy as adjunct.
Hersh 1998	USA	Abuse or dependence (92%) by DSM-III-R. 92% male, 87% also cocaine dependent, 81% employed.	Naltrexone 50mg/day vs placebo, 8 weeks. Relapse prevention psychotherapy as adjunct.
Kiefer 2003	Germany	Dependence by DSM-IV. Abstinent 12-15 days before study. 74% male, 27% married, 61% employed.	Naltrexone 50mg/day vs placebo, 12 weeks. Abstinence-oriented group therapy as adjunct.
Kranzler 2000B	USA	Dependence by DSM-III-R. Abstinent 3-28 days before study. 77% male	Naltrexone, 50mg/day vs placebo, 11 weeks. Coping skills training as adjunct.
Krystal 2001	USA	Dependence by DSM-IV. Abstinent ≥5 days before study. 98% male, 35% married.	Naltrexone, 50mg/day 3 months or 12 months, vs placebo. (3 month data used and naltrexone groups combined.) 12-step facilitation counselling.
Landabaso 1999	Spain	Dependence or abuse by DSM-IV. 73% male, 53% married, 77% employed.	Naltrexone 25mg/day plus aversion agent (disulfiram or calcium cyanamide) vs aversion agent only, 1 year. Supportive psychotherapy as adjunct.
Latt 2002A	Australia	Dependence by DSM-IV. Abstinent mean 12 days before study. 69% male.	Naltrexone 50mg/day vs placebo, 12 weeks. Counselling and/or AA available but not obligatory.
Lee 2001	Singapore	Dependence by DSM-IV. Entered study 1 week after detox. All male, 72% married, 40% employed.	Naltrexone 50mg/day vs placebo, 12 weeks. 12-step oriented program as adjunct. 1 month inpatient, rest outpatient.
Monterosso 2001	USA	Dependence by DSM-III.R. Abstinent 3 days before study. 73% male	1 week placebo, then naltrexone 100mg/day or placebo, 12 weeks. Psychosocial therapy as adjunct.
Morris 2001	Australia	Dependence by DSM-III-R. Abstinent 3-30 days at entry. All male, 55% psychiatric comorbidity, 48% married.	Naltrexone 50mg/day vs placebo, 12 weeks. Group psychoeducation and social support as adjunct.

Study	Country	Participant characteristics	Intervention
Niederhofer 2003A	Austria	Chronic or episodic dependence by DSM-III-R. Abstinent ≥5 days at entry. All adolescents (15- 19).	Naltrexone 50mg/day vs placebo, 90 days. Adjunct treatment not reported.
O'Malley 1992	USA	Dependence by DSM-III-R. Abstinent mean 9.4 days before study. 74% male, 73% unemployed, 66% unmarried.	Naltrexone 50mg/day vs placebo, 12 weeks. Coping skills/relapse prevention or supportive therapy as adjunct.
O'Malley 2003	USA	Dependence by DSM-III-R, <2 heavy drinking days in last 28 days of treatment with naltrexone. 75% employed, 52% unmarried.	Naltrexone 50mg/day vs placebo, 6 months. Two separate studies of primary care management or cognitive behavioural therapy as adjunct.
Oslin 1997	USA	Dependence by DSM-III-R. 16% married. Gender not reported – all veterans.	Naltrexone 100mg Mon & Wed, 150mg Fri, vs placebo, 12 weeks. Group therapy and case management as adjunct.
Petrakis 2004	USA	Abuse or dependence (97%) by DSM-IV. Abstinent <29 days at entry. All male. 16% employed. All with schizophrenia or schizoaffective disorder.	Naltrexone 50mg/day vs placebo, 12 weeks. Cognitive-behavioural relapse prevention plus skills training and usual psychiatric treatment as adjuncts.
Rohsenow 2000A	USA	Abuse or dependence by DSM-IV. Partial inpatient treatment prior to study. 76% male, 84% employed.	Naltrexone 50mg/day, vs placebo, 9 months. Cue exposure, coping & communication skills training during inpatient phase. 3 month data used.
Rubio 2002	Spain	Mild alcohol dependence by DSM-III-R and Severity of Alcohol Dependence Scale. All male.	Naltrexone 50mg/day plus controlled drinking program vs controlled drinking program only.
Volpicelli 1992	USA	Dependence by DSM-III-R. All male. 34.2% (naltrexone) and 48.9% (placebo) employed. 44% married.	Naltrexone 50mg/day vs placebo, 12 weeks. Partial day treatment first month.
Volpicelli 1997	USA	Dependence by DSM-III-R. Abstinent <21 days before study. 77% male, 68% employed, 44% married.	Naltrexone 50mg/day vs placebo, 12 weeks. Relapse prevention therapy as adjunct.

## (b) Depot or implant naltrexone

Study	Country	Participant characteristics	Intervention
Johnson 2004	USA, France, Netherlands	Dependence by DSM-IV. Abstinent 5 days before study. Naltrexone: 68% male, placebo: all male	Naltrexone 400mg depot preparation or placebo by intramuscular injection every 28 days. Psychosocial therapy as adjunct. 4 month study.
Kranzler 1998	USA	Dependence by DSM-IV. Abstinent ≥3 days at entry. 75% male, 45% employed, 80% married in naltrexone group, 40% in placebo group.	2 weeks oral naltrexone, 2 week placebo washout, then naltrexone 206mg or placebo, sustained release preparation as single subcutaneous injection. Coping skills as adunct. 12 week study.
Kranzler 2004	USA	Dependence by DSM-IV. Abstinent ≥3 days at entry. 65% male.	Naltrexone, 300mg first injection, 150mg/month subsequently, or placebo, intramuscular injection of depot formulation. Motivational enhancement as adjunct. Self-help groups encouraged. 12 week study.

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## (c) Nalmefene

Study	Country	Participant characteristics	Intervention
Anton 2004	USA	Dependence by DSM-IV. Abstinent ≥3 days at entry. 72% male, 43% to 64% married.	Nalmefene, 5, 20 or 40 mg/day, or placebo, 12 weeks. Motivational enhancement therapy as adjunct. Individualised goal of total abstinence or drinking reduction.
Mason 1994	USA	Dependent by DSM-III-R. 71% male.	Nalmefene 10 or 40mg/day, vs placebo, 12 weeks. No psychosocial treatment.
Mason 1999	USA	Dependence by DSM-III-R. 67% male, 38% married, 70% employed.	Nalmefene 20 or 80mg/day, vs placebo, 12 weeks. Cognitive behavioural therapy as adjunct.

## Table 2Studies involving Acamprosate

Study	Country	Participant characteristics	Intervention
Baltieri 2004	Brazil	Dependent by ICD-10. All male, 1 week detoxification before study.	Acamprosate 1998 mg/day vs placebo, 12 weeks. Encouraged to attend AA.
Barrias 1997	Portugal	8% female, 73% married.	Acamprosate vs placebo, 12 months.
Besson 1998	Switzerland	Dependence by DSM-III, $\geq$ 5 days abstinence before study. 80% male.	Acamprosate 1332 or 1998mg/day (by bodyweight) vs placebo, 1 year. Optional disulfiram and supportive psychosocial treatment as adjuncts.
Borg 1994	Sweden	All male, 70% married.	Acamprosate vs placebo, 6 months.
Chick 2000A	UK	Depedence by DSM-III. One-third episodic drinkers. 32% drank in week between detox and study. 84% male, 44% unmarried, 48% unemployed.	Acamprosate, 1998mg/day vs placebo, 6 months. Variable psychosocial treatment as adjunct.
Combine 2003	USA	Dependence by DSM-IV, abstinent <21 days at entry. 67-81% male, 35-47% married, 56-78% employed.	Acamprosate, 3g vs placebo, 16 weeks. Medical Management or Combined Behavioural Intervention as adjunct.
Geerlings 1997	Netherlands, Belgium, Luxembourg	Dependent by DSM-III-R, ≥5 days abstinence before study. 76% male, 51% married.	Acamprosate, 1998 or 1332 mg/day (by bodyweight) vs placebo, 6 months. Variable psychosocial support as adjunct.
Gual 2001	Spain	Dependent by DSM-III-R. Medication from start of withdrawal. 80% male, 68% married.	Acamprosate 1998mg/day vs placebo, 6 months. Adjunct treatments unclear.
Kiefer 2003	Germany	Dependent by DSM-IV. Abstinent 12-15 days at entry. 74% male, 73% unmarried, 61% employed.	Acamprosate, 1998mg/day, vs placebo, 12 weeks. Abstinence-oriented group therapy as adjunct.
Ladewig 1993	Switzerland	Dependence by DSM-III-R, ≥5 days abstinence before study. 23% female.	Acamprosate 1998 or 1332mg/day (by bodyweight) vs placebo, 6 months.
Lhuintre 1985	France	Severe dependence. Study entry at end of 5-day inpatient detoxification. 89% male.	Calcium bis acetyl homotaurine 25mg/kg/day vs placebo, 3 months. Meprobomate 1 month as adjunct.

(a) Acamprosate compared with placebo or no medication

Study	Country	Participant characteristics	Intervention
Lhuintre 1990	France	Dependence by clinical history. 5-30 days abstinence before study. 82% male.	Acamprosate 1.3g/day vs placebo, 12 weeks. Adjunct treatment not reported.
Namkoong 2003A	Korea	Dependence by DSM-IV. 65-71% had alcohol in 2 days before study. 96% male, 76% married, 60% employed.	Acamprosate 1998 or 1332mg/day (by bodyweight) vs placebo, 2 months. Variable psychosocial intervention as adjunct.
Niederhofer 2003	Austria	Chronic or episodic dependence by DSM-IV, ≥5 days abstinence before study. 65% male, aged 16-19.	Acamprosate 1332mg/day vs placebo, 90 days. Adjunct treatment unclear.
Paille 1995	France	Dependence by DSM-III-R. 7-22 days abstinence before study. 80% male, 68% employed.	Acamprosate 1.3 or 2g/day vs placebo, 12 months. Supportive psychotherapy as required.
Pelc 1992	Belgium	31% female, 79% married.	Acamprosate vs placebo, 6 months.
Pelc 1997	Belgium	Dependence by DSM-III-R. 14.9% female, 49.5% married.	Acamprosate 1332 or 1998mg/day vs placebo, 3 months. Supportive counselling, social support.
Poldrugo 1997	Italy	Dependence by DSM-III, ≥5 days abstinence before study. 73% male, 58% married.	Acamprosate, 1332 or 1998mg/day (by bodyweight) vs placebo, 6 months. Rehabilitation program and optional disulfiram.
Roussaux 1996	Belgium	Dependence by DSM-III, ≥14 days abstinence before study. 30% female, 32% married.	Acamprosate 1998mg/day vs placebo, 3 months. Group, individual and family counselling as adjunct.
Sass 1996	Germany	Dependence by DSM-III-R. 14-28 days abstinence before study. 78% male, 46% married, 26% unemployed.	Acamprosate 1332 or 1998mg/day (by bodyweight) vs placebo, 48 weeks. Variable counselling and psychotherapy as adjunct.
Tempesta 2000	Italy	Dependence by DSM-III-R, ≥5 days abstinence before study. 17% female, 68% married.	Acamprosate 1998mg/day vs placebo, 6 months. Medical counselling, psychotherapy, self-help groups available.
Whitworth 1996	Austria	Chronic or episodic dependence, ≥5 days abstinence at entry. 78% male, 52% married.	Acamprosate 1332 or 1998mg/kg (by bodyweight) vs placebo, 1 year.

## (b) Acamprosate compared with naltrexone

Study	Country	Participant characteristics	Intervention
Combine 2003	USA	Dependent by DSM-IV, <21 days abstinence at entry. 67-81% male, 35-47% married, 56-78% employed.	Acamprosate, 3g as 3 doses/day vs naltrexone 100mg as 2 doses/day, 16 weeks. Medical Management or Combined Behavioural Intervention as adjunct.
Kiefer 2003	Germany	Dependence by DSM-IV and Severity of Alcohol Dependence Scale. 12-15 days abstinence before study. 74% male, 73% unmarried, 61% employed.	Acamprosate, 1998mg/day, vs naltrexone 50mg/day, 12 weeks. Abstinence-oriented group therapy as adjunct.
Rubio 2001	Spain	Dependence by DSM-III-R. Mean 16 days abstinence before study. All male, 93% married, 75% employed full-time.	Acamprosate 1665-1998mg/day (by bodyweight) vs naltrexone 50 mg/day, 12 months. Supportive group therapy weekly. Accompanied by family member to appointments.

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#### Table 3Studies of naltrexone combined with acamprosate

Study	Country	Participant characteristics	Intervention
Combine 2003	USA	Dependent by DSM-IV, <21 days abstinence at entry. 67-81% male, 35-47% married, 56-78% employed.	Acamprosate 3g/day vs naltrexone 100mg/day vs acamprosate plus naltrexone vs placebo. Medical management or combined Behavioural Intervention as adjunct. 16 week study.
Kiefer 2003	Germany	Dependent by DSM-IV. Abstinent 12-15 days before study. 74% male, 27% married, 61% employed.	Naltrexone 50mg/day vs acamprosate 1998 mg/day vs naltrexone plus acamprosate vs placebo. Abstinence- oriented group therapy as adjunct. 12 week study.

## Table 4Studies involving disulfiram

(a) Oral disulfiram compared with placebo

Study	Country	Participant characteristics	Intervention
Chick 1992	UK	84% male; 65% unemployed; 46% cohabiting. Participants aware of treatment group but assessors blind.	Disulfiram 200mg/day vs vitamin C, 100mg/day. Medication supervised by informant. 6 month study. Counselling and support.
Fuller 1979	USA	All male; 65% married; 44% employed.	Disulfiram 250mg/day vs disulfiram 1mg/day (inactive dose). Medical care and counselling. 1 year study.
Fuller 1986	USA	Alcoholic by National Council on Alcoholism criteria. <1 month abstinence at entry. All male, 72% married.	Disulfiram 250mg/day vs disulfiram 1mg/day (inactive dose). Counselling every 1-2 weeks. 1 year study.
Niederhofer 2003B	Austria	Chronic or episodic dependence by DSM-IV. Abstinence ≥5 days at entry. 65% male, all adolescents.	Disulfiram 200mg/day vs placebo, 90 days.

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(b) Disulfiram implant compared with placebo

Study	Country	Participant characteristics	Intervention
Johnsen 1987	Norway	Alcoholism by Short Michigan Screening test. Mean 1 previous implant. Participants not told some would receive placebo.	Disulfiram or calcium phosphate, 10 x 100mg tablet implant. 20 week study. No adjunct treatment reported.
Johnsen 1991	Norway	Dependent by DSM-III, requested disulfiram implant. Participants not told some would receive placebo.	Disulfiram, 10 x 100mg or placebo (9 x 100mg calcium phosphate, 1 x 100mg disulfiram) tablet implant. 10 month study. No adjunct treatment reported.
Wilson 1976	Canada	"Alcoholic", 17/20 from "Skid Row", 85% male.	Disulfiram 8 x 100mg tablets implanted, or sham operation.
Wilson 1980	Canada	"Alcoholic", weighted heavily towards "Skid Row". 89% male	Disulfiram or placebo implant.

(c) Oral disulfiram compared with no medication

Study	Country	Participant characteristics	Intervention
Carroll 1998	USA	Alcohol abuse or dependence (85%) by DSM- III-R. All cocaine dependent. 27% female, 41% cohabiting, 57% unemployed. Only assessors blinded.	Disulfiram 250-500mg/day vs no medication. Cognitive behavioural, twelve-step facilitation or clinical management as adjunct. 12 week study.
Fuller 1979	USA	All male; 65% married; 44% employed.	Disulfiram 250mg/day vs no medication. Medical care and counselling. 1 year study.
Fuller 1986	USA	Alcoholism by National Council of Alcoholism criteria. <1 month abstinence at entry. All male, 72% married.	Disulfiram 250mg/day vs riboflavin 50 mg/day (participants advised they were receiving vitamin not disulfiram). Counselling every 1-2 weeks. 1 year study.
Gerrein 1973	USA	Around 13 years if loss of control of drinking. 88% male, 10% with spouse, 21% living alone, 16% in a hospital, 35% in halfway house. 51% unemployment.	Disulfiram (dose not reported) vs no medication. Clinic visits once or twice weekly. 6 month study.
Powell 1985	USA	Abuse or dependence by DSM-III, 2-4 weeks inpatient treatment before study. All male, 40% married.	Disulfiram vs no medication. Tailored psychosocial support or medical monitoring only.

(d) Disulfiram implant compared with no medication

Study	Country	Participant characteristics	Intervention
Wilson 1980	Canada	"Alcoholic", weighted heavily towards "Skid Row". 89% male	Disulfiram implant or no operation.

# (e) Disulfiram compared with naltrexone

Study	Country	Participant characteristics	Intervention
Carroll 1993	USA	Alcohol abuse or dependence by DSM-III-R. All cocaine dependent. 72% male.	Disulfiram 250mg/day vs naltrexone 50mg/day. Weekly individual psychotherapy. 12 week study.

# Table 5Studies involving antidepressants

(a) SSRIs

Study	Country	Participant characteristics	Intervention
Angelone 1998	Italy	Dependent by DSM-IV. 68% male.	Fluvoxamine vs citalopram vs no medication (fluvoxamine and citalopram groups combined for this review). Cognitive behavioural therapy as adjunct. 12 week study. Commenced as inpatient.
Chick 2004	UK, Eire, Austria, Switzerland	Dependent by DSM-III-R. Abstinent 10-30 days at entry. 74% male.	Fluvoxamine, up to 300mg/day or placebo. 12 month study. Psychosocial treatment as adjunct.
Cornelius 1997	USA	Dependent by DSM-III-R. Actively drinking at entry. All with major depressive disorder. 51% male; 20% (antidepressant) or 4% (no medication) currently married; 27-36% employed.	Fluoxetine vs placebo, 12 weeks. Setting unclear.
Coskunol 2002	Turkey	Dependent by DSM-III-R. Withdrawn from alcohol 7-21 days before study. 60% (sertraline) or 35% (placebo) had first degree relative with alcoholism.	Sertraline 100mg/day or placebo. Thiamine 500mg/day and pyridoxine 500mg/day as adjuncts. Encouraged to attend AA. 6 month study. Commenced as inpatient.
Deas 2000	USA	"Alcohol use disorder". 80% male. All with primary depressive disorder.	Sertraline, 25mg/day to 100mg/day or placebo, 12 weeks. Cognitive behavioural therapy as adjunct.
Eriksson 2001	Sweden	73% dependent by DSM-IV. All male, 73% cohabiting, 94% employed.	2 week premedication period, then citalopram 40mg/day or placebo, 4 weeks.
Gual 2003	Spain	Dependence by DSM-IV and ICD-10. Abstinent 2 weeks at entry. 53% male. Current major depression or dysthymia.	Sertraline 50mg/day to max 150mg/day or placebo. 24 week study.
Janiri 1996	Italy	Dependent by DSM-III-R. Abstinent ≥7 days at entry. 80% male.	Fluoxetine 20mg/day or placebo, 2 months. Weekly psychological interviews, AA attendance.

Study	Country	Participant characteristics	Intervention
Kabel 1996	USA	Severe dependence. All male; multiple personality disorder diagnoses; 36% homeless at entry.	Fluoxetine 60mg/day vs placebo, 12 weeks. 3 weeks inpatient, then outpatient.
Kranzler 1993	USA	Dependent by DSM-III-R. 95% male.	Fluvoxamine 50mg/day at bed-time to max 200mg/day or placebo. Weekly medication monitoring and relapse prevention psychotherapy as adjuncts. 12 week study.
Kranzler 1995	USA	Dependence by DSM-III-R. 80% male; 14% current depression; 97% employed.	Fluoxetine max 60mg/day vs placebo. Individual or group cognitive behavioural therapy as adjunct. 12 week study. Outpatient treatment.
Moak 2003	USA	Abuse or dependence by DSM-III-R. Alcohol free 3 days at entry. All currently depressed.	Sertraline 50mg/day to max 200mg/day or placebo. 12 weeks medication. Cognitive behavioural therapy as adjunct.
Pettinati 2000	USA	Dependence by DSM-III-R. Abstinent ≥3 days at entry. Subgroups by history of major depression. 52% male, 42% married, most working.	Sertraline 200mg/day vs placebo, 14 weeks. 12-step facilitation therapy as adjunct, and encouraged to attend community support groups.
Tiihonen 1996	Finland	Dependence by DSM-III-R. Abstinent ≥1 week before study. All male.	Citalopram 20 to 40mg/day, or placebo. 3 month study. Psychobehavioural treatment as adjunct.

# (b) Tricyclic antidepressants

Study	Country	Participant characteristics	Intervention
Favre 1997	France	Dependence by DSM-III-R. 1-4 week withdrawal period prior to study. 85% male.	Tianeptine 32.5mg/day or placebo, 9 months.
Mason 1996	USA	Dependence by DSM-III-6. Median 8 days abstinence at entry. 83% male.	Desipramine, dose titrated (median 200mg/day), vs placebo, 6 months. Encouraged to attend AA and other psychosocial treatments.
McGrath 1996	USA	Dependence or abuse by DSM-III-R. Actively drinking. 51% male. All with primary depression.	Imipramine 50mg/day to max 300mg/day, or placebo at bedtime, 12 weeks. Relapse prevention counselling as adjunct. Attendance at AA encouraged.

# (c) Ritanserin

Study	Country	Participant characteristics	Intervention
Johnson 1996A	USA	Dependence by DSM-III-R. 77% male	1 week placebo, then ritanserin 2.5 or 5mg/day, or placebo, 11 weeks. Cognitive behavioural therapy as adjunct.
Wiesbeck 1999	International	Moderate or severe dependence by DSM-III-R. 2- 6 weeks abstinence at entry. 80% male.	Ritanserin 2.5, 5 or 10mg/day vs placebo, 6 months. Supportive psychotherapy as adjunct.

# (d) Nefazodone

Study	Country	Participant characteristics	Intervention
Kranzler 2000B	USA	Dependence by DSM-III-R, 3-28 days abstinence at entry. 78% male.	Nefazodone 400-600mg/day vs placebo, 11 weeks. Coping skills training as adjunct.
Roy-Byrne 2000	USA	Dependence by DSM-III-R; 9.5% stopped drinking prior to entry. 45% male, 27% married, 70% employed. All with major depression.	Nefazodone, 200mg/day to max 500mg/day, or placebo, 12 weeks. Cognitive behavioural skills training, psycheducational group as adjuncts.

### Table 6Other medications

(a) Baclofen compared with placebo

Study	Country	Participant characteristics	Intervention
Addolorato 2002	Italy	12-24 hours abstinence at entry. Dependent by DSM-IV.	Baclofen 15-30mg/day vs placebo. Baclofen or placebo entrusted to referred family member. 30 day study.

(b) Buspirone compared with placebo

Study	Country	Participant characteristics	Intervention
Bruno 1989	Italy	None abstinent at entry. Mild to moderate alcohol abuse by DSM-III. 48% male, 76% with mild to moderate anxiety, 32 % married, 14% unemployed.	Buspirone 15-30mg/day, vs placebo, 8 weeks.
Fawcett 2000	USA	Dependence by DSM-III-R. All male; 52% married or cohabiting; 80% employed.	Buspirone to max 40mg/day, or placebo, 6 months. Supportive interventions as adjunct. Encouraged to attend AA.
Kranzler 1994	USA	Dependent by DSM-III-R. 77% male, all with anxiety and mood disorders, 14% major depression; 57% cohabiting, 82% employed.	Buspirone vs placebo. Relapse prevention psychotherapy as adjunct. 12 week study.
Malcolm 1992	USA	Dependent by DSM-III-R. All male, all with anxiety syndrome by DSM-III-R.	Buspirone, 45-60mg/day vs placebo, 26 weeks. Encouraged to attend AA. 1 week inpatient then outpatient.
Malec 1996	Canada	Dependence by DSM-III-R. Abstinent <15 days at entry. 80% male. 47% cohabiting.	2 weeks placebo wash-out, then buspirone 20mg/day to max 40mg/day, or placebo, 12 weeks. Abstinence not required. Various adjunct treatments.
Tollefson 1992	USA	Abuse or dependence by DSM-III. 30-90 days abstinence at entry. 73% male, all with generalised anxiety disorder.	Buspirone to max 60mg/day vs placebo, 24 weeks. Controlled participation in AA as adjunct.

## (c) Ondansetron compared with placebo

Study	Country	Participant characteristics	Intervention
Johnson 2000	USA	Early (59%) or late onset alcoholism. Abstinence not required at entry. 70% male.	1 week single-blind placebo, then ondansetron, 1, 4 or 16ug/kg vs placebo, 11 weeks. Cognitive behavioural therapy as adjunct.

### (d) Combination naltrexone and ondansetron compared with placebo

Study	Country	Participant characteristics	Intervention
Johnson 2000C	USA	All early onset alcoholics, meeting 3 of 7 DSM-IV criteria for dependence. 75% male.	Naltrexone 50mg/day plus ondansetron 8ug/kg vs placebo. Cognitive behavioural therapy as adjunct. 8 week study.

(e) Antipsychotic or neuroleptic compared with placebo

Study Country		Participant characteristics	Intervention		
Marra 2002	France	Dependence by DSM-IV. 10-18 days inpatient detox before study. 69% male, 59% employed, 35% living alone.	Amisulpride (benzamide neuroleptic) 50mg/day vs placebo. Counselling as adjunct. 6 month study.		
Shaw 1987	UK	"Chemically dependent on alcohol". All with significant anxiety or depression. All male.	Tiapride 300 mg/day or placebo, 6 months. "Supportive follow-up interviews" as adjunct.		
Wiesbeck 2001	Germany, Austria	Moderate or severe dependence by DSM-III-R. Abstinent 14-42 days at entry. 72.6% male.	Flupenthixol 10mg or placebo as intramuscular injection every second week, 6 months. Supportive psychotherapy as adjunct. Participation in self-help groups recommended.		

# (f) Anticonvulsants

Study Country		Participant characteristics	Intervention
Brady 2002	USA	Dependent. 60% male.	Divalproex 1500mg/day or placebo, 12 weeks. Cognitive-behavioural therapy as adjunct.
Johnson 2003G	USA	Dependence by DSM-IV. Abstinence at study entry not required. 52% male.	Topiramate 25mg/day to max 300mg/day or placebo, 12 weeks. Weekly medication compliance management as adjunct.
Mueller 1997	USA	Dependence by DSM-III-R. 38% male, 31% married in carbamazepine group; 81% male, 69% married in placebo group.	Carbamazepine 300-600mg/day or placebo. 12 month study, follow-up data at 3 months.

# (g) GHB compared with naltrexone

Study	Country	Participant characteristics	Intervention
Caputo 2003	Italy	Dependence by DSM-IV. Abstinent about 5 days at entry. 77% male, 50% married, 60% employed.	GHB, oral, 150mg/kg/day, or naltrexone 50mg/day, 3 months. Medication entrusted to family member. Weekly counselling, self-help groups and AA offered.

# (h) Lithium compared with placebo

Study	Country	Participant characteristics	Intervention
Fawcett 2000	USA	Dependence by DSM-III-R. All male. 49% married or cohabiting. 80% employed.	Lithium to max 1200mg/day, or placebo, 6 months. Supportive interventions to maintain abstinence. Encouraged to attend AA.

# FIGURES

or sub-category	Antagonist n/N	Control n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl	
1 Oral naltrexone						
Lee 2001	14/35	4/19		0.62	1.90 [0.73, 4.97]	
Galarza 1997	5/10	6/10		0.87	0.83 [0.37, 1.85]	
Kiefer 2003	22/40	10/40	<b></b>	1.45	2.20 [1.20, 4.03]	
COMBINE 2003	10/18	13/17	_ <b>_</b>	2.08	0.73 [0.45, 1.19]	
D'Malley 2003	17/26	13/27		2.14	1.36 [0.84, 2.20]	
Oslin 1997	14/21	13/23	_ <b></b>	2.23	1.18 [0.74, 1.89]	
Hersh 1998	20/31	19/33	<b></b>	2.96	1.12 [0.76, 1.66]	
/olpicelli 1992	24/35	21/35	_ <b>+</b>	3.48	1.14 [0.80, 1.62]	
Chick 2000	37/90	36/85		3.49	0.97 [0.68, 1.38]	
Petrakis 2004	12/16	13/15	_ <b></b>	3.56	0.87 [0.61, 1.22]	
D'Malley 2003A	19/30	24/30	_ <b>_</b>	3.86	0.79 [0.57, 1.10]	
Ahmadi 2002	46/58	25/58		3.90	1.84 [1.33, 2.54]	
_att 2002	33/56	34/51	_ <b>_</b>	4.45	0.88 [0.66, 1.18]	
D'Malley 1992	37/52	31/52		4.64	1.19 [0.90, 1.58]	
Morris 2001	38/55	42/65		5.31	1.07 [0.83, 1.38]	
Kranzler 2000B	36/61	50/63		5.50	0.74 [0.58, 0.95]	
/olpicelli 1997	35/48	36/49		5.58	0.99 [0.78, 1.26]	
Sastpar 2002	56/84	54/87	<u> </u>	6.04	1.07 [0.86, 1.34]	
Guardia 2002	61/93	59/99		6.16	1.10 [0.88, 1.37]	
inton 1999	59/68	49/63	<u> </u>	7.93	1.12 [0.95, 1.31]	
		921		76.24	1.06 [0.96, 1.18]	
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*Figure 1.1 Opioid antagonist compared with placebo or no medication, number of participants completing the study* 

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3.10(8.80)       27         7.10(9.90)       30         0.30(2.60)       23         9.44(3.90)       99         1.10(2.60)       63         242         , I <sup>2</sup> = 0%         7.99(4.30)       5         5	16.10(9.20) 20.60(7.30) 9.50(4.00) 9.19(3.71) 10.50(3.10) 17.14(7.04)		1.61 1.95 9.65 32.46 38.98 84.64 0.92 0.92	2.00 [-2.85, 6.85] -3.50 [-7.90, 0.90] 0.80 [-1.18, 2.78] 0.25 [-0.83, 1.33] 0.60 [-0.38, 1.58] 0.42 [-0.25, 1.09] 0.85 [-5.55, 7.25]
7.10(9.90) 30 0.30(2.60) 23 0.44(3.90) 99 1.10(2.60) 63 242 1.1 <sup>2</sup> = 0%	20.60(7.30) 9.50(4.00) 9.19(3.71) 10.50(3.10)		1.95 9.65 32.46 38.98 84.64	-3.50 [-7.90, 0.90] 0.80 [-1.18, 2.78] 0.25 [-0.83, 1.33] 0.60 [-0.38, 1.58] 0.42 [-0.25, 1.09]
0.30(2.60)     23       0.44(3.90)     99       1.10(2.60)     63       242       1, I² = 0%	9.50(4.00) 9.19(3.71) 10.50(3.10)		9.65 32.46 38.98 84.64	0.80 [-1.18, 2.78] 0.25 [-0.83, 1.33] 0.60 [-0.38, 1.58] 0.42 [-0.25, 1.09]
9.44(3.90)     99       1.10(2.60)     63       242       , I² = 0%       7.99(4.30)     5	9.19(3.71) 10.50(3.10)		32.46 38.98 84.64	0.25 [-0.83, 1.33] 0.60 [-0.38, 1.58] 0.42 [-0.25, 1.09]
1.10(2.60) 63 242 ,   <sup>2</sup> = 0%	10.50(3.10)		38.98 84.64	0.60 [-0.38, 1.58] 0.42 [-0.25, 1.09] 0.85 [-5.55, 7.25]
242 , <b>I</b> <sup>2</sup> = <b>0%</b> 7.99(4.30) 5			0.92	0.42 [-0.25, 1.09]
, <b>I</b> <sup>2</sup> = <b>0%</b> 7.99(4.30) 5	17.14(7.04)		0.92	0.85 [-5.55, 7.25]
7.99(4.30) 5	17.14(7.04)			
7.99(4.30) 5	17.14(7.04)			
	17.14(7.04)			
	17.14(7.04)			
5			0.92	0.85 [-5.55, 7.25]
7.25(5.13) 7	5.66(5.74)		- 1.49	1.59 [-3.44, 6.62]
9.51(4.47) 35	9.79(4.07)	<b></b> _	12.94	-0.28 [-1.99, 1.43]
42			14.44	-0.09 [-1.70, 1.53]
$, l^2 = 0\%$				
289		•	100.00	0.35 [-0.26, 0.97]
$, I^2 = 0\%$				
,	.51(4.47) 35 42 1 <sup>2</sup> = 0% 289	.51(4.47) 42 1 <sup>2</sup> = 0% 289	.51(4.47) 35 9.79(4.07) 42 1 <sup>2</sup> = 0% 289 1 <sup>2</sup> = 0%	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

### Figure 1.2 Opioid antagonist compared with placebo or no medication, average weeks in treatment

Study or sub-category	Antagonist n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% Cl
01 Oral naltrexone					
Landabaso 1999	8/15	2/15	<b>_</b>	1.23	4.00 [1.01, 15.81]
O'Malley 2003	9/26	5/27	_ <b></b>	3.03	1.87 [0.72, 4.84]
Niederhofer 2003A	20/30	10/30	_ <b></b>	6.17	2.00 [1.14, 3.52]
O'Malley 1992	22/52	10/52	_ <b></b>	6.17	2.20 [1.16, 4.18]
O'Malley 2003A	17/30	13/30	- <b></b> -	8.02	1.31 [0.78, 2.19]
Oslin 1997	15/21	15/23	_ <b>_</b>	8.84	1.10 [0.73, 1.64]
Volpicelli 1992	19/35	15/35	- <b></b> -	9.26	1.27 [0.78, 2.06]
Chick 2000	16/90	16/85	_ <b>_</b>	10.16	0.94 [0.50, 1.77]
Volpicelli 1997	21/48	17/49	_ <b></b> _	10.39	1.26 [0.76, 2.08]
Kranzler 2000B	18/61	22/63		13.36	0.85 [0.51, 1.41]
Anton 1999	32/68	21/63		13.46	1.41 [0.92, 2.17]
Subtotal (95% CI)	476	472	•	90.09	1.35 [1.14, 1.59]
Test for overall effect: Z = 3.49	· · · ·				
02 Depot or implant naltrexone				0.01	
Kranzler 2004	28/158	16/157		9.91	1.74 [0.98, 3.08]
Subtotal (95% Cl) Total events: 28 (Antagonist), Test for heterogeneity: not app Test for overall effect: Z = 1.89	licable	157		9.91	1.74 [0.98, 3.08]
Total (95% CI)	634	629	•	100.00	1.39 [1.18, 1.63]
Total events: 225 (Antagonist),	, 162 (Control)		ľ		
Test for heterogeneity: Chi <sup>2</sup> = 1	13.52, df = 11 (P = 0.26), l <sup>2</sup>	= 18.6%			
Test for overall effect: Z = 3.95	(P < 0.0001)				
		0.0	1 0.1 1 10	100	
			Favours control Favours an	tagonist	

Figure 1.3 Opioid antagonist compared with placebo or no medication, number of participants continuously abstinent

Study or sub-category	Antagonist n/N	Control n/N				(fixeo 5% CI	'		Weight %	RR (fixed) 95% Cl
01 Oral naltrexone										
Morris 2001	8/55	4/65			-	_			7.82	2.36 [0.75, 7.43]
Gastpar 2002	45/84	44/87			-	<b>-</b>			92.18	1.06 [0.79, 1.41]
Subtotal (95% CI)	139	152				T			100.00	1.16 [0.87, 1.54]
Total events: 53 (Antagonist	), 48 (Control)					ľ				
Test for heterogeneity: Chi2	= 1.87, df = 1 (P = 0.17), l <sup>2</sup> = 4	46.6%								
Test for overall effect: $Z = 1$ .	03 (P = 0.30)									
			0.1	0.2	0.5	1	2	5	10	
				Favour	s control	Fa	avours	antado	nist	

#### Figure 1.4 Opioid antagonist compared with placebo or no medication, number of participants abstinent at follow-up

Favours control Favours antagonist

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Total events: 562 (Antagonist) 605 (Control)	Study or sub-category	Antagonist n/N	Control n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl	
Landabaso 1999 2/15 7/15 Okain 1997 3/21 8/23 Guardia 2002 7/93 19/99 Lee 2001 8/24 8/15 Lee 2001 1992 8/35 19/35 Achieved 2002 18/64 Lee 2001 1992 8/35 19/35 Achieved 2002 18/64 Lee 2001 1997 17/48 26/49 Latt 2002 19/55 27/51 Castpar 2002 32/84 33/87 Chastpar 2002 158/418 93/209 Chastpar 2001 52/63 54/58 Subtotal (95% Cl) 1166 955 Total events: 2004 (Attagonist), 449 (Control) Test for heterogeneity: Chi = 0.009), P = 51.5% Test for overall effect: Z = 4.52 (P = 0.009), P = 51.5% Test for overall effect: Z = 4.52 (P = 0.009), P = 51.5% Test for overall effect: Z = 1.54 (P = 0.02), P = 51.5% Test for overall effect: Z = 1.54 (P = 0.00), P = 0.00, P = 51.5% Test for overall effect: Z = 1.54 (P = 0.00), P = 0.00, P = 51.5% Test for overall effect: Z = 1.54 (P = 0.00), P = 0.00, P = 51.5% Test for overall effect: Z = 1.54 (P = 0.00), P = 0.00, P =	01 Oral naltrexone						
Oslin 1997 $3/21$ $8/23$ 1.16 $0.41$ $0.13$ , $1.35$ ]         Guardia 2002 $7/93$ $19/99$ $2.23$ $0.39$ $0.17$ , $0.89$ ]         Lee 2001 $8/24$ $8/15$ $2.65$ $0.63$ $0.30$ , $1.31$ ]         Valpicelli 1992 $8/35$ $19/35$ $3.01$ $0.42$ $0.22$ , $0.83$ ]         Rohsenow 2000 $18/64$ $21/64$ $4.40$ $0.86$ $0.51$ , $1.45$ ]         Kiefer 2003 $12/40$ $30/40$ $4.64$ $0.40$ $0.24$ , $0.66$ ]         Morris 2001 $19/55$ $26/65$ $5.10$ $0.67$ $0.42$ , $1.042$ ]         Volpicelli 1997 $17/48$ $26/49$ $5.19$ $0.67$ $0.44$ $0.42$ , $1.001$ Gastar 2002 $33/64$ $33/87$ $6.49$ $1.00$ $0.68$ , $1.471$ Omaley 1992 $22/68$ $38/63$ $6.67$ $0.63$ $0.44$ , $0.911$ Arton 1999 $26/68$ $38/63$ $10.75$ $0.92$ $0.82$ , $1.021$ Total events: 406 (Antagonist), 449 (Contro)) $1166$ $955$ $78.53$ $0.92$ $0.82$	Rubio 2002	4/30	3/30	<b>_</b>	0.84	1.33 [0.33, 5.45]	
Guardia 2002 7/93 19/99 Lee 2001 8/24 8/15 2.23 0.39 $[0.17, 0.89]$ Lee 2001 8/24 8/15 2.066 Rohsenow 2000 18/64 21/64 2.164 4.40 0.86 $[0.51, 1.45]$ Rohsenow 2000 18/64 2.164 4.40 0.86 $[0.51, 1.45]$ Korl 2003 12/40 30/40 4.64 0.40 $[0.24, 0.63]$ Morris 2001 19/55 26/65 5.10 0.86 $[0.54, 1.38]$ Morris 2002 19/56 27/51 5.42 0.64 $[0.41, 1.00]$ Gastpar 2002 32/84 33/87 6.49 1.00 $[0.66, 1.47]$ Ordaley 1992 21/52 37/52 6.668 0.57 $[0.39, 0.82]$ Anton 1999 26/68 38/63 6.87 0.63 $[0.44, 0.91]$ Heinala 2001 52/63 54/58 5.20 0.63 $[0.44, 0.91]$ Heinala 2001 52/63 54/58 5.20 0.63 $[0.59, 0.81]$ Total events: 42 (Anagonish), 429 (Control) Test for hereagoneity: Chi <sup>P</sup> = 30.92 df = 16 (P = 0.009), P = 51.5% Test for overall effect: Z = 1.54 (P = 0.12) 30 Naimelene Mason 1999 26/70 20/35 5.48 0.12 2.78 0.92 $[0.82, 1.02]$ Subtotal (95% CI) 158 132/157 12.78 0.92 $[0.82, 1.02]$ Subtotal (95% CI) 158 132/157 12.78 0.92 $[0.82, 1.02]$ Subtotal (95% CI) 158 132/157 12.78 0.92 $[0.82, 1.02]$ Total events: 42 (Antagonish), 42 (Control) Test for hereogeneity: Chi <sup>P</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for overall effect: Z = 1.54 (P = 0.09) Test for hereogeneity: Chi <sup>P</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for overall effect: Z = 1.86 (P = 0.09) Test for hereogeneity: Chi <sup>P</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for hereogeneity: Chi <sup>P</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for hereogeneity: Chi <sup>P</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for overall effect: Z = 1.86 (P = 0.09) Test for hereogeneity: Chi <sup>P</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for overall effect: Z = 1.86 (P = 0.09) Test for hereogeneity: Chi <sup>P</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for overall effect: Z = 1.86 (P = 0.09) Test for hereogeneity: Chi <sup>P</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for overall effect: Z = 1.86 (P = 0.09) Test for hereogeneity: Chi <sup>P</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for overall effect: Z = 1.86 (P = 0.09) Test for hereogeneity: Chi <sup>P</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for overal	Landabaso 1999	2/15	7/15	<b>_</b>	0.85	0.29 [0.07, 1.16]	
Lee 2001 8/24 8/15 2.65 0.63 [0.30, 1.31] Volpicelli 1928 8/35 19/35 4.64 2.1/64 4.64 0.66 [0.51, 1.65] Rohsenow 2000 18/64 2.1/64 4.64 0.40 [0.24, 0.66] Morris 2001 19/55 26/65 5.10 0.68 [0.54, 1.38] Volpicelli 1937 17/48 26/49 5.19 0.67 [0.42, 1.06] Lat 2002 32/84 33/87 6.49 1.00 [0.68, 1.47] Ordaley 1939 26/68 38/63 6.87 0.63 [0.30, 0.3] Heinala 2001 52/63 54/58 6.87 0.63 [0.44, 0.91] Kingtar 2002 15/56 27/51 6.68 0.75 [0.39, 0.82] Anton 1939 26/68 38/63 6.87 0.63 [0.44, 0.91] Subtrail (95% CI) 1166 955 7.0 0.65 [0.70, 1.03] Heinala 2001 52/63 54/58 12.25 0.89 [0.78, 1.01] Subtrail (95% CI) 1166 955 7.8% Fest for versal fetter Z = 1.54 (P = 0.00) Total events: 122 (Antagonist), 132 (Control) Fest for heterogeneity: Ch <sup>2</sup> = 3.09.2, df = 15 (P = 0.009) Total events: 122 (Antagonist), 132 (Control) Fest for heterogeneity: Ch <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 51.5% Fest for versal fetter Z = 1.54 (P = 0.012) 33 Nalmelee Mason 1939 26/70 20/35 5.88 0.55 [0.82, 1.02] 30 Nalmelee Test for versal effect Z = 1.54 (P = 0.00) Total events: 34 (Antagonist), 24 (Control) Fest for versal effect Z = 1.55 (P = 0.006) Total events: 34 (Antagonist), 24 (Control) Fest for versal effect Z = 1.55 (P = 0.006) Total events: 34 (Antagonist), 24 (Control) Fest for versal effect Z = 1.55 (P = 0.006) Total events: 34 (Antagonist), 24 (Control) Fest for versal effect Z = 1.55 (P = 0.006) Total (95% CI) 1407 1153 100.00 0.73 [0.64, 0.83]	Oslin 1997	3/21	8/23		1.16		
Valpicelli 1992 8/35 19/35 3/46 3/46 3/40 3/40 3/40 4.64 0.66 [0.51, 1.45] Keler 2003 12/40 3/40 4.64 0.66 [0.54, 1.38] Morris 2001 19/55 26/65 5.10 0.66 [0.54, 1.38] Morris 2002 19/55 27/51 5.42 0.66 [0.54, 1.38] Castpar 2002 32/44 33/87 6.49 1.00 [0.66, 1.47] O'Malley 1992 21/52 37/52 6.68 0.57 [0.39, 0.82] Anton 1999 26/68 38/63 6.87 0.63 [0.44, 0.91] Krystal 2001 158/418 93/209 10.75 0.68 [0.70, 1.03] Heinala 2001 25/63 54/58 12.25 0.89 [0.78, 1.01] Subtotal (95% CI) 1166 955 7.85 0.68 [0.59, 0.81] Fest for hetrogeneity: Ch <sup>2</sup> a 0.922 [0.82, 1.02] Subtotal (95% CI) 158 157 12.78 0.92 [0.82, 1.02] Subtotal (95% CI) 138 157 12.78 0.92 [0.82, 1.02] Subtotal effect: Z = 1.54 (P = 0.12) 37 Naimefene Mason 1999 26/70 20/35 5.88 0.55 [0.45, 0.89] Subtotal (95% CI) 83 41 Mason 1999 26/70 20/35 5.88 0.55 [0.45, 0.89] Subtotal effect: Z = 1.85 (P = 0.00), P = 0% Fest for hetrogeneity: Ch <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 0% Fest for hetrogeneity: Ch <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 0% Fest for hetrogeneity: Ch <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 0% Fest for hetrogeneity: Ch <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 0% Fest for hetrogeneity: Ch <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 0% Fest for hetrogeneity: Ch <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 0% Fest for hetrogeneity: Ch <sup>2</sup> = 0.73 (0.64, 0.83] Fotal events: 562 (Antagonish), 605 (Control) Fest for hetrogeneity: Ch <sup>2</sup> = 0.74 (f = 1 (P = 0.40), P = 0% Fest for noverall effect: Z = 1.85 (P = 0.06) Fotal (95% CI) 1407 1153 100.00 .73 [0.64, 0.83]	Guardia 2002	7/93	19/99	_ <b>-</b> -	2.23	0.39 [0.17, 0.89]	
Rohsenve 2000 187.64 21/44 4.40 0.66 [0.51, 1.45] Kiefer 2003 12/40 30/40 4.64 0.40 10.24, 0.66 [ Worris 2001 1975 267.65 4.0 0.66 [0.54, 1.38] Volpicelli 1997 17.748 267.49 5.19 0.67 [0.42, 1.06] Latt 2002 19/56 277.51 5.42 0.64 [0.41, 1.00] Gastpar 2002 327.84 33/87 6.49 1.00 [0.68, 1.47] O'Malley 1992 21/52 37.52 6.68 0.57 [0.39, 0.82] Anton 1999 267.68 38/63 6.87 0.63 [0.44, 0.91] Krystal 2001 158/418 93/209 10.75 0.85 [0.70, 1.03] Heinala 2001 527.63 547.58 122.25 0.89 [0.79, 1.03] Heinala 201 527.63 547.58 122.25 0.89 [0.79, 1.03] Heinala 201 166 955 78.53 0.69 [0.59, 0.81] Total events: 406 (Antagonist), 49 (Control) Total events: 406 (Antagonist), 132 (Control) Test for heterogeneity: Chi <sup>2</sup> = 30.92, df = 15 (P = 0.009), $\mu$ = 51.5% Test for overall effect: Z = 1.54 (P = 0.12) 31 Namedne Mason 1994 8/13 4/6 8.157 12.78 0.92 [0.82, 1.02] Subtotal (95% Cl) 158 157 12.78 0.92 [0.82, 1.02] Subtotal (95% Cl) 158 157 12.78 0.92 [0.82, 1.02] Subtotal (95% Cl) 83 41 9.2075 5.88 0.65 [0.43, 0.99] Subtotal (95% Cl) 83 41 9.2075 5.88 0.65 [0.43, 0.99] Subtotal (95% Cl) 83 41 9.2075 5.88 0.65 [0.43, 0.99] Subtotal (95% Cl) 83 41 9.2075 5.88 0.65 [0.43, 0.99] Subtotal (95% Cl) 83 41 9.2075 5.88 0.65 [0.43, 0.99] Subtotal (95% Cl) 83 41 9.2075 5.88 0.65 [0.43, 0.99] Subtotal (95% Cl) 83 41 9.2071 [0.50, 1.02] Subtotal (95% Cl) 107 1153 10.00 0.73 [0.64, 0.83] Subtotal (95% Cl) 1070 1153 10.00 0.73 [0.64, 0.83]	Lee 2001	8/24	8/15	<b></b>	2.65	0.63 [0.30, 1.31]	
Kiefer 2003 $12/40$ $30/40$ - $4.64$ $0.40$ $[0.24]$ , $0.66]$ Morris 2001 $19/55$ $26/65$ $5.10$ $0.67$ $[0.24]$ , $0.66]$ Latt 2002 $19/56$ $27/51$ $5.42$ $0.64$ $[0.41]$ , $1.00]$ Gaspar 2002 $32/84$ $33/87$ $6.49$ $1.00$ $[0.68, 1.47]$ O'Malley 1992 $21/52$ $37/52$ $6.68$ $0.57$ $[0.39, 0.82]$ Anton 1999 $26/68$ $38/63$ $6.87$ $0.63$ $[0.44, 0.91]$ Krystal 2001 $158/18$ $93/209$ $10.75$ $0.85$ $[0.70, 1.03]$ Heinala 2001 $52/63$ $54/58$ $12.25$ $0.89$ $[0.78, 1.01]$ Subtotal (95% Cl) $1166$ $955$ $78.53$ $0.69$ $[0.59, 0.81]$ Total events: 406 (Antagonist), 449 (Control) $122/158$ $132/157$ $12.78$ $0.92$ $[0.82, 1.02]$ Total events: 12 (Antagonist), 122 (Control) $158$ $157$ $12.78$ $0.92$ $[0.82, 1.02]$ Total events: 21 (Antagonist), 24 (Control) $83$ $41$ <	Volpicelli 1992	8/35	19/35	<b></b>	3.01	0.42 [0.21, 0.83]	
Morris 2001 1975 26/65 5.10 0.86 [0.54, 1.38] Volpicelli 1997 17/48 26/49 5.19 0.67 [0.42, 1.06] Latt 2002 19/56 27/51 6.49 1.00 [0.68, 1.47] Ordaley 1992 21/52 37/52 6.68 0.57 [0.39, 0.82] Anton 1999 26/68 38/63 6.87 0.63 [0.44, 0.91] Krystal 2001 158/418 93/209 10.75 0.85 [0.70, 1.03] Heinala 2001 52/63 54/58 12.25 0.89 [0.78, 1.01] Subtoal (95% CI) 116 955 78.5 0.69 [0.59, 0.81] Total events: 406 (Antagonist), 449 (Control) Test for heterogeneity: chi = 30.92, df = 15 (P = 0.009), P = 51.5% Test for overall effect: Z = 1.54 (P = 0.12) 3National (95% CI) 158 157 12.78 0.92 [0.82, 1.02] Subtoal (95% CI) 158 157 12.78 0.92 [0.82, 1.02] Total events: 422 (Antagonist), 24 (Control) Test for heterogeneity: chi = applicable Test for overall effect: Z = 1.54 (P = 0.12) 3Nationeffect Test for overall effect: Z = 1.54 (P = 0.40), P = 0% Test for overall effect: Z = 1.85 (P = 0.00) Subtoal (95% CI) 83 41 Cotal events: 422 (Antagonist), 24 (Control) Test for heterogeneity: chi = a.71, df = 1 (P = 0.40), P = 0% Test for overall effect: Z = 1.85 (P = 0.06) Total (95% CI) 1407 1153 100.00 0.73 [0.64, 0.83]	Rohsenow 2000	18/64	21/64		4.40	0.86 [0.51, 1.45]	
Volpicelli 1997 17.48 26.49 5.19 0.67 [0.42, 1.06] Latt 2002 19/56 27/51 5.42 0.64 [0.41, 1.00] Gaspar 2002 32.84 33.87 CMalley 1992 21.52 37/52 6.68 0.57 [0.39, 0.82] Anton 1999 26,68 38,63 6.68 0.57 [0.39, 0.82] Heinala 2001 158/418 93/209 10.75 0.65 [0.70, 1.03] Heinala 2001 52/63 54/58 12.25 0.99 [0.78, 1.01] Subtotal (95% Cl) 1166 955 78.53 0.69 [0.59, 0.81] Fotal events: 406 (Antagonist), 449 (Control) Fest for verall effect: Z = 4.52 ( $P < 0.0009$ ), $P = 51.5\%$ Fest for verall effect: Z = 4.52 ( $P < 0.0009$ ), $P = 51.5\%$ Fest for verall effect: Z = 1.54 ( $P = 0.12$ ) 3) Nalmefene Mason 1994 8/13 4/6 Mason 1994 8/13 4/6 Coll events: 40(Atagonist), 24 (Control) Fest for verall effect: Z = 1.54 ( $P = 0.40$ ), $P = 0\%$ Fotal events: 40(Atagonist), 24 (Control) Fest for verall effect: Z = 1.54 ( $P = 0.40$ ), $P = 0\%$ Fotal events: 40(Atagonist), 24 (Control) Fest for verall effect: Z = 1.54 ( $P = 0.40$ ), $P = 0\%$ Fotal (95% Cl) 83 41 Mason 1994 8.13 4/6 Mason 1994 8.69 0.71 [0.55, 1.02] Malmefere Mason 1994 8.13 4/6 Mason 1994 8.69 0.71 [0.55, 1.02] Malmefere Mason 1994 8.13 4/6 Mason 1994 8.69 0.71 [0.55, 1.02]	Kiefer 2003	12/40	30/40		4.64	0.40 [0.24, 0.66]	
Laft 2002 19/56 27/51 $\bullet$ 5.42 0.64 [0.41, 1.00] Gastpar 2002 32/84 33/87 $6.49$ 1.00 [0.68, 1.47] OMalley 1992 21/52 37/52 $\bullet$ 6.68 0.57 [0.39, 0.82] Anton 1999 26/68 38/63 $\bullet$ 6.87 0.63 [0.44, 0.91] Heinala 2001 158/418 93/209 10.75 0.85 [0.70, 1.03] Heinala 2001 52/63 54/58 12.25 0.99 [0.78, 1.01] Subtotal (95% Cl) 1166 955 78.53 0.69 [0.59, 0.81] Total events: 406 (Antagonist), 449 (Control) Fest for heterogeneity. Ch <sup>2</sup> = 3.092, df = 15 ( $P = 0.009$ ), $P = 51.5\%$ Fest for overall effect: Z = 4.52 ( $P < 0.00001$ ) 12 Depot or implant naltrexone Kranzler 2004 122/158 132/157 12.78 0.92 [0.82, 1.02] Total events: 122 (Antagonist), 132 (Control) Fest for heterogeneity. rot applicable Fest for overall effect: Z = 1.54 ( $P = 0.12$ ) 13 Nalmefene Mason 1994 8/13 4/6 2.81 0.92 [0.45, 1.88] Mason 1994 8/13 4/6 8.69 0.71 [0.50, 1.02] 13 Nalmefene Mason 1994 8/13 4/1 Total events: 34 (Antagonist), 24 (Control) Fest for heterogeneity. Ch <sup>2</sup> = 0.71, df = 1 ( $P = 0.40$ ), $P = 0\%$ Fest for overall effect: Z = 1.58 ( $P = 0.00$ ) Total events: 34 (Antagonist), 24 (Control) Fest for overall effect: Z = 1.85 ( $P = 0.00$ ) Total events: 562 (Antagonist), 265 (Control) Total events: 562 (Antagonist), 605 (Control)	Morris 2001	19/55	26/65	_ <b>_</b>	5.10	0.86 [0.54, 1.38]	
Lat 2002 $19/56$ $27/51$ Gaspar 2002 $32/84$ $33/87$ O'Malley 1992 $21/52$ $37/52$ 6.69 $1.00$ $[0.68, 1.47]O'Malley 1992 25/68 38/636.67$ $0.63$ $[0.44, 0.91]Krystal 2001 158/418 93/20910.75$ $0.85$ $[0.70, 1.03]Heinala 2001 52/63 54/5812.25$ $0.99$ $[0.78, 1.01]Subtoal (95% CI) 1166 955Total events: 406 (Antagonist), 449 (Control)Test for heterogeneity: ChiP = 30.92, df = 15 (P = 0.009), P = 51.5%Test for overall effect: Z = 4.52 (P < 0.00001)12 Depot or implant naturexoneKranzler 2004 122/158 132/15712.78$ $0.92$ $[0.82, 1.02]Subtoal (95% CI) 158 157Total events: 122 (Antagonist), 132 (Control)Test for heterogeneity: not applicableTest for verall effect: Z = 1.54 (P = 0.12)13 NalmefeneMason 1994 8/13 4/6Mason 1994$ $8/13$ $4/6S.88$ $0.65$ $[0.43, 0.99]26/70$ $20/355.88$ $0.65$ $[0.43, 0.99]Subtoal (95% CI) 83 41Total events: 34 (Antagonist), 24 (Control)Test for heterogeneity: ChiP = 0.71, df = 1 (P = 0.40), P = 0%Test for overall effect: Z = 1.85 (P = 0.00)Total events: 562 (Antagonist), 24 (Control)Total events: 562 (Antagonist), 24 (Control)Total events: 562 (Antagonist), 605 (Control)$	Volpicelli 1997	17/48	26/49		5.19	0.67 [0.42, 1.06]	
Gastpar 2002       32/84       33/87       6.49       1.00       [0.68, 1.47]         O'Malley 1992       21/52       37/52       6.68       0.57       [0.39, 0.82]         Anton 1999       26/68       38/63       6.68       0.57       [0.39, 0.82]         Krystal 2001       158/418       93/209       10.75       0.68       [0.70, 1.03]         Heinala 2001       52/63       54/58       12.25       0.89       [0.78, 1.01]         Valutati (95% CI)       1166       955       78.53       0.69       [0.59, 0.81]         rest for heterogeneity: ChP = 30.92, df = 15 (P = 0.009), P = 51.5%       rest for overall effect: Z = 4.52 (P < 0.00001)	-	19/56	27/51		5.42	0.64 [0.41, 1.00]	
Anton $1999$ 26/68 38/63 Krystal 2001 158/418 93/209 10.75 0.85 [0.70, 1.03] Heinala 2001 52/63 54/58 Subtotal (95% CI) 1166 955 Total events: 406 (Antagonist), 449 (Control) Test for heterogeneity: Chi <sup>2</sup> = 3.0.92, df = 15 ( $P = 0.009$ ), $P = 51.5\%$ Test for overall effect: Z = 4.52 ( $P < 0.00001$ ) 22 Depot or implant naltrexone Kranzler 2004 122/158 132/157 Total events: 122 (Antagonist), 132 (Control) Total events: 122 (Antagonist), 132 (Control) Total events: 122 (Antagonist), 24 ( $P = 0.12$ ) 33 Nalmefene Mason 1999 26/70 20/35 Subtotal (95% CI) 83 41 Subtotal (95% CI) 83 41 State thereogeneity: Chi <sup>2</sup> = 0.71, df = 1 ( $P = 0.40$ ), $P = 0\%$ Test for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 ( $P = 0.40$ ), $P = 0\%$ Test for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 ( $P = 0.40$ ), $P = 0\%$ Test for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 ( $P = 0.40$ ), $P = 0\%$ Total events: 54 (Antagonist), 24 (Control) Total events: 56 ( $P = 0.06$ ) Total (95% CI) 1407 1153 100.00 0.73 [0.64, 0.83]		32/84	33/87	+	6.49		
Anton $1999$ 26/68 38/63 Krystal 2001 158/418 93/209 10.75 0.85 [0.70, 1.03] Heinala 2001 52/63 54/58 Subtotal (95% CI) 1166 955 Total events: 406 (Antagonist), 449 (Control) Test for heterogeneity: Chi <sup>2</sup> = 0.59, d. 81] 22 Depot or implant naltrexone Kranzler 2004 122/158 132/157 Total events: 122 (Antagonist), 132 (Control) Total events: 42 (Antagonist), 419 (P = 0.40), P = 51.5% Test for versall effect: Z = 1.54 (P = 0.12) 33 Nalmefene Mason 1999 26/70 20/35 Subtotal (95% CI) 83 41 Contail events: 34 (Antagonist), 24 (Control) Test for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 (P = 0.40), P = 0% Test for verall effect: Z = 1.85 (P = 0.06) Total events: 562 (Antagonist), 605 (Control) Test for heterogeneity: Chi <sup>2</sup> = 0.761 Total events: 562 (Antagonist), 605 (Control)				-			
Krystal 2001       158/418       93/209       10.75       0.85       [0.78, 1.01]         Heinala 2001       52/63       54/58       12.25       0.89       [0.78, 1.01]         Jobbotal (95% CI)       1166       955       78.53       0.69       [0.59, 0.81]         Total events: 406 (Antagonist), 449 (Control)       8.50       78.53       0.69       [0.59, 0.81]         Y2 Depot or implant naltrexone       78.53       0.69       [0.59, 0.81]       10.75       0.85       [0.78, 1.01]         Y2 Depot or implant naltrexone       78.53       0.69       [0.59, 0.81]       10.75       0.82       1.02]         Y2 Depot or implant naltrexone       78.53       0.69       [0.59, 0.81]       10.75       0.92       [0.82, 1.02]         Y2 Depot or implant naltrexone       78.73       0.92       [0.82, 1.02]       10.75       0.92       [0.82, 1.02]         Y2 Depot or implant naltrexone       Y       12.78       0.92       [0.82, 1.02]       102.78       0.92       [0.82, 1.02]       102.78       0.92       [0.82, 1.02]       102.78       102.78       0.92       [0.45, 1.88]       102.78       102.78       0.92       [0.45, 1.88]       102.78       102.78       0.92       [0.45, 1.82]       102.78							
Heinala 2001 52/63 54/58 Subtotal (95% CI) 1166 955 Total events: 406 (Antagonist), 449 (Control) Test for heterogeneity: Chi <sup>2</sup> = 30.92, df = 15 (P = 0.009), l <sup>2</sup> = 51.5% Test for overall effect: Z = 4.52 (P < 0.00001) 12 Depot or implant naltrexone Kranzler 2004 122/158 132/157 Subtotal (95% CI) 158 157 Total events: 122 (Antagonist), 132 (Control) Test for heterogeneity: not applicable Test for overall effect: Z = 1.54 (P = 0.12) 13 Nalmefene Mason 1994 8/13 4/6 Mason 1999 2.6770 20/35 Subtotal (95% CI) 83 41 Total events: 34 (Antagonist), 24 (Control) Test for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 (P = 0.40), l <sup>2</sup> = 0% Test for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 (P = 0.40), l <sup>2</sup> = 0% Test for scrall effect: Z = 1.85 (P = 0.06) Total (95% CI) 1407 1153 100.00 0.73 [0.64, 0.83]				<b>_</b>			
Subtotal (95% Cl) 1166 955 Total events: 406 (Antagonist), 449 (Control) Test for heterogeneity: Chi <sup>2</sup> = 30.92, df = 15 (P = 0.009), l <sup>2</sup> = 51.5% Test for overall effect: Z = 4.52 (P < 0.0001) 12 Depot or implant naltrexone Kranzler 2004 122/158 132/157 Subtotal (95% Cl) 158 157 Total events: 122 (Antagonist), 132 (Control) Test for heterogeneity: not applicable Test for overall effect: Z = 1.54 (P = 0.12) 30 Nalmefene Mason 1994 8/13 4/6 Total events: 34 (Antagonist), 24 (Control) Total (95% Cl) 1407 1153 100.00 0.73 [0.64, 0.83]				_			
Total events: 406 (Antagonist), 449 (Control)         Test for heterogeneity: Chi <sup>2</sup> = 30.92, df = 15 (P = 0.009), I <sup>2</sup> = 51.5%         Test for overall effect: Z = 4.52 (P < 0.00001)							
Subtotal (95% CI)       158       157       12.78       0.92 [0.82, 1.02]         Total events: 122 (Antagonist), 132 (Control)       12.78       0.92 [0.82, 1.02]         Total events: 122 (Antagonist), 132 (Control)       12.78       0.92 [0.82, 1.02]         Total events: 122 (Antagonist), 132 (Control)       12.78       0.92 [0.82, 1.02]         Total events: 122 (Antagonist), 132 (Control)       12.78       0.92 [0.82, 1.02]         Total events: 122 (Antagonist), 132 (Control)       10.92 [0.45, 1.88]       10.92 [0.45, 1.88]         Mason 1994       8/13       4/6       2.81       0.92 [0.45, 1.88]         Mason 1999       26/70       20/35       5.88       0.65 [0.43, 0.99]         Subtotal (95% CI)       83       41       4       8.69       0.71 [0.50, 1.02]         Total events: 34 (Antagonist), 24 (Control)       100.00       0.73 [0.64, 0.83]       100.00       0.73 [0.64, 0.83]         Total events: 562 (Antagonist), 605 (Control)       1153       100.00       0.73 [0.64, 0.83]       100.00		122/158	132/157		12.78	0.92 [0.82, 1.02]	
Total events: 122 (Antagonist), 132 (Control)         Test for heterogeneity: not applicable         Test for overall effect: $Z = 1.54$ (P = 0.12)         D3 Nalmefene         Mason 1994 $8/13$ Mason 1999 $26/70$ $20/35$ Subtotal (95% Cl) $83$ Total events: 34 (Antagonist), 24 (Control)         Test for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 (P = 0.40), l <sup>2</sup> = 0%         Test for overall effect: Z = 1.85 (P = 0.06)         Total events: 562 (Antagonist), 605 (Control)				4			
Mason 1994 $8/13$ $4/6$ $2.81$ $0.92$ $[0.45, 1.88]$ Mason 1999 $26/70$ $20/35$ $5.88$ $0.65$ $[0.43, 0.99]$ Subtotal (95% CI) $83$ $41$ $8.69$ $0.71$ $[0.50, 1.02]$ Total events: 34 (Antagonist), 24 (Control) $est for heterogeneity: Chi^2 = 0.71, df = 1$ (P = 0.40), l <sup>2</sup> = 0% $100.00$ $0.73$ $[0.64, 0.83]$ Total (95% CI) $1407$ $1153$ $100.00$ $0.73$ $[0.64, 0.83]$	otal events: 122 (Antagonist), 13 est for heterogeneity: not applica	2 (Control) able					
Mason 1999 $26/70$ $20/35$ Subtotal (95% CI)       83       41         Fotal events: 34 (Antagonist), 24 (Control) $8.69$ $0.71 [0.50, 1.02]$ Fots for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 (P = 0.40), l <sup>2</sup> = 0% $8.69$ $0.71 [0.50, 1.02]$ Fotal (95% CI)       1407       1153 $100.00$ $0.73 [0.64, 0.83]$ Fotal events: 562 (Antagonist), 605 (Control) $100.00$ $0.73 [0.64, 0.83]$ $100.00$	03 Nalmefene						
Mason 1999 $26/70$ $20/35$ $\bullet$ $5.88$ $0.65$ $[0.43, 0.99]$ Subtotal (95% CI)       83       41 $\bullet$ $8.69$ $0.71$ $[0.50, 1.02]$ Total events: 34 (Antagonist), 24 (Control)       Fest for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 (P = 0.40), l <sup>2</sup> = 0% $\bullet$ $0.71$ $[0.50, 1.02]$ Fost for overall effect: Z = 1.85 (P = 0.06)       1407       1153 $\bullet$ $100.00$ $0.73$ $[0.64, 0.83]$ Fotal (95% CI)       1407       1153 $\bullet$ $100.00$ $0.73$ $[0.64, 0.83]$	Mason 1994	8/13	4/6	_ <b>_</b>	2.81	0.92 [0.45, 1.88]	
Subtotal (95% CI)       83       41       8.69       0.71 [0.50, 1.02]         Total events: 34 (Antagonist), 24 (Control)       Fest for heterogeneity: Chi <sup>2</sup> = 0.71, df = 1 (P = 0.40), l <sup>2</sup> = 0%       8.69       0.71 [0.50, 1.02]         Test for overall effect: Z = 1.85 (P = 0.06)       1407       1153       100.00       0.73 [0.64, 0.83]         Total events: 562 (Antagonist), 605 (Control)       1407       1153       100.00       0.73 [0.64, 0.83]		26/70	20/35		5.88	0.65 [0.43, 0.99]	
iotal events: 34 (Antagonist), 24 (Control)         iest for heterogeneity: Chi² = 0.71, df = 1 (P = 0.40), l² = 0%         iest for overall effect: Z = 1.85 (P = 0.06)         iotal (95% Cl)       1407         1153         iotal events: 562 (Antagonist), 605 (Control)		83	41		8.69		
Test for heterogeneity: Chi² = 0.71, df = 1 (P = 0.40), l² = 0%         Test for overall effect: Z = 1.85 (P = 0.06)         Total (95% Cl)       1407         1153         Total events: 562 (Antagonist), 605 (Control)		(Control)		•			
otal events: 562 (Antagonist), 605 (Control)	est for heterogeneity: Chi <sup>2</sup> = 0.71	1, df = 1 (P = 0.40), l <sup>2</sup> =	0%				
Fotal events: 562 (Antagonist), 605 (Control)			1153	•	100.00	0.73 [0.64, 0.83]	CLICK HE
1 + 51 + 101 + 1			l² = 55.3%				
							TO REPO

Figure 1.5 Opioid antagonist compared with placebo or no medication, number of participants who relapsed during treatment

Favours antagonist Favours control

Study or sub-category	Ν	Antagonist Mean (SD)	Ν	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% Cl
01 Oral naltrexone							
Guardia 2002	93	0.71(15.80)	99	1.22(21.09)		2.64	-0.51 [-5.76, 4.74]
O'Malley 2003	26	2.10(3.80)	27	3.03(4.80)		7.64	-0.93 [-3.26, 1.40]
Balldin 2003	56	9.10(6.50)	62	8.62(6.20)	<b>_</b>	7.73	0.48 [-1.82, 2.78]
O'Malley 2003A	30	1.80(4.80)	30	1.10(2.20)	_ <b></b>	9.06	0.70 [-1.19, 2.59]
Rohsenow 2000	64	4.94(3.36)	64	8.77(6.17)	_ <b>_</b>	9.66	-3.83 [-5.55, -2.11]
Morris 2001	55	6.00(3.00)	65	9.00(5.00)	<b></b>	10.64	-3.00 [-4.45, -1.55]
Anton 1999	68	2.50(3.30)	63	4.20(4.30)		11.12	-1.70 [-3.02, -0.38]
Krystal 2001	418	9.20(8.00)	209	9.00(6.00)	_ <b>_</b>	11.85	0.20 [-0.92, 1.32]
Subtotal (95% CI)	810		619			70.34	-1.18 [-2.44, 0.08]
02 Depot or implant naltrexon Johnson 2004 Subtotal (95% CI) Test for heterogeneity: not ap Test for overall effect: Z = 4.3	25 25 pplicable	3.80(1.80)	5 5	6.00(0.80)	•	12.27 12.27	-2.20 [-3.19, -1.21] -2.20 [-3.19, -1.21]
	0 (1 < 0.0001	,					
03 Nalmefene Mason 1994	14	4.05(2.98)	7	3.20(2.30)		7.69	0.85 [-1.46, 3.16]
Mason 1999	70	4.10(3.30)	35	5.30(4.60)		9.70	-1.20 [-2.91, 0.51]
Subtotal (95% CI)	84	1.10(5.50)	42	5.50(1.00)		17.39	-0.33 [-2.31, 1.66]
Test for heterogeneity: $Chi^2 =$ Test for overall effect: Z = 0.3	1.95, df = 1 (	P = 0.16), I <sup>2</sup> = 48.8%				11.00	0.00 ( 2.02, 2.00)
Total (95% CI) Test for heterogeneity: Chi² = Test for overall effect: Z = 2.4	,	0 (P = 0.0002), l <sup>2</sup> = 70.7	666 %		•	100.00	-1.16 [-2.11, -0.21]
	. ,				<u> </u>		
				-10	0 -5 0 5	10	

# *Figure 1.6 Opioid antagonist compared with placebo or no medication, average drinks per drinking day*

Favours antagonist Favours control

Study or sub-category	Ν	Antagonist Mean (SD)	N	Control Mean (SD)	WMD (random) 95% Cl	Weight %	WMD (random) 95% Cl
01 Oral naltrexone							
Chick 2000	90	12.25(28.50)	85	21.50(35.50)		2.90	-9.25 [-18.82, 0.32]
Morris 2001	55	11.58(14.75)	65	23.25(22.00)	-	5.39	-11.67 [-18.29, -5.05]
Petrakis 2004	16	4.73(7.03)	15	6.93(8.18)	<del>4</del>	7.34	-2.20 [-7.59, 3.19]
Heinala 2001	63	28.90(6.20)	58	34.20(7.03)	=	17.13	-5.30 [-7.67, -2.93]
O'Malley 1992	52	1.33(2.66)	52	4.69(6.09)	-	19.79	-3.36 [-5.17, -1.55]
Rubio 2002	30	2.11(1.08)	30	3.32(1.13)	•	24.56	-1.21 [-1.77, -0.65]
Subtotal (95% CI)	306		305		•	77.10	-4.13 [-6.57, -1.69]
02 Depot or implant naltrex							
Kranzler 1998	15	0.70(0.60)	5	0.90(1.20)	•	22.90	-0.20 [-1.29, 0.89]
Subtotal (95% CI)	15		5		•	22.90	-0.20 [-1.29, 0.89]
Test for heterogeneity: not	applicable						
Test for overall effect: $Z = 0$	0.36 (P = 0.72)						
Total (95% CI)	321		310		•	100.00	-2.97 [-4.71, -1.24]
Test for heterogeneity: Chi	<sup>2</sup> = 31.90, df = 6	(P < 0.0001), I <sup>2</sup> = 81.2%					
Test for overall effect: Z = 3	3.36 (P = 0.0008	3)					
					-100 -50 0 50	100	
					Equatre antagonist Equate on	ntrol	

### *Figure 1.7* Opioid antagonist compared with placebo or no medication, average drinks per week

Favours antagonist Favours control

Study or sub-category	Ν	Antagonist Mean (SD)	Ν	Control Mean (SD)	WMD (random) 95% Cl	Weight %	WMD (random) 95% Cl
01 Oral naltrexone							
Guardia 2002	93	34.70(218.30)	99	37.00(267.70)	<b>_</b>	0.08	-2.30 [-71.21, 66.61]
O'Malley 2003	26	10.20(17.90)	27	21.60(33.40)		1.56	-11.40 [-25.75, 2.95]
Niederhofer 2003A	30	22.44(30.60)	30	74.67(10.00)	<b></b>	2.26	-52.23 [-63.75, -40.71]
Hersh 1998	31	17.90(22.80)	33	19.80(22.40)	-4-	2.41	-1.90 [-12.98, 9.18]
Balldin 2003	56	38.60(25.70)	62	48.50(33.10)		2.57	-9.90 [-20.54, 0.74]
Morris 2001	55	25.00(28.00)	65	36.00(30.00)		2.67	-11.00 [-21.39, -0.61]
Petrakis 2004	16	6.30(8.20)	15	13.80(15.90)		3.31	-7.50 [-16.49, 1.49]
Kranzler 2000B	61	21.20(28.90)	63	15.70(21.30)		3.33	5.50 [-3.46, 14.46]
O'Malley 2003A	30	6.20(13.40)	30	6.50(16.40)	+	4.19	-0.30 [-7.88, 7.28]
Anton 1999	68	10.00(18.90)	63	18.00(22.90)		4.45	-8.00 [-15.22, -0.78]
Krystal 2001	418	11.30(21.00)	209	14.00(23.00)	-	8.25	-2.70 [-6.41, 1.01]
Latt 2002	56	31.40(8.60)	51	32.30(10.00)	+	8.47	-0.90 [-4.45, 2.65]
Rubio 2002	30	18.70(6.90)	30	21.80(4.30)	-	9.36	-3.10 [-6.01, -0.19]
Landabaso 1999	15	1.30(2.50)	15	2.40(1.30)	÷	11.17	-1.10 [-2.53, 0.33]
Rohsenow 2000	64	0.50(1.40)	64	1.70(2.90)		11.66	-1.20 [-1.99, -0.41]
Volpicelli 1997	48	6.20(1.59)	49	10.76(2.32)	-	11.66	-4.56 [-5.35, -3.77]
O'Malley 1992	52	4.30(1.40)	52	9.90(1.30)	•	11.79	-5.60 [-6.12, -5.08]
Subtotal (95% CI)	1149		957		•	99.20	-4.48 [-6.43, -2.54]
Test for heterogeneity: Chi Test for overall effect: $Z = 4$	4.52 (P < 0.0000		3%				
02 Depot or implant naltrex							
Johnson 2004	25	30.60(33.70)	5	37.40(51.40)		0.17	-6.80 [-53.75, 40.15]
Kranzler 1998	15	21.00(25.50)	5	28.40(34.50)		0.33	-7.40 [-40.28, 25.48]
Subtotal (95% CI)	40		10			0.50	-7.20 [-34.13, 19.73]
Test for heterogeneity: Chi Test for overall effect: Z = 0	, ,	P = 0.98), I <sup>2</sup> = 0%					
03 Nalmefene							
Mason 1994	14	49.30(30.70)	7	42.90(41.40)	<b> </b>	0.30	6.40 [-28.23, 41.03]
Subtotal (95% CI)	14		7			0.30	6.40 [-28.23, 41.03]
Test for heterogeneity: not	applicable						
Test for overall effect: Z = 0	0.36 (P = 0.72)						
Total (95% CI)	1203		974		•	100.00	-4.45 [-6.38, -2.52]
Test for heterogeneity: Chi Test for overall effect: Z = 4			7%		, i i i i i i i i i i i i i i i i i i i		

# Figure 1.8 Opioid antagonist compared with placebo or no medication, days of treatment with drinking (%)

Favours antagonist Favours control

Study or sub-category	Ν	Antagonist Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% Cl
01 Oral naltrexone							
Anton 1999	68	48.00(33.00)	63	40.00(40.00)	+ <b>-</b> -	11.85	8.00 [-4.61, 20.61]
Kranzler 2000B	61	42.00(32.90)	63	39.90(31.50)	_ <b>_</b>	14.66	2.10 [-9.24, 13.44]
Hersh 1998	31	14.70(18.20)	33	17.50(18.20)		23.69	-2.80 [-11.72, 6.12]
Guardia 2002	93	30.17(22.64)	99	29.23(20.74)	<b>+</b>	49.80	0.94 [-5.21, 7.09]
Subtotal (95% CI)	253		258		•	100.00	1.06 [-3.28, 5.40]
Test for heterogeneity: Chi	i² = 1.92, df = 3 (	P = 0.59), l <sup>2</sup> = 0%			ſ		
Test for overall effect: Z =	0.48 (P = 0.63)						
	. ,				-100 -50 0 5	0 100	
					Favours control Favours	antagonist	

#### *Figure 1.9* Opioid antagonist compared with placebo or no medication, average time to first drink (days)

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Study or sub-category	Ν	Antagonist Mean (SD)	Ν	Control Mean (SD)	WMD (random) 95% Cl	Weight %	WMD (random) 95% Cl
01 Oral naltrexone							
Rubio 2002	30	81.00(24.00)	30	30.00(21.00)		15.11	51.00 [39.59, 62.41]
Anton 1999	68	60.00(33.00)	63	48.00(32.00)		15.29	12.00 [0.87, 23.13]
Guardia 2002	93	78.80(18.60)	99	73.90(22.20)	<del>_</del>	18.40	4.90 [-0.88, 10.68]
Krystal 2001	418	72.30(36.00)	209	62.40(34.00)	-	18.41	9.90 [4.14, 15.66]
Balldin 2003	56	36.50(9.60)	62	19.90(5.00)	-	19.52	16.60 [13.79, 19.41]
Subtotal (95% CI)	665		463		•	86.74	17.94 [7.89, 27.98]
03 Nalmefene	70	46 20/27 50)	35	22 50/24 20)		12.26	
Mason 1999	70	46.30(37.50)	35 35	33.50(34.20)		13.26 13.26	12.80 [-1.54, 27.14]
Subtotal (95% CI) Test for heterogeneity: not Test for overall effect: Z =	applicable		35			13.20	12.80 [-1.54, 27.14]
Total (95% CI)	735		498		•	100.00	17.20 [8.16, 26.25]
Test for heterogeneity: Chi Test for overall effect: Z =			5				
				-1	00 -50 0 50	100	
					Favours control Eavours trea	atment	

#### Figure 1.10 Opioid antagonist compared with placebo or no medication, average time for relapse to heavy drinking (days)

Favours control Favours treatment

Study or sub-category	Antagonist n/N	Control n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl
01 Oral naltrexone					
Lee 2001	7/35	4/18	<b>_</b>	2.85	0.90 [0.30, 2.67]
O'Malley 2003A	14/56	16/57		6.79	0.89 [0.48, 1.65]
Heinala 2001	38/63	26/58	<b>⊢</b> ∎	12.14	1.35 [0.95, 1.91]
Croop 1997	214/570	52/295		14.32	2.13 [1.63, 2.79]
Gastpar 2002	52/84	54/87	+	15.25	1.00 [0.79, 1.26]
Chick 2000	81/90	71/85	<b>+</b>	18.16	1.08 [0.96, 1.21]
Subtotal (95% CI)	898	600	•	69.51	1.22 [0.88, 1.69]
Fotal events: 406 (Antagonist)	, 223 (Control)				
Test for heterogeneity: Chi <sup>2</sup> =		, l² = 86.2%			
Test for overall effect: Z = 1.18	B (P = 0.24)				
02 Depot or implant naltrexone	e				
Kranzler 1998	7/15	2/5		2.40	1.17 [0.35, 3.88]
Johnson 2004	23/25	4/5	<b></b>	9.66	1.15 [0.73, 1.81]
Kranzler 2004	140/167	132/166	<b>+</b>	18.43	1.05 [0.95, 1.17]
Subtotal (95% CI)	207	176	•	30.49	1.06 [0.96, 1.17]
otal events: 170 (Antagonist)	, 138 (Control)		ľ		
est for heterogeneity: Chi <sup>2</sup> =	0.16, df = 2 (P = 0.92), l <sup>2</sup> =	0%			
Test for overall effect: Z = 1.14	4 (P = 0.25)				
otal (95% CI)	1105	776	•	100.00	1.19 [0.97, 1.45]
otal events: 576 (Antagonist)	, 361 (Control)		•		
Fest for heterogeneity: Chi <sup>2</sup> =		, l² = 79.2%			
Test for overall effect: Z = 1.71	, ,				
			0.1 0.2 0.5 1 2 5	10	
			Favours antagonist Favours cont	1	

*Figure 1.11* Opioid antagonist compared with placebo or no medication, number of participants experiencing any adverse effects

Study or sub-category	Antagonist n/N	Control n/N			RR (fixed) 95% Cl		Weight %	RR (fixed) 95% Cl
01 Oral naltrexone								
COMBINE 2003	5/18	3/17				-	36.84	1.57 [0.44, 5.60]
Monterosso 2001	18/121	4/62				_	63.16	2.31 [0.82, 6.52]
Subtotal (95% CI)	139	79					100.00	2.04 [0.91, 4.58]
Total events: 23 (Antagonist	), 7 (Control)				-			
Test for heterogeneity: Chi <sup>2</sup>	= 0.21, df = 1 (P = 0.64), l <sup>2</sup> = 0	%						
Test for overall effect: $Z = 1$ .	72 (P = 0.09)							
			0.01	0.1	<b> </b> 1	10	100	
			Favo	ours treatm	ent Favo	urs contr	ol	

Figure 1.12 Opioid antagonist compared with placebo or no medication, number of participants requiring a dose reduction to manage adverse effects

Study or sub-category	Antagonist n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% Cl
01 Oral naltrexone					
Guardia 2002	8/93	1/99	<b>_</b>	9.08	8.52 [1.09, 66.78]
COMBINE 2003	4/18	2/17	_ <b></b>	12.96	1.89 [0.40, 9.01]
Balldin 2003	11/56	2/62	<b></b>	13.97	6.09 [1.41, 26.29]
Anton 1999	21/68	7/63	<b></b> _	22.91	2.78 [1.27, 6.09]
Kranzler 2000B	47/61	33/63	-	29.62	1.47 [1.12, 1.93]
Subtotal (95% CI)	296	304		88.54	2.60 [1.28, 5.28]
Total events: 91 (Antagonist)	), 45 (Control)		•		
	= 10.29, df = 4 (P = 0.04), l <sup>2</sup> =	61.1%			
Test for overall effect: $Z = 2.0$					
02 Depot or implant naltrexo	ne				
Kranzler 2004	9/158	0/157		5.57	18.88 [1.11, 321.63]
Johnson 2004	6/25	0/5	<b></b>	5.90	3.00 [0.19, 46.28]
Subtotal (95% CI)	183	162		11.46	7.28 [1.02, 52.17]
Total events: 15 (Antagonist)	), 0 (Control)		-		
Test for heterogeneity: Chi <sup>2</sup> =	= 0.88, df = 1 (P = 0.35), l <sup>2</sup> = 0	0%			
Test for overall effect: $Z = 1.9$	98 (P = 0.05)				
Total (95% CI)	479	466		100.00	3.02 [1.44, 6.33]
Total events: 106 (Antagonis	st), 45 (Control)		•		
	= 15.31, df = 6 (P = 0.02), l <sup>2</sup> =	60.8%			
Test for overall effect: $Z = 2.9$					
	. ,	0 (	001 0.01 0.1 1 10 10	0 1000	
		0.0	Favours treatment Favours cont		
			ravours treatment ravours com	101	

*Figure 1.13* Opioid antagonist compared with placebo or no medication, number of participants experiencing abdominal pain or gastrointestinal symptoms

Study or sub-category	Antagonist n/N	Control n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
01 Oral naltrexone					
Volpicelli 1992	2/35	0/35		- 0.53	5.00 [0.25, 100.53]
Croop 1997	56/570	0/295		0.70	58.58 [3.63, 944.69]
Heinala 2001	7/63	2/58		2.22	3.22 [0.70, 14.89]
Rohsenow 2000	14/64	5/64	_ <b></b>	5.32	2.80 [1.07, 7.32]
O'Malley 1992	17/52	7/52	_ <b></b>	7.45	2.43 [1.10, 5.36]
COMBINE 2003	10/18	8/17		8.76	1.18 [0.62, 2.27]
Ahmadi 2002	20/58	9/58		9.58	2.22 [1.11, 4.46]
Morris 2001	19/55	10/65	_ <b></b>	9.76	2.25 [1.14, 4.42]
Anton 1999	23/68	9/63	_ <b></b>	9.95	2.37 [1.19, 4.72]
Chick 2000	27/85	13/78		14.44	1.91 [1.06, 3.42]
Subtotal (95% CI)	1068	785	•	68.73	2.74 [2.10, 3.58]
Total events: 195 (Antagonist)	, 63 (Control)				
Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: Z = 7.45		34.4%			
02 Depot or implant naltrexon					
Johnson 2004	8/25	1/5	<b>+</b>	1.77	1.60 [0.25, 10.11]
Kranzler 2004	23/158	17/157		18.16	1.34 [0.75, 2.42]
Subtotal (95% CI)	183	162	•	19.94	1.37 [0.78, 2.39]
Total events: 31 (Antagonist), Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: Z = 1.10	0.03, df = 1 (P = 0.86), l <sup>2</sup> = 0	)%			
03 Nalmefene					
Mason 1999	9/70	0/35		0.71	9.63 [0.58, 160.88]
Anton 2004	36/169	7/68	<b>⊢</b> ∎−	10.63	2.07 [0.97, 4.42]
Subtotal (95% CI)	239	103	<b>•</b>	11.34	2.54 [1.23, 5.26]
Total events: 45 (Antagonist), Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: Z = 2.57	1.14, df = 1 (P = 0.29), l <sup>2</sup> = <sup>2</sup>	2.4%			
Total (95% CI)	1490	1050	•	100.00	2.45 [1.95, 3.07]
Total events: 271 (Antagonist) Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: Z = 7.73	16.37, df = 13 (P = 0.23), l <sup>2</sup>	= 20.6%			
		0.00	1 0.01 0.1 1 10 1	00 1000	
		-	vours antagonist Favours co		

Figure 1.14 Opioid antagonist compared with placebo or no medication, number of participants experiencing nausea or vomiting

Study or sub-category	Antagonist n/N	Control n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl
01 Oral naltrexone					
Morris 2001	6/55	0/65		<b>—</b> 1.12	15.32 [0.88, 266.02]
Guardia 2002	7/93	1/99		2.00	7.45 [0.93, 59.41]
Heinala 2001	6/63	10/58		6.46	0.55 [0.21, 1.42]
Croop 1997	38/570	5/295	<b></b>	6.66	3.93 [1.56, 9.89]
Ahmadi 2002	14/58	6/58	<b>⊢</b> ∎−	6.98	2.33 [0.96, 5.65]
COMBINE 2003	7/18	6/17	_ <b>_-</b>	7.15	1.10 [0.46, 2.62]
Gastpar 2002	9/84	10/87	_ <b>_</b>	7.30	0.93 [0.40, 2.18]
Latt 2002	8/55	16/50		8.19	0.45 [0.21, 0.97]
O'Malley 1992	18/52	8/52	<b></b>	8.38	2.25 [1.07, 4.71]
Kranzler 2000B	53/61	43/63	-	14.73	1.27 [1.05, 1.55]
Subtotal (95% CI)	1109	844	•	68.96	1.42 [0.91, 2.23]
Total events: 166 (Antagonist), 10 Test for heterogeneity: Chi <sup>2</sup> = 28.0 Test for overall effect: Z = 1.55 (P	02, df = 9 (P = 0.0009), I	<sup>2</sup> = 67.9%			
2 Depot or implant naltrexone					
Johnson 2004	8/25	1/5	<b></b>	2.45	1.60 [0.25, 10.11]
Kranzler 2004	37/158	33/157	+	12.28	1.11 [0.74, 1.69]
Subtotal (95% CI)	183	162	•	14.73	1.13 [0.76, 1.70]
Total events: 45 (Antagonist), 34 Test for heterogeneity: $Chi^2 = 0.14$ Test for overall effect: Z = 0.61 (P	4, df = 1 (P = 0.71), l <sup>2</sup> = 0	)%			
03 Nalmefene					
Mason 1999	12/70	7/35	_ <b>_</b>	7.39	0.86 [0.37, 1.98]
Anton 2004	54/197	8/68	_ <b>_</b> _	8.91	2.33 [1.17, 4.64]
Subtotal (95% CI)	267	103		16.30	1.45 [0.54, 3.92]
Total events: 66 (Antagonist), 15 Test for heterogeneity: Chi <sup>2</sup> = 3.34 Test for overall effect: Z = 0.74 (P	4, df = 1 (P = 0.07), l <sup>2</sup> = 7	70.0%			
Total (95% CI)	1559	1109	•	100.00	1.37 [1.00, 1.87]
Total events: 277 (Antagonist), 15 Test for heterogeneity: $Chi^2 = 31.9$ Test for overall effect: Z = 1.95 (P	99, df = 13 (P = 0.002), I	<sup>2</sup> = 59.4%			
		0.00	1 0.01 0.1 1 10 1	00 1000	
		Fa	avours antagonist Favours cor	ntrol	

*Figure 1.15* Opioid antagonist compared with placebo or no medication, number of participants experiencing headache or neuropsychiatric symptoms

or sub-category	Antagonist n/N	Control n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% CI	
01 Oral naltrexone						
Guardia 2002	2/93	0/99		- 1.20	5.32 [0.26, 109.35]	
O'Malley 2003	2/26	0/27		- 1.22	5.19 [0.26, 103.11]	
Kiefer 2003	4/40	0/40		- 1.24	9.00 [0.50, 161.86]	
O'Malley 2003A	2/30	0/30		- 1.24	5.00 [0.25, 99.95]	
COMBINE 2003	1/18	0/17		1.28	2.84 [0.12, 65.34]	
Latt 2002	3/56	0/51		- 1.30	6.39 [0.34, 120.71]	
Volpicelli 1997	2/48	1/49	<b>_</b>	2.46	2.04 [0.19, 21.78]	
O'Malley 1992	5/52	1/52		2.48	5.00 [0.60, 41.34]	
Petrakis 2004	1/16	1/15		2.56	0.94 [0.06, 13.68]	
Anton 1999	1/68	2/63	<b>_</b>	5.16	0.46 [0.04, 4.98]	
Gastpar 2002	4/84	3/87	<b></b>	7.32	1.38 [0.32, 5.99]	
Croop 1997	74/500	3/238	│ _ <b>_</b>	10.10	11.74 [3.74, 36.86]	
Chick 2000	13/90	11/85	_ <b>_</b>	28.10	1.12 [0.53, 2.35]	
Subtotal (95% CI)	1121	853		65.66	3.42 [2.18, 5.36]	
<b>3</b> ,	= 19.33, df = 12 (P = 0.08), l <sup>2</sup>	= 37.9%				
02 Depot or implant naltrexo Johnson 2004 Kranzler 2004 Subtotal (95% CI) Fotal events: 13 (Antagonist	ne 2/25 11/158 183 ), 8 (Control)	0/5 8/157 162 0%		2.02 19.93 21.95	1.15 [0.06, 21.05] 1.37 [0.56, 3.31] 1.35 [0.58, 3.14]	
02 Depot or implant naltrexo Johnson 2004 Kranzler 2004 Subtotal (95% CI) Fotal events: 13 (Antagonist Fest for heterogeneity: Chi <sup>2</sup>	ne 2/25 11/158 183 ), 8 (Control) = 0.01, df = 1 (P = 0.91), l <sup>2</sup> = 0	8/157 162		19.93	1.37 [0.56, 3.31]	
D2 Depot or implant naltrexo Johnson 2004 Kranzler 2004 Subtotal (95% CI) Total events: 13 (Antagonist Test for heterogeneity: Chi <sup>2</sup> Fost for overall effect: $Z = 0$ . D3 Nalmefene	2/25 11/158 183 ), 8 (Control) = 0.01, df = 1 (P = 0.91), l <sup>2</sup> = 0 69 (P = 0.49)	8/157 162 0%	•	19.93 21.95	1.37 [0.56, 3.31] 1.35 [0.58, 3.14]	
D2 Depot or implant naltrexo Johnson 2004 Kranzler 2004 Subtotal (95% CI) Fotal events: 13 (Antagonist Fest for heterogeneity: Chi <sup>2</sup> = Fest for overall effect: $Z = 0$ . D3 Nalmefene Mason 1999	nne 2/25 11/158 183 ), 8 (Control) = 0.01, df = 1 (P = 0.91), l <sup>2</sup> = 0 69 (P = 0.49) 3/70	8/157 162 0% 0/35	•	19.93 21.95 1.65	1.37 [0.56, 3.31] 1.35 [0.58, 3.14] 3.55 [0.19, 66.87]	
D2 Depot or implant naltrexo Johnson 2004 Kranzler 2004 Subtotal (95% CI) Total events: 13 (Antagonist Test for heterogeneity: Chi <sup>2</sup> : Test for overall effect: $Z = 0$ . D3 Nalmefene Mason 1999 Mason 1994	2/25 $11/158$ $183$ ), 8 (Control) = 0.01, df = 1 (P = 0.91), I <sup>2</sup> = 0 69 (P = 0.49) 3/70 $3/14$	8/157 162 0% 0/35 1/7		19.93 21.95 1.65 3.31	1.37 [0.56, 3.31] 1.35 [0.58, 3.14] 3.55 [0.19, 66.87] 1.50 [0.19, 11.93]	
D2 Depot or implant naltrexo Johnson 2004 Kranzler 2004 Subtotal (95% CI) Fotal events: 13 (Antagonist Fest for heterogeneity: Chi <sup>2</sup> = Fest for overall effect: $Z = 0$ . D3 Nalmefene Mason 1999 Mason 1994 Anton 2004	nne 2/25 11/158 183 ), 8 (Control) = 0.01, df = 1 (P = 0.91), l <sup>2</sup> = 0 69 (P = 0.49) 3/70 3/14 21/202	8/157 162 0% 0/35 1/7 2/68		19.93 21.95 1.65 3.31 7.43	1.37 [0.56, 3.31] 1.35 [0.58, 3.14] 3.55 [0.19, 66.87] 1.50 [0.19, 11.93] 3.53 [0.85, 14.68]	
D2 Depot or implant naltrexo Johnson 2004 Kranzler 2004 Subtotal (95% CI) Fotal events: 13 (Antagonist Fest for heterogeneity: Chi <sup>2</sup> : Fest for overall effect: $Z = 0$ . D3 Nalmefene Mason 1999 Mason 1994 Anton 2004 Subtotal (95% CI)	nne 2/25 11/158 183 ), 8 (Control) = 0.01, df = 1 (P = 0.91), l <sup>2</sup> = 0 69 (P = 0.49) 3/70 3/14 21/202 286	8/157 162 0% 0/35 1/7		19.93 21.95 1.65 3.31	1.37 [0.56, 3.31] 1.35 [0.58, 3.14] 3.55 [0.19, 66.87] 1.50 [0.19, 11.93]	
D2 Depot or implant naltrexo Johnson 2004 Kranzler 2004 Subtotal (95% CI) Total events: 13 (Antagonist Test for heterogeneity: Chi <sup>2</sup> : Test for overall effect: $Z = 0$ . D3 Nalmefene Mason 1999 Mason 1994 Anton 2004 Subtotal (95% CI) Total events: 27 (Antagonist Test for heterogeneity: Chi <sup>2</sup> :	nne 2/25 11/158 183 ), 8 (Control) = 0.01, df = 1 (P = 0.91), l <sup>2</sup> = 0 69 (P = 0.49) 3/70 3/14 21/202 286 ), 3 (Control) = 0.49, df = 2 (P = 0.78), l <sup>2</sup> = 0	8/157 162 0% 0/35 1/7 2/68 110		19.93 21.95 1.65 3.31 7.43	1.37 [0.56, 3.31] 1.35 [0.58, 3.14] 3.55 [0.19, 66.87] 1.50 [0.19, 11.93] 3.53 [0.85, 14.68]	
D2 Depot or implant naltrexo Johnson 2004 Kranzler 2004 Subtotal (95% CI) Total events: 13 (Antagonist Test for heterogeneity: Chi <sup>2</sup> : Test for overall effect: $Z = 0$ . D3 Nalmefene Mason 1999 Mason 1994 Anton 2004 Subtotal (95% CI) Total events: 27 (Antagonist Test for heterogeneity: Chi <sup>2</sup> : Test for overall effect: $Z = 1$ .	nne 2/25 11/158 183 ), 8 (Control) = 0.01, df = 1 (P = 0.91), l <sup>2</sup> = 0 69 (P = 0.49) 3/70 3/14 21/202 286 ), 3 (Control) = 0.49, df = 2 (P = 0.78), l <sup>2</sup> = 0	8/157 162 0% 0/35 1/7 2/68 110		19.93 21.95 1.65 3.31 7.43	1.37 [0.56, 3.31] 1.35 [0.58, 3.14] 3.55 [0.19, 66.87] 1.50 [0.19, 11.93] 3.53 [0.85, 14.68]	
Test for overall effect: $Z = 0$ . O3 Nalmefene Mason 1999 Mason 1994 Anton 2004 Subtotal (95% CI) Total events: 27 (Antagonist Test for heterogeneity: Chi <sup>2</sup> Test for overall effect: $Z = 1$ . Total (95% CI)	nne 2/25 11/158 183 ), 8 (Control) = 0.01, df = 1 (P = 0.91), l <sup>2</sup> = 0 69 (P = 0.49) 3/70 3/14 21/202 286 ), 3 (Control) = 0.49, df = 2 (P = 0.78), l <sup>2</sup> = 0 96 (P = 0.05) 1590	8/157 162 0% 0/35 1/7 2/68 110		19.93 21.95 1.65 3.31 7.43 12.39	1.37 [0.56, 3.31] 1.35 [0.58, 3.14] 3.55 [0.19, 66.87] 1.50 [0.19, 11.93] 3.53 [0.85, 14.68] 2.99 [1.00, 8.94]	CLICK HE
D2 Depot or implant naltrexo Johnson 2004 Kranzler 2004 Subtotal (95% CI) Total events: 13 (Antagonist Test for heterogeneity: Chi <sup>2</sup> Test for overall effect: $Z = 0$ . D3 Nalmefene Mason 1999 Mason 1994 Anton 2004 Subtotal (95% CI) Total events: 27 (Antagonist Test for heterogeneity: Chi <sup>2</sup> Test for overall effect: $Z = 1$ . Total (95% CI) Total events: 154 (Antagonist	nne 2/25 11/158 183 ), 8 (Control) = 0.01, df = 1 (P = 0.91), l <sup>2</sup> = 0 69 (P = 0.49) 3/70 3/14 21/202 286 ), 3 (Control) = 0.49, df = 2 (P = 0.78), l <sup>2</sup> = 0 96 (P = 0.05) 1590	8/157 162 0% 0/35 1/7 2/68 110 0% 1125		19.93 21.95 1.65 3.31 7.43 12.39	1.37 [0.56, 3.31] 1.35 [0.58, 3.14] 3.55 [0.19, 66.87] 1.50 [0.19, 11.93] 3.53 [0.85, 14.68] 2.99 [1.00, 8.94]	CLICK HE TO RETU

Figure 1.16 Opioid antagonist compared with placebo or no medication, number of participants withdrawing from treatment due to adverse effects

Favours antagonist Favours control

1

10 100 1000

0.001 0.01 0.1

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl
Niederhofer 2003	7/13	2/13		0.37	3.50 [0.89, 13.78]
Kiefer 2003	17/40	10/40	_ <b>_</b>	1.53	1.70 [0.89, 3.25]
Besson 1998	19/55	19/55	_ <b>_</b>	2.26	1.00 [0.60, 1.67]
COMBINE 2003	12/18	13/17	-	3.12	0.87 [0.57, 1.33]
Geerlings 1997	52/128	42/134	<b>+</b>	4.47	1.30 [0.94, 1.80]
Poldrugo 1997	65/122	47/124	-	5.42	1.41 [1.06, 1.86]
Pelc 1997	87/126	32/62	-	5.70	1.34 [1.02, 1.75]
Sass 1996	79/136	55/136	-	6.18	1.44 [1.12, 1.84]
Baltieri 2004	30/40	28/35	+	6.31	0.94 [0.73, 1.20]
Whitworth 1996	94/224	85/224	<b>–</b>	6.77	1.11 [0.88, 1.39]
Paille 1995	184/361	63/177	-	6.91	1.43 [1.15, 1.79]
Chick 2000A	102/289	108/292	+	7.10	0.95 [0.77, 1.18]
Namkoong 2003	53/72	48/70	<b>+</b>	7.28	1.07 [0.87, 1.32]
Lhuintre 1985	33/42	37/43	4	7.65	0.91 [0.75, 1.11]
Gual 2001	96/141	90/147	<b>_</b>	8.57	1.11 [0.94, 1.32]
Lhuintre 1990	175/279	181/290	<b>_</b>	10.16	1.00 [0.89, 1.14]
Tempesta 2000	124/164	122/166	+	10.20	1.03 [0.91, 1.17]
Fotal (95% CI)	2250	2025	•	100.00	1.12 [1.03, 1.22]
Total events: 1229 (Treatme	ent), 982 (Control)		ľ		
Test for heterogeneity: Chi <sup>2</sup> Test for overall effect: $Z = 2$	= 33.19, df = 16 (P = 0.007), .59 (P = 0.009)	l² = 51.8%			
		0.0	1 0.1 1 10	100	
			Favours control Eavours trea	atment	

*Figure 2.1 Acamprosate compared with placebo or no medication, number of participants completing treatment* 

Favours control Favours treatment

Study or sub-category	Acamprosate n/N	Naltrexone n/N				(fixed) 5% CI	)		Weight %		RR (fixed) 95% Cl	
COMBINE 2003	12/18	10/18			_	-	_		9.77	1.20	[0.71, 2.03]	
Kiefer 2003	17/40	22/40				+			21.50	0.77	[0.49, 1.22]	
Rubio 2001	62/80	69/77			•				68.73	0.86	[0.75, 1.00]	
Total (95% CI)	138	135							100.00	0.88	[0.76, 1.02]	
Total events: 91 (Acampros	sate), 101 (Naltrexone)					Ĭ						
Test for heterogeneity: Chi2	<sup>2</sup> = 1.70, df = 2 (P = 0.43), l <sup>2</sup> = 0	1%										
Test for overall effect: $Z = 1$	1.75 (P = 0.08)											
			0.1	0.2	0.5	1	2	5	10			
			Fav	vours na	altrexone	Fa	vours a	acampi	rosate			

*Figure 2.2 Acamprosate compared with naltrexone, number of participants completing treatment* 

	Acamprosate compared with placebo or no m	- dis a tisk was to an affin a utisk south	a sufficiency of the short of the sufficiency for strangers of
Figure 2.3	Acamprosate compared with placebo or no m	edication number of participants	continuousiv anstinent during treatment
1 19010 2.0	nounplocate compared with placese of ne m		

Study or sub-category	category n/N n/N		RR (random) 95% Cl	Weight %	RR (random) 95% Cl	
Borg 1994	2/5	2/5		0.94	1.00 [0.22, 4.56]	
Niederhofer 2003	7/13	2/13		1.14	3.50 [0.89, 13.78]	
Ladewig 1993	10/29	3/32	<b>_</b>	1.48	3.68 [1.12, 12.07]	
Pelc 1992	15/55	3/47		1.50	4.27 [1.32, 13.86]	
Besson 1998	19/55	4/55		1.97	4.75 [1.73, 13.06]	
Baltieri 2004	17/40	7/35	<b></b>	3.21	2.13 [1.00, 4.52]	
Pelc 1997	52/126	9/62	<b></b>	4.14	2.84 [1.50, 5.39]	
Geerlings 1997	25/128	13/134	<b></b>	4.28	2.01 [1.08, 3.76]	
Roussaux 1996	18/63	21/64		5.44	0.87 [0.52, 1.47]	
Namkoong 2003	26/72	22/70	_ <b>_</b>	6.35	1.15 [0.72, 1.83]	
Chick 2000A	35/289	32/292	_ <b>_</b> _	6.55	1.11 [0.70, 1.73]	
Sass 1996	58/136	29/136	-	7.93	2.00 [1.37, 2.92]	
Gual 2001	49/141	38/147		8.39	1.34 [0.94, 1.92]	
Poldrugo 1997	57/122	32/124	-	8.43	1.81 [1.27, 2.58]	
Whitworth 1996	63/224	45/224	+	8.84	1.40 [1.00, 1.96]	
Paille 1995	112/361	37/177		9.06	1.48 [1.07, 2.05]	
Barrias 1997	67/150	47/152	-	9.73	1.44 [1.07, 1.94]	
Tempesta 2000	79/164	58/166	-	10.63	1.38 [1.06, 1.79]	
Total (95% CI)	2173	1935	•	100.00	1.58 [1.36, 1.84]	CLICK HERI
Total events: 711 (Treatmer	nt), 404 (Control)					
Test for heterogeneity: Chi <sup>2</sup>	= 29.22, df = 17 (P = 0.03), l <sup>2</sup>	= 41.8%				TO RETURN
Test for overall effect: Z = 5.	.89 (P < 0.00001)					TO REPORT

Favours control Favours treatment

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl	
Ladewig 1993	12/29	7/32		2.20	1.89 [0.86, 4.15]	
Lhuintre 1985	20/42	12/43		3.92	1.71 [0.96, 3.03]	
Geerlings 1997	32/128	18/134	<b>_</b>	5.81	1.86 [1.10, 3.14]	
Pelc 1997	60/126	16/62	│ <b></b>	7.08	1.85 [1.16, 2.92]	
Besson 1998	40/55	26/55	<b></b>	8.58	1.54 [1.11, 2.12]	
Sass 1996	61/136	34/136	_ <b>_</b>	11.22	1.79 [1.27, 2.53]	
Poldrugo 1997	59/122	40/124	_ <b>_</b> _	13.10	1.50 [1.10, 2.05]	
Paille 1995	150/361	53/177		23.48	1.39 [1.07, 1.79]	
Tempesta 2000	95/164	75/166		24.61	1.28 [1.04, 1.59]	
Total (95% CI)	1163	929	•	100.00	1.52 [1.35, 1.70]	
Total events: 529 (Treatmen	t), 281 (Control)					
Test for heterogeneity: Chi2 -	= 5.55, df = 8 (P = 0.70), l <sup>2</sup> = 0	0%				

*Figure 2.4 Acamprosate compared with placebo or no medication, number of participants abstinent at follow-up* 

Favours control Favours treatment

Figure 2.5	Acamprosate compared with placebo or no medication, number of participants relapsing during treatment	
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Study or sub-category	Treatment n/N	Control n/N	I	RR (fixed) 95% CI	Weight %	RR (fixed) 95% Cl	
Niederhofer 2003	1/13	6/13			1.56	0.17 [0.02, 1.20]	
Gual 2001	4/96	7/90		•	1.88	0.54 [0.16, 1.77]	
Pelc 1997	15/126	10/62		<b></b>	3.48	0.74 [0.35, 1.55]	
Besson 1998	17/55	20/55		<b></b>	5.20	0.85 [0.50, 1.44]	
Poldrugo 1997	20/122	29/124		<b></b>	7.47	0.70 [0.42, 1.17]	
Kiefer 2003	17/40	30/40			7.79	0.57 [0.38, 0.85]	
Lhuintre 1985	22/42	31/43			7.96	0.73 [0.52, 1.02]	
Namkoong 2003	43/72	42/70		<b>+</b>	11.06	1.00 [0.76, 1.30]	
Whitworth 1996	52/224	52/224		<b>_</b>	13.51	1.00 [0.71, 1.40]	
Paille 1995	77/361	39/177		<b>_</b>	13.60	0.97 [0.69, 1.36]	
Sass 1996	75/136	102/136		=	26.50	0.74 [0.61, 0.88]	
Total (95% CI)	1287	1034		•	100.00	0.81 [0.72, 0.91]	CLICK HERE
Total events: 343 (Treatmen Test for heterogeneity: Chi <sup>2</sup>		2 - 20 0%					
Test for overall effect: $Z = 3$ .		- 20.370					
		(	0.01 0.1	1 10	100		
		(		1 10			

Favours treatment Favours control

Study or sub-category	Ν	Treatment Mean (SD)	Ν	Control Mean (SD)	WMD (random) 95% Cl	Weight %	WMD (random) 95% Cl
Niederhofer 2003	13	88.70(41.70)	13	36.40(21.10)		3.39	52.30 [26.90, 77.70]
Besson 1998	55	40.00(41.00)	55	21.00(30.00)	_ <b>_</b> _	7.18	19.00 [5.57, 32.43]
Poldrugo 1997	122	55.10(44.40)	124	39.10(41.20)	<b></b>	8.52	16.00 [5.29, 26.71]
Gual 2001	141	51.70(41.70)	147	41.10(41.70)	<b>⊢</b>	9.09	10.60 [0.97, 20.23]
Sass 1996	136	66.85(40.66)	136	48.20(39.30)		9.16	18.65 [9.15, 28.15]
Tempesta 2000	164	61.10(42.80)	166	49.40(42.80)	_ <b>_</b> _	9.30	11.70 [2.46, 20.94]
Geerlings 1997	128	33.90(38.90)	134	23.90(32.20)		9.61	10.00 [1.33, 18.67]
Namkoong 2003	72	81.20(23.70)	70	78.50(27.80)	<b>—</b>	9.69	2.70 [-5.81, 11.21]
Whitworth 1996	224	38.56(38.20)	224	28.80(33.06)	-	10.68	9.76 [3.14, 16.38]
Paille 1995	361	57.50(36.60)	177	47.40(34.50)	-	10.82	10.10 [3.77, 16.43]
Pelc 1997	126	60.30(5.00)	62	38.10(4.80)	•	12.54	22.20 [20.72, 23.68]
Total (95% CI)	1542		1308		•	100.00	14.41 [8.94, 19.88]
Test for heterogeneity: Ch Test for overall effect: Z =	,	( ,,	3%				
				-	100 -50 0 50	100	
					Eavours control Eavours tre	atment	

Figure 2.6 Acamprosate compared with placebo or no medication, average cumulative abstinence duration (%)

Favours control Favours treatment

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#### Figure 2.7 Acamprosate compared with naltrexone, number of participants relapsing during treatment

Study or sub-category	Acamprosate n/N	Naltrexone n/N				(randor 5% Cl	'		Weight %	RR (random) 95% Cl
Kiefer 2003 Rubio 2001	17/40 45/77	12/40 66/80			-	-			42.33 57.67	1.42 [0.78, 2.57] 0.71 [0.57, 0.88]
Total (95% CI) Total events: 62 (Acampros Test for heterogeneity: Chi Test for overall effect: Z = (	<sup>2</sup> = 5.03, df = 1 (P = 0.02), l <sup>2</sup> = 8	120 0.1%							100.00	0.95 [0.47, 1.91]
	5.14 (1 = 0.03)		0.1	0.2	0.5	1	2	5	10	
			Favo	urs acar	nprosate	ə Fa	vours	naltrex	one	

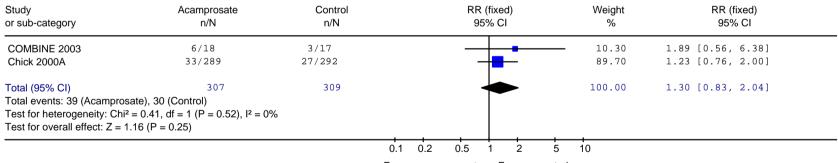
Study or sub-category	Treatment n/N	Control n/N		RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
Lhuintre 1985	7/42	2/43			- 0.76	3.58 [0.79, 16.27]
Paille 1995	136/361	61/177		<b>+</b>	31.67	1.09 [0.86, 1.39]
Chick 2000A	93/289	83/292		<b>_</b>	31.95	1.13 [0.88, 1.45]
Gual 2001	99/141	94/147		<b>+</b>	35.61	1.10 [0.93, 1.29]
otal (95% CI)	833	659		•	100.00	1.13 [0.99, 1.28]
otal events: 335 (Treatme	ent), 240 (Control)			*		
Test for heterogeneity: Chi Test for overall effect: Z =	i <sup>2</sup> = 2.40, df = 3 (P = 0.49), l <sup>2</sup> = 0 1.86 (P = 0.06)	0%				
			0.01 0.	1 1 10	100	
			<b>F</b>			

Figure 2.8 Acamprosate compared with placebo or no medication, number of participants experiencing adverse effects

Favours treatment Favours control

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Figure 2.9 Acamprosate compared with placebo or no medication, number of participants with dose reduced due to adverse effects



Favours acamprosate Favours control

Study or sub-category	Acamprosate n/N	Placebo n/N			(fixed) % CI	Weight %	RR (fixed) 95% CI
Baltieri 2004	4/40	1/35					3.50 [0.41, 29.86]
COMBINE 2003	8/18	6/17		_		22.71	1.26 [0.55, 2.87]
Sass 1996	7/136	9/136				33.12	0.78 [0.30, 2.03]
Tempesta 2000	12/164	11/166			╞╾	40.24	1.10 [0.50, 2.43]
Total (95% CI)	358	354				100.00	1.13 [0.70, 1.82]
Total events: 31 (Acampros	sate), 27 (Placebo)				Ĩ		
Test for heterogeneity: Chi	$^{2} = 1.72$ , df = 3 (P = 0.63), l <sup>2</sup> = 0	%					
Test for overall effect: $Z = 0$	0.48 (P = 0.63)						
			0.01	0.1	1 10	100	
			Favours	acamprosate	Favours pl	acebo	

Figure 2.10	Acamprosate compared with placebo or no medication, number of participants experiencing headaches
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Figure 2.11 Acamprosate compared with placebo or no medication, number of participants experiencing diarrhoea or other gastrointestinal effects

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% Cl	
Lhuintre 1985	4/42	1/43		- 0.54	4.10 [0.48, 35.14]	
Namkoong 2003	8/72	2/70		1.10	3.89 [0.86, 17.68]	
Besson 1998	17/55	4/55	<b></b>	2.17	4.25 [1.53, 11.82]	
Baltieri 2004	5/40	4/35		2.31	1.09 [0.32, 3.76]	
Tempesta 2000	5/164	5/166	<b></b>	2.69	1.01 [0.30, 3.43]	
Paille 1995	35/361	6/177		4.37	2.86 [1.23, 6.67]	
COMBINE 2003	11/18	10/17	_ <b>_</b>	5.58	1.04 [0.60, 1.79]	
Sass 1996	10/136	11/136		5.96	0.91 [0.40, 2.07]	
Geerlings 1997	25/128	15/128	<b>↓</b>	8.13	1.67 [0.92, 3.01]	
Lhuintre 1990	37/279	20/290	_ <b>_</b> _	10.64	1.92 [1.14, 3.23]	
Whitworth 1996	45/224	27/224	<b></b>	14.64	1.67 [1.07, 2.59]	
Pelc 1997	57/126	24/62	<b></b>	17.44	1.17 [0.81, 1.69]	
Gual 2001	61/141	46/147	-	24.42	1.38 [1.02, 1.88]	
Total (95% CI)	1786	1550	•	100.00	1.57 [1.34, 1.85]	CLICK HERE
Total events: 320 (Treatmen	it), 175 (Control)					
<b>č</b> ,	= 16.33, df = 12 (P = 0.18), l <sup>2</sup>	= 26.5%				TO RETURN
Test for overall effect: $Z = 5$ .	44 (P < 0.00001)					TO REPORT
		0.0	01 0.1 1 10	100		

Favours treatment Favours control

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
Kiefer 2003	3/40	0/40		- 0.74	7.00 [0.37, 131.28]
Tempesta 2000	2/164	0/166		- 0.74	5.06 [0.24, 104.61]
Namkoong 2003	2/72	0/70		• 0.75	4.86 [0.24, 99.52]
COMBINE 2003	1/18	0/17	<b>_</b>	0.76	2.84 [0.12, 65.34]
Gual 2001	2/141	1/147	<b></b>	1.46	2.09 [0.19, 22.74]
Niederhofer 2003	1/13	1/13		1.49	1.00 [0.07, 14.34]
Pelc 1997	3/126	1/62	<b></b>	2.00	1.48 [0.16, 13.90]
Geerlings 1997	7/128	4/134	_ <b></b>	5.82	1.83 [0.55, 6.11]
Whitworth 1996	6/224	4/224	_ <b></b>	5.95	1.50 [0.43, 5.24]
Poldrugo 1997	2/122	8/124	<b>_</b> _	11.81	0.25 [0.06, 1.17]
Paille 1995	28/361	15/177	<b>_</b>	29.97	0.92 [0.50, 1.67]
Chick 2000A	42/289	26/292	-	38.50	1.63 [1.03, 2.59]
Fotal (95% CI)	1698	1466	•	100.00	1.35 [1.00, 1.83]
Fotal events: 99 (Treatment)	, 60 (Control)		•		
,	= 10.15, df = 11 (P = 0.52), l <sup>2</sup>	= 0%			
est for overall effect: Z = 1.9					
			0.001 0.01 0.1 1 10 1	00 1000	
			Favours treatment Favours cor	ntrol	

*Figure 2.12 Acamprosate compared with placebo or no medication, number of participants withdrawing due to adverse effects* 

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#### Figure 2.13 Acamprosate compared with naltrexone, number of participants experiencing nausea

Study or sub-category	Acamprosate n/N	Naltrexone n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% Cl
COMBINE 2003	3/18	10/18	_ <b>_</b>	34.06	0.30 [0.10, 0.91]
Rubio 2001	3/80	19/77	<b>——</b>	65.94	0.15 [0.05, 0.49]
Total (95% CI)	98	95	•	100.00	0.20 [0.09, 0.46]
Total events: 6 (Acamprosa Test for heterogeneity: Chi <sup>2</sup> Test for overall effect: Z = 3	= 0.71, df = 1 (P = 0.40), l <sup>2</sup> = 0	%			
		C	<b>1 1 1</b> 0.01 0.1 1 1	0 100	

Favours acamprosate Favours naltrexone

Study or sub-category	Acamprosate n/N	Naltrexone n/N			(fixed) 5% CI		Weight %	RR (fixed) 95% Cl
COMBINE 2003	1/18	4/18	-	-	<u> </u>		17.90	0.25 [0.03, 2.02]
Rubio 2001	3/80	18/77		<b>—</b>			82.10	0.16 [0.05, 0.52]
Total (95% CI)	98	95					100.00	0.18 [0.06, 0.49]
Total events: 4 (Acamprosa	, · · · · /							
0,	<sup>2</sup> = 0.13, df = 1 (P = 0.72), l <sup>2</sup> = 0	%						
Test for overall effect: $Z = 3$	3.31 (P = 0.0009)							
			0.01	0.1	1	10 100	)	
			Favours	acamprosate	Favour	s naltrexone		

#### *Figure 2.14 Acamprosate compared with naltrexone, number of participants experiencing abdominal pain*

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#### Figure 2.15 Acamprosate compared with naltrexone, number of participants experiencing diarrhoea

Study or sub-category	Acamprosate n/N	Naltrexone n/N		R (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
Rubio 2001	3/80	1/77		-	9.25	2.89 [0.31, 27.16]
COMBINE 2003	11/18	10/18		+	90.75	1.10 [0.63, 1.91]
Total (95% CI) Total events: 14 (Acampros		95		•	100.00	1.27 [0.72, 2.22]
Test for overall effect: $Z = 0$	= 0.77, df = 1 (P = 0.38), l <sup>2</sup> = 0 .82 (P = 0.41)	%				
		(	0.01 0.1	1 10	100	

Favours acamprosate Favours naltrexone

Study or sub-category	Acamprosate n/N	Naltrexone n/N				R (fixed 95% Cl	'		Weight %	RR (fixed) 95% Cl
COMBINE 2003	8/18	7/18				-			40.72	1.14 [0.53, 2.48]
Rubio 2001	5/80	10/77			-	—			59.28	0.48 [0.17, 1.34]
Total (95% CI)	98	95							100.00	0.75 [0.40, 1.40]
Total events: 13 (Acampros	ate), 17 (Naltrexone)				-					
<b>o</b> ,	= 1.85, df = 1 (P = 0.17), l <sup>2</sup> = 4	5.9%								
Test for overall effect: Z = 0	.90 (P = 0.37)									
			0.1	0.2	0.5	1	2	5	10	
			Favo	urs acar	mprosate	e Fa	avours	naltrex	one	

#### *Figure 2.16 Acamprosate compared with naltrexone, number of participants experiencing headaches*

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Study or sub-category	Acamprosate n/N	Naltrexone n/N		RR (fixed) 95% Cl	Weight %	RR (fixed) 95% CI
COMBINE 2003	1/18	1/18			13.42	1.00 [0.07, 14.79]
Rubio 2001	0/77	2/80			32.91	0.21 [0.01, 4.26]
Kiefer 2003	3/40	4/40			53.67	0.75 [0.18, 3.14]
Fotal (95% CI)	135	138			100.00	0.61 [0.19, 1.88]
Total events: 4 (Acamprosa	ate), 7 (Naltrexone)			-		
Fest for heterogeneity: Chi2	$P = 0.70$ , df = 2 (P = 0.70), $I^2 = 0.00$	%				
Test for overall effect: Z = 0	0.87 (P = 0.39)					
			0.01 0.1	<b> </b> 1	10 100	
			_	. –		

Figure 2.17 Acamprosate compared with naltrexone, number of participants withdrawing from treatment due to adverse effects

Favours acamprosate Favours naltrexone

Study or sub-category	Combination n/N	Placebo n/N				(rando 5% CI	'		Weight %	RR (random) 95% Cl
Kiefer 2003	26/40	10/40				-			48.14	2.60 [1.45, 4.66]
COMBINE 2003	24/36	13/17			_	-			51.86	0.87 [0.61, 1.24]
Total (95% CI)	76	57							100.00	1.48 [0.44, 4.92]
Total events: 50 (Combinati Test for heterogeneity: $Chi^2$ Test for overall effect: $Z = 0$	= 12.58, df = 1 (P = 0.0004), l	<sup>2</sup> = 92.0%								
			0.1	0.2	0.5	1	2	5	10	
				Favours	placebo	o Fa	avours o	combin	ation	

#### Figure 3.1 Naltrexone plus acamprosate, compared with placebo, number of participants completing treatment

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# Figure 3.2 Naltrexone plus acamprosate, compared with acamprosate, number of participants completing treatment

Study or sub-category	Combined n/N	Acamprosate n/N				R (fixed) 5% CI	)		Weight %	RR (fixed) 95% CI
COMBINE 2003	24/36	12/18			_	+			48.48	1.00 [0.67, 1.49]
Kiefer 2003	26/40	17/40					<u> </u>		51.52	1.53 [1.00, 2.34]
Total (95% CI)	76	58							100.00	1.27 [0.95, 1.71]
Total events: 50 (Combined) Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: Z = 1.6	= 2.11, df = 1 (P = 0.15), l <sup>2</sup> = 5	52.6%								
			0.1	0.2	0.5	1	2	+ 5	10	
			Favou	urs acar	nprosate	ə Fav	vours	combine	ed	

Study or sub-category	Combined n/N	Naltrexone n/N				R (fixed 5% CI	,		Weight %	RR (fixed) 95% CI
COMBINE 2003	24/36	10/18			-		_		37.74	1.20 [0.75, 1.93]
Kiefer 2003	26/40	22/40				+	-		62.26	1.18 [0.82, 1.70]
Total (95% CI)	76	58					•		100.00	1.19 [0.89, 1.58]
Total events: 50 (Combined Test for heterogeneity: $Chi^2$ Test for overall effect: $Z = 1$	= 0.00, df = 1 (P = 0.96), l <sup>2</sup> = 0	)%								
			0.1	0.2	0.5	1	2	5	10	
			Fav	vours n	altrexon	ə Fa	avours	combin	ed	

#### Figure 3.3 Naltrexone plus acamprosate, compared with naltrexone, number of participants completing treatment

ours naitrexone Favours combined

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# Figure 3.4 Naltrexone plus acamprosate, compared with placebo, number of participants withdrawing from treatment due to adverse effects

Study or sub-category	Combination n/N	Placebo n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
Kiefer 2003	4/40	0/40		12.94	9.00 [0.50, 161.86]
COMBINE 2003	0/36	2/17		87.06	0.10 [0.00, 1.92]
Total (95% CI)	76	57	•	100.00	1.25 [0.36, 4.31]
Total events: 4 (Combinatio	n), 2 (Placebo)		Ť.		
Test for heterogeneity: Chi <sup>2</sup>	= 4.61, df = 1 (P = 0.03), l <sup>2</sup> = 7	8.3%			
Test for overall effect: Z = 0	.35 (P = 0.72)				
		0	.001 0.01 0.1 1 10 1	00 1000	
			Eavours combination Eavours pla	cebo	

Favours combination Favours placebo

# Figure 3.5 Naltrexone plus acamprosate, compared with acamprosate, number of participants withdrawing from treatment due to adverse effects

Study or sub-category	Combined n/N	Acamprosate n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
COMBINE 2003	0/36	1/18	<b>_</b>	39.78	0.17 [0.01, 4.00]
Kiefer 2003	4/40	3/40	_ <b>_</b>	60.22	1.33 [0.32, 5.58]
Total (95% CI)	76	58	•	100.00	0.87 [0.26, 2.90]
Total events: 4 (Combined), Test for heterogeneity: $Chi^2$ Test for overall effect: $Z = 0$ .	= 1.36, df = 1 (P = 0.24), l <sup>2</sup> =	26.6%			
		C	0.001 0.01 0.1 1 10 1	00 1000	
			Favours combined Favours ac	amprosate	

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# Figure 3.6 Naltrexone plus acamprosate, compared with placebo, number of participants withdrawing from treatment due to adverse effects

Study or sub-category	Combined n/N	Naltrexone n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
COMBINE 2003	0/36	1/18	<b>_</b>	33.13	0.17 [0.01, 4.00]
Kiefer 2003	4/40	4/40	_ <del></del>	66.87	1.00 [0.27, 3.72]
Total (95% CI)	76	58	•	100.00	0.73 [0.23, 2.29]
Total events: 4 (Combined),	5 (Naltrexone)				
Test for heterogeneity: Chi <sup>2</sup>	= 1.04, df = 1 (P = 0.31), l <sup>2</sup> = 3	.4%			
Test for overall effect: Z = 0.	.55 (P = 0.58)				
		0.00	1 0.01 0.1 1 10 1	00 1000	
		-			

Favours combined Favours naltrexone

Study or sub-category	Disulfiram n/N	Control n/N			•	andor % Cl	n)		Weight %	RR (random) 95% Cl	
01 Oral disulfiram											
Gerrein 1973	16/26	6/23					-		3.91	2.36 [1.11, 5.00]	
Powell 1985	98/116	50/58				<b>-</b>			41.36	0.98 [0.86, 1.12]	
Fuller 1986	194/208	186/199							54.73	1.00 [0.95, 1.05]	
Subtotal (95% CI)	350	280				•			100.00	1.02 [0.88, 1.19]	
Total events: 308 (Disulfirar	n), 242 (Control)					Ī					
Test for heterogeneity: Chi <sup>2</sup>	= 6.32, df = 2 (P = 0.04), l <sup>2</sup> =	68.4%									
Test for overall effect: $Z = 0$											
			0.1	0.2	0.5	1	2	5	10		
			F	avour	s control	Fa	vours d	lisulfira	m		

#### *Figure 4.1 Disulfiram compared with no medication, number of participants completing treatment*

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### *Figure 4.2 Disulfiram compared with placebo, number of participants continuously abstinent during treatment*

Study or sub-category	Disulfiram n/N	Placebo n/N		F	RR (fixed) 95% CI		Weight %	RR (fixed) 95% Cl
01 Oral disulfiram								
Niederhofer 2003B	7/13	2/13					3.40	3.50 [0.89, 13.78]
Fuller 1979	9/43	11/43			<b></b>		18.72	0.82 [0.38, 1.77]
Fuller 1986	38/202	46/204			-		77.88	0.83 [0.57, 1.22]
Subtotal (95% CI)	258	260			<b></b>		100.00	0.92 [0.66, 1.28]
Total events: 54 (Disulfiram), Test for heterogeneity: $Chi^2 =$ Test for overall effect: $Z = 0.4$	= 3.99, df = 2 (P = 0.14), l <sup>2</sup> =	49.9%						
			0.01	0.1	1	10	100	
			Fa	vours place	bo Favo	ours disul	firam	

Study or sub-category	Disulfiram n/N	Placebo n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
01 Oral disulfiram					
Fuller 1979	18/43	15/43	_ <b></b> _	47.95	1.20 [0.70, 2.06]
Subtotal (95% CI)	43	43	•	47.95	1.20 [0.70, 2.06]
Total events: 18 (Disulfiram) Test for heterogeneity: not a Test for overall effect: Z = 0.	pplicable				
02 Disulfiram implant					
Wilson 1976	5/10	1/10			5.00 [0.70, 35.50]
Johnsen 1991	6/33	6/30		20.09	0.91 [0.33, 2.52]
Wilson 1980	12/40	9/40	_ <b></b>	28.77	1.33 [0.63, 2.81]
Subtotal (95% CI)	83	80	•	52.05	1.39 [0.80, 2.44]
Total events: 23 (Disulfiram) Test for heterogeneity: Chi <sup>2</sup> : Test for overall effect: Z = 1.	= 2.32, df = 2 (P = 0.31), l <sup>2</sup> = 1	3.9%			
Total (95% CI) Total events: 41 (Disulfiram) Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: Z = 1.	= 2.38, df = 3 (P = 0.50), l <sup>2</sup> = 0	123 <b>)%</b>	•	100.00	1.30 [0.88, 1.92]
		0.0	1 0.1 1 10	100	
			Favours placebo Favours dis	ulfiram	

Figure 4.3 Disulfiram compared with placebo, number of participants abstinent at follow-up

Study or sub-category	N	Disulfiram Mean (SD)	N	Placebo Mean (SD)	WMD (random) 95% Cl	Weight %	WMD (random) 95% Cl
01 Oral disulfiram							
Niederhofer 2003B	13	76.11(41.67)	29	33.00(21.11)		27.94	43.11 [19.19, 67.03]
Fuller 1986	202	86.40(2.30)	204	79.10(3.30)		44.36	7.30 [6.75, 7.85]
Subtotal (95% CI)	215		233			72.30	23.13 [-11.73, 57.98]
Test for heterogeneity: Chi <sup>2</sup> =	8.61, df = 1 (	P = 0.003), l <sup>2</sup> = 88.4%			_		
Test for overall effect: Z = 1.3	0 (P = 0.19)						
02 Disulfiram implant							
Johnsen 1987	10	45.00(28.50)	11	33.50(28.00)	_ <b>+</b>	27.70	11.50 [-12.70, 35.70]
Subtotal (95% CI)	10		11			27.70	11.50 [-12.70, 35.70]
Test for heterogeneity: not ap	olicable				-		
Test for overall effect: Z = 0.93	3 (P = 0.35)						
Total (95% CI)	225		244			100.00	18.47 [-2.31, 39.25]
Test for heterogeneity: $Chi^2 =$ Test for overall effect: $Z = 1.74$		P = 0.01), I <sup>2</sup> = 77.1%			-		
					100 -50 0 50	100	
					Favours placebo Favours dis	ulfiram	

*Figure 4.4 Disulfiram compared with placebo, average cumulative abstinence duration (%)* 

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Study or sub-category	Disulfiram n/N	Control n/N			RR (fixed) 95% Cl		Weight %	RR (fixed) 95% Cl
01 Oral disulfiram								
Gerrein 1973	6/26	2/23					5.38	2.65 [0.59, 11.88]
Fuller 1979	9/43	5/42					12.83	1.76 [0.64, 4.81]
Fuller 1986	38/202	32/199			-		81.78	1.17 [0.76, 1.79]
Subtotal (95% CI)	271	264			•		100.00	1.33 [0.91, 1.93]
Total events: 53 (Disulfiram)	), 39 (Control)				ľ			
Test for heterogeneity: Chi <sup>2</sup>	= 1.45, df = 2 (P = 0.48), l <sup>2</sup> = 0	)%						
Test for overall effect: Z = 1.	.46 (P = 0.14)							
			0.01	0.1	1	10	100	
			Fa	avours cont	rol Favo	urs disul	firam	

*Figure 4.5 Disulfiram compared with no medication, number of participants continuously abstinent during treatment* 

Study or sub-category	Disulfiram Control RR (random) n/N n/N 95% CI		Weight %	RR (random) 95% Cl	
01 Oral disulfiram					
Fuller 1979	18/43	7/42		40.75	2.51 [1.17, 5.38]
Powell 1985	38/116	21/58	+	48.75	0.90 [0.59, 1.39]
Subtotal (95% CI)	159	100		89.50	1.43 [0.52, 3.92]
Total events: 56 (Disulfiram), 28 (C	Control)				
Test for heterogeneity: Chi <sup>2</sup> = 5.33	, df = 1 (P = 0.02), l <sup>2</sup> = 8	31.2%			
Test for overall effect: Z = 0.70 (P	= 0.48)				
02 Disulfiram implant					
Wilson 1980	12/40	0/10		10.50	6.71 [0.43, 104.63]
Subtotal (95% CI)	40	10		10.50	6.71 [0.43, 104.63]
Total events: 12 (Disulfiram), 0 (Co	ontrol)		_		
Test for heterogeneity: not applical	ble				
Test for overall effect: Z = 1.36 (P	= 0.17)				
Total (95% CI)	199	110		100.00	1.69 [0.63, 4.57]
Total events: 68 (Disulfiram), 28 (C	Control)		-		
Test for heterogeneity: $Chi^2 = 7.18$	,	72.2%			
Test for overall effect: $Z = 1.04$ (P	,.				
		0.00	01 0.01 0.1 1 10 1	00 1000	
			Favours control Favours dis	ulfiram	

Figure 4.6 Disulfiram compared with no medication, number of participants abstinent at follow-up

Study or sub-category			RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl	
01 Oral disulfiram						
Niederhofer 2003B	1/13	1/13	<b>_</b>	33.05	1.00 [0.07, 14.34]	
Subtotal (95% CI)	13	13		33.05	1.00 [0.07, 14.34]	
Total events: 1 (Disulfiram), 1 (I Test for heterogeneity: not appl Test for overall effect: $Z = 0.00$	licable					
02 Disulfiram implant						
Johnsen 1987	3/10	0/11		15.81	7.64 [0.44, 131.75]	
Wilson 1976	2/10	0/10	<b>_</b>	16.52	5.00 [0.27, 92.62]	
Johnsen 1991	5/33	1/30		34.62	4.55 [0.56, 36.72]	
Subtotal (95% CI)	53	51		66.95	5.39 [1.26, 23.01]	
Total events: 10 (Disulfiram), 1 Test for heterogeneity: $Chi^2 = 0$ Test for overall effect: Z = 2.27	.09, df = 2 (P = 0.96), $I^2 = 0$	%				
Total (95% CI)	66	64	•	100.00	3.94 [1.16, 13.34]	
Total events: 11 (Disulfiram), 2 Test for heterogeneity: $Chi^2 = 1$ Test for overall effect: Z = 2.20	.27, df = 3 (P = 0.74), $I^2 = 0$	%				
		0.00	1 0.01 0.1 1 10 10	0 1000		
		F	avours disulfiram Favours plac	ebo		

*Figure 4.7 Disulfiram compared with placebo, number of participants experiencing adverse effects* 

Figure 4.8 Disulfiram compared with placebo, number of participants discontinuing treatment due to adverse effects

Study or sub-category	Disulfiram n/N	Placebo n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% Cl	
01 Oral disulfiram						
Fuller 1986	3/208	0/204		33.20	6.87 [0.36, 132.09]	
Chick 1992	4/64	1/62		66.80	3.88 [0.45, 33.71]	
Subtotal (95% CI)	272	266		100.00	4.87 [0.86, 27.69]	CLICK HERE
Total events: 7 (Disulfiram),	1 (Placebo)					
Test for heterogeneity: Chi <sup>2</sup>	= 0.09, df = 1 (P = 0.76), l <sup>2</sup> = 0	%				TO RETURN
Test for overall effect: $Z = 1$	.78 (P = 0.07)					
		0.00	1 0.01 0.1 1 10 10	0 1000		
		F	avours disulfiram Eavours plac	eho		

Favours disulfiram Favours placebo

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl	
01 SSRIs						
Kranzler 1993	2/10	8/9		1.17	0.23 [0.06, 0.79]	
Tiihonen 1996	21/31	13/31		5.11	1.62 [1.00, 2.61]	
Gual 2003	24/44	22/39		6.41	0.97 [0.66, 1.42]	
Pettinati 2000A	32/50	26/50	I_	7.19	1.23 [0.88, 1.73]	
Janiri 1996	19/21	20/29		8.19	1.31 [0.99, 1.74]	
Moak 2003	31/38	28/44	<u> </u>	8.40	1.28 [0.98, 1.68]	
Chick 2004	72/243	116/249	- [	9.04	0.64 [0.50, 0.80]	
Subtotal (95% CI)	437	451	-	45.51	1.03 [0.74, 1.43]	
otal events: 201 (Treatment		497	Ť	45.51	1.05 [0.74, 1.45]	
	= 35.57, df = 6 (P < 0.00001)	), l <sup>2</sup> = 83.1%				
2 Tricyclic antidepressants						
Mason 1996	8/37	8/34	<b>4</b>	2.25	0.92 [0.39, 2.18]	
Favre 1997	58/170	78/172	-	8.47	0.75 [0.58, 0.98]	
McGrath 1996	27/36	29/33		9.19	0.85 [0.68, 1.07]	
Subtotal (95% CI)	243	239	•	19.91	0.81 [0.69, 0.96]	
est for overall effect: Z = 2.3	39 (P = 0.02)					
03 Ritanserin	100/201	E1 (100		10.00		
Wiesbeck 1999	198/371	71/122	1	10.08	0.92 [0.77, 1.10]	
Johnson 1996	171/283	90/140	7	10.47	0.94 [0.80, 1.10]	
	654	262		20.55	0.93 [0.83, 1.05]	
Total events: 369 (Treatment	t), 161 (Control)	00/				
Fotal events: 369 (Treatment Fest for heterogeneity: Chi² =	t), 161 (Control) = 0.04, df = 1 (P = 0.84), l² =	: 0%				
Total events: $369$ (Treatment Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: Z = 1.2	t), 161 (Control) = 0.04, df = 1 (P = 0.84), l <sup>2</sup> = 22 (P = 0.22)					
otal events: 369 (Treatmen est for heterogeneity: Chi <sup>2</sup> = est for overall effect: Z = 1.2 4 Nefazodone	t), 161 (Control) = 0.04, df = 1 (P = 0.84), l² =	11/32		4.35	1.82 [1.05, 3.15]	
otal events: 369 (Treatmen) est for heterogeneity: Chi <sup>2</sup> = est for overall effect: Z = 1.2 4 Nefazodone Roy-Byrne 2000	t), 161 (Control) = 0.04, df = 1 (P = 0.84), l <sup>2</sup> = 22 (P = 0.22) 20/32 43/59	11/32 50/63	-	9.68	1.82 [1.05, 3.15] 0.92 [0.75, 1.12]	
Total events: 369 (Treatment         Test for heterogeneity: Chi² =         Test for overall effect: Z = 1.2         14 Nefazodone         Roy-Byrne 2000         Kranzler 2000B         Subtotal (95% CI)	t), 161 (Control) = 0.04, df = 1 (P = 0.84), l <sup>2</sup> = 22 (P = 0.22) 20/32 43/59 91	11/32	•			
Total events: 369 (Treatmen) Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: Z = 1.2 04 Nefazodone Roy-Byrne 2000 Kranzler 2000B Subtotal (95% CI)	t), 161 (Control) = 0.04, df = 1 (P = 0.84), l <sup>2</sup> = 22 (P = 0.22) 20/32 43/59 91	11/32 50/63	•	9.68	0.92 [0.75, 1.12]	
Fotal events: 369 (Treatmen) Fest for heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Z = 1.2 04 Nefazodone Roy-Byrne 2000 Kranzler 2000B Subtotal (95% CI) Fotal events: 63 (Treatment) Fest for heterogeneity: Chi <sup>2</sup> =	t), 161 (Control) = 0.04, df = 1 (P = 0.84), l <sup>2</sup> = 22 (P = 0.22) 20/32 43/59 91 , 61 (Control) = 6.07, df = 1 (P = 0.01), l <sup>2</sup> =	11/32 50/63 95	•	9.68	0.92 [0.75, 1.12]	
Fotal events: 369 (Treatment Fest for heterogeneity: Chi <sup>2</sup> = Fest for overall effect: $Z = 1.2$ 04 Nefazodone Roy-Byrne 2000 Kranzler 2000B Subtotal (95% CI) Fotal events: 63 (Treatment) Fest for heterogeneity: Chi <sup>2</sup> = Fest for overall effect: $Z = 0.5$	t), 161 (Control) = 0.04, df = 1 (P = 0.84), l <sup>2</sup> = 22 (P = 0.22) 20/32 43/59 91 , 61 (Control) = 6.07, df = 1 (P = 0.01), l <sup>2</sup> =	11/32 50/63 95		9.68	0.92 [0.75, 1.12]	
Total events: 369 (TreatmentTest for heterogeneity: $Chi^2 =$ Test for overall effect: $Z = 1.2$ 14 NefazodoneRoy-Byrne 2000Kranzler 2000BSubtotal (95% CI)Total events: 63 (Treatment)Test for heterogeneity: $Chi^2 =$ Test for overall effect: $Z = 0.5$ Total (95% CI)	t), 161 (Control) = 0.04, df = 1 (P = 0.84), I <sup>2</sup> = 22 (P = 0.22) 20/32 43/59 91 , 61 (Control) = 6.07, df = 1 (P = 0.01), I <sup>2</sup> = 59 (P = 0.56) 1425	11/32 50/63 95 : 83.5%		9.68 14.03	0.92 [0.75, 1.12] 1.24 [0.61, 2.53]	CLICK F
Total events: 369 (Treatment Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: $Z = 1.2$ 04 Nefazodone Roy-Byrne 2000 Kranzler 2000B Subtotal (95% CI) Total events: 63 (Treatment) Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: $Z = 0.5$ Total (95% CI) Total events: 726 (Treatment)	t), 161 (Control) = 0.04, df = 1 (P = 0.84), I <sup>2</sup> = 22 (P = 0.22) 20/32 43/59 91 , 61 (Control) = 6.07, df = 1 (P = 0.01), I <sup>2</sup> = 59 (P = 0.56) 1425	11/32 50/63 95 <b>: 83.5%</b> 1047		9.68 14.03	0.92 [0.75, 1.12] 1.24 [0.61, 2.53]	
Fest for overall effect: $Z = 1.2$ 04 Nefazodone Roy-Byrne 2000 Kranzler 2000B Subtotal (95% CI) Fotal events: 63 (Treatment) Fest for heterogeneity: Chi <sup>2</sup> = Fest for overall effect: $Z = 0.5$ Fotal (95% CI) Fotal events: 726 (Treatment)	t), 161 (Control) = 0.04, df = 1 (P = 0.84), $l^2$ = 22 (P = 0.22) 20/32 43/59 91 , 61 (Control) = 6.07, df = 1 (P = 0.01), $l^2$ = 59 (P = 0.56) 1425 t), 570 (Control) = 43.69, df = 13 (P < 0.0001)	11/32 50/63 95 <b>: 83.5%</b> 1047		9.68 14.03	0.92 [0.75, 1.12] 1.24 [0.61, 2.53]	CLICK F TO RET

Figure 5.1 Antidepressant compared with placebo or no medication, number of participants completing treatment

Favours control Favours treatment

Study or sub-category	Ν	Treatment Mean (SD)	N	Control Mean (SD)	WMD (random) 95% Cl	Weight %	WMD (random) 95% Cl
01 SSRIs							
Chick 2004	243	24.71(20.43)	249	33.00(20.57)	-	17.41	-8.29 [-11.91, -4.67]
Moak 2003	38	10.20(3.70)	44	8.80(4.20)	Let a let	25.97	1.40 [-0.31, 3.11]
Kranzler 1995	51	8.70(4.30)	50	10.30(3.10)	4	27.01	-1.60 [-3.06, -0.14]
Gual 2003	44	20.54(1.47)	39	20.14(1.39)	•	29.61	0.40 [-0.22, 1.02]
Subtotal (95% CI)	376		382		4	100.00	-1.39 [-3.71, 0.93]
Test for heterogeneity: Chi	i² = 28.90, df = 3	(P < 0.00001), l <sup>2</sup> = 89.6%	6		1		
Test for overall effect: Z =							
	. ,					100	
					-100 -50 0 50	100	
					Favours control Favours trea	atment	

Figure 5.2 Antidepressant compared with placebo or no medication, mean time in treatment (weeks)

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*Figure 5.3 Antidepressant compared with placebo or no medication, number of participants continuously abstinent during treatment* 

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
01 SSRIs					
Cornelius 1997	7/25	4/26	<b>_</b>	8.99	1.82 [0.61, 5.46]
Janiri 1996	13/21	10/29	<b>⊢</b> ∎	19.27	1.80 [0.98, 3.28]
Pettinati 2000A	18/50	10/50	<b>⊢</b> ∎	22.94	1.80 [0.92, 3.50]
Subtotal (95% CI)	96	105	•	51.20	1.80 [1.18, 2.75]
Total events: 38 (Treatment), 2	24 (Control)		•		
Test for heterogeneity: Chi <sup>2</sup> = 0		)%			
Test for overall effect: $Z = 2.73$	B (P = 0.006)				
04 Nefazodone					
Kranzler 2000B	19/59	22/63	_ <u>+</u> _	48.80	0.92 [0.56, 1.52]
Subtotal (95% CI)	59	63	<b></b>	48.80	0.92 [0.56, 1.52]
Total events: 19 (Treatment), 2	22 (Control)		1		
Test for heterogeneity: not app	· · ·				
Test for overall effect: $Z = 0.32$					
Total (95% CI)	155	168	•	100.00	1.37 [1.00, 1.89]
Total events: 57 (Treatment), 4					
Test for heterogeneity: $Chi^2 = 4$		26.3%			
Test for overall effect: Z = 1.95	P = 0.05				
		0.	01 0.1 1 10	100	
			Favours control Favours tre	eatment	

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
01 SSRIs					
Tiihonen 1996	6/31	3/31		2.01	2.00 [0.55, 7.29]
Kabel 1996	8/15	9/13	<b>_</b> _	6.45	0.77 [0.42, 1.40]
Angelone 1998	31/58	7/23		6.70	1.76 [0.91, 3.41]
Chick 2004	102/243	115/249		75.95	0.91 [0.74, 1.11]
Subtotal (95% CI)	347	316	→	91.10	0.99 [0.82, 1.18]
Total events: 147 (Treatment), 134	4 (Control)		Ĭ		
Test for heterogeneity: $Chi^2 = 5.36$ Test for overall effect: $Z = 0.16$ (P	,.	44.0%			
02 Tricyclic antidepressants					
McGrath 1996	16/36	7/33	<b>_</b>	4.88	2.10 [0.99, 4.45]
Subtotal (95% CI)	36	33		4.88	2.10 [0.99, 4.45]
Total events: 16 (Treatment), 7 (C	control)				
Test for heterogeneity: not applica Test for overall effect: Z = 1.93 (P	ible				
04 Nefazodone					
Roy-Byrne 2000	8/32	6/32	<b>_</b>	4.01	1.33 [0.52, 3.41]
Subtotal (95% CI)	32	32		4.01	1.33 [0.52, 3.41]
Total events: 8 (Treatment), 6 (Co					
Test for heterogeneity: not applica	,				
Test for overall effect: Z = 0.60 (P					
Total (95% CI)	415	381		100.00	1.05 [0.89, 1.25]
Total events: 171 (Treatment), 147		501	T	100.00	1.00 [0.00] 1.20]
Test for heterogeneity: Chi <sup>2</sup> = 9.84		19 2%			
Test for overall effect: Z = 0.59 (P	,.	TU.270			
Test for overall effect. $\Sigma = 0.59$ (P	- 0.00)				
			0.1 0.2 0.5 1 2	5 10	
			Favours control Favours trea	tment	

*Figure 5.4 Antidepressant compared with placebo or no medication, number of participants abstinent at follow-up* 

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
01 SSRIs					
Gual 2003	14/44	9/39	_ <b></b>	2.90	1.38 [0.67, 2.83]
Coskunol 2002	15/30	20/29		6.18	0.73 [0.47, 1.12]
Chick 2004	112/243	100/249	<b>_</b>	30.04	1.15 [0.94, 1.41]
Subtotal (95% CI)	317	317	•	39.12	1.10 [0.92, 1.31]
otal events: 141 (Treatmen	t), 129 (Control)		ľ		
	= 4.09, df = 2 (P = 0.13), l <sup>2</sup> =	51.2%			
Test for overall effect: Z = 1.					
2 Tricyclic antidepressants					
Mason 1996	3/37	8/34	<b>_</b>	2.54	0.34 [0.10, 1.19]
Favre 1997	88/170	84/172	<b>+</b>	25.39	1.06 [0.86, 1.31]
Subtotal (95% CI)	207	206	•	27.93	1.00 [0.81, 1.23]
otal events: 91 (Treatment)	, 92 (Control)		Ĭ		
,	= 3.14, df = 1 (P = 0.08), l <sup>2</sup> =	68.2%			
Test for overall effect: $Z = 0.0$					
03 Ritanserin					
Wiesbeck 1999	197/371	72/122		32.95	0.90 [0.75, 1.07]
Subtotal (95% CI)	371	122		32.95	0.90 [0.75, 1.07]
Total events: 197 (Treatmen	t), 72 (Control)				
Test for heterogeneity: not a					
Test for overall effect: $Z = 1$ .	••				
Fotal (95% CI)	895	645	•	100.00	1.00 [0.90, 1.12]
Total events: 429 (Treatmen	t), 293 (Control)		Ĭ		
,	= 9.16, df = 5 (P = 0.10), l <sup>2</sup> =	45.4%			
Test for overall effect: $Z = 0.0$					
			0.01 0.1 1 10	100	
			Favours treatment Favours co	ontrol	

*Figure 5.5 Antidepressant compared with placebo or no medication, number of participants relapsing during treatment* 

Study or sub-category	Ν	Treatment Mean (SD)	Ν	Control Mean (SD)		WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% Cl
01 SSRIs								
Deas 2000	5	4.99(4.48)	5	2.81(4.81)			0.14	2.18 [-3.58, 7.94]
Cornelius 1997	25	2.40(2.90)	26	5.40(5.50)	_	_ <b>_</b>	0.79	-3.00 [-5.40, -0.60]
Kranzler 1995	51	3.20(5.20)	50	2.70(5.30)		_ <b></b>	1.09	0.50 [-1.55, 2.55]
Moak 2003	38	2.30(0.50)	44	3.50(0.50)		-	96.95	-1.20 [-1.42, -0.98]
Subtotal (95% CI)	119		125				98.97	-1.19 [-1.41, -0.98]
Fest for heterogeneity: Chi <sup>2</sup> Test for overall effect: Z = 10         22 Tricyclic antidepressants         McGrath 1996         Subtotal (95% Cl)         Test for heterogeneity: not a         Fest for overall effect: Z = 0.	36 36 36 36		33 33	4.10(4.10)		•	1.03 1.03	-0.40 [-2.50, 1.70] -0.40 [-2.50, 1.70]
otal (95% CI) est for heterogeneity: Chi <sup>2</sup> est for overall effect: Z = 10			158			•	100.00	-1.18 [-1.40, -0.97]
					-10 -	5 0 5	10	
					Favours t	reatment Favours co	ontrol	

Figure 5.6 Antidepressant compared with placebo or no medication, average drinks per drinking day

## Figure 5.7 Antidepressant compared with placebo or no medication, average drinks per week during treatment

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% Cl	
01 SSRIs								
Eriksson 2001	16	54.60(31.50)	17	60.20(26.60)		0.10	-5.60 [-25.55, 14.35]	
Subtotal (95% CI)	16		17			0.10	-5.60 [-25.55, 14.35]	
Test for heterogeneity: not app	licable				-			
Test for overall effect: Z = 0.55	(P = 0.58)							
02 Tricyclic antidepressants								
Favre 1997	170	2.47(2.58)	172	2.28(3.33)		99.90	0.19 [-0.44, 0.82]	
Subtotal (95% CI)	170		172		T	99.90	0.19 [-0.44, 0.82]	
Test for heterogeneity: not app	licable							
Test for overall effect: Z = 0.59	(P = 0.56)							
	186		189			100.00	0.18 [-0.45, 0.81]	CLICK HERE
Total (95% CI)			189			100.00	0.18 [-0.45, 0.81]	TO RETURN
Test for heterogeneity: $Chi^2 = 0$		P = 0.57, $P = 0%$						I O RETORN
Test for overall effect: Z = 0.57	(P = 0.57)							TO REPORT
					-100 -50 0 50	100		

Favours treatment Favours control

Study or sub-category	Ν	Treatment Mean (SD)	Ν	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% Cl
01 SSRIs							
Deas 2000	5	5.71(3.98)	5	7.62(12.42)	_ <del></del>	1.97	-1.91 [-13.34, 9.52]
Cornelius 1997	25	12.62(18.57)	26	24.17(21.79)		2.09	-11.55 [-22.65, -0.45]
Pettinati 2000A	50	19.20(29.10)	50	18.80(22.40)	<del>. +</del> -	2.48	0.40 [-9.78, 10.58]
Kranzler 1995	51	9.04(16.90)	50	5.24(10.70)	<b>⊢</b>	8.47	3.80 [-1.71, 9.31]
Moak 2003	38	18.90(4.40)	44	19.40(3.80)	<u>=</u>	79.82	-0.50 [-2.29, 1.29]
Subtotal (95% CI)	169		175		•	94.83	-0.36 [-2.01, 1.28]
Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: Z = 0.4		P = 0.18), l <sup>2</sup> = 35.6%					
02 Tricyclic antidepressants							
McGrath 1996	36	28.30(33.10)	33	30.80(32.90)		1.06	-2.50 [-18.09, 13.09]
Subtotal (95% CI)	36		33		<b>•</b>	1.06	-2.50 [-18.09, 13.09]
Test for heterogeneity: not ap Test for overall effect: Z = 0.3	•						
04 Nefazodone							
Kranzler 2000B	59	16.80(23.10)	63	15.70(21.30)	+	4.12	1.10 [-6.80, 9.00]
Subtotal (95% CI)	59		63		<b>•</b>	4.12	1.10 [-6.80, 9.00]
Test for heterogeneity: not ap Test for overall effect: Z = 0.2							
Total (95% CI)	264		271		•	100.00	-0.33 [-1.93, 1.28]
Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: Z = 0.4		P = 0.38), l <sup>2</sup> = 6.5%					

Figure 5.8 Antidepressant compared with placebo or no medication, days during treatment with drinking (%)

Favours treatment Favours control

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (random) 95% Cl	Weight %	WMD (random) 95% Cl
01 SSRIs							
Coskunol 2002	30	69.72(33.67)	29	51.06(36.89)	<b></b>	13.90	18.66 [0.62, 36.70]
Gual 2003	44	81.25(5.77)	39	83.69(6.13)	<b>_</b>	50.87	-2.44 [-5.01, 0.13]
Subtotal (95% CI)	74		68			64.77	6.14 [-14.17, 26.46]
Test for heterogeneity: Chi <sup>2</sup>	= 5.15, df = 1 (	P = 0.02), l <sup>2</sup> = 80.6%			-		
Test for overall effect: Z = 0	.59 (P = 0.55)						
02 Tricyclic antidepressants	5						
Favre 1997	170	45.93(35.56)	172	51.85(37.41)		35.23	-5.92 [-13.66, 1.82]
Subtotal (95% CI)	170		172		•	35.23	-5.92 [-13.66, 1.82]
Test for heterogeneity: not a	applicable						
Test for overall effect: Z = 1	.50 (P = 0.13)						
Total (95% CI)	244		240		•	100.00	-0.73 [-8.54, 7.08]
Test for heterogeneity: Chi <sup>2</sup>		P = 0.05), l <sup>2</sup> = 66.8%					
Test for overall effect: Z = 0	.18 (P = 0.85)						
					-100 -50 0 50	100	
					Favours control Favours trea	atment	

Figure 5.9 Antidepressants compared with placebo or no medication, cumulative abstinence duration (%)

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Study or sub-category	Ν	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% Cl	Weight %	WMD (fixed) 95% Cl
01 SSRIs							
Cornelius 1997	25	38.50(31.50)	26	27.30(28.00)	+ <b>-</b> -	12.97	11.20 [-5.18, 27.58]
Angelone 1998	58	56.70(21.00)	23	51.10(13.30)		59.22	5.60 [-2.07, 13.27]
Subtotal (95% CI)	83		49		•	72.19	6.61 [-0.34, 13.55]
Test for heterogeneity: Chi Test for overall effect: Z =		P = 0.54), l <sup>2</sup> = 0%					
4 Nefazodone							
Kranzler 2000B	59	37.10(31.50)	63	39.90(31.50)		27.81	-2.80 [-13.99, 8.39]
ubtotal (95% CI)	59		63		<b>•</b>	27.81	-2.80 [-13.99, 8.39]
est for heterogeneity: not est for overall effect: Z =							
<sup>-</sup> otal (95% CI) <sup>-</sup> est for heterogeneity: Chi <sup>-</sup> est for overall effect: Z =		P = 0.31), l <sup>2</sup> = 14.1%	112		•	100.00	3.99 [-1.91, 9.89]
				-	100 -50 0 50	100	
					Fourier control Fourier tra		

## *Figure 5.10* Antidepressant compared with placebo or no medication, average time to first drink (days)

Favours control Favours treatment

Study or sub-category	Ν	Treatment Mean (SD)	Ν	Control Mean (SD)	WMD (ra 95%	, 0	WMD (random) 95% Cl
01 SSRIs							
Pettinati 2000A	50	67.55(48.30)	50	52.64(46.20)	+	30.35	14.91 [-3.62, 33.44]
Cornelius 1997	25	56.00(33.60)	26	32.90(29.40)	-	31.19	23.10 [5.75, 40.45]
Gual 2003	44	153.00(7.90)	39	160.60(8.80)	=	38.46	-7.60 [-11.22, -3.98]
Subtotal (95% CI)	119		115			100.00	8.81 [-13.00, 30.61]
Test for heterogeneity: Chi	<sup>2</sup> = 16.39, df = 2	2 (P = 0.0003), I <sup>2</sup> = 87.8%					
Test for overall effect: Z =	0.79 (P = 0.43)						
					-100 -50 0 Fayours control	50 100 Fayours treatment	

*Figure 5.11* Antidepressant compared with placebo or no medication, average time to relapse (days)

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*Figure 5.12 Antidepressant compared with placebo or no medication, number of participants experiencing one or more adverse effects* 

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
01 SSRIs					
Deas 2000	1/5	1/5	<b>_</b>	0.35	1.00 [0.08, 11.93]
Eriksson 2001	12/16	4/17	<b>│</b> — <b>∎</b> —	1.36	3.19 [1.29, 7.86]
Subtotal (95% CI)	21	22		1.72	2.74 [1.19, 6.30]
Total events: 13 (Treatmen	t), 5 (Control)		-		
	$P^{2} = 0.74$ , df = 1 (P = 0.39), l <sup>2</sup> =	0%			
Test for overall effect: Z = 2	2.37 (P = 0.02)				
03 Ritanserin					
Wiesbeck 1999	241/371	79/122	<b>_</b>	41.82	1.00 [0.86, 1.17]
Johnson 1996	234/283	120/140	<b></b>	56.47	0.96 [0.89, 1.05]
Subtotal (95% CI)	654	262	•	98.28	0.98 [0.90, 1.06]
Total events: 475 (Treatme Test for heterogeneity: Chi <sup>2</sup> Test for overall effect: Z = 0	$P^2 = 0.23$ , df = 1 (P = 0.63), $I^2 =$	0%			
Total (95% CI)	675	284		100.00	1.01 [0.93, 1.10]
Total events: 488 (Treatme Test for heterogeneity: Chi <sup>2</sup> Test for overall effect: Z = 0	<sup>2</sup> = 7.38, df = 3 (P = 0.06), l <sup>2</sup> =	59.3%			
		+ 0.0	1 0.1 1 10	100	
			Favours treatment Favours cor	ntrol	

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
01 SSRIs					
Chick 2004	10/243	3/249		5.19	3.42 [0.95, 12.26]
Gual 2003	4/44	3/39	<b></b>	5.57	1.18 [0.28, 4.96]
Pettinati 2000A	28/50	19/50		33.30	1.47 [0.96, 2.27]
Subtotal (95% CI)	337	338	•	44.06	1.67 [1.11, 2.50]
Total events: 42 (Treatment), Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: Z = 2.4	1.74, df = 2 (P = 0.42), l <sup>2</sup> = 0	0%			
04 Nefazodone					
Kranzler 2000B	35/59	33/63	+	55.94	1.13 [0.83, 1.55]
Subtotal (95% CI)	59	63	•	55.94	1.13 [0.83, 1.55]
Fotal events: 35 (Treatment), Fest for heterogeneity: not ap Fest for overall effect: Z = 0.7	plicable				
Total (95% CI) Total events: 77 (Treatment), Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: Z = 2.4	3.49, df = 3 (P = 0.32), $I^2 = 1$	401 14.0%	•	100.00	1.37 [1.06, 1.76]
		0.0	1 0.1 1 10	100	

# *Figure 5.13* Antidepressant compared with placebo or no medication, number of participants experiencing nausea or gastrointestinal symptoms

Favours treatment Favours control

Figure 5.14 Antidepressant compared with placebo or no medication, number of participants experiencing headache or neuropsychiatric symptoms

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
01 SSRIs					
Pettinati 2000A	17/50	7/50		- 11.62	2.43 [1.10, 5.34]
Gual 2003	12/44	11/39		19.36	0.97 [0.48, 1.94]
Subtotal (95% CI)	94	89		30.97	1.52 [0.91, 2.52]
Total events: 29 (Treatment	), 18 (Control)				
est for heterogeneity: Chi <sup>2</sup>	= 2.98, df = 1 (P = 0.08), l <sup>2</sup> = 6	6.4%			
Test for overall effect: Z = 1.	.60 (P = 0.11)				
04 Nefazodone					
Kranzler 2000B	50/59	43/63		69.03	1.24 [1.02, 1.52]
Subtotal (95% CI)	59	63	•	69.03	1.24 [1.02, 1.52]
otal events: 50 (Treatment	), 43 (Control)				
est for heterogeneity: not a	applicable				
est for overall effect: Z = 2.	.12 (P = 0.03)				
otal (95% CI)	153	152	•	100.00	1.33 [1.07, 1.65]
otal events: 79 (Treatment	), 61 (Control)		-		
	= 3.47, df = 2 (P = 0.18), l <sup>2</sup> = 4	12.4%			
Test for overall effect: Z = 2.	.57 (P = 0.01)				
		0.1	0.2 0.5 1 2	5 10	
		F	Eavours treatment Eavours con	trol	

Favours treatment Favours control

Figure 5.15 Antidepressant compared with placebo or no medication, number of participants discontinuing treatment due to adverse effects

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl	
01 SSRIs						
Cornelius 1997	0/25	0/26			Not estimable	
Tiihonen 1996	1/31	0/31	<b>_</b>	1.15	3.00 [0.13, 70.92]	
Kranzler 1993	6/10	0/9		<b>—</b> 1.21	11.82 [0.76, 184.13]	
Moak 2003	3/38	1/44	_ <b></b>	2.14	3.47 [0.38, 32.02]	
Pettinati 2000A	6/50	4/50	_ <b></b>	9.24	1.50 [0.45, 4.99]	
Kranzler 1995	7/51	4/50	_ <b>_</b>	9.33	1.72 [0.54, 5.50]	
Chick 2004	34/243	11/249		25.09	3.17 [1.64, 6.11]	
Subtotal (95% CI)	448	459		48.16	2.79 [1.73, 4.52]	
otal events: 57 (Treatment),		100		10.110	2	
Test for heterogeneity: $Chi^2 =$ Test for overall effect: Z = 4.1	= 2.94, df = 5 (P = 0.71), l <sup>2</sup> = 0	0%				
2 Tricyclic antidepressants						
Mason 1996	3/37	1/34	<b>+</b>	2.41	2.76 [0.30, 25.25]	
McGrath 1996	9/36	4/33	+	9.64	2.06 [0.70, 6.07]	
Favre 1997	15/170	11/172		25.25	1.38 [0.65, 2.92]	
Subtotal (95% CI)	243	239	•	37.29	1.64 [0.91, 2.97]	
Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: Z = 1.6		0%				
03 Ritanserin						
Johnson 1996	14/283	4/144		12.24	1.78 [0.60, 5.31]	
Subtotal (95% CI)	283	144		12.24	1.78 [0.60, 5.31]	
Total events: 14 (Treatment), Test for heterogeneity: not ap Test for overall effect: Z = 1.0	plicable					
04 Nefazodone						
Roy-Byrne 2000	1/32	1/32		2.31	1.00 [0.07, 15.30]	
Subtotal (95% CI)	32	32	I	2.31	1.00 [0.07, 15.30]	
Fotal events: 1 (Treatment), 1		52		4.91	1.00 [0.077 10.00]	
Fest for heterogeneity: not ap	( )					
Test for overall effect: $Z = 0.0$						
Fotal (95% CI)	1006	874	•	100.00	2.20 [1.55, 3.11]	CLICK HE
Total events: 99 (Treatment),	41 (Control)		•			
	= 5.40, df = 10 (P = 0.86), l <sup>2</sup> =	- 0%				TO RETU
est for overall effect: Z = 4.4	5 (P < 0.00001)					TO REPO

Favours treatment Favours control

Study or sub-category	Buspirone n/N	Placebo n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl
Tollefson 1992	10/26	4/25		8.70	2.40 [0.87, 6.68]
Malcolm 1992	10/33	10/34		12.95	1.03 [0.49, 2.15]
Bruno 1989	20/25	9/25	<b></b>	16.61	2.22 [1.27, 3.88]
Fawcett 2000	21/48	27/52	_ <b></b>	20.11	0.84 [0.56, 1.27]
Malec 1996	16/28	20/29	_ <b>_</b>	20.38	0.83 [0.55, 1.24]
Kranzler 1994	26/31	16/30		21.25	1.57 [1.09, 2.27]
Total (95% CI)	191	195	•	100.00	1.27 [0.88, 1.83]
Total events: 103 (Buspiron	ie), 86 (Placebo)				
Test for heterogeneity: $Chi^2$ Test for overall effect: $Z = 1$	= 14.77, df = 5 (P = 0.01), l <sup>2</sup> = .27 (P = 0.21)	= 66.2%			
		0.	1 0.2 0.5 1 2	5 10	
			Favours placebo Favours bus	pirone	

## Figure 6.1 Buspirone compared with placebo, number of participants completing treatment

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Figure 6.2 Buspirone compared with placebo, days during treatment with drinking (%)

Study or sub-category	Ν	Buspirone Mean (SD)	Ν	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Kranzler 1994	31	4.28(13.10)	30	11.43(15.80)	-	29.69	-7.15 [-14.45, 0.15]
Fawcett 2000	48	7.00(10.00)	52	8.00(14.00)	<b>=</b>	70.31	-1.00 [-5.74, 3.74]
Total (95% CI)	79		82		•	100.00	-2.83 [-6.80, 1.15]
Test for heterogeneity: Cl	ni² = 1.92, df = 1 (I	P = 0.17), l² = 47.9%					
Test for overall effect: Z =	= 1.39 (P = 0.16)						
					-100 -50 0 50	100	
					Favours huspiropo - Favours pl	acaba	

Favours buspirone Favours placebo

Study or sub-category	Buspirone n/N	Placebo n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
Bruno 1989	5/25	7/25	<b>_</b>	11.54	0.71 [0.26, 1.95]
Tollefson 1992	21/26	12/25	<b></b>	20.16	1.68 [1.07, 2.64]
Malcolm 1992	22/23	24/34	- <b>-</b> -	31.92	1.36 [1.07, 1.71]
Fawcett 2000	33/48	23/52		36.39	1.55 [1.08, 2.23]
otal (95% CI)	122	136	•	100.00	1.42 [1.16, 1.74]
otal events: 81 (Buspirone	e), 66 (Placebo)		•		
	<sup>2</sup> = 2.74, df = 3 (P = 0.43), l <sup>2</sup> =	0%			
Test for overall effect: Z = 3	3.41 (P = 0.0006)				
			0.1 0.2 0.5 1 2	<del>; ;</del> 5 10	
			Favours treatment Favours con	trol	

## *Figure 6.3 Buspirone compared with placebo, number of participants reporting adverse effects*

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# Figure 6.4 Buspirone compared with placebo, number of participants experiencing dizziness

Study or sub-category	Buspirone n/N	Placebo n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
Malcolm 1992	15/33	0/34		9.12	31.91 [1.99, 512.50]
Malec 1996	16/28	5/29		90.88	3.31 [1.40, 7.83]
Total (95% Cl) Total events: 31 (Buspirone Test for heterogeneity: Chi <sup>2</sup> Test for overall effect: Z = 4	= 3.17, df = 1 (P = 0.08), l <sup>2</sup> = 6	63 8.4%	•	100.00	5.92 [2.59, 13.56]
		0.0	001 0.01 0.1 1 10 10	0 1000	

Favours buspirone Favours placebo

Study or sub-category	Buspirone n/N	Placebo n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
Fawcett 2000	2/48	0/52		13.85	5.41 [0.27, 109.87]
Malcolm 1992	1/33	0/34	<b>_</b>	14.21	3.09 [0.13, 73.20]
Tollefson 1992	3/26	1/25	<b>_</b>	29.41	2.88 [0.32, 25.92]
Malec 1996	0/28	1/29		42.53	0.34 [0.01, 8.12]
Total (95% CI)	135	140		100.00	2.18 [0.63, 7.59]
Total events: 6 (Buspirone),	, 2 (Placebo)		-		
Test for heterogeneity: Chi <sup>2</sup>	= 1.77, df = 3 (P = 0.62), l <sup>2</sup> = 0	%			
Test for overall effect: $Z = 1$	.23 (P = 0.22)				
		0.0	001 0.01 0.1 1 10 10	0 1000	
			Favours buspirone Favours place	cebo	

#### *Figure 6.5* Buspirone compared with placebo, number of participants discontinuing treatment due to adverse effects

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# *Figure 6.6 Antipsychotic or neuroleptic compared with placebo, number of participants completing treatment*

Study or sub-category	Neuroleptic n/N	Placebo n/N				(fixed) 5% Cl			Weight %	RR (fixed) 95% Cl
Shaw 1987	8/13	12/19				<b>_</b>			11.33	0.97 [0.56, 1.69]
Marra 2002	14/37	17/34				+-			20.58	0.76 [0.44, 1.29]
Wiesbeck 2001	33/142	58/139			-				68.09	0.56 [0.39, 0.80]
Total (95% CI)	192	192			•				100.00	0.65 [0.49, 0.84]
Total events: 55 (Neurolept	, · · · · ·	06 50/			÷					
Test for overall effect: $Z = 3$	<sup>2</sup> = 3.15, df = 2 (P = 0.21), l <sup>2</sup> = 3 3.22 (P = 0.001)	50.3%								
			0.1	0.2	0.5	1	2	5	10	
			I	Favours	placebo	Favo	ours n	eurole	eptic	

Study or sub-category	Neuroleptic n/N	Placebo n/N			(fixed) % CI	Weight %	RR (fixed) 95% Cl	
Marra 2002 Wiesbeck 2001	4/37 15/126	8/34 30/118		-	-	21.20 78.80	0.46 [0.15, 1.39] 0.47 [0.27, 0.83]	
Total (95% CI) Total events: 19 (Neurolept Test for heterogeneity: Chi <sup>2</sup> Test for overall effect: Z = 2	= 0.00, df = 1 (P = 0.98), $I^2 = 0\%$	152		•		100.00	0.47 [0.28, 0.77]	
			0.1 0.2 Favo	2 0.5 urs placebo	1 2 Favours	5 10 neuroleptic		

#### Figure 6.7 Antipsychotic or neuroleptic compared with placebo, number of participants abstinent at follow-up

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#### *Figure 6.8* Antipsychotic or neuroleptic compared with placebo, days during study with drinking (%)

Study or sub-category	N	Neuroleptic Mean (SD)	Ν	placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% Cl
Shaw 1987	13	42.84(39.08)	19	68.10(37.20)		31.04	-25.26 [-52.30, 1.78]
Marra 2002	37	44.90(37.20)	34	37.20(40.50)	- <del> =</del>	68.96	7.70 [-10.44, 25.84]
Total (95% CI) Test for heterogeneity: Cl Test for overall effect: Z =		P = 0.05), l <sup>2</sup> = 74.6%	53		•	100.00	-2.53 [-17.59, 12.53]
					-100 -50 0	50 100	
					Favours neuroleptic Favo	urs placebo	

Study or sub-category	Neuroleptic n/N	Placebo n/N		I	RR (fixed) 95% CI		Weight %	RR (fixed) 95% Cl
Wiesbeck 2001	3/126	2/118		_		_	49.77	1.40 [0.24, 8.26]
Marra 2002	6/37	2/34			-		50.23	2.76 [0.60, 12.74]
Total (95% CI)	163	152					100.00	2.08 [0.66, 6.54]
Total events: 9 (Neuroleptic	c), 4 (Placebo)				-			
Test for heterogeneity: Chi <sup>2</sup>	= 0.32, df = 1 (P = 0.57), l <sup>2</sup> = 0%	6						
Test for overall effect: Z = 1	.26 (P = 0.21)							
			0.01	0.1	1	10	100	
			Favou	rs neurolep	otic Favo	ours place	ebo	

*Figure 6.9 Antipsychotic or neuroleptic compared with placebo, number of participants discontinuing treatment due to adverse effects* 

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Figure 6.10	Anticonvulsant compared with placebo, number of participants completing treatment
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Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
Mueller 1997	7/13	12/16		14.66	0.72 [0.40, 1.28]
Brady 2002	14/19	15/20	_ <b>_</b>	19.92	0.98 [0.68, 1.42]
Johnson 2003G	55/75	48/75		65.42	1.15 [0.92, 1.42]
Total (95% CI)	107	111	•	100.00	1.05 [0.88, 1.26]
Total events: 76 (Treatment	), 75 (Control)		Ť		
Test for heterogeneity: Chi <sup>2</sup>	= 2.41, df = 2 (P = 0.30), l <sup>2</sup> =	16.9%			
Test for overall effect: $Z = 0$	.54 (P = 0.59)				
			0.1 0.2 0.5 1 2	5 10	

Favours control Favours treatment

Study or sub-category	Treatment n/N	Control n/N				(fixed 5% CI	,		Weight %	RR (fixed) 95% Cl
Mueller 1997	3/13	8/16			_	_			32.92	0.46 [0.15, 1.40]
Brady 2002	14/19	15/20			_	<b>-</b>			67.08	0.98 [0.68, 1.42]
Total (95% CI)	32	36							100.00	0.81 [0.55, 1.19]
Total events: 17 (Treatment Test for heterogeneity: $Chi^2$ Test for overall effect: Z = 1	= 2.03, df = 1 (P = 0.15), l <sup>2</sup> = 5	50.8%								
			0.1	0.2	0.5	1	2	5	10	
			Fa	avours t	reatment	t Fa	vours	control		

Figure 6.11 Anticonvulsant compared with placebo, number of participants relapsing to heavy drinking during treatment

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Figure 6.12	Anticonvulsants compa	ared with place	ebo. number of pa	participants discontinuin	g treatment due to adverse effects

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
Mueller 1997	3/13	0/16		8.28	8.50 [0.48, 151.05]
Johnson 2003G	3/75	5/75		91.72	0.60 [0.15, 2.42]
Total (95% CI)	88	91	•	100.00	1.25 [0.43, 3.70]
Total events: 6 (Treatment),		0.00/	-		
Test for overall effect: $Z = 0$ .	= 2.77, df = 1 (P = 0.10), l <sup>2</sup> = 6 .41 (P = 0.68)	3.9%			
		0.	001 0.01 0.1 1 10	100 1000	
			Favours treatment Favours co	ontrol	