Pharmacotherapies for Relapse Prevention in Alcohol Dependence

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DASSA Monograph No. 17
Research Series

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April 2005

ISBN
0-9751253-5-4

This monograph can be downloaded in pdf format from www.dassa.sa.gov.au.
It is intended that the content of the monograph will be updated on a regular basis.
The text of this version was finalised in December 2004.

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TABLE OF CONTENTS

SECTION 2: ACAMPROSATE

SECTION 3: COMBINATION DRUG THERAPY: NALTREXONE PLUS ACAMPROSATE

SECTION 4: DISULFIRAM

SECTION 5: ANTIDEPRESSANTS

LIST OF TABLES

LIST OF FIGURES

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.*[1] 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,[2–9] 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 intervention is more effective than the comparison intervention.

The **Absolute Risk Reduction**, or **Risk Difference**, is the difference between the event rates in the active and comparison groups. The absolute risk reduction is a decimal fraction, which is not easy to grasp. This review instead uses the **Number Needed to Treat (NNT)**, which is the inverse of the Absolute Risk Reduction. The NNT is the number needed to treat to prevent, or gain, one additional event in the active group relative to the comparison group. That is, the NTT indicates the number needed to treat to prevent one individual from 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 I^2 value indicates the extent to which this heterogeneity contributes to the combined variance. Below that is the test for overall effect – a P-value less than 0.05 indicates the difference is statistically significant.

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[10]

Anton 1999[11; 12]

Balldin 2003[13]

Chick 2000[14]

Combine 2003[15; 16]

Croop 1997[1]

Galarza 1997[17] (cited by Srisurapanont *et al.*[2])

Gastpar 2002[18]

Guardia 2002[19]

Heinala 2001[20]

Hersh 1998[21; 22]

Kiefer 2003[23]

Kranzler 2000B[24]

Krystal 2001[25]

Landabaso 1999[26]

Latt 2002A[27]

Lee 2001[28]

Monterosso 2001[29]

Morris 2001[30]

Niederhofer 2003A[31]

O'Malley 1992[32–35]

O'Malley 2003[36]

Oslin 1997[37; 38]

Petrakis 2004[39]

Rohsenow 2000[40; 41]

Rubio 2002[42]

Volpicelli 1992[43; 44]

Volpicelli 1997[45]

(b) Depot or implant naltrexone

Johnson 2004[46]

Kranzler 1998[47]

Kranzler 2004[48]

(c) Nalmefene

Anton 2004[49]

Mason 1994[50]

Mason 1999[51]

2. Acamprosate

(a) vs placebo or no medication

Baltieri 2004[52]

Barrias 1997 (cited by Mann[5])

Besson 1998[53]

Borg 1994 (cited by Mann[5])

Chick 2000A[54]

Combine 2003[15; 16]

Geerlings 1997[55]

Gual 2001[56]

Kiefer 2003[23]

Ladewig 1993[57] (cited by Mann *et al.*5 and Carmen *et al.*[6])

Lhuintre 1985[58]

Lhuintre 1990[59]

Namkoong 2003A[60]

Niederhofer 2003[61]

Paille 1995[62]

Pelc 1992 (cited by Mann[5])

Pelc 1997[63]

Poldrugo 1997[64]

Roussaux 1996[65] (cited by Mann *et al.*[5])

Sass 1996[66]

Tempesta 2000[67]

Whitworth 1996[68]

(b) *vs naltrexone*

Combine 2003[15; 16]

Kiefer 2003[23]

Rubio 2001[69]

3. Combination naltrexone and acamprosate

(a) *vs placebo or no medication*

Combine 2003[15; 16]

Kiefer 2003[23]

(b) *vs acamprosate*

Combine 2003[15; 16]

Kiefer 2003[23]

(c) *vs naltrexone*

Combine 2003[15; 16]

Kiefer 2003[23]

4. Disulfiram

(a) *oral vs placebo*

Chick 1992[70]

Fuller 1979[71–73]

Fuller 1986[74]

Niederhofer 2003[75]

(b) *implant vs placebo*

Johnsen 1987[76]

Johnsen 1991[77]

Wilson 1976[78; 79]

Wilson 1980[80]

(c) *oral vs no medication*

Carroll 1998[81; 82]

Fuller 1979[71–73]

Fuller 1986[74]

Gerrein 1973[83]

Powell 1985[84]

(d) *implant vs no medication*

Wilson 1980[80]

(e) *vs naltrexone*

Carroll 1993[85]

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[99; 100]

Tiihonen 1996[101]

(b) Tricyclic antidepressants

Favre 1997[102]

Mason 1996[103]

McGrath 1996[104]

(c) Ritanserin

Johnson 1996A[105]

Wiesbeck 1999[106]

(d) Nefazodone

Kranzler 2000B[24]

Roy-Byrne 2000[107]

6. Other medications

(a) baclofen vs placebo

Addolorato 2002[108]

(b) buspirone vs placebo

Bruno 1989 [109]

Fawcett 2000[110]

Kranzler 1994[111]

Malcolm 1992[112]

Malec 1996[113]

Tollefson 1992[114]

(c) ondansetron vs placebo

Johnson 2000[115]

(d) combination naltrexone and ondansetron vs placebo

Johnson 2000C[116]

(e) *antipsychotics (neuroleptics) vs placebo*

Marra 2002[117]

Shaw 1987[118]

Wiesbeck 2001[119; 120]

(f) *anticonvulsants*

Brady 2002[121]

Johnson 2003G[122]

Mueller 1997[123]

(g) *GHB vs naltrexone*

Caputo 2003[124]

(h) *lithium*

Fawcett 2000[110]

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.[3; 9]

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[9] and a single daily dose of 50mg (oral) is usually considered sufficient.

The COMBINE study Research Group[15], 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 (μ, δ, and κ) that are thought to reinforce drinking.[51]

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

1.2 Evidence of effectiveness

Brief information about the trials included in this group of studies is given in Table 1.

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 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[11; 43; 45] of significantly lower craving in participants treated with naltrexone, compared to those receiving placebo. In addition participants in three studies[32; 43; 45] 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% CI 1.44, 6.33) and nausea or vomiting (Figure 1.14: RR 2.45, 95% CI 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% CI 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% CI 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.[1]

It is possible that people of Asian ethnicity may be more susceptible to adverse effects than people of Caucasian background. Wilkin and Hazelrigg[125] 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.*[126] 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;[3]
- type of adjunct psychosocial therapy.[3; 9]

1.3.1 Adverse effects

Oncken *et al.*[127] 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.*[40] 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 (±SD) duration of the four most common side effects was: nausea 17.9±27.0 days; headache 10.1±14.8 days; dizziness 8.7±7.3 days; fatigue 17.7±20.8 days. They reported the most effective methods of managing nausea were advising patients to take their dose with meals, take their dose at bedtime, or take an antacid daily. Bedtime dosing was suggested to help with fatigue if side effects usually occur within two hours of a dose.

***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.*[45] 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.*[14] 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.*[128] from an analysis of data from an RCT comparing naltrexone with placebo[25], 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[12]. 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.*[33] also found that some, but not all, of the benefits resulting from short-term naltrexone treatment persist after discontinuation of treatment.

Rohsenow *et al.*[40] 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.*[13] 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.*[32] 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[20] 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.*[27] 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.*[129] 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.*[35] analysed data from study by O'Malley *et al.*[32] 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.*[130] 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.*[29] 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.*[130] 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.*[39] 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.[6] 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.[3]

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

Based on a review of European studies of acamprosate, Mason *et al.*[9] 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.[15] Full results from this study are not yet available.

2.2 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.

2.2.1 *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*,[55] also reported the mean (±SD) time in treatment: 102±71 days for those treated with acamprosate, compared to 88±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[53;55;60;62;67] reported a longer time to first drink for participants treated with acamprosate, compared to those receiving placebo. Two studies[63;66] reported a longer time to relapse, while one study[60] 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[69]) 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±35.3 % days for acamprosate, compared to 66.6±31.5 % 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±38 days compared to 42±32 days for the

acamprosate group, P<0.001). However, there was no difference in the days to first drink (39±28 days for acamprosate, 44±36 days for naltrexone, P=0.33).

Rubio *et al.*[69] reported numbers who had not relapsed at 1 year (41.5% naltrexone compared to 17.5% acamprosate). Kiefer *et al.*[23] 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.[6; 9] 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.[9]

Soyka *et al.*[131] 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[15]) 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.*[132] 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.*[133] 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.*[134] 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.*[135] 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.*[136] 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.*[54] 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.*[67] 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.[16;137]

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

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,[23] significantly more participants treated with combination medications completed treatment. In Combine 2003,[15; 16] 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,[15; 16] there was no difference in completion rates for the combination therapy and acamprosate groups. In Kiefer 2003,[23] 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).

(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.[3]

The severity of the disulfiram-ethanol reaction is dependent upon the dose of each compound.[140]

4.2 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

(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.*[81] 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.*[70] 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 one-third 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.*[53], 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±8.41 drinks/week for participants receiving an active disulfiram implant, compared to 11.99±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±36.8 days for the disulfiram implant group, compared to 37.40±38.70 days for the placebo group (P = 0.45). In a subsequent study by the same group[77], 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[75] 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[81; 82] reported a significant difference in the maximum number of weeks of consecutive abstinence – 4.45±4.27 weeks in the disulfiram group, compared to 1.75±2.64 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.*[84] 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±3.3, compared to 1.6±1.4, P < 0.001), less drinks per week (2.3±6.2 compared with 27.0±36.5, P = 0.06), and significantly less days with drinking during treatment (4.0±0.04 compared to 26.3±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[75] 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 naltrexone

No 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 disulfiram-alcohol interaction varies from a slight flush to a distressing state of nausea, headache, dizziness and tightness in the chest. Very rarely, when larger amounts of disulfiram have been taken, the reaction has been fatal. Because of this risk, disulfiram should normally not be offered to patients with heart disease or taking hypotensive medication. Deaths from the disulfiram-alcohol interaction have not been reported in recent years, possibly because the doses used are now lower and patients with cardiac disease are excluded.[7]

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.[141]

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

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.[7] Animal and human data indicate that the concomitant use of MAO inhibitors and disulfiram is not safe.[141]

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.[141]

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.[7] Fuller and Gordis[141] 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.[7]

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.[7]

***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.[3] Methodological rigour of studies of disulfiram is generally poor.[141] 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.[142]

However, a key factor appears to be compliance. Fuller *et al.*[74], 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.[141] Mattick and Jarvis[140] 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.*[73] 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.[3; 143] 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[64] 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.*[53] 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.*[143] 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[144] 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.*[84] 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.[86] 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.[137]

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.[3]

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_2 receptor which has been implicated in alcohol drinking behaviour.[24]

The SSRIs themselves are not a homogeneous class of drugs and hence may differ in their efficacy.[86] 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[95] and Chick 2004[87]) 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% CI 1.18, 2.75). One study of nefazodone found no difference between nefazodone and placebo on this outcome (RR 0.92, 95% CI 0.56, 1.52). The overall effect from all four studies is statistically significant, favouring antidepressant treatment (RR 1.37, 95% CI 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[104] 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[88] and Moak 2003[98]) 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.*[107] found significant time effects, but no treatment group effects, for drinks consumed per day for nefazodone compared with placebo. Johnson *et al.*[105] and Kranzler *et al.*[96] 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.*[98] 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.*[86] 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[86] stated there was no difference in overall adverse effects without reporting specific data. Mason 1996[103] 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[86] 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.*[105] 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,[88; 96; 103] the timeframe for follow-up and evaluation, severity of dependence and patient gender.[3]

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.*[97] found Type B alcoholics treated with fluoxetine drank more during treatment compared to placebo group. Pettinati *et al.*[145] found less alcohol use in Type A individuals treated with sertraline and no effect of sertraline in the type B group.[137]

Chick *et al.*[87] 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.*[97] 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.*[99] who found that sertraline benefited Type A alcoholics but had no effect in Type B alcoholics.

In a crossover study, Gerra *et al.*[136] compared ethanol intake during treatment with fluoxetine, acamprosate or placebo, for participants with familial or non-familial 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.*,[103] 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.*[88] reported that depressive symptoms were also reduced in the fluoxetine group, indicating possible vale for antidepressants in this population.

Kranzler *et al.*[96] 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.*[103] 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.*[100] 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 γ-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.[108]

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.*[108] 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.*[108] 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.[114] Hence control of anxiety may reduce relapse. Buspirone is a non-benzodiazepine anxiolytic (a 5-HT_{1A} 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[110] and Malec 1996[113]) 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±2.66 weeks for those treated with buspirone, compared to 8.17±4.53 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±6 for the buspirone group, compared to 6.6±8.2 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±11.90 for the buspirone group and 5.67±10.50 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[114] also identified dizziness as the most frequent adverse effect. Malec 1996[113] 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,[115] and the other compared the combination of naltrexone and ondansetron with placebo.[116]

Ondansetron is a 5-HT_3 antagonist that has been shown to reduce alcohol-induced positive subjective effects and craving in healthy social drinkers, and to diminish drinking and increase abstinence among alcoholics with a biological disease predisposition. 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.[146]

For ondansetron compared with placebo, there was no significant difference in the proportion of participants completing treatment (RR 0.88, 95% CI 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.*[147] 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.*[148] 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[149] note that ondansetron has antiemetic and anti-nausea 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.[117–119]

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±34.44 %days) compared to those receiving placebo (67.78±36.67 %days, P = 0.007). In addition significantly more participants treated with antipsychotic relapsed to drinking during treatment (97/126 compared to 69/118, P = 0.003) but there was no significant difference in the time to relapse (48±39 days for those treated with antipsychotic and 48±40 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±43.2 compared with 36.5±38.1, 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.[150] Most of the research on the use of anticonvulsants to treat alcohol dependence relates to the management of alcohol withdrawal.[151] 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[121] 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±3.8) compared to those receiving placebo (5.4±3.7) but the difference did not achieve statistical significance (P = 0.11).

Johnson *et al.*[122] 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.*[121] stated there were no group differences in side effects, but Johnson *et al.*[122] 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.**

6.6 GHB compared with naltrexone

In the only study making this comparison[124] 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[110] 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.*[6] 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[8] found that there is no statistical difference in the efficacy of acamprosate and naltrexone. Mason[9] 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*.[152] and Rubio *et al*.[42] involving early problem drinkers with lesser severity of dependence. Davidson *et al*.[153] 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,[4] 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 1 Studies 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.

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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.

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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.

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(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.

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Table 2 Studies involving Acamprosate

(a) Acamprosate compared with placebo or no medication

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, ≥ 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.

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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.

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(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 3 Studies 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.

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Table 4 Studies 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.

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(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.

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(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.

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Table 5 Studies 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.

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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.

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(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.

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Table 6 Other 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.

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(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.

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(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.

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Figure 1.1 Opioid antagonist compared with placebo or no medication, number of participants completing the study

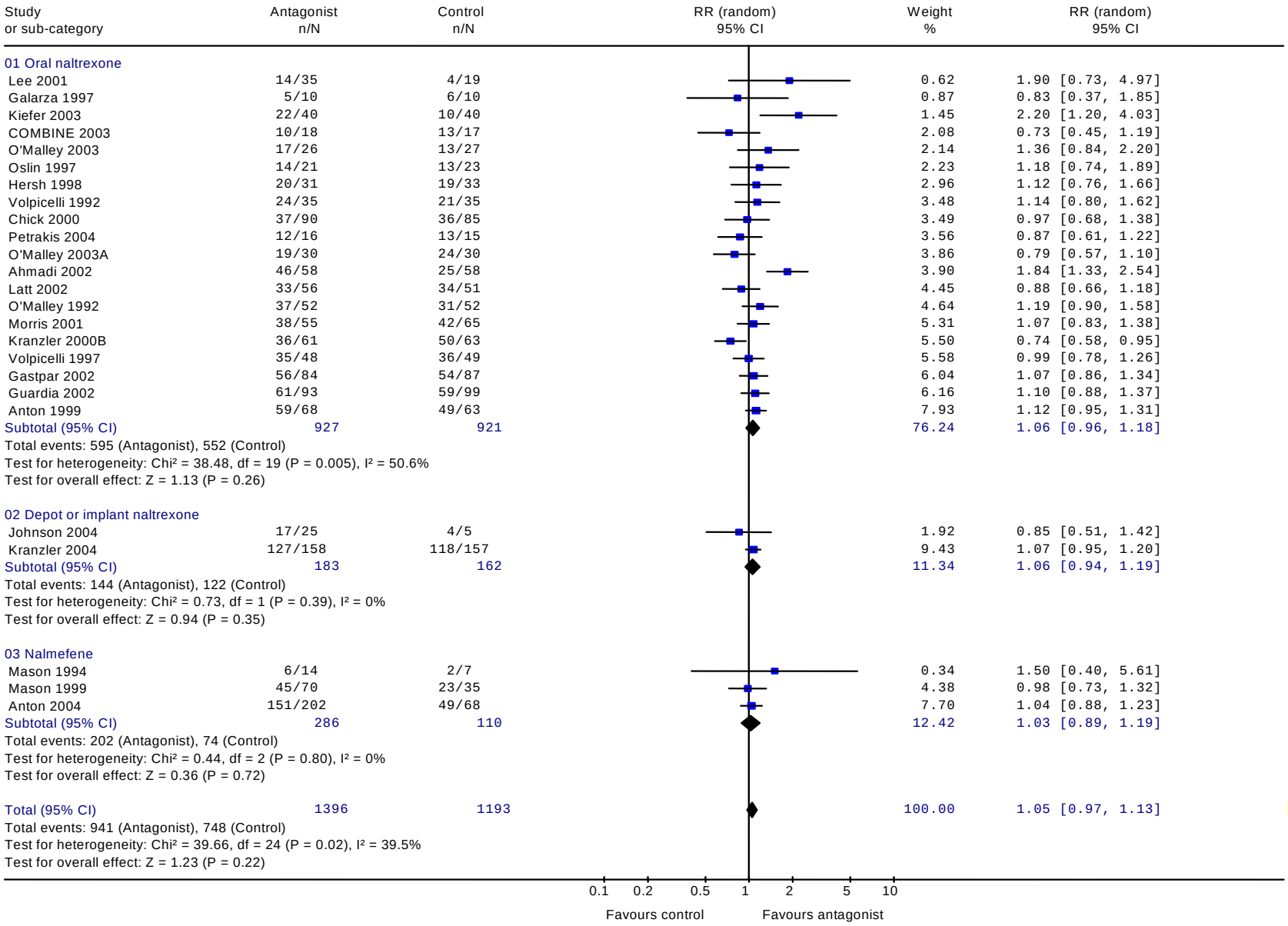

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Figure 1.2 Opioid antagonist compared with placebo or no medication, average weeks in treatment

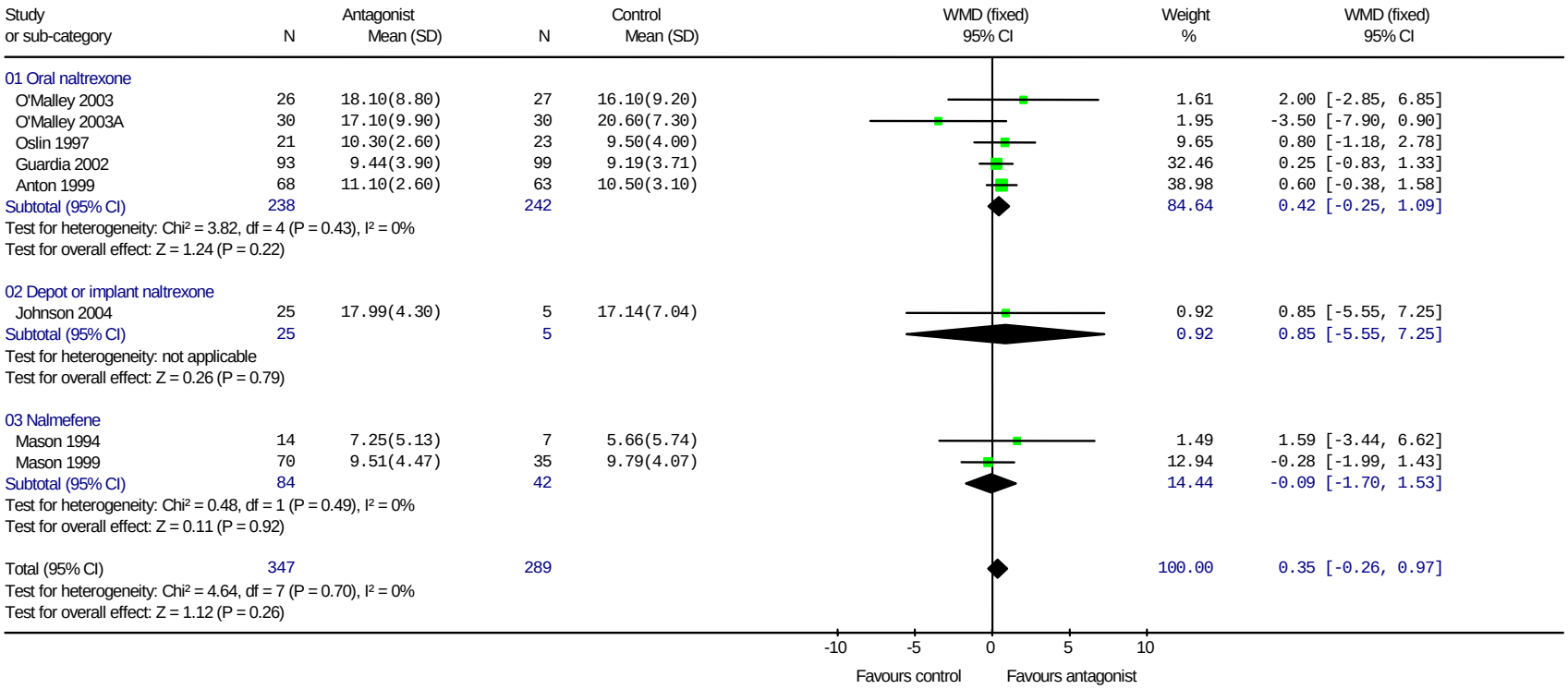

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Figure 1.3 Opioid antagonist compared with placebo or no medication, number of participants continuously abstinent

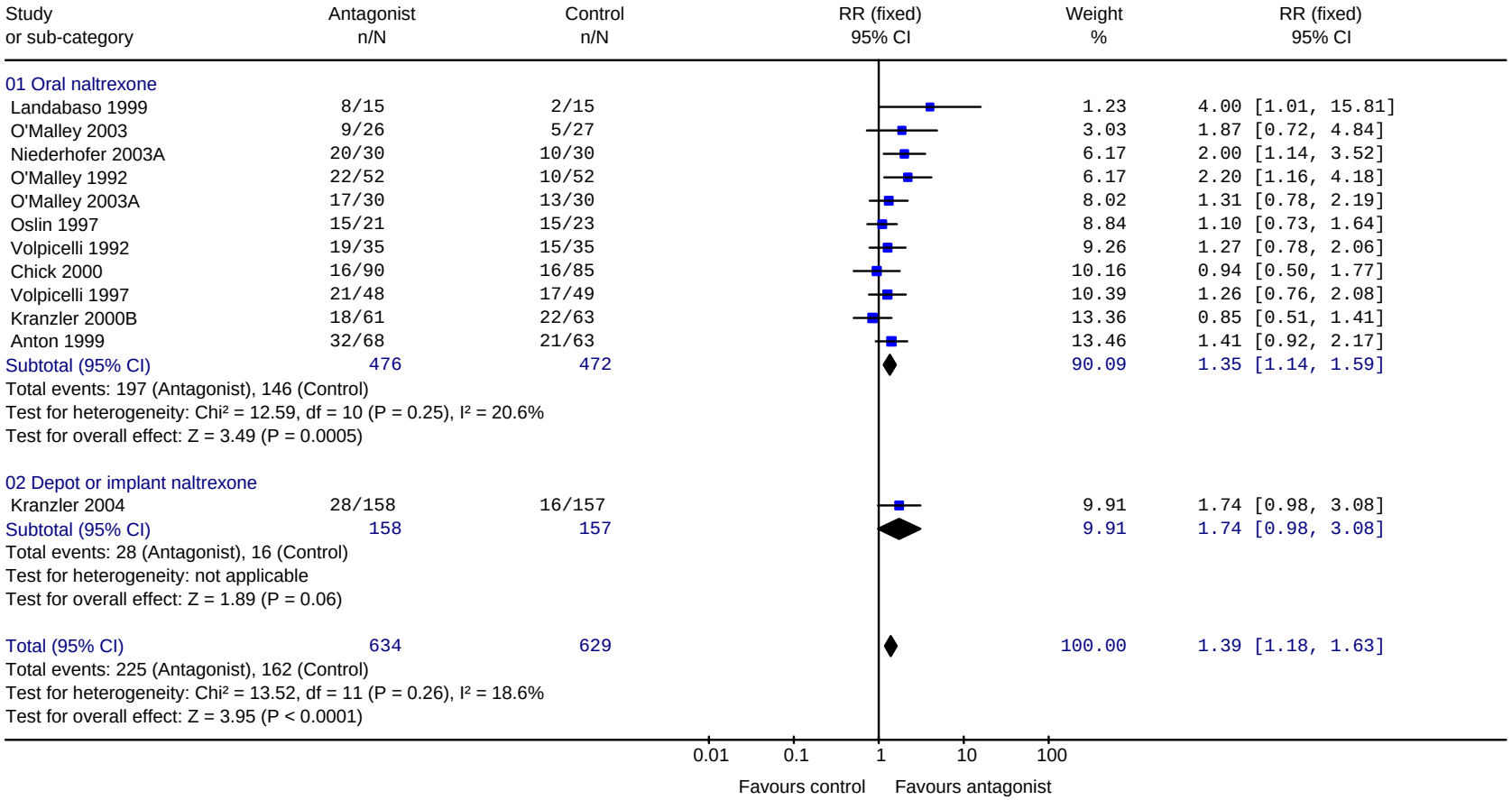

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Figure 1.4 Opioid antagonist compared with placebo or no medication, number of participants abstinent at follow-up

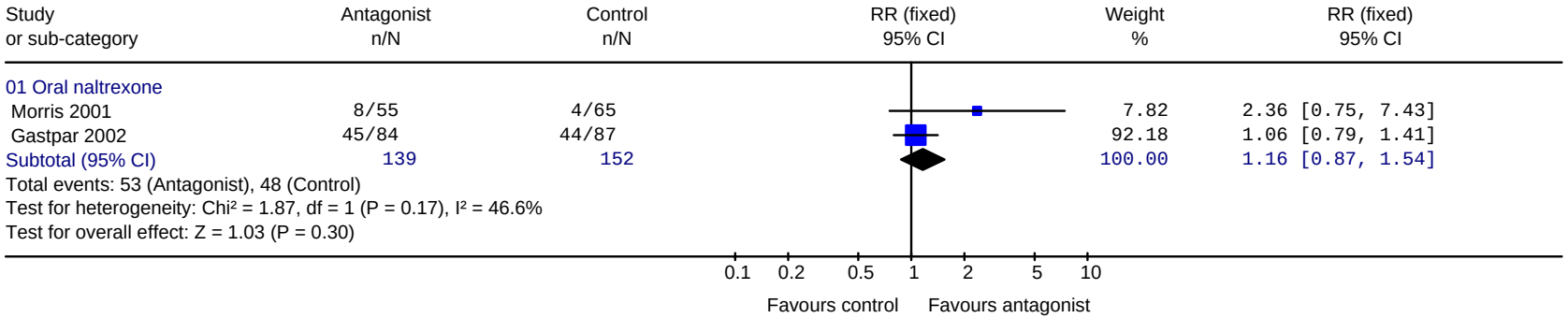

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Figure 1.5 Opioid antagonist compared with placebo or no medication, number of participants who relapsed during treatment

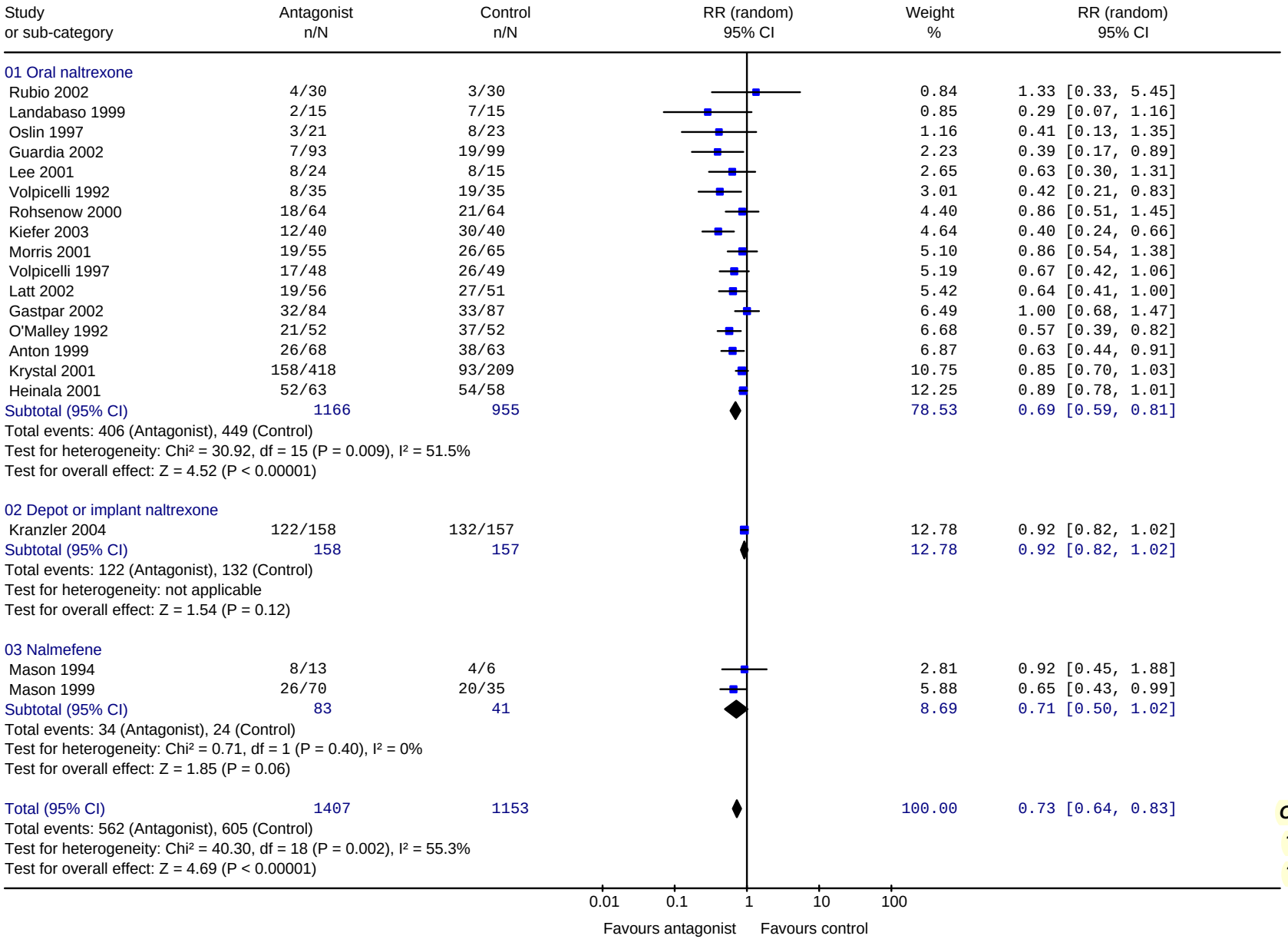

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Figure 1.6 Opioid antagonist compared with placebo or no medication, average drinks per drinking day

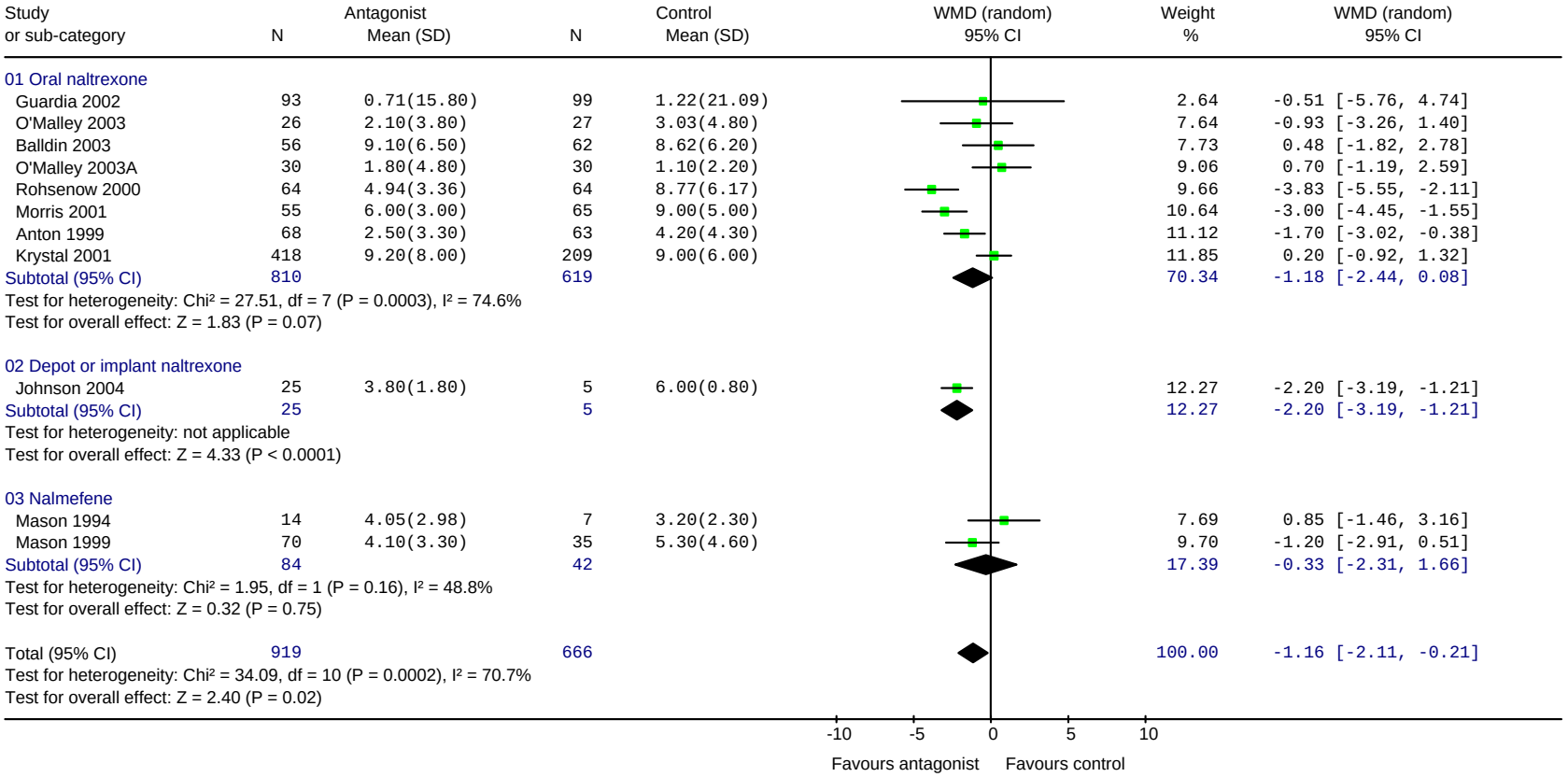

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Figure 1.7 Opioid antagonist compared with placebo or no medication, average drinks per week

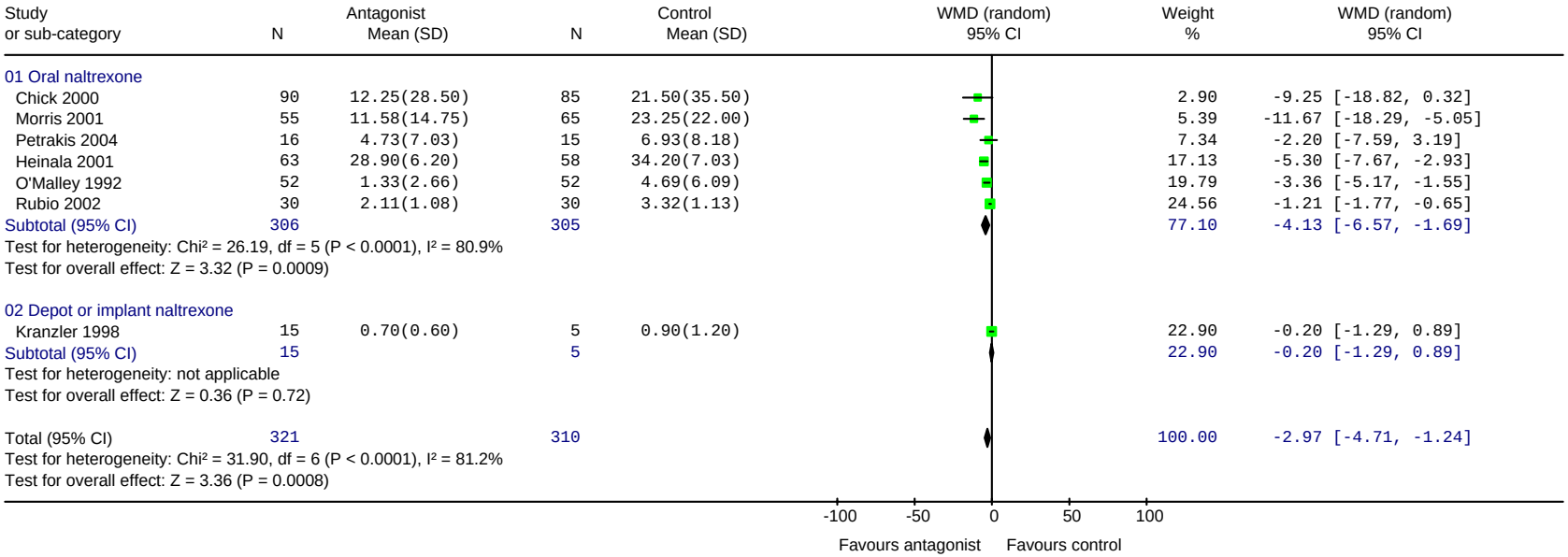

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Figure 1.8 Opioid antagonist compared with placebo or no medication, days of treatment with drinking (%)

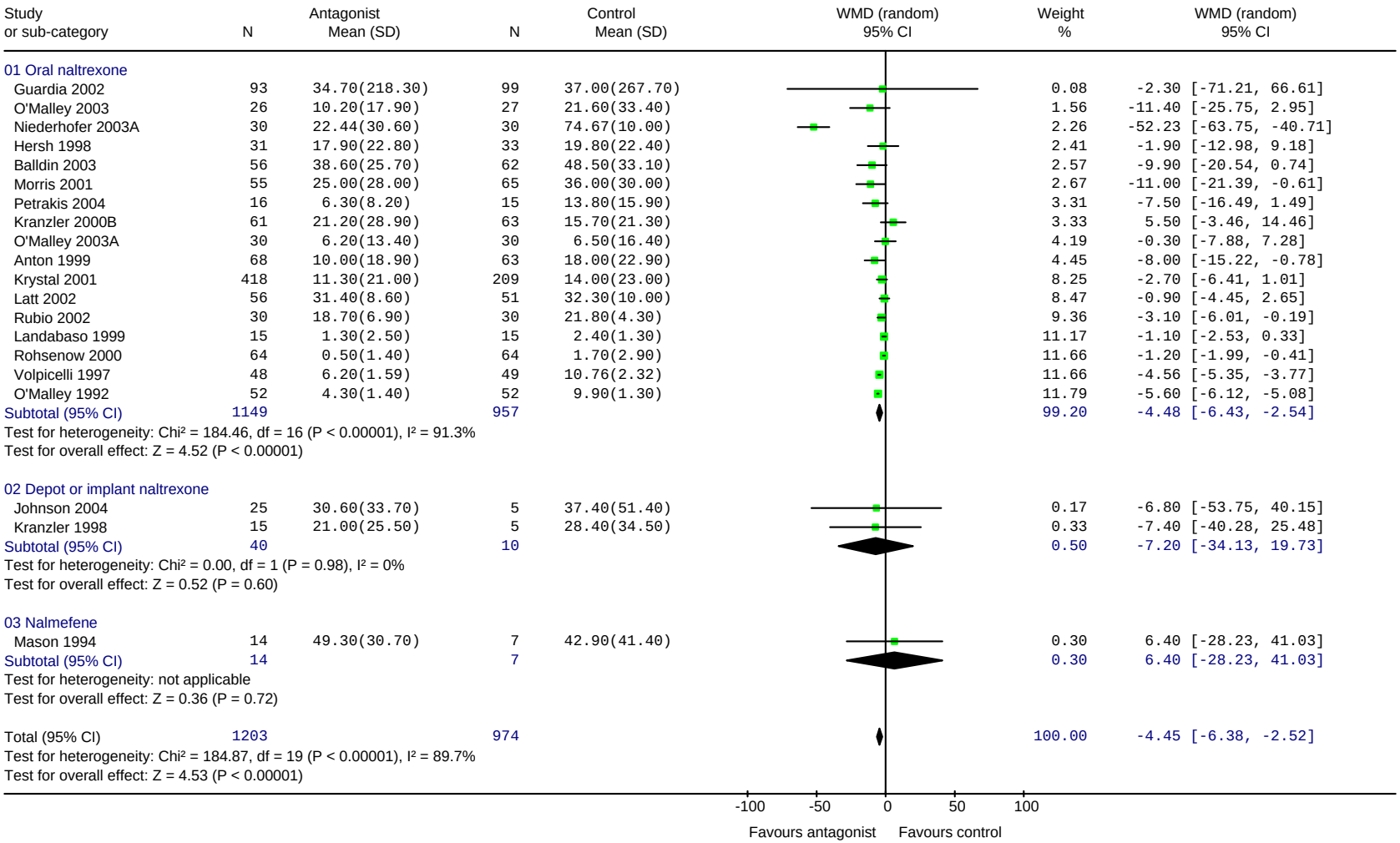

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Figure 1.9 *Opioid antagonist compared with placebo or no medication, average time to first drink (days)*

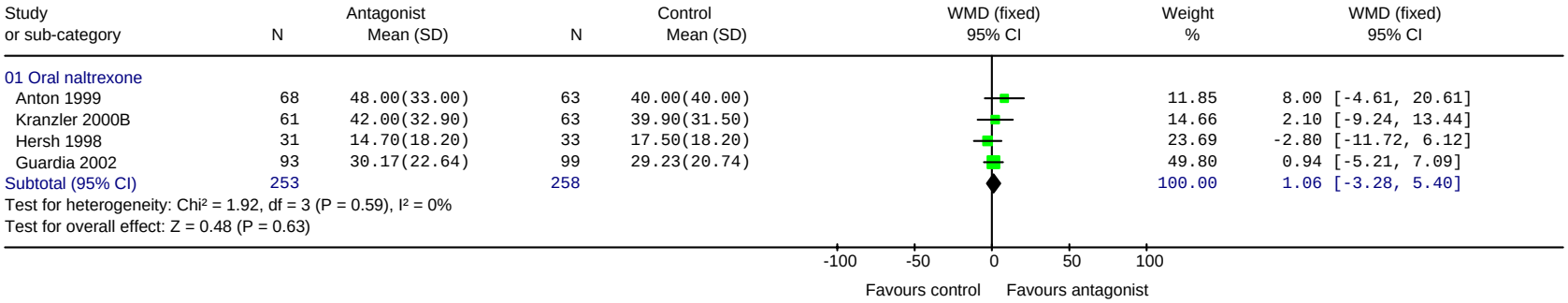

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Figure 1.10 *Opioid antagonist compared with placebo or no medication, average time for relapse to heavy drinking (days)*

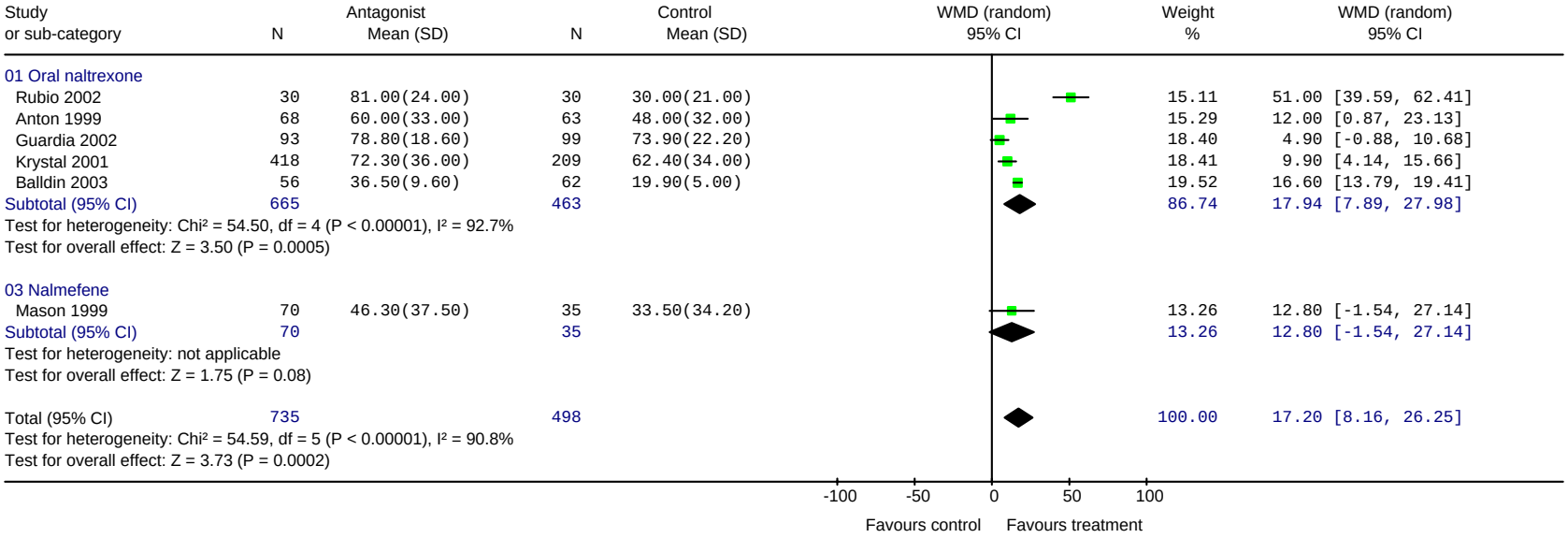

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Figure 1.11 Opioid antagonist compared with placebo or no medication, number of participants experiencing any adverse effects

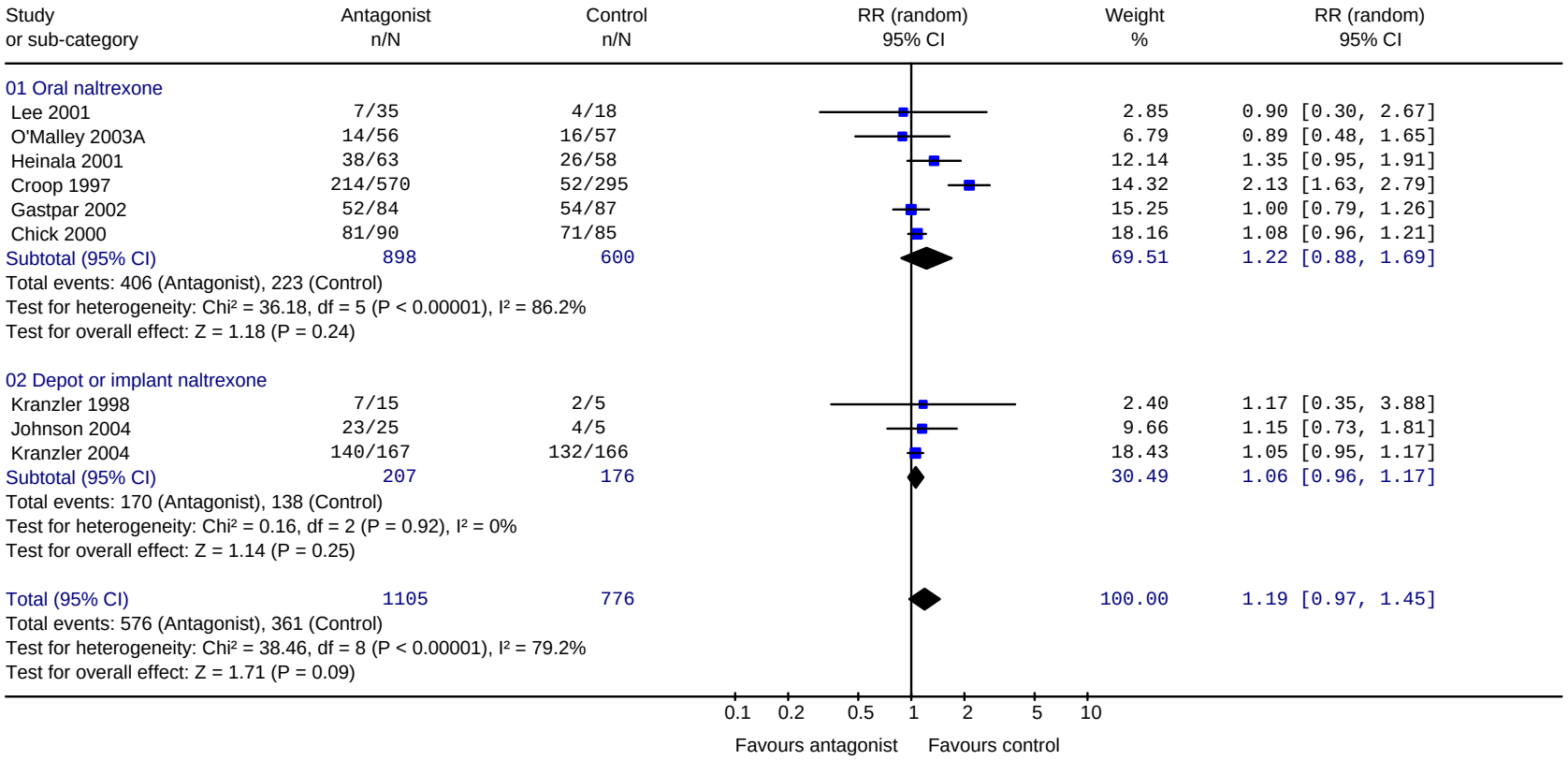

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Figure 1.12 *Opioid antagonist compared with placebo or no medication, number of participants requiring a dose reduction to manage adverse effects*

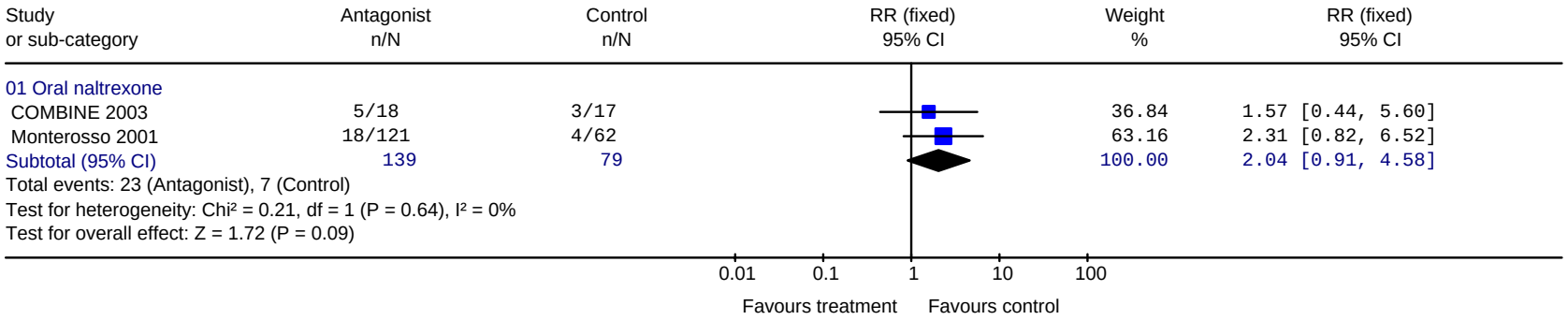

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Figure 1.13 *Opioid antagonist compared with placebo or no medication, number of participants experiencing abdominal pain or gastrointestinal symptoms*

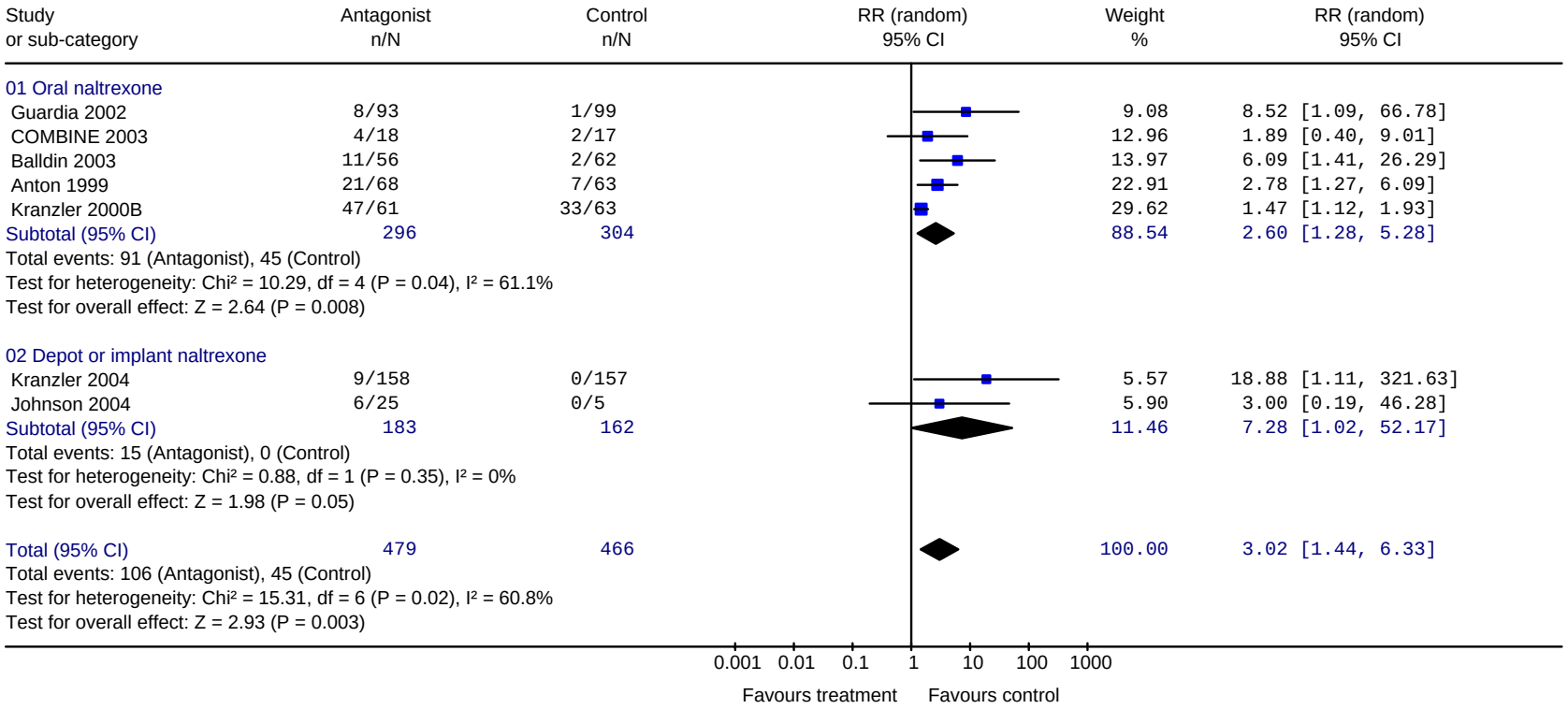

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Figure 1.14 Opioid antagonist compared with placebo or no medication, number of participants experiencing nausea or vomiting

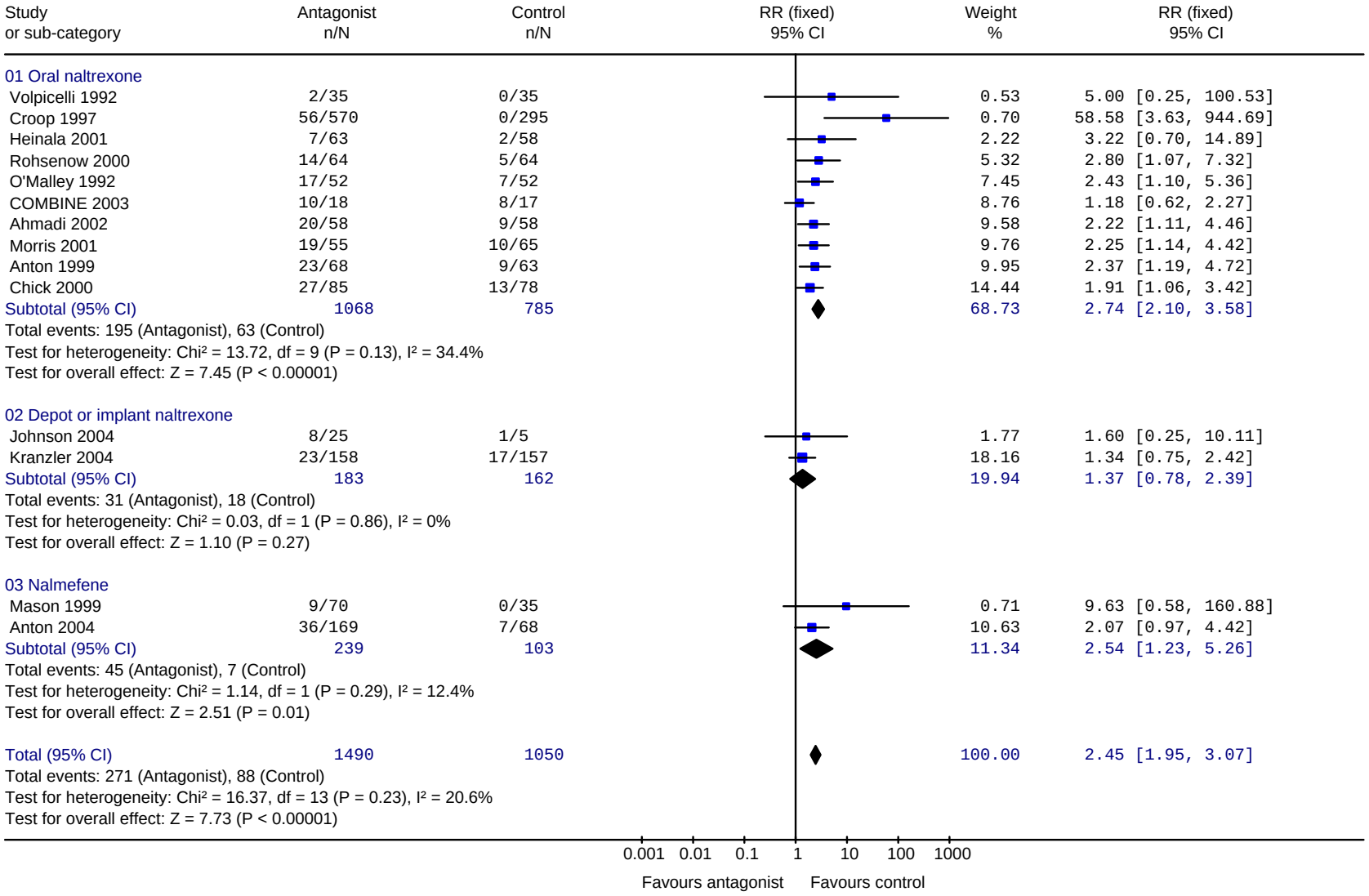

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Figure 1.15 *Opioid antagonist compared with placebo or no medication, number of participants experiencing headache or neuropsychiatric symptoms*

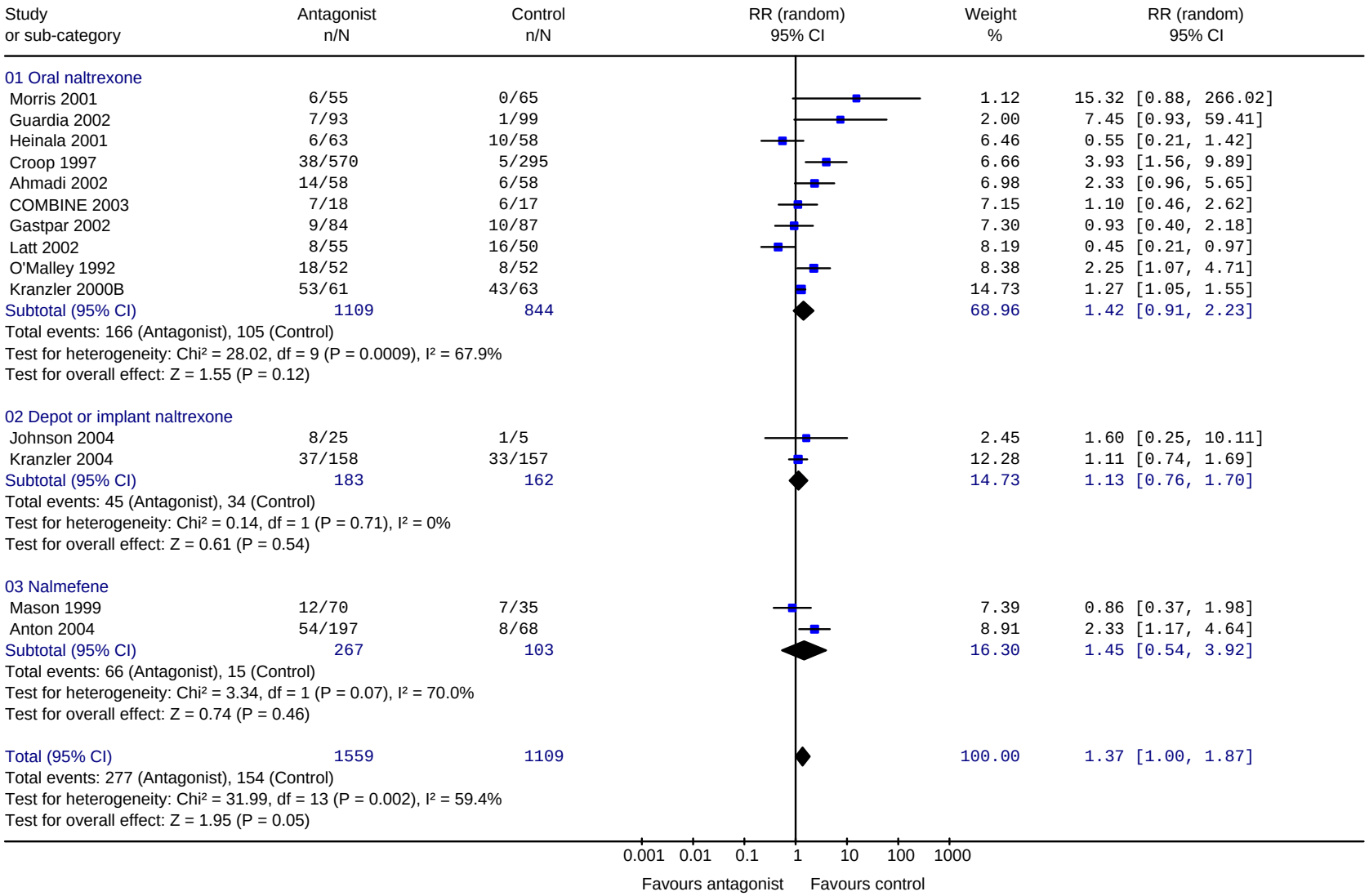

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Figure 1.16 *Opioid antagonist compared with placebo or no medication, number of participants withdrawing from treatment due to adverse effects*

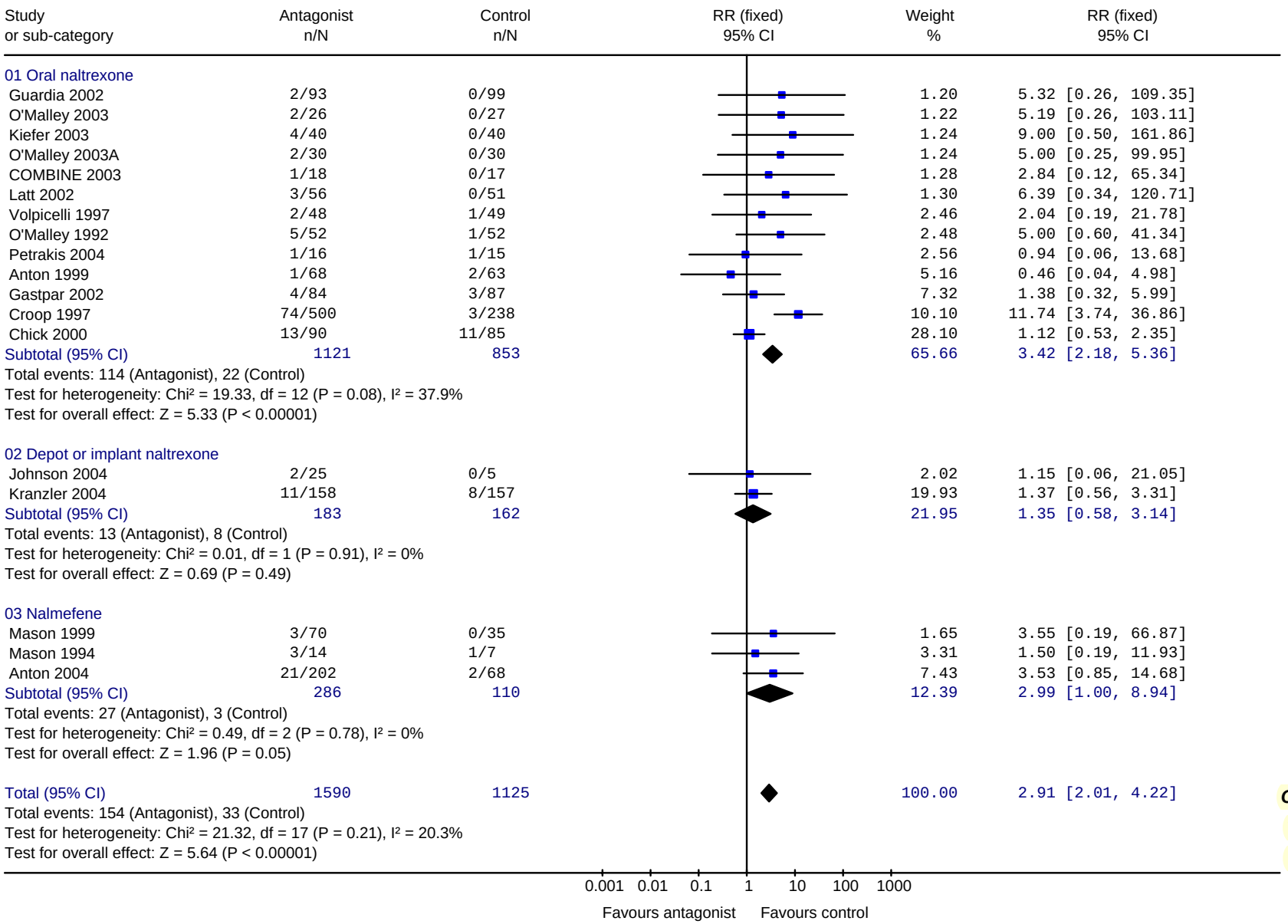

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Figure 2.1 Acamprosate compared with placebo or no medication, number of participants completing treatment

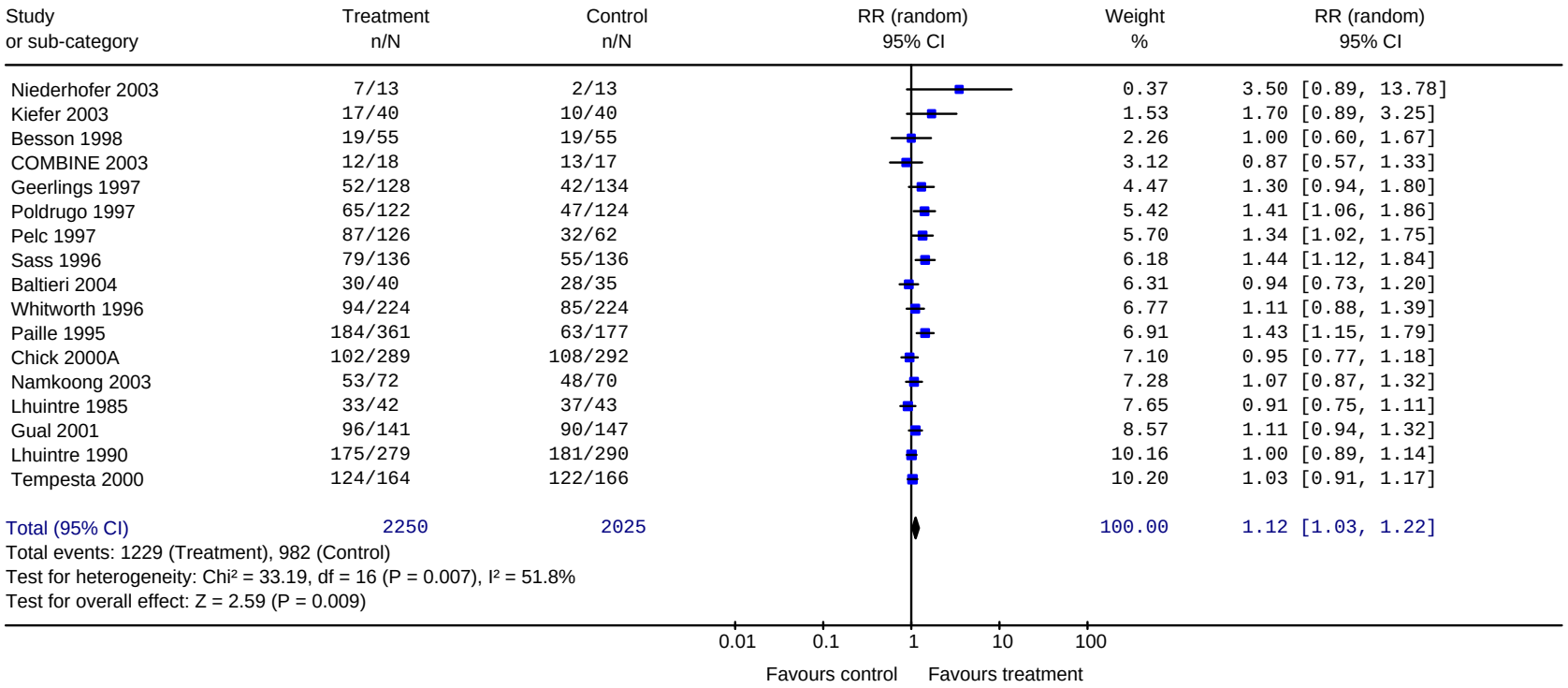

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Figure 2.2 *Acamprosate compared with naltrexone, number of participants completing treatment*

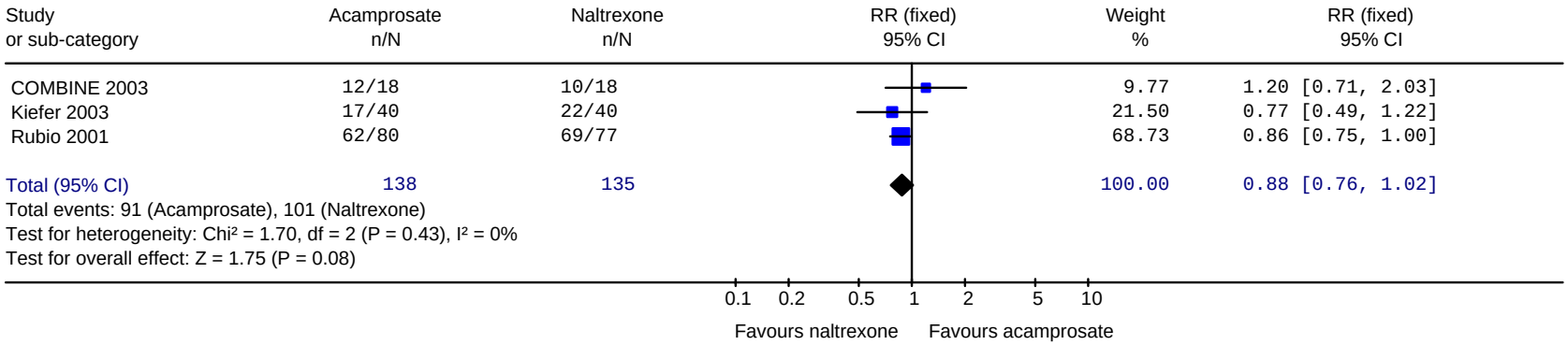

Figure 2.3 *Acamprosate compared with placebo or no medication, number of participants continuously abstinent during treatment*

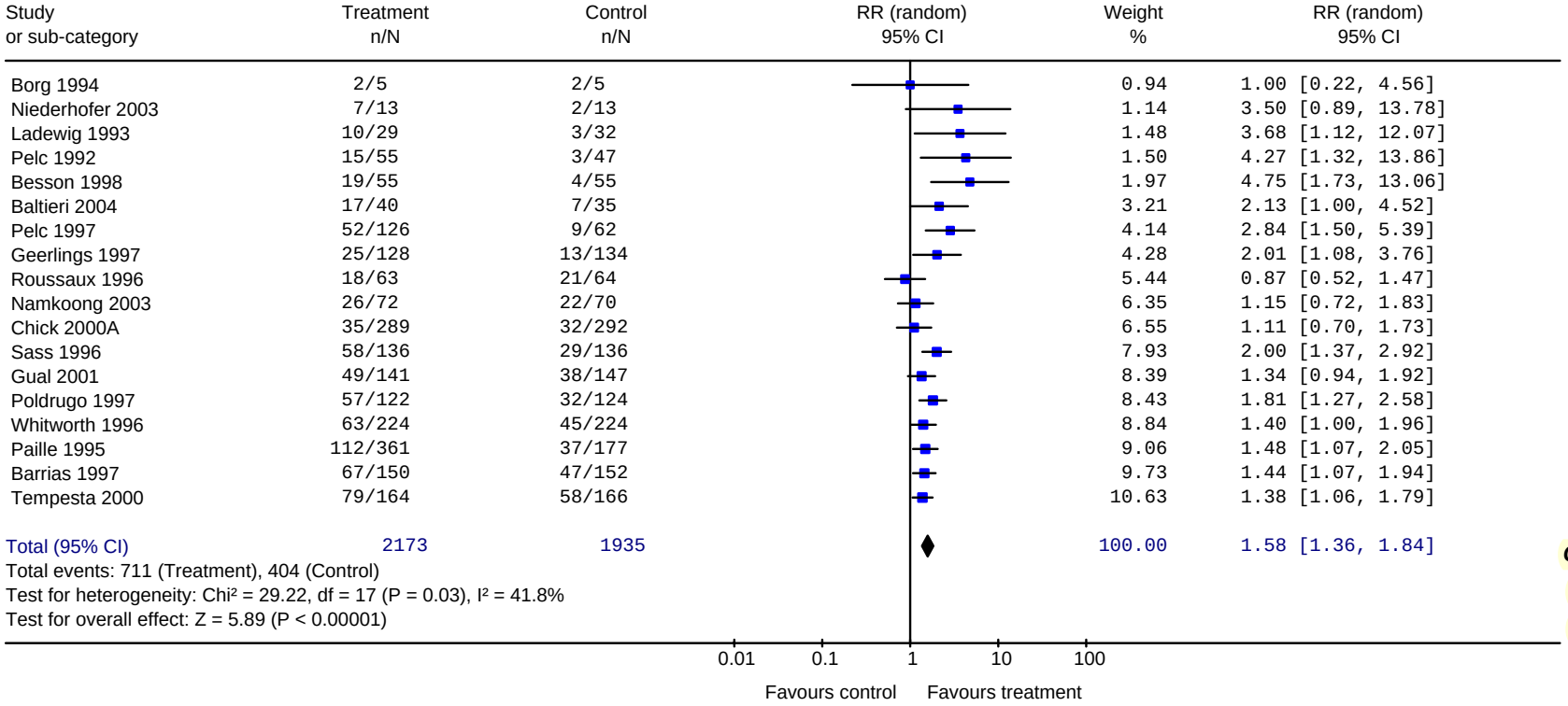

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Figure 2.4 *Acamprosate compared with placebo or no medication, number of participants abstinent at follow-up*

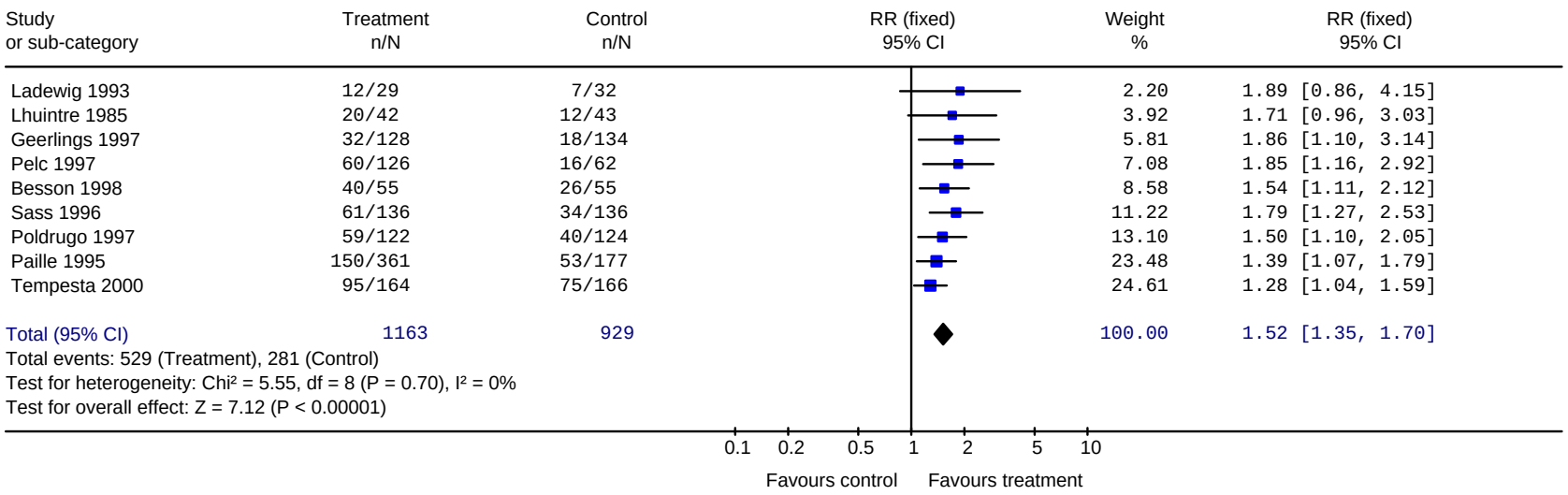

Figure 2.5 *Acamprosate compared with placebo or no medication, number of participants relapsing during treatment*

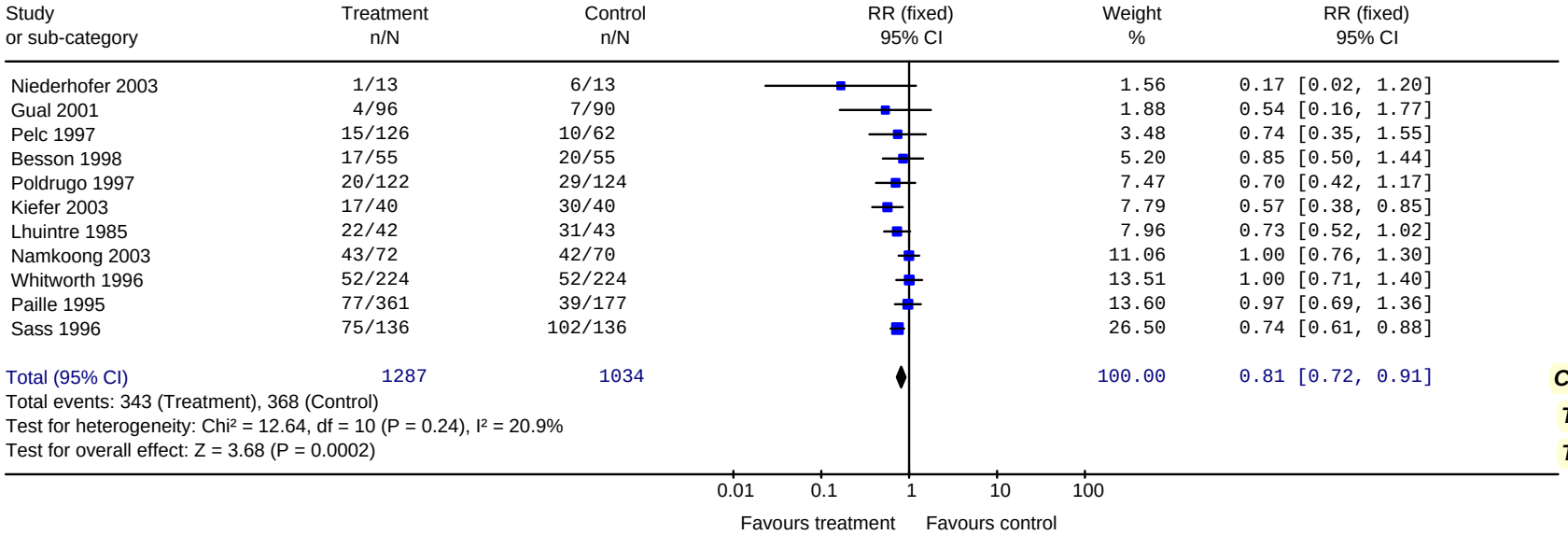

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Figure 2.6 *Acamprosate compared with placebo or no medication, average cumulative abstinence duration (%)*

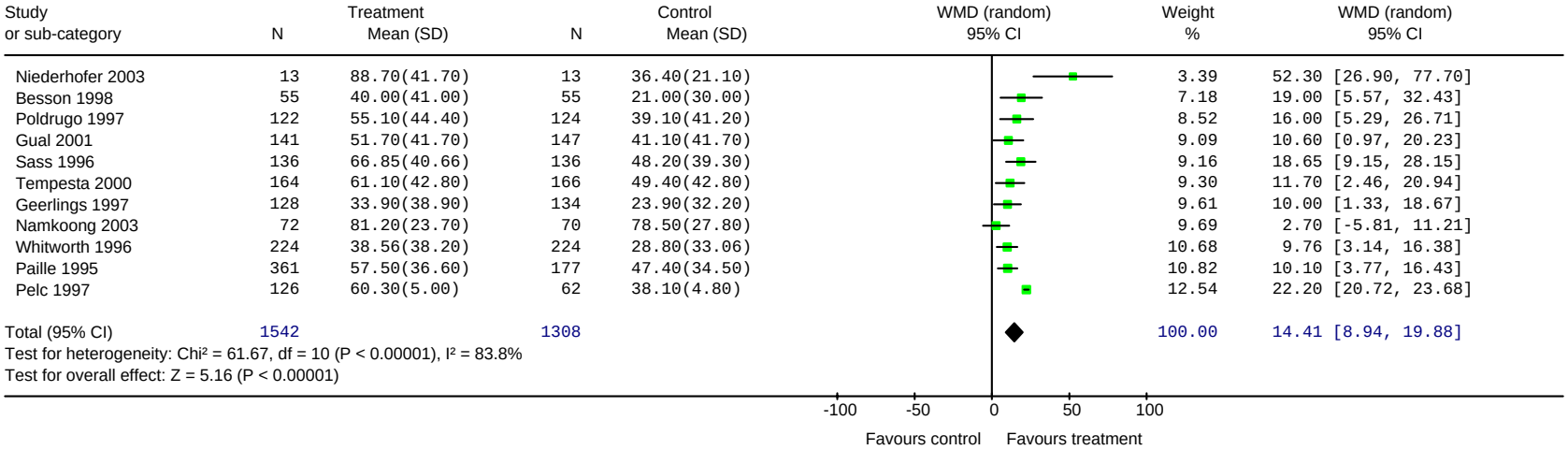

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Figure 2.7 *Acamprosate compared with naltrexone, number of participants relapsing during treatment*

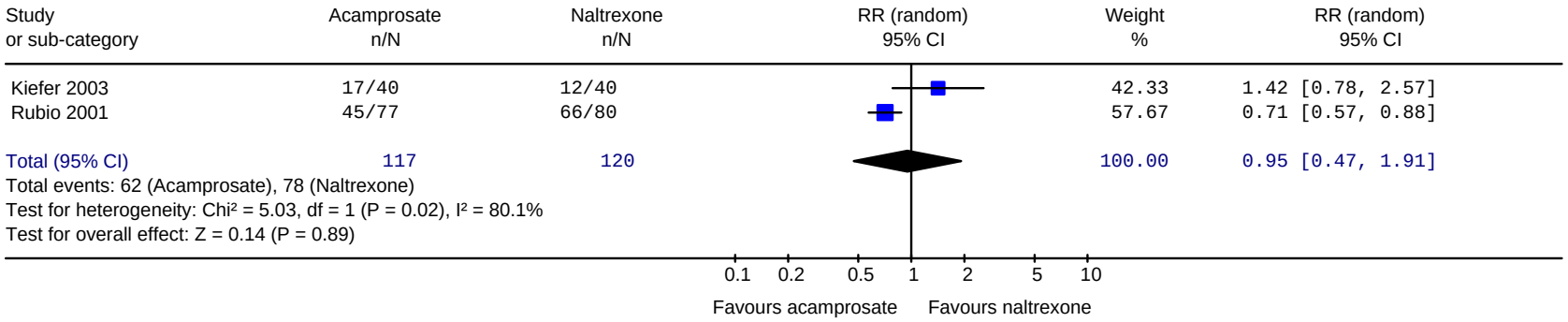

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Figure 2.8 *Acamprosate compared with placebo or no medication, number of participants experiencing adverse effects*

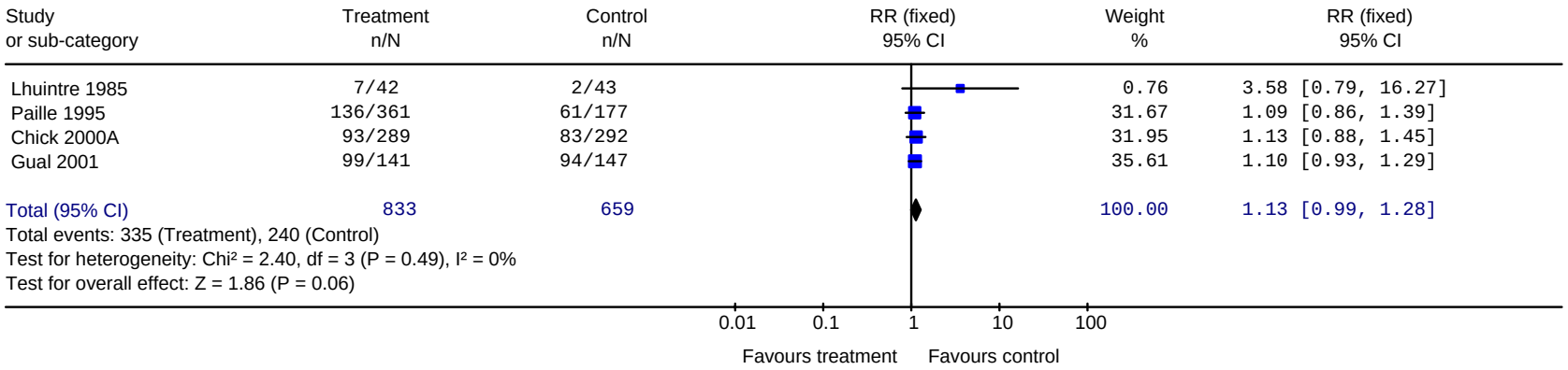

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Figure 2.9 *Acamprosate compared with placebo or no medication, number of participants with dose reduced due to adverse effects*

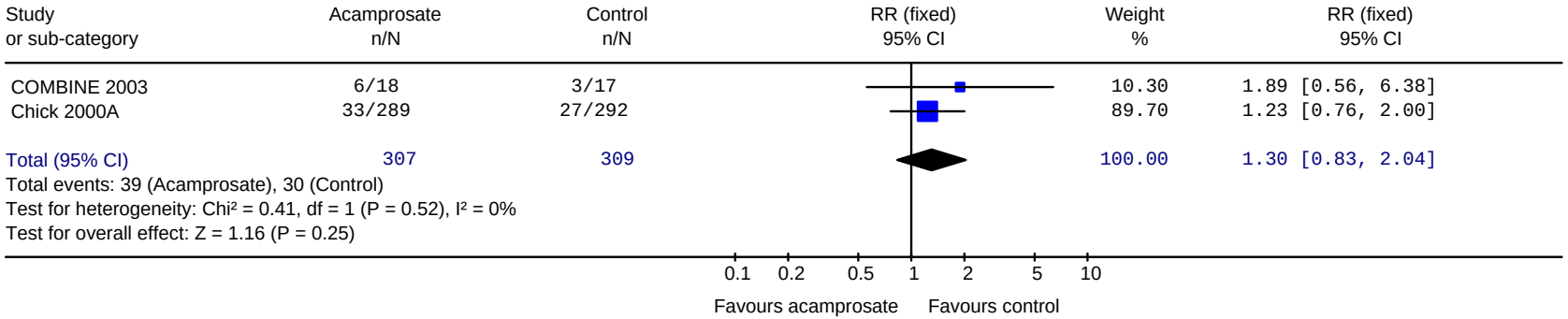

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Figure 2.10 Acamprosate compared with placebo or no medication, number of participants experiencing headaches

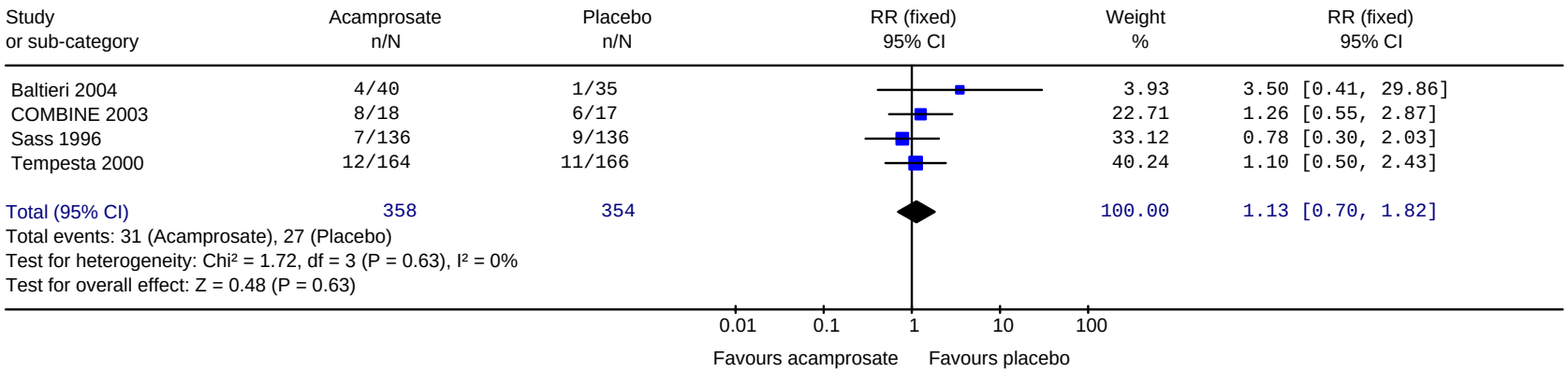

Figure 2.11 Acamprosate compared with placebo or no medication, number of participants experiencing diarrhoea or other gastrointestinal effects

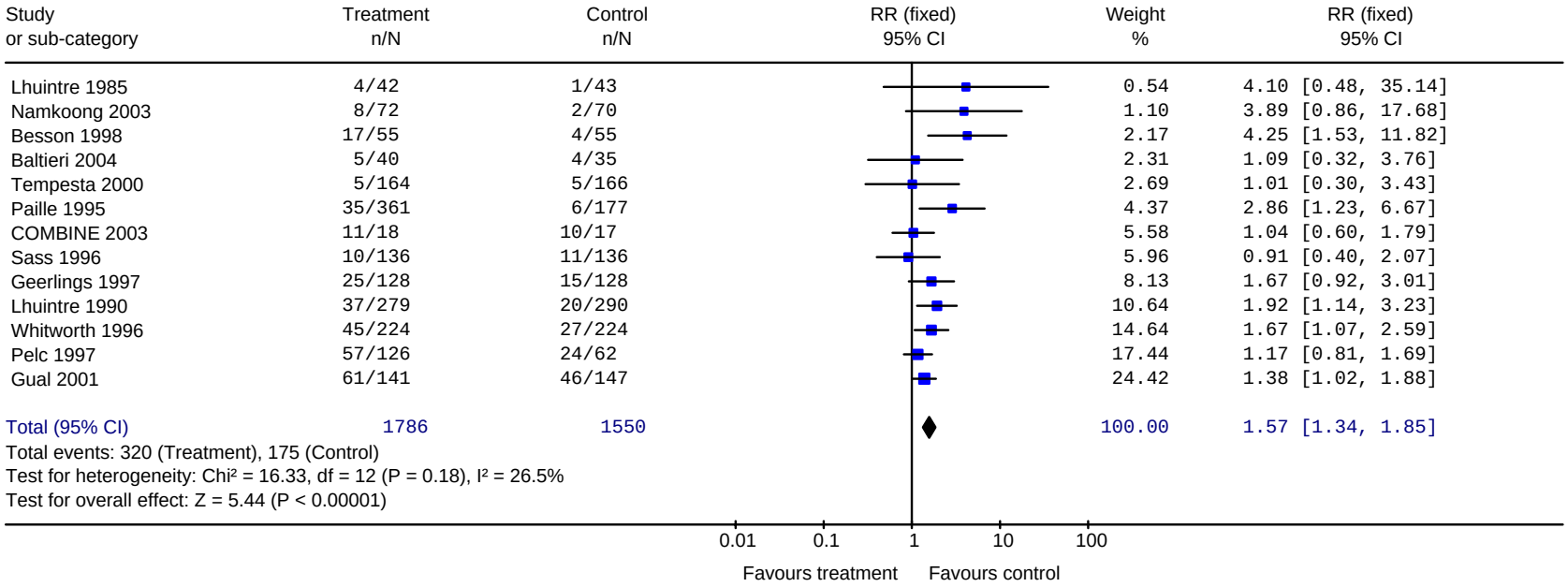

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Figure 2.12 Acamprosate compared with placebo or no medication, number of participants withdrawing due to adverse effects

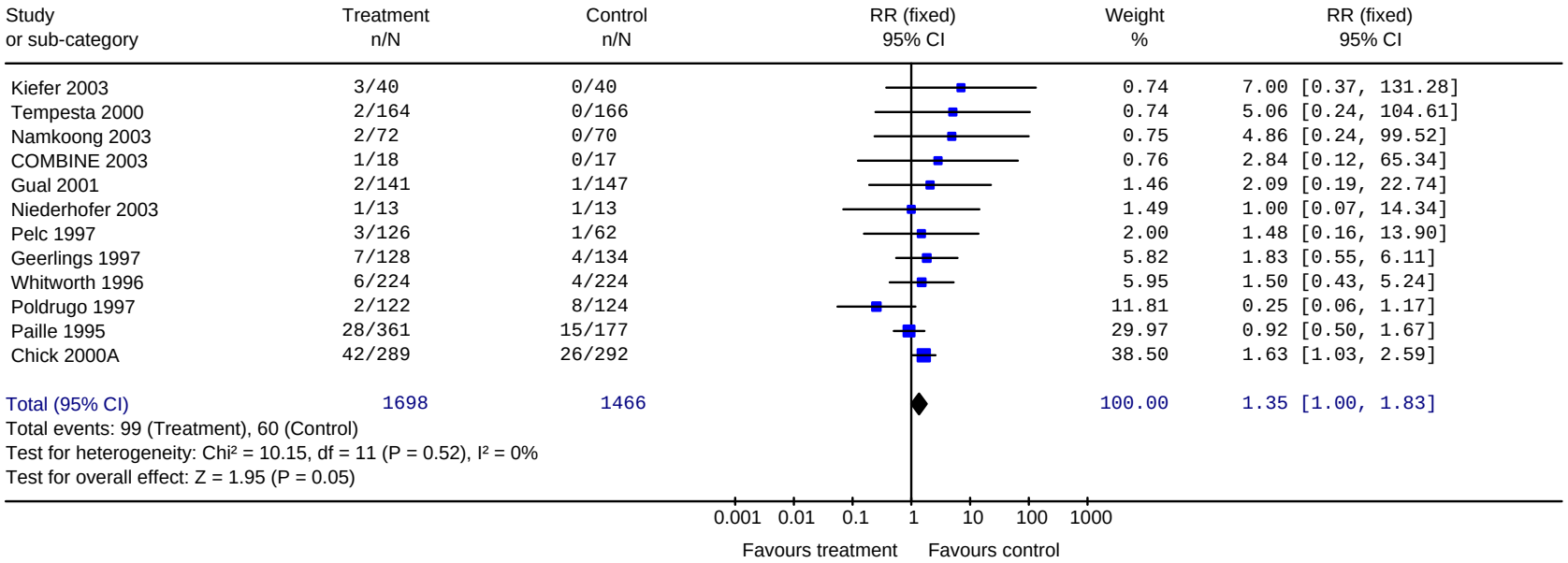

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Figure 2.13 Acamprosate compared with naltrexone, number of participants experiencing nausea

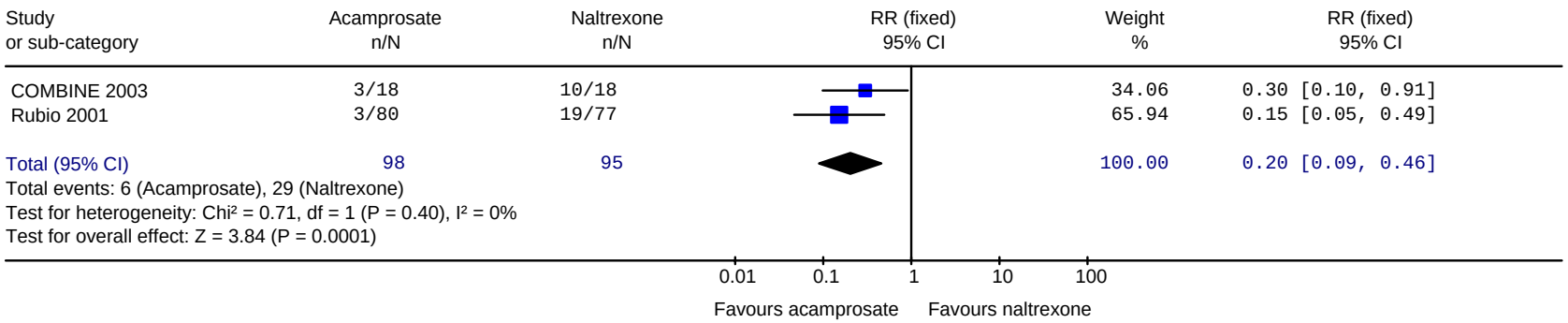

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Figure 2.14 Acamprosate compared with naltrexone, number of participants experiencing abdominal pain

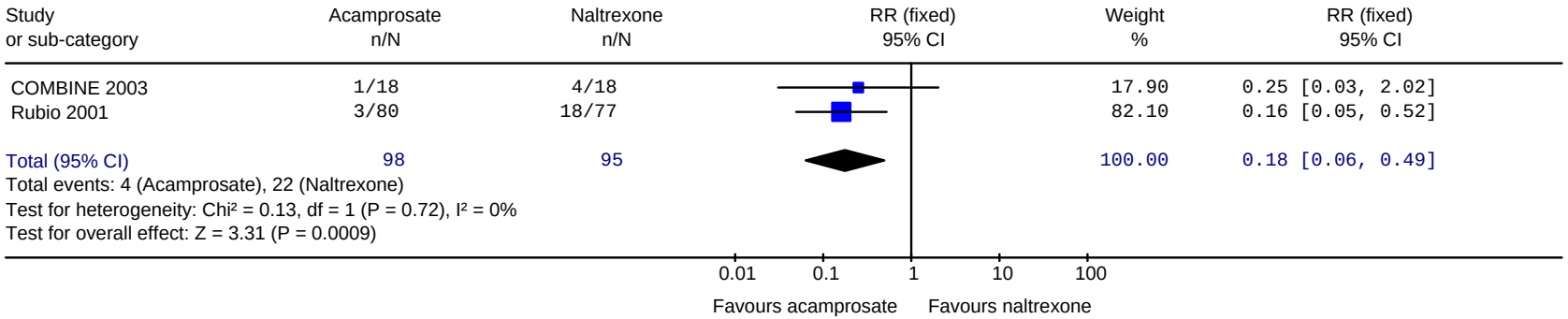

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Figure 2.15 Acamprosate compared with naltrexone, number of participants experiencing diarrhoea

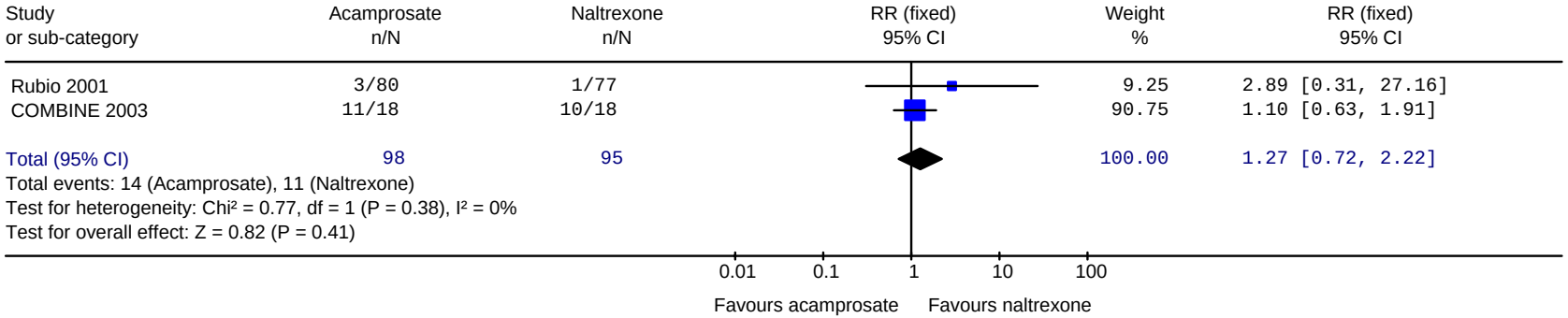

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Figure 2.16 Acamprosate compared with naltrexone, number of participants experiencing headaches

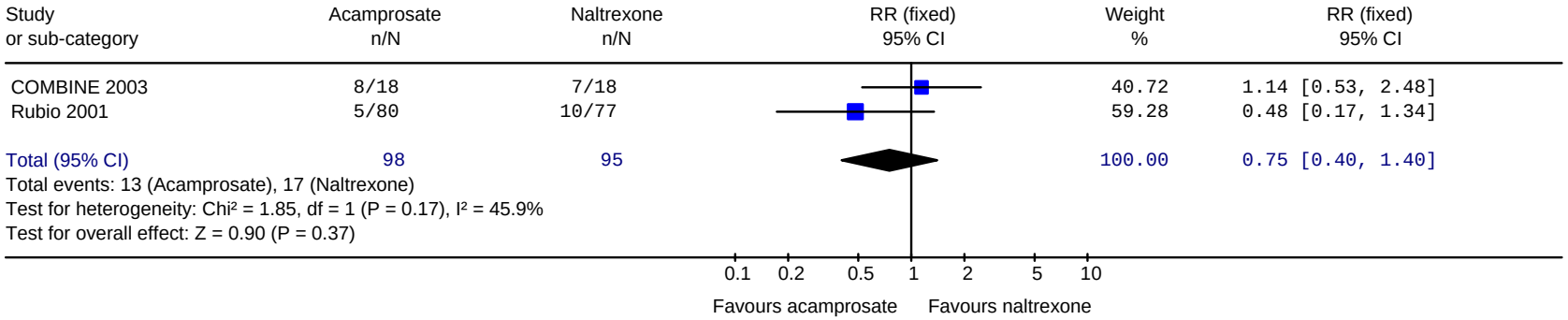

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Figure 2.17 Acamprosate compared with naltrexone, number of participants withdrawing from treatment due to adverse effects

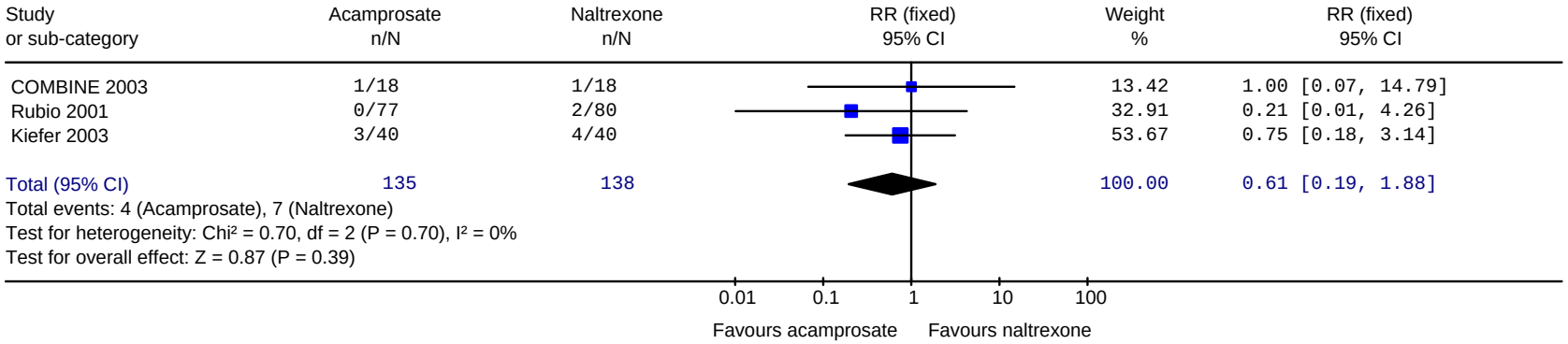

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Figure 3.1 *Naltrexone plus acamprosate, compared with placebo, number of participants completing treatment*

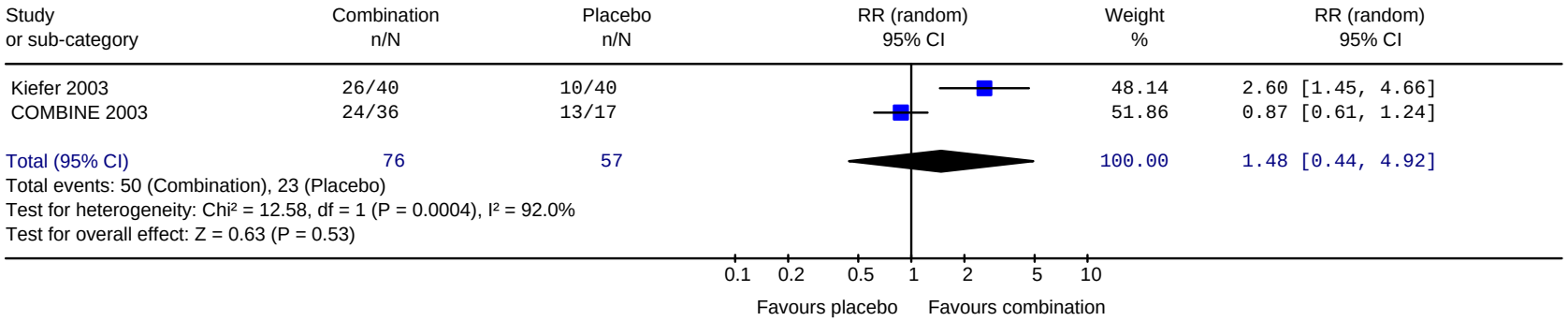

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Figure 3.2 *Naltrexone plus acamprosate, compared with acamprosate, number of participants completing treatment*

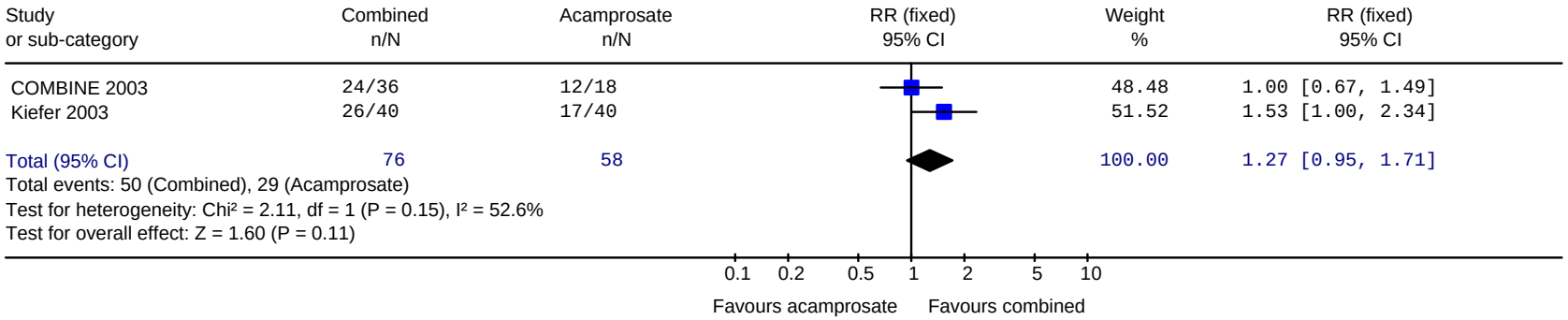

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Figure 3.3 *Naltrexone plus acamprosate, compared with naltrexone, number of participants completing treatment*

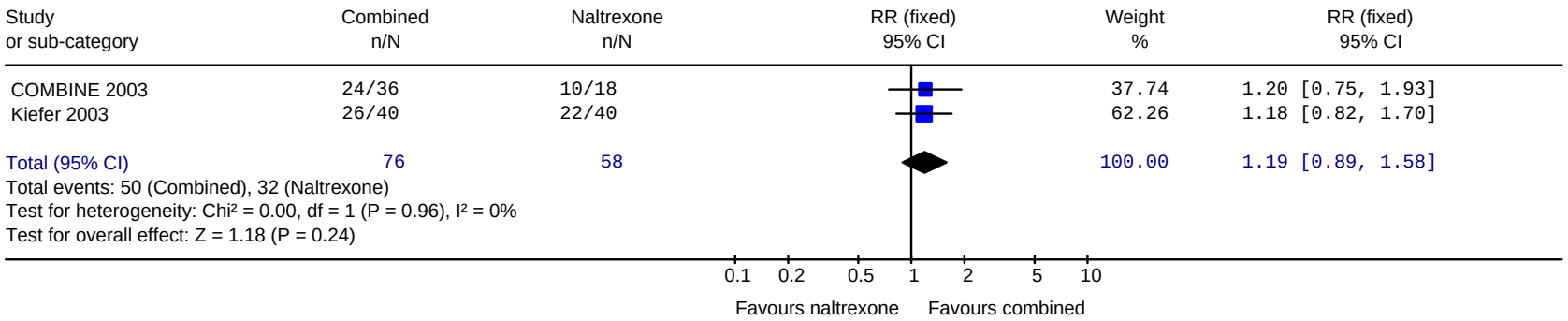

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Figure 3.4 *Naltrexone plus acamprosate, compared with placebo, number of participants withdrawing from treatment due to adverse effects*

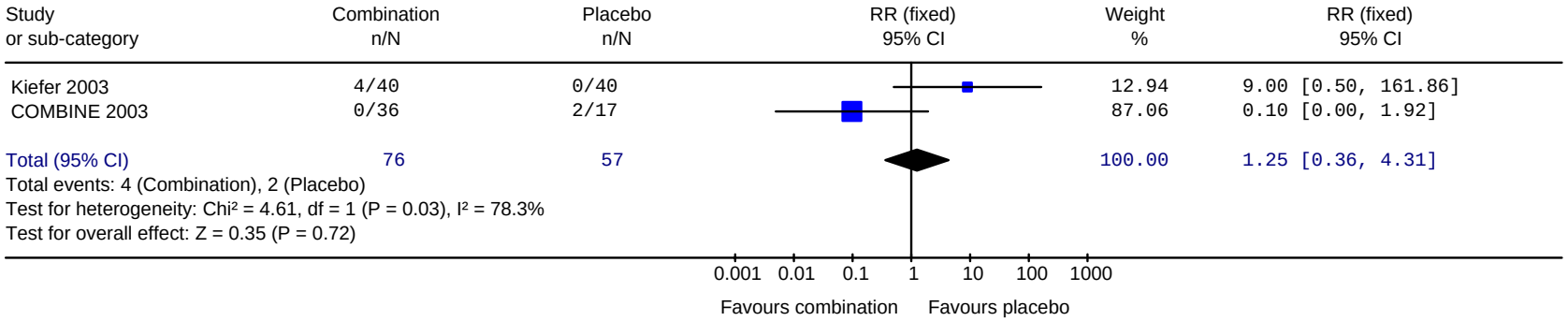

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Figure 3.5 *Naltrexone plus acamprosate, compared with acamprosate, number of participants withdrawing from treatment due to adverse effects*

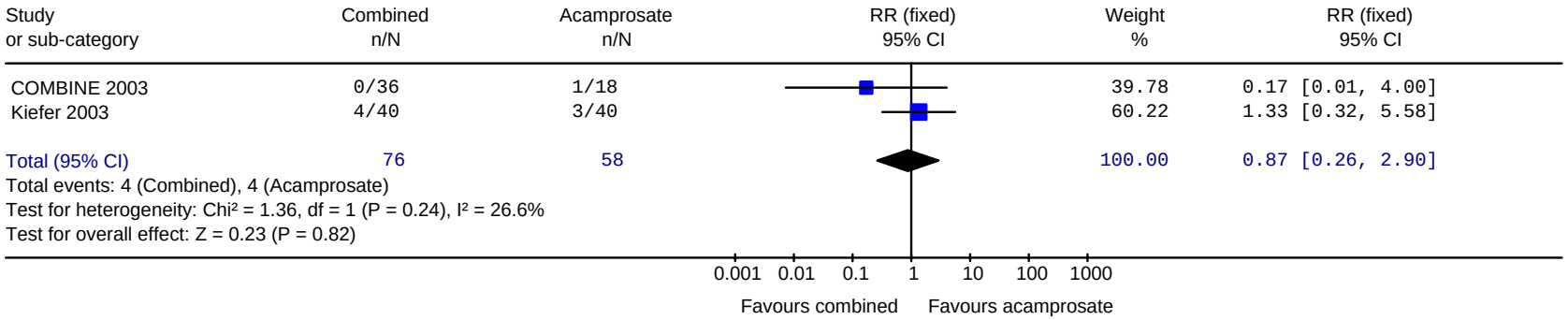

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Figure 3.6 *Naltrexone plus acamprosate, compared with placebo, number of participants withdrawing from treatment due to adverse effects*

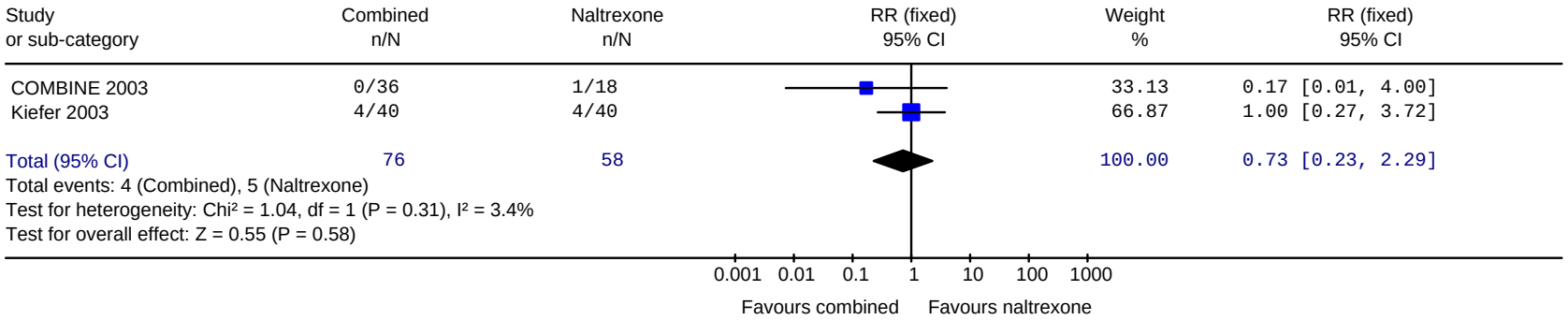

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Figure 4.1 Disulfiram compared with no medication, number of participants completing treatment

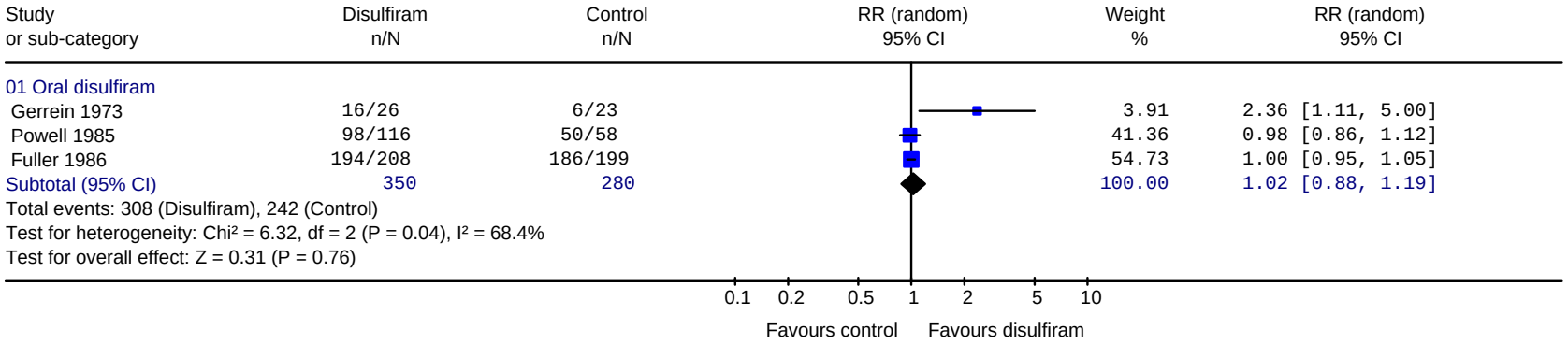

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Figure 4.2 Disulfiram compared with placebo, number of participants continuously abstinent during treatment

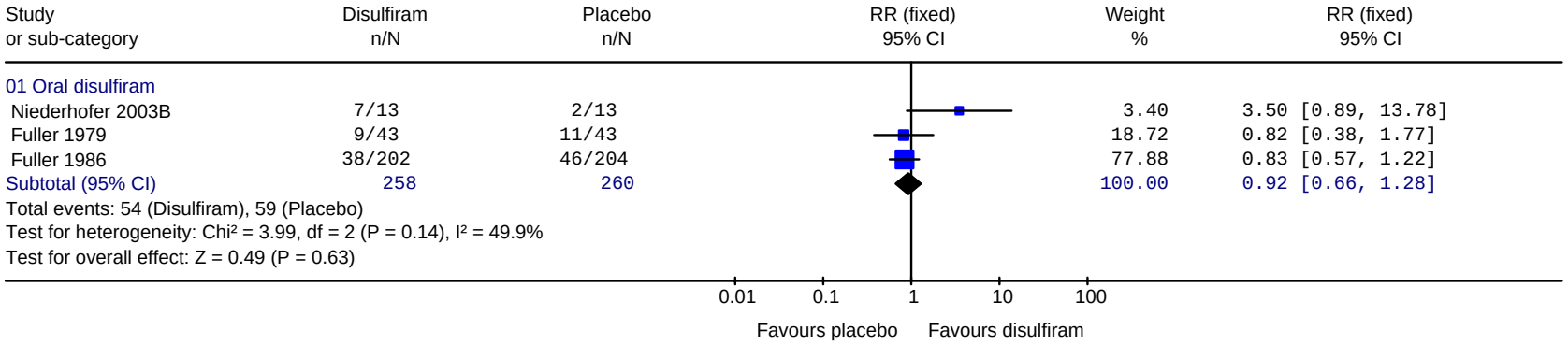

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Figure 4.3 Disulfiram compared with placebo, number of participants abstinent at follow-up

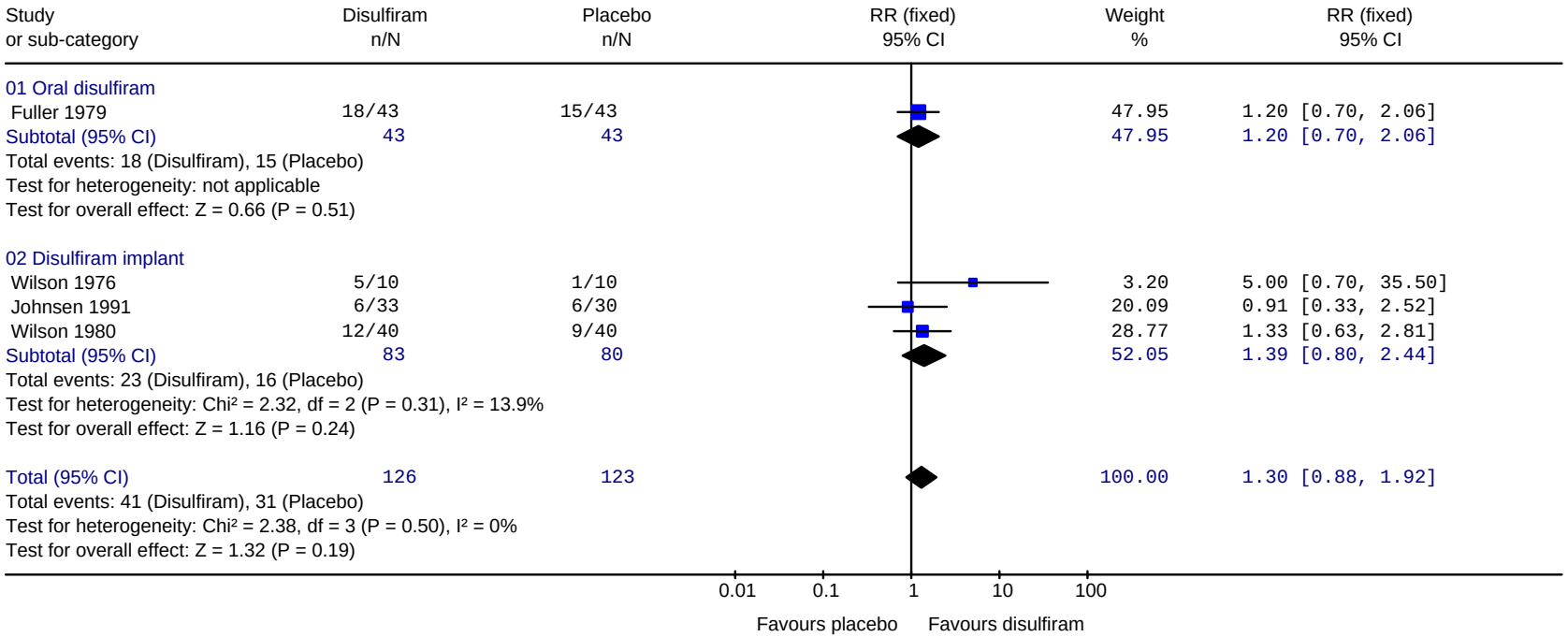

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Figure 4.4 *Disulfiram compared with placebo, average cumulative abstinence duration (%)*

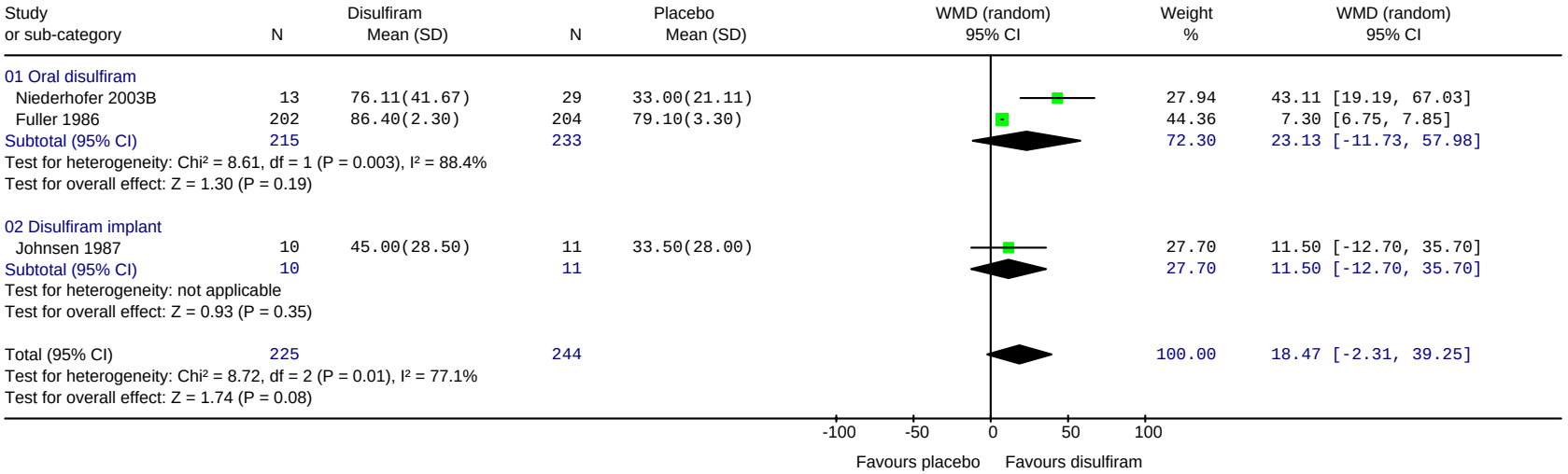

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Figure 4.5 *Disulfiram compared with no medication, number of participants continuously abstinent during treatment*

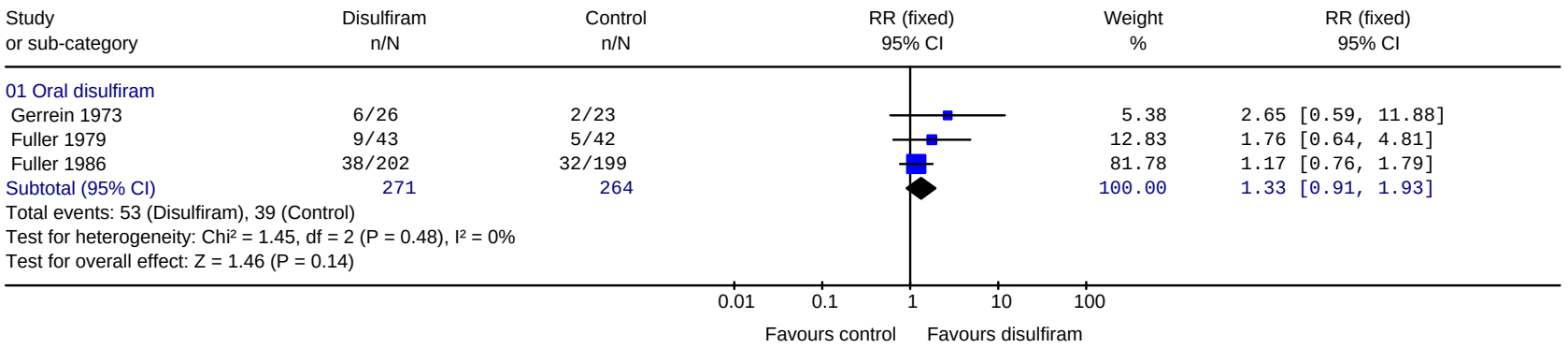

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Figure 4.6 Disulfiram compared with no medication, number of participants abstinent at follow-up

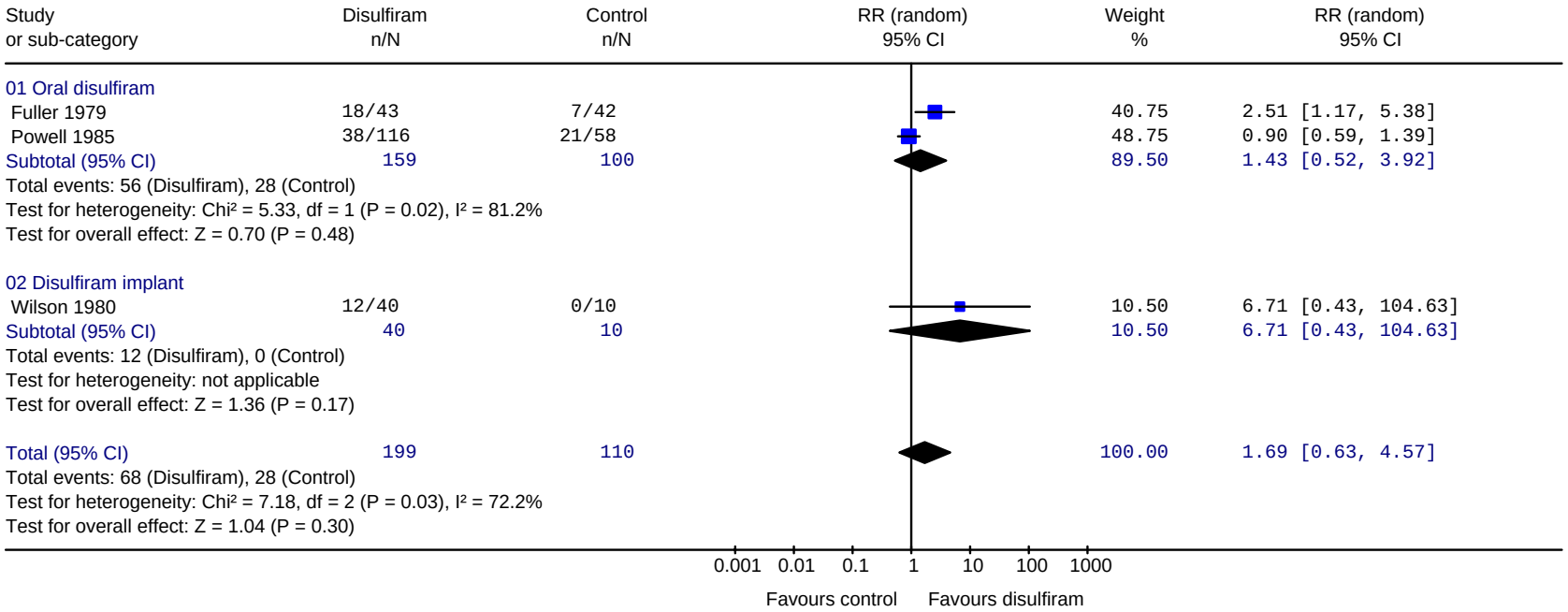

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Figure 4.7 *Disulfiram compared with placebo, number of participants experiencing adverse effects*

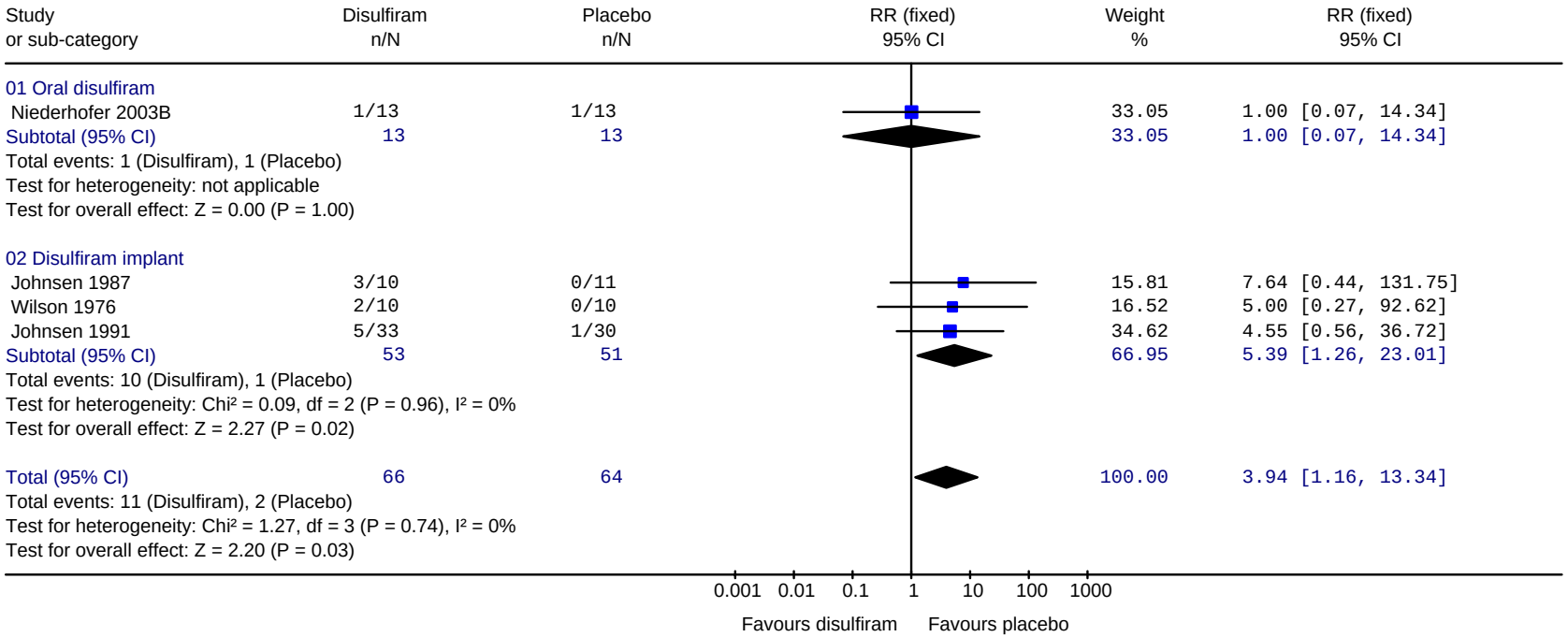

Figure 4.8 *Disulfiram compared with placebo, number of participants discontinuing treatment due to adverse effects*

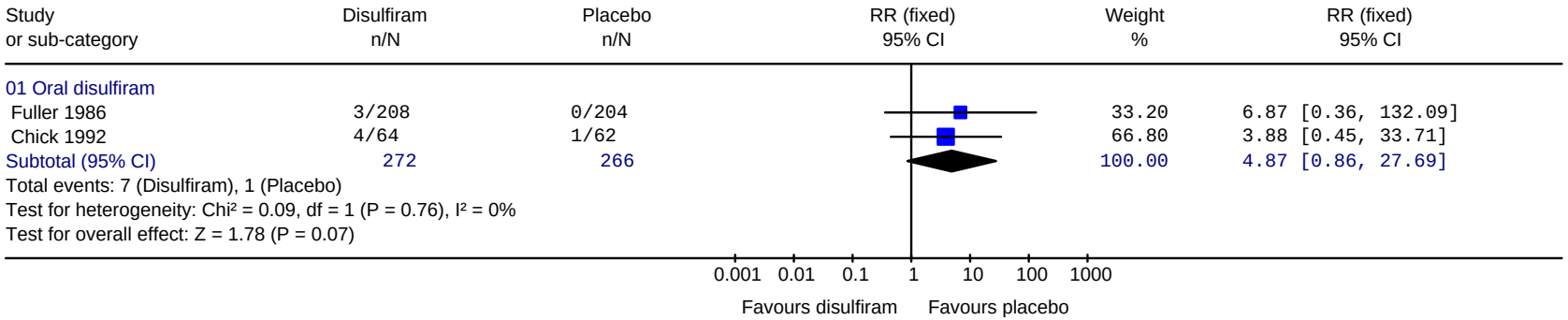

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Figure 5.1 Antidepressant compared with placebo or no medication, number of participants completing treatment

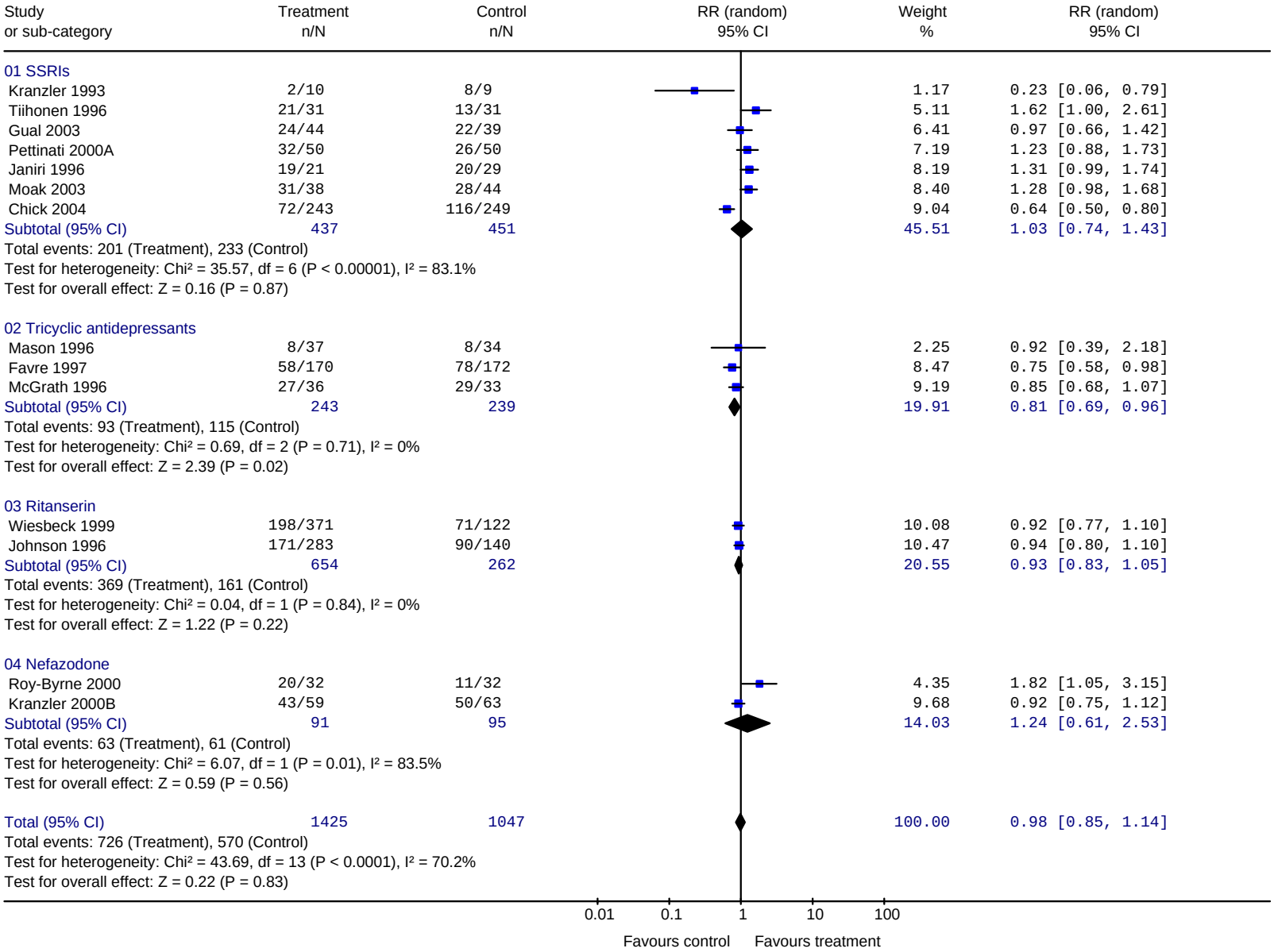

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Figure 5.2 *Antidepressant compared with placebo or no medication, mean time in treatment (weeks)*

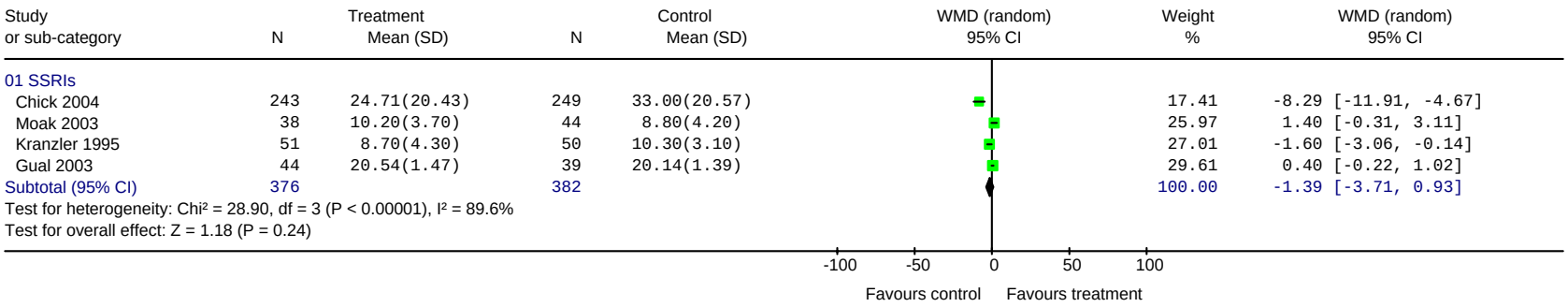

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Figure 5.3 *Antidepressant compared with placebo or no medication, number of participants continuously abstinent during treatment*

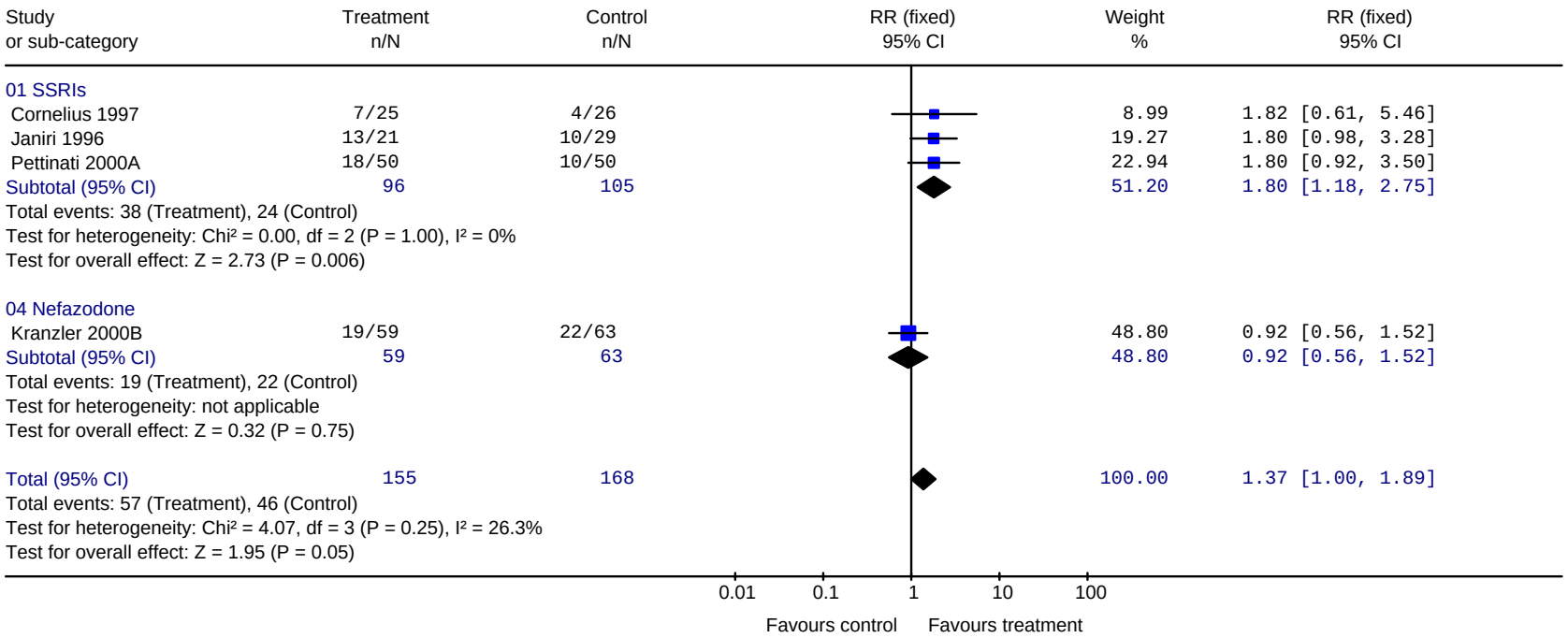

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Figure 5.4 *Antidepressant compared with placebo or no medication, number of participants abstinent at follow-up*

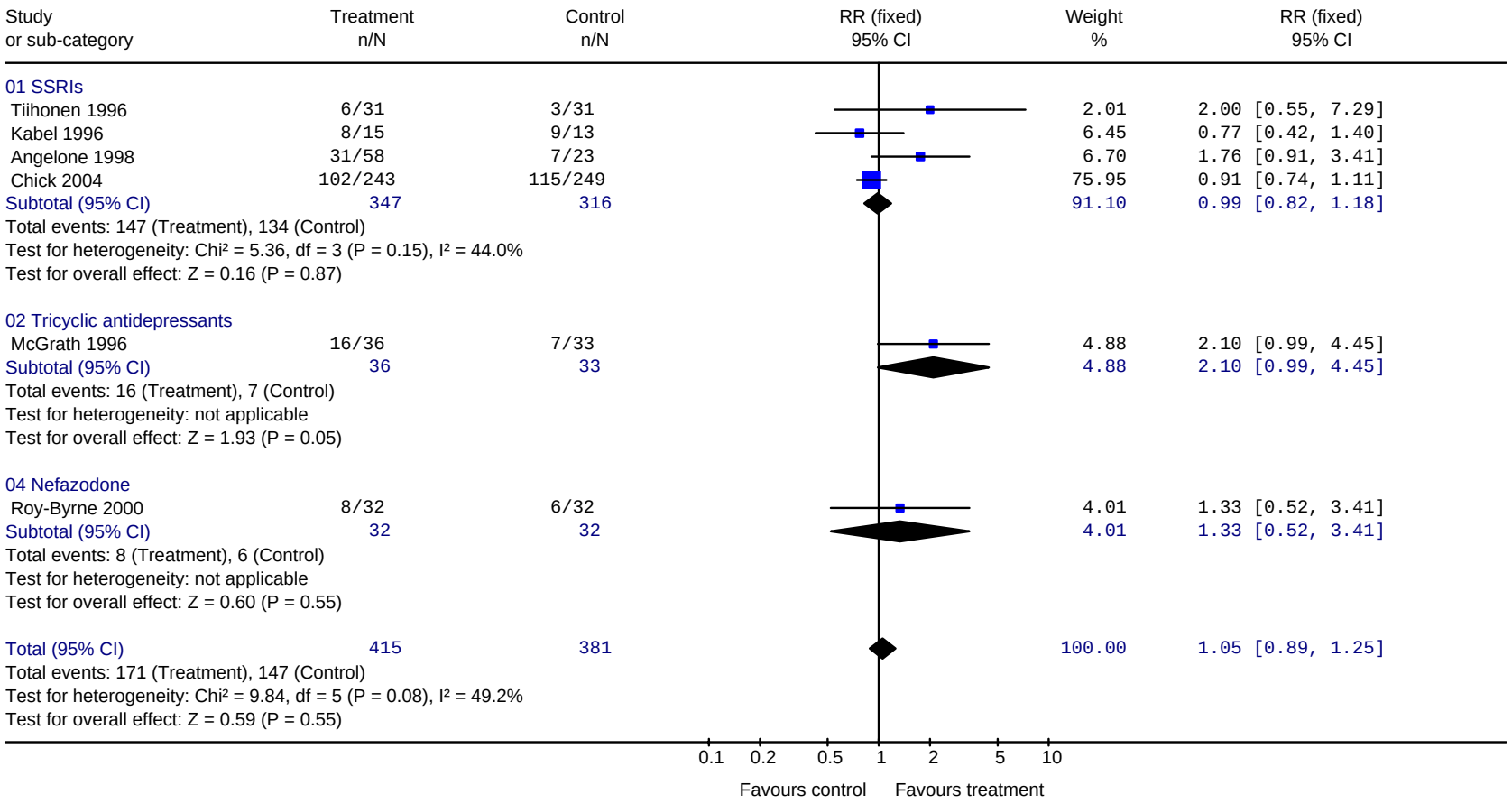

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Figure 5.5 Antidepressant compared with placebo or no medication, number of participants relapsing during treatment

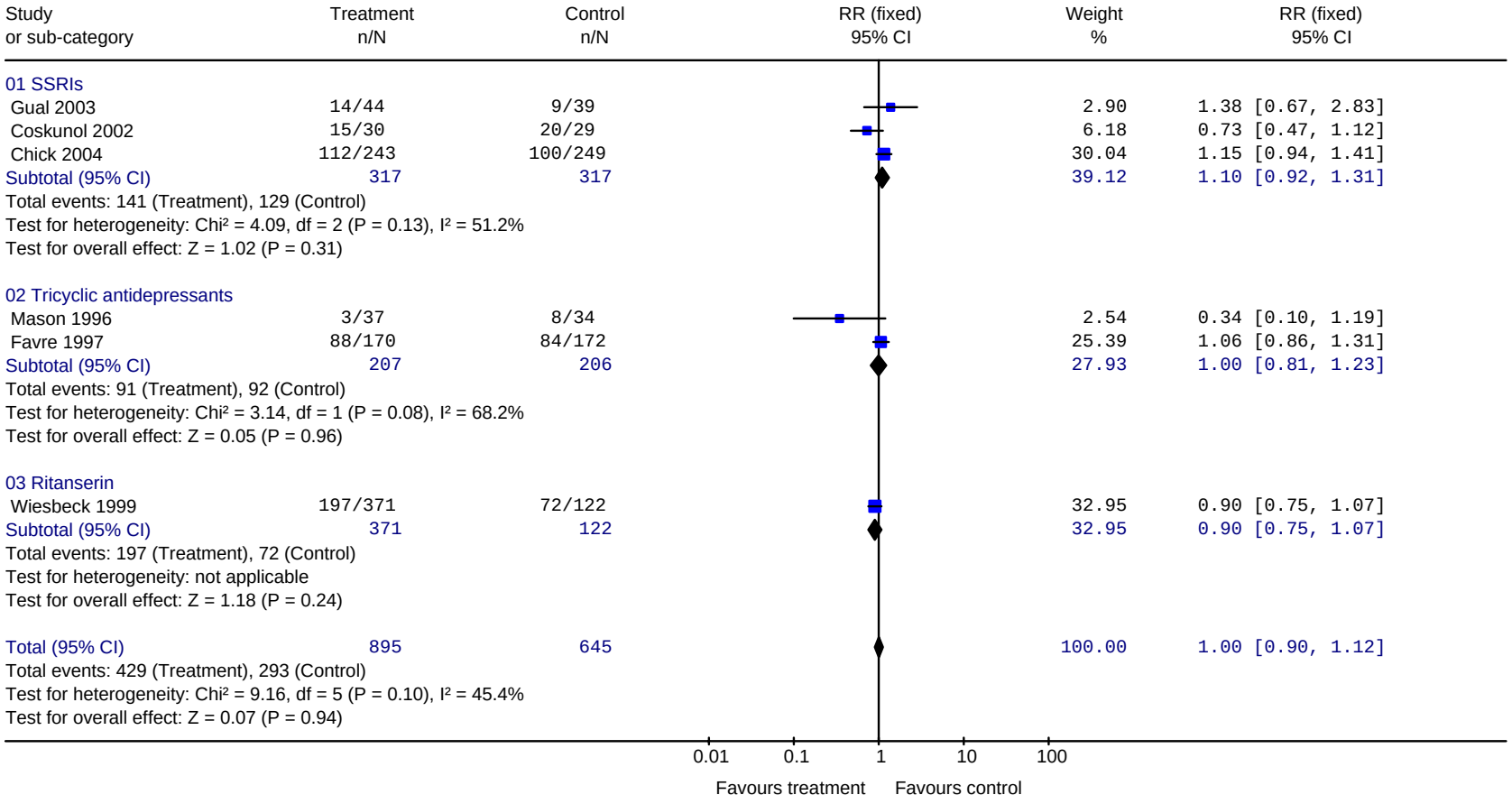

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Figure 5.6 *Antidepressant compared with placebo or no medication, average drinks per drinking day*

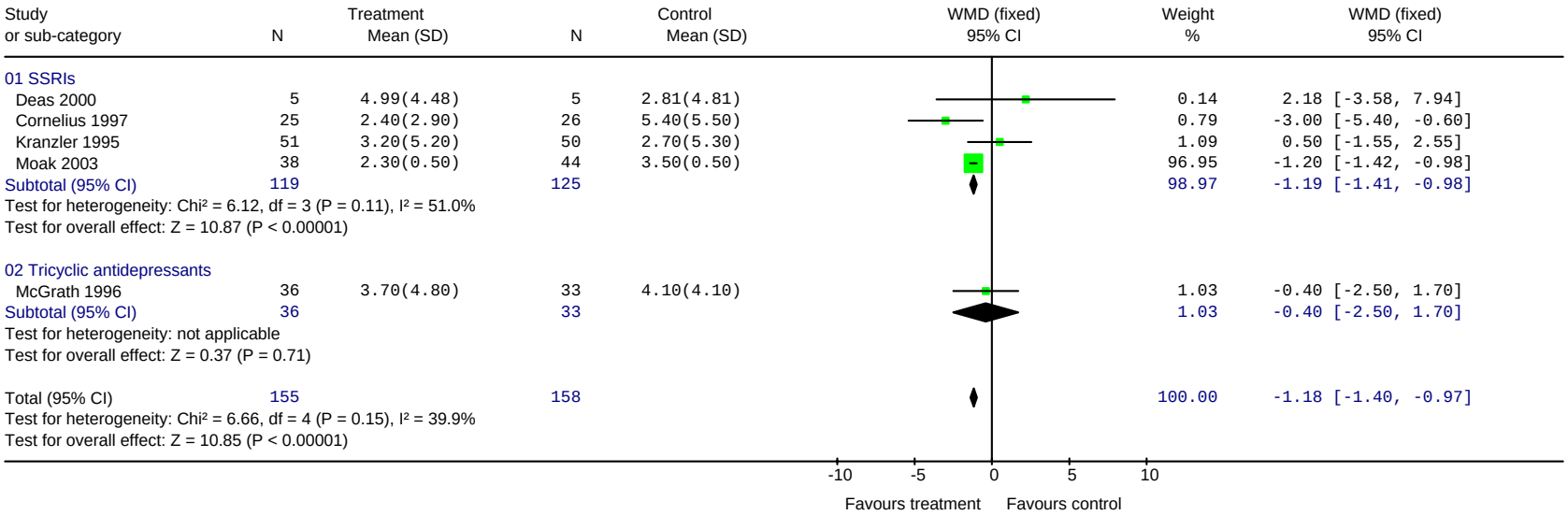

Figure 5.7 *Antidepressant compared with placebo or no medication, average drinks per week during treatment*

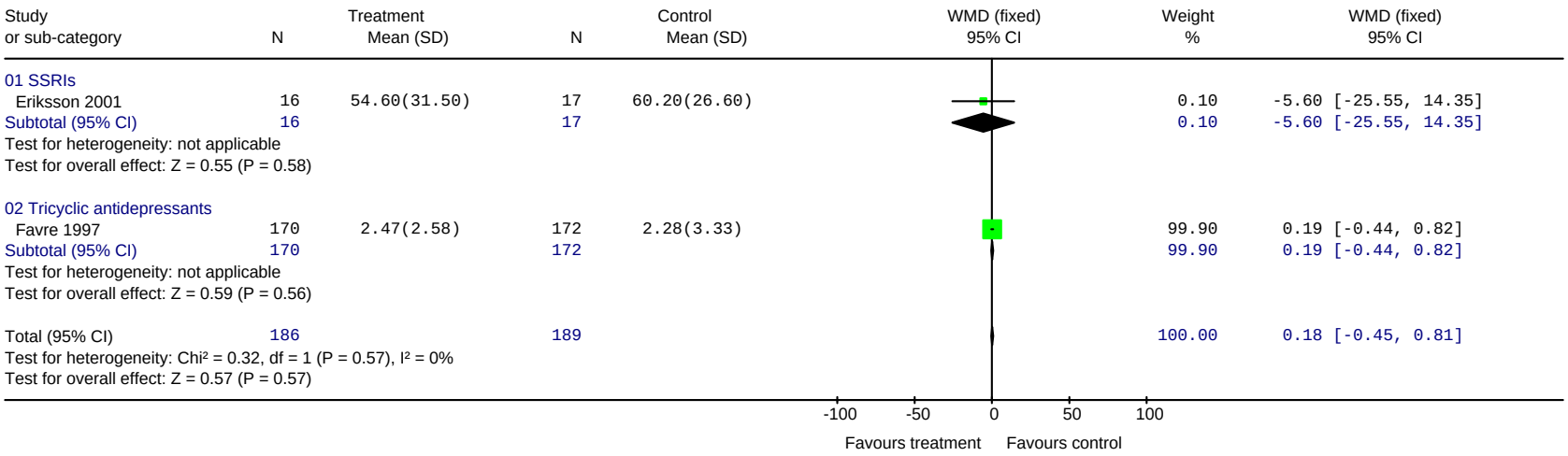

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Figure 5.8 Antidepressant compared with placebo or no medication, days during treatment with drinking (%)

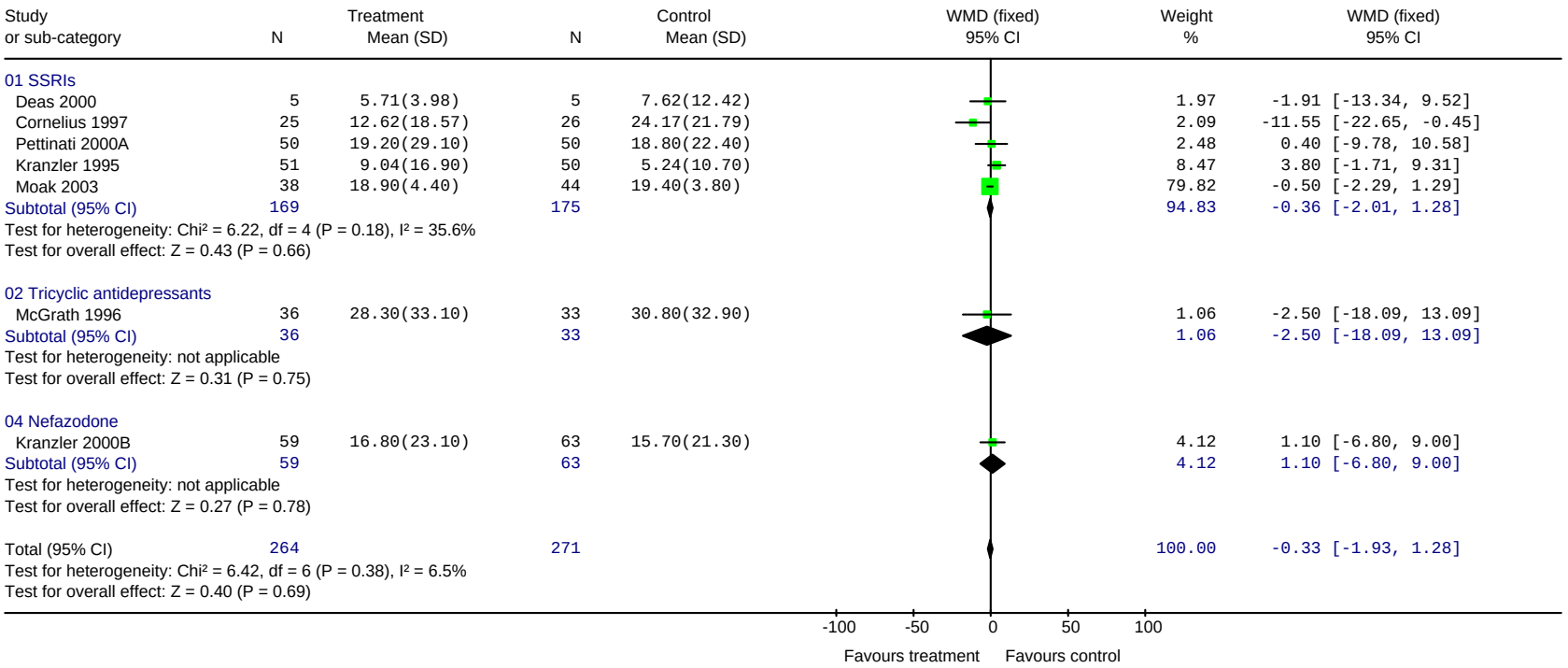

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Figure 5.9 *Antidepressants compared with placebo or no medication, cumulative abstinence duration (%)*

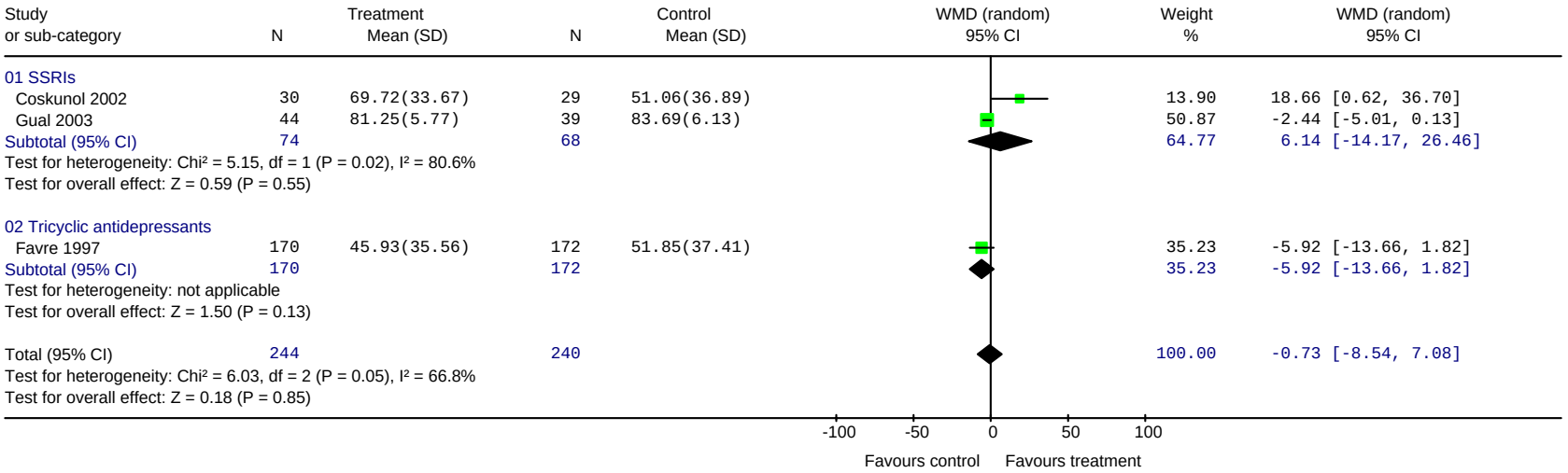

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Figure 5.10 *Antidepressant compared with placebo or no medication, average time to first drink (days)*

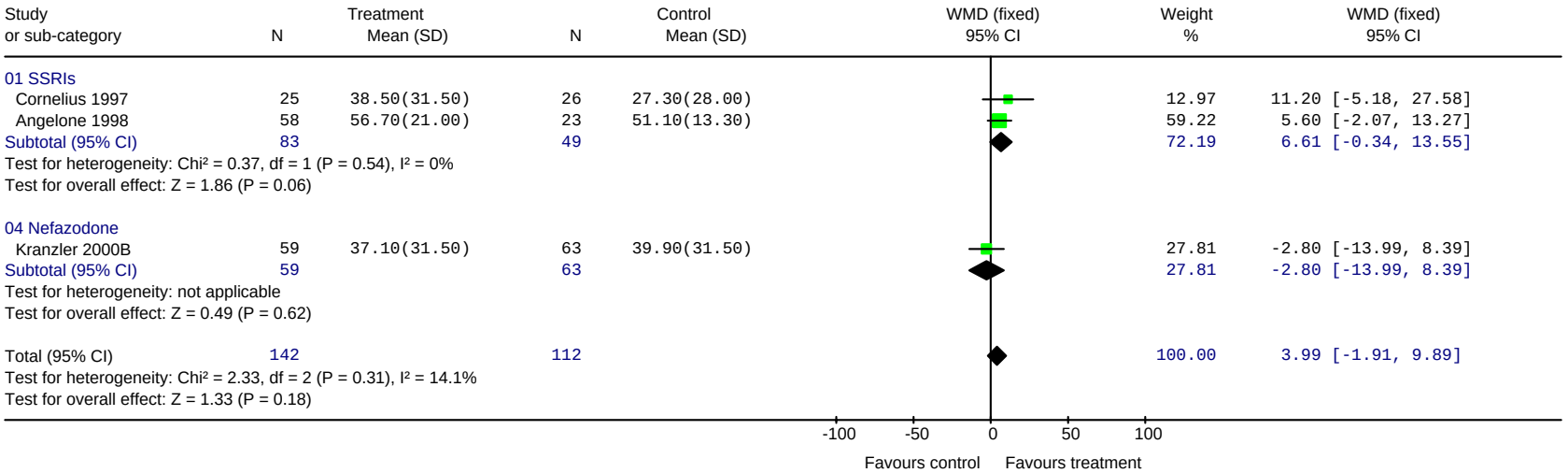

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Figure 5.11 Antidepressant compared with placebo or no medication, average time to relapse (days)

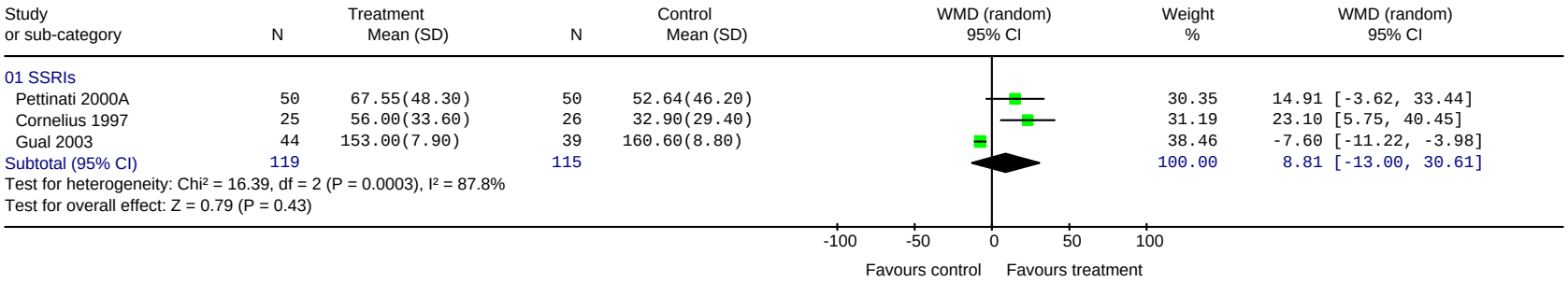

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Figure 5.12 Antidepressant compared with placebo or no medication, number of participants experiencing one or more adverse effects

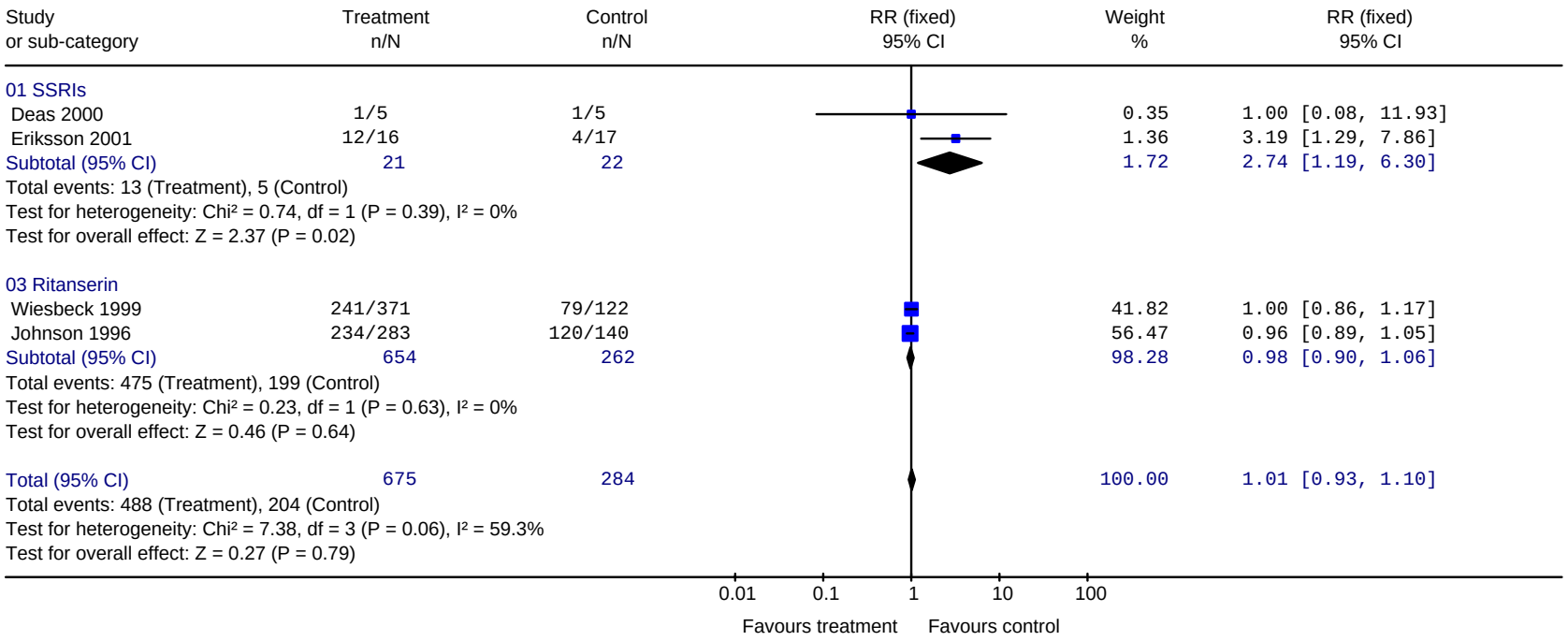

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Figure 5.13 *Antidepressant compared with placebo or no medication, number of participants experiencing nausea or gastrointestinal symptoms*

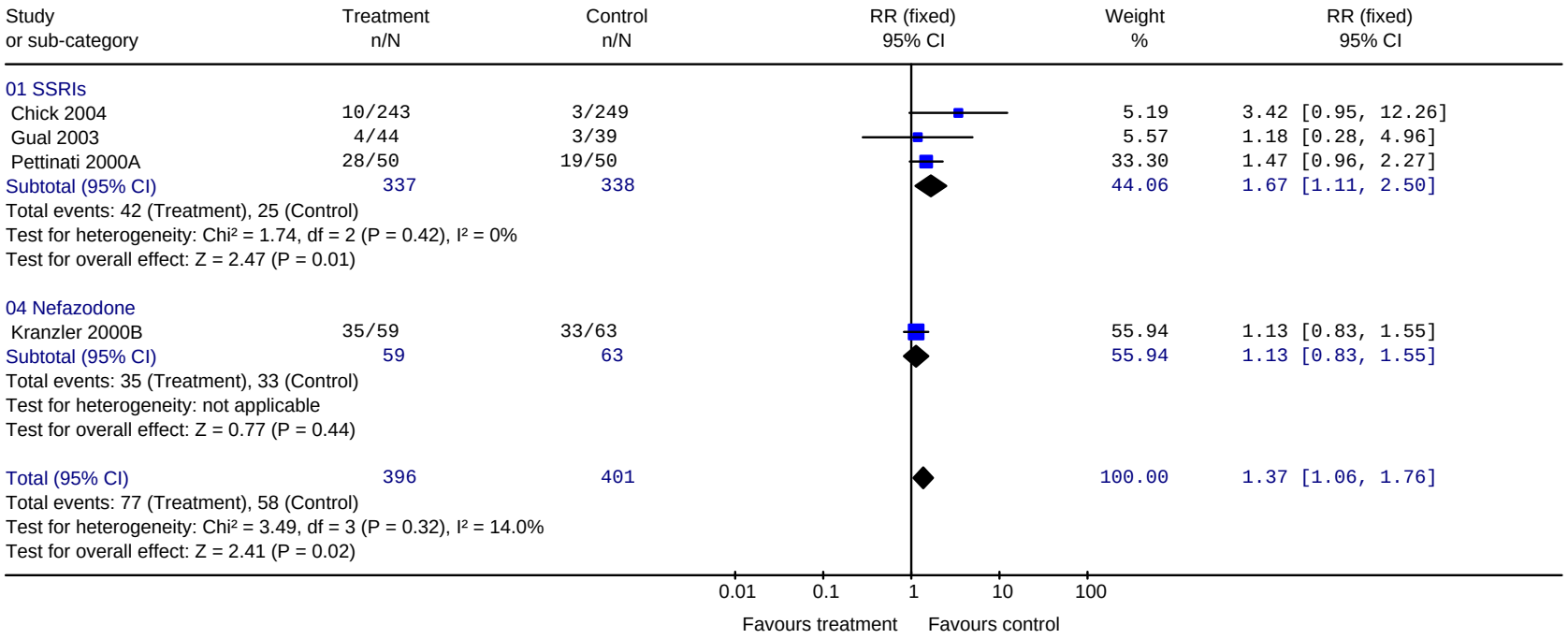

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Figure 5.14 *Antidepressant compared with placebo or no medication, number of participants experiencing headache or neuropsychiatric symptoms*

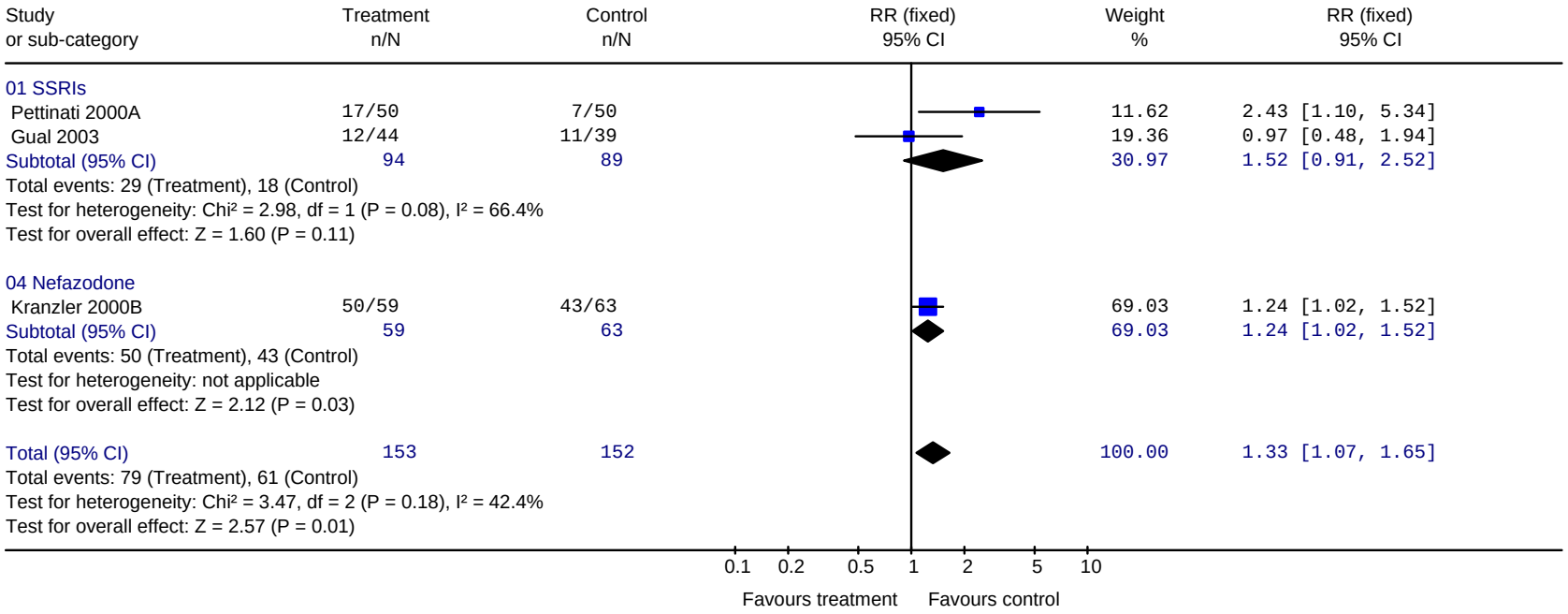

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Figure 5.15 *Antidepressant compared with placebo or no medication, number of participants discontinuing treatment due to adverse effects*

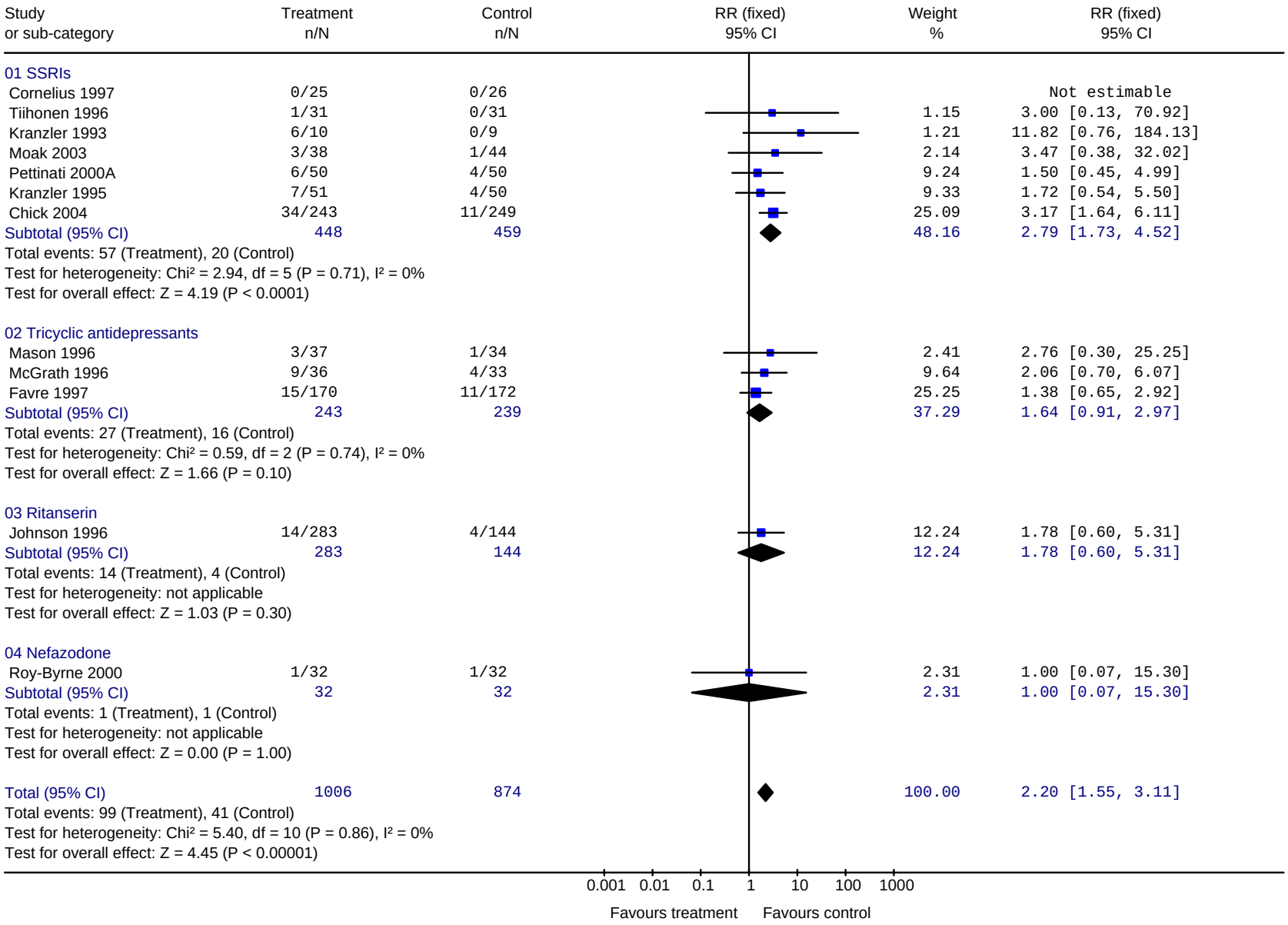

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Figure 6.1 *Buspirone compared with placebo, number of participants completing treatment*

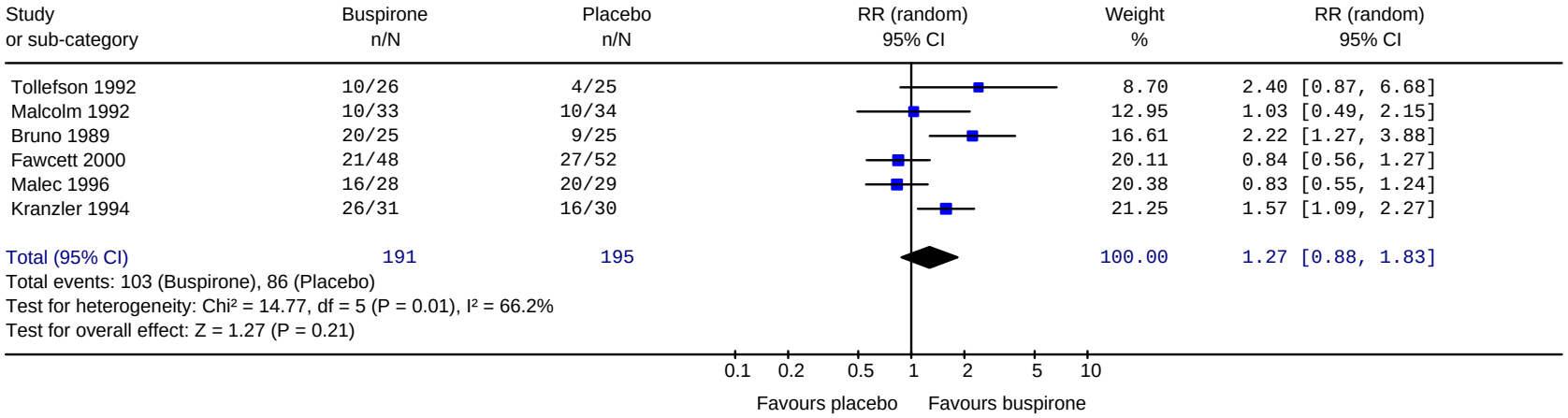

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Figure 6.2 *Buspirone compared with placebo, days during treatment with drinking (%)*

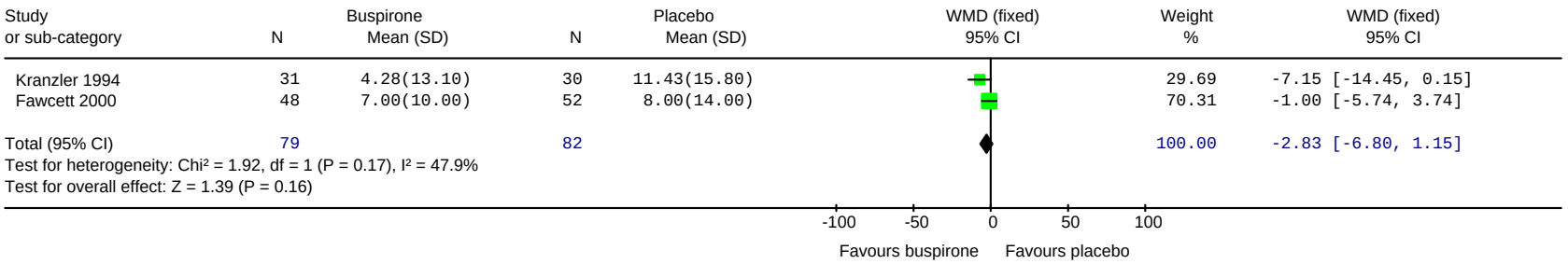

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Figure 6.3 *Buspirone compared with placebo, number of participants reporting adverse effects*

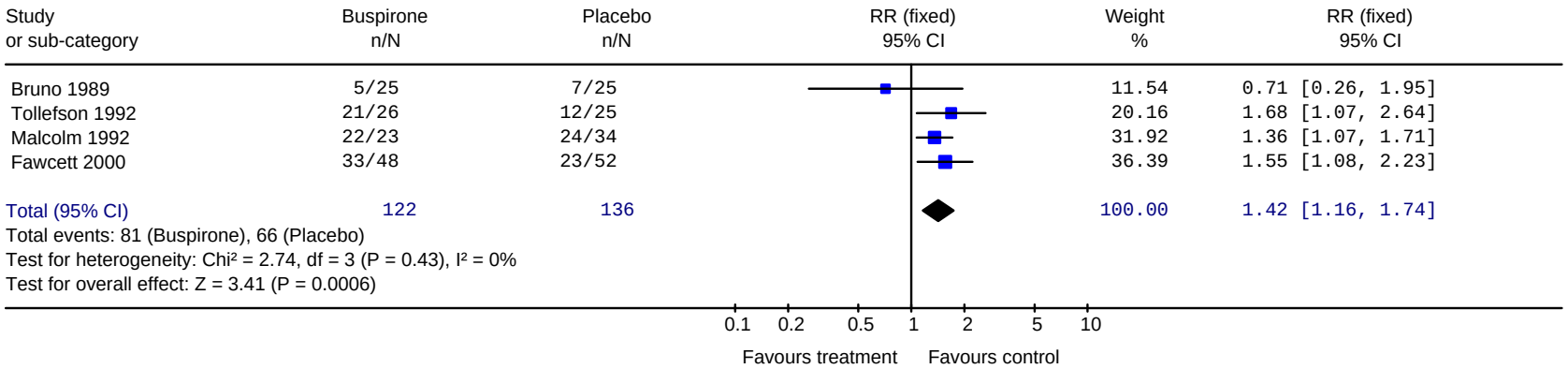

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Figure 6.4 *Buspirone compared with placebo, number of participants experiencing dizziness*

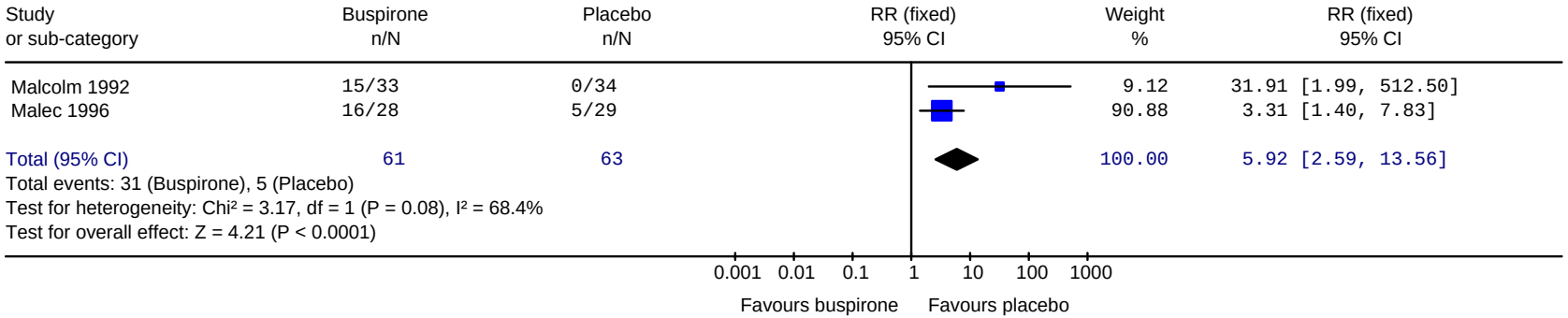

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Figure 6.5 *Buspirone compared with placebo, number of participants discontinuing treatment due to adverse effects*

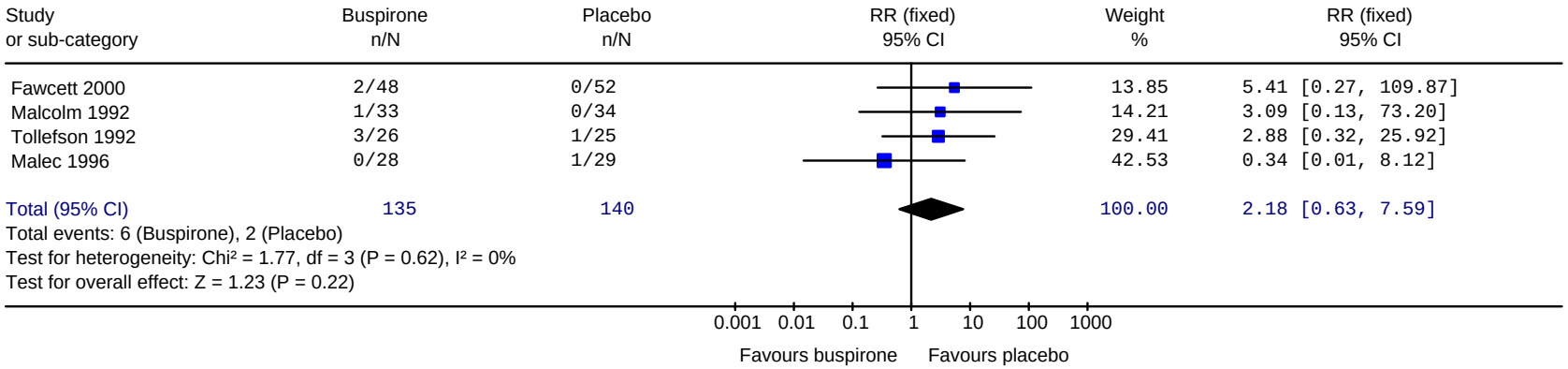

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Figure 6.6 *Antipsychotic or neuroleptic compared with placebo, number of participants completing treatment*

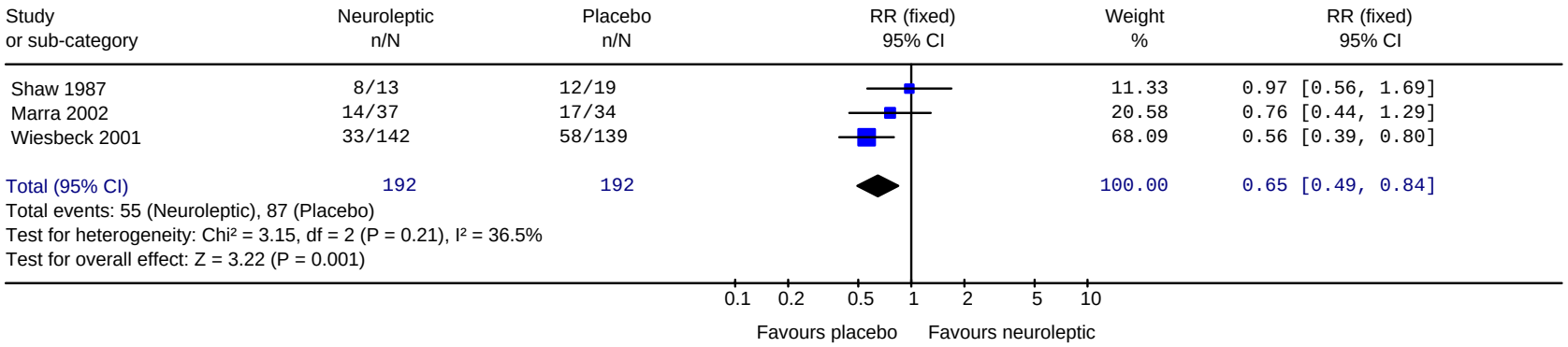

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Figure 6.7 *Antipsychotic or neuroleptic compared with placebo, number of participants abstinent at follow-up*

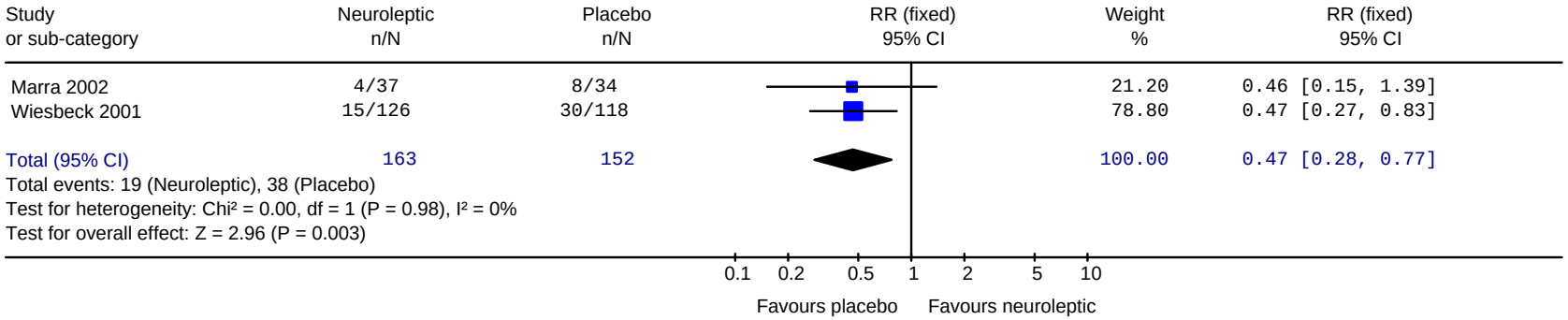

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Figure 6.8 *Antipsychotic or neuroleptic compared with placebo, days during study with drinking (%)*

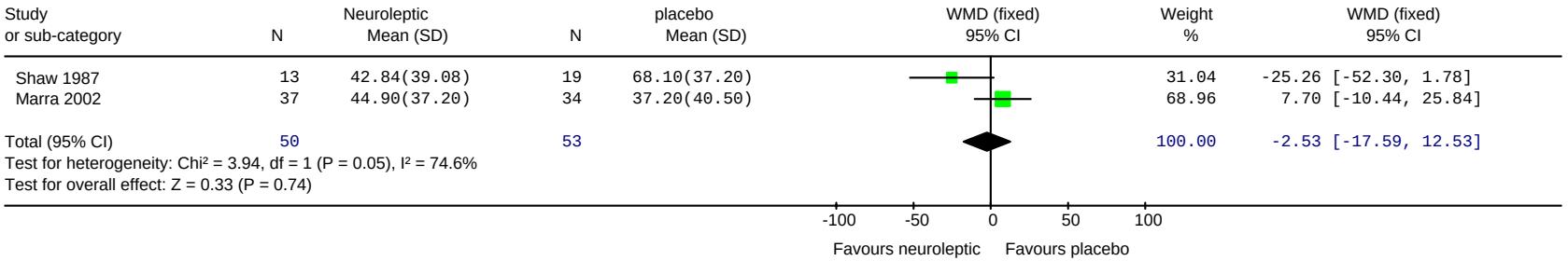

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Figure 6.9 *Antipsychotic or neuroleptic compared with placebo, number of participants discontinuing treatment due to adverse effects*

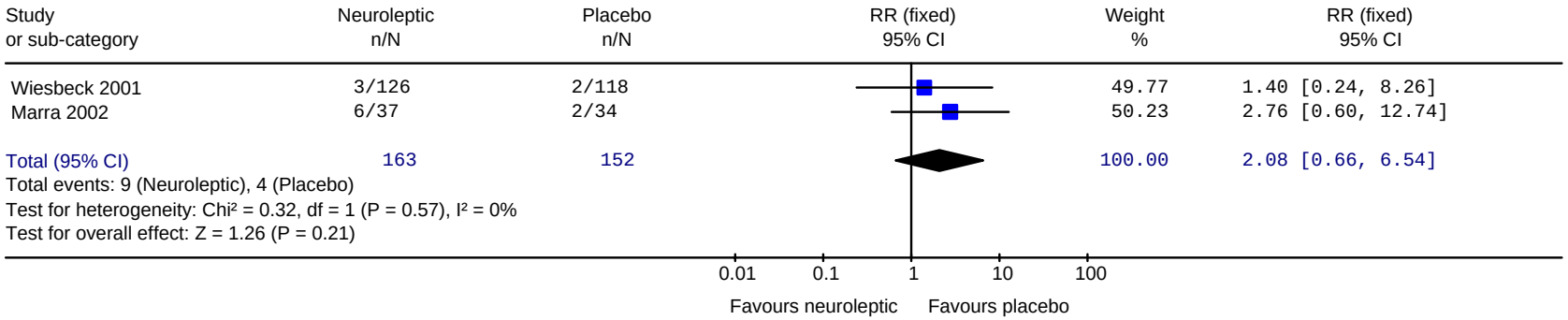

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Figure 6.10 *Anticonvulsant compared with placebo, number of participants completing treatment*

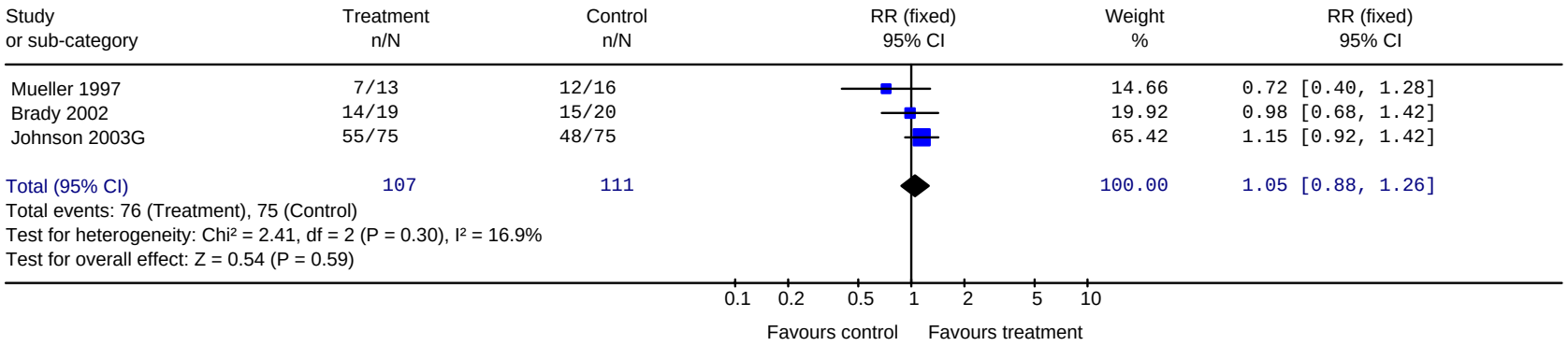

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Figure 6.11 Anticonvulsant compared with placebo, number of participants relapsing to heavy drinking during treatment

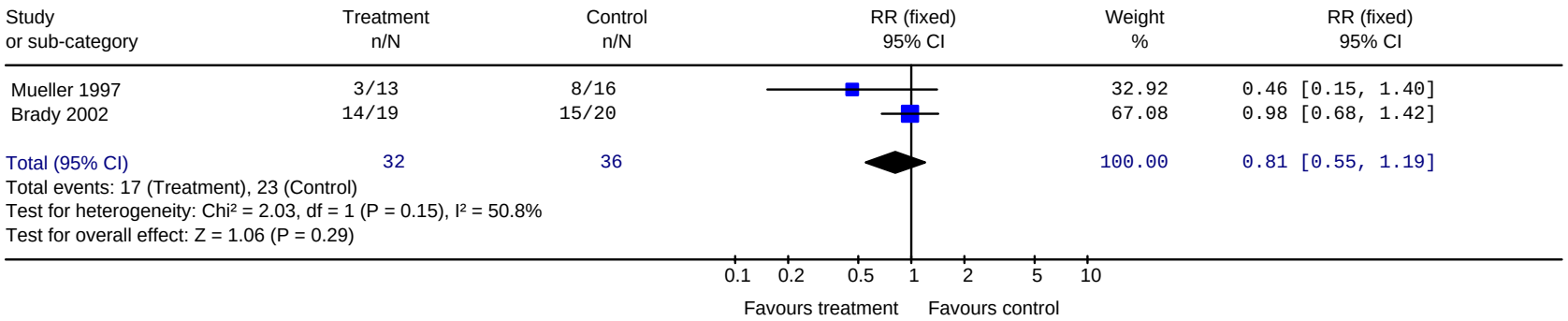

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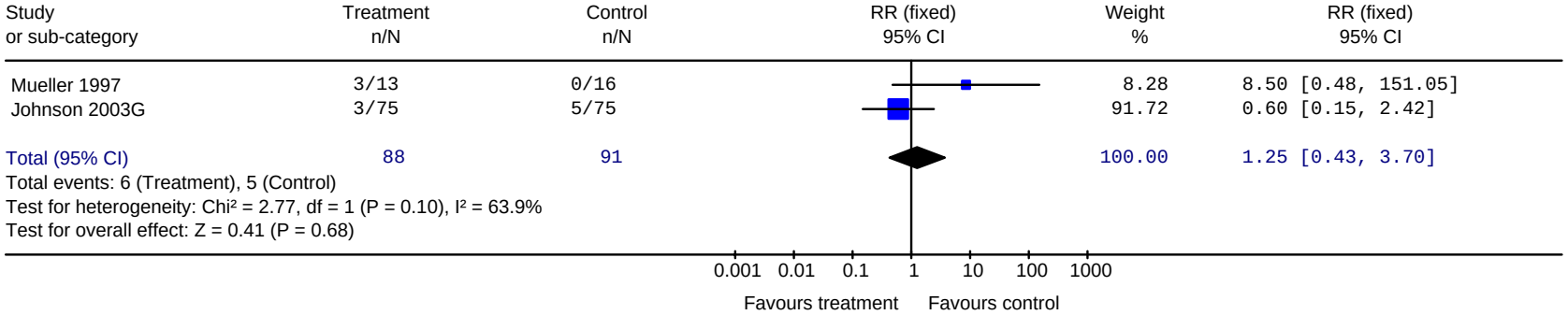
Figure 6.12 Anticonvulsants compared with placebo, number of participants discontinuing treatment due to adverse effects



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