

Methods of Detoxification and Their Role in Treating Patients With Opioid Dependence

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OPIOID DEPENDENCE AND ITS ASSOCIATED MORBIDITY, mortality, and social costs continue to plague societies around the world. Opioid dependence is characterized by physical dependence as evidenced by tolerance and withdrawal and by behavioral problems, including the inability to control opioid use, opioid use despite adverse consequences, and social dysfunction. The 2003 National Survey on Drug Use and Health reported that 3.7 million Americans had used heroin at some time in their lives.¹ The Monitoring the Future Survey noted that approximately 1.2% of 10th- and 12th-graders reported ever using heroin in 2004.² In addition, the recent trend of increasing abuse of prescription opioids including oxycodone, propoxyphene, hydrocodone, hydromorphone, and meperidine has been a major concern since the late 1990s. The National Survey on Drug Use and Health¹ estimated that as of 2003, more than 31.2 million Americans had used narcotic pain relievers in a “nonmedicinal” manner sometime in their lives and 11.7 million were “past year” nonmedicinal users in 2003.¹ The Monitoring the Future Survey indicated that 6.2% of 10th-graders and 9.3% of 12th-graders used hydrocodone and 3.5% of 10th-graders and 5.0% of 12th-graders used oxycodone in 2004.² These statistics and the overall lack of access to high-quality treatment resources for opioid-dependent individuals³ point directly to the urgent need to develop new treatment strategies for opioid dependence while expanding access to established treatment approaches known to be effective.

Medication-based treatment for opioid dependence consists of 2 distinct approaches: detoxification and maintenance.⁴ Detoxification involves the use of medications to bring a patient from an opioid-dependent to an opioid-free state. The medications used are designed to decrease withdrawal-related discomfort and complications. Maintenance therapy involves the substitution of an abused opioid such as heroin or narcotic analgesics, which are often used intravenously or intranasally several times a day, by a medically prescribed opioid such as methadone or buprenorphine that can be taken orally and administered once a day in combination with counseling.

Detoxification-based treatments for opioid dependence have been studied over many decades. Among the early treat-

ment approaches were some in which opioid withdrawal occurred in patients who were rendered unconscious during detoxification.⁵ These treatments included “bromide sleep treatment,” “hibernation therapy,” and “insulin-induced hypoglycemia” and were subsequently noted to be ineffective and dangerous.⁵ More rational approaches using methadone and clonidine were demonstrated to be relatively safe and effective in the short term (measured in days) but of questionable long-term value due to exceedingly high dropout and relapse rates following detoxification. More recently, “rapid” detoxification techniques in which opioid withdrawal is precipitated by opioid antagonists such as naloxone or naltrexone have attempted to speed up the detoxification process to improve retention in withdrawal treatment and initiate induction of naltrexone to prevent relapse. Naltrexone, an orally administered opioid antagonist, is designed to prevent relapse by blocking the effects of opioids. The US Food and Drug Administration (FDA) approval of buprenorphine in 2002 for the treatment of opioid dependence (for both detoxification and maintenance) offers a new option for opioid detoxification,⁶ although data concerning its long-term effectiveness in detoxification are also lacking. In fact, all detoxification approaches are only partially effective in controlling the symptoms of opioid withdrawal and are often not followed with effective relapse prevention treatment.⁷

In a relatively new approach for treating opioid dependence, “ultrarapid” opioid detoxification is induced with an opioid antagonist while the patient is under anesthesia or heavy sedation.⁸ This approach offers patients the possibility of a rapid and “painless” withdrawal under anesthesia, after which they awaken in a non-opioid-dependent state, thereby, at least in theory, avoiding the discomfort of withdrawal. Thus, like the other “sleep” and “hibernation” therapies of the past,⁵ anesthesia-assisted detoxification is designed to limit patients’ withdrawal-related discomfort by rendering them unconscious during withdrawal.

However, the effectiveness and safety of anesthesia-assisted detoxification have been called into question. A systematic review published in 1998 noted a lack of evidence to support this approach: of the 9 studies published in peer-reviewed journals, only 3 included a control group, only 2

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used randomization, and only 3 followed up patients for more than 12 days.⁸ Safety concerns have also been raised. Along with the risks inherent in general anesthesia, complications such as pulmonary and cardiac problems occurring during this procedure have been reported.⁸⁻¹⁰ Despite this lack of evidence and significant safety concerns, the availability of opioid detoxification under anesthesia expanded across the United States and Europe in the 1990s.¹¹

Since that time, there have been additional studies concerning the effectiveness and safety of ultrarapid opioid detoxification under anesthesia. While most of the recent data on this treatment are from case series and nonrandomized studies,¹²⁻¹⁴ 2 randomized trials have been published: one compared ultrarapid detoxification with clonidine-based treatment¹⁵ and the other compared it with rapid detoxification without general anesthesia.¹⁶ The former study found equivocal results after 3 to 6 months but did not systematically assess withdrawal severity,¹⁵ while the latter study found that detoxification under anesthesia was no more effective than that done without anesthesia and was associated with adverse events necessitating hospitalization.¹⁶

The article by Collins et al¹⁷ in this issue of *JAMA* provides a methodologically rigorous assessment of opioid detoxification under anesthesia and yields convincing evidence that this procedure is neither effective nor safe. These authors randomly assigned heroin-dependent patients to 1 of 3 inpatient interventions: anesthesia-assisted rapid opioid detoxification, buprenorphine-assisted opioid detoxification, or clonidine-assisted opioid detoxification. Clonidine, an α -adrenergic agonist, suppresses autonomically mediated signs and symptoms of opioid withdrawal.⁴ Carefully selected and measured short-term outcomes in this study including withdrawal severity scores and the proportion of patients successfully receiving naltrexone induction therapy provide critical insight into how these approaches compare over the first few days of treatment. In addition, outcomes including retention in treatment and urine toxicology for opioids provide more detailed and longer-term (in this case 12 weeks) results than have been typically reported in studies on detoxification under anesthesia.

The results of the study by Collins et al are striking and convincing. Anesthesia-assisted detoxification did no better than buprenorphine or clonidine in improving the primary outcome—withdrawal severity.¹⁷ In addition, while patients in the anesthesia-assisted detoxification and buprenorphine groups both had significantly greater rates of naltrexone induction than did those receiving clonidine, this finding is not surprising given that the anesthesia and buprenorphine groups were given naltrexone before they left the inpatient treatment unit (on days 1 and 2, respectively), while patients in the clonidine treatment group had to come back as outpatients several days later (on day 7) to receive their naltrexone, thus leaving plenty of time for dropout before the medication could be given. More significantly, treatment retention did not differ between the 3

groups and was exceedingly low across the board: by week 3 more than 50% of patients in each group had dropped out of treatment and the overall dropout rate at the end of the 12-week study was 82%. In addition, not only was anesthesia-assisted detoxification no more effective than the other treatments, it was also less safe. All 3 serious adverse events in this study occurred in the anesthesia-assisted group. The overall outcome is undeniable: as compared with the other approaches studied, anesthesia-assisted detoxification appears to be no more effective and less safe.

This study should be viewed in the larger context of what is known about treatment of opioid dependence. Because medical detoxification addresses only the very first steps of treatment and many programs do not provide ongoing treatment beyond detoxification, this approach can be fundamentally flawed for most patients, especially those with chronic relapsing opioid dependence. Even in the study by Collins et al, in which careful steps were taken to begin ongoing treatment in the form of maintenance with naltrexone and psychotherapy, the overall treatment results in all 3 groups were poor, as evidenced by the exceedingly high dropout rate and the finding that the majority of urine samples continued to be positive for opioids.¹⁷ In fact, overall only 11% of patients both were retained in treatment for 12 weeks and provided no more than 2 opioid-positive urine samples. This is a remarkably high rate of failure and suggests that beyond the comparisons made in this study, detoxification-based approaches that are not followed by effective means of postdetoxification treatment are overwhelmingly likely to fail for patients such as those enrolled in this study.

A major limitation of this and other detoxification-based approaches is the fact that no widely effective strategies are available to help patients remain free of illicit drugs after detoxification. The approach used by Collins et al, providing naltrexone plus twice-weekly psychotherapy, represents close to the “state of the art” for outpatient treatment of detoxified patients.¹⁸ However, naltrexone has been associated with poor adherence and poor treatment outcomes, as was seen in this study.^{19,20} Thus, for a significant proportion of opioid-dependent patients, especially those with a high level of dependency and long-term drug use, all detoxification-based approaches, regardless of the specific method used, are likely to be ineffective.

Opioid maintenance treatment, on the other hand, has been demonstrated to be effective for the treatment of opioid-dependent patients.⁷ Since the mid-1960s, methadone maintenance has been the gold standard for the treatment of opioid dependence.^{4,21-25} Research has consistently demonstrated that methadone maintenance effectively decreases drug use, reduces medical comorbidity, decreases transmission of human immunodeficiency virus, reduces mortality, and improves social functioning. One study comparing methadone maintenance with an “enriched” 180-day methadone detoxification found that patients receiving methadone maintenance had much greater treatment retention (439 days vs

174 days) and were much less likely to use heroin.²⁶ In addition, the more intensive maintenance approach was actually more cost-effective than detoxification.²⁷

Since its approval by the FDA in 2002, buprenorphine has become an additional option for maintenance treatment of opioid dependence.²⁸ Maintenance treatment with buprenorphine, a partial opioid agonist, has been demonstrated to be as effective as methadone maintenance in reducing opioid use and supporting treatment retention.²⁹ In addition, like methadone, buprenorphine has been shown to be much more effective when used in maintenance treatment than for detoxification. In one study 1-year retention was 75% in buprenorphine-maintained patients and 0% in those given a 6-day buprenorphine detoxification.³⁰

The approval of buprenorphine along with the passage of the Drug Abuse Treatment Act of 2000 allowed the further expansion of effective opioid maintenance treatments into physician office settings.^{6,31} Office-based treatment now allows for the substantial expansion of opioid maintenance treatment beyond the highly regulated environment of methadone maintenance programs into the offices of appropriately trained and qualified primary care and specialty physicians, thus increasing access to this therapy. Early research supports office-based buprenorphine maintenance treatment as a highly effective alternative to maintenance program-based treatment.³²⁻³⁴

The study by Collins et al¹⁷ in this issue of *JAMA* contributes significantly to the growing body of evidence concerning effective and safe treatment for opioid dependence by further documenting that anesthesia-assisted opioid detoxification is no more effective than opioid detoxification without anesthesia and that it can be unsafe. Thus, anesthesia-assisted detoxification should have no significant role in the treatment of opioid dependence. When detoxification is provided to patients, other approaches using clonidine, methadone, or buprenorphine are likely to be at least as effective as anesthesia-assisted detoxification and also are safer and far less costly. In the larger context of treating opioid dependence, the major implication of the overall results of this study and other studies^{26,30} is that regardless of the protocol used, detoxification-based treatment of opioid dependence has a low likelihood of long-term success for most opioid-dependent patients. Further research on detoxification-based treatment should focus on how to provide effective relapse prevention treatment. In the meantime, for the majority of individuals with chronic relapsing opioid dependence, opioid maintenance using methadone or buprenorphine is much more effective than detoxification in terms of decreasing drug use, supporting treatment retention, improving health outcomes, and improving social functioning. Thus, maintenance therapy should be considered first-line treatment for such patients.

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