

Infectious Disease (ID) Learning Unit: What the ID Clinician Needs to Know About Buprenorphine Treatment for Opioid Use Disorder

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In the context of an escalating opioid epidemic, infectious disease clinicians increasingly treat the infectious complications of injection drug use. In this learning unit, we review the history, pharmacology, and clinical use of buprenorphine as maintenance therapy for opioid use disorder, and we describe the process by which clinicians can obtain a buprenorphine waiver.

Keywords. addiction; buprenorphine; opioid use disorder.

A 32-year-old man is referred to infectious disease clinic for treatment of human immunodeficiency virus (HIV) and hepatitis C, newly diagnosed during a recent hospitalization for a methicillin-sensitive Staphylococcus aureus hand abscess. He has a 6-year history of opioid use disorder and currently injects heroin twice daily. He wants to stop using; he mentions that he previously bought Suboxone (buprenorphine/naloxone) on the street and found it helpful.

Amidst an evolving opioid epidemic, infectious disease (ID) clinicians frequently treat the infectious sequelae of opioid use. However, treating the complications of injection drug use without the tools to address the underlying addiction feels frustrating and futile—like treating *Pneumocystis jirovecii* pneumonia without starting antiretrovirals. This learning unit provides an overview of medication-assisted treatment with buprenorphine, which is increasingly prescribed by ID clinicians as an integral component of care for HIV and other infections.

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OPIOID AGONIST MAINTENANCE THERAPY: METHADONE AND BUPRENORPHINE

Medication-assisted treatment with an opioid agonist is the cornerstone of managing opioid use disorder as a chronic, relapsing disease. In light of opioid-related risks of lethal overdose and infectious disease, an abstinence-only approach (such as that which has been widely adopted for alcohol use disorder) is inadequate [1]. Compared with psychological interventions alone, opioid agonist therapy has been shown to reduce the risk of fatal overdose by 50% [2]. It has been similarly demonstrated to decrease incident HIV infections through reductions in injection drug use [3]. Opioid maintenance treatment is prescribed in concert with psychosocial interventions and is embedded within a harm reduction framework. Treatment additionally aims to reduce opioid use to repair interpersonal relationships, restore ability to work, and decrease crime used to pay for drugs [4].

In the United States, 2 opioid agonists are available for the treatment of opioid use disorder: methadone and buprenorphine. Methadone, widely used for treatment of opioid addiction since 1965, is a Schedule II controlled substance restricted by federal law to specialized opioid treatment programs. Within such programs, patients must present every day for administration of their methadone dose. In 2002, buprenorphine was approved by the US Food and Drug Administration (FDA) as a Schedule III controlled substance for the treatment of opioid use disorder in a routine office-based setting (ie, providing a prescription for buprenorphine rather than observed daily dosing) [5]. Several studies have shown that methadone and buprenorphine have similar efficacy in terms of suppressing illicit opioid use [6–8]. Despite benefits, treatment with methadone can be burdensome, stigmatizing, and punitive.

HISTORY, POLITICS, AND LICENSURE REQUIREMENTS: THE BUPRENORPHINE WAIVER

In 1973, President Nixon created the Drug Enforcement Agency (DEA) by executive order as part of a campaign branded the “War on Drugs.” Congress subsequently passed the Narcotic Addict Treatment Act of 1974, restricting methadone maintenance prescribing to addiction specialists registered with the DEA. Twenty-six years later, the Drug Addiction Treatment Act of 2000 made provisions for nonspecialists to prescribe buprenorphine for the treatment of opioid addiction. Under this legislation, physicians who complete an 8-hour training can register with the DEA under a unique identifier known as an “X number” and are granted a waiver to prescribe buprenorphine for the treatment of opioid addiction (Table 1) [9]. Buprenorphine trainings are available online and in person, offered by several physician

Table 1. Three Steps to Becoming a Buprenorphine Prescriber

1. Confirm eligibility. All physicians who meet the following criteria are eligible to apply for a waiver:
 - licensed under state law
 - registered with the Drug Enforcement Agency (DEA) to dispense controlled substances
 - able to refer patients to counseling and other support services
2. Complete an 8-hour training course.
 - Courses available online, in person, or as a blended live/webinar format
 - Offered by American Academy of Addiction Psychiatry, American Society of Addiction Medicine and others.
 - Course offerings can be found here on the website of the Substance Abuse and Mental Health Services Administration (SAMHSA).^a
3. Apply for physician waiver.
 - Brief online application can be found here on the SAMHSA website.^b

^a<http://www.samhsa.gov/medication-assisted-treatment/training-resources/buprenorphinephysician-trainin>.

^b<http://www.samhsa.gov/medication-assisted-treatment/buprenorphinewaiver-management/apply-for-physician-waiver>.

organizations including the American Academy of Addiction Psychiatry and the American Society of Addiction Medicine.

The original legislation limited the number of patients a physician could treat within the first year of buprenorphine prescribing to 30, with up to 100 patients per prescriber in subsequent years. In the summer of 2016, the Comprehensive Addiction and Recovery Act expanded waiver eligibility to nurse practitioners and physician assistants and increased the patient limit from 100 to 275. Nevertheless, physicians have been slow to adopt office-based opioid treatment and bring it to scale. Between 2010 and 2014, the median monthly patient census for buprenorphine prescribers in high-volume states was only 13, with 22% of prescribers treating just 1–3 patients [10].

PHARMACOLOGY OF BUPRENORPHINE

Buprenorphine acts as a partial agonist at the mu opioid receptor, effectively curbing opioid cravings. High affinity for the mu receptor and slow dissociation kinetics mean that it largely blocks the effects of concomitantly administered full agonists (eg, a patient taking maintenance buprenorphine who injects heroin will feel only attenuated effects of heroin). As a partial agonist, buprenorphine shows a dose-ceiling effect for all opioid properties including euphoria, analgesia, and respiratory depression [11]. This ceiling effect dramatically reduces the risk of respiratory arrest, although fatal overdose can occur if buprenorphine is taken in conjunction with other central nervous system depressants such as alcohol and benzodiazepines [12].

As a result of high affinity, buprenorphine out-competes most other opioids for a site at the mu receptor, with fentanyl being the notable exception. If administered after use of a full agonist (eg, heroin, methadone, or oxycodone), it displaces the full agonist. In this setting, buprenorphine precipitates opioid withdrawal (ie, there is a net decrease in activation as receptors shift from being occupied by a full agonist to partial agonist). To avoid precipitated withdrawal, buprenorphine must be initiated when a patient is in a moderate state of withdrawal.

In the context of withdrawal, a partial agonist provides symptomatic relief.

Due to significant first-pass hepatic metabolism, buprenorphine is administered sublingually [12]. Naloxone, an opioid antagonist that has negligible bioavailability when absorbed sublingually, is coformulated with buprenorphine to attenuate potential for injection misuse and diversion [13]. Buprenorphine and naloxone are coformulated in a 4:1 ratio as a sublingual tablet (generic, Suboxone, Zubsolv), sublingual film (Suboxone), or buccal film (Bunavail). Buprenorphine alone (generic; previously marketed under the brand name Subutex) is available as a sublingual tablet. Use of the monoformulation is generally limited to pregnancy, where concerns regarding teratogenicity of naloxone preclude use of the combination pill. A subdermal buprenorphine implant (Probuphine), which provides a constant, low-level dose of buprenorphine over 6 months, was approved by the FDA in May 2016 but is not in widespread clinical use.

PRINCIPLES OF BUPRENORPHINE INDUCTION AND MAINTENANCE

As discussed above, buprenorphine precipitates withdrawal if administered while opioid receptors are occupied by a full agonist such as heroin. To avoid precipitated withdrawal, initiation of buprenorphine maintenance therapy—often referred to as buprenorphine induction—must take place when the patient is in a state of opioid withdrawal. For short-acting opioids (eg, heroin, oxycodone), withdrawal symptoms begin within 6–12 hours after the last dose and peak at 36–72 hours. For opioids with long half-lives (eg, methadone), withdrawal symptoms begin 36–72 hours after the last dose and peak at several days [4]. Patients who are dependent on short-acting opiates should abstain from use for 12 hours before buprenorphine induction. Patients who are transitioning from methadone maintenance should taper methadone to 30 mg daily for a minimum of 1–2 weeks and then stop all opioids for ~96 hours before induction. Objective tools such as the Clinical Opiate Withdrawal Scale (COWS) can be used to quantitate withdrawal symptoms; a score of >8 reflects mild to moderate withdrawal, appropriate for buprenorphine induction [14].

For most opioid-dependent patients, the initial induction dose is 4 mg buprenorphine/1 mg naloxone. If symptoms of opioid withdrawal are not relieved within 2 hours, an additional dose of 4 mg/1 mg is given. Patients return to clinic the following day for re-evaluation and to titrate the dose to withdrawal symptoms. Many patients stabilize at a dose of 12–24 mg buprenorphine daily [6]. The FDA-approved dose range is up to 24 mg/6 mg daily; in clinical practice, maximum daily dose is often considered 32 mg/8 mg. The stabilization dose is the dose at which withdrawal symptoms are absent, cravings are controlled, and opioid use is markedly reduced

or absent. Therapy is continued long-term (at minimum, 12 months); indefinite therapy can be considered, because the risks of relapse and overdose return upon buprenorphine discontinuation [4]. Drug-drug interactions are minimal, including those with most antiretrovirals and direct-acting antivirals for hepatitis C.

Toxicology screens should be performed (1) regularly and (2) at random during buprenorphine treatment. Routine toxicology screen serves as an objective measure of treatment response. If used within the past 12 hours, heroin will be detected as its metabolites 6-monoacetylmorphine and morphine. Many routine screens do not detect synthetic opioids; in such cases, an expanded opioid toxicology panel is required to detect drugs such as oxycodone, fentanyl, and buprenorphine [15]. A positive toxicology screen should not prompt discontinuation of treatment; rather, it is a sign that treatment intensification is required (eg, in the form of a dose increase, increased visit frequency, referral to a drug rehabilitation facility, or transition to methadone).

CONCLUSIONS

Infectious disease clinicians are uniquely positioned to prescribe buprenorphine as an integrated part of care for HIV, hepatitis C, and endocarditis. Treating addiction with buprenorphine can be as satisfying as reversing advanced AIDS with antiretrovirals. Barriers to buprenorphine prescribing can be readily overcome: obtaining a waiver is a straightforward process, and there are ample resources to assist novice buprenorphine prescribers (eg, Providers' Clinical Support System for Medication Assisted Treatment; www.pcssmat.org).

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