Review: methadone dose reduction is better than α_2 adrenergic agonists for treatment retention in opioid dependence

Gowing LR, Farrell M, Ali RL, et al. ***α_2–Adrenergic agonists in opioid withdrawal.*** *Addiction 2002 Jan;**97**:49–58.*

Gowing L, Farrell M, Ali R, et al. ***Alpha2 adrenergic agonists for the management of opioid withdrawal.*** *Cochrane Database Syst Rev 2001;(1):CD002024 (latest version 17 Nov 2000).*

QUESTION: In patients with opioid dependence, are α_2 adrenergic agonists more effective than the reduction of methadone doses for managing opioid withdrawal?

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Data sources

Studies were identified by searching 12 databases; hand searching reviews, reference lists, and conference proceedings; and contacting pharmaceutical companies.

Study selection

Studies in any language were selected if they were controlled clinical trials that compared α_2 adrenergic agonists with each other, another treatment, or placebo for managing opioid withdrawal in patients who were opioid dependent.

Data extraction

Data were extracted on study design and setting, participant characteristics, drug regimens, and outcomes.

Main results

13 studies (11 randomised controlled trials [RCTs]) fufilled the criteria. 10 studies compared methadone dose reduction with α_2 adrenergic agonists (6 comparisons of clonedine, 3 of lofexidine, and 2 of guanfacine), and 3 RCTs compared lofexidine with clonidine. Intensity of withdrawal was similar for methadone dose reduction and α_2 adrenergic agonists but peak intensity occurred earlier for α_2 adrenergic agonists. In the methadone dose reduction studies, more patients receiving methadone than those receiving α_2 adrenergic agonists completed the treatment period with active medication (4 of 10 RCTs) (table). The mean duration of treatment was longer for the methadone group than the α_2 adrenergic agonist group (3 of 4 RCTs). 6 RCTs reported on the number of participants completing the withdrawal. The definition for withdrawal completion differed, and the results were not combined. Only 1 of the 6 RCTs showed a difference: methadone dose reduction led to more patients completing withdrawal than did α_2 adrenergic agonists. More patients in the clonidine group than in the methadone dose reduction group had adverse events and orthostatic hypertension (2 RCTs). Mean blood pressure was reduced in the clonidine group relative to the methadone dose reduction group (2 RCTs) but did not differ between lofexidine and methadone dose reduction (2 RCTs). Lofexidine and clonidine did not differ for intensity and pattern of withdrawal (3 RCTs). The median treatment duration was 5 days for lofexidine (range 1–9 d) and 4 days for clonidine (range 1–8 d) (1 RCT). No statistically significant difference existed between lofexidine and clonidine for the number of patients who completed withdrawal (65% *v* 50%) (1 RCT). Hypotension occurred more frequently in the clonidine group than in the lofexidine group (2 RCTs). Patients in the clonidine group were more likely than those in the lofexidine group to have low blood pressure and to miss doses because of low blood pressure, although no patients had clinically significant hypotension (1 RCT).

Conclusions

In patients with opioid dependence, methadone dose reduction is better than α_2 adrenergic agonists for improving treatment retention. Clonidine and lofexidine are equally effective but hypotension is less likely to occur with lofexidine.

*α_2 adrenergic agonists v methadone dose reduction for opioid dependence**

Outcome	Weighted event rates: α_2 adrenergic agonists	Weighted event rates: Methadone dose reduction	RBR (95% CI)	NNH (CI)
Completed drug treatment	53%	77%	30% (19 to 40)	5 (4 to 7)

*RBR = relative benefit reduction. Other abbreviations defined in glossary; RBR, NNH, and CI calculated from data in article. Follow up not reported.

COMMENTARY

Gowing *et al* review the literature on α_2 adrenergic agonists for the treatment of opiate withdrawal. These medications provide an important tool for opiate detoxification treatment. Although methadone is also effective in this regard, various governmental agencies regulate its use for this purpose, thus limiting its availability and use.

The interpretation of the findings that methadone is superior to α_2 adrenergic agonists with respect to completion of active medication or withdrawal, but inferior in terms of length of treatment, is complex. For example, withdrawal symptoms typically peak after the methadone is terminated but while the α_2 adrenergic agonist treatment is being continued. Furthermore, certain aspects of the withdrawal technique strongly influence the length of the withdrawal, the period on active medication, and when the withdrawal process is over; these 3 factors vary for the 2 types of drug. Clonidine and guanfacine, approved by the US Food and Drug Administration for the treatment of hypertension, are not approved for opiate withdrawal treatment. None the less, clonidine has been widely used off label for this purpose since the 1960s and has become the standard of care in much of the world as a pharmacological agent for the non-narcotic treatment of opiate withdrawal. It is considered to be effective in attenuating opiate withdrawal signs, but has a side effect profile (primarily orthostatic hypotension, sedation, and dizziness) that can limit aggressive treatment and may prevent adequate dosing during the peak period of withdrawal signs and symptoms (doses may have to be withheld or decreased to minimise these side effects).

Lofexidine is currently approved in the UK for opiate detoxification treatment and will likely soon have European Union approval. It is not approved as an antihypertensive agent and is not approved for any indication in the US, although it is currently in phase III trials for opiate withdrawal treatment. Lofexidine appears to be an effective medication for opiate detoxification. It has also been associated with fewer qualitative and quantitative cardiovascular changes than clonidine (eg, less hypotension); blood pressure changes are usually well tolerated and are dose dependent. If lofexidine is eventually approved in the US, it will provide US clinicians (as well as those in Europe) with a non-opiate alternative to methadone with a more favourable side effect profile than clonidine.

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