TAKE-HOME MESSAGE

Compared with α2-adrenergic agonists (eg, clonidine), buprenorphine improves withdrawal scores and has higher rates of adherence to withdrawal regimen completion.

Should Buprenorphine Be Administered to Patients With Opioid Withdrawal in the Emergency Department?

EBEM Commentators
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METHODS

DATA SOURCES

The authors searched the Cochrane Central Register of Controlled Trials (Issue 11, 2016), MEDLINE (1946 to December, 2016), EMBASE (to December 22, 2016), PsycINFO (1806 to December, 2016), and Web of Science (to December 22, 2016). Ongoing clinical trials and conference summaries with relevant trials were also included.

STUDY SELECTION

Authors selected randomized controlled trials examining the use of buprenorphine to manage withdrawal in opioid-dependent patients. Some studies included primary buprenorphine-based interventions; others compared buprenorphine with methadone, α2-adrenergic medications (eg, clonidine), or placebos. In some studies, adjunct medications (eg, antiemetics, nonsteroidal anti-inflammatories) were available for withdrawal symptom management. Exclusion criteria included studies that combined buprenorphine with opioid antagonists. The primary outcomes included intensity of withdrawal based on withdrawal scores (Clinical Opiate Withdrawal Scale [0 to 48],[1] Subjective Opiate Withdrawal Scale [0 to 64],[2] and Objective Opiate Withdrawal Scale [0 to 13][2]), treatment duration, adverse effects, and completion of treatment.

Results

Buprenorphine versus α2-adrenergic agonists for acute opioid withdrawal.

Outcome	Relative Effect (95% CI)	No. of Participants (Studies)
Mean overall withdrawal score	SMD −0.4 (−0.6 to −0.3)	902 (7)
Completing withdrawal treatment	RR 1.6 (1.2 to 2.1)	1,264 (11)

CI, Confidence interval; *SMD*, standardized mean difference; *RR*, risk ratio.

Of 3,573 studies identified, 27 met all inclusion criteria for meta-analysis: 6 studies evaluated buprenorphine versus tapered methadone, 7 evaluated tapering buprenorphine, and 14 evaluated buprenorphine versus α2-adrenergic agonists (primarily clonidine).

The quality of evidence (study allocation and blinding biases) within each subgroup analysis varied greatly. Quality of evidence for all 7 studies on tapering doses of buprenorphine was assessed as low or very low. Quality of evidence for studies of methadone versus buprenorphine was considered low for all outcomes except "number of patients who completed treatment."

In the buprenorphine vs α2-adrenergic agonists group, the quality of evidence was considered moderate for 3 outcomes: mean withdrawal scores, mean days in treatment, and number of patients who completed treatment. These 14 studies demonstrated significant variation in their treatment protocols, medication dosing, study design, study location, and route of medication administration. Thirteen of 14 studies compared clonidine with buprenorphine treatment. No studies occurred in the emergency

DATA EXTRACTION AND SYNTHESIS

One of 2 reviewers completed a data extraction form; study inclusion was evaluated by all reviewers. Eligible studies were separated into 3 treatment comparison groups: buprenorphine versus tapered methadone, tapering buprenorphine, and buprenorphine versus α2-adrenergic agonists. Individual subgroup analyses were performed for each of the 3 treatment groups. Up to 6 patient outcomes were analyzed, including withdrawal score, days in treatment, adverse effects, and treatment completion. Summary statistics differed for each outcome variable. Risk ratios were calculated for outcomes with dichotomous data, and mean differences were calculated for outcomes with consistently measured continuous data. Standardized mean differences were used for outcomes with continuous data with variable measurement (eg, withdrawal scores).

department (ED): 10 studies occurred in inpatient detoxification clinics and 4 occurred in outpatient clinics. Most studies treated patients with oral medication doses, but a few studies included intramuscular clonidine (1), intramuscular buprenorphine (2), and transdermal clonidine (2). Medication dosing, along with ancillary medications to treat withdrawal adverse effects, also varied across the 14 studies.

Subgroup results revealed that patients treated with buprenorphine had lower overall withdrawal scores and a greater number of days in treatment compared with patients treated with clonidine (Table). For buprenorphine and methadone subgroups, results suggested similar rates of treatment completion (risk ratio 1.04; 95% confidence interval 0.9 to 1.2).

Commentary

During the last 20 years, the opioid epidemic has surged significantly, and by 2015, approximately 63% of 52,400 drug overdose deaths were related to opioids.[3] Additionally, opioid-related ED visits have increased by almost 8% annually during 10 years.[4] Treating opioid use disorder is a multimodal process with interventions that occur in various health care settings. The ED serves as an essential transition point for opioid use disorder patients presenting with overdose, acute withdrawal, or associated medical complications.

This systematic review suggests that treatment of acute opioid withdrawal with buprenorphine is superior at decreasing the withdrawal syndrome and keeping patients in treatment longer compared with clonidine. The results suggest that the number needed to treat is 4 with buprenorphine for 1 additional patient to reach withdrawal treatment completion compared with clonidine. However, there was substantial clinical heterogeneity with respect to medication dose, dosing frequency, clinical treatment setting, and administration route. Thus, the subgroup analysis must be interpreted with caution, given that patient treatment regimen and adjunctive medication availability may affect treatment completion. Additionally, the included studies were conducted outside the ED.

Despite these limitations, initiating buprenorphine in the ED may decrease the acute withdrawal syndrome better than current symptom-based therapies, reduce illicit opioid use, and protect patients from opioid overdose.[5-7] Although methadone and buprenorphine appear to have similar treatment success, the safety, ease of administration, and referral options of the latter may make it a better ED-based treatment.[5,6] Perhaps most consequentially, initiating buprenorphine in the ED bridges patients to medication-assisted treatment, particularly if coordinated treatment follow-up is used (a "warm handoff").[8]

In summary, studies comparing buprenorphine and clonidine suggest that buprenorphine treatment improves withdrawal scores and number of days in treatment for patients with opioid abuse disorder. Ideally, buprenorphine treatment initiation should not be delayed until the patient accesses a treatment program or requires an inpatient hospital admission.[9]

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, Ali R, White JM, et al. Buprenorphine for managing opioid withdrawal. *Cochrane Database Syst Rev.* 2017;2:CD002025.

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4. Weiss AJ, Elixhauser A, Barrett ML, et al. *Opioid-Related Inpatient Stays and Emergency Department Visits by State, 2009-2014*. Rockville, MD: Agency for Healthcare Research & Quality; 2016. HCUP Statistical Brief #219. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb219-Opioid-Hospital-Stays-ED-Visits-by-State.jsp. Accessed October 26, 2017.
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Michael Brown, MD, MSc, Jestin N. Carlson, MD, MS, and Alan Jones, MD, serve as editors of the SRS series.