TAKE-HOME MESSAGE

α_2-Adrenergic agonists (eg, clonidine) are associated with lower rates of severe withdrawal symptoms and higher rates of adherence; however, this must be balanced with known adverse effects such as hypotension.

Do α_2-Adrenergic Agonists Decrease the Symptoms Associated With Opioid Withdrawal?

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METHODS

DATA SOURCES

Electronic searches were performed with the Cochrane Central Register of Controlled Trials (Issue 11, 2015), MEDLINE (1946 to November week 2, 2015), EMBASE (January 1985 to November week 2, 2015), PsycINFO (1806 to November week 2, 2015), and Web of Science (as of November 23, 2015). The authors also searched the reference lists of all relevant articles, conference proceedings, and multiple clinical trial registries, and they contacted investigators to seek information about additional trials.

STUDY SELECTION

This systematic review included randomized controlled clinical trials that compared the administration of an α_2-adernergic agonist with other interventions such as placebo or methadone to reduce symptoms of opioid withdrawal. Outcomes included withdrawal signs and symptoms, adverse effects, or treatment course completion. Four review authors developed a set of inclusion and exclusion criteria by which studies were chosen. One review author assessed potential studies according to this list; however, all 4 authors confirmed these decisions.

DATA EXTRACTION AND SYNTHESIS

One author extracted data with a standardized data extraction form, with assistance from other review

Results

Meta-analytic comparison of α_2-adrenergic agonist treatment to placebo.

Outcome	Number of Studies (Number of Patients)	RR (95% CI)	I^2, %
Participants with severe withdrawal	3 (148)	0.3 (0.2–0.6)	21
Completion of treatment	3 (148)	2.0 (1.3–2.8)	0

RR, Risk ratio; *CI*, confidence interval.

The search strategy identified 3,377 articles, of which 26 studies (n=1,728 participants) met the inclusion criteria for this review. Among these studies, 1,012 participants were randomized to receive an α_2-adrenergic agonist (607 clonidine, 215 lofexidine, 174 guanfacine, and 16 tizanidine). Twelve studies compared α_2-adrenergic agonists to tapering doses of methadone, 6 studies to placebo, and 4 to targeted medications for symptom management, and 5 studies compared different α_2-adrenergic agonist medications (ie, clonidine versus lofexidine in 3 studies and clonidine versus guanfacine in 2 studies). In 16 of the studies, treatment was provided on an inpatient basis, one study was conducted in a prison health center, and the remaining 9 were outpatient settings. Nineteen of the studies involved participants withdrawing from heroin, 5 studies involved methadone, one included either heroin or methadone withdrawal, and one involved withdrawal from opium. Duration of α_2-adrenergic agonist treatment was less than 1 week in 4 studies, 1 to 2 weeks in 15 studies, and greater than 2 weeks in 5 studies. In 2 studies, the treatment length was unclear. Route of administration of medication was unclear in a majority of the studies. Most studies were determined to be at low risk of bias with respect to blinding, incomplete outcome data, selective reporting, and other forms of bias. Although the majority of studies had an unclear risk of bias in regard to random-sequence generation and allocation concealment, 25% of the trials were at low risk of

authors when there was uncertainty. Outcomes of interest were recorded on the form and key findings were summarized descriptively and then considered for quantitative meta-analysis. Risk of bias was assessed with the approach recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*.[1] Risk ratios were calculated for dichotomous data, whereas standardized mean differences were calculated for continuous data. Statistical heterogeneity was assessed with the χ^2 test, visual inspection of forest plots, and the I^2 statistic. A random-effects model was used to combine results for all analyses.

bias and 2 studies were determined to be at high risk of bias on these 2 critical parameters.

When α_2-adrenergic agonists were compared with placebo, there was a lower degree of severe withdrawal and higher rate of treatment completion in the 3 studies that assessed these outcomes (Table). Withdrawal severity was measured with the Modified Himmelsbach Opiate Withdrawal Scale,[2] a previously validated, 13-item scale assessing various symptomatic and physiologic parameters. Two studies also demonstrated lower peak withdrawal scores, although the data were not combined because of a high degree of heterogeneity. When compared with tapering doses of methadone, α_2-adrenergic agonists demonstrated no difference in peak withdrawal severity (2 studies), overall withdrawal severity (3 studies), or occurrence of severe withdrawal (5 studies). α_2-Adrenergic agonists were associated with quicker onset and resolution of withdrawal symptoms, as well as shorter overall treatment duration (3 studies). There was no significant difference between clonidine, lofexidine, and guanfacine in regard to severity of withdrawal or time course (5 studies). However, clonidine was associated with increased rates of hypotension compared with lofexidine in all 3 trials assessing these 2 medications.

Commentary

The prevalence of heroin abuse and dependence has increased considerably during the past decade, especially among young adults.[3] Patients who are experiencing heroin overdose or withdrawal often present to the emergency department (ED), where emergency physicians may have opportunities to facilitate detoxification and abstinence. Although the rates of relapse after heroin detoxification are high,[4] detoxification remains an important initial step and can help reduce the likelihood of immediate relapse.[5-7] Signs and symptoms of heroin withdrawal include anxiety, irritability, rhinorrhea, piloerection, nausea, vomiting, diarrhea, yawning, generalized weakness, and insomnia.[7] Symptoms usually begin within 6 to 12 hours of use for shorter-acting drugs (eg, heroin, morphine) and 36 to 48 hours for longer-acting ones (eg, methadone).[8] During this period, patients are at high risk for relapse.[7] Controlling symptoms and referring the patient to a rehabilitation center can have a significant effect on his or her life.

This systematic review demonstrated that patients receiving an α_2-adrenergic agonist experienced a reduction in the severity of withdrawal symptoms and had a greater likelihood of treatment completion for their opioid misuse. The review also demonstrated that α_2-adrenergic agonists had an efficacy similar to that of a course of tapering doses of methadone, which is unlikely to be initiated in an ED setting.

It is important to consider several limitations to this meta-analysis. The number of studies and patients comparing an α_2-adrenergic agonist with placebo (the outcome of interest for most ED providers) was small, comprising only 148 total patients. Additionally, the majority of the data assessed the use of clonidine, whereas guanfacine, lofexidine, and tizanidine provided much smaller contributions, limiting the applicability to other α_2-adrenergic agonists. Moreover, none of the studies were specifically performed in the ED setting. Because patients presenting to the ED may have different motivations to quit than those already enrolled in a rehabilitation program, it is unclear whether similar outcomes would be demonstrated in this patient population. Furthermore, 6 studies received financial support from the pharmaceutical industry and another 14 studies had unclear sources of funding, which may have biased the conclusions. Finally, one must consider the potential for adverse effects from the initiation of α_2-adrenergic agonists. The most common adverse effects were dry mouth, drowsiness, and dizziness. Although there were also higher rates of orthostatic hypotension in the clonidine group compared with the methadone group, no patients actually withdrew from treatment because of adverse effects.

This systematic review provides evidence that α_2-adrenergic agonists decrease withdrawal symptoms and reduce the likelihood of

opioid misuse relapse. Future studies should assess different formulations of α_2-adrenergic agonists (eg, topical patch versus pills), the addition of pharmacologic adjuncts, and efficacy for withdrawal from different types of opioids (eg, heroin, morphine, methadone).

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals*' Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Gowing L, Farrell M, Ali R, et al. Alpha$_2$-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev.* 2016;(5):CD002024.**

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