

Suboxone: Rationale, Science, Misconceptions

Jennifer R. Velander, MD

Department of Psychiatry, Ochsner Clinic Foundation, New Orleans, LA and The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, LA

The United States is in the middle of a historically unprecedented opioid epidemic. Today, more people die of drug overdoses than any other form of accidental death, and opioid overdose rates surpass historic peak death rates from human immunodeficiency virus (HIV), gun violence, and motor vehicle accidents.^{1,2} Opioid addiction rates are at all-time high. In 2014, 4.3 million people abused prescription opioids, 1.9 million people had an opioid use disorder related to prescription pain relievers, and another 586,000 people had an opioid use disorder related to heroin.³ This epidemic is attributable to a confluence of circumstances, primarily overprescribing by physicians combined with an influx of potent heroin from Mexico. The epidemic has received additional fuel and urgency from the rise of extremely potent synthetic opioids such as fentanyl, carfentanil, and others. These synthetic drugs are often consumed unknowingly, mixed in illicit street heroin or compounded in fake versions of prescription opioids. As with other chronic medical illnesses, opioid addiction, once developed, has no cure and requires ongoing monitoring and treatment. Therapy alone and abstinence-based models rather than medication-assisted treatment have dominated opioid treatment until now. Despite detoxification combined with psychosocial treatment, relapse rates remain at 90% or higher.⁴ These high relapse rates have been confirmed in populations that abuse heroin as well as prescription opioids.^{5,6} Renewed use after abstinence is associated with a high overdose risk, likely the result of the loss of previous tolerance and misjudgment of safe amounts.

HISTORIC CONTEXT

To understand the legal and medical framework for treating this epidemic, it is necessary to examine a smaller, yet not insignificant, opioid epidemic. In the late 19th and early 20th centuries, laudanum treatment for pain and opium dens associated with Chinese immigrants led to alarm and racist hysteria.⁷ Physicians attempted to detoxify and safely maintain these patients with opioid medications. The Harrison Narcotics Tax Act of 1914 restricted the use of opioids to pain treatment and outlawed their use for addiction management.⁸ The act framed opioid dependence and substance abuse in general as a criminal or moral rather than as a medical issue. Thirty thousand physicians, some engaged in unethical practice, some not, were prosecuted under this act.⁷ Opioid addiction remained a difficult-to-treat problem, with very low recovery rates.

The work of Dole and Nyswander at Rockefeller University in the 1960s showed that the treatment of opioid addiction with methadone, a high-affinity, long-acting opioid, led to reduced criminal behavior and improved function.^{9,10} The success of their research paved the way for methadone to become the first legally allowed opioid treatment for addiction since 1914. The Controlled Substances Act of 1970¹¹ and the Narcotic Addict Treatment Act of 1974¹² allowed dispensation of specific opioids from federally waived clinics. This legal dispensation saved lives and improved public health outcomes by helping to limit the spread of hepatitis C and HIV.^{13,14} However, the utility of methadone was limited by strict regulation and the need for patients to attend special clinics—typically on a daily basis—that was undesirable for many potential patients and impossible for those who lacked access.

Buprenorphine, the opioid in Suboxone, was developed in the 1970s as a safer opioid than morphine or heroin for the treatment of pain. Studies suggested that buprenorphine could be an attractive alternative to methadone, as it could require fewer regulations because of its inherent abuse deterrence properties as a partial opioid agonist-antagonist.¹⁵ The drug's manufacturer and the addiction treatment community lobbied for an exception to the Narcotic Addict Treatment Act to allow individual providers, rather than federally designated clinics, to prescribe buprenorphine. The Drug Addiction Treatment Act of 2000 authorized physicians via a new individual waiver to prescribe specific opioids for the treatment of opioid use disorder.¹⁶ Buprenorphine is currently the only opioid authorized under this waiver.

BUPRENORPHINE PHARMACOLOGY/ MECHANISM

Buprenorphine is a long-acting, high-affinity partial agonist at the mu-opioid receptor. As a long-acting agonist, buprenorphine prevents withdrawal and craving and stabilizes opioid receptors. As a high-affinity agonist, buprenorphine blocks other opioids from binding, preventing abuse of other opioids. As a partial agonist, it has a smaller effect with a ceiling, a low overdose risk, and no intoxication in the opioid dependent. Buprenorphine is available in many formulations (Table 1). The most common formulation is buprenorphine and naloxone (Suboxone) in a 4:1 ratio.¹⁷ As an opioid antagonist with high first-pass hepatic metabolism, naloxone has no effect on sublingual use of buprenorphine but blocks intravenous or intranasal abuse of buprenorphine. In contrast, naltrexone is another opioid

Table 1. Formulations and Indications of Buprenorphine With and Without Naloxone

Formulation	Route	Indication
Buprenorphine + naloxone		
Suboxone	Sublingual film	Opioid use disorder
Zubsolv	Sublingual tablet	Opioid use disorder
Bunavail	Buccal film	Opioid use disorder
Buprenorphine		
Subutex	Sublingual tablet	Opioid use disorder
Belbuca	Buccal film	Pain management
Buprenex	Intravenous	Pain management
Butrans	Transdermal patch	Pain management
Probuphine	30-day subcutaneous implant	Opioid use disorder

antagonist with greater oral bioavailability that blocks all opioids regardless of delivery method and is also US Food and Drug Administration (FDA) approved for treatment of opioid use disorder. Buprenorphine without naloxone is used for pain management and can be prescribed for opioid use disorder in sublingual film or tablet form. Except in the case of severe hepatic impairment or pregnancy, prescription of isolated buprenorphine is discouraged given the potential for intravenous abuse.

BUPRENORPHINE DOSING

The most common dosing of buprenorphine is 8-24 mg daily. Patients need to be in sufficient opioid withdrawal for induction, typically 12-24 hours after last use. The starting dose is 4-8 mg on the first day with gradual titration. The requirement to be in withdrawal and the need for gradual titration may limit the use of buprenorphine in patients with acute pain in hospital settings. Buprenorphine is a Schedule III medication requiring special waiver (X number). Physicians can obtain waivers by taking an 8-hour course that is available online and in person.¹⁸ Advanced practice professionals can apply for waivers as well but need a supervising physician with an X number. The initial limit is 30 patients, but this limit can be increased to 100 and then 275 patients after year-long periods. The physician must be able to offer concurrent counseling or to refer patients to counseling. In the hospital, a physician does not need to have an X number to continue buprenorphine for opioid-dependent patients with acute medical conditions as is the case with methadone.

EVIDENCE FOR USE OF BUPRENORPHINE

As elaborated below, current evidence shows buprenorphine is superior to methadone for tolerability but equivalent for treatment retention and other outcomes. The data also indicate that buprenorphine is equal or superior to antagonist-based treatment (depot intramuscular and oral naltrexone). US Department of Veterans Affairs guidelines currently recommend either buprenorphine or methadone vs depot intramuscular naltrexone, oral naltrexone, or abstinence-based treatment.¹⁹

Several placebo-controlled studies document the general efficacy of buprenorphine for opioid use disorder. Patients

in a Swedish treatment program randomized to buprenorphine had 1-year retention of 75% and negative urine drug tests in 75% of patients compared to 0% of patients randomized to placebo.²⁰ One major randomized placebo-controlled trial was terminated early because of the clear superiority of buprenorphine to placebo, with 4 times the rate of negative urine drug tests and significantly less craving in patients on buprenorphine.²¹ The follow-up open-label study showed continued benefit and no increase in adverse events compared to placebo.²¹ In another study of 110 patients initiated on buprenorphine, those who remained on buprenorphine after 18 months were more likely to be sober, employed, and involved in 12-step groups.²²

Buprenorphine significantly lowers the risk of mortality and adverse outcomes. In a metaanalysis, both methadone and buprenorphine maintenance were found to be superior to detoxification alone in terms of treatment retention, adverse outcomes, and relapse rates.⁶ Studies have also shown a reduction in all-cause and overdose mortality and significantly improved quality-of-life ratings with maintenance buprenorphine.^{23,24} Patients on buprenorphine had reduced rates of HIV and hepatitis C transmission compared to abstinence-based therapy or detoxification alone.^{13,14} Maintenance buprenorphine is also associated with better hepatitis C treatment outcomes.²⁵

Suboxone has been shown to have similar efficacy to methadone when treatment conditions are similar and when patients take higher doses of Suboxone. One early study suggested that methadone was associated with better treatment retention and more negative urine drug tests than buprenorphine.²⁶ These findings were hypothesized to be attributable to increased dependence on the medication because of the full agonist activity and the support provided by the daily visits required for methadone treatment.^{27,28} However, this study and other early studies typically underdosed buprenorphine, prescribing only 8 mg to many participants. When the subgroups on lower doses were excluded in later analyses, the outcomes between buprenorphine and methadone were the same.^{26,29} This equipoise argues for buprenorphine instead of methadone, given the better safety profile of the former. As a full agonist, methadone has more than 4 times the risk of overdose than buprenorphine.³⁰ Buprenorphine has rarely been linked to overdoses outside of concurrent alcohol or other sedative abuse and lacks the QTc prolongation and drug-drug interactions of methadone.³¹

Oral naltrexone has been established as inferior to the extended-release depot form of naltrexone (Vivitrol) and to buprenorphine. Rates of relapse for oral naltrexone and placebo at 6 months were similar, and both were 3 times higher than the relapse rate for patients on buprenorphine maintenance.³² Several recent studies indicate that buprenorphine and extended-release naltrexone are equally efficacious. Two naturalistic studies showed better treatment retention for buprenorphine products compared to extended-release naltrexone.^{33,34} An outpatient-based randomized open-label study in Norway showed similar treatment retention and rates of negative urine drug screens between extended-release naltrexone and buprenorphine-naloxone, with significantly fewer days of heroin and illicit opioid use.³⁵ This study was limited in that it only followed

patients for 12 weeks. A 2017 randomized controlled study of buprenorphine and extended-release naltrexone conducted for 6 months found both medications to be equally efficacious in the per-protocol analysis.³⁶ However, the intention-to-treat sample showed buprenorphine to be superior to extended-release naltrexone because of the relative difficulty of induction on antagonist-based therapy, which carries a higher probability of eliciting withdrawal symptoms even weeks after the last illicit opioid use. Of the 283 patients randomized to extended-release naltrexone, 79 failed induction and ultimately relapsed.³⁶ Buprenorphine may also be a safer option than antagonist-based treatment. A longitudinal study showed 8 times the risk of overdose after patients left naltrexone treatment compared to agonist treatment.³⁷

According to 2017 American College of Obstetricians and Gynecologists guidelines, buprenorphine is the treatment of choice for opioid-dependent women in pregnancy and is safer than methadone or medical withdrawal.³⁸ This recommendation for buprenorphine rather than abstinence-based or antagonist treatment is based on the high risk associated with opioid withdrawal and detoxification in pregnancy. Studies have shown higher birth weight, larger head circumference, less preterm birth, and less neonatal withdrawal symptoms in the babies of patients on buprenorphine vs methadone.³⁹ Of note, naltrexone is contraindicated in pregnancy, as it typically requires or precipitates opioid withdrawal. To treat opioid use disorder in pregnancy, providers historically were recommended to prescribe buprenorphine without naloxone (Subutex) given the theoretical risk of naloxone crossing the placenta.³⁸ However, because of the extensive first-pass hepatic metabolism of naloxone, many researchers conclude that Suboxone is as safe as or safer than Subutex in pregnancy, except in cases of severe hepatic impairment. Recent studies show little placental transfer of naloxone and equivalent safety between buprenorphine/naloxone and buprenorphine alone.⁴⁰⁻⁴³

In line with the move toward maintenance and chronic opioid treatment rather than detoxification and abstinence, studies suggest that treatment duration should be years rather than weeks to months for most patients. The FDA recently adjusted its labeling to state that some patients will benefit from indefinite buprenorphine treatment.⁴⁴ Tapers should be individualized because of the potential for worsened outcomes with forced tapers. The risk of relapse is equally high after 2-week and 12-week stabilization periods before taper, with no further benefit from counseling posttaper.⁴ Young adults randomized to 12 weeks of maintenance buprenorphine before taper had fewer positive urine drug tests, adverse outcomes, and dropouts than those randomized to detoxification alone. No significant difference in relapse rates persisted at follow-up, suggesting that the benefit to maintenance, at least for the short term, only lasts as long as the maintenance treatment.⁴⁵

Waiver guidelines dictate that physicians have the ability to refer patients to adjunctive psychosocial therapy. The benefit of psychosocial treatment in addition to buprenorphine maintenance, however, is uncertain, with only 4 of 8 studies showing benefit.⁴⁶ Certain subgroups, such as heroin users or those with severe disease, may benefit more.⁴⁷ Therapy-based outcomes are difficult to measure,

particularly in this population because of the chronic nature of addiction, and therapy and support needs may wax and wane over time. Further, studies often exclude patients with other substance use disorders, selecting more stable patients than typically present in the general population. In my experience as an addiction psychiatrist, patients commonly need more support in the initial stages of treatment, such as that provided in intensive outpatient programs, to maintain engagement and address risk factors.

SYSTEM-BASED TREATMENT WITH BUPRENORPHINE

The multiple models for buprenorphine treatment range from minimal support to extensive scaffolded systems. Most commonly, buprenorphine is prescribed by solo practitioners (41.6% psychiatrists, 36.7% primary care physicians) in private practice or small clinic settings who leave the responsibility for psychotherapy largely up to the patient.⁴⁸ This practice allows for greater access but also runs the risk of inadequate treatment and diversion. Several system-based approaches have been developed with numerous levels of expertise, providers, and support (Table 2).⁴⁹⁻⁵⁴ The benefits of system-based approaches include expanded and rapid access to treatment, more support for prescribers, and the ability to adjust levels of care based on the patient's stability. Ideally, a healthcare system would incorporate elements of several models with routes to treatment initiation in emergency rooms, inpatient medical floors, and primary care and psychiatry offices, in addition to higher levels of psychiatric and addiction care in inpatient and intensive outpatient substance abuse programs.

MISCONCEPTIONS ABOUT BUPRENORPHINE

Despite substantial evidence for its efficacy and well-developed models of care, buprenorphine remains underutilized. The need for further prescribers is particularly evident in the rural United States and the South.⁵⁵ As of 2015, the majority of US counties (53.4%), most of them rural, were without a buprenorphine prescriber.⁴⁸ Louisiana has only 209 providers statewide, with the vast majority concentrated in the New Orleans area.⁵⁶ Most waived physicians treat far fewer patients than the 275 potential maximum. Studies suggest that lack of experience and education in the use of buprenorphine is a major reason for its underutilization.⁵⁷ As an addiction psychiatrist, I have encountered several misconceptions among colleagues and patients who are unfamiliar with buprenorphine that have led to resistance to utilizing it. I discuss 5 of these misconceptions below.

Misconception 1: Suboxone just substitutes one drug for another. If used as directed, buprenorphine-naloxone is a medication, not a substance. It is a stable, safe, long-acting medication with a ceiling effect. It is prescribed for the specific effect of improving patients' physical and mental health and preventing HIV, hepatitis C, other infectious diseases, and death. Thus, it has a clear indication, unlike substances of abuse. Suboxone would likely be more widely accepted as a medication if analogous treatments were available for other addictions. However, no partial-agonist treatment or similarly effective medication is available for alcohol or cocaine use disorders.⁵⁸

Table 2. System-Based Models of Buprenorphine Maintenance Treatment

Model	Description	Evidence
Vermont Hub and Spoke ⁴⁹	The state of Vermont was divided into 5 administrative sections, each with a hub clinic, led by an addiction psychiatrist who initiates treatment and then refers to a local hub of waived primary care practitioners who can refer patients back to the hub if they destabilize.	Of 7,212 people identified in the state with a diagnosis of opioid use disorder, 5,298 were receiving opioid agonist treatment. Sixty-four percent more physicians were waived to prescribe buprenorphine, and waived physicians provided treatment to 50% more patients.
Massachusetts Nursing Care Model ⁵⁰	In this statewide system, specially trained nurse care managers support prescribing physicians, providing clinical and administrative care with psychiatric resources available onsite or nearby.	The number of waived physicians increased by 375%.
Project Echo ⁵¹	Via this telemedicine system in New Mexico, specialists provide video-based education and mentoring to primary care physicians in rural communities.	In terms of having the most buprenorphine-waivered physicians per capita, New Mexico's state ranking progressed from fourteenth to fourth.
Inpatient-Initiated, Medication-Assisted Treatment ^{52,53}	Hospitalists induce patients on buprenorphine during admissions for other medical issues and refer them to affiliated addiction clinics.	Patients randomized to maintenance buprenorphine treatment during hospitalization were much more likely to follow through with outpatient treatment than those randomized to detoxification (72.2% vs 11.9%). Of 40 patients induced on buprenorphine, 49% linked to a clinic, with 39% remaining in treatment after 30 days, 27% after 90 days, and 18% after 180 days.
Emergency Department (ED)-Initiated, Medication-Assisted Treatment ⁵⁴	In the ED, take-home doses of buprenorphine are dispensed to bridge patients to appointments with outpatient substance abuse clinics within 3 days.	Compared to screening and referral alone, initiation of buprenorphine maintenance in the ED led to higher treatment engagement rates (78% vs 45%).

Misconception 2: Suboxone is a "failure of willpower" or "giving up." Addiction is a medical disease, not a moral failure. Treatment with a partial agonist allows stabilization of opioid receptors so that patients are able to make changes in lifestyle, behaviors, and psychiatric condition to allow ultimate recovery rather than cycles of relapses. The mortality associated with any relapse on opioids is too high and too final.

Misconception 3: Suboxone is incompatible with 12-step groups like Alcoholics Anonymous and Narcotics Anonymous. The 12-step groups distinguish between taking medications as prescribed and substance use. Alcoholics Anonymous and Narcotics Anonymous were previously hostile to antidepressants and disulfiram (Antabuse), stating that patients on those medications were not really sober, but the organizations have changed their stance. Numerous substance abuse treatment programs combine Suboxone use with 12-step facilitation. The Hazelden Betty Ford Foundation, possibly the most respected substance abuse treatment institution, has been pioneering integration of partial-agonist therapy with 12-step groups.⁵⁹ However, real stigma to partial-agonist therapy exists and exerts undue

pressure on 12-step participants to prematurely discontinue a lifesaving medication.⁶⁰

Misconception 4: Patients can get "high" or "loaded" on Suboxone. Intoxication from Suboxone does not occur if a patient is opioid dependent. Intoxication occurs only in patients who combine Suboxone with other substances, do not take it as directed, or use it to medicate withdrawal between episodes of full-agonist opioid abuse. This misuse can be addressed with increased monitoring, urine drug testing, and film/pill counts. Patients are safe to drive while on maintenance doses, and cognitive function in patients on buprenorphine maintenance is likely improved compared to other opioid users.³¹

Misconception 5: Patients will just sell Suboxone. Physicians can monitor for diversion of Suboxone by instituting film/pill checks and checking urine buprenorphine levels. Furthermore, diversion of medications is not unique to opioids or buprenorphine. The rates of diversion are similar between buprenorphine and antibiotics, both approximately 20%.⁶¹ Also the vast majority of diverted buprenorphine is used to self-treat addiction; 64% of opioid users in one

study reported using illicit buprenorphine because they were unable to afford or to access treatment.⁶²

CONCLUSION

Buprenorphine-naloxone remains an underutilized treatment for opioid use disorder despite its efficacy, safety, and relative ease of use. To fully address the vast opioid epidemic, more physicians other than addiction subspecialists should be enlisted to diagnose and treat opioid use disorder. With familiarization, training, and formation of support networks, buprenorphine could become a vital part of the community practice and health system response to the opioid epidemic.

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