

## REVIEWS

# USE OF BUPRENORPHINE IN THE PREHOSPITAL SETTING

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*Recommended Citation:* Spadaro, A., Huo, S., & Bar, J. (2024). Use of Buprenorphine in the prehospital setting. *International Journal of Paramedicine*. (7), 125-130. <https://doi.org/10.56068/CRDE9788>. Retrieved from <https://internationaljournalofparamedicine.com/index.php/ijop/article/view/2948>.

*Keywords:* EMS protocols, substance use disorder, opioid use disorder, EMS physicians, emergency medical services, EMS, paramedicine

*Received:* October 10, 2023

*Revised:* April 4, 2024

*Accepted:* April 29, 2024

*Published:* July 8, 2024

*Funding:* None.

*Disclosures:* None.

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## ABSTRACT

*Purpose:* Buprenorphine is a lifesaving medication in opioid use disorder (OUD). Emergency Medical Services (EMS) play a crucial role in responding to opioid overdoses. The prehospital use of buprenorphine by EMS can expand access to this important medication. This article aims to provide a narrative review of the use of buprenorphine in the prehospital setting.

*Methods:* This is a narrative review of recent publications that describe the use of buprenorphine to treat opioid withdrawal in the prehospital setting.

*Results:* There are a few well done studies that describe protocols, safety, and efficacy of the administration of buprenorphine in the prehospital setting by EMS providers. The pharmacology of buprenorphine makes it advantageous in treating opioid use disorder. Proper patient selection and protocols for the administration of buprenorphine are key to the success of implementing prehospital buprenorphine programs.

*Conclusions:* The prehospital administration of buprenorphine for opioid use disorder should be considered by EMS agencies.

## INTRODUCTION

Opioid overdoses are a major cause of mortality in the United States and around the world. Emergency Medical Services (EMS) play a crucial role in responding to opioid overdoses in the prehospital setting. Naloxone (Narcan®) is the mainstay of therapy for opioid overdose (Carrieri et al., 2006). As a competitive antagonist at the opioid receptor, naloxone reverses the effects of opioid agonists such as fentanyl and heroin (Geiger et al., 2020). Due to the antagonist effects of naloxone, its use can precipitate withdrawal in people with opioid dependence (Spadaro et al., 2022). Naloxone-precipitated withdrawal can lead to severe myalgias, diarrhea, vomiting, and anxiety (Spadaro et al., 2022). The discomfort from naloxone-precipitated withdrawal can increase patient reluctance to call EMS or lead to patients refusing transport to medical facilities (Geiger et al., 2020). This can result in a lost chance for medical providers to intervene. While naloxone is used for acute opioid intoxication, medications such as buprenorphine and methadone are used to treat opioid withdrawal and

opioid use disorder (OUD) itself (Spadaro et al., 2022). There is an increasing interest in the use of buprenorphine in the prehospital setting. The aim of this article will be to review the existing literature on the use of buprenorphine in the prehospital setting. This article will also review the pharmacology of buprenorphine and the management of opioid withdrawal to contextualize the use of buprenorphine in the prehospital setting. This article will explain why EMS medical directors should consider developing a prehospital buprenorphine program.

## **METHODS**

This article is a narrative review of literature on the use of buprenorphine in the prehospital setting. Articles selected for review were based on consensus among the authors who had expertise in EMS (J.B.), addiction medicine (S.H. and A.S), and medical toxicology (A.S). A PubMed search of Prehospital Buprenorphine found 11 articles, of which 7 were excluded for not being relevant as determined by the authors. The remainder of the articles selected to review were based off the authors content expertise. The authors have no financial conflicts of interest to disclose.

## **RESULTS**

### **PHARMACOLOGY OF BUPRENORPHINE**

Buprenorphine is a partial mu-opioid receptor agonist with high affinity for the opioid receptor (Spadaro et al., 2022). Through its opioid agonist activity, buprenorphine manages opioid cravings and has some analgesic effects (Herring et al., 2019). As a partial agonist there is a ceiling effect that it can have on respiratory depression and sedation, making it an exceedingly safe drug (Spadaro et al., 2022). Because of its high affinity for the mu-opioid receptor, buprenorphine binds more tightly to the receptor than agonists such as fentanyl and heroin (Spadaro et al., 2022). This high affinity means that buprenorphine will displace any full agonists present, and therefore patients must be in withdrawal and abstain from full agonists for a period of time to avoid precipitated withdrawal when initiating buprenorphine (Spadaro 2022). Similar to naloxone-precipitated withdrawal, precipitated withdrawal from buprenorphine can be distressing to patients. Recent guidelines from the Substance Abuse and Mental Health Services Administration (SAMHSA) recommend waiting 12-24 hours from last opioid use before starting buprenorphine (SAMHSA, n.d.). Chronic fentanyl use is thought to increase the risk of precipitated withdrawal (Spadaro et al., 2022). The degree of opioid withdrawal a patient is experiencing can be quantified using the Clinical Opioid Withdrawal Scale (COWS). SAMHSA (2023) recommends starting buprenorphine when a patient reaches a COWS score of at least 13.

Buprenorphine treats the cravings and withdrawal symptoms that patients with OUD experience when they stop using full agonists (Herring et al., 2019). Use of buprenorphine leads to decreased illicit drug use, decreased opioid overdoses, and improved morbidity and mortality (Herring et al., 2019). Although traditionally used in the outpatient and inpatient settings, initiation of buprenorphine in the emergency department has been shown to improve retention in treatment (Herring et al., 2019). Buprenorphine comes in many different formulations, some are combined with naloxone as an abuse deterrent to prevent intravenous use. Suboxone is the trade name of a commonly used buprenorphine-naloxone sublingual preparation. For the remainder of this article, we

will refer to these products as just buprenorphine; though many of the protocols discussed use the combination products containing buprenorphine-naloxone, the activity of naloxone is presumed to be limited.

#### MANAGEMENT OF OPIOID WITHDRAWAL

Several U.S. EMS agencies have adopted protocols to administer buprenorphine to patients who are experiencing opioid withdrawal (Wakeman, 2022; Hern et al., 2022a; Carroll et al., 2021). A case series from California reported the use of prehospital buprenorphine in three patients (Hern et al., 2022a). In this pilot study, EMS providers received a four-hour training on the use of buprenorphine and measuring of COWS scores (Hern et al., 2022a). If a patient experiencing opioid withdrawal was interested in buprenorphine, the provider on scene called a medical command physician and, if approved, administered 16mg of sublingual buprenorphine. If opioid withdrawal symptoms worsened or persisted an additional 8mg of buprenorphine could be administered (Hern et al., 2022a). Of the three cases they reported, two patients had developed withdrawal after receiving naloxone and one patient had developed withdrawal from opioid abstinence (Hern et al., 2022a). The authors of this study went on to publish a larger study of their prehospital buprenorphine program (Hern et al., 2022b). Patients were administered buprenorphine if they were in opioid withdrawal with a COWS score greater than 7, the patient was interested in buprenorphine, and the command physician approved the order (Hern et al., 2022b). All patients were followed up by the California Department of Public Health and connected to a navigator who could follow patients for clinical outcomes (Hern et al., 2022b). Of 36 patients that were treated, 17 received naloxone prior to receiving buprenorphine and 19 received buprenorphine first (Hern et al., 2022b). Three cases received 8mg of buprenorphine, 30 cases received 16mg of buprenorphine, and three cases received 24mg of buprenorphine (Hern et al., 2022b). Thirty-one of the 36 cases were ultimately discharged from the ED, and five cases were admitted to the hospital (Hern et al., 2022b). Half of the patients were engaged in treatment at seven days, and 14 out of 36 were engaged in treatment at 30 days, similar to retention in treatment in other healthcare settings (Hern et al., 2022b).

Prehospital buprenorphine has also been implemented in several EMS agencies around the U.S including Camden County in New Jersey, Buncombe County in North Carolina, San Antonio in Texas, and New Haven in Connecticut (Wakeman, 2022; Hern et al., 2022a; Carroll et al., 2021, Winkler, 2023).

#### MANAGEMENT OF NALOXONE-PRECIPIATED WITHDRAWAL

In addition to the management of opioid withdrawal that has developed from abstaining from opioid use, buprenorphine can also be used in the prehospital environment to treat precipitated withdrawal from naloxone after an overdose (Carroll et al., 2021). Naloxone-precipitated withdrawal can lead to refusal of transport to a hospital, with rates as high as 36% in one system (Carroll et al., 2022). While multifactorial, this high rate of refusal represents a missed opportunity and could be improved upon by managing precipitated withdrawal symptoms (Geiger et al., 2022). There are case reports of buprenorphine improving the symptoms of precipitated withdrawal in both the prehospital and hospital environment (Carroll et al., 2021). Due to the long half-life and high affinity of buprenorphine, it may also protect against re-sedation and repeat overdose in the acute

setting (Carroll et al., 2022). In a case study of three patients that received prehospital buprenorphine after naloxone-precipitated withdrawal, 16mg-32mg of buprenorphine was given after naloxone (Carroll et al., 2021). All three patients made it to their first outpatient addiction medicine visit, and two of the three were still engaged in treatment at 30 days (Carroll et al., 2021).

Another study from the same EMS agency based in Camden, New Jersey described a protocol for ambulances to carry buprenorphine (Carroll et al., 2022). For patients to receive buprenorphine they had to have a COWS score of at least 5 or a last use of opioid greater than 72 hours (Carroll et al., 2022). The initial dose of buprenorphine was 16mg, with an additional 8mg given if withdrawal symptoms persisted (Carroll et al., 2022). The authors reported that of the 1841 drug overdoses they responded to that required naloxone during the study period, 1230 patients were treated by an ambulance that could prescribe buprenorphine, and 611 were treated by an ambulance that could not (Carroll et al., 2022). Patients who received buprenorphine had a 12-fold increase in being engaged in treatment at 30 days (Carroll et al., 2022). Administering buprenorphine was associated with an increase in time on scene by nine minutes (Carroll et al., 2022). There are several limitations to the studies discussed above. These studies occurred in areas of high prevalence of fentanyl in the opioid supply and may not be generalizable to other regions. The protocols in these studies utilized a COWS score to determine the state of withdrawal. EMS agencies that do not see as many patients with OUD may be less accurate in determining a COWS score before initiating buprenorphine, which may also limit the generalizability of these studies.

#### LEGAL CONSIDERATIONS

In the U.S., the Protecting Patients Access to Emergency Medications Act (PPEMA) was passed in 2017, which explicitly allowed EMS providers to administer controlled substances (Davis et al., 2021). As part of this act, three criteria must be met by EMS organizations to provide controlled substances: 1) the EMS organization must be registered with the DEA, 2) state law must authorize EMS professionals to administer the controlled substances, and 3) the EMS personnel must act in accordance with either a standing order issued by the EMS organization's medical director or receive a patient-specific verbal order by the agency's medical director (Davis et al., 2021). Although previously a DATA-2000, or X-Waiver, was required for a provider to prescribe buprenorphine, the Mainstreaming Addiction Treatment Act of 2023 eliminated the requirement for the X-Waiver to increase access to buprenorphine (Linas & Linas, 2023). This act also eliminated the caps on the number of patients to whom a provider can prescribe buprenorphine (Linas & Linas, 2023). All providers with a DEA license can now prescribe buprenorphine. Thus, most EMS personnel in the US should be able to administer buprenorphine through a standing order or verbal order from a medical command physician.

Regulation of buprenorphine around the world is variable (Carrieri et al., 2006). In France any physician can prescribe buprenorphine making it widely available. Conversely, in Italy buprenorphine is distributed from specialized pharmacies. Further, in Russia buprenorphine is prohibited for the treatment of OUD (Carrieri et al., 2006). Thus, it is prudent to ensure new EMS protocols are compliant with state and national regulations prior to implementation (see Figure 1 for an example buprenorphine flowchart).

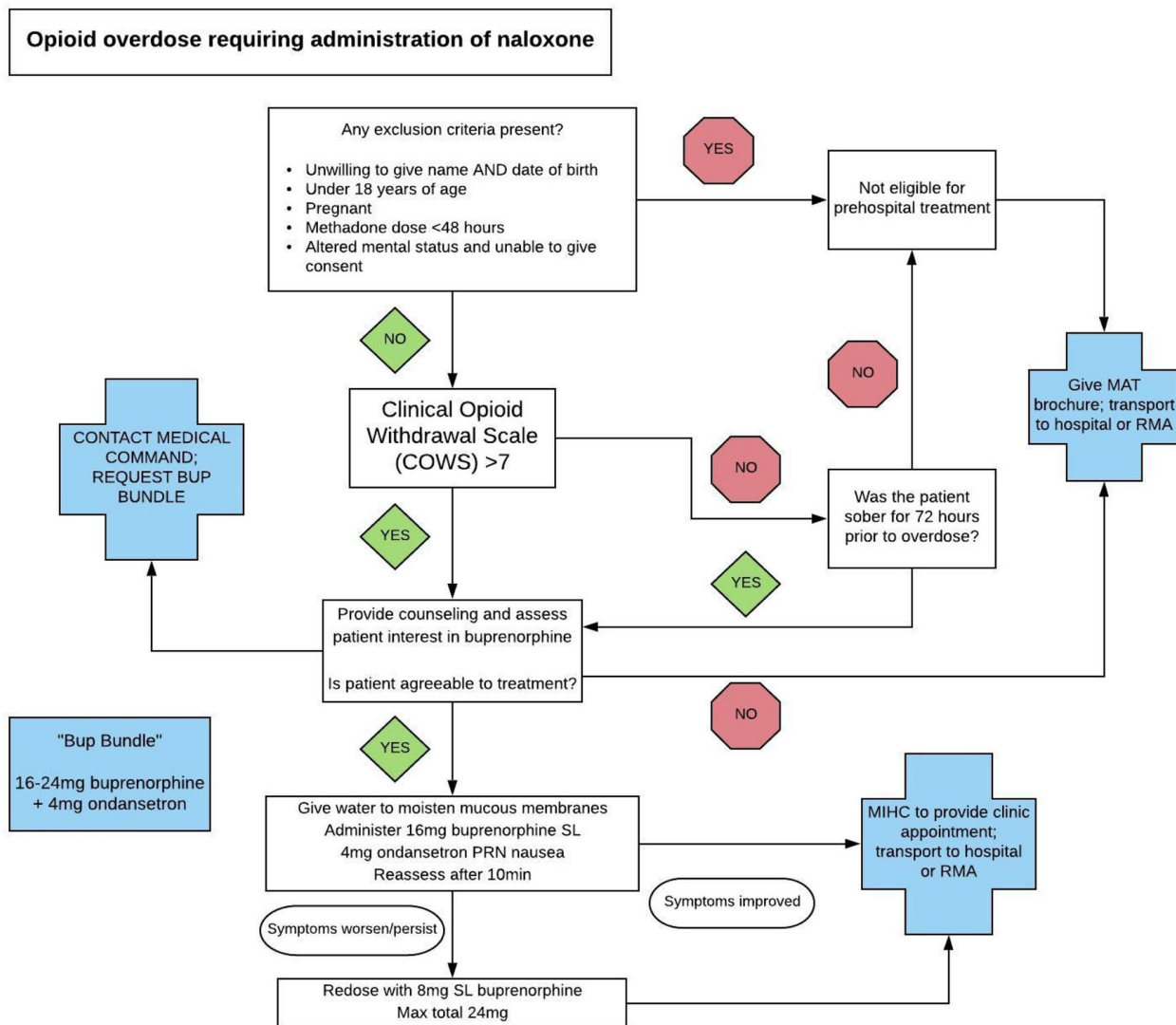


Figure 1. Example flowchart for prehospital Buprenorphine (Carroll, 2021).

CONCLUSIONS

Buprenorphine is a safe and effective medication for opioid use disorder. There is emerging but limited evidence that buprenorphine can be safely used by EMS personnel to treat patients experiencing opioid withdrawal, whether precipitated by naloxone administration or gradually developed through opioid abstinence. Overall, these studies demonstrate that administering 8mg-32mg of buprenorphine by prehospital providers was safe, could reduce symptoms of opioid withdrawal, and increase the rate at which patients remained engaged in addiction treatment without significantly increasing the length of time on scene (Carroll et al., 2021; Carroll et al., 2022; Hern et al., 2022a; Hern et al., 2022b). Agencies should develop protocols to correctly identify patients in opioid withdrawal who are appropriate for buprenorphine and connect these patients to ongoing addiction treatment. While there are some regions where EMS agencies have a lot of experience with administering buprenorphine, it is still an evolving field, but one worth considering putting into practice now.

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