



Review Article

Buprenorphine initiation to treat opioid use disorder in emergency rooms

Stephen Jaeger Jr*, Brian Fuehrlein

^a Yale University School of Medicine, Yale-New Haven Hospital, United States^b Psychiatric Emergency Room, VA Connecticut, Yale University, United States

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ABSTRACT

Emergency rooms across the United States regularly treat patients with opioid use disorder and patients experiencing opioid overdose. Four to six million people in the US are estimated to have opioid use disorder. Over half of overdose related deaths in 2016 resulted from the use of opioids. The majority of deaths involved the use of fentanyl. There is an opioid epidemic plaguing the nation and with emergency rooms at the forefront of the proverbial battlefield; they can potentially play a key role in addressing the problem. Currently, there are three FDA approved, evidence-based medications for the treatment of opioid use disorder. These are buprenorphine, methadone and extended-release naltrexone. Buprenorphine induction in emergency room settings has shown great promise. Research suggests that it is an effective, safe and cost-effective treatment to initiate in emergency rooms. In order to successfully treat opioid use disorder and overdose in emergency rooms, they must have waived providers and they must be equipped with the necessary resources. The VA Connecticut has been able to overcome some of the challenges to initiating buprenorphine in the emergency room setting and has established a feasible model for treating opioid overdose and managing opioid use disorder.

Currently, psychiatric and substance use related emergencies constitute a large and growing percentage of individuals seen in emergency rooms across the United States. In 2017, the Agency for Healthcare Research and Quality reported that psychiatric and substance-use related emergencies grew by 44% between 2006 and 2014 [20]. Emergency rooms are a common entry point for patients with mental illness and substance use disorders. Given the high rates of overdose, the opioid epidemic should be of particular interest to emergency room providers. Additionally, emergency rooms should be adequately staffed with providers who understand these disorders and who understand the available resources in their community. Despite ample evidence supporting its efficacy, the initiation of buprenorphine in the emergency room setting represents a paradigm shift for many providers.

This review article will focus on the emergency management of opioid use disorder, with a specific focus on buprenorphine induction. It will conclude with a discussion of the VA Connecticut Model for buprenorphine induction in the emergency room as an example of the feasibility of such a model. Readers are encouraged to understand the emergency presentations of opioid use disorder and how they may play a role in its treatment, operating within the limitations of their system of care. The role that emergency rooms play in the context of the broader system is critical to understand and a very important part of this special issue on substance use disorders and treatments.

1. Part 1 – Prevalence of substance use disorders with a focus on opioid use disorder

Substance use disorders are a growing health concern in the United States [4]. It was estimated that 2.5 million emergency room visits were related to drug misuse or abuse in 2011; over half of these visits involved the use of illicit drugs and over 1.2 million resulted from the non-medical use of pharmaceuticals ([12]; *National Estimates of Drug-Related Emergency Department Visits*, 2013). More recently, in 2016, nearly 2.2 million people indicated that they received treatment for illicit drug use in the previous year [1]. The increasing death toll has resulted in a growing need to prioritize the diagnosis and treatment of opioid use disorder [16].

Trends in the prevalence of opioid and other substance use disorders are tracked through epidemiological surveys including the National Survey on Drug Use and Health (NSDUH). The latest NSDUH survey data collected in 2016 indicates that roughly 20.1 million people age 12 or older in the United States suffered from substance use disorder in the prior year. Of this group, 7.4 million had illicit drug use disorder. Among the 7.4 million experiencing illicit drug use disorder, opioid use disorder was the second most prevalent after cannabis use disorder; 2.1 million people had opioid use disorder. Of the 2.1 million individuals with opioid use disorder, 1.8 million were using prescription pain

* Corresponding author.

E-mail address: Stephen.Jaeger@yale.edu (S. Jaeger).

relievers and 0.6 million were using heroin [2].

In addition to tracking substance use disorders, the NSDUH tracks substance misuse. The 2016 NSDUH survey reported 11.8 million misusers ages 12 and older in the prior year. The majority of misusers, 11.5 million people, were using prescription pain relievers while 948,000 individuals used heroin. Of the total 11.8 million misusers, 10.9 million solely misused pain relievers, nearly 307,000 individuals solely misused heroin and 641,000 individuals misused both [2].

According to the 2018 CDC Annual Surveillance Report of Drug-Related Risks and Outcomes, in 2016 there were 63,632 overdose related deaths and approximately 64% of them involved opioids. Most opioid related deaths (19,413) involved the use of synthetic opioids excluding methadone. Fentanyl was the most common cause of death. Recently, fentanyl has become a growing problem with extremely high potency and rapid onset. Of the 63,632 overdose related deaths, 17,087 resulted from the use of prescription opioids and 15,469 resulted from heroin use. Prescription opioid related deaths consisted of 14,487 deaths resulting from natural and partly synthetic opioids and 3373 deaths resulting from methadone [1]. According to a Morbidity and Mortality Weekly Report by the CDC, the opioid epidemic is reported to have caused over 70,237 deaths in the United States in 2017 [23]. Furthermore, opioid use disorder is frequently undiagnosed and under reported, hence it is estimated that 4–6 million people in the US may have opioid use disorder [7].

2. Part 2 – Overview of opioid use disorder

Opioid use disorder is characterized by a pattern of uncontrolled, continued use of opioids despite consequences and craving. Additional diagnostic modifiers include: the duration of remission, whether or not the patient is on maintenance therapy and whether or not the patient is in a controlled environment where opioid access is restricted [22]. Opioid related psychiatric emergencies can result from opioid intoxication or withdrawal.

Opioid intoxication causes drowsiness, unintelligible speech, coma, decreased respiration, blue appearance, pinpoint pupils, hyperemic nasal mucosa, pulmonary edema, cardiac arrhythmias and/or seizures. These symptoms are commonly complicated by the concomitant use and withdrawal of other drugs [22]. Opioid withdrawal is rarely life threatening, unless it is coupled with significant medical complications. Depending on the opioid, withdrawal symptoms can last between 7 and 14 days. Opioid withdrawal symptoms include nausea, vomiting, diarrhea, dilated pupils, muscle pain, insomnia and flu-like symptoms.

2.1. Treatment

Currently methadone, buprenorphine and extended-release naltrexone are the only three evidence-based medications indicated for opioid use disorder. Methadone and buprenorphine occupy opioid receptors to decrease cravings and withdrawal without producing acute intoxication. Extended-release naltrexone blocks the opioid receptors. All three medications have been shown to reduce opioid use and medical complications. Methadone was associated with a 53% reduction and buprenorphine a 37% reduction in all deaths among patients with opioid use disorder in the 12 months following an overdose. Nonetheless, these medications are not widely available. It is thought that only 20 to 40% of individuals diagnosed with opioid use disorder are currently receiving treatment and thus it is critical to expand access to care [16].

Methadone can only be initiated and administered for opioid use disorder in federally-regulated opioid treatment programs. Individuals who have established methadone treatment may seek continued dosing in an emergency room, however, emergency rooms cannot initiate methadone for opioid use disorder. Buprenorphine can be prescribed in an office-based setting, emergency room setting and an opioid treatment program setting. Prescribers must complete training and receive a

waiver by the federal Substance Abuse and Mental Health Services Agency. Unlike methadone and buprenorphine, extended-release naltrexone may be prescribed by all licensed prescribers, however, patients must be opioid free for 7–10 days before the initiation of treatment.

Buprenorphine is administered sublingually and comes in two forms – with or without the presence of naloxone. Naloxone is added to prevent diversion and abuse of buprenorphine. However, naloxone is excluded when treating pregnant patients with buprenorphine in order to avoid fetal withdrawal [13]. Common side effects of buprenorphine include body aches, dizziness, constipation, perspiration, sleep difficulty, upset stomach, vomiting and mood swings [10].

While buprenorphine is more widely available than methadone, it remains subject to considerable restrictions. In addition to requiring 8 h of training to obtain a waiver, prescribers are limited in the number of patients that they can treat with buprenorphine for opioid use disorder [24]. Many believe that such limitations are too restrictive and may prevent proper treatment for the opioid use epidemic. Fifty six percent of rural counties in the United States did not have any buprenorphine prescribers in 2017 [3]. Deregulation of buprenorphine is hypothesized to dramatically increase access to treatment and lead to a reduction in the epidemic. Furthermore, buprenorphine has low risk of over-dose and is overwhelmingly used for its intended purpose as a medication for addiction treatment (MAT). Analysis of the Researched Abuse, Diversion and Addiction-Related Surveillance data showed that less than 5% of those using buprenorphine without a prescription were using it to get high [8].

The evidence overwhelmingly suggests that buprenorphine is both safe and effective in treating opioid use disorder. A 1995 study demonstrated that buprenorphine was associated with less dose adjustments and fewer positive urine drug screens than those taking placebo [17]. A 2003 study showed that buprenorphine led to decreased opioid use compared to those taking placebo [15]. A 2010 study demonstrated that patients receiving buprenorphine implants had more negative urine drug screens and fewer withdrawal symptoms than those receiving placebo [21]. A 2012 study examining the effects of buprenorphine versus methadone on 39 full-term newborns found that the infants exposed to buprenorphine were less stressed, less excitable, less over stimulated, less hypertonic and better able to self-regulate [9].

2.2. Emergency room initiation of buprenorphine

While evidence suggests that buprenorphine treatment is safe and effective, emergency rooms are rarely able to initiate treatment. To treat opioid withdrawal, emergency room physicians typically administer symptom-based treatment followed by a referral to an outpatient MAT facility. Data is beginning to emerge, however, that suggests emergency room initiation of buprenorphine is safe and effective.

There are a variety of clinical and administrative challenges to the initiation of buprenorphine in the emergency room setting. Many emergency rooms have length-of-stay limitations, which preclude waiting the appropriate amount of time before buprenorphine can be successfully dosed without precipitating opioid withdrawal. Many emergency room providers do not have a waiver to prescribe buprenorphine and may feel that it is not their role. A great deal of areas of the country do not have buprenorphine providers readily accessible for outpatient follow up following discharge from the emergency room.

Despite these limitations, D'Onofrio et al. demonstrated improved engagement in treatment when buprenorphine was initiated in the emergency room compared to referral to treatment and brief intervention [11]. It has also been shown that buprenorphine maintenance treatment demonstrated significantly higher rates of engagement in treatment at one-year compared to detoxification from opioids only [18].

A study from 2017 and 2018 evaluated buprenorphine initiation and outpatient referral in the emergency room of Denver Health Medical Center by looking at the percentage of patients enrolled in an

outpatient MAT program 30 days following the referral. Of the 219 patients receiving buprenorphine induction in the emergency room, 49.3% were enrolled in a MAT program at 30 days. Unlike previous research regarding buprenorphine induction in the emergency room, this study also mentioned the use of advanced practice providers managing buprenorphine treatment in the emergency room. This is a practical solution to challenges such as cost of treatment and lack of providers and resources to manage treatment [19].

Similarly, a 2019 review by Dunkley, et al. aimed to evaluate a new model for treating opioid use disorder in the emergency room setting of a large public hospital. The hospital also established its own MAT clinic for follow-up care. The study revealed that twelve of the 19 participants who received buprenorphine initiation in the emergency room attended their follow-up visit in the MAT clinic. Nine participants were still engaged in MAT services 30 days after being discharged from the emergency room. Finally, 4 patients remained engaged at the 6-month mark. It is critical to note that the physicians who saw the patients for buprenorphine induction are the same physicians who carried out the MAT services in the clinic, contributing to positive outcomes [14].

A 2018 clinical review examined the details of identification, management and referral to outpatient MAT programs for patients experiencing opioid use disorder in the emergency room setting. Given the busy nature of emergency rooms, identification of opioid use must fit seamlessly and efficiently into emergency management of opioid use disorder. There are currently several reliable screening tools such as the Opioid Risk Tool (ORT), Screener and Opioid Assessment for Patients with Pain (SOAPP-R), Current Opioid Misuse Measure (COMM) and Addiction Behaviors Checklist (ABC) [13].

The ORT evaluates patient and family history of substance abuse, sexual abuse and psychological disease. The SOAPP-R is a patient questionnaire assessing opioid use and pain; this screening tool is particularly conducive to a busy emergency room environment, as it generally requires less than 5 min to complete. The COMM assesses the risk of opioid abuse in patients experiencing pain before beginning opioid therapy. Finally, the ABC is a questionnaire which assesses addictive behaviors exhibited between and during visits. While there are various screening tools for the identification of opioid use disorder in the emergency room, there aren't any strict guidelines on who to screen. Many states mandate drug monitoring programs and screening for individuals who are at-risk or are being prescribed opioids [13]. Comparably, identifying opioid withdrawal can occur in the emergency room through several screening tools. Most clinicians and experts believe that the Clinical Opiate Withdrawal Scale is the most reliable and efficient screening tool for opioid withdrawal in the emergency room [13].

Data clearly shows that buprenorphine is a safe and effective option for managing opioid use disorder in the emergency room setting. To initiate buprenorphine, there must be evidence of moderate opioid withdrawal symptoms, otherwise withdrawal symptoms can worsen. Physicians typically initiate treatment with a 2 to 4 mg sublingual dose, observe the patient for 60–90 min and titrate dosage as necessary [13].

Once buprenorphine has been successfully initiated in the emergency room, physicians must facilitate the transition of patients to a MAT program. Some emergency rooms have affiliated MAT clinics making for a smooth transition, but many do not. Medication for addiction treatment is necessary for long-term success in patients with opioid use disorder. Participation in MAT reduces relapse rates and the chance of overdose death. To maximize positive outcomes, MAT should be combined with psychological intervention such as personal or group therapy as well as follow-up support through case management [13].

In addition to its efficacy, emergency room-initiated buprenorphine is a cost-effective. A cost-effectiveness analysis compared the average healthcare expense, crime expense and patient time expense of three different groups in an urban emergency room setting in the US. The three groups included those for whom buprenorphine was initiated in the emergency room, those who received a brief intervention and those

who were referred to a community-based treatment program. The results showed that emergency room-initiated buprenorphine costs significantly less than the other treatment options and had better outcomes as determined by a previously conducted clinical trial. At a time in which most insurance plans are required to cover addiction treatment, they too will be in support of the most cost-effective treatment [5].

Opioid use disorder is a deadly illness with only three FDA approved medications. Access to methadone is restricted to federally-regulated opioid treatment programs, which are not available in all communities and are subject to significant restrictions. Buprenorphine is only available through waived physicians, who may not be available in all communities and who are also subject to restrictions. Extended-release naltrexone is an opioid antagonist that is not subject to restrictions, however, the patient must be opioid-free for 7–10 days, which may be a significant barrier to initiation. Given the mounting evidence for their efficacy and the difficulties with access to these medications, it is critical to initiate them whenever the opportunity arises. Often, that opportunity is in the emergency room setting.

3. Part 3 – Emergency room initiation of buprenorphine: the VA Connecticut model

The United States Department of Veterans Affairs (VA) is a federal agency that provides healthcare services to eligible military veterans at VA medical centers and outpatient clinics throughout the country. VA Connecticut Healthcare System encompasses an inpatient facility and ambulatory care center in West Haven, an ambulatory care center in Newington and six primary care community-based outpatient clinics: Danbury, New London, Stamford, Waterbury, Willimantic and Winsted. VA Connecticut also provides community care through the Errera Community Care Center, which provides a continuum of psychosocial, medical and educational services that range from acute to long-term rehabilitation and includes job training. VA Connecticut is affiliated with the Yale University School of Medicine and the University of Connecticut Schools of Medicine and Dentistry. More than 675 physicians and dentists and more than 685 students in allied health disciplines are trained at VA Connecticut every year.

The mental health service line of VA Connecticut provides a variety of resources to veterans. First is a wide range of specialized outpatient services. These services include specialized treatment for PTSD, mood disorders, anxiety, psychosis, and others. Specifically for substance use disorders, there is a range of specialized outpatient care available. These services include a general outpatient clinic for substance use and dual diagnosis, specialized group therapies including cognitive behavioral therapy and contingency management, a buprenorphine clinic with specialized providers and clinicians, an opioid treatment program for the administration of methadone and a day program providing an intensive outpatient level of care. In addition, there is an extensive telepsychiatry network, including tele-buprenorphine and buprenorphine in primary care. There is also an ambulatory detoxification and addiction stabilization service (DASS) providing walk-in clinical care for veterans seeking detoxification from substances or stabilization on buprenorphine. The mental health inpatient service provides a range of inpatient care and a consult-liaison service provides mental health care to patients admitted to other services. Finally, there is a psychiatric emergency room (PER) which is in close proximity to, though distinctly separate from the medical emergency room (MER).

The VA Connecticut PER functions 24 h per day, 7 days per week. There are approximately 120 new patient encounters per month with a capacity of 14. Patients may present voluntarily or involuntarily, though the vast majority of patients are voluntary. The unit can function as a brief-stay observation unit, caring for veterans for 48 h or longer if needed. Common diagnoses seen in the PER include (patients often have multiple diagnoses hence percentage add to greater than 100%): alcohol use disorder (~60%), PTSD (~40%), cocaine use

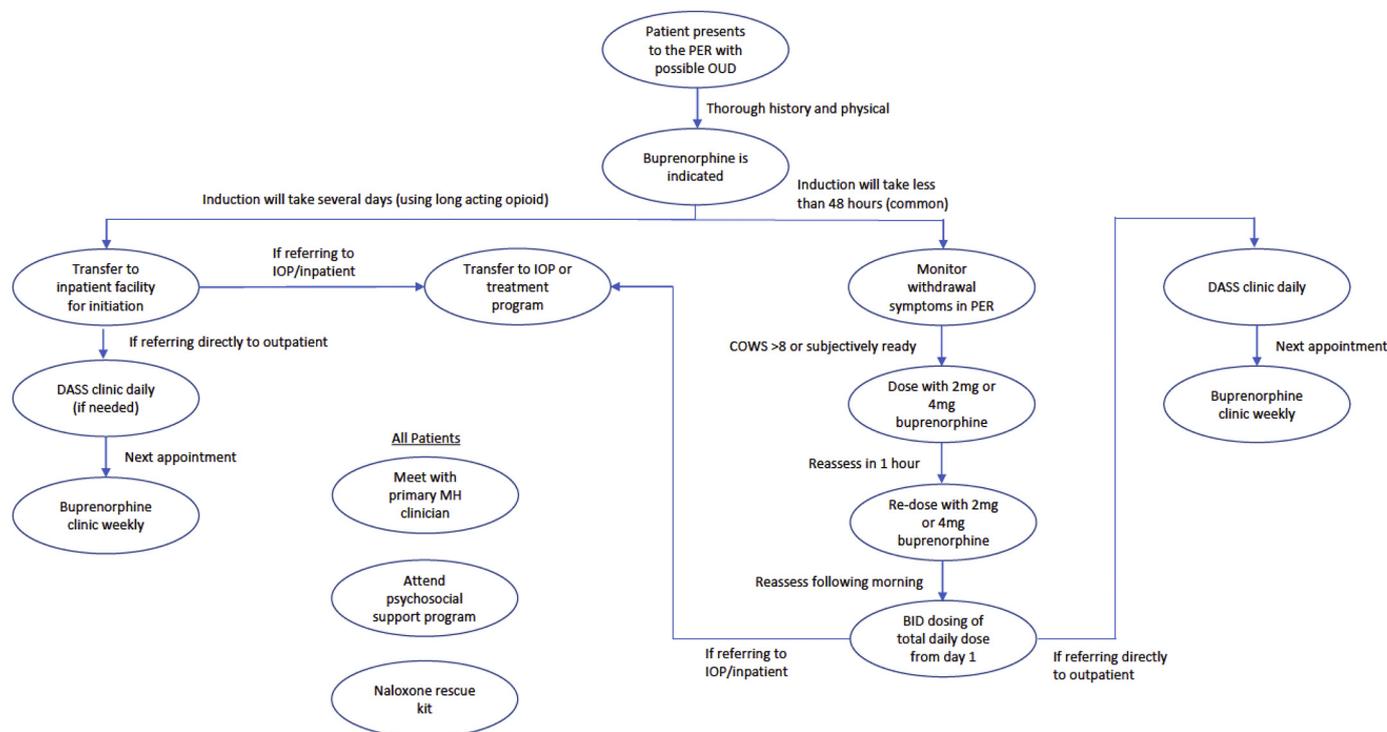


Fig. 1. VA Connecticut PER buprenorphine management model (PER = psychiatric emergency room, OUD = opioid use disorder, DASS = detox and stabilization service, IOP = intensive outpatient program).

disorder (~30%), depressive disorder (~30%), opioid use disorder (~20%) and bipolar disorder (~20%). The PER is staffed 24/7 by in-house attending psychiatrists, all of whom are required to have a buprenorphine waiver. The PER is a common entry-point to the VA Connecticut system and also provides care to many veterans with poor outpatient followup, hence it represents an opportunity to provide care to a vulnerable population that might otherwise be missed.

As mentioned above, acute opioid overdoses commonly present to emergency rooms. Providing a life-saving opioid antagonist to reverse an overdose is a critically important step, though without a system in place for providing long-term care for the underlying opioid use disorder, opioid use is very likely to continue upon discharge. Those with opioid use disorder may also seek treatment for comorbid medical and psychiatric conditions. The emergency room visit may represent the only opportunity to provide care for the opioid use disorder. And with the current rates of overdose death and the ubiquitous nature of fentanyl, without an immediate intervention, death may be imminent. Emergency rooms represent a critical resource in the battle against the opioid epidemic. Traditionally, emergency rooms are only able to provide a referral to addiction treatment services. Given that the data overwhelmingly supports buprenorphine as a treatment for opioid use disorder, and that emergency rooms may be the only interaction with the health care system, it would follow that emergency rooms initiate buprenorphine. This is not dissimilar to hypertension, diabetes or asthma in which the emergency room clinicians initiate or restart treatment.

When a veteran presents to the PER, a thorough history and physical examination are completed. A diagnosis of opioid use disorder must be established. It must be determined that buprenorphine is appropriate and indicated. The veteran is educated about the risks and benefits of buprenorphine treatment, as well as the alternatives, extended-release naltrexone and methadone. The PER is typically unable to initiate extended-release naltrexone as patients must be opioid free for 7–10 days, which is rarely the case upon presentation. Methadone can only be initiated in a opioid treatment program setting. PER clinicians always discuss these medication options for all veterans with an opioid use

disorder diagnosis. If the veteran is determined to be appropriate for buprenorphine, and agreeable to initiation, a standard induction process occurs. The veteran is held in the PER until withdrawal is sufficient for initial dosing of buprenorphine, which varies based upon the type of opioid used. Most veterans are able to be dosed with a maximum of 8 mg of buprenorphine on day 1 and can be fully stabilized with 8-16 mg by day 2 (usually less than 48 h in the PER). Veterans using long acting opioids may require additional time in the PER to be fully stabilized.

Following induction and stabilization, veterans are discharged from the PER and referred to the appropriate setting. Some of the patients require the structure of the intensive outpatient program and others are stable for outpatient care. Following discharge from the PER, regardless of the treatment setting, patients present daily to the DASS clinic for continued stabilization/maintenance. DASS is a walk-in clinic that provides daily dosing of buprenorphine while titration and stabilization is occurring. DASS is staffed by an attending psychiatrist, advanced practice nurse practitioner, nurses and administrative support. DASS provides service during business hours, Monday-Friday. Once clinically stable and an appointment is available, patients are then referred from the DASS clinic to the buprenorphine clinic for continued care. The buprenorphine clinic will typically transition patients to a weekly prescribing. Following a period of stability, patients are seen less frequently, often once per month for prescriptions. In addition, the buprenorphine clinic provides a variety of counseling and therapy options and patients are also encouraged to attend Narcotics Anonymous and other self-help programs. See Fig. 1 below for a flow chart of patient management in the VA Connecticut PER.

The process of initiation of buprenorphine in the PER is possible for several key reasons. First, all providers have a buprenorphine waiver. While it may seem easy to require providers to become buprenorphine waived, educating the staff about the importance of the treatment is essential for provider buy-in. Second is the role of the DASS clinic for daily followup. This eliminates the burden on the PER staff of arranging outpatient followup. It also eliminates the burden of PER clinicians from writing prescriptions for buprenorphine. And with a dedicated

buprenorphine clinic, DASS rarely has to manage the buprenorphine prescribing beyond several days. Lastly is the ability to hold patients in the PER for a sufficient period of time to allow for the onset of withdrawal symptoms and stabilization on buprenorphine, which often takes more than 24 h, something that may be challenging in traditional medical emergency rooms.

4. Conclusion

Emergency room providers are at the forefront of the opioid epidemic. Patients routinely present to emergency rooms following an overdose or with the intention to be connected to outpatient care. Emergency room providers should be familiar with basic mental health and substance-related emergencies that may be comorbid with opioid use disorder. Three evidence-based medications are highly effective for opioid use disorder and should be used aggressively when indicated. There is ample evidence that the emergency room initiation of buprenorphine is effective. VA Connecticut has adopted a system for emergency room initiation of buprenorphine that takes advantage of the various resources available. Readers should think about the resources available within their system of care and consider the possibility of emergency room initiation of buprenorphine as a way to expand access to this very important medication.

References

- [1] Annual Surveillance Report of Drug-Related Risks and Outcomes — United States. Surveillance Special Report. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services(Rep.) (August 31). Retrieved., 2018. <https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf>.
- [2] R. Ahrnsbrak, J. Bose, S.L. Hedden, R.N. Lipari, E. Park-Lee, Key substance use and mental health indicators in the United States: results from the 2016 National Survey on Drug Use and Health, Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, 2017 Retrieved from <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.htm>.
- [3] C.H. Andrilla, T.E. Moore, D.G. Patterson, E.H. Larson, Geographic distribution of providers with a DEA waiver to prescribe buprenorphine for the treatment of opioid use disorder: a 5-year update, *J. Rural. Health* 35 (1) (2018) 108–112, <https://doi.org/10.1111/jrh.12307>.
- [4] A.M. Brown, C. DeFrances, E. Crane, R. Cai, S. Naeger, Identification of substance-involved emergency department visits using data from the National Hospital Care Survey, *Nat. Health Stat. Rep.* 115 (2018) Retrieved from <https://www.cdc.gov/nchs/data/nhsr/nhsr114.pdf>.
- [5] S.H. Busch, D.A. Fiellin, M.C. Chawarski, P.H. Owens, M.V. Pantalon, K. Hawk, S.L. Bernstein, P.G. O'Connor, G. D'Onofrio, Cost-effectiveness of emergency department-initiated treatment for opioid dependence, *Addiction* 112 (11) (2017) 2002–2010, <https://doi.org/10.1111/add.13900>.
- [7] S. Charumilind, T. Latkovic, R. Lewis, E. Mendez-Escobar, Why we need bolder action to combat the opioid epidemic, Healthcare Systems and Services Practice, McKinsey & Company, 2018 Retrieved from <https://healthcare.mckinsey.com/sites/default/files/Why-we-need-bolder-action-to-combat-the-opioid-epidemic.pdf>.
- [8] T.J. Cicero, M.S. Ellis, H.D. Chilcoat, Understanding the use of diverted buprenorphine, *Drug Alcohol Depend.* 193 (2018) 117–123, <https://doi.org/10.1016/j.drugalcdep.2018.09.007>.
- [9] M.G. Coyle, A.L. Salisbury, B.M. Lester, H.E. Jones, H. Lin, K. Graf-Rohrmeister, G. Fischer, Neonatal neurobehavior effects following buprenorphine versus methadone exposure, *Addiction* 107 (Suppl 1(0 1)) (2012) 63–73, <https://doi.org/10.1111/j.1360-0443.2012.04040.x>.
- [10] Department of Health and Human Services USA, The Facts about Buprenorphine for Treatment of Opioid Addiction, Substance Abuse and Mental Health Services Administration, 2015 Retrieved from www.samhsa.gov.
- [11] G. D'Onofrio, P.G. O'Connor, M.V. Pantalon, M.C. Chawarski, S.H. Busch, P.H. Owens, S.L. Bernstein, D.A. Fiellin, Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial, *JAMA* 313 (16) (2015) 1636–1644, <https://doi.org/10.1001/jama.2015.3474>.
- [12] Drug Abuse Warning Network, National estimates of drug-related emergency department visits (2013), U.S. Department of Health And Human Services Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality, 2011 Retrieved from <https://www.samhsa.gov/data/sites/default/files/DAWN2k11ED/DAWN2k11ED/DAWN2k11ED.pdf>.
- [13] H.C. Duber, I.A. Barata, E. Cioè-Peña, S.Y. Liang, E. Ketcham, W. Macias-Konstantopoulos, et al., Identification, management, and transition of care for patients with opioid use disorder in the emergency department, *Ann. Emerg. Med.* 72 (4) (2018) 420–431, <https://doi.org/10.1016/j.annemergmed.2018.04.007>.
- [14] C.A. Dunkley, J.E. Carpenter, B.P. Murray, E. Sizemore, M. Wheatley, B.W. Morgan, T.P. Moran, A. Steck, Retrospective review of a novel approach to buprenorphine induction in the emergency department, *J. Emerg. Med.* 57 (2) (2019) 181–186.
- [15] P.J. Fudala, T.P. Bridge, S. Herbert, et al., Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone, *N. Engl. J. Med.* 349 (2003) 949–958.
- [16] R.L. Haffajee, L.A. Lin, A.S.B. Bohnert, J.E. Goldstick, Characteristics of US counties with high opioid overdose mortality and low capacity to deliver medications for opioid use disorder, *JAMA Netw. Open* (2019), <https://doi.org/10.1001/jamanetworkopen.2019.6373>.
- [17] R.E. Johnson, T. Eissenberg, M.L. Stitzer, E.C. Strain, I.A. Liebson, G.E. Bigelow, A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence, *Drug Alcohol Depend.* 40 (1995) 17–25.
- [18] J. Kakko, K.D. Svanborg, M.J. Kreek, M. Heilig, 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trial, *Lancet* 361 (9358) (2003) 662–668.
- [19] K.A. Kaucher, E.H. Caruso, G. Sungar, L. Gawenus, K. Hurlbut, D.C. Sanchez, K. Broderick, Evaluation of an emergency department buprenorphine induction and medication-assisted treatment referral program, *Am. J. Emerg. Med.* (2019), <https://doi.org/10.1016/j.ajem.2019.158373> Retrieved from.
- [20] B.J. Moore, C. Stocks, P.L. Owens, Trends in emergency department visits, 2006–2014, HCUP Statistical Brief #227, Agency for Healthcare Research and Quality, 2017 Retrieved from www.hcup-us.ahrq.gov/reports/statbriefs/sb227-Emergency-Department-Visit-Trends.pdf.
- [21] R.N. Rosenthal, W. Ling, P. Casadonte, F. Vocci, G.L. Bailey, K. Kampman, A. Patkar, S. Chavoustie, C. Blasey, S. Sigmon, K.L. Beebe, Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone, *Addiction* 108 (12) (2013) 2141–2149, <https://doi.org/10.1111/add.12315>.
- [22] B.J. Sadock, V.A. Sadock, P. Ruiz (Eds.), *Kaplan & Sadocks Comprehensive Textbook of Psychiatry*, Wolters Kluwer, Philadelphia, 2017.
- [23] L. Scholl, P. Seth, M. Kariisa, N. Wilson, G. Baldwin, Drug and Opioid-Involved Overdose Deaths - United States, 2013–2017 | *MMWR*, January 4. Retrieved from, 2019. <https://www.cdc.gov/mmwr/volumes/67/wr/mm675152e1.htm>.
- [24] R.C. Walters, The case for buprenorphine deregulation, *Fam. Pract. Manag.* 26 (4) (2019) 6–8 Retrieved from <https://www.aafp.org/fpm/2019/0700/p6.html>.