CME/MOC

Buprenorphine Pharmacology Review: Update on Transmucosal and Long-acting Formulations

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Buprenorphine is an effective treatment for opioid use disorder. As a high-affinity, partial agonist for the mu-opioid receptor, buprenorphine suppresses opioid withdrawal and craving, reduces illicit opioid use, and blocks exogenous opioid effects including respiratory depression. Other pharmacologic benefits of buprenorphine are its superior safety profile compared with full opioid agonists and its long half-life that allows daily or less-than-daily dosing. New and innovative buprenorphine formulations, with pharmacokinetic profiles that differ from the original tablet formulation, continue to be developed. These include higher bioavailability transmucosal tablets and films and also 6-month implantable and monthly injectable products. This growing array of available formulations allows more choices for patients and increased opportunity for clinicians to individualize treatment; thus, it is important for buprenorphine prescribers to understand these differences.

Key Words: buprenorphine depot injections, buprenorphine implants, clinical pharmacology, opioid use disorder, pharmaceutical technology, pharmacokinetics, sublingual buprenorphine, sustained-release

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Buprenorphine, a semisynthetic opioid, was developed in the 1970s by Reckitt & Colman, as an analgesic (Cowan et al., 1977), and subsequently investigated by clinical researchers at the Addiction Research Center in Lexington, Kentucky. Their work resulted in a landmark paper (Jasinski et al., 1978), which correctly predicted that buprenorphine had potential for the treatment of opioid use disorder (OUD) due to its unique pharmacology. Despite this, buprenorphine was not approved in the United States for OUD until 2002, although a parenteral formulation was approved for analgesic use in 1989. Before 2000, the US Food and Drug Administration (FDA) and Drug Enforcement Administration regulations limited delivery of treatment with opioid agonist therapy (ie, methadone) to highly regulated federally licensed clinics, and the pharmaceutical company was hesitant to bring buprenorphine to the US market under those regulations (it was already marketed abroad for OUD at this time [Auriacombe et al., 1994]). In 2000, the Drug Addiction Treatment Act (DATA 2000) was passed, allowing qualified physicians to obtain a federal waiver to prescribe schedule III to V opioids US FDA-approved for OUD treatment in settings outside of opioid treatment programs (ie, methadone clinics), introducing a new US treatment paradigm. Sublingual (SL) buprenorphine was placed in schedule III and approved for opioid dependence treatment (the contemporary Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition nomenclature). Buprenorphine products have undergone continual innovation, leading to development and marketing of SL films, other transmucosal products, 6-month implants, and a monthly subcutaneous (SC) depot injection formulation. Another injection depot formulation is in late-phase development.

Utilization of US FDA-approved medication for OUD treatment in general, and buprenorphine specifically, is associated with positive outcomes for both patients and society. In a recent analysis of persons prescribed buprenorphine in France, patients who discontinued treatment were approximately 29 times more likely to die than those who remained on buprenorphine (Dupouy et al., 2017). Likewise, heroin-related overdose deaths in Baltimore from 1995 to 2009 decreased significantly as access to methadone and buprenorphine treatment expanded (Schwartz et al., 2013). Moreover, utilization of buprenorphine treatment is associated with reductions in illicit opioid-related crime and decreased transmission of communicable diseases, such as HIV and hepatitis C virus (Sullivan and Fiellin, 2005; Volkow et al., 2014). Buprenorphine is efficacious and effective for OUD because it provides relief of craving and withdrawal, produces opioid blockade, has an excellent safety profile, has reduced abuse liability compared to full opioid agonists, and is suitable for daily or less-than-daily dosing. Each of these treatment outcomes and beneficial characteristics can be directly explained by its pharmacology. As innovative buprenorphine formulations are marketed, it is important for providers to have a complete understanding of buprenorphine formulations and

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pharmacology to make well-informed prescribing and therapeutic decisions.

The aims of this narrative review are to synthesize available published evidence (peer-reviewed journal articles, guidance documents, drug monographs, etc) to:

1. review buprenorphine pharmacology (of both transmucosal and long-acting formulations),
2. explain how aspects of buprenorphine pharmacology manifest as clinical effects, and
3. provide practical information about each buprenorphine formulation, with a focus on how these formulations differ.

BUPRENORPHINE PHARMACOLOGY

This section will describe the physiological basis for the clinical effects of buprenorphine. The properties of buprenorphine contributing to its efficacy in OUD treatment include: mu-opioid receptor-related factors (eg, high-affinity, low-efficacy, and slow dissociation kinetics) and non-mu-opioid receptor-related factors (eg, long terminal half-life, lipophilicity). While buprenorphine also binds the delta and opioid-receptor-like 1 receptors and is a high-affinity kappa opioid receptor antagonist, the contribution of these interactions in OUD treatment is unknown and likely minimal; however, buprenorphine is under investigation for depression treatment (Karp et al., 2014) due to kappa opioid receptor involvement in stress systems implicated in depression pathophysiology (Crowley and Kash, 2015). For each pharmacologic property discussed below, the corresponding clinical effects are summarized and differences (or lack thereof) in pharmacology between transmucosal and long-acting buprenorphine formulations are noted.

Buprenorphine Interaction With Mu-opioid Receptors (Pharmacodynamics)

Formulation differences? No. Buprenorphine exhibits the same interaction with the mu opioid receptor regardless of the route by which it is administered.

Low-efficacy Agonist

As an agonist (a compound that can elicit cellular response) at the mu-opioid receptor, buprenorphine produces typical opioid effects (eg, euphoria, analgesia, decreased gastrointestinal motility, miosis, respiratory depression, etc). This results in both beneficial (eg, suppression of withdrawal and craving) and adverse (eg, constipation, sedation) clinical effects. Buprenorphine is a partial (or low efficacy) agonist, meaning that the maximal effect produced by buprenorphine will be less than that produced by a full (or high-efficacy) mu-opioid receptor agonist. This is illustrated in Fig. 1: buprenorphine does not reach the same peak effect as measured on the y-axis as full agonists (fentanyl and morphine). Clinically, this partial agonism translates to a ceiling effect for mu-opioid receptor-mediated effects of buprenorphine, such as respiratory depression and euphoria (Walsh et al., 1994). In preclinical models, buprenorphine exhibits a bell-shaped dose-response curve for both respiratory depression and analgesia (ie, at high enough doses, respiratory depression, and analgesia decrease), but the descending limb of this curve has not been reproduced in human studies (for review, see Cowan, 2003). This could be due, in part, to the fact that much higher relative doses can be administered in animal models than in humans. The ceiling effect observed clinically is the basis for its improved safety profile and reduced abuse potential compared with full mu-opioid receptor agonists. The exact dose at which this ceiling is observed may vary among persons (see ' Buprenorphine pharmacokinetics' section below), but clinical laboratory studies have shown that intravenous doses of up to 0.6 mg/70 kg did not significantly decrease respiration more than 0.2 mg/70 kg (Dahan et al., 2005), and respiratory depression was no greater after 32 mg than 16 mg SL among persons without physical dependence on opioids (Walsh et al., 1994). The best evidence for buprenorphine safety perhaps lies in the relative dearth of buprenorphine overdose deaths compared with those with full opioid agonists. While the abuse potential of buprenorphine is less than that of high-efficacy agonists (Jasinski et al., 1978), it still has intrinsic reinforcing effects as a partial agonist and can be misused and diverted (for review, see Lofwall and Walsh, 2014).

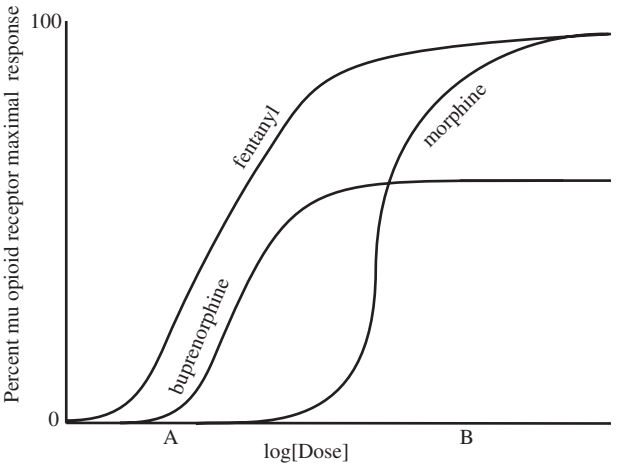

FIGURE 1. Dose-response curve schematic of 3 opioid agonists. At a low dose (dose A), fentanyl and buprenorphine produce significantly greater responses than morphine (ie, fentanyl and buprenorphine are more potent than morphine). While fentanyl response is dose-related until reaching 100% maximal response, buprenorphine effects reach a ceiling, at which point further increases in dose do not increase the magnitude of response. Because buprenorphine is a partial agonist, it cannot not produce a 100% response like a full agonist (ie, fentanyl) can. At higher doses (dose B), morphine (a full agonist with low potency) produces greater response than buprenorphine.

High Affinity

Buprenorphine affinity (a measure of the attractive force between a compound and a receptor) for the mu-opioid receptor is approximately 1.7 times that of hydromorphone,

5.4 times that of morphine, 6.2 times that of fentanyl, and 120 times that of oxycodone (Volpe et al., 2011). This high affinity means that buprenorphine is difficult (but not impossible) to displace from the mu-opioid receptor, which explains its ability to block subjective and physiological effects of other opioids. As receptor theory suggests and clinical observation confirms, blockade of the mu-opioid receptor by buprenorphine is surmountable with higher doses (Bickel et al., 1988; Strain et al., 2002) or with high-affinity opioids, such as fentanyl. Its high affinity is also the primary reason that buprenorphine can precipitate withdrawal when given to individuals physically dependent on opioids. Precipitated withdrawal can be avoided, particularly among persons dependent on short-acting opioids, by waiting to administer buprenorphine until signs of opioid withdrawal emerge (a time of low receptor occupancy)—this is the common clinical strategy for buprenorphine induction.

High Potency

Buprenorphine is a high-potency medication. Potency is simply a measure of drug activity expressed as the absolute dose required to produce a given effect. For example, if drug A produces effect X at 10 mg and drug B produces X at 100 mg, drug A is 10 times more potent than drug B. Potency depends on both efficacy and affinity. While comparatively low doses of buprenorphine may elicit some degree of respiratory depression compared with morphine, the potency of buprenorphine does not significantly increase with doses within the clinical range (Fig. 1). This concept of potency is important for understanding why buprenorphine should not be converted to morphine milligram equivalents (MME) either for purposes of opioid analgesic rotations or for assessing overdose risk based on daily opioid dose. While the Centers for Disease Control and Prevention (CDC) Guidelines for Prescribing Opioids for Chronic Pain (Dowell et al., 2016) caution against daily opioid doses >90 MME due to overdose risk, buprenorphine dose escalation does not pose increasing overdose risk like the full opioid agonists due to its low efficacy. This explains why CDC guidelines do not include buprenorphine in the MME conversion table and why the American Society of Addiction Medicine does not support legislation limiting buprenorphine prescribing based upon MMEs (ASAM, 2017).

Slow Dissociation From Mu-opioid Receptor

Buprenorphine has slow dissociation kinetics (~166 min) (Boas and Villiger, 1985), contributing to its long duration of action and allowing daily or less-than-daily dosing. Studies testing the efficacy of administering higher-than-normal daily buprenorphine doses on less-than-daily dosing schedules suggest that patients can be maintained on alternate-day or thrice-weekly dosing with minimal withdrawal and similar rates of illicit opioid use compared with daily dosing (Amass et al., 1994; Eissenberg et al., 1997; Bickel et al., 1999). Duration of opioid blockade closely mirrors that of withdrawal suppression. Subjects maintained on SL buprenorphine (8, 12, 16, or 32 mg) for 2 weeks, and then administered placebo under blinded conditions displayed attenuated subjective responses (eg, drug liking) to hydromorphone (6, 12, and 18 mg IM) up to 98 hours after the last active buprenorphine dose. Withdrawal increased, but was mild, with time since last dose, but severity of withdrawal was not related to buprenorphine dose (Correia et al., 2006).

Buprenorphine Pharmacokinetics

Formulation differences? Yes. Buprenorphine PKs are altered when taken by different routes of administration.

Bioavailability

Interperson variability in transmucosal buprenorphine pharmacokinetics (PKs) is high, with estimates of bioavailability (the amount of parent drug to reach systemic circulation) commonly ranging by 3-fold or more after both acute and chronic administration (Kuhlman et al., 1996; Strain et al., 2004; Chawarski et al., 2005; Compton et al., 2007). These differences may be partly due to individual variability in absorption. Buprenorphine bioavailability is high after IV or SC administration, considerably lower by the sublingual and buccal (transmucosal products) routes and very low orally.

Half-life

The half-life ($t^1/_2$) of buprenorphine is variable after transmucosal administration, ranging from 24 to 42 hours reported in buprenorphine product package inserts. This long $t^1/_2$ allows daily or less-than daily transmucosal dosing schedules, but the variability underscores the need for individualized dosing based on clinical response. The $t^1/_2$ is much longer after transmucosal compared with IV (3 hours) administration (Kuhlman et al., 1996), possibly due to sequestration of buprenorphine in the oral mucosa and lipid storage sites when administered transmucosally (Welsh and Valadez-Meltzer, 2005). The reported $t^1/_2$ of SC and implantable buprenorphine formulations also exceeds transmucosal, but this is due to continuous release and absorption of buprenorphine from the indwelling implant and/or depot matrix, not because of a fundamental change in metabolism.

Metabolism

When administered via routes that undergo first-pass metabolism (ie, sublingual/buccal), buprenorphine is metabolized to norbuprenorphine via CYP450 3A4/5-mediated N-dealkylation, and both buprenorphine and norbuprenorphine undergo glucuronidation to buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide—metabolites that are generally considered inactive (Kuhlman et al., 1998; Elkader and Sproule, 2005). While norbuprenorphine is a potent mu-opioid receptor agonist (Huang et al., 2001), brain concentrations of norbuprenorphine are very low (Brown et al., 2012), suggesting that norbuprenorphine does not contribute to the clinical effects of buprenorphine. Because this metabolite is found in high concentrations in urine, urine toxicology for patients receiving buprenorphine frequently includes testing norbuprenorphine to ensure patients are not simply adding buprenorphine directly into the urine sample. Routes

of administration that bypass first-pass metabolism (eg, IV, IN, SC) result in significantly lower norbuprenorphine formation (Kuhlman et al., 1996; Harris et al., 2000). If using urine norbuprenorphine concentrations as a marker of medication adherence, it must be understood that patients receiving SC or subdermal buprenorphine may have low urine concentrations of norbuprenorphine.

Drug-drug Interactions

Concomitant use of CYP450 inhibitors and inducers can affect the metabolism of buprenorphine, leading to possible over or undermedication (especially relevant for patients with moderate-to-severe hepatic impairment). This is one reason that monitoring of liver function enzymes before initiation and during treatment is recommended in all buprenorphine product package inserts. Notably, the NIDA Clinical Trials Network START (Starting Treatment With Agonist Replacement Therapies) study enrolled patients with OUD who had AST and ALT values less than 5 times the upper limits of normal and alkaline phosphatase levels less than 3 times the upper limits of normal and randomized them to either SL buprenorphine/naloxone or methadone for 24 weeks (Saxon et al., 2013). Liver function tests were evaluated over time. There was no evidence of liver damage induced by SL buprenorphine doses up to 32 mg SL daily. Extreme increases in liver function tests were uncommon and associated with seroconversion to hepatitis B and C; and illicit drug use during the first 2 months of treatment. Thus, this study suggests that monitoring when prescribing transmucosal buprenorphine among patients with normal to elevated (but not more than 5× AST/ALT or 3× alkaline phosphatase) may be clinically relevant as a screening measure to suggest newly contracted hepatitis C and/or B or ongoing illicit drug use (if urine tests and clinical manifestation of hepatitis are undetected). Because the SC route bypasses first-pass metabolism, buprenorphine interactions with CYP450 inducers and/or inhibitors should be limited.

The concomitant use of benzodiazepines with buprenorphine does increase the risk of serious adverse events and death, but the mechanism of this interaction remains unclear. Benzodiazepines alone do not cause respiratory depression, but there is synergistic effect that occurs when they are combined with opioids. It has been speculated that both benzodiazepines (via GABA) and opioids (via mu-opioid receptor agonism) depress medullary controls for respiration (White and Irvine, 1999); however, in a Drug Safety Communication (FDA, 2017c), the US FDA has advised that *careful medication management* can reduce these risks and that buprenorphine should not be uniformly withheld from OUD patients taking benzodiazepines. Harms caused by withholding effective medication treatment with buprenorphine may outweigh the risks of concomitant prescribed and supervised use of these two medications.

Naloxone in Buprenorphine Combination Products

The incorporation of naloxone to transmucosal buprenorphine products was designed to decrease misuse of buprenorphine products via IN and IV routes of administration. Naloxone is a high-affinity mu-opioid receptor antagonist with a short half-life and rapid dissociation (~6.5 minutes) from the mu-opioid receptor. When buprenorphine/naloxone is ingested via prescribed routes, naloxone is essentially inert due to poor oral and sublingual bioavailability followed by first-pass metabolism and elimination; however, when insufflated or injected, naloxone is bioavailable and can precipitate withdrawal. Sublingual bioavailability of naloxone has been estimated to be about 3% in the first US FDA-approved buprenorphine/naloxone formulation (FDA, 2002), whereas naloxone intranasal bioavailability (ie, of the crushed and snorted SL tablet) is estimated to be 30% (Middleton et al., 2011). Laboratory studies reliably report reduced abuse liability of buprenorphine/naloxone compared with buprenorphine alone (Comer and Collins, 2002; Comer et al., 2010; Middleton et al., 2011; Walsh et al., 2016). A review of available epidemiological evidence also reports that buprenorphine/naloxone is injected less frequently than the buprenorphine monoproducts (Lofwall and Walsh, 2014).

OVERVIEW OF SUBLINGUAL AND OTHER TRANSMUCOSAL BUPRENORPHINE PRODUCTS

The safety of transmucosal buprenorphine formulations has been well established and is similar among products. Side effects listed in transmucosal buprenorphine package inserts include common mu-opioid receptor agonist effects (eg, constipation, abdominal pain, nausea, sweating, headache, drowsiness, insomnia, dizziness, respiratory depression). While transmucosal products vary modestly in bioavailability, C_{max}, area under the curve (AUC), dissolve time, and flavoring, they are otherwise largely comparable. Year of US FDA approval, available doses, cost per month, and dissolution time are listed in Table 1.

Before development and US FDA approval of the SL buprenorphine tablet in 2002, research was conducted using a SL liquid consisting of buprenorphine dissolved in an ethanol/water solution (Kuhlman et al., 1996) and administered directly under the tongue. It was never commercially available. This solution had greater bioavailability than the subsequently marketed SL tablets. The first US FDA-approved buprenorphine SL tablets have a relative bioavailability of 0.70 to the ethanol/water solution (FDA, 2002) that was used in early buprenorphine studies (Walsh et al., 1994).

After the initial buprenorphine tablet products were approved (buprenorphine [Subutex, Reckitt Benckiser Healthcare, Slough, UK] and buprenorphine/naloxone [Suboxone, Indivior UK Limited, Slough, UK]), others entered the market through the US FDA 502b pathway. This pathway allows new medications with the same active ingredient as an approved product to use safety and efficacy data from that product as long as the new product is bioequivalent (ie, no significant difference between the drugs in acute dosing pharmacokinetic parameters, such as $AUC_{0\text{-inf}}$ and C_{max} using a 90% confidence interval (FDA, 2013). Consequently, chronic dosing pharmacokinetics are unavailable for most of the transmucosal buprenorphine products marketed subsequent to the original.

As there are small differences in transmucosal products' PK parameters, it is possible that patients switching formulations (eg, when insurance coverage changes) may

TABLE 1. Approved Buprenorphine Products

Formulations	US FDA Approval Year	Available Doses (mg)	Total Cost Per Month*	Dissolution Time (min)
Buprenorphine/Naloxone tablet	2002 for brand name products†	2/0.5 and 2	$154	7–12.4
	2013 and after for generics	8/2 and 8	$164	
Buprenorphine/Naloxone film	2010	2/0.5	$131	5–6.6
		4/1	$222	
		8/2	$222	
		12/3	$432	
Buprenorphine/Naloxone tablet (Zubsolv)	2013	0.7/0.18	$131	5
		1.4/0.36	$131	
		2.9/0.71	$254	
		5.7/1.4	$254	
		8.6/2.1	$377	
		11.4/2.9	$499	
Buprenorphine/Naloxone film (Bunavail)	2014	2.1/0.3	$252	30
		4.2/0.7	$252	
		6.3/1.0	$495	
6-month Buprenorphine implant (Probuphine)	2016	320	$825	N/A
Monthly Buprenorphine depot (Sublocade)	2017	100	$1580	N/A
		300	$1580	

N/A, not applicable.

*Total cost for transmucosal products is assuming once daily use for 30 days. Total cost for the 6-month product is $4950. Prices taken from drugs.com on February 1, 2018.

†The brand name mono-product tablet was no longer marketed after 2011, but the generic mono-product remains available and is still used for patients with naloxone sensitivities and for pregnant women. The brand name combination product is also no longer available.

note differences in response and dose adjustments could be needed. For example, if a patient maintained comfortably on 4.2 mg of the higher bioavailability film is switched to 8 mg of the generic tablet and complains of mild withdrawal, the physician can consult Table 2 and see that the new medication may produce lower buprenorphine plasma concentrations than the previous one; thus, the report of withdrawal is not unexpected. Of course, individual differences in absorption and metabolism mean that PK values can only be used as guidelines and ultimately dosing regimens should be titrated to individual patient needs. The next section discusses each transmucosal formulation and how it compares with the original buprenorphine/naloxone tablet formulation approved in 2002.

Buprenorphine/Naloxone Film (Suboxone, Indivior Inc., Richmond, VA) delivers higher peak and plasma buprenorphine concentrations compared with the 2/0.5 and 8/2 tablet product (Table 2).

Buprenorphine/Naloxone sublingual tablets (Zubsolv, Orexo US, Inc., Morristown, NJ) have higher bioavailability than the original buprenorphine/naloxone tablets. A 5.4/1.7 mg and 1.4/0.36 dose produce exposure bioequivalent to 8/2 mg and 2/0.5 buprenorphine/naloxone tablet, respectively (per package insert). Notably, the 0.7/0.18 mg buprenorphine/naloxone dose is the lowest dose available.

Buprenorphine/Naloxone buccal film (Bunavail, Biodelivery Sciences International, Inc., Raleigh, NC) has higher bioavailability than all other transmucosal products. According to the US FDA, a 4.2/0.69 mg dose produces buprenorphine concentrations approximately equivalent (3.4 ng/ml C_{max}) to 8 mg buprenorphine/naloxone tablet (3.0 ng/mL C_{max}; Table 2).

OVERVIEW OF IMPLANTABLE AND INJECTABLE BUPRENORPHINE FORMULATIONS

Novel buprenorphine products with unique delivery systems are being developed at a rapid pace. Two long-acting products were approved in the past 2 years—a 6-month subdermal implant and a monthly injectable sustained-release formulation. Another weekly and monthly injectable is in late-stage development (see Table 3 for indications, common adverse events, excipient toxicology).

Buprenorphine Subdermal Implant (Probuphine, Titan Pharmaceuticals, San Francisco, CA)

The product consists of 4 matchstick-sized rods each containing 80 mg (total 320 mg). A short office-based procedure for insertion and removal is needed, and training for insertion and removal is required by the pharmaceutical company. A provider can be certified to prescribe, insert, or both prescribe and insert the implant; both require a waiver. The steady-state plasma buprenorphine concentration is slightly less than that produced by 8 mg daily SL buprenorphine (Ling et al., 2010); thus, it is recommended for patients already stable on $\leq$8 mg buprenorphine. While clinical judgment can be used to extend treatment duration, the package insert recommends only 2 successive implants (ie, 1 year of treatment) before transitioning back to transmucosal buprenorphine, primarily because there is inadequate experience with repeated insertions and removals to date.

TABLE 2. Pharmacokinetics of Buprenorphine Formulations

Formulations	Doses (mg)	Single Dose		Steady State		
		C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (h*ng/mL)	C_{min} (ng/mL)	C_{avg} (ng/mL)	C_{max} (ng/mL)
Buprenorphine/Naloxone tablet						
Brand name*	2/0.5 and 2	–	–	–	–	–
	8/2 and 8	3.00	20.22†	0.65	1.19	4.74
	12	–	–	0.81	1.71	5.35
	24	–	–	1.54	2.91	8.27
Generic group 1‡	2/0.5	0.95	8.65	–	–	–
	8/2	3.37	30.45	–	–	–
Generic group 2§	2/0.5	0.78	7.65	–	–	–
	8/2	2.58	25.31	–	–	–
Generic group 3‖	2/0.5	1.25	10.93	–	–	–
	8/2	2.88	28.39	–	–	–
	16/4	4.70	47.09	–	–	–
Buprenorphine/Naloxone film	2/0.5	1.07	8.43	–	–	–
	4/1	1.66	14.62	–	–	–
	8/2	3.55	30.66	–	–	–
	12/3	4.80	41.74	–	–	–
Buprenorphine/Naloxone tablet (Zubsolv)	0.7/0.18	–	–	–	–	–
	1.4/0.36	0.81	7.01	–	–	–
	2.9/0.71	–	–	–	–	–
	5.7/1.4	2.66	23.51	–	–	–
	8.6/2.12	3.68	32.27	–	–	–
	11.4/2.9	4.58	41.51	–	–	–
Buprenorphine/Naloxone film (Bunavail)	2.1/0.3	–	–	–	–	–
	4.2/0.7	3.41	27.17	–	–	–
	6.3/1.04	4.90	38.47	–	–	–
Buprenorphine implant (Probuphine)	320	~2.6¶	19.6**	~0.6¶	~0.82	~2.6¶
Monthly Buprenorphine depot (Sublocade)	100	1.54	1557.40	2.48	3.21	4.88
	300	5.37	–	5.01	6.54	10.12
Buprenorphine depot (CAM2038)						
	16	3.08	335	0.84	2.09	4.30
Weekly	24	3.64	–	–	–	–
	32	5.27	638	2.63	4.17	6.87
Monthly	64	3.81	1360	–	–	–
	96	5.47	1830	–	–	–
	128	6.59	2550	2.09	3.89	11.1
	160			2.66	5.27	15.4

Unless otherwise noted, data are taken from product package inserts and Center on Drug Evaluation Research Clinical Biopharmaceutical Review Packages.

*The brand name product is no longer marketed. The generic products are bioequivalent; thus, pharmacokinetic parameters are similar for all buprenorphine/naloxone tablets.

†$AUC_{0\text{-}48}$, $not_{0\text{-}inf}$.

‡Manufacturers using these pharmacokinetic data in their package inserts are Amneal Pharmaceuticals, LLC, and Ethypharm SA.

§Manufacturers using these pharmacokinetic data in their package inserts are Kremers Urban Pharmaceuticals, and SpecGx LLC.

‖Manufacturers using these pharmacokinetic data in their package inserts are: Actavis Pharma Inc.; Sun Pharmaceutical Industries Limited; Teva Pharmaceuticals USA, Inc.; and West-Ward Pharmaceuticals Corp.

¶Estimated based on graph from Beebe et al. (2009) poster: Safety, Efficacy, and Pharmacokinetics of Probuphine, a 6-Month Implantable Sustained-Release Formulation of Buprenorphine, for the Treatment of Opioid Addiction.

**$AUC_{0\text{-}24}$, $not_{0\text{-}inf}$.

Efficacy

An initial study in new-to-treatment patients with OUD demonstrated that the implant was superior to placebo at suppressing withdrawal and craving and reducing illicit opioid use (Ling et al., 2010). A second small study with new-to-treatment patients compared the active implant versus placebo implant versus open-label SL buprenorphine and similarly found superiority over placebo and no differences between the active implant and SL buprenorphine (Rosenthal et al., 2013). A larger 6-month, double-blind, double-dummy, noninferiority study enrolled patients who were already in treatment and stable on transmucosal buprenorphine at $\leq$8 mg and randomized to either the active implant (plus placebo SL tablets) or 8 mg SL buprenorphine/naloxone (and placebo implants). The implant was non-inferior to SL buprenorphine/naloxone at suppressing withdrawal and craving and reducing illicit opioid use, and more implant patients maintained illicit opioid abstinence for the duration of the study (81%) compared with those on SL buprenorphine/naloxone (67%) (Rosenthal et al., 2016).

Because the implant reduces patient burden by limiting reliance on daily medication, treatment adherence may be higher with the implant than with SL dosing regimens. Retention rates for the 6-month studies (which required monthly visits) were 65.7% and 96.4% (Rosenthal et al., 2013; Rosenthal et al., 2016), with the observed difference likely attributable to the earlier study enrolling unstable patients.

TABLE 3. Long-acting Buprenorphine Formulations

	Indication (s)	Adverse Events Occurring in >5% of Patients	Excipients and Toxicology	Delivery System	Storage and Administration
6-mo Buprenorphine implant (Probuphine)	Maintenance for patients who have achieved prolonged stability on ≤8 mg TM buprenorphine	Headache, depression, constipation, nausea, vomiting, back pain, toothache, oropharyngeal pain and injection site reactions (pain, pruritus, & erythema)	N/A	Ethylene vinyl acetate (EVA) implants 11 US FDA-approved products*	Subdermal insertion of 4 flexible matchstick-sized rods in upper arm under local anesthetic by trained provider.
Monthly Buprenorphine depot (Sublocade)	Maintenance treatment (to be used after initiation on TM buprenorphine)	Constipation, nausea, vomiting, fatigue, elevated liver enzymes, headache, and injection site reactions (pain, pruritus, and erythema)	NMP at doses equivalent to those in the depot, reproductive harms† were reported in animal studies.	ATIRGEL (Tolmar Inc.) 7 US FDA-approved products‡	Prefilled syringe (refrigeration required). SC abdominal injection by trained provider. Injection volume of .5 and 1.5 mL.
Weekly and monthly Buprenorphine depot (CAM2038)	Proposed: induction and maintenance treatment	Headache, nausea, urinary tract infection, constipation, nasopharyngitis, and injection site reactions (pain, swelling, and erythema)	NMP† dose used has a 3-fold safety margin for reproduction	FluidCyrstal Technology (Camurus) 1 US FDA-approved product||	Prefilled syringe (no refrigeration required) with injection volume of 0.16 to 0.64 mL. SC injection into buttock by trained provider.

BUP, buprenorphine; NMP, N-methyl-2-pyrrolidase (a biocompatible solvent); SC, subcutaneous; TM, transmucosal.

*Examples of approved products with EVA: etonogestrel/ethinyl estradiol vaginal ring [NuvaRing, Organon/Merck & Co. Kenilworth, NJ], birth control implants [Implanon, Organon/Merck & Co. Kenilworth, NJ], and pilocarpine - ophthalmic ocular system [Ocusert Alza Mountain View, CA].

†Preimplantation losses, delayed ossification, reduced fetal weight, developmental delays and reduced cognitive function.

‡Examples of approved products with Atrigel: leuprolide acetate suspension for subcutaneous injection [Eligard, Tolmar Inc. Fort Collins, CO] and doxycycline hyclate [Atridox, Tolmar Inc. Fort Collins, CO].

§NMP is present in the monthly formulation only.

||Oral spray for oral mucositis pain [Episil, Camurus Lund, Sweden].

Safety

Implant site adverse events (AEs) occurred in 23% (Rosenthal et al., 2016) to 56.5% (Ling et al., 2010) of subjects. In the outpatient trials, there were no AEs related to respiratory depression or overdose in the persons receiving implants. In the control groups receiving SL buprenorphine/naloxone and placebo, 2 volunteers were admitted to inpatient treatment programs, 1 hospitalized for circumstances related to illicit opioid use, and 1 experienced nonfatal respiratory failure. While improper implant insertion/removal can theoretically lead to complications including nerve damage, implant migration, and protrusion and expulsion, none of these events occurred in the outpatient trials (n = 309 and n = 198 active and placebo implants, respectively) (Ling et al., 2010; Rosenthal et al., 2013; Rosenthal et al., 2016).

Monthly Subcutaneous Buprenorphine Injection Depot (Sublocade, formerly RBP-6000 [Indivior Inc., Richmond, VA])

The product was approved by the US FDA in late 2017 and is now available in two doses: 100 and 300 mg. The recommended treatment regimen is two 300 mg monthly doses followed by 100 mg doses thereafter; however, the US FDA is requiring the pharmaceutical company to conduct a postmarketing study to determine if the depot is effective when administered at interdose intervals exceeding the currently approved 1-month interval. Its' long $t^1/_2$ (~38 days [FDA, 2017a]) and the observation that the depot produces higher buprenorphine plasma concentrations with each subsequent dose suggest that patients may be adequately treated at longer dosing intervals.

Efficacy

In a phase II trial (Nasser et al., 2016), assessing the ability of the depot to block effects of an opioid agonist, nontreatment-seeking volunteers with OUD were inducted and stabilized on 8 to 24 mg SL buprenorphine and then administered two doses of the 300 mg depot four weeks apart. Hydromorphone (6 and 18 mg, IM) was administered before and up to 8 weeks after the second depot injection. The 300 mg depot produced complete blockade of 6 mg hydromorphone for four weeks after the first injection and complete blockade of 18 mg hydromorphone for 3 weeks (with partial blockade during the fourth week). During phase III outpatient trials evaluating the efficacy of the depot to reduce withdrawal, craving, and illicit opioid use, participants with OUD

were inducted onto SL buprenorphine for up to 2 weeks and were then randomized to receive 6 once-monthly injections of 300 mg depot; two doses of 300 mg followed by four doses of 100 mg; or matched-volume placebo injections. Withdrawal severity, as measured by the clinical opiate withdrawal scale, was low throughout the 24-week treatment period for all participants (<2 with active buprenorphine, <4 with placebo). The low withdrawal scores in the placebo group may be explained by the ongoing use of illicit opioids.

Significantly more patients receiving either active dosing regimen (300/300 or 300/100) of the depot provided illicit opioid-negative urine samples with corroborating self-report on at least 80% of testing days compared to placebo (active: 28.4%, placebo: 2%). There were no differences in efficacy between the 2 dosing regimens (ie, no dose-dependency in abstinence rates or reduction in withdrawal), but AEs were more frequent with the higher dose. These findings suggested that the lower dosing regimen is likely appropriate for most patients, and this is what is recommended in the package insert. Secondary analyses suggested that certain sub-populations (eg, people who inject drugs) may benefit from the higher dose regimen, and the pharmaceutical company is required to conduct a postmarketing study to identify those for whom the benefits of the 300 mg per month dose outweigh the risks of the higher dose (ie, clinically meaningful hepatotoxicity, see below) (FDA, 2017d).

Safety

The overall safety profile of this monthly depot product is generally consistent with the safety profile of buprenorphine, with the addition of injection site adverse events and buprenorphine exposures for the 300 mg dose that exceed what is recommended by the US FDA (ie, equivalent up to 24 mg SL buprenorphine). Long-term safety data for patients administered multiple doses of the 300 mg injection are not available. The local tolerability of the abdominal injection was similar to other approved products using the sustained-release delivery system, and most injection site reactions were of mild-to-moderate severity. The 300 mg regimen produced greater dropout and more AEs related to injection site reactions and elevations in hepatic enzymes compared with the 100 mg dosing regimen. Thirty percent of participants receiving the 300 mg depot in the phase III study required dose reductions to 100 mg; a quarter of these dose reductions were necessary because of AEs. The most common AEs leading to dose reduction included abnormal liver function tests, sedation, constipation, nausea, fatigue, and headache. Specifically, the incidence of elevations 3 times the upper limits of normal in AST were 11.4% (300 mg depot doses each month for 3 months), 7.9% (300 mg depot dose first 2 months then 100 mg in the third month), and 1.0% (placebo depot dose each month). Results for incident ALT elevations 3 times the upper limits of normal were similar (300 mg depot doses each month for 3 months: 12.4%, 300 mg depot dose first 2 months then 100 mg in third month: 5.4%, and placebo: 4.0%). The most common AEs leading to medication discontinuation included elevated liver enzymes, injection site reactions, sedation, constipation, somnolence, lethargy, and drug withdrawal syndrome. In two cases, surgical removal of the depot was necessary. The US FDA package insert states: ''Liver function tests, prior to initiation of treatment, are recommended to establish a baseline. Monthly monitoring of liver function during treatment, particularly with the 300 mg maintenance dose, is also recommended. An etiological evaluation is recommended when a hepatic event is suspected. . .If signs and symptoms of toxicity or overdose occur within 2 weeks of administration, removal of the depot may be required.'' Surgical removal of the depot is possible within 14 days of injection: after 14 days, the depot is likely not removable.

Weekly and Monthly Subcutaneous Buprenorphine Injection Depot (CAM2038 [Braeburn Pharmaceuticals, Princeton, NJ])

The product is in development and not yet US FDA-approved, although a US FDA Advisory Committee voted in favor of approval in November, 2017. The company received a Complete Response Letter from the US FDA on January 19, 2018, indicating that the agency had outstanding questions related to the CAM2038 product (PRNewswire, 2018). While the letter is not publicly available, no further clinical trials were mandated, making it possible that this product could still be approved in the near future. Doses in development and PK parameters are listed in Table 2.

Efficacy

In an inpatient laboratory study, nontreatment-seeking adults with OUD and physical dependence received 2 SC weekly injections of either 24 or 32 mg (estimated equivalence to 16 and 24 mg daily SL buprenorphine, respectively) and were challenged with hydromorphone (0, 6, and 18 mg, IM) before and up to 6 days after each injection. Both doses produced complete blockade of 18 mg hydromorphone for 6 days (Walsh et al., 2017). In a 6-month outpatient trial evaluating the efficacy of the SC depot compared with SL buprenorphine/naloxone (Lofwall et al., 2018), patients with OUD were randomized to receive 12 injections of the weekly depot followed by three injections of the monthly depot, or to receive daily SL buprenorphine/naloxone. Both SL and SC depot dosing was flexible and based on patient needs using clinical judgment, as would occur in clinical practice (FDA, 2017b). In both groups, withdrawal and craving were suppressed on day 1 and remained low throughout the study, including during the transition to monthly injections. Retention was similar between groups, and a significantly greater percentage of patients who received the SC depot provided illicit opioid-negative urine samples in weeks 4 through 24 of the study than those who received SL buprenorphine/naloxone. The authors concluded that CAM was an efficacious treatment for OUD with potential advantages over SL buprenorphine/naloxone.

Safety

Among patients with OUD, the SC depot produced a safety profile consistent with that of transmucosal buprenorphine, with additional AEs related to the injections. Localized injection site reactions occurred in ~7 (Haasen et al., 2017) to 9% (Walsh et al., 2017) of subjects. The highest doses of the

depot produced buprenorphine exposures that exceed what is recommended by the FDA (i.e., ~ 24 mg SL buprenorphine; see Table 2) and long-term safety data for patients exposed to these doses are lacking. No incidences of serious respiratory depression were reported for persons receiving the SC depot. Notably, in the 6-month outpatient trial comparing the SC depot to SL buprenorphine/naloxone, five drug overdoses occurred in the group randomized to receive SL buprenorphine/naloxone while none occurred in the SC depot group (Lofwall et al., 2018).

CONCLUSIONS

Buprenorphine can now be administered in daily, monthly, and twice-yearly doses, and clinicians have a growing number of treatment options for patients new to treatment and those who are more stable. Theoretically, implantable and injectable buprenorphine products should increase adherence and reduce diversion or misuse, but empirical data are not yet available to confirm these potentially important patient and public health benefits. These products may also obviate several patient concerns, including the risk of having their prescription stolen, traveling while carrying a controlled substance (this is illegal in some countries), needing to safely store their medication away from children, and the daily reminder of their OUD that comes with daily medication. It will be important for clinicians to consider patient status in choosing the most beneficial option. Because the buprenorphine implant produces comparatively lower plasma concentrations, it is most suited for patients already stabilized on buprenorphine at $\leq$8 mg. While it may be very convenient because of low patient burden, acquiring, inserting, and removing the implant places more initial burden on the provider. The approved monthly injectable produces the highest buprenorphine plasma concentrations of the marketed products; therefore, it may be most appropriate for those with greater physical dependence or already on higher daily doses. The injectable product may be helpful too for patients transitioning between different treatment settings. For example, patients leaving the hospital after treatment for a complication related to OUD (eg, endocarditis) and stabilized on buprenorphine in-hospital may have a delay connecting to outpatient care after discharge, and the injectable could provide coverage during the treatment gap. This product provides higher buprenorphine concentrations and could be beneficial for patients who are at high risk of illicit opioid use and overdose. As this product has been used only after stabilization on SL buprenorphine, it may not be suitable for direct induction (eg, in an emergency department setting) unless further data verify that direct induction is safely tolerated. The as-yet unapproved depot product is being developed in multiple doses, and as both weekly and monthly formulations, which would provide further flexibility for both patients and providers. Experience to date with that product has shown that direct induction onto the weekly injectable is well tolerated as is initiation of treatment after a test dose of SL buprenorphine (ie, prior stabilization on SL buprenorphine is not required). The highest doses of both injectable depot products do raise some concerns as they expose patients to buprenorphine at much higher concentrations than what has been previously deemed safe by the US FDA (Table 2). Because buprenorphine exhibits a ceiling effect (due to its low efficacy), increasing doses beyond a certain point may provide no additional clinical benefit. That ceiling effect has been suggested to occur at or near the equivalent of 24 mg/d transmucosal buprenorphine by both the US FDA and ASAM.

Treatment outcomes (and the corresponding buprenorphine dose prescribed) must be determined on a case-by-case basis, and not all outcomes are equally important in all phases of treatment. Reducing the risk of relapse to illicit opioid use by buprenorphine is achieved through withdrawal suppression, craving suppression, and blockade of agonist effects, but the relative importance of each may change depending on patient status. For example, withdrawal suppression is critical throughout treatment as the anticipation and experience of withdrawal are highly stressful and key risk for relapse. Likewise, reducing a patient's desire to use illicit opioids (ie, craving) is critically important, but, with time in treatment, the frequency or intensity of craving may diminish. Opioid blockade is an important benefit of treatment, especially for patients new to treatment and unstable or for those who continue to use illicit opioids intermittently while in treatment. Blockade may be less critical for those who are stable and abstaining from illicit use successfully. For example, it would be expected that the implant product would produce limited blockade because it yields lower plasma concentrations, but it was quite effective in patients already stable and abstaining. Similarly, treatment with lower daily SL buprenorphine (mean 9.6 mg [Dupouy, private communication]) was associated with an ~30 times lower mortality rate among persons with OUD compared with those not in treatment (Dupouy et al., 2017). Thus, both lower and higher doses of buprenorphine have been shown to be efficacious, and doses can vary considerably based on patient needs. Prescribers should, as always, use the lowest effective dose to achieve the desired treatment outcomes and now have more options from which to choose.

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