

# Prescribing Buprenorphine for Opioid Use Disorders in the ED: A Review of Best Practices, Barriers, and Future Directions

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**Abstract:** ED-initiated addiction treatment holds promise for enhancing access to treatment for those with opioid use disorder (OUD). We present a literature review summarizing the evidence for buprenorphine induction in the ED including best practices for dosing, follow-up care, and reducing implementation barriers. A literature search of Pubmed, PsychInfo, and Embase identified articles studying OUD treatment in the ED published after 1980. Twenty-five studies were identified including eleven scientific abstracts. Multiple studies suggest that buprenorphine induction improves engagement in substance treatment up to 30 days after ED treatment. Many different induction protocols were presented, but no particular approach was best supported as criteria for induction and initial dosing vary widely. Similarly, transition of care models focused on either a “hub and spoke” model or “warm hand-offs” model, but no studies compared these approaches. Common barriers to implementing induction programs were provider inexperience, discomfort with addiction treatment, and limited time during the ED visit. No studies described the number of EDs offering induction. While ED buprenorphine induction is safe and enhances adherence to addiction treatment, uncertainty persists in how to best identify patients needing treatment, how to initiate buprenorphine, and how to enhance follow-up after ED-initiated treatment.

**Keywords:** buprenorphine, opioid use disorder, opioid overdose, emergency department

## Introduction

Emergency services are well-positioned to provide effective treatment to patients with opioid use disorder (OUD). There is a significant need to deliver OUD treatment: in 12 months from February 2018 to February 2019, 69,209 people died in the United States from opioid overdose.<sup>1</sup> Every year, an additional 11 million American misuse opioids by taking the medication in a manner other than prescribed.<sup>2</sup> Opioid-related emergency department (ED) visits in the United States have doubled since 2010; these visits often involve treatment after an overdose or other substance abuse-related complication.<sup>3</sup> Many more visits are complicated by concurrent opioid misuse, as when patients with OUD awaiting hospital admission require management of withdrawal symptoms while still in the ED.

OUD is a biological and behavioral disorder characterized by signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or, if another medical condition is present that requires opioid treatment, that are used in doses greatly in excess of the amount needed for that medical condition.<sup>4</sup> Patients with OUD often spend significant time acquiring, using, and recovering from opioid use while suffering

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impairment across multiple personal, occupational, and health domains. Illegal opioid use can be detected with a high degree of sensitivity with a one question screener – “In the past year, how often have you used prescription drugs for non-medical reasons or illegal drugs?”<sup>5</sup> Patients who report misuse at least once in the past year merit further assessment. Predicting the risk of potential misuse of prescribed opioids requires longer screening tools such as the five question Opioid Risk Tool.<sup>6</sup>

Traditionally the standard of care for OUD has been daily dosing of methadone as part of a robust addiction treatment program. As a full mu-opioid agonist, methadone provides patients relief from withdrawal and inhibits the euphoria induced by intravenous heroin use. The routine of daily dosing provides behavioral structure and obviates the continual seeking and recovering from opioids that causes significant social impairment in OUD. Additional treatments include psychotherapy to aid in relapse prevention, management of concurrent medical illnesses (such as hepatitis C virus), and treatment for co-occurring psychiatric disorders. Methadone maintenance treatment reduces patients’ risk of infectious disease, social dysfunction, and death due to opioid addiction.<sup>7,8</sup> However, prescribing methadone for daily dosing must occur within a highly monitored setting to avoid the risk of diversion or adverse side effects such as over-sedation.<sup>9,10</sup> The need to observe patients for extended periods after their first dose and the risk of subsequent sedation make methadone problematic for treating OUDs in the ED setting.

The availability of the partial mu-opioid agonist buprenorphine has made it possible to safely treat opioid withdrawal and initiate OUD treatment from the ED with greater success than motivational interviewing and referral to treatment alone.<sup>7</sup> Buprenorphine’s partial agonism allows a safer therapeutic index that achieves symptomatic resolution of opioid withdrawal without methadone’s associated risk of overdose, particularly in the setting of additional opioid use.<sup>11,12</sup> Buprenorphine is often combined with naloxone for outpatient maintenance therapy; the naloxone addition is not bioavailable when taken orally and has no impact on the therapeutic efficacy of the drug. Rather, naloxone is added as a deterrent to misuse, as naloxone becomes bioavailable only once injected to induce immediate and uncomfortable withdrawal.<sup>11</sup>

Since the publication of a landmark trial demonstrating the efficacy of buprenorphine induction for ED patients with OUDs, EDs across the country have developed protocols for facilitating buprenorphine induction.<sup>13</sup>

D’onofrio et al demonstrated that among opioid dependent patients, induction of buprenorphine in the ED compared to control resulted in higher engagement in addiction treatment. However, there remains a great deal of variation in ED practice for patients with OUD, and subsequent articles have added nuance to inform clinical practice. A significant gap in providing ED-based induction still remains: one analysis suggested that only one in three patients who had screened positive for OUD actually receive effective treatment for OUD.<sup>14</sup>

This review summarizes the evidence and best practices for initiating buprenorphine treatment for OUDs in the ED. We also identify barriers to implementing ED-based buprenorphine induction, limitations in the extant literature, and opportunities for enhancing the care of these patients in the ED.

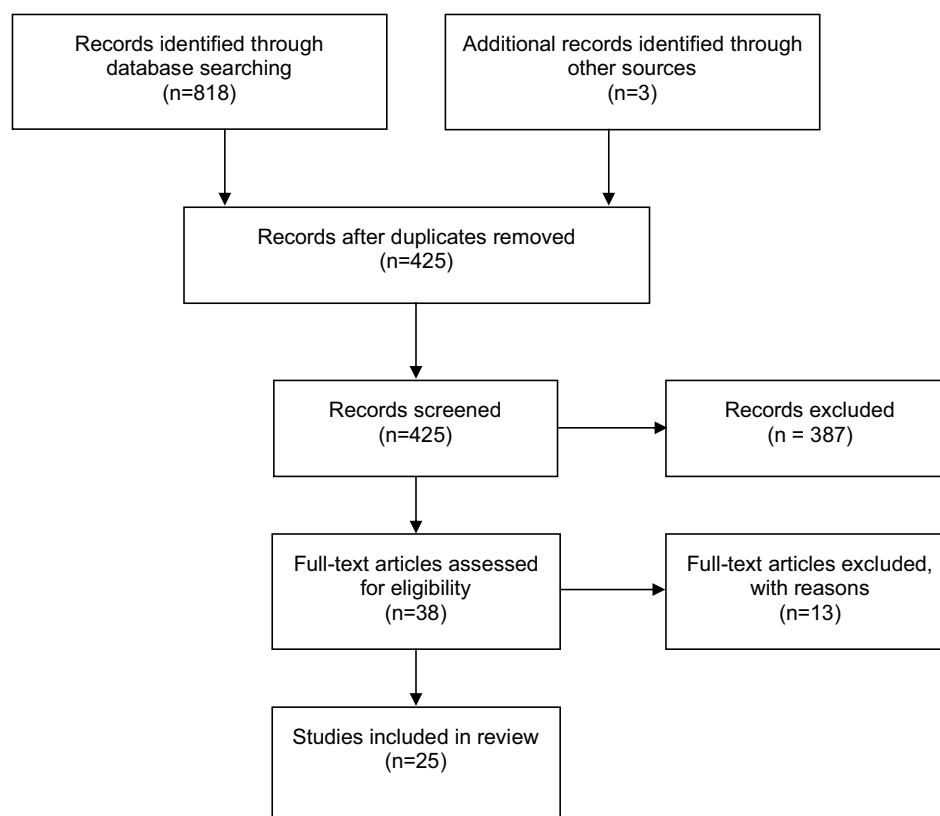
## Methods

A search of the Pubmed, PsychInfo, and Embase databases was conducted to identify articles related to OUD treatment in the emergency department using a combination of terms “buprenorphine” and “emergency service, hospital.” References from included articles and similar articles sections on Pubmed were utilized to identify additional literature. Results were narrowed to include English-titled articles published after 1980 through March 2020. Finally, the authors selected articles that included all three elements: OUD treatment, emergency department, and buprenorphine. Study quality was assessed using the Cochrane risk of bias for randomized controlled trials and the Newcastle-Ottawa Scale for cohort studies.<sup>15,16</sup> Two authors independently rated all of the trial and cohort studies; inter-rater reliability was assessed using the kappa statistic.<sup>17</sup> Disagreements were resolved by consensus to produce a final assessment.

## Results

### Article Selection

An initial database search yielded 818 academic products, and of those studies, 25 were applicable to this report. These studies included 14 peer-reviewed manuscripts and 11 scientific abstracts. Figure 1 illustrates the article selection process.<sup>18</sup> Of the 14 manuscripts, two were randomized controlled trials and seven were cohort studies. The inter-rater reliability was 91% (kappa=0.77, suggesting substantial agreement) in scoring cohort studies and 100% in scoring the randomized trials.<sup>17</sup>



**Figure 1** Study selection process.

## Effectiveness of Buprenorphine Induction for OUD in the ED

After induction, the most commonly studied outcome of interest is initial patient follow-up at an outpatient appointment after discharge from the ED and whether these patients are still enrolled in outpatient treatment at 30 days. Initial visit follow-up rates ranged from 63% to 83%<sup>19–23</sup> compared to 38%<sup>21</sup> among control conditions. Follow-up rates at 30 days ranged from 47% to 78%, which is higher than the 7.6% to 37% range for control-group patients in all studies.<sup>13,19–22</sup>

Two randomized trials evaluated the efficacy of buprenorphine induction in the ED. D’Onofrio et al randomized 328 ED patients with OUD and found patients receiving buprenorphine induction were more likely to be retained in treatment at 30 days (95%) than those in a referral to treatment (37%) or enhanced psychotherapeutic intervention (45%) control cohorts.<sup>13</sup> Patients receiving buprenorphine followed up in a primary care setting. The buprenorphine intervention was associated with less frequent use of inpatient addiction services as well, but the incidence of negative urine toxicology tests was similar across cohorts. Subsequent

analyses of the trial have revealed that buprenorphine induction proved cost-effective,<sup>24</sup> although retention rates did not vary among groups by 6 months.<sup>25</sup> A second trial randomized 26 ED patients in opioid withdrawal to receive buprenorphine or clonidine treatment along with a discharge prescription and follow-up instructions.<sup>21</sup> Clonidine is a non-opioid sedative used for withdrawal management. Patients in the buprenorphine cohort were more likely to be receiving agonist treatment at one month (62%) than the clonidine cohort (8%). Table 1 details the quality of these studies.

Seven cohort studies described the outcomes from buprenorphine induction programs. The highest quality cohort study is a retrospective analysis of 219 patients who underwent induction in an urban Level I Trauma Center; 75% of patients used intravenous opioids, and the mean total dose received in the ED was 8mg.<sup>20</sup> Follow-up retention at 30 days was 49%. The investigators found a decrease in median length of ED stay of 40% for induction patients since the beginning of the program, which suggests that familiarity with the practice among clinicians may reduce the impact of long induction stays for other patients. No other medical outcomes including infection incidence or overdoses were assessed. Another

**Table 1** Quality Assessment of Included Studies

Author	Random Assignment	Allocation Concealment	Blinding of Participants	Blind Evaluation for Outcomes	Incomplete Outcome Data	Selective Reporting	Other Bias
Quality Assessment of Included Randomized Controlled Trials							
D'Onofrio et al 2015 <sup>13</sup>	Low	High	High	High	Low	Low	n/a
Srivastava et al 2019 <sup>21</sup>	Low	High	High	Unclear	Low	Low	n/a
Author	Selection			Outcome			
	How Representative	Selection of Nonexposed Cohort	Ascertainment of Exposure	Demonstration of Novel Outcome	Comparability Basis of Design and Analysis (Max. 2)	Assessment of Outcome	Follow-Up Long Enough
Newcastle-Ottawa Scale for Assessing the Quality of Included Cohort Studies							
Berg et al 2007 <sup>42</sup>	✓		✓	✓	✓	✓	4/9
Dunkley et al 2019 <sup>19</sup>	✓		✓	✓	✓	✓	5/9
Kaucher et al 2019 <sup>20</sup>	✓		✓	✓	✓	✓	7/9
Kelly et al 2019 <sup>29</sup>	✓		✓	✓	✓	✓	5/9
Kawasaki et al 2019 <sup>41</sup>	✓		✓	✓	✓	✓	6/9
Bogan et al 2020 <sup>22</sup>	✓		✓	✓	✓	✓	6/9
Carroll et al 2020 <sup>35</sup>	✓		✓	✓	✓	✓	5/9

**Notes:** ✓ = presence of specific rating criteria; comparability basis is rated 0–2, while other columns are rated 0–1.

high quality cohort study described outcomes among 231 ED patients among multiple sites who were induced with a single dose of buprenorphine 8mg.<sup>22</sup> In this study, 77% of patients arrived to next-day appointments, and 60% were retained in treatment at 30 days. A third cohort study of note described the implementation of a multisite buprenorphine induction program across 12 sites including 2 emergency departments. They found an overall retention rate of 43% at 6-month follow-up, although these numbers exclude patients who receiving an induction but failed the first follow-up appointment. Study outcomes and quality of additional cohort studies are described in [Table 1](#).

## Identification of Patients for Induction

Clinical guidelines suggest that patients should have a diagnosis of OUD and exhibit at least mild acute opioid withdrawal.<sup>26</sup> Among the research literature, there are variable inclusion and exclusion criteria for providing ED-based induction. Inclusion criteria have most often been a diagnosis of OUD,<sup>13,19,21–23,27</sup> age over 16<sup>21</sup> or 18,<sup>13,27</sup> a positive urine test for opioids,<sup>13</sup> recent or multiple visits related to overdose,<sup>23</sup> intoxication,<sup>23</sup> or admission to an ED observation unit.<sup>19</sup> Exclusion criteria were pregnancy,<sup>13,21,23,27</sup> current enrollment in an OUD treatment program,<sup>13,21,23,27</sup> abuse of benzodiazepines or alcohol,<sup>21,23</sup> liver disease,<sup>21</sup> critically ill patients,<sup>13</sup> active suicidality,<sup>13</sup> police custody,<sup>13</sup> or an inability to communicate due to dementia or psychosis.<sup>13</sup> While ED studies have often excluded pregnant patients, research outside of emergency settings has shown that buprenorphine is safe and effective for pregnant patients.<sup>28</sup>

Few studies examined additional clinical factors associated with improved treatment outcomes. Two cohort studies reported on factors associated with a decreased likelihood of remaining in treatment. These factors were unstable housing,<sup>19</sup> unemployment,<sup>19</sup> poor social support system,<sup>19</sup> heroin use,<sup>19</sup> lack of transportation,<sup>20</sup> and receiving a referral to follow-up care to a different health system.<sup>29</sup>

## Optimal Procedure for Buprenorphine Induction

Studies offered general guidance for dosing and timing. Most protocols use the Clinical Opioid Withdrawal Scale (COWS) to assess withdrawal severity. The COWS is a clinician-administered tool for assessing a patient's

level of opioid withdrawal by rating 11 commonly seen opioid withdrawal symptoms.<sup>30</sup>

Clinical assessment of withdrawal is imperative to ensuring that patients are in withdrawal to induction and decreasing the risk of precipitated withdrawal. Precipitated withdrawal is a particularly worrisome adverse effect in the ED. Precipitated withdrawal occurs when a patient takes buprenorphine too soon after another opioid agonist, and the patient experiences an immediate withdrawal syndrome due to displacement of that agonist by buprenorphine, a partial agonist. Precipitated withdrawal can largely be avoided by only commencing induction in a patient with objective evidence of opioid withdrawal on physical examination or by adhering an opioid withdrawal scale. There are no strict cutoff criteria based on COWS score; [Table 2](#) reports cutoffs used by different studies. Precipitated withdrawal is most concerning among pregnant patients, for whom clinicians should feel utterly confident as to the presence of acute opioid withdrawal before initiating buprenorphine. Patients misusing long-acting opioids may evince opioid withdrawal yet remain at risk for precipitated withdrawal. In these cases, the clinician should have a discussion of risks and benefits with the patient.

Just as there are no concrete rules for initiation based on COWS scores, neither is there clear guidance for the initial dosing of buprenorphine. In studies, initial induction doses ranged from 2 mg to 4 mg and up to a maximum of 16 mg over the ED course.<sup>19,20,22,23,27,31–33</sup> Timing of buprenorphine administration included waiting 24 hours after the last known use of extended-release opioids,<sup>27,31,32,34</sup> 6–12 hours after the last known use of short-acting opioids,<sup>27,32,34</sup> and 48 hours following the use of methadone after that agent had been substantially tapered.<sup>34</sup> No studies compared different induction regimens or different practices for subsequent dosing, so the optimal induction regimen for improving outcomes remains unknown. [Table 2](#) describes specific induction regimens reported in the literature.

One study described immediate initiation of buprenorphine after opioid overdose reversal with naloxone in the field by trained emergency medical technicians (EMT). The investigators did not report any complications with subsequent induction of buprenorphine once the patients reached the ED. This novel two-step induction suggests that immediate administration of buprenorphine after naloxone is a safe and of value for emergency medical service clinicians.<sup>35</sup>

In summary, an initial dose of 4 mg appears to be well-tolerated and effective for starting patients on buprenorphine therapy for OUD; an additional 4–8 mg may be administered if the patient continues to experience withdrawal symptoms

**Table 2** Published Protocols for Emergency Department Buprenorphine Induction

Author	Method	Clinical Assessment and Induction Threshold	Dosing	Plan for Follow-Up	Outcomes
Berg et al 2007 <sup>42</sup>	Retrospective cohort study of 158 patients investigating adverse outcomes of buprenorphine when treating patients with OUD in the ED	<ul style="list-style-type: none"> <li>• SOWS</li> <li>• OOWS</li> </ul>	Initial: 0.3mg – 0.9mg IM Maximum: Not specified	<ul style="list-style-type: none"> <li>• Patients were given IM doses of buprenorphine after being evaluated with either SOWS or OOWS to assess for withdrawal symptoms</li> <li>• The buprenorphine group was compared to a symptom management group and a group that did not receive pharmacological intervention</li> </ul>	8% (7/88) of patients who were treated with buprenorphine had a drug-related return to the ED within 30 days compared with 17% (5/29) of patients who received only symptomatic treatment
D'Onofrio et al 2015 <sup>13</sup>	RCT of 329 patients using three different treatments arms to assess patient retention in MAT after ED treatment	<ul style="list-style-type: none"> <li>• Presences of DSM-IV OUD by MINI</li> <li>• COWS to determine moderate/severe withdrawal</li> <li>• If no symptoms, consider unobserved induction</li> </ul>	Initial: 8 mg on day one Follow up: 16 mg on days two and three	<ul style="list-style-type: none"> <li>• Scheduled appointment with hospital primary care within 72 hours</li> <li>• Prescribed 16 mg on day two and three until appointment</li> </ul>	78% (89/114) of patients induced with buprenorphine in the ED were still in addiction treatment at 30-day mark when compared to 37% (38/102) in the referral only group
Duber et al 2018 <sup>32</sup>	Clinical review summarizing strategies for identifying, treating, and transitioning patients with OUD	<ul style="list-style-type: none"> <li>• COWS</li> <li>• Induction threshold not specified</li> </ul>	Initial: 2–4 mg (but can start at 8 mg) Second: 2–4 mg if symptoms persist Max: 8–12 mg (increase if heavy user)	<ul style="list-style-type: none"> <li>• Recommend SOAPP-R or NIDA-m-ASSIST for screening of OUD in the ED</li> <li>• Follow up appointments should happen ASAP within 72 hours</li> <li>• There needs to be a robust bridge between ED and MAT</li> <li>• Warm hand-offs utilizing social workers</li> </ul>	N/A
Dunkley et al 2019 <sup>19</sup>	Retrospective cohort study of 18 patients with OUD investigating the feasibility of using buprenorphine in an ED CDU setting and retention of patients in MAT programs	<ul style="list-style-type: none"> <li>• Presence of DSM-5 OUD determined by toxicology fellow</li> <li>• COWS score <math>\geq</math> 10</li> </ul>	Initial: 2–0.5 mg of buprenorphine-naloxone Max: 8:2 mg maximum dose	<ul style="list-style-type: none"> <li>• Discharge at 24 hours with follow up appointment in the MAT clinic</li> <li>• MAT clinic with same provider who initiated buprenorphine in the ED-CDU</li> </ul>	63% (n = 12/19) of patients induced in ED attend initial MAT visit. 47% (9/19) still active at 1 month, and 21% (4/9) still active at 6 months.

(Continued)

Table 2 (Continued).

Author	Method	Clinical Assessment and Induction Threshold	Dosing	Plan for Follow-Up	Outcomes
Kaucher et al 2019 <sup>20</sup>	Retrospective study of 219 patients with OUD investigating the retention of patients in MAT programs after induction of buprenorphine in the ED	<ul style="list-style-type: none"> <li>• COWS 6–12</li> <li>• COWS <math>\geq</math> 13</li> </ul>	Initial COWS 6–12: 2–4 mg Initial COWS $\geq$ 13: 4–6 mg Max: 16 mg	<ul style="list-style-type: none"> <li>• Next day MAT follow up with intranasal naloxone and SBIRT resources</li> <li>• If X-waivered: prescribe up to buprenorphine/naloxone 16 mg if next day appointment cannot be made</li> </ul>	At the 30-day mark, 49.3% (108/219) of patients induced with buprenorphine were retained in MAT programs.
Srivastava et al 2019 <sup>21</sup>	RCT of 26 patients investigating effectiveness of buprenorphine vs clonidine in retaining patients in MAT program	<ul style="list-style-type: none"> <li>• Presence of opioid withdrawal</li> <li>• Optional COWS</li> </ul>	Initial: Not specified Maximum: 12 mg	<ul style="list-style-type: none"> <li>• 5-day supply of buprenorphine (8 mg/day) dispensed at one time in 8 mg tablets</li> <li>• Map given to patients showing nearest pharmacy open 7 days a week</li> <li>• Printed information and map with location of addiction facility</li> </ul>	Patients induced with buprenorphine in the ED were more likely to receive opioid agonist treatment at 1-month mark when compared to clonidine, 62% (8/13) vs 8% (1/13), respectively.
Reuter et al 2019 <sup>23</sup>	Scientific abstract detailing a prospective study of 212 patients with OUD who were treated with buprenorphine in the ED and followed into MAT programs	<ul style="list-style-type: none"> <li>• COWS</li> <li>• Induction threshold not specified</li> </ul>	Initial: 4 mg Second: 4 mg dose if COWS $>$ 8	<ul style="list-style-type: none"> <li>• Patients discharged to “close opioid treatment provider” for next day follow up</li> <li>• Patient can come back to ED for buprenorphine treatment on weekends and holidays</li> </ul>	Included 89 patients, only 71 actually began MAT. 83% (59/71) of patients went to first follow up appointment, and of those 59, 95% (56/59) were still in program at 6 months
Melnick et al 2019 <sup>27</sup>	Planned randomized trial to be carried out in 20 ED across 5 healthcare systems	<ul style="list-style-type: none"> <li>• Presence of DSM-5 OUD</li> <li>• COWS <math>\geq</math> 8</li> <li>• COWS <math>&lt;</math> 8 consider unobserved induction and referral</li> </ul>	Initial COWS 8–12: 4 mg Initial COWS $\geq$ 13: Consider 8 mg Max: Not specified	<ul style="list-style-type: none"> <li>• If X-waivered: physician prescribes 16 mg of buprenorphine for each day until appointment with outside addiction treatment</li> <li>• If not X-waivered: consider instructing patient to return to ED for 2 days of 16 mg of buprenorphine dosing with referral for addiction treatment</li> <li>• Warm handoff to outside addictions provider within 24–72 hours</li> </ul>	Not yet published

(Continued)

Table 2 (Continued).

Author	Method	Clinical Assessment and Induction Threshold	Dosing	Plan for Follow-Up	Outcomes
Cisewski et al 2019 <sup>31</sup>	Narrative review that discusses the approach to initiating buprenorphine use in the ED for opioid-abuse recovery	<ul style="list-style-type: none"> <li>• COWS &gt; 7</li> </ul>	Initial: 4mg Max: 16 mg	<ul style="list-style-type: none"> <li>• Provide patient with MAT clinic information within 48–72 hours</li> <li>• If X-waivered: prescribe 3-day course at equal dosage to that used in the ED (8–16mg)</li> <li>• If possible, discharge patient with bridging dose (2–4mg)</li> </ul>	N/A
Herring et al 2019 <sup>34</sup>	Review article analyzing treatment options and different induction protocols for the use of buprenorphine in an ED setting	<ul style="list-style-type: none"> <li>• Uncomplicated Opioid Withdrawal</li> <li>• COWS ≥ 8</li> <li>• COWS &lt; 8 reassess in 1–2 hours</li> </ul>	Initial: 4–8 mg (based on severity) Max: 32 mg	<ul style="list-style-type: none"> <li>• If X-waivered: prescribe max 16 mg SL buprenorphine/naloxone for 3–7 days or until appointment with outside addiction facility</li> <li>• Provide patients with the highest level of care navigation and shortest appointment wait time</li> </ul>	N/A
Bogan et al 2020 <sup>22</sup>	Article reviewing the implementation of an emergency department-initiated buprenorphine program aimed at treating opioid use disorder	<ul style="list-style-type: none"> <li>• Presence of OUD</li> <li>• COWS &gt; 8</li> <li>• If COWS &lt; 8 patients were excluded</li> </ul>	Initial: 8 mg buprenorphine or 8:2 mg buprenorphine-naloxone Maximum: Not specified	<ul style="list-style-type: none"> <li>• All patients with OUD were offered naloxone kit upon discharge from ED</li> <li>• Patient navigator arranged outpatient follow up within 24 hours of discharge</li> </ul>	78% (187/241) showed up for initial outpatient visit. 59% (111/187) of those who showed up for initial visit were still in treatment at 30 days post discharge. Of the 535 patients eligible for naloxone kits 39% (209/535) elected to receive a kit.
Jaeger and Fuehrlein 2020 <sup>33</sup>	Narrative review of the safety and efficacy of buprenorphine induction that is started in the ED	<ul style="list-style-type: none"> <li>• OUD established through history and physical</li> <li>• COWS &gt; 8 or subjectively ready</li> </ul>	Initial: 2 or 4 mg Max: Not specified	<ul style="list-style-type: none"> <li>• Connecticut veterans hospital: Patients present daily to detox and stabilization service regardless of outpatient/inpatient or intensive outpatient follow-up</li> </ul>	N/A
Carroll et al 2020 <sup>35</sup>	Case-series that looks at the feasibility of using EMS to assess and treat OUD with buprenorphine in the field under the direction of a supervising physician	<ul style="list-style-type: none"> <li>• Presence of OUD</li> <li>• X-waivered physician approval</li> <li>• COWS &gt; 7 or opioid free &gt;72 hours</li> </ul>	Initial: 16 mg Maximum: 24 mg	<ul style="list-style-type: none"> <li>• Patients may either be admitted to ED or refuse further care</li> <li>• All patients provided with resources and next-day MAT clinic appointment</li> </ul>	18 patients were administered buprenorphine through this protocol. 100% (18/18) demonstrated improvement of symptoms. 0% (0/18) demonstrated precipitated withdrawal.

**Abbreviations:** CDU, clinical decision unit; COWS, Clinical Opiate Withdrawal Scale; MINI, Mini-international Neuropsychiatric Interview; OOWS, Objective Opiate Withdrawal Scale; OUD, opioid use disorder; RCT, randomized control trial; SBIRT, screening brief intervention, and referral for treatment; SOWS, Subjective Opiate Withdrawal Scale.

based on a COWS score of greater than 8. Emergency clinicians can use either buprenorphine or a buprenorphine-naloxone, which are pharmacologically equivalent in the ED as naloxone is not orally bioavailable. In the United States, clinicians do not need a license waiver (“X-waiver”) to prescribe medication for induction in a hospital setting. A waiver is only required to write an outpatient prescription including for any prescriptions written on discharge from the ED. The need for a waiver is a barrier for implementing OUD treatment programs with buprenorphine: only 2.2% of United States physicians have waivers to prescribe buprenorphine for OUD.<sup>36</sup>

Clinicians should also consider giving patients with OUD a prescription for intranasal or intramuscular naloxone to take home with them when discharged. When giving patients naloxone upon discharge is done in the context of a take-home-Naloxone program the number of opioid-based overdoses is significantly reduced.<sup>35</sup> This harm reduction intervention may be life-saving not only for the patient at risk of opioid overdose but also for acquaintances of the patient—in one survey study, 53% of ED patients with OUD had witnessed another person overdosing.<sup>37</sup> If naloxone is offered, patients should be offered training and a filled prescription, as fill rates of ordered prescriptions are low. While several studies and a review endorse this practice, another review of ED-distributed naloxone found that the high variability of the implementation methods between these studies highlights a need for further research to determine best-practices.<sup>38</sup>

## Adverse Effects of Induction

Buprenorphine is a safe and well tolerated medication. Several studies described side effects of buprenorphine induction in the ED. However, like full opioid agonists, buprenorphine can cause side effects such as constipation, nausea, vomiting, headache, and drowsiness in addition to the aforementioned risk of precipitated withdrawal. Research studies found these side effects to be relatively infrequent. Adverse effects of induction in the ED included precipitated withdrawal,<sup>13,20,31,33,34</sup> sedation,<sup>31,34</sup> QT prolongation (lengthening of a segment of the heart beat that can lead to arrhythmias),<sup>31,32</sup> and potential P450 medication interactions.<sup>32</sup> No studies reported adverse events during follow-up periods after the ED induction.

## Follow-Up Arrangements After Induction

Follow-up arrangements varied by study, and there were no comparative studies looking at the different follow-up

interventions separately from buprenorphine treatment. Some studies described X-waivered ED providers prescribing a 3-day supply of buprenorphine-naloxone to bridge patients to outpatient care<sup>13,23,31,34</sup> or medication-assisted therapy (MAT) clinics.<sup>31–33</sup> In some cases, the prescribing physician in the ED may also see the patient in clinic.<sup>19</sup> More intensive follow-up support includes coordination with psychological or case management services in the ED,<sup>23,32–34</sup> and warm handoffs with social workers and case managers are a particularly popular choice in EDs.<sup>27,29,32,39,40</sup> Recommendations for follow-up arrangements included having ED personnel make outpatient MAT appointments for patients<sup>32,34</sup> and having follow-up within-network such as with a “hub and spoke” model.<sup>20,41</sup> The timing of follow-up differed among articles, but all arranged follow-up within 72 hours between ED discharge and initial MAT follow-up visit.<sup>27,31,32,34</sup> Table 3 summarizes the different care transition models described in the literature.

Optimal follow-up arrangements depend in large part on a particular ED’s community setting. Emergency providers should feel confident that a 3-day course of buprenorphine-naloxone may be safely prescribed on discharge to facilitate connection to follow-up care. The availability of a care coordinator who can make explicit follow-up arrangements is optimal.

## Alternatives to Buprenorphine Induction

The search strategy revealed several treatment options for patients with OUD besides buprenorphine induction including methadone continuation,<sup>31–33</sup> clonidine for withdrawal symptoms,<sup>21,32,34,42</sup> or crystalloid replacement combined with adjunctive symptomatic treatments.<sup>31,32,34,42</sup> Aside from the aforementioned trial finding buprenorphine superior to clonidine for opioid withdrawal,<sup>21</sup> no studies compared alternative active treatments to buprenorphine in emergency settings.

One medical treatment option of potential interest to emergency clinicians may be naltrexone. Naltrexone is an opioid antagonist with mixed evidence for use treating OUD outside emergency settings; no studies have assessed the drug’s utility in emergency practice. Naltrexone is available in multiple formulations including orally and in a long-acting injectable. While naltrexone itself is quite safe, the long-acting formulation has not demonstrated substantial efficacy for reducing opioid use,<sup>43</sup> and the oral formulation was not considered effective in a meta-analysis of 13 studies.<sup>44</sup> One finding of these studies was that participants discontinued

**Table 3** Models of Care for Transition from the Emergency Department to Medication-Assisted Treatment Programs

Author	Transition Model
Kaucher et al 2019 <sup>20</sup>	<ul style="list-style-type: none"> <li>• Hub-and-spoke model where ED and hospital's onsite MAT center served as hub and affiliated community providers were the spokes</li> <li>• Patients initially treated at a hub</li> <li>• Patients initiated in the ED were given next day follow up at the MAT clinic</li> </ul>
Kelly et al 2019 <sup>29</sup>	<ul style="list-style-type: none"> <li>• Social work follow-up in the ED after initial induction with buprenorphine</li> <li>• Patients were screened for this study by MI and DSM-V to find patients with OUD who were motivated to engage in treatment</li> <li>• SW worked with surrounding community teams to set up follow-up care for patients</li> <li>• Outcome of study was patient engagement 30 days post ED course</li> <li>• Also looked at ED length of stay, success rate of patients showing up to 1st outpatient appointment, and median number of days until this first outpatient follow up</li> </ul>
Ahmed et al 2019 <sup>39</sup>	<ul style="list-style-type: none"> <li>• Although not implemented, stakeholders suggest three recommendations for a successful warm hand-off:               <ul style="list-style-type: none"> <li>○ Designing "an automated, rapid, and flexible" referral system</li> <li>○ Quality assurance through aggregate metrics</li> <li>○ Providing urgent follow up with community clinics</li> </ul> </li> </ul>
Sholl et al 2019 <sup>40</sup>	<ul style="list-style-type: none"> <li>• Social work driven process designed to lessen the burden on physicians in terms of arranging follow up for patients to community resources               <ul style="list-style-type: none"> <li>○ MAT centers, primary care, etc.</li> </ul> </li> <li>• Patients identified for eligibility for social worker by provider referral and nurse screening</li> <li>• Physician involvement was decreased, only including brief screening and buprenorphine prescribing until follow up appointment</li> </ul>
Kawasaki et al 2019 <sup>41</sup>	<ul style="list-style-type: none"> <li>• All ED physicians waived</li> <li>• ED social workers schedule appointments within 1–2 days</li> <li>• ED has a reliable after-care model consisting of a series of "spoke" clinics connected to a central "hub"</li> <li>• Both spokes and the hub provide pharmacy and psychiatric services               <ul style="list-style-type: none"> <li>○ Higher acuity patients and more severe patients receive treatment at the hub.</li> </ul> </li> <li>• Integrated so that spoke clinics can refer to hub with minimal wait time</li> <li>• If spoke or hub does not have time to initiate, patients can initiate at a partnered urgent care centers (bridge clinics) and return to spoke after</li> <li>• This model allows for shorter wait time for higher risk patients</li> <li>• Integrated peer-based recovery support services were also offered</li> </ul>

naltrexone treatment at a higher rate, and significantly sooner than those participants who were placed on a sublingual preparation of buprenorphine-naloxone. Another study found that people on naltrexone were twice as likely to discontinue treatment "for any reason" compared with "adverse events."<sup>45</sup> However, the authors of this paper did not fully specify what reasons for discontinuation they included under "for any reason," but mentioned that some of the reasons included relapse, dropping out of treatment programs, and feeling that the medication was not adequately controlling their cravings. One potential downside of the early discontinuation discussed in these studies is an increase a person's risk of accidental overdose if they begin using non-prescribed opioids because they have a reduced opioid

tolerance after using Naloxone.<sup>43–45</sup> Therefore, efforts to improve adherence to naltrexone may enhance its efficacy and increase its value for emergency practices that lack strong partners to support aftercare for buprenorphine induction. Naltrexone may also be of particular benefit for adolescents with OUD.<sup>46</sup>

## Barriers to Implementing Induction Programs

ED-based buprenorphine induction faces logistical, systemic, and clinical challenges to implementation. Physicians have cited lack of clinical familiarity prescribing buprenorphine, concerns about legal regulations, and the impact on ED length of stay and patient flow as reasons for not initiating

**Table 4** Barriers to Buprenorphine Induction in the Emergency Department

Author	Method	Barriers to Induction
Medcalf et al 2015 <sup>51</sup>	27 ED physician responders to a 24-question survey sent to emergency physicians in one academic ED	<ul style="list-style-type: none"> <li>• Unfamiliarity with standardized methods of severity for acute opioid withdrawal.</li> <li>• Unfamiliar with timing of buprenorphine in relation to moderate opioid withdrawal</li> <li>• Unfamiliarity with prescribing indications and nuances</li> <li>• Clinical volume combined with patient acuity</li> <li>• Uncertainty with side effects</li> </ul>
Hawk et al 2019 <sup>47</sup>	Organizational Readiness to Change Assessment administered in three different hospitals settings. Followed by in-person focus groups with ED physicians, PA/APRNs, nurses, social workers, and community providers	<ul style="list-style-type: none"> <li>• Lack of experience with buprenorphine</li> <li>• Difficulties with workflow integration</li> <li>• Increased time needed to treat these patients.</li> <li>• Limited knowledge of available treatment options for patients</li> </ul>
Hernandez-Meier 2019 <sup>48</sup>	21-question survey sent to 98 providers including physicians, physicians' assistants, and nurse practitioners	<ul style="list-style-type: none"> <li>• Gaps in knowledge and understanding of buprenorphine induction in the ED</li> <li>• Need for further education in pharmacology, dosages, efficacy, outcome information, and legal implications</li> </ul>
Lowenstein et al 2019 <sup>49</sup>	Cross-sectional survey of physicians in two EDs. These barriers are physician perceived	<ul style="list-style-type: none"> <li>• Lack of comfort counseling about buprenorphine</li> <li>• Lack of comfort ordering buprenorphine</li> <li>• Regulatory concerns</li> <li>• Time constraints</li> <li>• Concerns about diversion, misuse, and safety</li> </ul> <p>These concerns differed between X-waiver and non-X-waivered physicians</p>
Martin et al 2019 <sup>50</sup>	Semi-structured interviews with ED providers in a hospital with MAT protocol. Also interviewed 10 patients with OUD	<ul style="list-style-type: none"> <li>• Time pressure and lack of cues to know what to ask about opioid misuse</li> <li>• Uncertainty with treatment protocols</li> <li>• Uncertainty about responsibility of OUD treatment</li> <li>• Patient focus on present not future</li> <li>• Stigma surrounding treatment programs</li> <li>• Mistrust of health system</li> </ul>
Wiercigroch et al 2019 <sup>52</sup>	Semi- structured interviews of 19 self-selected physicians at single Toronto ED	<ul style="list-style-type: none"> <li>• Provider inexperience causing missed subtle presentations of withdrawal</li> <li>• Lacking feedback on treatment effectiveness</li> <li>• Uncertainty about protocol from nursing staff</li> <li>• Fast paced ED limits amount of time for counseling</li> <li>• ED environment discourages taking up a bed to wait for withdrawal symptoms</li> <li>• Worries about precipitating withdrawal</li> <li>• Reluctance for prescribing chronic medications in acute setting</li> </ul>
Hawk, McCormack et al 2019 <sup>47</sup>	Focus groups of patients with OUD chosen from recent ED visits. 29 patients from Baltimore, NYC, Cincinnati, and Seattle.	<ul style="list-style-type: none"> <li>• Key themes from the focus groups</li> <li>• Perception that ED staff did not understand OUD as a disease</li> <li>• Dehumanizing experiences in the past due to OUD</li> </ul> <p>Long history of feeling stigmatized</p>
Dora-Laskey and Sadler 2019 <sup>57</sup>	Compared locations of MATs to that of emergency departments in Michigan.	<ul style="list-style-type: none"> <li>• Found that 43.5% of EDs had a MAT facility within 5 miles</li> <li>• Found that 50.4% had a MAT facility within 10 miles</li> </ul> <p>Concluded that only half of Michigan's EDs were within 10 miles of a MAT, limiting patients' access to long term care</p>

ED-based induction programs.<sup>47–52</sup> Prescribers are also concerned about misuse and diversion among patients.<sup>49</sup> These concerns are not without cause: a review of patients treated in community settings suggest 16–46% had misused buprenorphine and 18–28% diverted medications.<sup>53</sup> The most frequent reasons for misuse were continuing opioid use habits (eg, injecting or snorting medication), addressing concern for under-dosing, alleviating withdrawal, achieving positive effects (eg, euphoria), and relieving negative states. Reasons for diversion of buprenorphine were peer pressure, desire to help an addicted friend or family member, and making money. Use of buprenorphine-naloxone decreases the risk of misuse and diversion compared to buprenorphine without naloxone. When compared to methadone, the rates of misuse and diversion for buprenorphine are much lower.<sup>54</sup> These risks of misuse and diversion must be weighed with the substantial morbidity and mortality of untreated OUD.

Another barrier that patients have reported is their reluctance to accept treatment due to fear of stigmatization and general mistrust in the health system.<sup>47,50</sup> ED administrators have voiced concern that offering ED-based buprenorphine induction might increase the volume of patients presenting with substance use disorders, but an analysis of ED volumes after introduction of induction services at one ED suggests this not to be the case.<sup>55</sup>

In rural areas, the physical distance between ED and medicated-assisted treatment (MAT) facilities and sparse distribution of X-waivered providers to provide follow-up care pose major barriers to successful buprenorphine programs.<sup>56,57</sup> In the US, 56% of rural counties lack a X-waivered physician to prescribe buprenorphine.<sup>56</sup> Some interventions to ameliorate these barriers have been described: one program trained first responders to administer buprenorphine in the community.<sup>35</sup> Table 4 summarizes barriers to implementation of ED-based buprenorphine induction.

## Discussion

Buprenorphine is a safe and effective treatment for patients with OUD in the ED. Multiple studies demonstrate improved rates of follow-up in substance treatment and decreased illicit substance use among patients receiving buprenorphine induction versus usual care. ED administrators and clinicians should be familiar with buprenorphine induction and build care processes to make induction feasible within the limitations of community resources.

Despite the strong evidence supporting induction programs, there remain notable gaps in knowledge. The quality of included studies varied in quality as well as scope. Insufficient knowledge exists as to optimal ED dosing regimens, psychosocial interventions that improve follow-up from the ED, and which patients are at risk for adverse events and sub-optimal outcomes. No included studies describe buprenorphine use for detoxification in the ED setting (rather than initiation of maintenance treatment.) Moreover, studies are limited to a short follow-up time-frame—typically initial visit and 30 day follow-up—and continued care support is almost certainly necessary to improve outcomes. Indeed, extended follow-up of the original D’Onofrio study revealed that intervention patients receiving ED-based induction were not more likely to remain in treatment by 6 months than those in control cohorts.<sup>25</sup>

Effectiveness research of buprenorphine induction may include more heterogeneous populations including with comorbid psychiatric illness. In practice, clinicians are anecdotally challenged to manage inductions in the context of complex clinical scenarios such as after recent naloxone reversals, while misusing long-acting oral opioids, or in the context of polysubstance withdrawal.<sup>48,50–52</sup> More evidence is needed to inform safe, effective management of these patient presentations. One such challenging example is the malingering patient; little guidance is provided by the scientific evidence of treatment for these patients despite clinicians’ frequently cited concerns around the risk of buprenorphine misuse.

Maximizing the potential for ED buprenorphine treatment will require further research on optimal induction protocols—particularly for complex presentations—and psychosocial interventions to mitigate barriers to follow-up. Clear barriers were found among physicians and health systems in implementing ED induction programs, but no studies described strategies to ameliorate cultural and institutional resistance to program development. Indeed, many of the concerns cited by clinicians related to ambiguous presentations of opioid withdrawal, impact on length of ED stay, and safety treatment of highly co-morbid patients remain unanswered by the literature. In response to these concerns, a new multi-site pragmatic trial is studying how a package of systematic interventions, including incorporating induction protocols into the electronic medical record, may facilitate access to buprenorphine treatment through the ED.<sup>27</sup>

These outstanding questions do not obscure the fact that patients with OUD will continue to present to emergency medical services. The capacity to provide ED-based buprenorphine induction programs represents an important advancement in the care of these patients, and the lessons learned from these programs hold lessons for the treatment of other substance use disorders.

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