The New Kid on the Block—Incorporating Buprenorphine into a Medical Toxicology Practice

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Abstract Buprenorphine represents a safe and effective therapy for treating opioid dependence, alleviating craving and withdrawal symptoms in opioid-dependent patients. Buprenorphine has a “blocking” effect against the action of other opioids at the mu-receptor, preventing not only opioid-induced euphoria, but CNS and respiratory depressant effects as well. Buprenorphine was approved for the treatment of opioid dependence in 2002 after the passage of Drug Abuse Treatment Act 2000 (DATA 2000) which allowed clinicians to treat opioid-dependent patients with specifically named opioid agonist therapies in an office setting. Buprenorphine programs reduce the prevalence of HIV and hepatitis C and reduce criminal behaviors associated with illicit drug use. Patients stabilized on buprenorphine have increased employment, enhanced engagement with social services, and better overall health and well-being.

Keywords Buprenorphine · Medical Toxicology · Opioid dependence · Addiction · Drug treatment

Introduction

Prescriptions of buprenorphine for opioid-dependent patients have increased dramatically in the USA since it was first ap-

proved for this indication in 2002. There were 50,000 prescriptions in 2002; more than 5.7 million in 2009; and in 2012, there were 9.3 million buprenorphine prescriptions in the USA [1]. The increasing numbers of individuals treated with this medication necessitate that providers in emergency departments and other hospital settings become familiar with its use [2].

Medical toxicologists are comfortable using a variety of medications as antidotes and for the treatment of intoxication and withdrawal. Familiarity with pharmacology and toxicology can be of particular use when the unique pharmacology of buprenorphine creates a complication or necessitates a deviation from standard protocol in patient care. Questions related to acute or perioperative pain management for patients maintained on buprenorphine and treatment of precipitated withdrawal arise frequently and can be challenging clinical scenarios that represent opportunities for the medical toxicologist. In addition to performing consultations on hospitalized patients with buprenorphine-related issues, the medical toxicologist can also expand their practice to include treatment of opioid dependence in the clinic setting in an office-based opioid treatment model.

To prescribe buprenorphine for the treatment of opioid dependence, a physician must obtain an X-waiver certification by completing 8 hours of training and passing a test regarding the treatment of opioid dependence [3]. There are exemptions to the waiver requirements accorded to non-waivered physicians, including (1) emergency use and (2) use in the hospital setting for opioid-dependent patients that are being treated for other medical conditions [4]. Additionally, a patient maintained on buprenorphine by an X-waivered physician in an outpatient setting can have it continued in the hospital setting, even if the treating providers do not have a waiver to prescribe buprenorphine [4]. There is also an emergency rule that allows for a treating physician to dispense not more than 3 days of the

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medication in an emergency in order to facilitate entry into a detoxification or treatment program [4].

Pharmacology

Buprenorphine is a partial mu-receptor agonist and a kappa-receptor antagonist. Compared to full agonists (such as morphine, methadone, or oxycodone), buprenorphine only partially activates the mu-receptor (Fig. 1). As the concentration of buprenorphine increases, the receptor activation starts to plateau. This plateau is called a “ceiling effect.” The ceiling effect confers some degree of safety with regard to risk for overdose compared to full agonists. A standard dose/response curve comparing full agonist (e.g., morphine) to partial agonists (buprenorphine) is included in Fig. 2. While buprenorphine behaves like a partial agonist with a ceiling effect for respiratory depression, there is emerging evidence that it behaves like a full agonist for analgesic effect [5]. Buprenorphine also has a very high affinity for the mu-receptor, along with a very slow dissociation from it. This high affinity and slow dissociation allow for buprenorphine to produce a blockade effect when other opioid agonists are administered [2].

In addition to its mu-receptor effects, buprenorphine is an antagonist at the kappa-opioid receptor. By blocking this receptor, buprenorphine may provide some degree of mood stabilization, as well as relief from dysphoria and discomfort beyond its effect at the mu-receptor [6]. The partial agonist activity and kappa-receptor antagonism may also be responsible for buprenorphine’s mitigation of opioid-induced hyperalgesia and underlie its effectiveness in controlling neuropathic pain [5, 7–9].

Buprenorphine is administered sublingually for the treatment of opioid dependence. Its sublingual bioavailability approaches 30 % of an intravenous dose [2, 10]. Oral administration of buprenorphine still results in some absorption; however, it undergoes extensive first-pass metabolism with little of the drug reaching systemic circulation when taken by this route. The time to peak plasma concentration after sublingual administration ranges from 40 minutes to 3.5 hours [11]. Buprenorphine has an elimination half-life of 4–6 hours, and all but one of its main metabolites is inactive. Norbuprenorphine, produced by *N*-dealkylation, is more potent than buprenorphine; higher levels of this metabolite have been associated with greater risk of respiratory depression [2]. Similar to methadone, the peak duration of analgesia for buprenorphine is 4–6 hours. The analgesic effect is much shorter than the duration of overall effect on craving and withdrawal. When a dependent patient has a need for acute pain management, buprenorphine dosing can be changed from once or twice daily to every 6–8 hours in order to maximize this effect [12].

Fig. 1 The ceiling effect of a mu-receptor ligand

Formulations

Buprenorphine is available in several different formulations for the treatment of opioid dependence [13]. It was first available in a 4:1 ratio of buprenorphine/naloxone (Suboxone[®]) in 2/0.5-mg and 8/2-mg dosage forms. Recently 4/1 and 12/3 mg strengths have also become available [14]. There is also Zubsolv[®], an oral-dissolving tablet, with 5.7/1.4 mg buprenorphine/naloxone strength [15] and Bunivail[®], a buccal formulation of buprenorphine/naloxone available in 4.2/0.7 buprenorphine/naloxone dose [16]. There are also generic forms of buprenorphine/naloxone available. Buprenorphine is available without naloxone; however, in the USA, this use is largely relegated to treatment of opioid dependence during pregnancy [2]. In most areas, Suboxone[®] tends to be the most prescribed form of buprenorphine, more due to prescriber familiarity and insurance coverage than any other reason. Buprenorphine is also available as a transdermal patch, called Butrans[®] and intravenously as Buprenex[®]. These formulations are used either for acute or chronic pain, and are not approved for use in treatment of opioid dependence [17].

Getting the Waiver

Passage of the Drug Abuse Treatment Act of 2000 permitted physicians to treat opioid addiction with “schedule III, IV, and V, narcotic medications that had been specifically approved by the Food and Drug Administration.” After a physician obtained their X-waiver certification, they could treat opioid dependence in settings other than the traditional opioid treatment program or methadone clinic [18].

Fig. 2 Dose/response curve for buprenorphine illustrating the ceiling effect with regard to changes in PCO₂ compared to morphine

In order to obtain an X-waiver, physicians must have an active DEA license and pass at least 8 hours of training in approved coursework related to buprenorphine use and treatment of opioid dependence. After completing the appropriate course work and passing an exam, the physician must submit a “notice of intent” to the Centers for Substance Abuse Treatment (CSAT) at Substance Abuse and Mental Health Services Administration (SAMHSA). The physician later receives an X-waiver license to be used instead of their standard DEA number when writing a prescription for buprenorphine to treat opioid dependence [18].

The initial Drug Abuse Treatment Act 2000 (DATA 2000) limited physicians to prescribing buprenorphine for a maximum of 30 individual patients at any given time. This limit applied not only to individual physicians, but also entire faculty groups. Large physician practices (such as medical groups, or the faculty practice affiliated with a medical school in an academic setting) were limited to 30 patients across the entire group under this restriction. In 2006, SAMHSA responded to requests to lift the overall practice restriction, and the ceiling limit was lifted to 100 patients for physicians that (1) qualified under the original DATA 2000 criteria and had already obtained an X-waiver, (2) had let at least 1 year elapse since their initial qualifications and X-waiver certification, and (3) certified that they had the capacity to refer patients for counseling and referral services when they required these services [18].

The most common buprenorphine prescribers are general practice (GP) and family medicine physicians followed by psychiatry, internal medicine, and anesthesiology. Emergency medicine physicians represent a smaller overall percentage of X-waivered physicians; however, emergency medicine represents an increasing area from which physicians transition to addiction medicine as their careers progress [19].

Induction, Stabilization, and Maintenance

To start buprenorphine, the patient needs to be in mild to moderate opioid withdrawal. Most patients are fully aware of the potential for precipitated withdrawal; the overall risk is quite low when patients are properly informed. Preceding an induction, the provider typically confirms recent opioid use through history and use of a urine drug screen (UDS). Some providers do this in order to document actual opioid dependence, as diversion of buprenorphine has increased along with prescription rates.

The Clinical Opioid Withdrawal Scale (COWS) (Table 1) can be used to document a baseline level of withdrawal and improvement in symptoms after buprenorphine administration. After completing the COWS, the physician can administer a low dose of buprenorphine (e.g., 2/0.5-mg test dose of any buprenorphine/naloxone formulation such as Suboxone®)

sublingually. There are several useful videos for patients that describe appropriate sublingual administration, as well as the storage and use of buprenorphine prescriptions. In fact, each of the specific buprenorphine/naloxone brands includes a patient video and educational packet for patients. There are also “test” strips without active ingredient that are available from the pharmaceutical companies for teaching and education.

After 1–2 hours have elapsed, the COWS is rescored. Improvement in symptoms without any sedation or dysphoria indicates a favorable response. The vast majority of patients will eventually be stable at a maximum dose of 16–24 mg/day, with higher doses unlikely to produce greater effects [21]. Many patients are stabilized at lower doses. Patients should be told that the induction will start in the morning and may take 4–5 hours to complete, assuming the medication is readily available from a nearby pharmacy.

Many patients, particularly in areas where buprenorphine providers are more heavily represented, may have had previous prescriptions or even a supply of diverted medication available to them for purchase “on the street.” There are many patients taking this illicit buprenorphine while they are waiting for an opening in a treatment program or an appointment with an X-waivered physician.

In patients transitioning from methadone to buprenorphine, the inductions can be more complex. Some protocols suggest that methadone be decreased to 40 mg/day for several days prior to buprenorphine induction. When transitioning from methadone, the first dose of buprenorphine should be a 2-mg or even 1-mg dose. Easing the patient onto buprenorphine with a stepwise induction limits the chance of precipitated withdrawal.

Home Versus Office Induction

While most physicians perform in-office buprenorphine inductions, some evidence suggests a subset of patients will do well with more flexibility and autonomy with home-induction of buprenorphine [22]. One study found less overall drug use in patients who underwent home-inductions [23].

Stabilization and Duration of Buprenorphine Therapy

The “stabilization” phase of buprenorphine treatment involves days to weeks after the induction when patients are getting used to the medication, and compliance is confirmed. Urine monitoring for illicit drug use (particularly opioid use) is important as is confirming that the patient is taking their buprenorphine. The stabilization phase may last from a few

Table 1 Clinical Opiate Withdrawal Scale (COWS) *Source: Wesson et al. [20]

Serial measurements of withdrawal score

Patient name: _____

Induction
date: _____

Times: _____

Score A.) Before medication, B.) 30 min after medication, and C.) 2 h after medication

Resting pulse rate: measured after patient is sitting or lying for 1 min

0 Pulse rate 80 or below

1 Pulse rate 81–100

2 Pulse rate 101–120

4 Pulse rate greater than 120

Sweating: over past 1/2 h not accounted for by room temperature or patient activity

0 No report of chills or flushing

1 Subjective report of chills or flushing

2 Flushed or observable moistness on face

3 Beads of sweat on brow or face

4 Sweat streaming off face

Restlessness: observation during assessment

0 Able to sit still

1 Reports difficulty sitting still but is able to do so

3 Frequent shifting or extraneous movements of legs/arms

5 Unable to sit still for more than a few seconds

Pupil size

0 Pupils pinned or normal size for room light

1 Pupils possibly larger than normal for room light

2 Pupils moderately dilated

5 Pupils so dilated that only the rim of the iris is visible

Bone or joint aches: if patient was having pain previously, only the additional component attributed to opiate withdrawal is scored

0 Not present

1 Mild diffuse discomfort

2 Patient reports severe diffuse aching of joints/muscles

4 Patient is rubbing joints or muscles and is unable to sit still because of discomfort

Runny nose or tearing: not accounted for by cold symptoms or allergies

0 Not present

1 Nasal stuffiness or unusually moist eyes

2 Nose running or tearing

4 Nose constantly running or tears streaming down cheeks

GI upset: over last 1/2 h

0 No GI symptoms

1 Stomach cramps

2 Nausea or loose stool

3 Vomiting or diarrhea

5 Multiple episodes of diarrhea or vomiting

Tremor: observation of outstretched hands

0 No tremor

1 Tremor can be felt but not observed

2 Slight tremor observable

4 Gross tremor or muscle twitching

Yawning: observation during assessment

0 No yawning

Table 1 (continued)

Serial measurements of withdrawal score

Patient name: _____

Induction
date: _____

Times: _____

Score A.) Before medication, B.) 30 min after medication, and C.) 2 h after medication

1 Yawning once or twice during assessment

2 Yawning three or more times during assessment

4 Yawning several times/minute

Anxiety or irritability

0 None

1 Patient reports increasing irritability or anxiousness

2 Patient obviously irritable anxious

4 Patient so irritable or anxious that participation in the assessment is difficult

Gooseflesh skin

0 Skin is smooth

3 Piloerection of skin can be felt or hairs standing up on arms

5 Prominent piloerection

Total scores A.) _____, B.) _____, C.) _____

Score: 5–12=mild withdrawal; 13–24=moderate withdrawal; 25–36=moderately severe withdrawal; >36=severe withdrawal

weeks to months. Stable patients are compliant with their dosing, not using illicit opioids or other drugs, or are at least attempting to address relapses and other issues in treatment. While patients are not required to be actively engaged in counseling for chemical dependency, they should at least undergo an evaluation or assessment by a specialist in addiction counseling. Many providers mandate that this occurs with the treatment contract, specifying the need for ongoing compliance with a drug treatment program in order to receive buprenorphine prescriptions. The most successful patients also incorporate lifestyle modifications including exercise, and have family support or self-help program attendance, such as Alcoholics Anonymous (AA) or Narcotics Anonymous (NA). A typical outpatient treatment program may last a few months and involve stages of treatment (phase 1, 2, and aftercare) with decreasing levels of intensity. The group and individual sessions provide education about addiction as a disease, and address lifestyle modifications and other strategies that will help an individual cope with craving, relapse, and a life without chemicals. Treatment programs often include assistance finding primary care physicians or contacts with psychiatric care. Stabilization of physical and mental health is another important aspect of recovery from chemical dependency. X-waivered providers need not provide all of these services; however, they should be familiar with the resources available in their community. Some providers have contracts that mandate ongoing counseling or other care. The optimal duration of opioid agonist therapy is unknown. Many studies have shown

abysmal effectiveness in terms of long-term sobriety when buprenorphine, or methadone for that matter, is used simply for detoxification purposes [24].

Effectiveness of Buprenorphine for Treatment of Opioid Dependence

Transmission of HIV in intravenous drug users remains a significant concern. Between 2004 and 2007, 13 % (19,687) of over 152,000 individuals newly diagnosed with HIV infections were from intravenous drug use [25]. A recent outbreak of HIV infections in rural Indiana was attributed primarily to injection of prescription opioids, heroin, and other drugs as well as associated behaviors [26]. Research has shown that buprenorphine is one of the tools which can be used to effectively reduce spread of HIV in these patients. Comparison of drug-related and sex-related risk behaviors in 166 buprenorphine-treated individuals at baseline, 4 weeks, and 12 weeks showed that intravenous drug use declined with initiation of buprenorphine. There was 37 % at baseline, 12 % at 12 weeks, and 7 % at 24 weeks [27]. In the treatment of opioid dependence, the effectiveness of treatment is measured in not only sobriety and compliance, but also in return to functionality, decreases in rates of infectious complications associated with intravenous drug use (e.g., HIV or HCV transmission), and in drops in criminality and crime. Whether individuals are able to avoid legal complications, complete

treatment, stay married and in healthy relationships, or gain back employment are all considered in the effectiveness of medication-assisted treatment.

The Partial Agonist and Precipitated Withdrawal

Opioid users who take buprenorphine before the onset of withdrawal symptoms run the risk of precipitating acute withdrawal. The risk of precipitated withdrawal increases with the degree of opioid dependence, and when little time has elapsed between the buprenorphine induction and time of last full agonist use. More severe reactions happen when more heavily opioid-dependent individuals use buprenorphine shortly after, or even on top of, full agonists (e.g., heroin or methadone) mistaking the expected effect as additive [28]. Because the relative affinity of buprenorphine for the mu-receptor is much higher than all of the full receptor agonists, the buprenorphine displaces the other opioid from the receptor and the drop in activation from “full” effect to the “partial” effect induces a withdrawal syndrome [28]. Individuals that use buprenorphine intravenously run the risk of precipitating the most severe abstinence syndromes, especially if they use it in tandem or right after other opioid agonists [29]. Despite the risk for precipitated withdrawal, severe reactions requiring intensive care unit admission are uncommon. When precipitated withdrawal occurs, very high doses of full opioid agonists can be used to overcome the symptoms (e.g., fentanyl). Adjunctive medications aimed at symptomatic control can also be administered. Clonidine (e.g., 0.1–0.2 mg PO q 4 h) along with benzodiazepines (diazepam 5–10 mg PO QID), and antihistamines (hydroxyzine 50 mg 1–2 mg PO QID) have been used for symptomatic control. In severe withdrawal, the dosing should be titrated to clinical endpoint in order to effectively mitigate the patient’s symptoms.

Buprenorphine and Pediatric Ingestions

Buprenorphine is one of the most frequently identified medications in pediatric patients hospitalized after accidental exposure to prescription medications [30]. Children are typically opioid naïve and vulnerable to an opioid’s sedative and respiratory depressant effects. A single dose of buprenorphine, even at the smallest dosage increment, has potency approaching 50-fold higher than morphine. Even very brief exploratory ingestions in infants and toddlers can cause significant intoxication. Despite exposure in a very vulnerable population, however, the toxic effects are less severe compared to other opioids, such as methadone. Pediatric fatalities are uncommon with buprenorphine but have been reported [31, 32]. Any pediatric exposure to buprenorphine no matter how small or brief needs to be monitored for 12–24 hours in a hospital setting. Naloxone

has been used effectively to reverse buprenorphine-induced CNS and respiratory depression in these patients.

Misuse of Buprenorphine

All opioid agonists have abuse liability. Buprenorphine, however, is less “likeable” than other opioids due to its partial agonist effect. Despite this, some populations have much higher rates of abuse of buprenorphine than the general population.

Evidence of buprenorphine abuse and diversion has been increasing since it first became available for the treatment of opioid dependence. While some providers ask for additional relaxation of requirements in prescribing buprenorphine, others cite a growing problem related to the medication and caution increasing availability. The truth is most likely a balance in between the two positions. It is thought that much of the motivation for illicit buprenorphine use is as an attempt to self-treat withdrawal [33]. It is uncommon that buprenorphine is a primary drug of abuse, except in special populations such as incarcerated individuals and in clusters of teens/adolescents with first exposure to buprenorphine products [34].

A Better Opioid

Buprenorphine has many favorable pharmacologic and clinical features compared to other opioids. It is associated with less tolerance and is associated with less physical dependence than other opioids; it has a much more mild withdrawal syndrome if discontinued [35]. There is less constipation associated with buprenorphine, and cognitive impairment is less frequent with buprenorphine than with many other opioids. Buprenorphine is not immunosuppressive and it has less effect on the hypothalamic-pituitary-adrenal axis; it does not inhibit gonadotropin-releasing hormone to the same extent as other opioids, and sexual side effects are less than other opioids [35].

Conclusions

Buprenorphine is an effective treatment for opioid dependence. In order to prescribe it for this indication, physicians must complete special training and obtain their X-waiver certification. Treatment of patients with buprenorphine can be done in a clinic or an office-based setting with much more flexibility than the methadone maintenance programs offer. There are fewer side effects associated with buprenorphine compared to full agonists, and buprenorphine is less abused than these medications as well; however, abuse and diversion of buprenorphine do occur.

Despite the X-waiver criteria, buprenorphine is another tool in the medical toxicologist's armamentarium. It can be a useful component of supportive care, and effective in the prevention of disease and death. Medical toxicologists already possess familiarity with the pharmacology of buprenorphine; general familiarity with the clinical use of buprenorphine as well as the policy and law surrounding the treatment of opioid dependence creates opportunities for the medical toxicologist to provide value and improve outcomes in patient care. Buprenorphine treatment of opioid dependence is a natural extension of medical toxicology practice.

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