



Cochrane
Library

Cochrane Database of Systematic Reviews

Opioid antagonists with minimal sedation for opioid withdrawal (Review)

Gowing L, Ali R, White JM

Gowing L, Ali R, White JM.

Opioid antagonists with minimal sedation for opioid withdrawal.

Cochrane Database of Systematic Reviews 2017, Issue 5. Art. No.: CD002021.

DOI: [10.1002/14651858.CD002021.pub4](https://doi.org/10.1002/14651858.CD002021.pub4).

www.cochranelibrary.com

Opioid antagonists with minimal sedation for opioid withdrawal (Review)

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

[Intervention Review]

Opioid antagonists with minimal sedation for opioid withdrawal

Linda Gowing¹, Robert Ali¹, Jason M White²

¹Discipline of Pharmacology, University of Adelaide, Adelaide, Australia. ²School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia

Contact: Linda Gowing, Discipline of Pharmacology, University of Adelaide, Frome Road, Adelaide, South Australia, 5005, Australia. linda.gowing@adelaide.edu.au.

Editorial group: Cochrane Drugs and Alcohol Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 5, 2017.

Citation: Gowing L, Ali R, White JM. Opioid antagonists with minimal sedation for opioid withdrawal. *Cochrane Database of Systematic Reviews* 2017, Issue 5. Art. No.: CD002021. DOI: [10.1002/14651858.CD002021.pub4](https://doi.org/10.1002/14651858.CD002021.pub4).

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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 alpha₂-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 alpha₂-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.