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[Intervention Review]

Alpha$_2$-adrenergic agonists for the management of opioid withdrawal

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ABSTRACT

Background

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

Objectives

To assess the effectiveness of interventions involving the use of alpha$_2$-adrenergic agonists compared with placebo, reducing doses of methadone, symptomatic medications, or an alpha$_2$-adrenergic agonist regimen different to the experimental intervention, for the management of the acute phase of opioid withdrawal. Outcomes included the withdrawal syndrome experienced, duration of treatment, occurrence of adverse effects, and completion of treatment.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1946 to November week 2, 2015), EMBASE (January 1985 to November week 2, 2015), PsycINFO (1806 to November week 2, 2015), Web of Science, and reference lists of articles.

Selection criteria

Randomised controlled trials comparing alpha$_2$-adrenergic agonists (clonidine, lofexidine, guanfacine, tizanidine) with reducing doses of methadone, symptomatic medications or placebo, or comparing different alpha$_2$-adrenergic agonists to modify the signs and symptoms of withdrawal in participants who were opioid dependent.

Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration.

Main results

We included 26 randomised controlled trials involving 1728 participants. Six studies compared an alpha$_2$-adrenergic agonist with placebo, 12 with reducing doses of methadone, four with symptomatic medications, and five compared different alpha$_2$-adrenergic agonists. We assessed 10 studies as having a high risk of bias in at least one of the methodological domains that were considered.

We found moderate-quality evidence that alpha$_2$-adrenergic agonists were more effective than placebo in ameliorating withdrawal in terms of the likelihood of severe withdrawal (risk ratio (RR) 0.32, 95% confidence interval (CI) 0.18 to 0.57; 3 studies; 148

participants). We found moderate-quality evidence that completion of treatment was significantly more likely with alpha$_2$-adrenergic agonists compared with placebo (RR 1.95, 95% CI 1.34 to 2.84; 3 studies; 148 participants).

Peak withdrawal severity may be greater with alpha$_2$-adrenergic agonists than with reducing doses of methadone, as measured by the likelihood of severe withdrawal (RR 1.18, 95% CI 0.81 to 1.73; 5 studies; 340 participants; low quality), and peak withdrawal score (standardised mean difference (SMD) 0.22, 95% CI -0.02 to 0.46; 2 studies; 263 participants; moderate quality), but these differences were not significant and there is no significant difference in severity when considered over the entire duration of the withdrawal episode (SMD 0.13, 95% CI -0.24 to 0.49; 3 studies; 119 participants; moderate quality). The signs and symptoms of withdrawal occurred and resolved earlier with alpha$_2$-adrenergic agonists. The duration of treatment was significantly longer with reducing doses of methadone (SMD -1.07, 95% CI -1.31 to -0.83; 3 studies; 310 participants; low quality). Hypotensive or other adverse effects were significantly more likely with alpha$_2$-adrenergic agonists (RR 1.92, 95% CI 1.19 to 3.10; 6 studies; 464 participants; low quality), but there was no significant difference in rates of completion of withdrawal treatment (RR 0.85, 95% CI 0.69 to 1.05; 9 studies; 659 participants; low quality).

There were insufficient data for quantitative comparison of different alpha$_2$-adrenergic agonists. Available data suggest that lofexidine does not reduce blood pressure to the same extent as clonidine, but is otherwise similar to clonidine.

Authors' conclusions

Clonidine and lofexidine are more effective than placebo for the management of withdrawal from heroin or methadone. We detected no significant difference in efficacy between treatment regimens based on clonidine or lofexidine and those based on reducing doses of methadone over a period of around 10 days, but methadone was associated with fewer adverse effects than clonidine, and lofexidine has a better safety profile than clonidine.

PLAIN LANGUAGE SUMMARY

Clonidine, lofexidine, and similar medications for the management of opioid withdrawal

Review question

We reviewed the evidence about the effect of alpha$_2$-adrenergic agonists (clonidine, lofexidine, guanfacine, and tizanidine) in managing withdrawal in people who are dependent on opioid drugs (for example heroin, methadone).

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 completion of opioid withdrawal difficult for most people. For many years, the main approach to detoxification involved suppression of withdrawal with methadone and gradual reduction of the methadone dose. The use of methadone in this way has been limited by government restrictions on prescription of methadone and dislike of the drawn-out nature of methadone withdrawal. Clonidine and similar medications (known as alpha$_2$-adrenergic agonists) offer an alternative approach. This review considered whether alpha$_2$-adrenergic agonists are more effective than reducing doses of methadone, and whether there are any differences in the effectiveness of different types of alpha$_2$-adrenergic agonist.

Search date

The evidence is current to November 2015.

Study characteristics

We identified 26 randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups), involving 1728 opioid-dependent participants. The studies were undertaken in 12 different countries and involved treatment with an alpha$_2$-adrenergic agonist (clonidine, lofexidine, guanfacine, and in one study, tizanidine) compared with reducing doses of methadone (12 studies), placebo (six studies), or symptomatic medications (four studies). Five studies compared different alpha$_2$-adrenergic agonists. Treatment was scheduled to last for one to two weeks in most studies; the shortest duration was three days, and the longest was 30 days.

Six studies received some financial support from a pharmaceutical company.

Key results

Opioid withdrawal was similar with alpha$_2$-adrenergic agonists and reducing doses of methadone, but the duration of treatment was longer and there were fewer adverse effects with methadone. Withdrawal signs and symptoms occurred earlier with alpha$_2$-adrenergic agonists, within a few days of cessation of the opioid drugs. The chances of completing withdrawal treatment were similar.

Clonidine and lofexidine were more effective than placebo in managing withdrawal from heroin or methadone, and were associated with higher chances of completing treatment.

Lofexidine had less effect on blood pressure than clonidine.

Quality of the evidence

For alpha$_2$-adrenergic agonists compared with placebo, the evidence was very low to moderate quality, indicating that further evidence would be likely to change the estimates of relative effect made in this review. However, the evidence is sufficient to indicate that alpha$_2$-adrenergic agonists are more effective than placebo, making further comparisons of this nature inappropriate on ethical grounds.

For the comparison of alpha$_2$-adrenergic agonists with reducing doses of methadone, the evidence was low to moderate quality. The key reasons for the low quality were small numbers of studies reporting some outcomes, low rates of occurrence of some events (for example drop-out due to adverse effects), and variability between studies.