Challenges with current diagnosis and treatment strategies for precipitated opioid withdrawal in the emergency department and the role of the pharmacist

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Purpose: To demonstrate the challenges with current diagnosis and treatment strategies for precipitated opioid withdrawal secondary to naloxone the emergency department (ED) setting and describe the role of the emergency medicine (EM) pharmacist in its management.

Summary: There are no standardized criteria to define precipitated opioid withdrawal syndrome, so the diagnosis is typically based on sentinel signs and symptoms and time course. Complicating factors include a positive urine toxicology screen for nonopioid substances, comorbidities and associated medications prior to admission, medications given in the ED, and a fluctuating patient course during the ED stay that likely involves all these issues. Although buprenorphine is frequently recommended as the primary treatment for precipitated withdrawal, its use can be complicated if patients are on methadone maintenance or other long-acting opioids. The EM pharmacist plays a key role in managing patients with precipitated withdrawal.

Conclusion: Practice changes related to the diagnosis and treatment of opioid use disorder (OUD) with precipitated withdrawal in the ED are needed. EM pharmacists as part of the interprofessional care team have an important role in the management of patients with OUD, including those patients undergoing possible precipitated withdrawal.

Keywords: analgesia, buprenorphine, critical care, opioid use disorder, pain, precipitated withdrawal

Am J Health-Syst Pharm. 2025;82:60-64

The number of cases of precipitated withdrawal is likely to increase as access to naloxone increases in conjunction with a perceived need for higher doses of naloxone for synthetic opioid overdoses, particularly fentanyl and high-potency fentanyl analogs such as carfentanil.[1] Additionally, buprenorphine can cause precipitated withdrawal in patients who regularly use opioids by displacing lower-affinity agonists from opioid receptors.[2] As suggested by the name, patients experiencing precipitated opioid withdrawal generally have a more fulminant, abbreviated time course than patients undergoing spontaneous withdrawal after stopping an opioid.[3] The associated catecholamine surge can result in life-threatening pulmonary edema and cardiac arrythmias in addition to the unpleasant combination of vomiting, agitation, and tachycardia.[4] Patients in precipitated withdrawal may present to the emergency department (ED) in such extremis that they can be difficult to diagnosis and manage, especially if they are not able to provide a history.[2] As they look so ill, clinicians may be hesitant to attribute their condition simply to withdrawal.

Often, these patients' undifferentiated agitation is treated with medications such as diphenhydramine, haloperidol or droperidol, and lorazepam, often in conjunction with intubation to secure the airway. Although buprenorphine is often recommended as the first-line treatment

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https://doi.org/10.1093/ajhp/zxae212

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for precipitated withdrawal,[5-8] emergency medicine (EM) clinicians may not be comfortable recognizing precipitated withdrawal using instruments such as the Clinical Opiate Withdrawal Scale (COWS) or the Subjective Opiate Withdrawal Scale (SOWS) or treating withdrawal with medications such as buprenorphine.[2] Additionally, buprenorphine may only be available in tablet or film formulations, and sublingual (SL) administration may present challenges in acutely ill patients.[9] Moreover, for patients who are on methadone maintenance, buprenorphine is rarely the ideal treatment. This clinical consultation demonstrates the challenges with current diagnosis and treatment strategies for precipitated opioid withdrawal secondary to naloxone use in the ED setting and describes the role of the EM pharmacist in its management.

KEY POINTS

- Cases of opioid-related precipitated withdrawal are likely to increase with a perceived need for higher doses of naloxone for synthetic opioid overdoses.
- There are no standardized diagnostic criteria for defining precipitated withdrawal, so the diagnosis is based on signs and symptoms and the time course of withdrawal.
- Care of patients experiencing suspected precipitated withdrawal is challenging from both diagnostic and treatment perspectives, and consultation with addiction and pain specialists is recommended.

Potential factors complicating initial diagnosis and ongoing management

Potential factors complicating the diagnosis and management of patients presenting to the ED with suspected opioid use disorder (OUD) and precipitated withdrawal include a urine drug screen that is positive for nonopioid substances (as polysubstance use is increasingly common among people who use drugs) or even negative because it did not screen for fentanyl, comorbidities, prior administration of long-acting opioids (methadone) that may not be known on presentation, and a persistently altered mental status, possibly secondary to all the above issues.[10-12] The negative urine screen for opiates is not unexpected since standard urine assays only test for naturally occurring opioids and not synthetic opioids such as fentanyl, but it does make diagnosis more confusing. This has led to calls for more point-of-care testing with assays that do detect fentanyl.[13]

Additionally, patients presenting in such extremis and with such a persistently altered mental status raise questions with regards to differential diagnosis, even when the past medical history and time course of events is consistent with precipitated withdrawal. For example, some patients in precipitated withdrawal have such significant tachycardia, leukocytosis, and rigid abdomens (secondary to the gastrointestinal distress of withdrawal) that differential diagnosis can be quite broad. In such a situation, many ED clinicians might prefer to sedate and intubate a patient to expedite the diagnostic workup and rule out life-threatening causes such as intracranial hemorrhage, a surgical abdomen, or sepsis.

Criteria for defining precipitated opioid withdrawal syndrome

There are no standardized criteria to define precipitated opioid withdrawal syndrome,[3] so the diagnosis is typically based on history, sentinel signs and symptoms, and time course. Signs and symptoms of opioid withdrawal include eye tearing, yawning, lacrimation, rhinorrhea, perspiring, and hot flashes, which ideally should be diagnosed with a validated instrument such as the COWS or SOWS.[3] The abbreviated time course from provoking agent to symptom onset helps differentiate precipitated withdrawal from spontaneous withdrawal.[3]

The duration of precipitated withdrawal is a function of the half-life of the precipitating agent, which is approximately 2 hours for a dose of naloxone given naloxone's half-life of approximately 60 minutes. However, this duration of withdrawal is likely to be extended when large and/or multiple naloxone doses are administered due to drug accumulation, or when the long-acting opioid antagonist nalmefene is administered, given that its terminal elimination half-life is approximately 11 hours.[14] The potential for severe, prolonged opioid withdrawal with nalmefene versus naloxone has led the American College of Medical Toxicology and the American Academy of Clinical Toxicology to publish a position statement recommending against the use of nalmefene as a primary opioid antidote until more supportive studies are available.[15] The half-life of sublingual buprenorphine is more variable, with a mean of 24 to 48 hours in most studies.[16] Thus, if buprenorphine is the agent that precipitates withdrawal, its effects can last quite a bit longer.

Naloxone dosing issues

The most appropriate dose of naloxone for opioid reversal has been the subject of debate ever since the initial labeled dose of 0.4 mg of intramuscular IM naloxone was increased to 2 mg following recommendations from a US Food and Drug Administration advisory committee in 2016.[17] One of the currently available naloxone products is a 10-mg/0.4 mL solution in a single-dose, prefilled auto-injector intended for subcutaneous (SC) or IM administration when use of high-potency opioids such as fentanyl analogs is suspected.[18] It has been theorized that higher doses of naloxone are routinely needed for the reversal of high-potency synthetic opioids, and escalating dosing regimens suggested in the literature

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could lead to more than 30 mg of intravenous (IV) naloxone being administered within a 10-minute period.[19] The evidence base supporting this contention is weak.[20]

A notable downside of excessive naloxone doses is the likelihood of highly symptomatic precipitated withdrawal that can complicate treatment in the ED and hinder attempts to convince patients to seek subsequent outpatient care for OUD given their poor experience. Some of the potential adverse effects associated with naloxone are not trivial. For example, product labeling refers to the need to monitor for serious adverse events including hypotension, ventricular tachycardia or fibrillation, and pulmonary edema. The latter problem is thought to be a centrally mediated massive catecholamine response leading to increased blood volume in the pulmonary vascular bed and resulting in high-pressure edema.[18] Although a clear dose-effect relationship for naloxone has not been demonstrated for serious adverse effects, a recent systematic review demonstrates the need for caution with high doses of naloxone.[21] Tachycardia and pulmonary edema were found in a higher percentage of patients receiving high-dose (>2 mg) compared to standard-dose (0.4 to 2 mg) naloxone (22.1% [21/95] vs 100% [2/2], P = 0.404, and 4.2% [4/95] vs 50% [1/2], P = 0.10, respectively). Although these differences were not statistically significant, likely due to sample size issues, they raise potential concerns about unnecessarily high naloxone doses.

Medications for treating undifferentiated anxiety and agitation

Common treatments for acute, undifferentiated anxiety and agitation in the ED include antipsychotics such as haloperidol or droperidol, lorazepam for sedation, anticholinergics such as diphenhydramine for additional sedation and to prevent extrapyramidal symptoms, and α agonists such as dexmedetomidine.[22] Many of these agents are also used as supportive treatments for opioid withdrawal. There is limited evidence supporting the notion that the benefits of such regimens exceed their associated risks,[23] particularly in patients undergoing opioid withdrawal, for whom escalating doses of benzodiazepines or antipsychotics will only increase the likelihood of adverse effects while not addressing the underlying problem. Combinations of these agents with opioids such as buprenorphine may lead to additive or synergistic sedation that may complicate the diagnosis of possible comorbidities and prolong the time to patient discharge. Of note, there are studies that suggest that ketamine also has potential usefulness in treating precipitated withdrawl.[24,25]

Buprenorphine for precipitated opioid withdrawal

Buprenorphine is a partial opioid mu-opioid receptor agonist and antagonist of the kappa-opioid receptor that is available in variety of forms in the US, including buprenorphine SL, buccal film, transdermal patch, SC extended release, and a subdermal implant.[26] Implementation of buprenorphine protocols in EDs for patients with OUD is considered a public health priority, but initiating buprenorphine in patients on lower-affinity opioid receptor agonists such as fentanyl may lead to precipitated withdrawal in patients not experiencing at least moderate spontaneous withdrawal from the lower-affinity agonist.[27] Therefore, buprenorphine induction was traditionally withheld until a patient was experiencing moderate withdrawal. Similarly, it used to be believed that smaller initial doses of buprenorphine were more likely to prevent precipitated withdrawal, but this tenet is also being called into question as more ED studies successfully utilize macroinductions of 16 or 32 mg.[28] Additionally, there have been studies supporting the use of microinduction/cross-taper inductions that do not require patients to cease their full opioid agonists or enter withdrawal before initiating buprenorphine.[29-31]

In appropriately selected patients, high doses of SL buprenorphine have been recommended as the first-line treatment for patients undergoing precipitated withdrawal secondary to buprenorphine or naloxone administration.[2,7,8,32] Although most cases of precipitated withdrawal resolve after administration of 32 mg of SL buprenorphine,[2] there are case reports that describe patients needing much higher doses.[8] In addition to resolving the patient's constellation of symptoms, it also is the first step towards maintenance therapy for OUD.

Buprenorphine IV has the most rapid onset of action and does not have the bioavailability limitations (ie, reduced absorption) noted with products given by other routes, making it an attractive option in acutely ill patients unable to use other formulations. However, IV buprenorphine is only indicated for severe pain necessitating long-term treatment when other pain control options are inadequate. The IV product is not widely available, is costly, and is only available in one dosing formulation (ie, 0.3 mg/mL for injection).[33]

Because buprenorphine is a partial mu-opioid receptor agonist, it has a ceiling effect for respiratory depression with doses above approximately 16 mg but does not appear to have a similar ceiling effect for analgesia or alleviating withdrawal.[34] For example, there was a randomized trial in which 90 patients with OUD were randomly assigned to receive buprenorphine in single SL doses of 32, 64, or 96 mg during withdrawal.[35] Craving, as defined by a visual analog scale (0 = no craving and 10 = severe desire, craving, or temptation all the time), decreased from baseline in each of the groups (P < 0.0001), with higher doses of buprenorphine associated with greater reductions in craving. Inexperienced providers in the ED setting who are less familiar with the literature concerning buprenorphine may be reluctant to prescribe such high doses, particularly in patients who have alterations in mental status along with an inability to provide a history or follow

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commands. A more comprehensive evaluation of possible buprenorphine dosing regimens is available for the interested reader.[26]

Despite the potential advantages of buprenorphine over other treatment options for OUD and for precipitated withdrawal, for patients who are on methadone maintenance, buprenorphine is rarely the best treatment option. Buprenorphine may replace methadone at opioid receptors but not activate the receptors to the same degree, leading to precipitated withdrawal.[36] Additionally, both buprenorphine and methadone are long-acting, which could lead to a prolonged state of precipitated withdrawal. An alternative strategy for patients on methadone is to give push doses of fentanyl instead of buprenorphine to counteract the precipitated withdrawal until the naloxone wears off. However, there is little evidence to support such a practice. As indicated by this discussion, the treatment of patients experiencing withdrawal secondary to methadone use is complicated, so addiction and pain specialists should be consulted if available.[37]

Role of the EM Pharmacist

EM pharmacists as part of the interprofessional care team have an important role in the management of patients with OUD, including those patients undergoing possible precipitated withdrawal. The relatively recent relaxation of prescribing requirements for medications used for OUD represents an educational opportunity for pharmacists since some of these medications are likely to be unfamiliar to other care team members. This can include education of emergency services personnel on the appropriate dosing of naloxone in the prehospital setting. As experts in medication optimization, EM pharmacists are particularly likely to be helpful in providing recommendations for the selection, dosing, and ongoing monitoring of the effectiveness and safety of medications used for opioid withdrawal, including precipitated withdrawal. As noted earlier, buprenorphine is commercially available in a wide range of formulations and the EM pharmacist can be helpful in knowing which products are available in their ED setting, as well as potential product limitations (eg, the IV injection is only available in a 0.3-mg/mL formulation with no indication for OUD). Similarly, the EM pharmacist can evaluate potential drug interactions, such as those between medications often used for treating undifferentiated agitation and anxiety and medications such as buprenorphine used for managing OUD and withdrawal. EM pharmacists also have an important role in helping to develop clinical decision support tools that have the potential to lead to more appropriate prescribing of medications for OUD and opioid withdrawal. Importantly, the EM pharmacist can also help to recognize when additional expertise, such as that of addiction and pain specialists, is needed. Finally, there remains a paucity of research publications concerning the use of buprenorphine for precipitated withdrawal in the ED, so this is an excellent opportunity for those EM pharmacists who have the willingness and opportunity to be involved in such scholarship activities.

Conclusion

Practice changes related to the diagnosis and treatment of OUD with precipitated withdrawal in the ED are needed, beginning with education of EM clinicians by EM pharmacists and addiction and pain specialists. EM pharmacists can provide recommendations for the selection, dosing, and ongoing monitoring of the effectiveness and safety of medications used for opioid withdrawal, including precipitated withdrawal. EM pharmacists can also play a role in developing clinical decision support tools such as order sets that have treatment algorithms for opioid withdrawal.

Data availability

No new data were generated or analyzed in support of this article.

Disclosures

The authors have declared no potential conflicts of interest.

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