Managing Opioid Withdrawal in the Emergency Department With Buprenorphine

Andrew A. Herring, MD; Jeanmarie Perrone, MD; Lewis S. Nelson, MD*

*Corresponding Author. E-mail: lewis.nelson@rutgers.edu, Twitter: @LNelsonMD.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2018.11.032

A **podcast** for this article is available at www.annemergmed.com.

Continuing Medical Education exam for this article is available at http://www.acep.org/ACEPeCME/.

[Ann Emerg Med. 2019;73:481-487.]

OVERVIEW

Emergency departments (EDs) provide acute treatment for patients with opioid use disorder, including opioid overdose and opioid withdrawal, and serve as access portals for the initiation of medication-assisted therapy (also called medication for addiction treatment, or medication for opioid use disorder).[1] To combat the public health crisis associated with opioid use disorder, the surgeon general, the Centers for Disease Control and Prevention, state governments, and many others have called on EDs to improve the quality of care offered to this patient population, particularly through the expanded use of buprenorphine.[1]

Although much attention has focused on treatment of patients with opioid overdose, opioid withdrawal is a high-risk period that is associated with elevated mortality after discharge.[2–4] More than half of patients who died from an opioid overdose were noted to have had a medical visit in the year before their death.[5] Abstinence without medical intervention, whether voluntary (eg, "cold turkey," abstinence-based treatment) or involuntary (eg, incarceration), further increases the risk for overdose.[6]

Because treatment of opioid withdrawal is a starting point for induction into medication-assisted therapy, the two are difficult to disentangle. In fact, they do not need to be separated, and they are discussed here together.

PATHOPHYSIOLOGY: WHO IS AT RISK FOR OPIOID WITHDRAWAL?

Opioid dependence must be present, by definition, for an individual to develop opioid withdrawal. The time course for the development of opioid dependence is variable, generally from days to weeks, contingent on factors such as the specific opioid formulation and routes and frequency of administration.[7] Use of short-acting opioids such as heroin or oxycodone several times daily for at least 2 weeks is needed before opioid dependence develops. Furthermore, the degree of dependence, and thus the severity of opioid withdrawal, is directly related to the intensity (eg, dose, duration, continuity) of exposure. After sustained exposure, μ-opioid receptors adapt to the presence of opioid agonists, which tonically suppress neuronal excitability. When the μ-opioid receptors are unbound, neuronal disinhibition and hyperexcitability result in the clinical findings of opioid withdrawal.

OPIOID WITHDRAWAL SYNDROMES

Opioid withdrawal manifests as 2 distinct yet reinforcing subsyndromes, psychological and physiologic. The physiologic findings include restlessness, nausea, vomiting, diarrhea, piloerection, diaphoresis, yawning, mydriasis, and mild autonomic hyperactivity. The psychological effects, including pain, anxiety, stress intolerance, irritability, and drug craving, coincide with the physiologic signs but may persist for weeks to months after physiologic normalization.[8]

Abstinence-related opioid withdrawal results from the discontinuation of opioid use in a patient with opioid dependence and is generally not life threatening. The onset varies according to the opioid (Table 1). Clinicians should explore the underlying reason for abstinence (eg, medical illness, desire for abstinence).

Precipitated opioid withdrawal develops abruptly after administration of an opioid antagonist, partial agonist, or agonist-antagonist (Table 2). Depending on the specific precipitant and the dose and rate of administration, the clinical effects of precipitated opioid withdrawal range from mild, self-limited discomfort to more concerning findings such as vomiting and agitation. Among the most severe manifestations are delirium and autonomic instability. The latter effect, caused by massive catecholamine release, may lead to cardiovascular complications such as pulmonary edema.[9]

Table 1. Typical time course following last use of physiologic opioid withdrawal for common opioids.

Drug	Onset, Hours	Peak	Resolution, Days
Buprenorphine	4–48	96 h	14–21
Fentanyl (intravenous)	2–5	8–12 h	4–5
Heroin	6–12	24–72 h	7–10
Short-acting prescription opioids	6–12	24–72 h	7–10
Long-acting prescription opioids	12–36	2–5 days	10–14
Methadone	24–72	4–6 days	14–21

The psychological effects (ie, postacute withdrawal syndrome) may last for several months.

DIAGNOSIS AND ASSESSMENT OF OPIOID WITHDRAWAL

Opioid withdrawal is a clinical diagnosis based on the physical examination and patient history. There are several tools that may be used to assist in evaluation of opioid withdrawal severity. The most widely used tool is the Clinical Opiate Withdrawal Scale. The scale grades severity from 0 to 36 points in accordance with the evaluation of typical effects, including pulse, pupillary size, restlessness, and yawning. Although the scale was not developed for use as a guideline for buprenorphine initiation, its long-standing use in this role has been valuable.[10] Unobserved or "home" induction, which is finding increasing use from the ED, is often guided by the Subjective Opioid Withdrawal Scale.[11]

TREATMENT OF OPIOID WITHDRAWAL

Although very uncomfortable, opioid withdrawal is rarely life threatening. However, untreated opioid withdrawal commonly results in return to high-consequence opioid use, with a high risk of overdose death after discharge from the ED.[6,12,13] There is increasing pressure to make medication-assisted therapy a standard practice; Massachusetts recently mandated ED treatment of opioid use disorder.[14] Nevertheless, despite the strong evidence supporting the benefit of medication-assisted therapy, there remains substantial variation in personal, institutional, and regional culture in opioid use disorder treatment approaches.[11]

Nonopioid Treatments

Self-treatment of opioid withdrawal (eg, kratom) and nonopioid pharmacologic treatment are described in Table 3.[15,16]

Opioid Agonist Treatment

The evidence-based approach and growing consensus in the ED is to use an opioid agonist (a form of medication-assisted therapy) to both treat opioid withdrawal and bridge to long-term treatment. Buprenorphine and methadone are both widely used and highly effective in safely stemming the physiologic and psychological effects of opioid withdrawal.[17] Although hospital logistics often dictate the decision, buprenorphine is the preferred option in the ED.

Methadone is a full agonist at the μ-opioid receptor and commonly used through opioid treatment programs for maintenance treatment, with daily oral doses ranging from 10 mg to greater than 100 mg. A methadone dose of 10 mg intramuscularly or 20 mg orally significantly reduces the Clinical Opiate Withdrawal Scale score in ED patients with opioid withdrawal.[18] At this recommended dose, methadone will not lead to consequential sedation or respiratory depression in awake patients.

Buprenorphine is a unique μ-opioid receptor partial agonist with minimal euphoric reward and a ceiling effect on both sedation and respiratory depression. It is generally administered as a sublingual (not swallowed) tablet or strip and is available for intravenous use as an analgesic.

Table 2. The pharmacology of precipitated opioid withdrawal.

Precipitant	Class	Typical Route*	Onset of Opioid Withdrawal, Minutes	Duration of Opioid Withdrawal	Treatment
Butorphanol or nalbuphine	Agonist-antagonist	Parenteral (intramuscular)	15	90 min	Supportive
Naloxone	Antagonist	Parenteral	1–3	30–60 min	Supportive†
Naltrexone	Antagonist	Oral	15–30	12–24 h	Buprenorphine or high-dose opioids‡
Buprenorphine	Partial agonist	Sublingual	10–15	12–24 h	Buprenorphine

*All of these agents can be administered by multiple routes, affecting the pharmacokinetics, clinical effects, and necessary treatment approaches.
†The potential benefit of buprenorphine in patients with naloxone-precipitated opioid withdrawal is being investigated.
‡High-dose opioids: fentanyl is frequently used because of titratability; start with 50 μg (adult) intravenously and increase.

Table 3. Pharmacologic and dietary supplement options to treat opioid withdrawal.

Medication	Class	Clinical Use	Dose	Comments*
Clonidine	α-2 agonist	Autonomic hyperactivity	0.1 mg PO; can repeat	Hypotension and bradycardia common but generally inconsequential
Kratom *(Mitragyna speciosa)*	Opioid agonist mitragynine and 7-hydroxymitragynine	Opioid agonist (unregulated)	Undefined	Can reduce craving because of its opioid agonism. Significant abuse potential.
Lofexidine	α-2 agonist	Autonomic hyperactivity	0.54 mg PO	FDA approved, $1,700. Less hypotension than with clonidine.
Loperamide	Nonabsorbed opioid agonist†	Diarrhea	2–4 mg PO	Abuse potential at high doses
Metoclopramide	Dopamine antagonist	Vomiting	10 mg PO; can repeat	QT prolongation
Ondansetron	Serotonin antagonist	Vomiting	4 mg PO; can repeat	QT prolongation

PO, Orally; *FDA*, Food and Drug Administration.
*None of the nonopioid pharmacologic options reduce craving.
†Can be absorbed at high doses, leading to its popular use as self-treatment for opioid withdrawal.

There is currently no definitive approach to the ED dosing strategies for buprenorphine. Office-based clinical guidelines for induction are not practical for ED use because of their low dosing and slow titration.[19]

There are few formal studies of buprenorphine for the treatment of opioid withdrawal. In 2 small studies, patients with a history of heroin use who presented in withdrawal (Clinical Opiate Withdrawal Scale score ≥13) and were receiving 8 mg SL and had a mean reduction in Clinical Opiate Withdrawal Scale score of 7 points (from 15 to 8),[20] whereas those treated with 24 mg SL buprenorphine experienced a larger mean reduction in Clinical Opiate Withdrawal Scale score (from 17 to 2).[21] Given the paucity of approaches that are ED specific, there is variation in current practice.[22–24] In general, patients in the ED can be expected to require buprenorphine at at least 8 mg SL to achieve substantive relief, and the majority of patients markedly improve with a 16-mg SL total dose; the maximum is 32 mg SL.

Excessive buprenorphine dosing causes mild sedation, but the use of insufficient buprenorphine risks the premature return of opioid withdrawal and craving during the high-risk period immediately after discharge from the ED. For this reason, certain guidelines recommend up to 32 mg SL as an induction dose to prolong the duration of opioid withdrawal suppression after discharge.[24] Reasonable caution, particularly in regard to the elderly, patients with decreased respiratory function, or those with co-occurring sedative use, should be exercised when higher doses are used.

An immediate concern with initiating buprenorphine is the displacement of a full agonist by a partial agonist that can result in precipitated opioid withdrawal. The development of precipitated opioid withdrawal depends on several factors, including the relative plasma concentrations and receptor affinities of the agonist and partial agonist.[25–27] For example, the relative antagonism after administration of a large dose of buprenorphine (partial agonist/high binding affinity) to a patient receiving methadone (full agonist/low binding affinity) will likely result in precipitated opioid withdrawal, whereas patients receiving buprenorphine can receive full-agonist opioids for analgesia without concern for precipitated opioid withdrawal.[28–30]

The relief provided by buprenorphine increases with worsening opioid withdrawal severity and increased dose of buprenorphine. Although a Clinical Opiate Withdrawal Scale score of 8 is a suggested minimum for initiation by some guidelines, at least one objective sign of opioid withdrawal indicates readiness to initiate buprenorphine. More conservative guidelines suggest withholding buprenorphine until the Clinical Opiate Withdrawal Scale score is 13. Particular caution should be taken with patients receiving methadone; most guidelines recommend waiting at least 48 hours since last use and until objective signs of withdrawal are present.

There is no consensus for the optimal initial buprenorphine dose. Some guidelines recommend a lower initial dose of buprenorphine (eg, 2 to 4 mg SL). However, because the treatment for buprenorphine-precipitated opioid withdrawal is administration of additional buprenorphine, a larger initial dose may carry less risk of precipitated opioid withdrawal. This seemingly paradoxic effect occurs because of optimization of partial agonist stimulation as the buprenorphine dose increases before reaching its ceiling dose.[31]

Although no single algorithm can account for the clinical complexity encountered in emergency practice, a

reasonable approach is shown in Figures 1 and 2. A common induction target dose before ED discharge is 16 mg SL, which may be comfortably increased as provider experience and judgment increase.[22,32,33]

A recently available injectable depot formulation provides several weeks of opioid withdrawal suppression, but it is costly and has not yet been studied for use in the ED.[34,35]

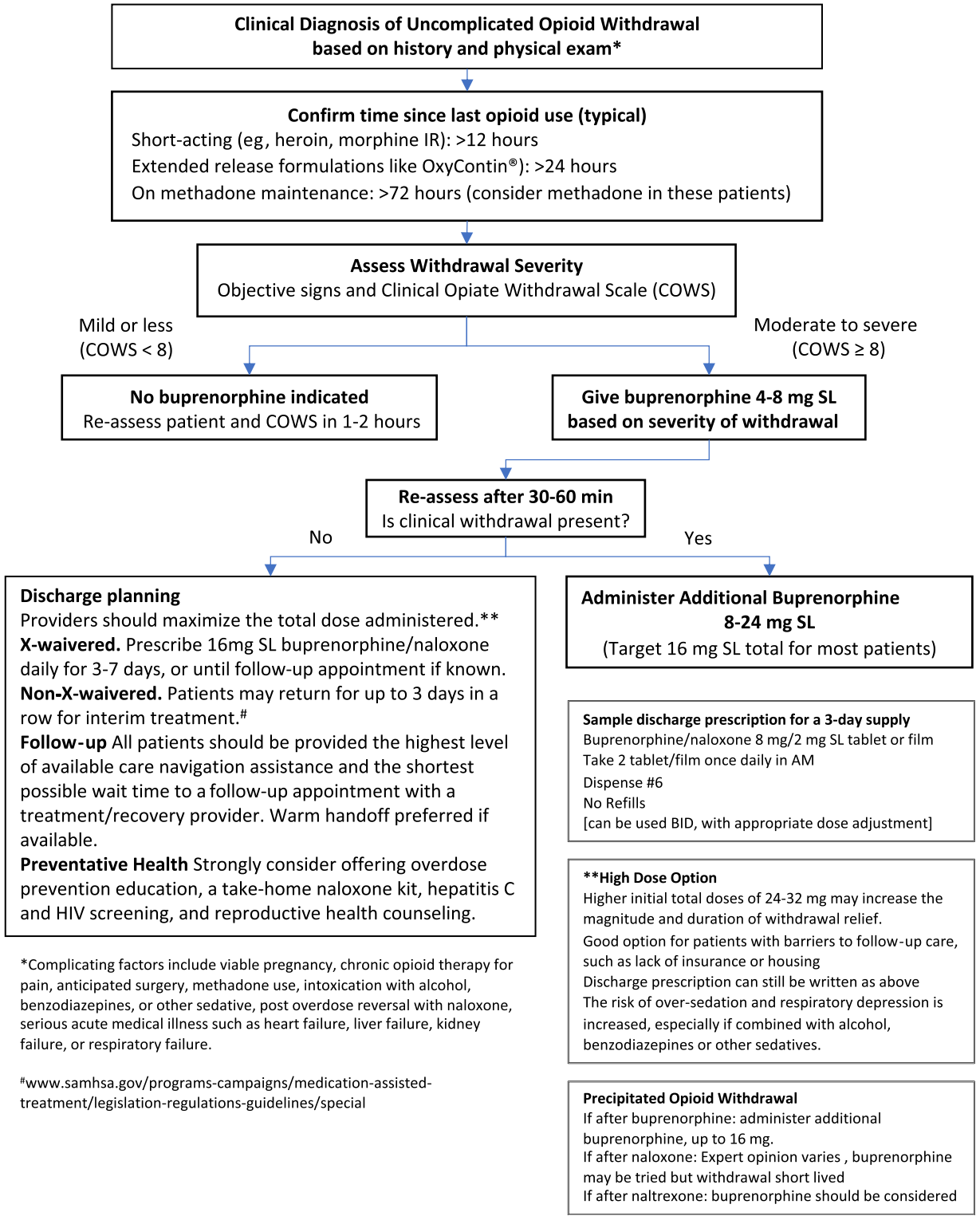

Figure 1. Algorithm for treatment of opioid withdrawal. *BID*, Twice a day.

Initial clinical assessment

- Is the patient experiencing moderate opioid withdrawal (OW)? The clinical opioid withdrawal scale (COWS) may be used if unsure,
- Is the time since last use of opioid consistent with OW?
- Is there a complicating factor to be addressed prior to administration of buprenorphine?
  - Mild withdrawal—is it too early for buprenorphine administration?
  - Altered mental status—co-intoxicant, decompensated psychiatric disease
  - Methadone use—methadone is usually a better option
- No laboratory testing is required, pregnancy testing, Hepatitis C and HIV, and urine drug screening may be offered.
- No initial counseling or psychosocial intervention is required.
- Interest in long-term treatment is not required.

First dose

- Typically, 4-8 mg sublingual (SL) buprenorphine or buprenorphine/naloxone
- Initial doses ranging from 2-32 mg SL may be considered depending on the clinical situation

Clinical Reassessment at 30-60 minutes

- Marked and unequivocal improvement in signs and symptoms confirms clinical diagnosis of OW and that buprenorphine is well tolerated.
- Lack of improvement should provoke reassessment of the clinical situation and treatment.
  - Is there a primary medical issue such as sepsis from an injection-related infection?
  - Is there persistent or worsening (precipitated) withdrawal suggesting insufficient partial agonism (higher buprenorphine dose needed, up to 16 mg)?
  - Is there worsening withdrawal suggesting antagonist effects (POW?)

Completion of treatment and discharge

- If the patient is comfortable after the first dose no additional treatment is required.
- Additional doses can be administered in the ED to prolong duration and magnitude of effect; typical daily doses of SL buprenorphine range from 8-32 mg.
- X-waivered
  - Prescribe for patients wishing to continue buprenorphine treatment or as a harm reduction rescue measure
  - Prescribe sufficient days of buprenorphine for patients awaiting entry into a treatment program
  - In general, the prescribing X-waiver provider must have a face-to-face visit with the patient. Under emergency circumstances a two-way audio-visual encounter (Telehealth) can be used to provide up to a 5-day prescription.
- Non-X-waivered
  - Provide a patient awaiting entry to a treatment program with once-daily direct administrations of buprenorphine for up to three consecutive days from the ED.
- Care navigation will increase rates of engagement in long-term treatment for OUD and should be provided if local resources allow.

Complicating factors

- Is there a viable pregnancy? If so, fetal monitoring during treatment may be considered. Pregnancy is not a contraindication to the use of buprenorphine with our without naloxone.
- Is the patient under full agonist treatment for either pain or OUD? If so, methadone may be the more appropriate treatment.
- Will the patient require surgery or full agonist opioids for acute pain? If so, full agonist opioid may be the more appropriate treatment. Alternatively, buprenorphine can be started and continued as a lower dose, more frequently dosed regimen, such as 2-4mg Q 4-8 hours, with additional high-affinity full agonist opioids as needed.
- Opioid withdrawal co-occurring with sedative intoxication (alcohol, benzodiazepines) may require complex management not easily protocolized. The PDMP may include information about other controlled substance prescriptions that may contribute to substantive withdrawal.
- Expert opinion varies on the optimal timing for buprenorphine administration after naloxone-POW. Better understanding of both the complex pharmacokinetic interactions involved and clinical study is required before evidence-based clinical recommendations are possible. Buprenorphine should be strongly considered in a patient with naltrexone-POW.

Figure 2. Guideline for treatment of opioid withdrawal. *OUD*, Opioid use disorder; *PDMP*, prescription drug monitoring program.

REGULATORY AND LEGAL ISSUES

It is a common misconception that the administration of buprenorphine requires a Drug Addiction Treatment Act of 2000 X-waiver. In fact, short-term treatment with *direct administration* of any opioid approved for use in maintenance or detoxification treatment (typically buprenorphine or methadone) is permitted under the "3-day rule" (Title 21, Code of Federal Regulations, Part 1306.07). Under this rule, discharged patients may return to the ED daily to receive the medication for up to 72 hours.[36]

An X-waiver is required to prescribe buprenorphine for the treatment of opioid use disorder. Any provider who holds a Drug Enforcement Administration registration may apply for an X-waiver after an 8-hour training program and examination.[37] Although abbreviated training programs designed for emergency physicians may provide the needed tools for ED buprenorphine use, they currently do not suffice to gain prescribing privileges. Prescribing methadone for opioid use disorder is not covered by an X-waiver and is not allowed outside of an opioid treatment program. However, admitted patients with opioid use disorder may receive buprenorphine or methadone indefinitely to permit the ongoing treatment of a concomitant medical issue.[38]

Buprenorphine diversion may occur, but its abuse potential and risk profile remain substantially better than that of full-agonist opioids. State prescription drug monitoring programs typically collect buprenorphine dispensing data and specifically omit data on opioid treatment program dispensing of methadone (by law).

State law and insurance providers vary in their requirements for previous authorization and other administrative expectations. These sometimes impede the ability to readily obtain prescribed buprenorphine, although an ED pharmacist or care coordinator may provide assistance.

DISPOSITION

Local resources determine the available options for patients who would like to continue buprenorphine treatment. As noted, providers with an X-waivercan prescribe buprenorphine until the next available treatment appointment. If no waivered provider is available, a systematic plan for next-day or at least rapid follow-up should be developed. This may include a warm handoff to a treatment provider (eg, face-to-face interaction), which results in better treatment engagement than an appointment or a referral.[11] More advanced programs include care coordinators, a "bridge clinic" (perhaps as part of the ED) for immediate treatment access, or a recovery coach program to assist in navigating the health care system. Although long-term engagement in outpatient opioid use disorder treatment is always the goal, because of the fragmented system of care return visits to the ED should be not discouraged.

For admitted patients, buprenorphine or methadone will reduce craving and the risk of leaving against medical advice because of untreated opioid withdrawal.[39] As with many ED therapies, those started in the ED are often continued in the hospital; ED partnership with hospital-based care teams will promote continuity of treatment and engagement in long-term treatment after discharge.

SUMMARY

Because EDs have the opportunity to influence opioid-related morbidity and mortality, developing a systematic approach is increasingly important to optimize patient outcomes. The best-practice approach supports the administration of buprenorphine in the ED, with adequate titration to both quell withdrawal and mitigate the risk of opioid use after discharge. This initial dosing serves as induction into medication-assisted therapy, and rapid referral, preferably directly to a treatment program, is optimal. Return visits for buprenorphine dosing for up to 3 days or prescribing buprenorphine for a duration needed to ensure treatment access is an alternative.

Supervising editor: Steven M. Green, MD. Specific detailed information about possible conflict of interest for individual editors is available at https://www.annemergmed.com/editors.

Author affiliations: From the Department of Emergency Medicine, Substance Use Disorder Program, Highland Hospital–Alameda Health System, University of California, San Francisco, San Francisco, CA (Herring); the Department of Emergency Medicine, Division of Medical Toxicology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA (Perrone); and the Department of Emergency Medicine, Division of Medical Toxicology, Rutgers New Jersey Medical School, Newark, NJ (Nelson).

Authorship: All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

REFERENCES

1. Houry DE, Haegerich TM, Vivolo-Kantor A. Opportunities for prevention and intervention of opioid overdose in the emergency department. *Ann Emerg Med*. 2018;71:688-690.

2. Doran KM, Raja AS, Samuels EA. Opioid overdose protocols in the emergency department: are we asking the right questions? *Ann Emerg Med*. 2018;72:12-15.
3. Weiner SG, Baker O, Bernson D, et al. One-year mortality of opioid overdose victims who received naloxone by emergency medical services. *Ann Emerg Med*. 2017;70:S158.
4. Scheuermeyer FX, DeWitt C, Christenson J, et al. Safety of a brief emergency department observation protocol for patients with presumed fentanyl overdose. *Ann Emerg Med*. 2018;72:1-8.e1.
5. Larochelle MR, Bernson D, Land T, et al. Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. *Ann Intern Med*. 2018;169:137-145.
6. Ravndal E, Amundsen EJ. Mortality among drug users after discharge from inpatient treatment: an 8-year prospective study. *Drug Alcohol Depend*. 2010;108:65-69.
7. Delvaux B, Ryckwaert Y, Van Boven M, et al. Remifentanil in the intensive care unit: tolerance and acute withdrawal syndrome after prolonged sedation. *Anesthesiology*. 2005;102:1281-1282.
8. Substance Abuse and Mental Health Services Administration. Protracted withdrawal. Available at: https://store.samhsa.gov/system/files/sma10-4554.pdf. Accessed December 9, 2018.
9. Kienbaum P, Thürauf N, Michel MC, et al. Profound increase in epinephrine concentration in plasma and cardiovascular stimulation after mu-opioid receptor blockade in opioid-addicted patients during barbiturate-induced anesthesia for acute detoxification. *Anesthesiology*. 1998;88:1154-1161.
10. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*. 2003;35:253-259.
11. D'Onofrio G, O'Connor PG, Pantalon MV, et al. Emergency department–initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. *JAMA*. 2015;313:1636-1644.
12. Binswanger IA, Blatchford PJ, Mueller SR, et al. Mortality after prison release: opioid overdose and other causes of death, risk factors, and time trends from 1999 to 2009. *Ann Intern Med*. 2013;159:592-600.
13. Gossop M, Stewart D, Treacy S, et al. A prospective study of mortality among drug misusers during a 4-year period after seeking treatment. *Addiction*. 2002;97:39-47.
14. Goldfine C. State legislation requiring emergency medication assisted therapy for opioid use disorder. Available at: http://www.acep.org/how-we-serve/sections/toxicology/news/september-2018/state-legislation-requiring-emergency-medication-assisted-therapy-for-opioid-use-disorder/. Accessed November 18, 2018.
15. U.S. Food & Drug Administration. Statement from FDA Commissioner Scott Gottlieb, MD, on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm595622.htm. Accessed December 9, 2018.
16. Gowing L, Farrell M, Ali R, et al. Alpha$_2$-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2016;5:CD002024.
17. Love JS, Perrone J, Nelson LS. Should buprenorphine be administered to patients with opioid withdrawal in the emergency department? *Ann Emerg Med*. 2018;72:26-28.
18. Su MK, Lopez JH, Crossa A, et al. Low dose intramuscular methadone for acute mild to moderate opioid withdrawal syndrome. *Am J Emerg Med*. 2018;36:1951-1956.
19. Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Rockville, MD: Substance Abuse & Mental Health Services Administration; 2004. SAMHSA/CSAT Treatment Improvement Protocols. Available at: http://www.ncbi.nlm.nih.gov/books/NBK64245/. Accessed November 18, 2018.
20. Oreskovich MR, Saxon AJ, Ellis MLK, et al. A double-blind, double-dummy, randomized, prospective pilot study of the partial mu opiate agonist, buprenorphine, for acute detoxification from heroin. *Drug Alcohol Depend*. 2005;77:71-79.
21. Kathleen A-L, Oreskovich MR, Saxon AJ, et al. Single dose of 24 milligrams of buprenorphine for heroin detoxification: an open-label study of five inpatients. *J Psychoactive Drugs*. 2006;38:505-512.
22. National Institute of Drug Abuse. Emergency department (ED) initiated buprenorphine & referral to treatment: a brief guide for ED practitioners. Available at: https://d14rmgtrwzf5a.cloudfront.net/sites/default/files/edbuprenorphinehandout.pdf. Accessed December 9, 2018.
23. E-QUAL Network. E-QUAL Network opioid initiative: buprenorphine initiation in the ED. Available at: https://www.acep.org/administration/quality/equal/e-qual-opioid-initiative/#sm.001mdzsbg12h5cr0zas1j032zukm9. Accessed November 18, 2018.
24. Herring AA. Emergency department initiation of buprenorphine with a loading dose. *Acad Emerg Med*. 2018;25(suppl 1):S8-S298.
25. Müller H, Gerlach H, Gips H, et al. [Intra- and postoperative interactions between the 2 opioids fentanyl and buprenorphine]. *Anaesthesist*. 1986;35:219-225.
26. Boysen K, Hertel S, Chraemmer-Jørgensen B, et al. Buprenorphine antagonism of ventilatory depression following fentanyl anaesthesia. *Acta Anaesthesiol Scand*. 1988;32:490-492.
27. Boas RA, Villiger JW. Clinical actions of fentanyl and buprenorphine. The significance of receptor binding. *Br J Anaesth*. 1985;57:192-196.
28. Davis M. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. *J Support Oncol*. 2012;10:209-219.
29. Leighton B, Crock L. Case series of successful postoperative pain management in buprenorphine maintenance therapy patients. *Anesth Analg*. 2017;125:1779-1783.
30. Lembke A, Ottestad E, Schmiesing C. Patients maintained on buprenorphine for opioid use disorder should continue buprenorphine through the perioperative period. *Pain Med*. 2018.
31. Kraus ML, Alford DP, Kotz MM, et al. Statement of the American Society of Addiction Medicine Consensus Panel on the use of buprenorphine in office-based treatment of opioid addiction. *J Addict Med*. 2011;5:254-263.
32. Herring A, Synder H, Moulin A, et al. ED-bridge buprenorphine guide. Available at: https://ed-bridge.org/. Accessed November 18, 2018.
33. National Institute of Drug Abuse. Buprenorphine treatment algorithm. Initiating buprenorphine treatment in the emergency department. Available at: https://www.drugabuse.gov/nidamed-medical-health-professionals/initiating-buprenorphine-treatment-in-emergency-department/buprenorphine-treatment-algorithm. Accessed October 22, 2018.
34. Sobel B-FX, Sigmon SC, Walsh SL, et al. Open-label trial of an injection depot formulation of buprenorphine in opioid detoxification. *Drug Alcohol Depend*. 2004;73:11-22.
35. Walsh SL, Comer SD, Lofwall MR, et al. Effect of buprenorphine weekly depot (cam2038) and hydromorphone blockade in individuals with opioid use disorder: a randomized clinical trial. *JAMA Psychiatry*. 2017;74:894-902.
36. Drug Enforcement Administration. Emergency narcotic addiction treatment. Available at: https://www.deadiversion.usdoj.gov/pubs/advisories/emerg_treat.htm. Accessed September 22, 2018.
37. Substance Abuse and Mental Health Services Administration. Buprenorphine waiver management. Available at: https://www.samhsa.gov/programs-campaigns/medication-assisted-treatment/training-materials-resources/buprenorphine-waiver. Accessed November 18, 2018.
38. Winetsky D, Weinrieb RM, Perrone J. Expanding treatment opportunities for hospitalized patients with opioid use disorders. *J Hosp Med*. 2018;13:62-64.
39. Gritsenko K, Khelemsky Y, Kaye A, et al. Multimodal therapy in perioperative analgesia. *Best Pract Res Clin Anaesthesiol*. 2014;28:59-79.