Balancing Benefits and Harms on the Frontier of Buprenorphine Initiation

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Emergency clinicians are expanding their role in turning the tide of America's opioid addiction and overdose epidemic by preventing the development of addiction through responsible prescribing, harm reduction practices such as take-home naloxone, and initiation of effective treatment for opioid use disorder with buprenorphine. The needs of opioid use disorder patients that are observed in the emergency department (ED) differ from the needs of those treated by office-based clinicians, and ED-initiated buprenorphine is evolving to account for—and take advantage of—these differences and ED capabilities.

Opioid overdose fatalities continue to increase,[1] and most Americans who would benefit from opioid agonist treatment for opioid addiction are not receiving it.[2] When communities expand access to opioid agonist treatment, overdose mortality decreases substantially.[3,4] In addition to removing regulatory barriers to buprenorphine prescribing,[5,6] effectively responding to the current epidemic requires expanding the pool of clinicians who treat patients with buprenorphine and promoting innovation and progress in strategies to engage and retain patients in opioid use disorder treatment.[7,8] The unexpected severity and persistence of the current opioid epidemic is rightfully spurring reconsideration of restrictive patient selection practices. In the current low-threshold model, many patients previously considered poor candidates for buprenorphine therapy are reframed as having the highest priority for engagement in opioid agonist treatment.[9] Emergency medicine is ideally positioned to reach the most at-risk patients at a critical moment and on a population scale not feasible within the specialty addiction treatment system.

Phillips et al[10] describe an opioid-dependent person in the ED who regularly uses intravenous heroin and is interested in starting opioid agonist treatment with buprenorphine. However, because he last used heroin only 7 hours before, he was not yet in withdrawal. The patient was appropriately offered a buprenorphine prescription for home induction, but declined, reporting that he had previously been unable to tolerate spontaneous withdrawal. Prolonged observation to permit the development of withdrawal was not feasible in the typically crowded ED. To expedite the induction process, the ED treating team intentionally precipitated withdrawal by administering intravenous naloxone 0.5 mg, which they then attempted to "rescue" with sublingual buprenorphine.

Using buprenorphine to treat ED patients with opioid withdrawal syndrome is a straightforward practice that simultaneously alleviates opioid withdrawal syndrome and transitions the patient to addiction recovery with opioid agonist treatment.[11] However, many opioid use disorder patients seek emergency care for problems indirectly related or unrelated to opioid use and are not withdrawing at presentation. Because buprenorphine can precipitate withdrawal in opioid-dependent patients not in sufficient spontaneous withdrawal, most initiation pathways recommend waiting until a Clinical Opiate Withdrawal Scale score of 8 or greater develops before buprenorphine administration. Providing these patients with a prescription for buprenorphine and simple instructions on how to start the medication at home after the development of withdrawal symptoms is a successful and cost-effective approach widely used in outpatient primary care.[12]

Waiting in the ED (or at home) for the development of very unpleasant symptoms of spontaneous withdrawal is an important barrier for some opioid use disorder patients, and seeking novel solutions as Phillips et al have done is laudable. Others have reported intentionally precipitating withdrawal to facilitate buprenorphine initiation, using multiday protocols supplemented with nonagonist withdrawal treatments.[13,14] However, the balance of benefit and harm when compared with alternatives, as well as concerns around patient understanding and consent to this intensely unpleasant procedure, does not presently support the practice of elective naloxone-induced opioid

withdrawal in the ED as a buprenorphine induction strategy.

The administration of naloxone is indicated when there is risk of harm because of sedation or respiratory depression from opioid overdose, or to address diagnostic uncertainty in the patient who might have occult opioid toxicity. The clinical effects that accompany reversal of an opioid agonist are highly unpredictable, and although abstinence-related opioid withdrawal syndrome is generally considered not to be life threatening, precipitated withdrawal, including naloxone doses as low as 0.1 mg,[15] can be dangerous.[16,17] It is difficult to justify electively assuming these risks, given the alternatives, and difficult to defend care if there were to be a bad outcome.

Every hour people with opioid use disorder are at therapeutic levels while receiving buprenorphine is an hour they are safe from withdrawal, cravings, and overdose, and we endorse efforts to treat as many opioid use disorder patients with buprenorphine as feasible. However, despite the sense of urgency that both clinicians and patients feel during crisis moments, opioid use disorder is, in fact, a chronic relapsing-remitting disorder. Buprenorphine treatment typically involves multiple episodes of return to illicit opioid use before long-term recovery is achieved. We therefore cannot yet endorse assuming the risks and harms of urgently inducing precipitated withdrawal even to enable immediate buprenorphine treatment until the true clinical value is better understood.

Although a very intriguing and supportable concept to allow expedited buprenorphine initiation, the case described may not provide sufficient evidence to suggest that the approach used was effective. Once naloxone-precipitated withdrawal occurred, 4 mg sublingual buprenorphine and 8 mg intravenous ondansetron were administered. However, the patient did not experience sufficient relief of the precipitated withdrawal until almost 2 hours after the dose of naloxone (greater than 9 hours after last heroin use). This is much longer than expected from sublingual buprenorphine, which typically provides significant relief within 30 minutes after an adequate dose. Furthermore, because intravenous naloxone has a duration of action of 1 to 2 hours, another credible interpretation of this patient's experience may be that the naloxone simply wore off and the patient was back to baseline. Rather than discarding this treatment as ineffective, however, this case serves as a call for further study of its value. The intended outcome, return for substance abuse treatment, was accomplished, highlighting the critical role that buprenorphine plays in the process.

Like Phillips et al, we are eager to develop strategies to quell withdrawal precipitated by naloxone administered for opioid overdose in the field and transition these patients rapidly to buprenorphine. Although this approach may prove to be effective, the potential interactions among naloxone, buprenorphine, and heroin complicate the treatment approach. For example, if the opioid agonist is still present after termination of naloxone's antagonism, the buprenorphine may itself precipitate withdrawal independently of the previous administration of naloxone. In the reported case, the second dose of buprenorphine 4 mg was administered more than 9 hours after last heroin use, which is when withdrawal from heroin abstinence usually develops, and may explain why the buprenorphine was well tolerated rather than itself precipitating withdrawal.

Not surprisingly, there is a sense of urgency to get high-risk patients to a therapeutic buprenorphine level because this likely confers significant short-term protection from overdose and is a first step toward long-term engagement in treatment. The concept of using buprenorphine in the ED to treat naloxone-precipitated withdrawal in opioid overdose victims and as a starting point for long-term buprenorphine treatment is promising but ultimately not supported by this case. In actual practice, the pathway from recognition of a patient in need and initiation of buprenorphine treatment is complex, and many lessons are yet to be learned.

Nearly all opioid overdose deaths are preventable. Emergency clinicians are uniquely positioned to redirect the lives of people with opioid use disorder because the ED is where these patients come for help. Central to this mission is treating appropriate patients with buprenorphine and catalyzing their sustained engagement in comprehensive addiction care. The majority of these patients can be treated within established protocols and guidelines. For individuals who require an alternative approach, providers must keep their view focused on the balance of benefit and harm as they navigate the frontiers of buprenorphine pharmacology.

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