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[Intervention Review]

Opioid antagonists with minimal sedation for opioid withdrawal

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ABSTRACT

Background

Managed withdrawal is a necessary step prior to drug-free treatment or as the endpoint of long-term substitution treatment.

Objectives

To assess the effects of opioid antagonists plus minimal sedation for opioid withdrawal. Comparators were placebo as well as more established approaches to detoxification, such as tapered doses of methadone, adrenergic agonists, buprenorphine and symptomatic medications.

Search methods

We updated our searches of the following databases to December 2016: CENTRAL, MEDLINE, Embase, PsycINFO and Web of Science. We also searched two trials registers and checked the reference lists of included studies for further references to relevant studies.

Selection criteria

We included randomised and quasi-randomised controlled clinical trials along with prospective controlled cohort studies comparing opioid antagonists plus minimal sedation versus other approaches or different opioid antagonist regimens for withdrawal in opioid-dependent participants.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

Ten studies (6 randomised controlled trials and 4 prospective cohort studies, involving 955 participants) met the inclusion criteria for the review. We considered 7 of the 10 studies to be at high risk of bias in at least one of the domains we assessed.

Nine studies compared an opioid antagonist-adrenergic agonist combination versus a treatment regimen based primarily on an alpha₂-adrenergic agonist (clonidine or lofexidine). Other comparisons (placebo, tapered doses of methadone, buprenorphine) made by included studies were too diverse for any meaningful analysis. This review therefore focuses on the nine studies comparing an opioid antagonist (naltrexone or naloxone) plus clonidine or lofexidine versus treatment primarily based on clonidine or lofexidine.

Five studies took place in an inpatient setting, two studies were in outpatients with day care, two used day care only for the first day of opioid antagonist administration, and one study described the setting as outpatient without indicating the level of care provided.

The included studies were heterogeneous in terms of the type of opioid antagonist treatment regimen, the comparator, the outcome measures assessed, and the means of assessing outcomes. As a result, the validity of any estimates of overall effect is doubtful, therefore we did not calculate pooled results for any of the analyses.

The quality of the evidence for treatment with an opioid antagonist-adrenergic agonist combination versus an α_2 -adrenergic agonist is very low. Two studies reported data on peak withdrawal severity, and four studies reported data on the average severity over the period of withdrawal. Peak withdrawal induced by opioid antagonists in combination with an adrenergic agonist appears to be more severe than withdrawal managed with clonidine or lofexidine alone, but the average severity over the withdrawal period is less. In some situations antagonist-induced withdrawal may be associated with significantly higher rates of treatment completion compared to withdrawal managed with adrenergic agonists. However, this result was not consistent across studies, and the extent of any benefit is highly uncertain.

We could not extract any data on the occurrence of adverse events, but two studies reported delirium or confusion following the first dose of naltrexone. Delirium may be more likely with higher initial doses and with naltrexone rather than naloxone (which has a shorter half-life), but we could not confirm this from the available evidence.

Insufficient data were available to make any conclusions on the best duration of treatment.

Authors' conclusions

Using opioid antagonists plus α_2 -adrenergic agonists is a feasible approach for managing opioid withdrawal. However, it is unclear whether this approach reduces the duration of withdrawal or facilitates transfer to naltrexone treatment to a greater extent than withdrawal managed primarily with an adrenergic agonist.

A high level of monitoring and support is desirable for several hours following administration of opioid antagonists because of the possibility of vomiting, diarrhoea and delirium.

Using opioid antagonists to induce and accelerate opioid withdrawal is not currently an active area of research or clinical practice, and the research community should give greater priority to investigating approaches, such as those based on buprenorphine, that facilitate the transition to sustained-release preparations of naltrexone.

PLAIN LANGUAGE SUMMARY

Use of opioid antagonists with minimal sedation to manage opioid withdrawal

Review question

We reviewed the evidence on the effects of opioid antagonists (naltrexone, naloxone) plus minimal sedation for managing withdrawal in people who are dependent on opioid drugs (for example, heroin or pharmaceutical opiates).

Background

Managed withdrawal, or detoxification, is a required first step for longer-term treatments of opioid dependence. The combination of uncomfortable symptoms and intense craving makes completing withdrawal difficult for most people. The rationale underlying the use of opioid antagonists to induce withdrawal is that a faster transition from dependence to abstinence might make completing withdrawal easier. This review considered the effects of treatment with opioid antagonists versus other approaches for withdrawal.

Search date

The evidence is current to December 2016.

Study characteristics

We identified 10 studies, including six randomised controlled trials (where people are randomly put into one of two or more treatment groups) and four prospective cohort studies (where participants could choose which treatment they received) involving 955 opioid-dependent participants. Four of the studies took place in the UK, three in the USA, two in Italy and one in Australia. Nine of the 10 studies compared treatment with an opioid antagonist (naltrexone or naloxone) plus an adrenergic agonist (clonidine or lofexidine) versus a regimen based on clonidine or lofexidine alone. Other comparisons (placebo, reducing doses of methadone, buprenorphine) made by included studies were too diverse for any meaningful analysis.

Four studies received some financial support from a pharmaceutical company.

Key results

We are uncertain whether peak withdrawal induced by opioid antagonists plus clonidine or lofexidine is more severe than withdrawal managed with clonidine or lofexidine alone, or whether the average severity over the withdrawal period is less, as the certainty of the evidence is very low.

Clinicians should warn people of the possibility of delirium in the first day of administration of naltrexone, particularly with higher doses (> 25 mg). People should also know that withdrawal will be moderately severe and that symptoms such as muscle aches, vomiting and diarrhoea, and insomnia are likely to persist despite medication.

Quality of the evidence

The studies included in this review were diverse and generally of very low quality. As a result there is considerable uncertainty about the value of approaches using opioid antagonists to induce opioid withdrawal as a means of managing withdrawal from opioid dependence.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Antagonist-adrenergic combination compared to adrenergic agonist for opioid withdrawal

Antagonist-adrenergic combination compared to adrenergic agonist for opioid withdrawal

Patient or population: opioid dependent adults

Setting: inpatient or outpatient

Intervention: antagonist-adrenergic combination

Comparison: adrenergic agonist

Outcomes	Impact	Nº of participants (studies)	Quality of the evidence (GRADE)
Peak withdrawal severity - Naltrexone	In 1 study peak withdrawal severity was similar for the 2 types of intervention. In the other study peak withdrawal was more severe in the group receiving antagonist-adrenergic combination.	184 (2 RCTs)	⊕⊕⊕⊕ Very low ^{a,b,c}
Peak withdrawal severity - Naloxone	This comparison reported by only 1 study, which found more severe withdrawal with naloxone-clonidine combination.	91 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,c}
Overall withdrawal severity - Naltrexone	No difference in overall withdrawal severity for 2 studies; in 1 study overall severity significantly less for antagonist-adrenergic combination.	256 (3 observational studies)	⊕⊕⊕⊕ Very low ^{b,c,d}
Overall withdrawal severity - Naloxone	This comparison reported by only 1 study, which found less severe overall withdrawal with naloxone-lofexidine combination.	49 (1 observational study)	⊕⊕⊕⊕ Very low ^{a,c}
Completion rate - Naltrexone	Completion rate with adrenergic agonist only ranged from 42% to 94%. Completion rate with antagonist-adrenergic agonist combination ranged from 73% to 95%	330 (4 RCTs)	⊕⊕⊕⊕ Very low ^{b,c,d,e}
Completion rate - Naloxone	Completion rate with adrenergic agonist only ranged from 28% to 94%. Completion rate with antagonist-adrenergic agonist combination ranged from 73% to 98%	463 (6 RCTs)	⊕⊕⊕⊕ Very low ^{b,c,e,f}

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio; OR: odds ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^aOne study at high risk of bias.

^bUnexplained inconsistency in results.

^cSmall studies.

^dTwo studies not randomised.

^eStudies at high risk of bias.

Opioid antagonists with minimal sedation for opioid withdrawal (Review)

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^fOne study not randomised.

BACKGROUND

Description of the condition

Dependence on opioid drugs is a major health and social issue in most societies. While only around 0.2% of adults report unsanctioned use of opioid drugs globally (Gowing 2015), these substances contribute more to the burden of disease than other illicit psychoactive drugs. The burden to the individual user and the community of opioid dependence arises from premature mortality and disability associated with dependent use (with the greatest impact in younger drug users; Gowing 2015), transmission of human immunodeficiency virus (HIV) and hepatitis C, healthcare costs, crime and law enforcement costs, and the less tangible costs of family disruption and lost productivity (Mark 2001).

Treatment is central to reducing the harms incurred by individuals and the community from opioid dependence. Managed withdrawal, or detoxification, by itself is not an effective treatment for dependence (Lipton 1983; Mattick 1996). Rates of withdrawal completion tend to be low, whereas rates of relapse to opioid use following detoxification are high (Broers 2000; Gossop 1989; Vaillant 1988). However, withdrawal remains a required first step for many forms of longer-term treatment such as residential rehabilitation and naltrexone maintenance (Kleber 1982). It may also represent the endpoint of an extensive period of substitution treatment such as methadone maintenance. As such, managed withdrawal is an essential part of an effective and comprehensive treatment system.

The signs and symptoms of the opioid withdrawal syndrome include irritability, anxiety, apprehension, muscular and abdominal pains, chills, nausea, diarrhoea, yawning, lacrimation, sweating, sneezing, rhinorrhoea, general weakness, and insomnia. Symptoms of opioid withdrawal usually begin two to three half-lives after the last opioid use, that is, 6 to 12 hours after taking short half-life opioids such as heroin and morphine, and 36 to 48 hours after taking long half-life opioids such as methadone. Following cessation of a short half-life opioid, symptoms reach peak intensity within two to four days, with most of the obvious physical withdrawal signs no longer observable after 7 to 14 days. As with onset of withdrawal, its duration also varies with the half-life of the opioid used and the history of regular use (Tetrault 2009). Opioid withdrawal is rarely life-threatening or associated with significant aberrations of mental state (Farrell 1994), but the combination of uncomfortable symptoms and intense craving makes completing withdrawal difficult for most people (Mattick 1996; Tetrault 2009).

Description of the intervention

For many years routine procedures involved suppression of withdrawal with methadone and gradual reduction of the methadone dose (Kleber 1982). This approach derived from observations that the withdrawal syndrome from methadone was milder, though longer, than from morphine. Methadone's high oral bioavailability, efficacy and long duration of withdrawal relief (24 to 36 hours) were additional factors that contributed to the widespread use of methadone in specialist withdrawal programmes.

Ambivalence to using a drug of dependence to treat opioid dependence, government restrictions on prescriptions, and

consumer dislike of the protracted nature of methadone withdrawal have all limited, to some extent, the use of methadone for managing opioid withdrawal (Farrell 1994). The α_2 -adrenergic agonist clonidine has been widely used as a non-opioid alternative for managing opioid withdrawal because of its capacity to ameliorate some signs and symptoms of opioid withdrawal (Gossop 1988), but it is associated with adverse effects of sedation and hypotension. Disatisfaction with methadone and clonidine have driven research into a variety of alternative approaches. This review focuses on approaches that involve administering opioid antagonists to induce withdrawal, in combination with medication to ameliorate withdrawal symptoms with minimal sedation.

How the intervention might work

The rationale underlying the use of opioid antagonists to induce withdrawal is that a faster transition from dependence to abstinence might increase rates of withdrawal completion. Initial experiments with opioid antagonists to induce withdrawal date back to the 1970s (Bearn 1999). While initial studies showed that the objective signs of withdrawal reduce rapidly with successive injections of naloxone (the only opioid antagonist available at that time), there was little further interest in the approach until clonidine became available. It seems likely that the use of antagonists alone was limited by poor acceptability to opioid users. Experience with the capacity of clonidine to ameliorate the signs and symptoms of opioid withdrawal led to studies investigating clonidine (and subsequently other α_2 -adrenergic agonists as well as other medications) plus opioid antagonists for managing opioid withdrawal.

Rapid detoxification techniques have seen further development with the administration of opioid antagonists in conjunction with sedation or anaesthesia to suppress people's awareness of withdrawal (Bearn 1999; Simon 1997). This approach of anaesthetic-assisted accelerated withdrawal is the subject of a separate Cochrane Review (Gowing 2010).

There is a complex range of variables that can potentially influence the course and subjective severity of withdrawal, including the type of opioid used, dose taken, concomitant use of other drugs including alcohol, duration of use, general physical health, and psychological factors, such as the reasons for undertaking withdrawal and fear of withdrawal (Farrell 1994; Phillips 1986; Preston 1985). Outcomes of a withdrawal episode may also be influenced by a prior period of substitution treatment, since such treatment is likely to result in a degree of stabilisation in health and social functioning that may facilitate successful withdrawal. Where information is available, we consider the influence of these variables.

The first, or acute, phase of withdrawal is followed by a period of six months or so of a secondary or protracted withdrawal syndrome. This protracted syndrome is characterised by a general feeling of reduced well-being that is reflected in measurable abnormal physiological functioning. During this phase, people may experience strong periodic cravings for opioids. The malaise associated with protracted abstinence is thought to be a major factor in relapse (Satal 1993). The protracted nature of withdrawal typically lengthens the recovery period, in which a range of factors – both social- and treatment-related – are at play. The types of intervention offered in the acute phase of withdrawal differ substantially from those offered afterwards to promote recovery

and prevent relapse. These may include psychological and lifestyle counselling, support groups, and pharmacological and medical treatment. We thus excluded this long-term aspect of treatment of opioid dependence from this review.

Why it is important to do this review

This review is one of a series relating to managing opioid withdrawal. Other reviews consider the use of α_2 -adrenergic agonists (Gowing 2016), opioid antagonists under heavy sedation or anaesthesia (Gowing 2010), buprenorphine to manage opioid withdrawal (Gowing 2017), tapered doses of methadone (Amato 2013), treatments in inpatient versus other settings (Day 2005), detoxification treatments for adolescents (Minozzi 2014), and psychosocial and pharmacological treatments for opioid detoxification (Amato 2011).

OBJECTIVES

To assess the effects of opioid antagonists plus minimal sedation for opioid withdrawal. Comparators were placebo as well as more established approaches to detoxification, such as tapered doses of methadone, adrenergic agonists, buprenorphine and symptomatic medications.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), quasi-randomised controlled clinical trials (CCTs) and prospective controlled cohort studies. To better control the risk of bias, it is desirable to limit systematic reviews to randomised and quasi-randomised controlled trials. However, because there are relatively few RCTs of antagonist-induced withdrawal, this review also includes prospective cohort studies.

Types of participants

Participants who were primarily opioid dependent, as defined by diagnostic criteria in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or the International Classification of Diseases (ICD) or by clinical assessment, who underwent managed withdrawal.

Types of interventions

Experimental interventions involved administering an opioid antagonist (naloxone, naltrexone or nalmefene) in the first three days of treatment or within three days of last opioid use to induce opioid withdrawal, in combination with medication to ameliorate the symptoms but with no or minimal sedation.

We excluded studies of interventions involving opioid antagonists under heavy sedation or anaesthesia. A separate Cochrane Review covers this approach (Gowing 2010).

Sedation differs from anaesthesia in that it is still possible to rouse the patient. In addition, the pharmacological agent used to induce sedation is usually different from anaesthetising agents. The studies included in this review involved either no sedation or light sedation as an adjunct to treatment to aid sleep or reduce anxiety.

Comparators involved tapered doses of methadone, an α_2 -adrenergic agonist, buprenorphine, symptomatic medications or placebo to manage withdrawal, or antagonist-based regimens differing in the type or dose regimen of opioid antagonist. For the purpose of this review, we define symptomatic medications as benzodiazepines, anti-emetics, anti-diarrhoeals, anti-psychotics, anti-spasmodics, muscle relaxants or non-opioid analgesics, administered in combination as needed, or according to a defined regimen.

Types of outcome measures

Primary outcomes

We assessed the included studies on the basis of a number of measures.

1. Severity of the withdrawal syndrome experienced (peak withdrawal scores and average withdrawal score over the duration of withdrawal treatment).
2. Duration of treatment.
3. Nature and incidence of adverse effects.
4. Completion of treatment.

The rationale for antagonist-induced withdrawal is that a faster transition from dependence to abstinence might increase rates of withdrawal completion. Hence we considered duration of treatment, in addition to rates of treatment completion to assess the extent to which the withdrawal process was shortened by the use of opioid antagonists.

It is difficult to differentiate treatment side effects from the signs and symptoms of opioid withdrawal. We have defined adverse effects as clinically significant signs and symptoms of opioid withdrawal (such as vomiting and diarrhoea) plus any incidents that are not typical components of the opioid withdrawal syndrome (delirium, hypotension, dry mouth).

Secondary outcomes

We also sought to assess data on the number of participants engaged in further treatment following completion of the withdrawal intervention. Managed withdrawal by itself is not an effective treatment for dependence. Hence we consider engagement in further treatment to be an outcome of interest. Engagement in naltrexone maintenance treatment is of particular interest as transition to naltrexone is the main reason for selecting antagonist-induced withdrawal.

Search methods for identification of studies

All searches included non-English language literature. We assessed studies with English abstracts on the basis of the abstract. If we thought the study was likely to meet inclusion criteria we translated it sufficiently to extract study methods and results.

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 11), MEDLINE (1946 to December week 1, 2016), Embase (1974 to 22 December 2016), PsycINFO (1806 to December week 3, 2016) and the Web of Science (1945 to 22 December 2016).

We developed a search strategy to retrieve references for all the Cochrane Reviews relating to the management of opioid withdrawal in one operation. We adapted this strategy to each of the major databases and the supporting platform. See [Appendix 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#); [Appendix 5](#).

Searching other resources

We also searched:

1. the reference lists of all relevant papers to identify further studies;
2. some of the main electronic sources of ongoing trials: ISRCTN registry (www.isrctn.com), ClinicalTrials.gov (clinicaltrials.gov/) and Trialsjournal.com (www.trialsjournal.com/);
3. conference proceedings likely to contain trials relevant to the review.

We contacted investigators to seek information about unpublished or incomplete trials.

Data collection and analysis

Selection of studies

One author (LG) assessed each potentially relevant study for inclusion according to the identified inclusion and exclusion criteria. All authors confirmed the inclusion and exclusion decisions.

Data extraction and management

We developed a form for recording data on the outcomes of interest, taking into account the different ways that studies might report such data. The outcomes specified in the form were:

- intensity of withdrawal (peak withdrawal score, overall withdrawal score, number with severe withdrawal, other data such as amount of adjunct medication);
- duration of withdrawal treatment (days in treatment, other data such as time of dropout);
- adverse effects (number experiencing any adverse effects, number with hypotensive effects, number with delirium, number withdrawn from treatment due to adverse effects, other);
- completion of treatment (number completing the scheduled period of treatment, number abstinent at completion of treatment);
- postdetoxification (number engaged in further treatment, other such as number abstinent at follow-up).

One author (LG) extracted key information, in consultation with other authors where there was any uncertainty. We contacted study authors if we required additional information to include studies in meta-analyses.

Assessment of risk of bias in included studies

We assessed the risk of bias of included studies according to the approach recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* and criteria developed by the Cochrane Drugs and Alcohol Group for assessing prospective observational studies ([Higgins 2011](#); [Appendix 6](#)).

We evaluated seven specific methodological domains (namely, sequence generation, allocation concealment, blinding of participants and providers, blinding of outcome assessor, incomplete outcome data, selective outcome reporting, and other issues). For each study we analysed the seven domains as reported in the study and provided a final judgement on the likelihood of bias in terms of low, high or unclear risk. We based these judgements on the criteria indicated in [Higgins 2011](#) and their applicability to the addiction field. We also incorporated criteria drawn from the Newcastle-Ottawa Scale for observational studies ([Wells 2010](#)). We operationalised the 'Risk of bias' tables for assessing RCTs, CCTs and prospective observational studies using this approach.

We considered blinding for subjective and objective outcomes separately. Lack of blinding is a source of serious risk of bias for subjective outcomes but is less significant with objective outcomes such as treatment completion and duration. We only considered incomplete outcome data for intensity of withdrawal and the nature and incidence of adverse effects. Retention in treatment (duration of treatment) and completion of treatment are frequently primary outcome measures in addiction research. See [Appendix 6](#) for a detailed description.

Details of the assessments of risk of bias are in the [Characteristics of included studies](#).

Measures of treatment effect

For dichotomous data (e.g. number completing treatment), we calculated risk ratios (RR), and for continuous data with consistent methods of measurement (e.g. time in treatment), we calculated mean differences (MD). For continuous data with differences between studies in the method of measurement (e.g. withdrawal scores), we calculated standardised mean differences (SMD). We used 95% confidence intervals (CI) to express the uncertainty in each result.

Unit of analysis issues

Where there were trials with multiple arms, we excluded any arms that involved an intervention not defined by the inclusion criteria for this review. Where there were trials with multiple arms relevant to meta-analyses, we considered whether it was appropriate to combine or separate the arms in analyses.

Assessment of heterogeneity

We assessed statistical heterogeneity using the Chi² test and its P value, by visual inspection of the forest plots and the I² statistic. We regarded heterogeneity as substantial if the I² was greater than 50% or the P value lower than 0.10 for the Chi² test for heterogeneity. Following guidance in [Higgins 2011](#), we distinguished the values to denote heterogeneity as unimportant (0% to 40%), moderate (30% to 60%), substantial (50% to 90%) and considerable (75% to 100%).

Data synthesis

We used Review Manager 5 for statistical analyses ([RevMan 2014](#)). In all analyses we used a random-effects model.

We suppressed the calculation of overall effects in all meta-analyses. Studies included in this review were heterogeneous in design (six randomised controlled trials and three prospective cohort studies) as well as in methods for assessing outcomes and

study findings. This heterogeneity made the validity of calculating overall effects doubtful.

Subgroup analysis and investigation of heterogeneity

This review also aimed to consider the following potential sources of heterogeneity through subgroup analyses, as this approach is considered to be associated with less risk of bias: drug of dependence and severity of dependence (as indicated by duration and level of use); poly-drug use; concurrent physical and psychiatric illness; precipitants to the withdrawal episode; the nature of the treatment setting; and the nature of adjunct treatment, including other medications to manage symptoms. Insufficient studies met the inclusion criteria to support such analyses.

Sensitivity analysis

We did not use risk of bias as a criterion for inclusion in the review. However, we intended to assess the impact of risk of bias through sensitivity analysis. This would have involved considering the overall estimate of effect when including or excluding studies at high risk of bias, but there were insufficient studies with data for such analyses to be undertaken.

Summary of findings table

We assessed the overall quality of the evidence for the primary outcome using the GRADE system. The Grading of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) developed a system for grading the quality of evidence that takes into account issues related to both internal and external validity, such as directness, consistency, imprecision of results and publication bias (Guyatt 2008; Guyatt 2011; Oxman 2004).

The 'Summary of findings' table presents the main findings in a transparent and simple tabular format. In particular, they provide key information concerning the quality of evidence, the magnitude of effect of the interventions examined and the sum of available data on the main outcomes.

The GRADE system uses the following criteria for assigning grades of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

- Low: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

We downgraded the certainty of evidence for the following reasons.

- Serious (–1) or very serious (–2) study limitation for risk of bias.
- Serious (–1) or very serious (–2) inconsistency between study results.
- Some (–1) or major (–2) uncertainty about directness (the correspondence between the population, the intervention, or the outcomes measured in the studies actually found and those under consideration in our systematic review).
- Serious (–1) or very serious (–2) imprecision of the pooled estimate (–1).
- Publication bias strongly suspected (–1).

We would have upgraded the certainty of evidence in observational studies for the following reasons.

- Strong evidence of association – significant relative risk of more than 2.0 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+ 1).
- Very strong evidence of association – significant relative risk of more than 5.0 (< 0.2) based on direct evidence with no major threats to validity (+ 2).
- Evidence of a dose response gradient (+ 1).
- All plausible confounders would have reduced the effect (+ 1).

RESULTS

Description of studies

Results of the search

This is an update of a Cochrane Review that was first published in 2000 under the title 'Opioid antagonists and adrenergic agonists for the management of opioid withdrawal'. We substantially updated the review in 2009 to incorporate a modified search strategy and changed the title to the current version.

In the present update, we again modified the search strategy, adding the Web of Science to the databases searched. We also removed the term 'Metabolic Detoxification, Drug' from the MEDLINE and CENTRAL searches as this term now maps to 'metabolic inactivation', which is not relevant to this review. We have also amended the review to meet current Cochrane requirements and included a flow diagram of the search process (Figure 1).

Figure 1. Flow diagram of literature search

As indicated in the flow diagram (Figure 1), we identified 3573 records relevant to the management of opioid withdrawal in general. Of these, we excluded 3269 on the basis of title and abstract. We assessed 304 full-text articles, excluding 244 without listing reasons and 47 records (37 studies) with reasons. Thirteen articles (10 studies) satisfied all the criteria to be included in the review. We had previously considered one of the included studies to be a secondary report of one of the other studies, but this update treats it as a separate, primary study. As a result, this update has 10 included studies, compared to 9 in the 2009 version. We did not identify any new studies relevant to the review published since 2009.

Included studies

Ten studies (13 reports) involving 955 participants met the inclusion criteria for this review (see [Characteristics of included studies](#)). In

total, 458 participants received treatment with an opioid antagonist to induce withdrawal.

Six of the studies were randomised controlled trials ([Arnold-Reed 2005](#); [Beswick 2003](#); [Gerra 1995](#); [Gerra 2000](#); [O'Connor 1997](#); [Umbricht 1999](#)), and three were prospective cohort studies with participants able to choose which treatment modality they received ([Bearn 2001](#); [Buntwal 2000](#); [O'Connor 1995](#)). In [McCambridge 2007](#), participants who did not consent to or were excluded from randomisation received methadone. We excluded this group from the review, so this study is effectively a randomised controlled trial.

Four studies received some financial support from a pharmaceutical company, four studies reported funding from government research grants, and two studies did not report funding arrangements.

Comparisons

Nine of the 10 studies that met the inclusion criteria compared an opioid antagonist-adrenergic agonist combination treatment with a regimen based primarily on either an α_2 -adrenergic agonist, clonidine (Arnold-Reed 2005; Gerra 1995; Gerra 2000; O'Connor 1995; O'Connor 1997), or on an analogue of clonidine: lofexidine (Bearn 2001; Beswick 2003; Buntwal 2000; McCambridge 2007).

Studies comparing clonidine and lofexidine as the primary medication have reported similar effectiveness in terms of ameliorating signs and symptoms of opioid withdrawal. However, lofexidine is associated with fewer hypotensive side effects than clonidine (Gowing 2016). Gerra 2001 directly compared clonidine and lofexidine as adjunct medications in withdrawal induced by opioid antagonists. Outcomes were similar for the clonidine- and lofexidine-based regimens in terms of craving levels, morphine metabolites in urine and dropout rate. However, participants receiving lofexidine showed lower levels of withdrawal symptoms, fewer mood problems, less sedation and less hypotensive effects. Overall we consider it reasonable to combine clonidine and lofexidine-based regimens in analyses but note the potential for heterogeneity in analyses of withdrawal severity and adverse effects.

Like most included studies, this review focuses primarily on an opioid antagonist-adrenergic agonist combination versus treatment based on an α_2 -adrenergic agonist for withdrawal.

Four studies compared antagonist-induced withdrawal with treatment regimens other than α_2 -adrenergic agonists: in Gerra 1995 the comparator was placebo; in Gerra 2000, tapered doses of methadone; and in O'Connor 1997 and Umbricht 1999, a regimen based primarily on buprenorphine, although in O'Connor 1997 participants in the buprenorphine group were transferred to 25 mg naltrexone plus clonidine on day 4 of treatment.

Because of the small number of studies investigating each of these comparisons, we could draw few conclusions. We did not include these comparisons in analyses, therefore, but we do discuss them where relevant to the review.

Treatment setting

Of the 10 studies that met the inclusion criteria, 5 carried out detoxification on a full inpatient basis (Bearn 2001; Beswick 2003; Buntwal 2000; McCambridge 2007; Umbricht 1999), and two used an outpatient setting with day care (Gerra 1995; Gerra 2000). Arnold-Reed 2005 and O'Connor 1995 used an outpatient setting with full day care for the first day of administration of naltrexone. O'Connor 1997 described the setting as outpatient without indicating whether it also involved an extended period of care on the first day of naltrexone treatment.

Four of the studies took place in the UK, three in the USA, two in Italy and one in Australia.

Participant characteristics

In 6 of the 10 studies that met the inclusion criteria, all participants were withdrawing from heroin. Participants in Umbricht 1999 were atypical for heroin users in the USA in that only 30% were injectors. Participants in four studies were using heroin, methadone or both (Bearn 2001; Beswick 2003; Buntwal 2000; McCambridge 2007).

All participants in these studies were stabilised on methadone for three days prior to detoxification. The mean stabilisation doses were 32.0, 34.3 and 40.0 mg/day, respectively, for Bearn 2001, Beswick 2003 and Buntwal 2000, whereas McCambridge 2007 did not report them.

Opioid use is more common amongst men than women. Consistent with this, between 55% and 82% of participants in the included studies were men. (Beswick 2003 did not report details of sex.)

Treatment regimens

Six of the 10 included studies used a treatment regimen based on naltrexone. Four of these studies administered an initial dose of 12.5 mg, given orally as a single dose on day 1 of treatment in O'Connor 1995 and O'Connor 1997 or day 2 in Gerra 1995 and Umbricht 1999. Buntwal 2000 used a similar starting dose (14 mg) but administered it orally in five divided doses over the first day of treatment. Participants also received 0.8 mg naloxone intramuscularly (IM) just prior to the first oral dose of naltrexone (1 mg). Authors reported using this approach in case of a severe withdrawal reaction.

The treatment protocols of three studies called for a maintenance dose of 50 mg/day naltrexone to be reached on day 3 (Gerra 1995; O'Connor 1995; O'Connor 1997). In Buntwal 2000 participants were scheduled to receive 50 mg naltrexone in two divided doses on day 4, with a single daily dose of 50 mg from day 5. Umbricht 1999 discontinued use of buprenorphine on day 4, with a 50 mg dose of naltrexone scheduled for day 5.

Six studies used naloxone to induce withdrawal. In Bearn 2001, Beswick 2003 and McCambridge 2007, participants received a single injection of 0.8 mg naloxone in the morning of days 3 to 6. Bearn 2001 offered participants 25 mg of oral naltrexone on day 7, the day after completion of withdrawal treatment. the following day. Beswick 2003 and McCambridge 2007 did not report the use of naltrexone.

Participants in Gerra 1995 received 0.2 mg naloxone intravenously (IV) on day 2, then 0.4 mg twice a day on days 3 and 4, before commencing naltrexone 50 mg/day on day 5. Participants in Gerra 2000 received repeated IV injections of 0.04 mg naloxone to a total of 0.4 mg/day on days 1 and 2 of treatment. This regimen of repeated injections was followed by 5 mg oral naltrexone at 6:00 pm on day 1 and 50 mg on day 2.

Arnold-Reed 2005 administered 0.8 mg naloxone in repeated doses until no significant withdrawal was apparent. After a rest of 20 to 30 minutes, participants received oral naltrexone in doses of 4 mg, 8 mg, 15 mg and 23 mg at 30-minute intervals.

Because the naltrexone and naloxone regimens differ substantially, we performed separate analyses for each of these opioid antagonists. We included Arnold-Reed 2005 in the naloxone group as this was the antagonist used to induce withdrawal.

Clonidine and lofexidine are usually administered orally. However, Gerra and colleagues used intravenous infusion in their two studies for administering clonidine as an adjunct to antagonist-induced withdrawal. In Gerra 1995 they infused 0.15 mg clonidine three times a day, giving a total dose of 0.45 mg/day as an adjunct to either naloxone- or naltrexone-based withdrawal. Gerra 2000 administered 0.15 mg clonidine six times a day in 100 mL saline for

two days, with an additional oral dose of 0.15 mg in the evening. This equates to 1.05 mg/day for two days. The dose was reduced to 0.15 mg orally three times on day 3 (0.45 mg/day).

Other than [Gerra 1995](#), all studies reported the use of a range of additional adjunct medications, including benzodiazepines, non-steroidal anti-inflammatory drugs (analgesics), anti-emetics and muscle relaxants.

Excluded studies

After a detailed assessment, we excluded 37 studies (47 reports) that we considered potentially relevant to the review (see [Figure 1](#) and [Characteristics of excluded studies](#)). The reasons for exclusion

were: no treatment comparison (20 studies), retrospective data collection (2 studies), case reports other than controlled study design (4 studies), insufficient data on outcomes defined for this review (9 studies), comparison of interventions other than those defined by the inclusion criteria (6 studies); and a primary focus on aspects other than the management of withdrawal (4 studies). We excluded some studies for more than one reason.

Risk of bias in included studies

For summary results of the 'Risk of bias' assessment across the included studies for each domain, see [Figure 2](#) and [Figure 3](#). The following sections summarise our judgements of the risk of bias for the included studies.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and providers (performance bias): Objective outcomes	Blinding of participants and providers (performance bias): Subjective outcomes	Blinding of outcome assessor (detection bias): Objective outcomes	Blinding of outcome assessor (detection bias): Subjective outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias: Comparability of cohorts	Other bias: Selection of comparison cohort	Other bias: Protection against contamination
Arnold-Reed 2005	?	?	+	-	+	-	-	-	+	+	+
Bearn 2001	-	-	+	-	+	-	+	+	+	+	?
Beswick 2003	?	+	+	+	+	+	+	+	+	+	+
Buntwal 2000	-	-	+	-	+	-	+	+	+	+	?
Gerra 1995	-	?	+	-	+	-	+	-	?	+	?
Gerra 2000	?	?	+	-	+	?	?	+	+	+	?
McCambridge 2007	+	?	+	+	+	+	+	+	+	+	+
O'Connor 1995	-	-	+	-	+	-	-	+	+	+	?
O'Connor 1997	?	?	+	?	+	?	+	+	+	+	?
Umbricht 1999	?	?	+	+	+	+	-	?	+	+	?

Allocation

We judged 4 of the 10 studies to be at high risk of selection bias due to random sequence generation (Bearn 2001; Buntwal 2000; Gerra 1995; O'Connor 1995). We judged three studies to be at high risk of selection bias due to allocation concealment (Bearn 2001; Buntwal 2000; O'Connor 1995). We considered that only McCambridge 2007 was at low risk of selection bias due to sequence generation, and only Beswick 2003 was at low risk for allocation concealment. We considered the risk of bias to be unclear in the remaining studies.

Blinding

We deemed the risk of performance and detection bias for objective outcomes (duration and completion of treatment) to be low for all studies, as these outcomes are unlikely to be affected by an awareness of group allocation. This section therefore focuses on the risk of performance and detection bias in relation to subjective outcomes (intensity of withdrawal, occurrence and severity of adverse effects).

We judged six studies to be at high risk of performance bias for subjective outcomes (Arnold-Reed 2005; Bearn 2001; Buntwal 2000; Gerra 1995; Gerra 2000; O'Connor 1995). We considered the risk of performance bias to be low in three studies (Beswick 2003; McCambridge 2007; Umbricht 1999), while it was unclear in O'Connor 1997.

We judged five studies to be at high risk of detection bias for subjective outcomes (Arnold-Reed 2005; Bearn 2001; Buntwal 2000; Gerra 1995; O'Connor 1995). In three studies, we considered the risk of detection bias to be low (Beswick 2003; McCambridge 2007; Umbricht 1999), while in two studies the risk was unclear (Gerra 2000; O'Connor 1997).

Incomplete outcome data

Retention (duration of treatment) and completion of treatment are primary outcome measures for opioid withdrawal interventions. Hence we only considered the risk of bias due to incomplete data for the outcomes of intensity of withdrawal and adverse effects.

We deemed three studies to be at high risk of bias due to incomplete outcome data (Arnold-Reed 2005; O'Connor 1995; Umbricht 1999). In Gerra 2000, the risk of bias due to incomplete outcome data was unclear, while it was low in the remaining studies.

Selective reporting

We judged two studies to have a high risk of bias due to selective reporting (Arnold-Reed 2005; Gerra 1995), while the risk was unclear in Umbricht 1999. We judged the risk to be low for the other studies.

Other potential sources of bias

We considered that seven studies were at unclear risk of other bias due to insufficient information on the comparability of the groups in Gerra 1995 and unclear protection against contamination of the groups in Bearn 2001, Buntwal 2000, Gerra 1995, Gerra 2000, O'Connor 1995, O'Connor 1997 and Umbricht 1999.

Effects of interventions

See: [Summary of findings for the main comparison](#) Antagonist-adrenergic combination compared to adrenergic agonist for opioid withdrawal

We present results in two sections. The first considers the major comparison between withdrawal induced by an opioid antagonist-adrenergic agonist combination and withdrawal managed primarily with an adrenergic agonist. The second section considers other comparisons. Within each section, we address the four types of outcome measures of interest: intensity of withdrawal syndrome, duration of withdrawal treatment, nature and incidence of adverse effects and completion of treatment and postdetoxification outcomes.

Antagonist-adrenergic agonist combination versus adrenergic agonist

Severity of withdrawal

The capacity for and strength of meta-analysis for this outcome was limited by:

- the small number of studies reporting data on the severity of withdrawal;
- different approaches to the assessment of the severity of withdrawal; and
- different ways of presenting the data.

The two studies by O'Connor and colleagues used the same rating instrument comprising 24 items, each graded for severity on a four-point scale (O'Connor 1995; O'Connor 1997). Gerra 1995 and Gerra 2000 used a scale that comprised nine items, primarily objective signs assessed by an observer and graded zero to five for severity. Bearn 2001, Beswick 2003 and Buntwal 2000 all used the Short Opiate Withdrawal Scale, which has 10 patient-reported items, each graded zero to three for severity (Gossop 1990). Arnold-Reed 2005 reported using part 1 of the Severity of Dependence Questionnaire to assess physical withdrawal. This scale usually asks respondents to consider a recent month and to assess the frequency with which they experienced 10 symptoms on waking, before the first dose of opiates. Presumably Arnold-Reed 2005 adjusted this scale to record symptoms at the time of assessment.

Studies also varied in the way they reported assessments of withdrawal severity. Gerra 1995 reported total mean (standard deviation (SD)) withdrawal scores at time points of 48 hours and 72 hours after commencement of detoxification. O'Connor 1995 reported the withdrawal score at admission only. However, they reported the amount of oxazepam used by participants in each group during detoxification as an alternative indicator of severity. O'Connor 1997 reported the mean (SD) overall withdrawal score and the mean (SD) peak withdrawal score. Buntwal 2000 and Bearn 2001 both undertook an area-under-the-curve analysis of daily withdrawal scores. Beswick 2003 and Gerra 2000 reported withdrawal scores only as graphs of mean daily scores and statistical analyses that were not suitable for inclusion in analyses. Arnold-Reed 2005 assessed physical withdrawal immediately prior to and postdetoxification.

Gerra 1995 presented graphs of withdrawal scores at 24 hours, 48 hours and 72 hours after commencement of treatment, and a table of mean withdrawal score at 48 hours and 72 hours. The 24-

hour assessment point was prior to the administration of opioid antagonist. The score at 48 hours was higher than that at 72 hours for all except the placebo group. On this basis we have taken the 48-hour score to represent the peak mean score, making it equivalent to the mean peak withdrawal scores reported in [O'Connor 1997](#). We present data from these studies in [Analysis 1.1](#). (Note that we have entered peak withdrawal data from [Gerra 1995](#) for the group treated with clonidine twice: once for comparison with the naltrexone-clonidine combination, and once for comparison with the naloxone-clonidine combination. As we did not calculate an overall result, there is no double-counting of these participants.)

Similarly, we have taken the data reported in [O'Connor 1995](#) on oxazepam use during detoxification to be an indicator of overall withdrawal severity. While substantially different in nature, the mean overall withdrawal scores from [O'Connor 1997](#) and the area-under-the-curve data from [Bearn 2001](#) and [Buntwal 2000](#) similarly indicate the overall severity experienced. These data are therefore presented together in [Analysis 1.2](#).

The studies that provide data on peak withdrawal severity provide quite different results ([Gerra 1995](#); [O'Connor 1997](#); [Analysis 1.1](#)). In [O'Connor 1997](#) peak withdrawal severity was similar for the two groups [28 (SD 13.1) versus 29.9 (SD 14.9), using a scale with a maximum possible score of 72]. However, in [Gerra 1995](#) peak withdrawal severity is significantly higher in the groups treated with an antagonist [22.88 (SD 11.06) for clonidine-naltrexone and 15.22 (SD 9.49) for clonidine-naloxone compared to 5.44 (SD 1.87) for the group treated with clonidine only, using a scale with a maximum possible score of 45].

[Gerra 1995](#) and [O'Connor 1997](#) differ in two aspects: the use of adjunct medications and the method for assessing withdrawal severity. These differences could explain the different results. Participants in [O'Connor 1997](#) rated withdrawal using a 24-item scale. This scale comprised a mix of signs and symptoms but was predominantly subjective. In [Gerra 1995](#) observers rated each of nine items (pulse rate, tremor, rhinorrhoea, mydriasis, aching muscles, shiver, vomiting, anxiety and insomnia) from zero to five for severity. Graphical presentation of withdrawal at 48 hours (the first day of administration of the opioid antagonist) indicated a significant contribution to the score by pulse rate, an item that was not rated in [O'Connor 1997](#).

[Gerra 2000](#) assessed withdrawal severity with the same rating system used in [Gerra 1995](#). Authors reported mean daily withdrawal scores graphically and in terms of statistical tests, not in a form that enabled data extraction. However, the graphs and statistical tests show no difference in peak withdrawal severity in the group treated with naloxone, naltrexone and clonidine compared to the group treated with clonidine alone. This finding suggests that the rating scale is not sufficient to explain the different results. The treatment regimen used in [Gerra 2000](#) differed from those used in [Gerra 1995](#) in the pattern of administration of naloxone and naltrexone, in the doses of clonidine, and in the use of adjunct medication. [Gerra 1995](#) did not report use of adjunct medications, while in [Gerra 2000](#), the group treated with naloxone and naltrexone received oxazepam, baclofen and ketoprofen over the two days of initial antagonist treatment. The authors note that this group, as a result, experienced more sedation and suggested that this countered the affective distress and dysphoria of withdrawal. [O'Connor 1995](#) also used adjunct medications on the first day of antagonist administration, in this case oxazepam, ibuprofen, ketorolac and

prochlorperazine. Hence it would seem likely that the differing result reported in [Gerra 1995](#) compared to [O'Connor 1997](#) and [Gerra 2000](#) reflects the use of adjunct medications.

[Beswick 2003](#) report mean daily withdrawal scores to be significantly lower for the group receiving naloxone and lofexidine compared to lofexidine alone, from day 5 (with the first injection of naloxone or placebo occurring on day 3). However, withdrawal was more pronounced in the naloxone-lofexidine group one hour after injection of naloxone on day 3.

The four studies that provide data indicating overall withdrawal severity also produced differing results ([Analysis 1.2](#)). Two studies found overall withdrawal severity to be significantly less in the groups treated with an opioid antagonist combined with an adrenergic agonist, compared to those treated primarily with the adrenergic agonist alone ([Bearn 2001](#); [Buntwal 2000](#)). However, data from [O'Connor 1995](#) and [O'Connor 1997](#) indicate no significant difference in overall withdrawal severity. These studies differed in:

- the opioid antagonist used ([Bearn 2001](#) used naloxone whereas the other three used naltrexone);
- the adrenergic agonist used ([Bearn 2001](#) and [Buntwal 2000](#) used lofexidine, while [O'Connor 1995](#) and [O'Connor 1997](#) used clonidine);
- the drug of dependence (in [Bearn 2001](#) and [Buntwal 2000](#) participants were stabilised on methadone for three days prior to withdrawal, while all participants in [O'Connor 1995](#) and [O'Connor 1997](#) were withdrawing from heroin);
- the means of assessing withdrawal severity ([Bearn 2001](#) and [Buntwal 2000](#) used the 10-item Short Opiate Withdrawal Scale with multiple assessments each day while [O'Connor 1997](#) used a 24-item scale completed once a day, and [O'Connor 1995](#) only provided data on the use of oxazepam);
- the means of calculating an overall statistic ([Buntwal 2000](#) and [Bearn 2001](#) undertook an area-under-the curve analysis while [O'Connor 1997](#) calculated the mean overall score, and [O'Connor 1995](#) provided mean overall doses of oxazepam); and
- study design ([O'Connor 1997](#) was a randomised controlled trial while the other studies were prospective cohort studies with participants able to choose the treatment received).

With only four studies, it was not possible to determine the extent to which these differences may be contributing to the variability in findings.

Duration of treatment

[Bearn 2001](#) provided detoxification as part of a structured programme of inpatient care. While not specifically stated, this is likely to also be the case in [Beswick 2003](#) and [Buntwal 2000](#), which involved the same inpatient facility and research team. As a consequence of this approach, the duration of treatment reflects both detoxification and after-care. There was no significant difference in any of these studies between the mean length of stay for the group receiving an antagonist-based regimen and the group receiving an adrenergic agonist only, with the mean length of stay ranging from 15 days for the lofexidine-naltrexone group in [Buntwal 2000](#) to 17.5 days for the lofexidine-naloxone group in [Beswick 2003](#). [McCambridge 2007](#) again involved the same inpatient facility and research team. In this study, participants in the lofexidine-naloxone group remained in treatment for an average 10.2 days

after detoxification, while those in the lofexidine-placebo group remained in treatment for an average 6.7 days.

Arnold-Reed 2005, O'Connor 1995, Gerra 1995 and Gerra 2000 did not report any data on the duration of treatment.

Nature and incidence of adverse effects

O'Connor 1995 reported that 4 of 68 (6%) participants treated with clonidine-naltrexone experienced mild to moderate delirium on the first day of treatment, compared to none of the 57 treated with clonidine only. One of the clonidine-only group experienced symptoms of hypotension, but this may have been due to an unrelated medical condition.

Bearn 2001 reported the development of a "transient, self-limiting confusional state" in 2 of 26 (8%) of those treated with naltrexone and lofexidine. Buntwal 2000 reported that one participant in the lofexidine group experienced dizziness and was given a lower dose. Authors reported no other adverse effects. In both these studies prochlorperazine was used as an adjunct medication. Although used as an anti-emetic, prochlorperazine has some anti-psychotic activity which may have helped reduce delirium in these studies.

Arnold-Reed 2005, Gerra 1995, Gerra 2000, McCambridge 2007 and O'Connor 1997 did not discuss adverse effects.

Completion of treatment and postdetoxification outcomes

Four studies reported data on treatment completion with naltrexone regimens versus an adrenergic agonist, and six studies with naloxone regimens, with data from Gerra 1995 included in both subcategories (Analysis 1.3). There is significant heterogeneity in these data. Two studies reported significantly higher rates of treatment completion for antagonist-induced withdrawal compared to regimens based on alpha₂-adrenergic agonists alone (Arnold-Reed 2005; O'Connor 1995), but in the remaining studies the difference was not significant.

Three of the nine studies providing data on treatment completion were prospective cohort studies and hence are at high risk of allocation bias (Bearn 2001; Buntwal 2000; O'Connor 1995). We consider Gerra 1995 to be at high risk of allocation bias, while the risk was unclear in O'Connor 1997 and Beswick 2003.

A further point of variability in the studies reporting data on completion of withdrawal was the definition of 'completion'. O'Connor 1995 and O'Connor 1997 defined completion by the administration of a 50 mg dose of naltrexone. Gerra 1995 did not define the endpoint, but they reported the number of participants who completed one week of treatment, at which time participants in all treatment groups were scheduled to have achieved a 50 mg dose of naltrexone. Gerra 2000 defined the endpoint as commencement of extended naltrexone treatment, which would also equate to achievement of a 50 mg dose of naltrexone.

The nature of the endpoint used in Gerra 2000 introduces some risk of bias favouring the naloxone-clonidine group. Participants in this group were scheduled to receive 50 mg naltrexone at the end of the second day of treatment, whereas participants in the clonidine group did not commence naltrexone until day 6. However, this schedule reflects the way in which these treatment regimens would be used in a context of routine service delivery, so the comparison is realistic.

Bearn 2001, Beswick 2003, Buntwal 2000 and McCambridge 2007 stated the number of participants who completed treatment without defining how this was determined. However, these studies took place in an inpatient setting with regular urine screening throughout treatment. Hence, it is likely that completion of withdrawal was determined on the basis of abatement of signs and symptoms of withdrawal along with opioid-negative urine tests.

Arnold-Reed 2005 did not define treatment completion.

The lack of studies at low risk of bias along with the heterogeneity in study design and findings makes any conclusions on relative rates of completion of detoxification treatment highly uncertain.

Bearn 2001 reported that 17 of 26 (65%) participants treated with the naloxone-lofexidine combination elected to take naltrexone on day 7. Naltrexone was continued for a mean of 4.5 days (range 1 to 17). Participants in the comparison lofexidine group were not routinely offered naltrexone.

Buntwal 2000 reported that participants in the group treated with the naltrexone-lofexidine combination continued to take naltrexone for a mean of 9.8 days (range 1 to 29). Three participants refused to continue naltrexone treatment while still receiving inpatient treatment.

Gerra 2000 reported that 15 of 32 participants (47%) treated with the clonidine-naloxone combination had relapsed to opioid use at six months after detoxification, compared to 18 of 32 (56%) from the clonidine group. However, they reported no difference in opioid-positive urine samples between the two groups at the six-month follow-up.

McCambridge 2007 reported that 9 of 45 (20%) in the lofexidine-naloxone group were abstinent at follow-up, compared to 4 of 46 (9%) in the lofexidine-placebo group. Follow-up occurred on average 8.7 months following discharge from treatment. These data are at some risk of attrition bias, with only 75% of study participants contacted at follow-up.

Gerra 1995, O'Connor 1995 and O'Connor 1997 did not report any information on postdetoxification outcomes.

Other comparisons

Four studies compared antagonist-induced withdrawal with other interventions.

- Placebo (Gerra 1995).
- Tapered doses of methadone (Gerra 2000).
- Buprenorphine (Umbricht 1999).
- Buprenorphine for three days followed by naltrexone plus clonidine (O'Connor 1997).

Severity of withdrawal

In Gerra 1995 withdrawal scores were significantly higher for the group receiving placebo than either of the groups treated with an opioid antagonist.

In Gerra 2000, peak withdrawal scores were higher and occurred later (day 12 compared to day 3) for the group treated with reducing doses of methadone compared to the group treated with the clonidine-naloxone combination.

Participants in [Umbricht 1999](#) received tapering doses of buprenorphine on days 1 to 4 of treatment (a total of 26 mg over the four days). In addition, one group received naltrexone 12.5 mg on day 2, increasing to 50 mg on day 5, while the comparison group commenced naltrexone 50 mg on day 8. Withdrawal severity was assessed primarily by observers (11 items, possible range of scores 0 to 30). These withdrawal ratings indicated that mean peak withdrawal severity was similar in the two groups but occurred at different times: 5.2 (SD 3.3) points on day 2 for the group commencing naltrexone on day 2, and 4.0 (SD 3.9) on day 8 for the group commencing naltrexone on day 8. Authors reported that withdrawal symptoms were of moderate intensity.

In [O'Connor 1997](#), overall and peak withdrawal scores were significantly lower in the group receiving buprenorphine prior to naltrexone on day 4 compared to the group commencing naltrexone on day 1.

Duration of treatment

The only study to report data on the duration of treatment was [Umbricht 1999](#). In this study the average length of stay was significantly shorter in the group commencing naltrexone on day 2: 5.9 (SD 0.5) days compared to 7.4 (SD 0.3) days for the comparison group that commenced naltrexone on day 8.

Nature and incidence of adverse effects

No studies reported data on adverse effects.

Completion of treatment and postdetoxification outcomes

In [Gerra 2000](#), 24 of 32 participants (75%) treated with the clonidine-naloxone combination accepted naltrexone treatment, compared with 9 of 24 (38%) of those treated with tapering doses of methadone. Six months after detoxification, 15 of 32 (47%) in the clonidine-naloxone group and 29 of 42 (69%) in the methadone group had relapsed to opioid use.

In [Umbricht 1999](#) there were more dropouts from the group administered naltrexone from day 2; 18 of 32 participants (56%) from this group completed the study, compared to 21 of 28 participants (75%) from the group administered naltrexone on day 8. However, in the absence of studies investigating similar treatment approaches, it is not possible to draw any conclusions as to the basis of this result. [Umbricht 1999](#) did not report any postdetoxification outcomes.

In [O'Connor 1997](#), the proportion of participants successfully completing detoxification was the same (81%) in the buprenorphine and antagonist-induced withdrawal groups.

DISCUSSION

Summary of main results

Severity of withdrawal

The small number of studies, the low quality of the evidence, variability in treatment regimen, and variability in the means of assessing and reporting withdrawal severity make it impossible to draw firm conclusions as to the nature and severity of withdrawal induced by an opioid antagonist-adrenergic agonist combination compared to withdrawal managed primarily with an α_2 -adrenergic agonist. However, the findings of the studies that met

the inclusion criteria for this review suggest that, when combined with an α_2 -adrenergic agonist, the severity of antagonist-induced withdrawal is, at worst, similar to withdrawal managed primarily with an adrenergic agonist, and at best it is less severe. This is probably because of earlier resolution of the signs and symptoms of withdrawal.

Initial administration of an opioid antagonist, particularly naltrexone, may be associated with a peak in withdrawal severity that is greater than the peak that occurs with adrenergic agonist-based regimens. This difference is most marked with the two antagonist-based regimens used in [Gerra 1995](#). This was the only study not to report the use of other adjunct medication in addition to the adrenergic agonist. The research team subsequently adopted the use of adjunct medication in [Gerra 2000](#) and considered the higher degree of sedation that resulted to be a factor in countering the "affective distress and dysphoria of withdrawal".

The type of opioid used prior to detoxification could potentially influence the nature and severity of withdrawal. The small number of studies involving participants withdrawing from methadone and the variability in treatment regimens and means of assessing withdrawal, prevented any exploration of the effect of the drug of dependence on withdrawal severity based on studies included in this review. However, [Bell 1999](#) reports the use of naltrexone with adjunct medication (flunitrazepam, clonidine, octreotide, buscopan, quinine) to induce withdrawal in 15 participants withdrawing from heroin and 15 withdrawing from methadone. On day 7, participants rated the acceptability of the treatment on a 10-point Likert scale where zero was completely acceptable. Of those withdrawing from heroin, 82% (compared to 60% of those withdrawing from methadone) rated acceptability as less than five, indicating the procedure was more acceptable to those withdrawing from heroin compared to those withdrawing from methadone. On the same day, investigators asked participants to rate severity on a 10-point Likert scale where zero is minimally severe. Of those withdrawing from heroin, 27% (compared to 7% of those withdrawing from methadone) rated severity as less than five. Participants withdrawing from methadone experienced more gastrointestinal symptoms than those withdrawing from heroin. These data suggest less severe symptoms in the cohort withdrawing from heroin, compared to those withdrawing from methadone.

Duration of treatment

Data reported on this aspect were minimal. Consequently it is currently not possible to determine whether antagonist-induced withdrawal reduces the duration of withdrawal treatment.

Nature and incidence of adverse effects

In addition to vomiting and diarrhoea, some opioid-dependent people may experience a degree of delirium or confusion following administration of an opioid antagonist. Only two of the studies included in this review reported delirium. However, six studies that did not meet the criteria for inclusion in this review reported delirium as an adverse effect of antagonist-induced withdrawal ([Bell 1999](#); [Charney 1986](#); [Golden 2004](#); [London 1999](#); [Senft 1991](#); [Silverstone 1992](#)). Other studies have reported delirium or confusion after accidental ingestion of naltrexone by people who are opioid dependent ([Boyce 2003](#); [Galloway 1993](#); [Mannelli 1999](#); [Tornabene 1974](#)). In all cases the opioid antagonist administered

was naltrexone, and in most cases the initial dose of naltrexone was 25 mg or greater. There are no reports of delirium as an adverse effect of treatment regimens involving low doses of naloxone, suggesting that the risk of delirium may be related to the dose and duration of action of the opioid antagonist. While the risk of delirium is probably reduced by the use of lower doses of naltrexone, it can still occur ([Charney 1986](#); [Silverstone 1992](#)). The use of other drugs in addition to opioids, particularly benzodiazepines, is one possible risk factor ([Bell 1999](#); [Golden 2004](#)).

Adverse effects of α_2 -adrenergic agonists (dizziness, sedation, dry mouth) are likely to be experienced in the first few days of treatment when high doses of drug are required to ameliorate the withdrawal symptoms induced by the opioid antagonist. However, it appears that hypotension necessitating cessation of adrenergic agonist may be rare when the drug is administered in combination with an opioid antagonist, and even less likely with lofexidine than with clonidine, although [London 1999](#) reported that 1 of 20 participants had a late hypotensive reaction to withdrawal induced by naltrexone administered in conjunction with lofexidine and a range of other adjunct medications.

[Bell 1999](#) reported that vomiting was common with antagonist-induced withdrawal, but participants treated with the drug octreotide did not require fluid replacement. [London 1999](#), in their review of 20 cases of antagonist-induced withdrawal, reported that two participants experienced severe vomiting, and five had severe diarrhoea. (The opioid drug, or drugs, from which participants were withdrawing was not specified.)

The studies included in this review did not report any other serious adverse effects.

While a number of studies considered for this review provided antagonist-based treatment in an outpatient setting, all provided extended care at least for the first day on which the opioid antagonist was administered. This reflects the desirability of providing a high level of monitoring and support until patients are comfortable and development of delirium is considered unlikely (at least several hours after administration of the antagonist).

Completion of treatment and postdetoxification outcomes

The use of naltrexone maintenance in relapse prevention treatment for opioid-dependent people has been limited by two factors: low rates of commencement on naltrexone, and low rates of retention in treatment ([Minozzi 2006](#); [Tucker 2000](#)). Antagonist-induced withdrawal with minimal sedation is seen as one way in which rates of commencement on naltrexone might be increased.

The data reported in this review suggest that in some situations, antagonist-induced withdrawal may be associated with significantly higher rates of treatment completion compared to regimens based primarily on an adrenergic agonist, but results are inconsistent, and the extent of any benefit is highly uncertain.

As indicated in the Results, the studies varied in their definitions of treatment endpoint, with only some studies clearly reporting the number of participants achieving maintenance doses of naltrexone, and hence initiating naltrexone maintenance treatment. Hence it is not possible, on the basis of the studies included in this review, to determine whether antagonist-induced withdrawal helps to increase rates of commencement in naltrexone

maintenance treatment. However, any such benefit appears to be relatively short-lived, with [Buntwal 2000](#) and [Bearn 2001](#) reporting the mean duration of naltrexone treatment to be less than 10 days, and [Gerra 2000](#) reporting no differences in opioid-positive samples at a six-month follow-up for the group detoxified by an antagonist-based regimen compared to one based on an adrenergic agonist. [McCambridge 2007](#) did not report data on engagement in naltrexone maintenance treatment but did report a higher rate of abstinence at follow-up for the group receiving antagonist-based treatment. The authors considered the difference in rates of abstinence at follow-up to be generally associated with the length of stay postdetoxification rather than the detoxification procedure.

Treatment regimen

A notable feature of the studies included in the review is the variability in the treatment regimens based on opioid antagonists to induce withdrawal. Points of variability include:

- the use of naloxone or naltrexone, or a combination of both, to induce withdrawal;
- initial dose, frequency of administration, and rate of increase of the dose of opioid antagonist;
- the medication used to ameliorate the signs and symptoms of withdrawal (most commonly clonidine or lofexidine but also buprenorphine); and
- the nature and extent of use of additional adjunct medications.

Due to this degree of variability, it is not possible to describe a standard regimen for this form of antagonist-induced withdrawal. The small number of studies also prevented sub-comparisons to determine the effect of the above variations in treatment protocol.

It is of interest that two of the most recent studies adopted an approach of repeated small doses of opioid antagonist with a 50 mg dose of naltrexone achieved on day 4 and the end of day 2 (in [Buntwal 2000](#) and [Gerra 2000](#), respectively). The authors of these studies do not report the reasoning behind their choice of dose regimen; presumably clinical experience with opioid antagonists was a factor. This approach is also reminiscent of some of the earliest studies of antagonist-induced withdrawal (e.g. [Charney 1986](#); [Kleber 1987](#)).

[Arnold-Reed 2005](#), [Bearn 2001](#), [Beswick 2003](#) and [Gerra 2000](#) used repeated doses of naloxone to induce withdrawal. [Bearn 2001](#) and [McCambridge 2007](#) administered a single dose of 0.8 mg IM in the mornings of the first three days after cessation of methadone. This antagonist regimen reduced the overall withdrawal severity compared to treatment with an adrenergic agonist alone, but Bearn and colleagues note that the response to naloxone was variable. Based on the graph of mean withdrawal score from [Bearn 2001](#), the difference in overall withdrawal severity is unlikely to be clinically significant. The authors themselves note that the "addition of naloxone did not confer substantial benefit over lofexidine monotherapy".

In [Gerra 2000](#), multiple doses of naloxone 0.04 mg IV were administered to a total of 0.4 mg/day for two days. Naltrexone was commenced with a single 5 mg dose on day 1, after the doses of naloxone were completed, and it increased to 50 mg by day 3. Graphs of mean daily withdrawal scores in [Gerra 2000](#) show peak withdrawal severity on day 2. Gerra and colleagues note that mean

withdrawal scores were higher for the group treated with opioid antagonist compared to those receiving a clonidine-based regimen, but the difference was not statistically significant. This suggests that low doses of naloxone, while apparently having little effect on the course of withdrawal, may help to prepare opioid-dependent people to tolerate subsequent doses of naltrexone.

Overall completeness and applicability of evidence

The studies included in this review provided some information on the severity of withdrawal induced by opioid antagonists with minimal sedation, but this information remains scarce. There is little information on the nature of withdrawal signs and symptoms experienced by patients, the duration of significant symptoms, the overall severity, or the acceptability to patients of this approach to the management of opioid withdrawal. The studies included in this review were too small to provide accurate information on the risks of adverse effects associated with antagonist-induced withdrawal. It remains uncertain to what extent the type and dose of opioid antagonist, the use of adjunct medications, the person's drug use history (including use of heroin or methadone) may contribute to both withdrawal severity and adverse effects.

Buprenorphine has been shown to be more effective than clonidine or lofexidine for managing opioid withdrawal (Gowing 2017). Eight of the studies included in this review compared antagonist-induced withdrawal with a regimen based primarily on an α_2 -adrenergic agonist, and only two studies used buprenorphine as a comparison. Some authors have suggested that due to its pharmacological properties, buprenorphine can facilitate the transition from dependent opioid use to naltrexone maintenance treatment (O'Connor 1997). However, evidence of the effectiveness of antagonist-induced withdrawal relative to withdrawal managed with buprenorphine is scarce and inconclusive.

Quality of the evidence

The available studies of antagonist-induced withdrawal with minimal sedation are relatively small and have design limitations with consequent risk of bias. These limitations, together with diversity in the nature of outcomes and findings reported, make it impossible to draw firm conclusions. Both the extent of potential benefits and the risk of harms associated with antagonist-induced withdrawal remain uncertain.

Potential biases in the review process

The review draws together studies of diverse design and some risk of internal bias. The review itself is consequently exposed to some risk of bias.

AUTHORS' CONCLUSIONS

Implications for practice

The use of an opioid antagonist (naltrexone, naloxone or both) to induce withdrawal in combination with an α_2 -adrenergic agonist (clonidine or lofexidine) to ameliorate the signs and symptoms of withdrawal is a feasible approach to managing opioid withdrawal. Most studies investigating this approach have involved participants withdrawing from heroin, but the approach is probably also feasible for withdrawal subsequent to administration of low to moderate doses of methadone (around 40 mg/day or less).

The peak withdrawal severity induced by an opioid antagonist in combination with an α_2 -adrenergic agonist may be more severe than withdrawal managed with clonidine or lofexidine alone, while the average severity over the withdrawal period is less. However, we are uncertain of this result because we assessed the quality of the evidence as very low. If the overall severity is less, this is probably because signs and symptoms of withdrawal resolve more quickly.

Some people may experience vomiting, diarrhoea and delirium following administration of the first dose of opioid antagonist, particularly when naltrexone is commenced at doses of 25 mg or more. To manage such side effects it is desirable to provide a high level of monitoring and support for several hours following administration of the first dose of opioid antagonist. Adjunct medications, in addition to adrenergic agonists, are likely to be required to manage the period of peak withdrawal induced by the opioid antagonist.

Clinicians should warn people of the possibility of delirium in the first day of administration of naltrexone. People should also know that withdrawal will be moderately severe and that symptoms such as muscle aches, vomiting and diarrhoea, and insomnia are likely to persist despite medication.

The data reported in this review suggest that in some situations antagonist-induced withdrawal may be associated with significantly higher rates of treatment completion than regimens based primarily on an adrenergic agonist, but results are inconsistent, and the extent of any benefit is highly uncertain. There are insufficient data to determine whether opioid antagonists plus adrenergic agonists reduce the duration of withdrawal treatment or increase rates of transfer to maintenance treatment with an opioid antagonist.

Implications for research

The evidence is insufficient to establish a detailed picture of the nature of the opioid withdrawal syndrome induced by opioid antagonist treatment compared to that managed with an adrenergic agonist alone. Information is particularly lacking for withdrawal from methadone. There are a number of aspects of treatment regimens based on opioid antagonists for managing opioid withdrawal that would need to be explored for this approach to become established as an effective approach. However, it is notable that in undertaking this review update we did not identify any new studies to include compared to the 2009 version. Clearly, this is not an active area of research, and we believe the approach is not being used in clinical practice.

Buprenorphine has been shown to be more effective than clonidine or lofexidine for managing opioid withdrawal (Gowing 2017), and buprenorphine may facilitate the transition from dependent opioid use to naltrexone maintenance treatment (O'Connor 1997). There is active research in this area, particularly related to the use of buprenorphine to aid the transition to sustained-release preparations of naltrexone (Mannelli 2014; Mogali 2015; Sullivan 2015). The rationale for sustained-release preparations of naltrexone is that they overcome the issue of patient adherence to the treatment regimen that has been experienced with oral naltrexone (Sullivan 2007). Facilitating the transition from opioid dependence to naltrexone maintenance is particularly important with sustained-release preparations, as any prolonged experience

of opioid withdrawal would be likely to make this treatment approach unacceptable to people who are opioid dependent. It appears that this is the direction currently being taken by research. Given that the main reason for considering using opioid antagonists to induce withdrawal would be to initiate naltrexone maintenance treatment, we consider this direction to be appropriate.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Arnold-Reed 2005

Methods	Randomised controlled trial
Participants	<p>Setting: day surgery or mixed inpatient and outpatient, community-based treatment, Australia</p> <p>N = 80 heroin dependent by DSM-IV, similar on age, sex, socioeconomic status, and total length of heroin use</p> <p>Average age: 30.6 years</p> <p>64% men</p> <p>95% used heroin at least once daily, 6.2% reported using other opioids in addition to heroin, 91% used tobacco, 64% cannabis, 51% alcohol, 45% tranquilizers, 26% amphetamines; 57.8% known to be unemployed</p>

Arnold-Reed 2005 (Continued)

Interventions	<p>Group 1 (n = 41): naloxone (IV) 800 µg in repeated doses plus clonidine, under midazolam sedation; when no withdrawal apparent, oral naltrexone in increasing doses at 30-minute intervals. Day surgery procedure at private, community-based clinic</p> <p>Group 2 (n = 39): clonidine, oral 75-150 µg/day on inpatient (5-7 days) or outpatient (7-10 days) basis at a community-based public facility</p>
Outcomes	Number commencing and number completing detoxification, number commencing naltrexone treatment, number abstinent from heroin in 4 weeks postdetoxification
Notes	<p>Physical withdrawal assessed immediately prior to, and immediately postdetoxification, using part 1 of the Severity of Dependence Questionnaire</p> <p>Source of funding: Department of Health (Western Australia)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...subjects were randomly assigned to one of two detoxification treatment groups." Method of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding of participants and providers (performance bias) Objective outcomes	Low risk	No blinding, but these outcomes considered unlikely to be affected by knowledge of group allocation
Blinding of participants and providers (performance bias) Subjective outcomes	High risk	No blinding, and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	No blinding, but measurement of these outcomes unlikely to be influenced by lack of blinding
Blinding of outcome assessor (detection bias) Subjective outcomes	High risk	No blinding, and the measurement of these outcomes is likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Data on patient satisfaction with detoxification, physical withdrawal scores and craving reported only for participants who completed detoxification, and there was a significant difference in rates of completion for the 2 groups (87.8% vs 28.2%).
Selective reporting (reporting bias)	High risk	Most outcomes (withdrawal severity, acceptability of treatment, engagement in further treatment) only reported for those who completed detoxification
Other bias: Comparability of cohorts	Low risk	Random allocation and groups similar on baseline characteristics
Other bias: Selection of comparison cohort	Low risk	Groups drawn from same population

Arnold-Reed 2005 (Continued)

Other bias: Protection
against contamination

Low risk

2 groups were treated by different personnel in different settings: in private and in public, community-based treatment facility

Bearn 2001

Methods	Prospective cohort study; treatment allocation open and by participant choice
Participants	<p>Setting: inpatient, dedicated unit in psychiatric teaching hospital, UK</p> <p>N = 49 opioid dependent by DSM-IV; groups similar in clinical characteristics, except higher levels of alcohol consumption in group 1.</p> <p>4 participants allocated to group 1 decided not to continue with the regimen and switched to group 2; analysis based on n= 26 (group 1) and n = 23 (group 2)</p> <p>Average age 32</p> <p>71% men</p>
Interventions	<p>Stabilised for 3 days on mean 32 mg (group 1) or 33 mg (group 2) methadone; diazepam prescribed for concurrent alcohol or benzodiazepine dependence</p> <p>Methadone stopped abruptly, then</p> <p>Group 1 (n = 30): lofexidine 2 mg/day for 2 days, plus naloxone 0.8 mg in morning days 3-6; or</p> <p>Group 2 (n = 19): lofexidine, 1.8 mg day 1, then 1 mg twice a day for 5 days, 0.6 mg twice on day 7.</p> <p>All offered 25 mg naltrexone day 7</p> <p>Structured care programme targeted at relapse prevention as adjunct before and during detoxification. Up to 28 days inpatient care</p>
Outcomes	Average withdrawal severity (AUC of mean withdrawal score), days in treatment, participants experiencing hypotension, transient delirium, number completing scheduled treatment
Notes	<p>Withdrawal assessed by Short Opiate Withdrawal Scale. Urine screening throughout study.</p> <p>Source of funding: Britannia Pharmaceuticals, UK</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Treatment allocation ... was by patient choice."
Allocation concealment (selection bias)	High risk	Quote: "Treatment allocation was open and was by patient choice."
Blinding of participants and providers (performance bias) Objective outcomes	Low risk	No blinding, but these outcomes considered unlikely to be affected by awareness of group allocation
Blinding of participants and providers (performance bias)	High risk	No blinding, and these outcomes are likely to be influenced by lack of blinding

Bearn 2001 (Continued)

Subjective outcomes

Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	No blinding, but measurement of these outcomes unlikely to be influenced by lack of blinding
Blinding of outcome assessor (detection bias) Subjective outcomes	High risk	No blinding, and measurement of these outcomes likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Level of missing data insufficient to affect outcomes
Selective reporting (reporting bias)	Low risk	None apparent
Other bias: Comparability of cohorts	Low risk	Groups similar on clinical characteristics at baseline
Other bias: Selection of comparison cohort	Low risk	Experimental and control groups drawn from same population
Other bias: Protection against contamination	Unclear risk	It is possible that communication between groups could have occurred.

Beswick 2003

Methods	Randomised controlled, double-blind trial
Participants	Setting: inpatient treatment in drug and alcohol unit, UK N = 89, opioid dependent by DSM-IV. Severity of dependence marginally less in naloxone group, groups otherwise similar Gender and age not reported.
Interventions	Stabilised for 3 days on mean 34.3 mg/day (group 1, n = 45) and 37.8 mg/day (group 2, n = 44) methadone Methadone stopped abruptly, then lofexidine 1.8-2.0 mg/day as 3 doses, combined with naloxone 0.8 mg (group 1) or placebo solution by injection days 3-6 (group 2)
Outcomes	Mean length of stay and number completing treatment, mean withdrawal and craving scores (as graphs and results of statistical tests), number of injections received, use of additional medication
Notes	Withdrawal assessed by Short Opiate Withdrawal Scale. Daily urine screening. Source of funding: Charitable trust and Britannia Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "subjects ... were randomly assigned..."; method of sequence generation not reported

Beswick 2003 (Continued)

Allocation concealment (selection bias)	Low risk	Double-blind stated, with medication prepared by pharmacy
Blinding of participants and providers (performance bias) Objective outcomes	Low risk	Quote: "Antagonist medication was delivered directly from the in-house pharmacy for each individual patient in order to preserve the double-blind"
Blinding of participants and providers (performance bias) Subjective outcomes	Low risk	Quote: "Antagonist medication was delivered directly from the in-house pharmacy for each individual patient in order to preserve the double-blind"
Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	Quote: "Antagonist medication was delivered directly from the in-house pharmacy for each individual patient in order to preserve the double-blind"
Blinding of outcome assessor (detection bias) Subjective outcomes	Low risk	Quote: "Antagonist medication was delivered directly from the in-house pharmacy for each individual patient in order to preserve the double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No significant difference in retention rates of the 2 groups
Selective reporting (reporting bias)	Low risk	None apparent
Other bias: Comparability of cohorts	Low risk	Random allocation and groups stated to be similar at baseline
Other bias: Selection of comparison cohort	Low risk	Groups drawn from same population
Other bias: Protection against contamination	Low risk	Communication between groups could have occurred, but blinding would be expected to nullify the effect

Buntwal 2000

Methods	Prospective cohort study. Naltrexone/lofexidine group recruited pre-admission; lofexidine-only group recruited from routine admissions selecting this regimen rather than tapered methadone
Participants	<p>Setting: inpatient, UK</p> <p>N = 22, opioid dependent by DSM-IV, withdrawing from heroin or methadone or both. More women in group 2; groups otherwise similar in demographics and drug use</p> <p>Average age 31</p> <p>4/11 women in group 1, 0/11 women in group 2</p> <p>Co-dependence on benzodiazepines, alcohol or cocaine were exclusion criteria</p>
Interventions	<p>Stabilised for 3 days on mean 40.0 mg (group 1) and 34.72 mg (group 2) methadone</p> <p>Group 1 (n = 11): naloxone 0.8 mg IM day 1 only; naltrexone, 14 mg in 5 doses day 1, increasing to 50 mg day 4, then single dose 50 mg/day; lofexidine, 2.0 mg day 1, tapered to 0.8 mg day 4 then ceased</p>

Buntwal 2000 (Continued)

Group 2 (n = 11): lofexidine, 1.8 mg day 1, 2.0 mg days 2-6, 1.0 mg day 7.

Both groups able to request additional 0.4 mg lofexidine

Outcomes	Overall withdrawal severity (AUC analysis of withdrawal score), number requesting extra lofexidine, days in treatment, number with hypotensive side effects, number completing scheduled treatment
Notes	Short Opiate Withdrawal Scale completed by participants 4 times daily for 7 days, then once daily. Urine screening 3 times a week Source of funding: Britannia Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Patient choice
Allocation concealment (selection bias)	High risk	Open label
Blinding of participants and providers (performance bias) Objective outcomes	Low risk	No blinding, but these outcomes considered unlikely to be affected by knowledge of group allocation
Blinding of participants and providers (performance bias) Subjective outcomes	High risk	No blinding, and these outcomes likely to be influenced by knowledge of group allocation
Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	No blinding, but assessment of these outcomes considered unlikely to be affected by lack of blinding
Blinding of outcome assessor (detection bias) Subjective outcomes	High risk	No blinding, and assessment of these outcomes likely to be influenced by knowledge of group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	AUC analysis adjusts for missing data, and dropout similar in both groups
Selective reporting (reporting bias)	Low risk	None apparent
Other bias: Comparability of cohorts	Low risk	Groups similar on baseline characteristics
Other bias: Selection of comparison cohort	Low risk	Experimental and comparison cohort drawn from same population
Other bias: Protection against contamination	Unclear risk	It is possible that communication between the groups could have occurred.

Gerra 1995

Methods	Randomised controlled, double-blind trial
Participants	Setting: hospital outpatient clinic, Italy N = 152, drug abuse disorder by DSM-III-R, withdrawing from heroin. Similarity of groups not reported Age 18-32 years 82% men
Interventions	Group 1 (n = 33): clonidine (0.15 mg IV 3 times a day) Group 2 (n = 42): clonidine (as group 1) + naltrexone (12.5 mg day 2 then 50 mg/day 3 months) Group 3 (n = 58): clonidine (as group 1) + naloxone (0.2 mg IV day 2, 0.4 mg twice a day on days 3 and 4) then naltrexone (50 mg/day from day 5) Group 4 (n = 19): IV saline + oral placebo Daily clinic attendance with 4 hours IV therapy in morning, 3 hours in afternoon
Outcomes	Mean total withdrawal score at 48 and 72 hours; bar graphs for days 1, 2 and 3 showing ratings for individual items of withdrawal scale; morphine metabolites in urine; Hamilton scale for depression on day 1, day 8 and 6 months
Notes	Withdrawal assessed by observer only using 9-item scale, mainly of objective signs, each item rated 0 to 5 for severity Source of funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "All the patients were randomly divided into four groups..." Comment: group sizes differed and similarity of the characteristics of the groups was not discussed. The adequacy of sequence generation is doubtful.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding of participants and providers (performance bias) Objective outcomes	Low risk	Double-blind stated; these outcomes unlikely to be affected by inadequate blinding
Blinding of participants and providers (performance bias) Subjective outcomes	High risk	Double-blind stated, but given the differences in group sizes it is doubtful whether the blind was maintained, and these outcomes could be influenced by knowledge of group allocation.
Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	Double-blind stated; these outcomes unlikely to be affected by inadequate blinding
Blinding of outcome assessor (detection bias) Subjective outcomes	High risk	Adequacy of blind doubtful, and assessment of these outcomes likely to be influenced by knowledge of group allocation

Gerra 1995 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout in first week similar for 3 groups relevant to this review
Selective reporting (reporting bias)	High risk	Analysis on basis of treatment provided
Other bias: Comparability of cohorts	Unclear risk	No information about comparability of groups
Other bias: Selection of comparison cohort	Low risk	All participants drawn from same population
Other bias: Protection against contamination	Unclear risk	It is possible that communication between the groups could have occurred.

Gerra 2000

Methods	Randomised controlled trial
Participants	<p>Setting: outpatient clinic, Italy</p> <p>N = 98 withdrawing from heroin, dependent by DSM-IV, urine positive for morphine; groups similar in psychiatric and psychometric data</p> <p>Age 18-36 years</p> <p>72% men</p> <p>Duration of drug use 2-6 years</p>
Interventions	<p>Heroin use continued until 12 hours before treatment</p> <p>Group 1 (n = 32): clonidine 0.15 mg/100mL saline IV 6 times/day for 2 days, 0.15 mg 3 times a day for 3 days. Additional 0.15 mg orally each evening. Total 5 days treatment</p> <p>Group 2 (n = 32): clonidine as group 1 for 2 days, plus naloxone as repeated 0.04 mg injections to 0.4 mg 2 days. Naltrexone, orally, 5 mg at 6 pm day 1 (after naloxone injections completed), 50 mg day 2, after same procedure. Clonidine 0.15 mg orally 3 times day 3. Total 3 days treatment</p> <p>Group 3 (n = 34): methadone, oral, 40 mg/day in single dose, tapered over 10 days</p> <p>Treatment in outpatient clinic with those in groups 1 and 2 receiving 4 hours IV therapy morning and afternoon. Unclear whether extent of clinic care same for group treated with methadone.</p> <p>All received counselling. Naltrexone maintenance commenced day 6 (group 1), during detox (group 2) and 5 days after taper (group 3)</p>
Outcomes	Graphs of mean daily withdrawal scores, craving scores before and after detox, % of positive urine samples, number accepting naltrexone and % of participants in maintenance naltrexone treatment 3 months after detox
Notes	<p>Withdrawal rated by observer (9 items, 0-5 severity). Urine testing during detoxification and follow-up period</p> <p>Source of funding: not reported</p>

Risk of bias
Opioid antagonists with minimal sedation for opioid withdrawal (Review)

Gerra 2000 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All the subjects were randomly divided into three groups" but the method of sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding of participants and providers (performance bias) Objective outcomes	Low risk	These outcomes are considered unlikely to be affected by knowledge of group allocation.
Blinding of participants and providers (performance bias) Subjective outcomes	High risk	Blinding not discussed; the timing of naltrexone commencement in the treatment protocols differed. This suggests that there was probably no blinding of treatment personnel, and possibly not participants either
Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	Assessment of these outcomes are considered unlikely to be affected by knowledge of group allocation.
Blinding of outcome assessor (detection bias) Subjective outcomes	Unclear risk	Insufficient information to permit judgement of low or high risk
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The 3 groups differed in the proportions who accepted and continued extended naltrexone maintenance treatment, but it is unclear how this difference translates into missing data. It is also unclear whether differences in dropout may have influenced withdrawal scores. (This outcome was not used in this review.)
Selective reporting (reporting bias)	Low risk	None apparent
Other bias: Comparability of cohorts	Low risk	Groups similar on baseline characteristics
Other bias: Selection of comparison cohort	Low risk	All participants drawn from same population
Other bias: Protection against contamination	Unclear risk	It is possible that communication between groups could have occurred.

McCambridge 2007

Methods	Cohort study design with double-blind, random allocation to lofexidine + naloxone or lofexidine + placebo. Participants who did not consent to, or were excluded from randomisation received methadone.
Participants	<p>Setting: inpatient, UK</p> <p>N = 137, opiate-dependent, admitted for inpatient detoxification. No differences between groups 1 and 2, but some differences in group 3.</p> <p>Average age 32</p>

McCambridge 2007 (Continued)

77% men

Interventions	Group 1 (n = 45): lofexidine plus 0.8 mg naloxone on days 3-6 Group 2 (n = 46): lofexidine plus placebo Group 3 (n = 46): methadone tapered over 10 days
Outcomes	Number completing detoxification, length of stay, abstinence at follow-up, time to relapse
Notes	No use of rating scales reported Source of funding: charitable trust and Britannia Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...patients randomly allocated (by computer) to receive lofexidine + naloxone or lofexidine + placebo". This is the only comparison relevant to this review.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding of participants and providers (performance bias) Objective outcomes	Low risk	Double-blind stated for groups 1 and 2, and these outcomes considered unlikely to be influenced by knowledge of group allocation
Blinding of participants and providers (performance bias) Subjective outcomes	Low risk	Double-blind stated for groups 1 and 2
Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	Double-blind stated for groups 1 and 2, and assessment of these outcomes considered unlikely to be influenced by knowledge of group allocation
Blinding of outcome assessor (detection bias) Subjective outcomes	Low risk	Double-blind stated for groups 1 and 2
Incomplete outcome data (attrition bias) All outcomes	Low risk	Rates of dropout from groups 1 and 2 similar
Selective reporting (reporting bias)	Low risk	None apparent
Other bias: Comparability of cohorts	Low risk	Groups 1 and 2 similar on baseline characteristics
Other bias: Selection of comparison cohort	Low risk	Groups drawn from same population
Other bias: Protection against contamination	Low risk	Communication between groups could have occurred, but blinding would be expected to nullify the effect

O'Connor 1995

Methods	Prospective cohort study; participants able to choose treatment group
Participants	<p>Setting: outpatient treatment from primary care medical clinic, USA</p> <p>N = 125 injecting drug users with active opioid addiction, willing to enter long-term treatment after detoxification. Groups similar in terms of drug use history, craving and withdrawal scores at baseline</p> <p>Average age 33 years</p> <p>64% men</p> <p>Average age of first heroin use 22 years, average 1.4 prior detoxifications, 95% had history of cocaine use; history of dependence on alcohol, benzodiazepines or sedatives exclusion criterion; 50% employed</p>
Interventions	<p>Group 1 (n = 57): clonidine 0.1-0.2 mg 4 times a day, tapered over 12 days</p> <p>Group 2 (n = 68): clonidine as group 1, tapered over 5 days + naltrexone 12.5 mg day 1, 25 mg day 2, then 50 mg/day</p> <p>Daily clinic attendance except weekends. Participants in group 2 in clinic to 5 pm day 1 to manage withdrawal from first dose of naltrexone</p> <p>All had access to oxazepam as adjunct medication, with group 2 also receiving ibuprofen, ketorolac and prochlorperazine on day of first naltrexone dose</p>
Outcomes	Number successfully completing detoxification defined by 50 mg dose of naltrexone without acute withdrawal; amount of oxazepam required during detoxification; withdrawal scores reported for baseline only
Notes	<p>Opioid withdrawal scale of 24 items, each rated 0-3 by participants. No urine screening</p> <p>Source of funding: Research grant, US National Institute on Drug Abuse (NIDA)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Two protocols were offered to patients, who selected their own treatments."
Allocation concealment (selection bias)	High risk	Quote: "Two protocols were offered to patients, who selected their own treatments."
Blinding of participants and providers (performance bias) Objective outcomes	Low risk	No blinding, but these outcomes are considered unlikely to be influenced by knowledge of intervention
Blinding of participants and providers (performance bias) Subjective outcomes	High risk	No blinding, but no subjective data were reported
Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	No blinding, but assessment of these outcomes considered unlikely to be influenced by knowledge of intervention

O'Connor 1995 (Continued)

Blinding of outcome assessor (detection bias) Subjective outcomes	High risk	No blinding, but no subjective data were reported
Incomplete outcome data (attrition bias) All outcomes	High risk	The 2 groups differed significantly in rates of completion of detoxification. Data on the total amount of oxazepam used during treatment is at risk of bias as a result.
Selective reporting (reporting bias)	Low risk	None apparent
Other bias: Comparability of cohorts	Low risk	Groups similar on baseline characteristics
Other bias: Selection of comparison cohort	Low risk	All participants drawn from same population
Other bias: Protection against contamination	Unclear risk	It is possible that communication between groups could have occurred.

O'Connor 1997

Methods	Randomised controlled, double-blind trial
Participants	<p>Setting: outpatient treatment from primary care medical clinic, USA</p> <p>N = 162 heroin dependent with sufficient social support for outpatient detoxification. No substantial differences in sociodemographic or clinical features of groups at baseline</p> <p>Age not reported (between 18 and 50 years)</p> <p>71% men</p> <p>62% married, 35% employed</p>
Interventions	<p>Group 1 (n = 55): clonidine 0.1-0.2 mg every 4 hours as needed days 1-7, 50 mg naltrexone day 8</p> <p>Group 2 (n = 54): clonidine as group 1, 12.5 mg naltrexone day 1, increasing to 50 mg day 3</p> <p>Group 3 (n = 53): buprenorphine 3 mg sublingually days 1-3 then clonidine as group 1, 25 mg naltrexone day 4, 50 mg day 5</p> <p>Daily clinic attendance except at weekends</p>
Outcomes	Mean overall and peak withdrawal scores; number retained in treatment for 8 days, number achieving 50 mg maintenance dose naltrexone
Notes	<p>Withdrawal rated by participants (24 items, each rated 0-3)</p> <p>Source of funding: Research grant, US National Institute on Drug Abuse (NIDA)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were randomly assigned to a treatment group..."; method of sequence generation not reported

O'Connor 1997 (Continued)

Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding of participants and providers (performance bias) Objective outcomes	Low risk	Quote: "...staff and patients were blinded to the protocols. Study medications were prepared so that participants received either active or placebo preparations of all medications." However, maintenance of blind difficult due to differential effects of medications. However, these outcomes are considered unlikely to be affected by awareness of intervention.
Blinding of participants and providers (performance bias) Subjective outcomes	Unclear risk	Study undertaken double-blind, as indicated above, but maintenance of the blind was reported to be difficult
Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	Assessment of these outcomes considered unlikely to be influenced by knowledge of group allocation
Blinding of outcome assessor (detection bias) Subjective outcomes	Unclear risk	Insufficient information to permit judgement of low or high risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "[r]etention did not differ significantly among the groups."
Selective reporting (reporting bias)	Low risk	None apparent
Other bias: Comparability of cohorts	Low risk	Baseline characteristics of groups similar
Other bias: Selection of comparison cohort	Low risk	All participants drawn from same population
Other bias: Protection against contamination	Unclear risk	It is possible that communication between groups could have occurred. The implications of this are unclear given the difficulties in maintaining the blind.

Umbricht 1999

Methods	Randomised, placebo-controlled, double-blind trial
Participants	<p>Setting: inpatient treatment in research ward, USA.</p> <p>N = 60, heroin dependent by DSM-III-R. Groups similar on sociodemographic and drug use characteristics.</p> <p>Average age 32 years</p> <p>59% men in group 1, 36% men in group 2</p> <p>30% injecting users; alcohol dependence an exclusion criterion; average days employed in last 30: 8 (SD 2) days (group 1), 4 (SD 1) days (group 2)</p>
Interventions	Buprenorphine, sublingual solution, 12 mg in 2 doses day 1, then single daily dose of 8 mg day 2, 4 mg day 3, 2 mg day 4, plus

Umbricht 1999 (Continued)

Group 1 (n = 32): naltrexone, oral, 2 hours after buprenorphine, 12.5 mg days 2 and 3, 25 mg day 4, then 50 mg/day or

Group 2 (n = 28): 50 mg oral naltrexone day 8

Symptomatic treatment initiated when withdrawal score above median entry score

Outcomes	Proportion of patients remaining in treatment, day of dropout and reasons for leaving, mean withdrawal score at each time point and daily mean peak scores, proportion of patients with withdrawal scores exceeding median baseline score each day, AUC analysis of withdrawal score, medications used for symptomatic treatment, mean clonidine dose per patient by day of treatment, numbers completing study
Notes	Withdrawal rated by observers 9 times a day using adapted form of Clinical Institute Narcotic Assessment scale (11 items, score 0-30). Participants completed adjective checklist but results not reported (stated as not robust)
	Source of funding: research grant, US National Institute on Drug Abuse (NIDA)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "[c]omplete patient randomizations was used with a slightly higher probability to be assigned to the NB group to offset a potential for higher dropout rate in this group." Specific method of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding of participants and providers (performance bias) Objective outcomes	Low risk	Double-blind stated, with placebos used to maintain blind
Blinding of participants and providers (performance bias) Subjective outcomes	Low risk	Double-blind stated, with placebos used to maintain blind
Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	Double-blind stated, with placebos used to maintain blind
Blinding of outcome assessor (detection bias) Subjective outcomes	Low risk	Double-blind stated, with placebos used to maintain blind
Incomplete outcome data (attrition bias) All outcomes	High risk	76% in the placebo group and 56% in the naltrexone group completed withdrawal. This difference was not statistically significant, but there was a significant difference in the average length of stay. If participants with more severe withdrawal symptoms were more likely to drop out, data on severity of withdrawal after day 2, is at risk of bias
Selective reporting (reporting bias)	Unclear risk	Participants completed adjective checklist to rate withdrawal severity but results not reported (stated as not robust)

Umbricht 1999 (Continued)

Other bias: Comparability of cohorts	Low risk	Groups similar on baseline characteristics
Other bias: Selection of comparison cohort	Low risk	All participants drawn from same population
Other bias: Protection against contamination	Unclear risk	It is possible that communication between groups could have occurred.

AUC: area under the curve; **DSM:** *Diagnostic and Statistical Manual of Mental Disorders*; **IM:** intramuscularly; **IV:** intravenously; **SD:** standard deviation.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Armstrong 2003	Analysis of presentations to hospital emergency department for treatment of adverse effects of antagonist-induced withdrawal. Retrospective review of records, no treatment comparison
Azatian 1994	Study of effectiveness of antagonist-induced withdrawal prior to naltrexone maintenance treatment of heroin dependence; no treatment comparison
Bartter 1996	Reports outcomes of withdrawal induced by naltrexone with sedation. No treatment comparison. Case series, not controlled study
Beaini 2000	Reports treatment outcomes for 504 consecutive patients receiving sedation and fluid for 3 days followed by naltrexone for management of opioid withdrawal. No treatment comparison
Bell 1999	Cohort study comparing outcomes for heroin-dependent and methadone-maintained clients receiving antagonist-induced withdrawal. No treatment comparison.
Brewer 1988	Reports 2 case series treated with different regimens of naltrexone combined with clonidine. Not a controlled study. Insufficient data on outcomes defined for this review.
Camarasa 2007	Reports the use of a single dose of naltrexone with adjunct medications on day 2, after cessation of methadone, to accelerate opioid withdrawal. No treatment comparison
Carreno 2002	Describes procedure, demographics and symptoms of opioid-dependent patients undergoing antagonist-induced withdrawal at home. No treatment comparison
Charney 1986	Reports outcomes of 2 treatment protocols combining naltrexone and clonidine, but differing in timing of naltrexone commencement. Results combined by reporting outcomes against days of clonidine/naltrexone treatment. No treatment comparison.
Chen 2004	Reports outcomes of naltrexone-induced withdrawal with or without an amino acid supplement. Method of selection of the group receiving the amino acid supplement not reported and insufficient detail of participant characteristics to determine comparability of 2 groups. Insufficient outcome data, unclear whether data collection retrospective
Dakwar 2015	Reports use of naltrexone to facilitate withdrawal from buprenorphine in cohort who were unable to reduce below 2 mg buprenorphine due to withdrawal distress. No treatment comparison.
De Jong 2005	Comparison of antagonist-induced withdrawal with or without anaesthesia for management of opioid withdrawal. Comparison is not one of the modalities defined by the inclusion criteria

Study	Reason for exclusion
Dijkstra 2010	Compares outcomes of antagonist-induced withdrawal with minimal sedation for group of patients treated in everyday clinical practice compared with those treated as part of a clinical trial (De Jong 2005). No treatment comparison
Frownfelter 2001	Randomised controlled trial comparing 2 treatment regimens that differ only in the timing of commencement of naltrexone. Both regimens involve 3 days of buprenorphine (12 mg, 8 mg, 4 mg) with naltrexone commenced either day 2 or day 4. Trial incomplete at the time of this report, but no further report located. Insufficient outcome data
Gerra 2001	Randomised controlled trial comparing clonidine and lofexidine for managing symptoms of antagonist-induced withdrawal. Antagonist-induced withdrawal regimens identical except for adjunct medications
Gerra 2006	Observational study of 2 groups receiving naltrexone or naltrexone plus buprenorphine. Medication commenced in context of detoxification but focus of study on relapse prevention (12 weeks treatment)
Glasgow 2001	Open-label study investigating the acceptability of antagonist-induced withdrawal followed by naltrexone maintenance treatment. No treatment comparison
Golden 2004	Chart review of 20 consecutive patients to assess the incidence of delirium during antagonist-induced withdrawal. Retrospective data collection, no treatment comparison
Kleber 1987	Reports the use of clonidine and naltrexone to manage opioid withdrawal in an outpatient setting. No treatment comparison
Kurland 1976	Investigation of effects of repeated doses of naloxone in parolees participating in an aftercare abstinence programme. No treatment comparison, not a full withdrawal intervention
London 1999	Reports outcomes for 20 patients treated with antagonist-induced withdrawal with "high level" of sedation and various adjunct medications. No treatment comparison
Mannelli 2003	Reports the administration of naltrexone (0.125 mg initially then increasing) during 6-day tapered methadone detoxification. No treatment comparison. One of series of studies leading to Mannelli 2009 .
Mannelli 2009	Randomised controlled trial comparing tapered methadone plus: placebo versus naltrexone 0.125 mg versus naltrexone 0.25 mg. Intervention not one defined by selection criteria of review
Mannelli 2014	Reports the use of low dose naltrexone and buprenorphine to facilitate transition from opioid dependence to sustained release naltrexone (Vivitrol). No treatment comparison
Masini 1981	Comparison of 2 dose regimens of antagonist-induced withdrawal. Consecutive case series, not a controlled study. Insufficient data on outcomes and participants
Mogali 2015	Assessment of effectiveness of buprenorphine-clonidine to manage transition from opioid dependence to sustained-release naltrexone (Depotrex or Vivitrol). No treatment comparison
Montazeri 2002	Randomised controlled trial of antagonist-induced withdrawal with or without acupuncture. Investigation of effectiveness of acupuncture, not antagonist-induced withdrawal
Montoya 1994	Study of effects of naltrexone administered to patients receiving buprenorphine/naltrexone combination or buprenorphine alone. Focus on pharmacology of buprenorphine rather than management of withdrawal

Study	Reason for exclusion
Pozzi 2000	Comparison of trazodone and clonidine in management of symptoms associated with antagonist-induced withdrawal. Focus on capacity of trazodone to ameliorate withdrawal, not effectiveness of antagonist-induced withdrawal.
Resnick 1977	Comparison of 2 regimens of antagonist-induced withdrawal. 2 case series, not a controlled study. Insufficient outcome data
Rezaian 2014	Randomised controlled trial comparing very low dose naltrexone (0.125 mg) and placebo as adjuncts to standard clonidine-based regimen for managing withdrawal. Naltrexone dose insufficient to induce withdrawal. Insufficient data on outcomes defined for review. Conference abstract currently only information available
Riordan 1980	Reports use of antagonist-induced withdrawal for opioid dependence. No treatment comparison
Saunders 2002	Comparison of antagonist-induced withdrawal with minimal sedation or anaesthesia and continued methadone maintenance treatment. Comparisons not those defined by the criteria for this review
Senft 1991	Reports use of antagonist-induced withdrawal. No treatment comparison
Silverstone 1992	Comparison of nifedipine and clonidine as adjuncts to antagonist-induced withdrawal. Study abandoned after 2/2 treated with nifedipine experienced delirium following the introduction of naltrexone. Insufficient outcome data
Sullivan 2015	Preliminary (conference abstract) report of randomised controlled trial comparing graduated doses of oral naltrexone with a 7-day regimen of tapered buprenorphine, following a single day of buprenorphine treatment, to manage transition from opioid dependence to sustained-release (injectable) naltrexone. Trial ongoing. No data on withdrawal syndrome
Vining 1988	Comparison of 2 regimens of antagonist-induced withdrawal, differing in day on which naltrexone was administered (day 2 or day 3). Treatments offered consecutively making control of allocation and performance bias difficult. Limited data reported

DATA AND ANALYSES

Comparison 1. Antagonist-adrenergic combination versus adrenergic agonist

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 Peak withdrawal severity	2		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Naltrexone	2		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Naloxone	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Overall withdrawal severity	4		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Naltrexone	3		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Naloxone	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Completion rate	9		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Naltrexone	4		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Naloxone	6		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Antagonist-adrenergic combination versus adrenergic agonist, Outcome 1 Peak withdrawal severity.

Study or subgroup	Antagonist		Adrenergic		Std. Mean Difference	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
1.1.1 Naltrexone						
Gerra 1995	42	22.9 (11.1)	33	5.4 (1.9)	+	2.06[1.49,2.63]
O'Connor 1997	54	28 (13.1)	55	29.9 (14.9)	+	-0.13[-0.51,0.24]
1.1.2 Naloxone						
Gerra 1995	58	15.2 (9.5)	33	5.4 (1.9)	+	1.26[0.8,1.73]
					Favours antagonist	Favours adrenergic

Analysis 1.2. Comparison 1 Antagonist-adrenergic combination versus adrenergic agonist, Outcome 2 Overall withdrawal severity.

Study or subgroup	Antagonist		Adrenergic		Std. Mean Difference Random, 95% CI	Std. Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)		
1.2.1 Naltrexone						
Buntwal 2000	11	70 (12.4)	11	116.4 (35.1)		-1.7[-2.7,-0.69]
O'Connor 1995	68	361 (209)	57	352 (279)		0.04[-0.32,0.39]
O'Connor 1997	54	17.6 (9.3)	55	17.8 (10.3)		-0.02[-0.4,0.36]
1.2.2 Naloxone						
Bearn 2001	26	96.4 (33.9)	23	121.6 (49.9)		-0.59[-1.16,-0.01]
					Favours antagonist	Favours adrenergic

Analysis 1.3. Comparison 1 Antagonist-adrenergic combination versus adrenergic agonist, Outcome 3 Completion rate.

Study or subgroup	Antagonist n/N	Adrenergic n/N	Risk Ratio M-H, Random, 95% CI		Risk Ratio M-H, Random, 95% CI
1.3.1 Naltrexone					
Gerra 1995	40/42	30/32			1.02[0.91,1.14]
O'Connor 1997	44/54	36/55			1.24[0.99,1.57]
O'Connor 1995	64/68	24/57			2.24[1.64,3.05]
			Favours adrenergic	0.2 0.5 1 2 5	Favours antagonist

APPENDICES

Appendix 1. CENTRAL search strategy

#1 (opiate or opioid or heroin or narcotic) near/2 (abuse or addiction or dependence):ti,ab,kw in Trials

#2 MeSH descriptor: [Opioid-Related Disorders] explode all trees

#3 #1 or #2

#4 MeSH descriptor: [Substance Withdrawal Syndrome] explode all trees

#5 detoxification:ti,ab,kw in Trials

#6 #4 or #5

#7 #3 and #6

Appendix 2. MEDLINE search strategy via Ovid Online

1. exp Opioid-Related Disorders/
2. ((opiate\$ or opioid\$ or heroin\$ or narcot\$) adj2 (abus\$ or depend\$)).ti,ab
3. exp Substance Withdrawal Syndrome/
4. (detoxifi\$ or desintoxi\$ or disintoxi\$ or disintossi\$).ti,ab
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. exp clinical trial/ or exp comparative study/
9. random\$.ti,ab
10. exp Double-Blind Method/
11. (double adj2 blind).ti,ab
12. 8 or 9 or 10 or 11
13. 7 and 12
14. Limit 13 to humans

Appendix 3. Embase search strategy

#1 'opiate addiction'/exp

#2 'heroin dependence'/exp

#3 (opiate* or opioid* or heroin* or narcot*) NEAR/2 (abus* or depend*)

#4 'withdrawal syndrome'/exp

#5 detoxifi*.ab,ti or desintoxi*.ab,ti or disintoxi*.ab,ti or disintossi*.ab,ti

#6 'drug detoxification'/exp

#7 #1 or #2 or #3

#8 #4 or #5 or #6

#9 #7 and #8

#10 'clinical study'/exp

#11 random*.ab,ti

#12 'double blind procedure'

#13 double NEAR/1 blind

#14 #10 or #11 or #12 or #13

#15 #9 and #14 AND [humans]/lim

Appendix 4. PsycINFO search strategy via Ovid Online

1. exp drug dependency/
2. exp heroin addiction/
3. ((opiate\$ or opioid\$ or heroin\$ of narcot\$) adj2 (abus\$ or depend\$)).ti,ab
4. exp drug withdrawal/ or exp detoxification/
5. (detoxifi\$ or desintoxi\$ or disintoxi\$ or disintossi\$).ti,ab
6. 1 or 2 or 3
7. 4 or 5
8. 6 and 7
9. limit 8 to human
- 10.exp clinical trials/
- 11.random\$.ti,ab
- 12.(double adj2 blind).ti,ab
- 13.10 or 11 or 12
- 14.9 and 13

Appendix 5. Web of Science search strategy

1. TS="opioid-related disorders"
2. TS=opiate addiction
3. TS=opiate depend*
4. TS=heroin* depend*
5. TS=heroin* addict*
6. #5 or #4 or #3 or #2 or #1
7. TS="substance withdrawal syndrome"
8. TX=detox*
9. #8 or #7
- 10.#9 and #6
- 11.TS=clinical trial*
- 12.TS=random*
- 13.TS=double blind
- 14.#13 or #12 or #11
- 15.#14 and #10

Appendix 6. Criteria for 'Risk of bias' assessment

Item	Judgement	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation
	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention Observational prospective study
	Unclear risk	Insufficient information to permit judgement of low or high risk
2. Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because one of the following methods was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled, randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
	High risk	Investigators enrolling participants could possibly foresee assignments because one of the following methods was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure Observational prospective study
	Unclear risk	Insufficient information to permit judgement of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement
3. Blinding of participants and providers (performance bias) - Objective outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
4. Blinding of participants and providers (performance bias) - Subjective outcomes	Low risk	Blinding of participants and providers and unlikely that the blinding could have been broken
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding Blinding of participants and key study personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk
5. Blinding of outcome assessor (detection bias) - Objective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken

(Continued)

		Record linkage
6. Blinding of outcome assessor (detection bias) - Subjective outcomes	Low risk	<p>No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding</p> <p>Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken</p>
	High risk	<p>No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding</p> <p>Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding</p>
	Unclear risk	Insufficient information to permit judgement of low or high risk
7. Incomplete outcome data (attrition bias) For all outcomes except retention in treatment or dropout	Low risk	<p>No missing outcome data</p> <p>Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias)</p> <p>Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups</p> <p>For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate</p> <p>For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size</p> <p>Missing data have been imputed using appropriate methods</p> <p>All randomised participants are reported/analysed in the group they were allocated to by randomisation irrespective of non-adherence and co-interventions (intention-to-treat)</p>
	High risk	<p>Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups</p> <p>For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate</p> <p>For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size</p> <p>'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation</p>
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of dropouts not reported for each group)
8. Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way

(Continued)

The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)		
	High risk	<p>Not all of the study's pre-specified primary outcomes have been reported.</p> <p>One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified</p> <p>One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect)</p> <p>One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis</p> <p>The study report fails to include results for a key outcome that would be expected to have been reported for such a study</p>
	Unclear risk	Insufficient information to permit judgement of low or high risk
9. Other bias: comparability of cohorts for baseline characteristics and outcome measures on the basis of the design or analysis	Low risk	<p>Exposed and non-exposed individuals are matched in the design for most important confounding factors</p> <p>Authors demonstrated balance between groups for the confounders</p> <p>Analyses are adjusted for most important confounding factors and imbalance</p> <p>Randomised controlled trial</p>
	High risk	No matching or no adjustment for most important confounding factors
	Unclear risk	No information about comparability of cohorts
10. Other bias: selection of the non-exposed (control) cohort	Low risk	The sample has been drawn from the same community as the exposed cohort
	High risk	The sample has been drawn from a different source
	Unclear risk	No description of the derivation of the non-exposed cohort
11. Other bias: protection against contamination	Low risk	Allocation was by community, institution or practice and it is unlikely that the control group received the intervention
	High risk	It is likely that the control group received the intervention
	Unclear	It is possible that communication between intervention and control groups could have occurred

WHAT'S NEW

Date	Event	Description
3 May 2017	New citation required but conclusions have not changed	Conclusions not changed
21 February 2017	New search has been performed	New search. No new studies included, but one study previously considered secondary now treated as separate primary study.

Date	Event	Description
		New excluded studies. Amendments to comply with Cochrane requirements.

HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 2, 2000

Date	Event	Description
7 August 2009	New citation required but conclusions have not changed	new trials found, conclusions not changed
7 August 2009	New search has been performed	the review has been updated,
15 January 2009	Amended	New search, new trials, new assessment of included studies, conclusions modified.
20 March 2008	Amended	Converted to new review format
8 November 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Linda Gowing assessed each potentially relevant study according to identified inclusion and exclusion criteria, extracted key information and compiled a first draft of the review. Robert Ali and Jason White confirmed and commented on review content.

DECLARATIONS OF INTEREST

Linda Gowing: none known.

Robert Ali: none known.

Jason White: none known.

SOURCES OF SUPPORT

Internal sources

- Drug and Alcohol Services South Australia, Australia.

External sources

- Commonwealth Department of Health and Aging, Australia.

NOTES

The first version of this review was entitled 'Opioid antagonists and adrenergic agonists for the management of opioid withdrawal'.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic alpha-Agonists [*therapeutic use]; Clonidine [analogs & derivatives] [therapeutic use]; Naloxone [therapeutic use]; Naltrexone [therapeutic use]; Narcotic Antagonists [*therapeutic use]; Non-Randomized Controlled Trials as Topic; Opioid-

Related Disorders [*rehabilitation]; Prospective Studies; Randomized Controlled Trials as Topic; Severity of Illness Index; Substance Withdrawal Syndrome [*drug therapy]

MeSH check words

Humans