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Is Buprenorphine More Effective and Safer Than Other Medical Treatments for Managing Opioid Withdrawal? A Cochrane Review Summary With Commentary

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Key Points

- Buprenorphine is similar in efficacy to methadone (i.e., severity of withdrawal, withdrawal treatment retention, withdrawal completion, and lack of adverse events) and is superior to both clonidine and lofexidine for managing opioid withdrawal.
- The review authors did not reach conclusions about speed of tapering the dosing of buprenorphine.
- The commentary authors indicate that ongoing research to examine contextual factors in medication for opioid withdrawal will elucidate what characteristics are linked to better outcomes.
- The commentary suggests examining the efficacy of substitution treatment following medication for withdrawal.

Background

This paper summarizes the published Cochrane Review, "Buprenorphine for Managing Opioid Withdrawal," by L. Gowing, R. Ali, J. M. White, & D. Mbewe,[1] and discusses it through a treatment policy and practice lens.[a]

Recent statistics from the 2019 National Survey of Drug Use and Health[2] reported that more than 1.5 million US adults aged 18 years or older had an opioid use disorder (OUD). The costs of untreated OUD in health care, criminal justice, and reduced productivity to individuals, families, and society have been estimated to be close to $150 billion per year.[3] Treatment is critical to reducing the physical and economic burden of this disorder.

Withdrawal from opioid dependence remains a required first step for many forms of long-term treatment such as residential rehabilitation and naltrexone maintenance. Medication in this context is designed to reduce the adverse effects of withdrawal and the intense craving for the substance so that individuals can focus on behavioral changes. Medical management for withdrawal is also a possible first step for subsequent treatment including medications for opioid use disorder (MOUD),[4] previously known as "medication-assisted treatment." MOUD includes counseling along with maintenance-dose medications of methadone, buprenorphine, or naltrexone.

a This brief is one in a series prepared by RTI Press in agreement with the Cochrane Library/Wiley. These briefs summarize and add original commentary to research presented in Cochrane Reviews. This summary is based on a Cochrane Review previously published in the *Cochrane Database of Systematic Reviews* 2017, Issue 2, Art. No. CD002025, DOI: https://doi.org/10.1002/14651858.CD002025.pub5 (see https://www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and *Cochrane Database of Systematic Reviews* should be consulted for the most recent version of the review.

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This Cochrane Review examined the evidence for efficacy and safety of one commonly used medication—buprenorphine—for managing opioid withdrawal in comparison with other medications or placebo. Gowing and colleagues[1] rated the quality of the evidence for the primary outcomes using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, concluding that the strength of evidence ranged between very low and moderate, with the modal category low. We conducted a dual appraisal of the quality of the systematic review using AMSTAR2 (A MeaSurement Tool to Assess systematic Reviews)[5] and concluded that we had moderate confidence in the Cochrane Review.

Methods

The study population included adolescents and adults who were opioid dependent and who received either buprenorphine or a comparison medication for managing withdrawal symptoms. The experimental intervention was buprenorphine; the included comparators were tapered doses of methadone; clonidine; lofexidine; symptomatic medications (e.g., nonopioid analgesics, benzodiazepines); placebo; or buprenorphine differing in amount, duration, or tapering rate. The primary outcomes of the review included intensity of withdrawal, duration of withdrawal treatment, and nature and incidence of harms; the secondary outcome was engagement in further treatment.

Search Methodology

The Cochrane Review authors searched for relevant randomized controlled trials (RCTs) of interventions using buprenorphine to manage opioid withdrawal in several databases up to December 2016. They also hand-searched reference lists of included literature, ongoing trials, and conference proceedings. The authors included non-English literature.

Main Results

The review included 27 RCTs. Of these studies, 14 were in the United States, 6 were in Europe, 2 each were in India and Iran, and 1 each were in Australia and Israel. The settings included 13 inpatient, 10 outpatient, 2 both inpatient and outpatient, 1 prison, and 1 residential therapeutic setting. Overall, the review included 3,048 participants, of whom approximately 70% were male, with a median age of 31 years.

Comparison 1: Buprenorphine vs. Methadone for Managing Opioid Withdrawal (6 Studies)

Meta-analysis was not possible for the outcome of intensity of withdrawal or adverse effects. However, the data from most individual studies testing this outcome indicated that buprenorphine and methadone were similar in withdrawal severity (4 studies). The 3 studies examining harms found no significant adverse events in either group.

Meta-analysis suggested no difference between buprenorphine and methadone for the outcome of the average treatment duration (mean difference [MD]: 1.3 days, 95% confidence interval [CI]: -8.11 to 10.72; 2 studies) and no difference for treatment completion rates (risk ratio [RR]: 1.04, 95% CI: 0.91 to 1.20; 5 studies).

Comparison 2: Buprenorphine vs. Clonidine or Lofexidine for Managing Opioid Withdrawal (14 Studies)

The studies comparing either clonidine or lofexidine with buprenorphine found that patients treated with buprenorphine had less severe withdrawal during treatment (standardized mean difference (SMD) of withdrawal scores: -0.43, 95% CI: -0.58 to -0.28; 7 studies), stayed in treatment longer (SMD: 0.92, 95% CI: 0.57 to 1.27; 5 studies), and were more likely to complete treatment (RR: 1.59, 95% CI: 1.23 to 2.06; 12 studies). Although the authors did not detect a difference in harms, they acknowledged that in 3 studies, patients treated with clonidine were more likely to stop treatment because of adverse events than those treated with buprenorphine (RR: 0.20, 95% CI: 0.04 to 1.15).

Comparison 3: Rapid vs. Slow Taper of Buprenorphine for Managing Opioid Withdrawal (7 Studies)

In these studies, the analysis was conducted separately for inpatient and outpatient settings. Meta-analysis was possible only for the treatment completion outcome. For inpatient settings, the authors failed to find an effect of the rate of dose taper on treatment completion (RR: 1.00, 95% CI: 0.84 to 1.18; 2 studies). The authors also reported that they failed to find an effect of the rate of dose taper on treatment completion in outpatient settings (RR: 0.86, 95% CI: 0.44 to 1.70; 4 studies).

Neither of the 2 inpatient studies examining the intensity of withdrawal found differences attributable to the rate of dose reduction. The 4 studies in outpatient settings that examined withdrawal severity reported mixed findings. For the outcome of duration of withdrawal treatment, the 1 inpatient study examining this outcome found similar treatment durations in the rapid and slower taper groups. In the 1 outpatient study reporting duration of withdrawal treatment, the frequency of clinic attendance was confounded with tapering. Only 1 inpatient study reported on harms, finding no difference between the treatment regimens. The 2 outpatient studies reported on adverse events; 1 found no adverse events, and 1 found no serious adverse events related to tapering.

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Cochrane Review Authors' Conclusions

Buprenorphine was similar in efficacy to methadone for managing opioid withdrawal in terms of severity of withdrawal, withdrawal treatment retention, withdrawal completion, and lack of adverse events. The Cochrane authors judged the quality of the evidence as low to moderate. Conversely, buprenorphine was superior to both clonidine and lofexidine for managing opioid withdrawal with no increase in adverse events; these treatment effects included fewer withdrawal symptoms, longer treatment duration, and greater likelihood of completing treatment in patients receiving buprenorphine. The authors rated the quality of this evidence as very low to moderate. The authors did not draw any firm conclusions regarding rapid versus slower reduction in dosing of buprenorphine, rating the quality of the evidence as very low to low.

The authors recognized that a limitation of the review is the failure of the studies to report outcomes on the basis of sex, as males and females are known to respond differently to drug therapies.[6] Lacking information regarding potential sex differences limits the ability of clinicians to select the best withdrawal treatment for an individual. The authors noted that further research is needed to establish the most effective doses, frequency, and duration of buprenorphine administration using objective criteria. The authors also briefly discussed buprenorphine as a substitute treatment for opioids. They indicated that because buprenorphine can be administered in an outpatient setting, it can be extended into substitution treatment for those patients who did not achieve abstinence. However, the authors cautioned that including both withdrawal management and substitution treatment in the same study would blur the distinctions between them.

Commentary: Implications of the Cochrane Evidence for Policy and Practice

Conclusions from the Cochrane Review indicate the efficacy of buprenorphine for managing opioid withdrawal. However, because of the high rates of reuse following opioid withdrawal, the Substance Abuse and Mental Health Services Administration's (SAMHSA) Treatment Improvement Panel (TIP) does not recommend short-term medically supervised withdrawal.[7] If patients do want medication for withdrawal, SAMHSA's TIP recommends providing psychosocial treatment along with medication for withdrawal. However, data from the Cochrane Systematic Review reported that psychotherapy was only an aftercare adjunct in one of the included studies. How widespread this practice is in medically supervised withdrawal is not known.

Rather than using medication for withdrawal, the TIP panel recommends using substitution treatment that includes therapy with medication. This practice recommendation is facilitated by the US Drug Enforcement Administration waiver that permits health care providers to prescribe buprenorphine outside of opioid treatment programs after completing specialized training. However, as a recent report from the Pew Trust[8] indicates, because the federal regulations limit the number of providers with waivers, many US counties do not have any eligible providers, leaving many individuals with OUD without access to this important treatment. A recent study indicates that out of 2,595 counties in 38 US states, 36% of urban counties and 32% of rural counties have an undersupply of buprenorphine providers.[9] Moreover, despite the recommendation for MOUD, a study examining responses from more than 13,000 addiction facilities to the 2017 National Survey of Substance Abuse Treatment Services found that only 40% of the addiction treatment facilities offered any medication for OUD.[10] This fact and the fact that the number of medical providers is limited leave many patients without viable options for medication treatment for OUD. Results from a second study[11] that examined whether individuals with private medical insurance who were treated with buprenorphine received care adhering to American Society of Addiction Medicine[12] guidelines were disappointing. Data from more than 38,000 individuals who received buprenorphine and were continuously enrolled in private insurance for 6 months indicated that most patients did not receive guideline-specified care. On average, patients completed only an average of 7.4 visits over the 6-month period. In addition, fewer than half of the patients filled buprenorphine prescriptions for at least 6 months.

Commentary: Implications of the Cochrane Evidence for Research

Based on the findings from the Cochrane Review and the policy landscape, we have suggestions for future research. Because the studies included in the Cochrane Review varied in dosing, frequency, and duration of buprenorphine administration, its authors could not determine the most effective dose or regimen. Systematically varying the dosing of buprenorphine, perhaps in a clinical trial, would make a real contribution to the field. Also critical are establishing the duration of buprenorphine withdrawal treatment and determining what personal characteristics are linked to better outcomes.

Although the purpose of the Cochrane Review is not buprenorphine treatment for OUD, tying buprenorphine for withdrawal to buprenorphine for treatment of OUD may be helpful in light of the TIP recommendation cited previously.[7] Given that many patients with OUD who are treated with

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buprenorphine (or the other medications) for managing withdrawal start using opioids again,[6] assessing substitution treatment following withdrawal would provide a real-world examination of a common situation in treating patients with OUD.

One investigation that bridges the gap is RECOVER,[13] a cohort study that followed participants from one of two studies that examined long-acting buprenorphine, administered monthly for up to 12 months. The investigators found positive outcomes over the 12-month post-buprenorphine observation period. The study reported that half of the participants reported sustained abstinence over the 12-month follow-up period, and that 36% of the cohort indicated that they did not need any further treatment. Specifically, participants whose duration of buprenorphine was longer (either 6 to 11 months or 12 months) rather than shorter (3 to 5 months), who were female, or who were older had self-reported sustained abstinence at 12 months. Results of these studies suggest that substitution treatment lasting 12 months can lead to abstinence, the desired outcome of many who undertake withdrawal treatment.

The HEALing (Helping to End Addiction Long-term) Communities Study,[14,15] a multi-site cluster-RCT implemented in four states with the same protocol, is designed to examine the impact of a set of evidence—based practices that communities select to reduce opioid use disorder. Among the outcomes are expansion of MOUD (i.e., methadone, buprenorphine, naltrexone) by increasing demand for, access to, and retention for MOUD. This study will contribute to a greater understanding of the contextual factors affecting the use of buprenorphine and other evidence-based MOUD.

Conclusions

Buprenorphine is effective in managing opioid withdrawal without adverse effects, but unless buprenorphine is followed up with longer-term maintenance medication and psychosocial treatment, patients are liable to relapse. Data are still needed to examine for whom buprenorphine is most effective as a medication for withdrawal and to document the experience of moving from buprenorphine for managing opioid withdrawal to substitution treatment with buprenorphine. Addressing the limited number of eligible providers who can prescribe buprenorphine is critical for ensuring timely and appropriate management of opioid withdrawal as well as medical treatment for OUD.

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