Elective Naloxone-Induced Opioid Withdrawal for Rapid Initiation of Medication-Assisted Treatment of Opioid Use Disorder

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We present a case of elective naloxone-induced opioid withdrawal followed by buprenorphine rescue to initiate opioid use disorder treatment in the emergency department. This strategy may represent a safe alternative to prescribing buprenorphine for outpatient initiation, a method that puts the patient at risk for complications of unmonitored opioid withdrawal, including relapse. After confirmation that the naloxone-induced withdrawal was adequately treated with buprenorphine, the patient was discharged with prescribed buprenorphine to follow up in an addiction medicine clinic, where he was treated 2 days later. [Ann Emerg Med. 2019;74:430-432.]

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INTRODUCTION

In 2017, opioid overdose accounted for 68% of the 72,000 drug overdose deaths in the United States.[1] Despite growing awareness of the opioid epidemic, overdose deaths continue to increase.[2] Medication-assisted treatment with buprenorphine improves mortality for individuals with opioid use disorder.[3,4] Buprenorphine is often prescribed for outpatient initiation after onset of spontaneous withdrawal to avoid a buprenorphine-induced withdrawal state.[5] Such a strategy has been shown to be safe and effective for emergency department (ED) patients with opioid use disorder.[6]

Despite coupling of buprenorphine prescriptions with specific instructions for obtaining continued addiction treatment, many patients are lost to follow-up and likely continue to experience opioid use disorder.[6,7] Efforts to improve rates of follow-up might include strategies for administering a first dose of buprenorphine before patient discharge from the ED. This is problematic for patients with recent opioid use in that giving the first dose early may cause withdrawal and thus lead to patient dissatisfaction with the therapy. Alternatively, waiting for a patient to withdraw spontaneously can require long periods of observation that are inappropriate for the ED.

Some have advocated using a first buprenorphine dose to improve withdrawal symptoms caused by naloxone when given to reverse opioid-induced respiratory depression.[8] Simultaneous low-dose naloxone has a relatively insignificant effect on the actions of buprenorphine, suggesting that this is a reasonable approach.[9,10] Although this strategy has not been thoroughly studied, the authors have experienced anecdotal success, observing improvement in withdrawal symptoms, possible protection against return of respiratory depression, and patient willingness to attempt continued buprenorphine. Despite increasing experience with the use of buprenorphine after naloxone, there is a paucity of literature supporting the use of an opioid antagonist to induce withdrawal for the purpose of initiating buprenorphine.[11] To our knowledge, this has not been described in the emergency setting. Such a strategy might offer an alternative to the outpatient initiation of buprenorphine, allowing rapid conversion to medication-assisted treatment within the ED.

CASE REPORT

A homeless unemployed 31-year-old man with ongoing intravenous heroin use presented to the ED with a chief complaint of leg swelling for 2 days. Physical examination findings were consistent with cellulitis and the patient was prescribed oral antibiotics. He reported using intravenous heroin with occasional intravenous cocaine daily for 15 years. The patient expressed interest in discontinuing heroin and described previous attempts to discontinue drug use, including multiple inpatient rehabilitation stays and treatment with methadone, but never buprenorphine. He had once been prescribed buprenorphine for outpatient initiation but did not begin taking the medication because of fear of precipitated withdrawal.

At presentation, the patient was clinically sober and displayed no signs of opioid withdrawal, having last used heroin 7 hours earlier. On being offered a buprenorphine prescription, the patient expressed that he would be unable to tolerate spontaneous withdrawal and would likely relapse before starting treatment. The risks and benefits of inducing withdrawal with intravenous naloxone followed by rescue with sublingual buprenorphine were discussed. The patient agreed to the suggested therapy. Motivating factors for the patient seemed to be the potential for short duration of withdrawal symptoms, access to ameliorating intravenous medications, and his previous failure to begin taking buprenorphine as an outpatient.

Naloxone 0.5 mg was administered intravenously, with continuous ECG and pulse oximetry monitoring. Before administration, the patient displayed a Clinical Opiate Withdrawal Scale score of zero.[12] At 5 minutes after naloxone administration, the patient appeared ill, with a Clinical Opiate Withdrawal Scale score of 17 (maximum possible 48). Buprenorphine hydrochloride 4 mg was administered sublingually, along with ondansetron 8 mg intravenously. At 75 minutes after naloxone administration, the patient was clinically improving, with a Clinical Opiate Withdrawal Scale score of 7. An additional 4 mg of sublingual buprenorphine was administered. At 105 minutes after naloxone administration, the patient reported feeling well. A Clinical Opiate Withdrawal Scale score was not documented but retrospectively is estimated to have been equal to or less than 2. The patient was observed for a total of 3 hours and 15 minutes from time of naloxone administration, with no return of withdrawal symptoms.

At discharge, the patient was prescribed 8 mg of sublingual buprenorphine and 2 mg of sublingual naloxone daily to last until he could be treated in the hospital's outpatient addiction clinic. This clinic reserves appointments for patients referred from the ED, allowing them to be discharged with a specific date and time for their appointment. The patient was treated in the clinic 2 days later. He continued receiving buprenorphine and naloxone, with a dose increase to 8 mg of sublingual buprenorphine and 2 mg of sublingual naloxone sublingually twice daily.

DISCUSSION

We report a case of elective naloxone-induced opioid withdrawal followed by buprenorphine rescue, performed to initiate opioid use disorder treatment in the ED. Although ED use of naloxone is typically reserved for cases involving respiratory depression, it was used in this patient without signs of opioid toxicity. The risks of naloxone (vomiting, tachycardia, seizure, etc) were thought to be outweighed by the benefit of initiating medication-assisted treatment in a monitored setting.[13] Although simply providing a prescription for buprenorphine might be better aligned with the axiom "first do no harm," we believe that the current opioid epidemic demands creative solutions for assisting patients with opioid use disorder at the point of care.

By inducing immediate withdrawal with naloxone, we were able to observe the patient during the height of withdrawal, provide symptomatic control with nonopioid medications, and confirm tolerance of buprenorphine before patient discharge. Given that buprenorphine is a partial opioid agonist with high affinity for the opioid receptor and long elimination half-life (3 to 44 hours), it is thought that the doses given in the ED not only decreased the patient's desire to use heroin after discharge but also provided temporary protection against overdose were heroin to be used.[14] We infer that the treatment increased the likelihood of the patient's presenting for follow-up care. Further research in the form of a randomized controlled trial is necessary to demonstrate this effect.

An alternative approach would have been to give the patient buprenorphine without preceding naloxone. This also would have caused a withdrawal that would likely have been improved with increasing subsequent doses of buprenorphine.[15] Problems with this approach include that the time of maximum severity for buprenorphine-induced withdrawal would be difficult to predict and almost certainly delayed relative to that of the naloxone-induced withdrawal, perhaps causing a prolonged ED stay. Additionally, there is the concern that using buprenorphine to cause withdrawal may lead the patient to become disillusioned with buprenorphine and lose trust in the process. When naloxone is given first, the buprenorphine is viewed as a *rescue* medication instead of a cause of withdrawal symptoms. Regardless of approach, the use of intravenous buprenorphine, which can be more rapidly titrated, may provide an expedited treatment course and decrease time spent in withdrawal.

We administered an intravenous dose of 0.5 mg naloxone. This dose was selected to cause a withdrawal of an intensity significant enough to ensure improvement with subsequent buprenorphine. Our experience is that lower doses are often ineffective in our patient population, which includes highly dependent opioid users exposed to large doses of multiple opioid agonists simultaneously. Smaller doses might be considered in other populations or simply to limit the severity of withdrawal. Titrating the dose at bedside to a target Clinical Opiate Withdrawal Scale score might be considered. Further work is necessary to determine what level of precipitated withdrawal is ideal.

The patient in this case was asymptomatic after buprenorphine 8 mg. Because of the medication's partial

agonist activity, it could not necessarily be expected that all withdrawal symptoms would be relieved. A clinician prescribing a similar regimen must be prepared to treat symptoms of withdrawal and must discuss the potential for prolonged withdrawal with the patient before initiation.

Physicians with a Drug Enforcement Administration license can administer buprenorphine to patients in the ED, with few restrictions. Prescribing buprenorphine for outpatient use requires an X waiver from the Substance Abuse and Mental Health Services Administration. This is obtained after completion of an 8-hour training course. We encourage all emergency physicians to obtain an X waiver and to become familiar with local outpatient providers with the same waiver so that patients receiving buprenorphine in the ED can be referred appropriately.

An ED visit offers a unique opportunity for intervention against opioid use disorder. We recommend further investigation of the benefits of starting buprenorphine before patient discharge relative to providing a prescription only.

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