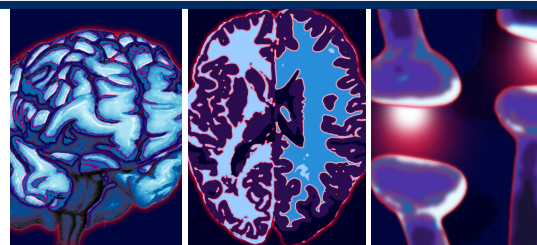# REVIEW

Buprenorphine for opioid addiction

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Practice points

- Buprenorphine is a partial μ opioid antagonist approved for the treatment of opioid dependence.

- Buprnenorphine for opioid dependence is available as a sublingual tablet or film formulation.

- Generic buprenorphine is available as a monoproduct in 2 mg or 8 mg doses, or as a combination product with 0.5 mg or 2 mg naloxone in a 4:1 ratio, respectively.

- Due to the ceiling on μ agonist activity, potential for overdose and respiratory suppression is limited.

- Due to a high affinity for the μ opioid receptor, buprenorphine inhibits the effects of exogenously administered opioids.

- Side effects of buprenorphine include headache, constipation, drowsiness, nausea, and sleep problems.

SUMMARY   Buprenorphine is a partial opioid agonist at the m receptor and is used as a daily-dose sublingual tablet or filmstrip for managing opioid addiction. In the United States, the Drug Addiction Treatment Act of 2000 made buprenorphine the only opioid medication for opioid addiction that can be prescribed in an office-based setting. Due to its high affinity for the μ receptor, buprenorphine inhibits the reinforcing effect of exogenous opioids. The ceiling on μ agonist activity of buprenorphine reduces potential for overdose and confers low toxicity even at high doses. Buprenorphine pharmacotherapy has proven to be a treatment approach that supports recovery from addiction while reducing or curtailing use of opioids. This review examines buprenorphine pharmacotherapy for opioid addiction, focusing on the situation in the United States, and is based on a review of pertinent literature and on the authors' research and clinical experience. The references in this paper were chosen according to the authors judgment of quality and relevance, and with respect to their familiarity and involvement in related research.

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Buprenorphine is one of the most important developments in pharmacotherapy for opioid addiction, preceded only by the broad implementation of methadone maintenance long before the approval of buprenorphine in the USA and in other countries. Distinct from methadone, buprenorphine may be prescribed by a qualified physician in an office setting instead of being dispensed only in federally authorized opioid treatment clinics, as required of methadone. Thus, the advent of buprenorphine permitted physicians to directly manage treatment for their opioid-addicted patients, making it possible for them to treat these patients with the same medical approach as would be appropriate for other patients with chronic conditions. Beyond the recognition that buprenorphine was pharmacologically different from methadone, with resultant greater safety and less addictive potential, buprenorphine was more readily embraced in large part due to the increasing understanding by scientists of addiction being a true brain disease rather than a deviant, criminal behavior reflecting corrupt morals. The approval of buprenorphine in 2002 and its clinical uptake were facilitated by commensurate changes in social philosophies toward addiction, but the availability of the medication also helped move these changes along.

In contrast, when methadone was the sole medication approved for opioid addiction treatment in the United States, clinical implementation of methadone maintenance reflected legal and public health philosophies concerning opioid addiction, with resulting stigma attached to both the medication and the opioid-dependent individual. Buprenorphine benefited from relaxed regulations compared with those pertinent to methadone [1]. Given its superior safety profile and ease of administration [2,101], buprenorphine enabled physicians to approach the treatment of addicted patients in a manner consistent with the care of patients with other chronic disorders, leading to changes in attitudes in the medical community that are filtering into the larger society.

Changes in attitudes attendant with the availability of buprenorphine elicited commensurate developments in clinical practices, as evident by the increase in treatment with buprenorphine. From 50,000 in 2002, prescriptions for buprenorphine in the USA increased to more than 5.7 million in 2009, of which more than 93% were for treatment of opioid use disorders for at least 330,000 patients with 'opioid type dependence' [3]. The clinical utility of buprenorphine for opioid addiction is further documented in the numbers of treated patients estimated to be more than 340,000 on Suboxone® (Reckitt Benckiser, Slough, UK) (the originally approved medication formulation that includes naloxone in a 4:1 ratio of buprenorphine to naloxone) plus more than 50,000 on generic buprenorphine [Pers comm] compared with about 268,000 on methadone in 2008 [4]. Clearly, office-based treatment with buprenorphine provides a viable alternative to methadone maintenance for many patients [5].

Buprenorphine in some ways is a victim of its own success, and its possession in the hands of hundreds of thousands of patients unavoidably has resulted in some illicit usage and diversion to individuals who are not under medical care; the drug can be abused and is being used illicitly. Increasing numbers of people misusing prescription opioid pain medications have provided a new market for diverted buprenorphine. Thus, buprenorphine-prescribing doctors and regulatory agencies are increasingly concerned about compliance and diversion of buprenorphine, which has worsened in step with the increasing number of patients. Another issue attendant with the widespread use of buprenorphine is potential accidental poisoning resulting from access by children and others who come into possession of prescribed buprenorphine that is not properly stored.

The problems and concerns about buprenorphine must be acknowledged, even in light of the clear benefits and utility of buprenorphine. Diversion and noncompliance with medication remain troublesome issues that require innovative solutions and diligence among clinicians. New developments in administration of buprenorphine offer promising alternatives, including the development of an implant form of buprenorphine that delivers six months of assured medication, although not yet approved in the USA. Sublingual buprenorphine will remain a widely used product for addiction treatment.

Indications & usage

Sublingual buprenorphine and sublingual buprenorphine:naloxone are approved for the treatment of opioid dependence in the USA and in several other countries (e.g., Australia, Britain and France), where they also are used for analgesia. Transdermal, intravenous, and

intramuscular formulations of buprenorphine are also approved for the treatment of chronic and acute pain, respectively. Other conditions for which sublingual buprenorphine may be useful include management of chronic pain and treatment of other substance use disorders, including cocaine use disorder, which has been under investigation in a recently completed clinical trial in the USA [6]; results are pending.

Dosage & administration

Generic buprenorphine is available in two sublingual tablet preparations, as a monoproduct containing only buprenorphine hydrochloride in 2 mg or 8 mg dosages or the combination-drug product in 2 mg or 8 mg of buprenorphine with 0.5 or 2 mg naloxone, respectively. Misuse liability is limited by the presence of naloxone, which is not well absorbed sublingually, yielding a clinical effect virtually identical to the mono-product. If injected, the naloxone will precipitate opioid withdrawal in opioid-dependent individuals, which inhibits injection use of the combination buprenorphine+naloxone product.

Buprenorphine (as Suboxone®) is available in a film form in varying dosages (2, 4, 8, 12 mg), which must be dissolved under the tongue. The formulation also includes naloxone in the same 4:1 ratio of buprenorphine:naloxone as in the tablet form, instilled into the product to inhibit misuse of buprenorphine by individuals who might dissolve the film and inject.

Procedures for induction onto sublingual buprenorphine are described in guidelines and in research literature [7]. An important initial element in this process is an accurate assessment of the patient's level of withdrawal symptoms, usually based on the Clinical Opiate Withdrawal Scale (COWS; [8,9]); a low COWS score (generally, below nine), stemming from inadequate time elapsed since previous opioid use, will compromise induction due to the potential for buprenorphine to precipitate withdrawal symptoms if administered in the presence of other opioids. As a partial agonist with very high binding affinity for μ opioid receptors, buprenorphine displaces other μ agonists from receptors.

For the induction, the first dose of sublingual buprenorphine varies from 2–4 mg and is administered after an individual has abstained from short-acting opioids for at least 12 h (or 36–72 h for longer-acting opioids such as methadone) and mild to moderate withdrawal symptoms have emerged. The dose may be titrated by 2–4 mg approximately every 2 h as needed for ongoing withdrawal symptoms with a dose of up to 8–16 mg on the first day, 8–16 mg on day 2, and 12–24 mg on day 3 (note: clinicians should regard these as guidelines, not mandates). Stabilization has occurred when objective and subjective measures indicate control of withdrawal symptoms and reduction in opioid craving. Buprenorphine has a high affinity for opiate receptors and a long half life (~37.5 h), and is effective when taken as infrequently as three times per week but is usually administered once or twice per day.

As noted before, a new depot formulation of buprenorphine marks a breakthrough in buprenorphine administration. Administration of buprenorphine by subcutaneous implant with 6 months of sustained effect eliminates the possibility of noncompliance and diversion [10].

Clinical pharmacology
■ Mechanism of action

Buprenorphine is a partial opioid agonist with strong affinity for the μ opioid receptor and is an antagonist at the kappa receptor. The high affinity for and limited intrinsic activity at the μ receptor inhibits the reinforcing effect of exogenous opioids. Although buprenorphine is a partial opioid agonist, its tight binding characteristic and slow rate of dissociation result in prolonged clinical effect and limited physical dependence. The ceiling on μ agonist activity of buprenorphine reduces potential for overdose and confers low toxicity even at high doses [11]. Buprenorphine can also block the effects of exogenous opioids [12], thus reducing illicit opioid use. An attribute of buprenorphine as pharmacotherapy for addiction is that its reinforcing effect is counterbalanced by the fact that it does not produce the 'rush' sought by addicted individuals. While reliably inhibiting opioid self-administration, buprenorphine dosing over time results in only a mild abstinence syndrome following abrupt cessation, which facilitates discontinuation of the medication as necessary or desired.

■ Pharmacodynamics & pharmacokinetics

As a pharmacotherapy for opioid addiction, buprenorphine is most commonly prescribed as a tablet or film containing buprenorphine hydrochloride mixed in a 4:1 ratio with naloxone for sublingual administration. Buprenorphine has poor oral bioavailability but high sublingual bioavailability; tablet administration under

the tongue produces up to 70% of the plasma concentration produced by the liquid preparation used in trials to support US FDA approval in the USA [13]. Peak plasma concentration occurs approximately 90 min after absorption, with a mean half-life of 37 h. Buprenorphine is metabolized via N-dealkylation and glucuronidation, with the resulting active metabolite norbuprenorphine conjugating with glucuronic acid [14]. Metabolites are excreted in the biliary system, with the major excretory route in feces and urine, regardless of route of administration. Acute administration results in small amounts of metabolite in plasma, while chronic dosing results in increased plasma levels of norbuprenorphine, the only biologically active metabolite [15].

In the combination product most commonly prescribed for opioid addiction treatment, the naloxone component does not affect the pharmacokinetics of buprenorphine [16]. Naloxone undergoes direct glucuronidation to naloxone 3-glocuronide as well as N-dealkylation and reduction of the 6-oxo group. Sublingual absorption of both buprenorphine and naloxone is subject to variations across individuals, but this variability was found to be clinically insignificant when administered to opioid-dependent individuals in clinical trials. Both C_{max} and the area under the curve of buprenorphine increase in a linear fashion with increased dosages in the 4–16 mg range, but the increase is not directly dose-proportional. Virtually all metabolites are undetectable by 11 days after dosing.

■ **Clinical evidence: overview of clinical trials**

Used in many countries for many years as an analgesic, buprenorphine was considered as a potential opioid addiction treatment in the late 1970s. The safety and efficacy of buprenorphine was established in early work [17] demonstrating buprenorphine's safety and efficacy in reducing illicit use of opioids, and showing equivalence to methadone in suppressing opioid withdrawal symptoms [18]. Initial work on buprenorphine for opioid addiction examined the drug as a liquid formulation, which was replaced by a more easily prepared and stored tablet form that ultimately included naloxone to dissuade injection use, using a 4:1 ratio after extensive investigation of the optimum proportions [19-21].

Development of buprenorphine as an addiction treatment was shepherded in the USA by the National Institute on Drug Abuse (NIDA), which supported extensive clinical research on its usefulness. Preceding FDA approval in 2002, buprenorphine had been extensively examined in clinical research [22,23]. NIDA had recognized the need for additional research on buprenorphine to facilitate implementation and took advantage of the NIDA Clinical Trials Network (CTN). The first CTN research focused on the matters of import to clinicians and patients regarding buprenorphine as a pharmacotherapy for opioid addiction. Clinicians who were reluctant to employ a new pharmacotherapy needed additional support to confirm the anecdotal reports and early-phase investigations of buprenorphine for addiction [24].

In the first CTN studies, the combination buprenorphine+naloxone product was compared with clonidine for short-term detoxification in an inpatient setting in one trial, and in an outpatient setting in another, documenting the superiority of buprenorphine as compared with the clonidine-assisted method of detoxification in multiple environments [25]. The studies substantiated the contention that clinical outcomes important in real-world practice were better than those after detoxification with clonidine in terms of retention, completion of treatment, and abstinence from illicit drugs.

A subsequent study, examined the issue of buprenorphine taper duration, in which a 7-day taper was compared with a 28-day taper. Individuals assigned to the 7-day taper had a greater proportion of opioid-free urine drug screens at the end of taper than those assigned to a 28-day taper, and outcomes were generally similar between the two groups at 1 and 3 month follow-ups, suggesting that a shorter taper duration is not inferior to a longer taper [26].

Opioid use disorders among youth populations became a recognized problem, resulting in a trial to examine buprenorphine in youths and young adults 15–21 years of age [27], comparing brief detoxification using buprenorphine plus counseling for 3 months versus 3 months of buprenorphine pharmacotherapy plus the same counseling. Better outcomes were achieved with three months of buprenorphine pharmacotherapy, with few safety or tolerability issues.

Comparing methadone as the standard pharmacotherapy versus buprenorphine (including the issue of potential side effects at the request of the FDA), a CTN trial examined liver enzymes in patients treated with the two medications. Findings indicated no evidence of liver damage during the 6 months of buprenorphine or

of methadone [28]. Based on data from the same sample, researchers determined the differential retention in the two groups, finding initially large numbers of dropouts in the buprenorphine patients, many of whom had been switched from methadone and preferred a return to that medication largely because of inadequate buprenorphine dosing and clinicians' lack of familiarity with buprenorphine. A Cochrane meta-analysis reported that treatment with methadone is associated with improved treatment retention than buprenorphine; however for individuals retained in treatment, buprenorphine and methadone yield equivalent opioid use outcomes [25].

A study of outcomes after 1 year of buprenorphine treatment (16 mg daily) or placebo given with psychosocial interventions showed a highly significant effect of buprenorphine in enhancing treatment retention in treatment and reducing use of illicit drugs [29]. Responding to need for information on treatment of rapidly increasing misuse of prescription opioid medications, the Prescription Opiate Addiction Treatment Study examined buprenorphine for such patients, providing additional substantiation for sustained pharmacotherapy rather than short-term treatment of several weeks. Approximately half of individuals attained successful opioid use outcomes during 12 weeks of sustained treatment with buprenorphine; however, relapse rates were greater than 90% when individuals were tapered after either 1 month or 3 months of buprenorphine treatment. The addition of drug counseling to standard medical management with a physician did not appear to improve treatment outcomes. The presence of chronic pain at baseline did not have a negative impact on opioid use outcomes [30].

Adverse reactions

Notable adverse reactions to sublingual buprenorphine include headache (36% compared with 22% for placebo), drowsiness, nausea, constipation, sleep problems, depression, and anxiety [22]. Other side effects are weight gain, sweating, skin rash, itching, abdominal pain, lassitude, menstrual effects, and decreased libido.

Drug interactions

Combining buprenorphine with alcohol, opioids, or other central nervous system depressants can result in respiratory depression. The combination of buprenorphine with intravenous benzodiazepines has resulted in deaths. Monoamine oxidase inhibitors and medications affecting the cytochrome system, specifically, CYP3A4 medications, can either increase or inhibit buprenorphine metabolism; common medications in this group include antifungals, protease inhibitors, macrolide antibiotics, and anticonvulsants [31]. Cardiac arrhythmias can be of concern among some populations, including individuals on HIV medications; taken with antiretrovirals, buprenorphine does prolong QT but without apparent clinically significant effects (i.e., QT interval less than 450 milliseconds in 100% of buprenorphine patients, whereas 49% of methadone patients exhibited QT intervals greater than 450 milliseconds) [32,33].

Use in specific populations
■ Patients on HIV/AIDS medications

Buprenorphine pharmacotherapy for HIV-infected opioid-dependent individuals has been shown to increase compliance with antiretroviral pharmacotherapy [34]. Furthermore, HIV patients on buprenorphine have increases in $CD4^+$ cell count and reductions in viral load [35]. The use of buprenorphine, whether delivered sublingually or as implant, in the presence of HIV medications has not posed a problem, given the minimal drug–drug interactions compared with those with methadone.

■ Women

Methadone maintenance has been the standard for opioid addiction, including for women who become pregnant. However, the safety of buprenorphine to treat opioid-dependent pregnant women has been supported by emerging data suggesting that buprenorphine in this population may be associated with less neonatal withdrawal among newborns. Research demonstrates that neonatal abstinence syndrome among buprenorphine-exposed newborns requires shorter hospital stays and less opioid-based medication for treatment than methadone-exposed newborns [36,37,38]. The risks of untreated opioid dependence and withdrawal in pregnancy outweigh those of treatment with maintenance medications.

■ Adolescents

The growing use of opioid medications and of heroin among children younger than age 18 has resulted in increased use of buprenorphine for these patients, although technically not

approved for children younger than 16 years old. The pharmacotherapy is reported to be effective in such populations, as noted above in the CTN trial, which included very few participants age 16 and younger, and there is continued concern for misuse and diversion as well as risk of accidental poisoning due to insecure storage and management of the medication.

Conclusion

The introduction of buprenorphine returned opioid addiction treatment to the hands of physicians, enabling them to care for opioid-addicted patients in an office-based setting similar to that employed for patients with other chronic conditions. In brief, buprenorphine can improve the lives of many opioid-dependent individuals, while the clinician understands the potential for the medication to be a source of problems if it is misused in a manner other than as prescribed. In contrast with such eventualities as diversion and misuse, adherence and outcomes of buprenorphine pharmacotherapy for treatment of opioid dependence are comparable to those of treatments for obesity, diabetes, asthma, and hypertension. Salient items of interest are noted below, derived from lessons learned during the authors' experience in clinical practice and in research.

■ Variations in practice

Clinicians often deviate from the dosing and procedural guidelines in the package insert for buprenorphine and from the Substance Abuse and Mental Health Services Administration guidelines, which recommend slow titration of dose and daily in-person clinical monitoring with multiple assessments of withdrawal symptoms during the early stages of induction. Over time, with greater knowledge and experience, practitioners have become comfortable with more rapid titration and unobserved at-home dosing practices [39]. Evidence from the literature supports positive treatment outcomes when a more rapid rate of induction is used [40,41]. At least one study found similar outcomes when a home-based buprenorphine induction strategy was used compared with traditional office-based inductions [42]. The ability to be flexible in dosing and induction procedures is a major strength of buprenorphine, to the benefit of clinicians and patients.

■ Induction issues

Before initiating buprenorphine treatment, it is important to establish a diagnosis of opioid dependence and review the risks and benefits of treatment. Urine drug screening is a valuable tool to collect objective evidence of recent opioid use. Prior to induction, patients should abstain from short-acting opioids at least 12 h and exhibit mild to moderate objective signs of opioid withdrawal (reflected by a COWS score of at least nine) before administration of the first dose of buprenorphine in order to avoid precipitation of withdrawal symptoms during induction.

■ For new buprenorphine-prescribing physicians

Physicians coming to the practice of addiction medicine involving buprenorphine are advised to join an informal network of reputable physicians with similar interests and learn from one another, thus establishing a good local standard of practice.

Due to the pharmacological profile of buprenorphine, which includes slow dissociation from its binding sites, buprenorphine may be dosed once per day. However many patients prefer to divide dosing at least twice per day. It is important to assess for evidence of functional improvement and progress toward treatment goals. Appropriateness of prescribed dosage over time and evidence of nonadherence to medication or of potential diversion should also be assessed. Monthly visits incorporating on-site urine drug screens and pill counts when appropriate may be useful. If indicated, smaller quantities of medication may be prescribed in conjunction with more frequent office visits; as a synthetic opioid, buprenorphine will not be detected on a basic drug screen for opioids, requiring a separate qualitative test specific for buprenorphine. Urine drug screens can be cost-effectively employed in many practice settings using tests authorized under federal Clinical Laboratory Improvement Amendments in the USA. These reliable tests almost instantly indicate the presence of a wide range of substances or substance metabolites such as morphine, oxycodone, methadone, buprenorphine, benzodiazepines, phenobarbital, cocaine, Tetrahydrocannabinol, phencyclidine, 3,4-methylenedioxy-N-methyl-amphetamine, amphetamine, methamphetamine and propoxyphene. Samples can be sent to the lab for quantitative analysis if necessary; psychosocial therapy may be recommended as an adjunct to buprenorphine pharmacotherapy.

The physician should emphasize aspects of medical management that he or she sees fit for the particular patient's needs, which in some cases may include participation in formal counseling or behavioral therapy. Research has not consistently documented improved outcomes associated with additional behavioral treatment over and above standard medical management [43].

Duration of buprenorphine pharmacotherapy: how long is long enough?

The package insert originally did not refer to 'maintenance' but reissuance of the insert now does, indicating the tentative nature of the original clinical sense of how the medication would be used. Buprenorphine has been and is being used as an aid to detoxification, but short-term use in that manner is often followed by relapse [30]. In general, the duration of buprenorphine pharmacotherapy should be tailored to the needs of the patient. Patients with unstable or untreated medical or psychiatric conditions may require ongoing buprenorphine pharmacotherapy. Whether discontinuation is appropriate is a matter of timing and of clinical judgment based on understanding the patient and the circumstances.

■ Discontinuation of buprenorphine

The limited physical dependence associated with the partial agonist makes tapering medically straightforward. Taper of buprenorphine doses is generally well tolerated with fewer, less intense physical symptoms than those associated with withdrawal from high affinity full opiate agonists. Since buprenorphine has a long half-life, mild withdrawal symptoms can last longer than those associated with withdrawal from sorter half life opiates. Some patients seem psychologically reliant on the presence of the medication, seeking to extend their involvement by taking doses as small as 0.5 mg/day. This may be due to the antidepressant effect of buprenorphine's κ-receptor antagonism, but further study of this topic is required. Clinicians familiar with sublingual buprenorphine should be capable of managing the care of patients after they have ceased buprenorphine. Usually, traditional outpatient opiate detoxification strategies are employed to alleviate withdrawal symptoms that require treatment (i.e., treatment of symptoms with nonopioid medications).

■ Use in pain management

Buprenorphine is a powerful analgesic with a long history of use in treating acute pain and chronic pain. Although the sublingual form is not yet approved for chronic pain, physicians are making use of the drug off label. Buprenorphine may offer an alternative to managing chronic pain in a safer and more tolerable manner than other opioid medications. Evidence suggests that chronic pain patients who have developed tolerance and diminished analgesia on full μ agonists in the 200–300 mg morphine-equivalents range may experience reduced pain when converted to buprenorphine therapy [44].

Future perspective

Use of buprenorphine as a pain control medication will be explored in future research.

Financial & competing interests disclosure

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