What are the pharmacological properties of Suboxone® that make it an appropriate agent for detoxification? Why not just a mixed agonist-antagonist (i.e., butorphanol, nalbuphine, pentazocine)?
What are the advantages/disadvantages of Suboxone® versus methadone?

March 1, 2016

Buprenorphine-containing products

Suboxone® is a combination product consisting of 2 drugs: buprenorphine, a partial agonist at the mu-opioid receptor (MOR) and antagonist at the kappa-opioid receptor (KOR), and naloxone, a potent MOR antagonist.[1] Per Goodman and Gilman, buprenorphine, itself, produces analgesia and other central nervous system (CNS) effects that are qualitatively similar to those of morphine.[2] Buprenorphine is highly lipophilic, and though it is a partial MOR agonist with limited intrinsic activity (i.e., it does not activate mu receptors fully), it is 25-50 times more potent than morphine. It also has a long duration of action.[3] When used in conjunction with a full opioid agonist, buprenorphine can display antagonism, as buprenorphine competes with other opioids for the MOR.[4] For example, in patients who have been using opioid receptor agonists for several weeks, administration of buprenorphine may cause symptoms of abstinence.[2] Buprenorphine will displace morphine, methadone, and other full opioid agonists from receptors and can also block the effects of other opioids.[5]

As mentioned previously, naloxone is an opioid antagonist.[2] Naloxone acts promptly to reverse the effects of opioid-receptor agonists. The duration of antagonistic effects depends on the dose, but it is typically 1 to 4 hours. When administered to patients who are opioid-dependent, naloxone may precipitate a moderate-to-severe withdrawal syndrome similar to that observed after abrupt discontinuation of opioids. However, naloxone-induced withdrawal typically appears within minutes of administration and is reduced in ~2 hours. Per the manufacturer, naloxone alone has not shown clinically significant effects when administered sublingually.[1] When administered sublingually in combination with buprenorphine, opioid agonist effects have been observed, whereas buprenorphine/naloxone administered IM has produced opioid antagonist effects similar to those expected of naloxone alone. Intravenous administration of buprenorphine/naloxone has also precipitated opioid withdrawal symptoms in methadone-maintained and heroin-dependent patients. These findings suggest that the naloxone component in the combination product may deter drug abuse by injection in patients with active heroin- or other opioid-dependence. In other words, if taken orally as directed, the patient will experience a predominant buprenorphine effect, but if he/she dissolves the formulation and injects it, the antagonistic effects of naloxone will prevail.[5]

Buprenorphine is available in several formulations, including a transdermal patch (Butrans®), buccal film (Belbuca®), injection solution (Buprenex® or generic), and sublingual tablet (generic product).[6] These formulations are approved by the Food and Drug Administration (FDA) for the management of pain, severe enough to require daily, around-the-clock, long-term opioid treatment (Butrans®, Belbuca®, Buprenex®), or the treatment of opioid dependence, particularly in the induction phase (buprenorphine sublingual tablet).[7-11] Buprenorphine combined with naloxone is also available in several formulations, including a sublingual film (Suboxone® or generic), buccal film (Bunavail®), and sublingual tablet (Zubsolv®).[12] Notably, these products are intended to decrease the potential for abuse via the injection route.[5] Use of these products is approved solely for the treatment of opioid dependence, by the Drug Addiction Treatment Act (DATA), passed in 2000 (21 USC 823(g)).[1,2,13-16]

Per the Substance Abuse and Mental Health Services Administration (SAMHSA), buprenorphine is useful for the treatment of opioid dependence because of its pharmacologic and safety profile.[5] Namely,

the SAMHSA identifies the following features: partial agonist properties, high affinity for MOR, low intrinsic activity at MOR, and slow dissociation rate. Although used for treatment of opioid dependence, the partial agonist properties of buprenorphine limit its use in treatment of opioid-dependent patients who require high maintenance doses of opioids.

Other partial agonists

In addition to buprenorphine, there are several other opioid drugs that act as mixed agonist-antagonists or partial agonists. These include pentazocine, nalbuphine, and butorphanol (see Table 1).[2] Importantly, these agents were developed to stimulate the analgesic portion of opioid receptors while blocking or having no effect on opioid toxicities.[17] The mixed agonist-antagonists or partial agonists produce analgesic effects while having the potential for less respiratory depression compared to opioid agonists. They are also thought to have a lower abuse potential, but their use is not prevalent due to issues such as psychomimetic responses (e.g., hallucinations and dysphoria with pentazocine), limited analgesia, and a risk of withdrawal (when used in opioid-dependent patients).

Table 1. Availability and indications of selected opioid agonist-antagonists.[18-21]

Drug	Available formulation	FDA-approved use(s)
Pentazocine	Injection solution (Talwin®)	• Relief of moderate-to-severe pain • Preoperative or pre-anesthetic analgesia • Supplement to balanced anesthesia
Pentazocine/acetaminophen	Oral tablets (Talacen®, generic)	• Relief of mild-to-moderate pain
Pentazocine/naloxone	Oral tablets (Talwin NX®, generic)	• Relief of moderate-to-severe pain
Nalbuphine	Injection solution (generic)	• Relief of moderate-to-severe pain • Supplement to balanced anesthesia • Preoperative and post-operative analgesia • Obstetrical analgesia during labor and delivery
Butorphanol	Injection solution (Stadol®, generic)	• Relief of pain where use of an opioid is appropriate • Preoperative or pre-anesthetic analgesia • Supplement to balanced anesthesia • Obstetrical analgesia during labor and delivery
	Nasal solution (generic)	• Relief of pain where use of an opioid is appropriate

FDA=Food and Drug Administration

Pentazocine acts as a weak opioid antagonist or partial agonist at opioid receptors.[2] While its CNS effects are similar to those of other pure opioid agonists (e.g., analgesia, sedation, respiratory depression), its cardiovascular effects differ, with high doses eliciting increases in blood pressure and heart rate. Higher doses (60-90 mg) may also result in dysphoric and psychomimetic effects, potentially due to activation of supraspinal receptors. Ceiling effects for analgesia and respiratory depression have been observed with pentazocine at doses in excess of 50-100 mg.

Nalbuphine is similar in structure to naloxone and oxymorphone and displays KOR agonist-MOR antagonist effects.[2] While qualitatively similar to pentazocine, nalbuphine is thought to be associated with a lower risk for dysphoria. Also, unlike pentazocine, higher doses of nalbuphine are not associated with increased cardiovascular effects. Ceiling effects for analgesia and respiratory depression have been observed with nalbuphine at doses beyond 30 mg.

Butorphanol is similar to pentazocine and nalbuphine in its KOR agonist-MOR antagonist effects.[2] Side effects of butorphanol are similar to those of pentazocine; psychomimetic effects have been reported with equianalgesic doses of butorphanol, and increased cardiovascular effects (e.g., pulmonary arterial pressure) have been reported at analgesic doses.

Pentazocine-, nalbuphine-, and butorphanol-containing products are solely FDA-approved for management of pain.[18-21] Though they display mixed opioid agonist-antagonist effects like buprenorphine, use of these agents for the treatment of opioid dependence may be discouraged due to the limitations outlined above. Additionally, based on a search of the published literature, there are few data to support use of pentazocine, nalbuphine, or butorphanol for treatment of opioid dependence. Of note, in their Treatment Improvement Protocol (TIP) addressing medication-assisted treatment for opioid addiction in opioid treatment programs (TIP 43), the SAMHSA states that all of these agents, including buprenorphine, should be avoided in patients maintained on methadone, due to the risk for opioid withdrawal.[4]

Pharmacologic treatment options for opioid addiction

According to the SAMHSA, there are 4 principal medications used to treat opioid addiction in opioid treatment programs: methadone, levo-alpha acetyl methadol (LAAM), buprenorphine, and naltrexone (see Table 2).[4] Among these, methadone is the most frequently used medication. LAAM traditionally has been used less frequently compared to methadone, especially since reports of cardiac arrhythmia were announced in 2001. These reports prompted the FDA to warn that LAAM use should be restricted to patients with unfavorable response to methadone.[22] Production of LAAM was also ceased in 2004.[4] Naltrexone has also been used less frequently compared to methadone. Per the SAMHSA, use of naltrexone in the United States has generally been limited to easing withdrawal symptoms for patients undergoing medically supervised withdrawal after maintenance treatment. Buprenorphine is the most recently approved medication, indicated for use in medical maintenance treatment of opioid addiction and medically supervised withdrawal. Buprenorphine is also the first agent to be made available for use by certified physicians outside of the traditional opioid treatment delivery system and requirements of the Narcotic Addict Treatment Act of 1974. Buprenorphine may be dispensed in opioid treatment programs that receive certification from the SAMHSA, and qualified physicians may dispense or prescribe buprenorphine-containing products for up to 30 patients at 1 time, initially, and up to 100 patients, subsequently, through the DATA of 2000.

Table 2. Pharmacotherapeutic medications for opioid addiction treatment. Adapted from TIP 43.[4]

Product	Formulations	Receptor pharmacology	Initial FDA-approval	Treatment settings
Methadone	Oral solution, liquid concentrate, tablet/diskette, powder	Full mu-opioid agonist	1970 (for detoxification) 1973 (for maintenance)	OTP
LAAM	Oral solution	Full mu-opioid agonist	1993	OTP
Buprenorphine	Sublingual tablet*	Partial mu-opioid agonist	2002	Physician's office, OTP, or other healthcare setting
Buprenorphine/ naloxone	Sublingual tablet, sublingual film, buccal film	Partial mu-opioid agonist/mu-antagonist	2002	Physician's office, OTP, or other healthcare setting
Naltrexone	Oral tablet	Mu-opioid antagonist	1984	Physician's office, OTP, or any substance abuse treatment program

*Approved formulation for opioid addiction treatment
FDA=Food and Drug Administration; LAAM=levo-alpha acetyl methadol; OTP=opioid treatment program

Buprenorphine vs. methadone

Comparing buprenorphine and methadone, there are several potential advantages and disadvantages to both. The drugs are described below.

Methadone is a full opioid agonist with extensive bioavailability and long half-life; when given IM or orally, analgesic effects may last for 4 to 6 hours.[4] An adequate daily oral dose of methadone may suppress opioid withdrawal and drug cravings for 24 to 36 hours in most opioid-dependent patients. After induction, steady-state concentrations are achieved in 5 to 7.5 days. Its sustained activity at MOR allows for substantial normalization of physiological changes observed after repeated intoxication and withdrawal associated with addiction to short-acting opioids. It is also thought that methadone, when administered at therapeutically appropriate doses, may attenuate the euphoric effects of heroin and other opioids.

Though methadone is associated with a long half-life in most individuals, its clearance rate varies widely among individuals.[4] Serum levels of methadone and its elimination are affected by several patient-specific factors (e.g., capacity for absorption, metabolism, and protein binding, urinary pH, use of medications, diet, physical condition, and age). There is also wide variability in the ratio of methadone dosage and serum concentrations achieved across patients. Tolerance to methadone may also take time to develop. As a result, unintentional overdose may occur, producing toxicities such as respiratory depression and, potentially, death.[3] Additionally, there are concerns for QT-prolongation with methadone, due to blockade of the human ether-a-gogo related gene (hERG) channel. Per *Goldfrank's Toxicologic Emergencies*, it is difficult to identify individuals at risk for life-threatening dysrhythmias from methadone-induced QT-prolongation. Screening patients for intrinsic heart disease or dysrhythmias and obtaining pre-treatment and follow-up electrocardiogram readings (e.g., at 30 days and yearly) may be necessary.

Prescription of methadone for maintenance therapy of opioid addiction is restricted to federally licensed programs, which may be inaccessible and inconvenient for patients.[3] In contrast, buprenorphine may be prescribed in a physician's office. Buprenorphine may also be administered 3 times weekly, as opposed to daily. There is potential for abuse and misuse of buprenorphine, but its safety profile is substantially better than that of methadone. Overdose of buprenorphine is associated with a lesser degree of respiratory depression than methadone and other full opioid agonists, and there have been no reports of QT prolongation with buprenorphine.[23]

As a partial opioid agonist, buprenorphine has a ceiling effect on respiratory depression as well as analgesic effects.[3] Per the SAMHSA, its partial agonist properties may limit its use in opioid-dependent patients who require high maintenance doses, but it may encourage adherence to the drug and regular administration.[5]

Treatment of opioid addiction with methadone or buprenorphine involves multiple stages: induction, stabilization, and maintenance.[4,16] With methadone, other opioid use should be discontinued completely prior to administration. Initial doses should be low and adjusted based on how patients feel at the peak period for their medication (e.g.., 2- to 4- hours post-dose of methadone).[4] Doses should be increased until withdrawal symptoms are suppressed at the peak period. Due to the risk of death in the first few days of treatment, careful dose adjustment of methadone is recommended under observation for 6-7 days/week. Stabilization is achieved when drug-seeking behavior or cravings no longer manifest. The focus is on determination of the appropriate dose of the medication. The maintenance stage begins when the patient is responding optimally and dose adjustments are no longer necessary. Patients may remain on the same dosage for extended periods (e.g., many months). Gradual dosage reduction may be attempted.

With regard to buprenorphine-containing products, induction with buprenorphine/naloxone is recommended for patients dependent on short-acting opioids, and buprenorphine monotherapy is recommended for tapering patients off of long-acting opioids.[16] The latter patients must have evidence of sustained medical and psychosocial stability. Buprenorphine/naloxone is recommended for induction, stabilization, and maintenance for most patients. For patients transferring from long-acting opioids, buprenorphine monotherapy should be initiated but switched to buprenorphine/naloxone soon thereafter. Induction involves switching the patient from the opioid(s) of abuse to buprenorphine, and the goal is to determine the minimum dose of buprenorphine at which the patient discontinues or markedly reduces use of the other opioid(s) and experiences no withdrawal symptoms or cravings. Though buprenorphine is less likely than methadone to produce respiratory depression, observation of the patient with the initial doses is advisable, and dosage monitoring early in treatment is strongly recommended.[4] Like methadone, maintenance treatment with buprenorphine may be indefinite.[16]

In general, choice of medication used for opioid addiction is based on safety and efficacy, patient preferences, and treatment goals.[4] Both methadone and buprenorphine have been shown to be effective for the maintenance treatment of opioid addiction. However, per the SAMHSA, methadone has been associated with the longest record for successful treatment of patients addicted to opioids for >1 year and has been shown to control withdrawal symptoms, stabilize physiologic processes, and improve functionality.

From a search of the literature, several meta-analyses were identified comparing buprenorphine to methadone. Among these, a recently published Cochrane review evaluated the 2 medications, including their ability to retain people in treatment and suppress illicit drug use.[24] Thirty-one randomized controlled trials were included in this review, involving 5,430 opioid-dependent patients. The trials were rated by the

reviewers as high to moderate quality. In low fixed-dose studies, methadone (≤40 mg) was more likely to retain patients than low-dose buprenorphine (2-6 mg; 3 studies, 253 patients, relative risk [RR] 0.67, 95% confidence interval [CI] 0.52 to 0.87). However, at medium doses (methadone 40-85 mg, buprenorphine 7-15 mg), there was no significant difference in retention (7 studies, 780 patients, RR 0.87, 95% CI 0.69 to 1.10) or suppression of illicit opioid use as measured by urinalysis (4 studies, 476 patients, standard mean difference 0.25, 95% CI -0.08 to 0.58). Similarly, at high doses (methadone ≥85 mg, buprenorphine ≥16 mg), there was no significant difference in retention (1 study, 134 patients, RR 0.79, 95% CI 0.20 to 3.16) or suppression of self-reported heroin use (standard mean difference -0.73, 95% CI -1.08 to 0.37). At flexible doses, adjusted to patient need, buprenorphine was less effective than methadone in retaining patients (5 studies, 788 patients, RR 0.83, 95% CI 0.72 to 0.95).

Based on these findings, Mattick et al concluded that buprenorphine appeared to retain fewer patients compared to methadone when doses were flexibly delivered and at low fixed doses.[24] With higher fixed doses, there appeared to be no significant difference in effectiveness of methadone and buprenorphine; however, the investigators asserted that flexible dosing may be more relevant to patient care.

In summary, there are several features and limitations to consider for both methadone and buprenorphine. Methadone is long-acting and its administration may lead to normalization of physiologic changes observed with opioid addiction.[4] However, its use is restricted to licensed programs, and its safety issues, particularly in relation to its wide inter-individual pharmacokinetic variability, are concerning. Buprenorphine may be more easily accessible, in comparison to methadone, as it may be prescribed/dispensed by certified providers, and it lacks some of the safety issues of methadone; however, its partial agonist properties may limit its use in treatment of opioid-dependent patients who require high maintenance doses of opioids.[5] Regardless of any potential differences in efficacy and safety, the SAMHSA recognizes that pharmacotherapy alone is rarely sufficient for treatment of opioid dependence. Clinicians are advised to refer patients to psychosocial services and consider other non-pharmacologic therapies. Regular physician visits are recommended with toxicology tests for all relevant substances and evaluation of maintenance treatment.

References

1. Suboxone® [package insert]. Richmond, VA: Indivior Inc.; 2015.
2. Yaksh TL, Wallace MS. Chapter 18: Opioids, analgesia, and pain management. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman and Gilman's: The Pharmacologic Basis of Therapeutics. 12th ed. New York, NY: McGraw-Hill; 2011. http://accesspharmacy.mhmedical.com/content.aspx?bookid=1613&Sectionid=102158872. Accessed February 5, 2016.
3. Nelson LS, Olsen D. Chapter 38: Opioids. In: Hoffman RS, Howland M, Lewin NA, Nelson LS, Goldfrank LR, eds. *Goldfrank's Toxicologic Emergencies*. 10th ed. New York, NY: McGraw-Hill; 2015. http://accesspharmacy.mhmedical.com/content.aspx?bookid=1163&Sectionid=65093560. Accessed February 8, 2016.
4. US Department of Health and Human Services. TIP 43: Medication-assisted treatment for opioid addiction in opioid treatment programs. Substance Abuse and Mental Health Services Administration Web site. http://store.samhsa.gov/shin/content//SMA12-4214/SMA12-4214.pdf. Accessed February 8, 2016.
5. US Department of Health and Human Services. TIP 40: Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Substance Abuse and Mental Health Services Administration Web site.

http://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/Bookshelf_NBK64245.pdf. Accessed February 8, 2016.
6. Buprenorphine. In: Facts and Comparisons. St. Louis, MO: Wolters Kluwer Health. [updated February 2015; accessed February 5, 2016]. http://online.factsandcomparisons.com.
7. Butrans® [package insert]. Stamford, CT: Purdue Pharma LP; 2014.
8. Belbuca® [package insert]. Malvern, PA: Endo Pharmaceuticals Inc.; 2015.
9. Buprenex® [package insert]. Richmond, VA: Reckitt Benckiser Pharmaceuticals; 2014.
10. Buprenorphine hydrochloride injection [package insert]. Spring Valley, NY: Par Pharmaceutical Companies, Inc.; 2015.
11. Buprenorphine hydrochloride tablet [package insert]. Parsippany, NJ: Actavis Pharma, Inc.; 2015.
12. Buprenorphine/naloxone. In: Facts and Comparisons. St. Louis, MO: Wolters Kluwer Health. [updated October 2015; accessed February 5, 2016]. http://online.factsandcomparisons.com.
13. Buprenorphine and naloxone tablet [package insert]. Parsippany, NJ: Actavis Pharma, Inc.; 2014.
14. Bunavail® [package insert]. Raleigh, NC: BioDelivery Sciences International, Inc.; 2014.
15. Zubsolv® [package insert]. Morristown, NJ: Orexo US, Inc.; 2015.
16. Doering PL, Li R. Chapter 48. Substance-related disorders I: overview and depressants, stimulants, and hallucinogens. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. *Pharmacotherapy: A Pathophysiologic Approach, 9e.* New York, NY: McGraw-Hill; 2014: 996-999.
17. Baumann TJ, Herndon CM, Strickland JM. Chapter 44: Pain management. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. *Pharmacotherapy: A Pathophysiologic Approach, 9e.* New York, NY: McGraw-Hill; 2014: 930-937.
18. Pentazocine. In: Facts and Comparisons. St. Louis, MO: Wolters Kluwer Health. [updated May 2014; accessed February 5, 2016]. http://online.factsandcomparisons.com.
19. Pentazocine combinations. In: Facts and Comparisons. St. Louis, MO: Wolters Kluwer Health. [updated May 2014; accessed February 5, 2016]. http://online.factsandcomparisons.com.
20. Nalbuphine. In: Facts and Comparisons. St. Louis, MO: Wolters Kluwer Health. [updated November 2015; accessed February 5, 2016]. http://online.factsandcomparisons.com.
21. Butorphanol. In: Facts and Comparisons. St. Louis, MO: Wolters Kluwer Health. [updated August 2014; accessed February 5, 2016]. http://online.factsandcomparisons.com.
22. US Food and Drug Administration. Important prescribing information for addiction treatment specialists. April 11, 2001. http://www.fda.gov/downloads/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm173871.pdf. Accessed February 8, 2016.
23. Crediblemeds.org. Combined list of drugs that prolong QT and/or cause Torsades de Pointes (TDP). https://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf. Accessed February 8, 2016.
24. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;2:CD002207.

Prepared by: Irene S Reilly, PharmD, BCPS
February 24, 2016