Opioids continue to be some of the most frequently reported prescription medications in substance abuse-related cases, according to recent data from the Drug Abuse Warning Network. In 2002, opioid pain relievers accounted for more than 119,000 emergency department (ED) drug mentions (i.e., drugs recorded during drug-related episode; four drugs can be mentioned during each episode). From 1994 to 2002, ED mentions of hydrocodone and oxycodone increased by 170% and 450%, respectively, and ED visits attributed to substance abuse and dependence continued to increase. Since 2002, death certificates have listed opioids as the most common cause of drug overdoses. Thus, initiatives to decrease sequelae of opioid abuse remain paramount.

There are several proposed theories regarding the physiological mechanisms of drug addiction. Although it is beyond the scope of this review to summarize all existing theories, most agree that addictive drugs either produce euphoria or alleviate symptoms of either withdrawal or dysphoria. Physicochemical properties of drugs (e.g., liposolubility, volatility, heat resistance) and pharmacologic and pharmacokinetic characteristics (e.g., rapid onset, short half-life) contribute to the potential for abuse. Personality and psychiatric disorders and genetic factors (e.g., aldehyde dehydrogenase deficiency, µ-opioid receptor polymorphisms) attenuate...
the risk of substance abuse. Although short-term use of opioids is associated with feelings of euphoria, sedation, and tranquility, regular repeated use (two weeks or longer) is associated with the development of tolerance and, ultimately, dependence. At the molecular level, opioids bind to and activate μ-, κ-, and δ-receptors that couple with G proteins (Figure 1). These receptors mediate slow synaptic transmission. G proteins are composed of two functional units. The binding of the agonist (e.g., opioids) activates a nearby G protein. The α subunit bound to guanosine triphosphate dissociates from its subunits to inhibit adenylyl cyclase, which synthesizes second messengers, such as cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate, inositol triphosphate, and diacylglycerol. In addition, the subunits and second messengers regulate calcium-, sodium-, and potassium-ion channels. After chronic exposure to opioids, receptor desensitization, internalization, and sequestration are thought to occur, necessitating greater quantities of opioids to obtain the same physiological effects. In addition, long-term tolerance is associated with increased adenylyl cyclase activity. Accumulated adenylyl cyclase acts in contrast to cAMP, inhibiting the desired opioid

Figure 1. Mechanisms of action of drugs of abuse. G protein-coupled receptors mediate slow synaptic transmissions. G proteins are trimeric structures composed of two functional units: an α subunit that catalyzes the activity of the enzyme that catalyzes the hydrolysis of guanosine triphosphate (GTPase) and a βγ dimer that interacts with the α subunit when bound to guanosine diphosphate (GDP). The binding of the agonist (e.g., opioids) activates a nearby G protein. The α subunit bound to guanosine triphosphate (GTP) dissociates from its subunits to inhibit adenylyl cyclase that synthesizes second messengers, such as cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate, inositol triphosphate, and diacylglycerol. In addition, the βγ subunits directly regulate calcium-, sodium-, and potassium-ion channels. Second messengers also regulate ion channels by activating protein kinases, which phosphorylate such channels. Protein kinases induce pharmacologic effects and produce changes in transcription factors, such as cAMP-responsive element-binding (CREB) and δFosB protein. Opioids bind to opioid receptors, which reduce cAMP levels, and cannabinoids bind to cannabinoid receptors. Classic hallucinogens are partial agonists of serotonin receptors. Amphetamines and cocaine have an indirect action on receptors, increasing the synaptic levels of dopamine, norepinephrine, and serotonin (facilitating release and inhibiting reuptake, respectively). These neurotransmitters activate different subtypes of dopaminergic, adrenergic, and serotonergic receptors. Reprinted with permission, from Cami J and Farré M. Mechanism of disease: Drug addiction. N Engl J Med. 2003; 349:975-86.
Levo-Methadone is still a partial µ-opioid receptor agonist and κ-receptor antagonist with a long duration of action.4,5 Buprenorphine is indicated for the maintenance treatment of opioid dependence.6 Several oral dosage forms of buprenorphine are commercially available, including buprenorphine 2- and 8-mg sublingual tablets (Subutex, Reckitt Benckiser Health care Ltd.), buprenorphine 2 mg combined with naloxone 0.5 mg, and buprenorphine 8-mg and naloxone 2-mg sublingual tablets (Suboxone, Reckitt Benckiser).6 Buprenorphine is also available in an injectable form (Buprenex, Reckitt Benckiser), which is indicated only for pain relief and cannot be legally used for detoxification or maintenance.

The pharmacokinetic and pharmacodynamic profiles of buprenorphine are not well characterized.6,7 One theory suggests that due to extensive binding to µ-opioid receptors with low intrinsic activity, a slow dissociation rate, and antagonistic effects at the κ-opioid receptor, a unique analgesic-ceiling effect occurs with escalating buprenorphine doses in vitro.6,7 However, in vivo studies in humans and animal models challenge this theory, citing a complex three-compartment pharmacokinetic model to explain the analgesic effects of buprenorphine that are observed.7 Yet, most sources state that buprenorphine produces partial antagonist effects by binding to the µ-opioid receptors and slowly dissociating from the receptor.3-8 Opioid-antagonist effects observed with buprenorphine treatment are similar to those observed with naloxone.6 As the buprenorphine dose increases, the antinociceptive (analgesic) effect decreases, and narcotic antagonism proportionally increases. Thus, analgesia is reversed, and opioid withdrawal effects ensue when buprenorphine is administered to patients under the influence of full opioid-receptor agonists (e.g., morphine, hydromorphone, fentanyl).5 The respiratory depressant effects of buprenorphine are similar to those of morphine when equipotent doses are prescribed. Because of the extended affinity for buprenorphine at the receptor site, naloxone may be of limited value for the treatment of buprenorphine overdose. A continuous infusion of naloxone may be necessary, since respiratory depression from buprenorphine may outlast the effects of small bolus doses of naloxone.9 The total of these pharmacologic characteristics decreases the recreational use potential of buprenorphine, and these characteristics are reflective of an ideal pharmacologic agent for the treatment of opioid dependence.

**Additional treatments**

Methadone, a full µ-opioid-receptor agonist with a complex pharmacokinetic profile, was the first opioid to receive approved labeling from the Food and Drug Administration (FDA) for the detoxification and maintenance treatment of opioid dependence.10,11 Methadone is still widely used for this purpose and considered the standard for therapeutic comparisons.11 In addition to its opioid-agonist effects, methadone has antagonist activity against N-methyl-D-aspartate receptors, which is advantageous in the treatment of neuropathic pain.12 Methadone use has been associated with a reduced tolerance for analgesia and less constipation compared with other opioids.11-13 As a full opioid-receptor agonist, methadone does have the potential for abuse and diversion.14

Another drug therapy with FDA-approved indications for the treatment of opioid dependence is naltrexone. Naltrexone is an opioid antagonist that is thought to decrease the euphoria associated with opioid use.15 Although naltrexone has little potential for abuse and diversion, its utility as monotherapy for opioid dependence is less than optimal.16 The limited efficacy of naltrexone monotherapy may be due to low rates of patient compliance and medication adherence. A newer depot formulation seeks to improve adherence to therapy, and preliminary data have shown the drug to be well tolerated.17 Another drug therapy approved for the treatment of opioid dependence is levomethadyl acetate.18 Levomethadyl acetate, a Schedule II pure opioid agonist, has a longer half-life than methadone. Although it was originally thought that the use of this drug at outpatient treatment programs might be associated with better adherence, its use fell out of favor after warnings and contraindications were added to the official labeling in 2001 (e.g., Q-T interval prolongation and cardiac arrest).18

**Legal considerations**

The ethical and legal issues associated with the maintenance treatment of opioid dependence are complex. Methadone cannot be prescribed for the treatment of opioid dependence outside of the confines of methadone clinics.10 While methadone can be prescribed for the treatment of pain in any setting, regulations restrict its use for maintenance therapy in acute care hospitals. Methadone is rarely used as first-line treatment of pain,19 in part due to the preconceived notion that methadone use is prevalent (and even favored) among substance abusers. Another deterrent to the use of methadone for pain management is its complex pharmacokinetic profile.20 Methadone has a large volume of distribution that increases its half-life.21 In addition, methadone is a Schedule II controlled substance in the United States, making long-term treatment cumbersome.

Buprenorphine is a Schedule III drug.6 The Drug Addiction Treatment Act of 2000 (DATA 2000) made it possible for physicians to...
treat opioid dependence from office-based practices with Schedule III, IV, or V opioids that have received FDA approval for that indication.\textsuperscript{22} Buprenorphine and buprenorphine–naloxone are the first drugs to meet the DATA 2000 criteria.\textsuperscript{23} To prescribe and dispense buprenorphine for the treatment of opioid dependence, physicians must meet certain qualifications and be granted a special waiver.\textsuperscript{22} However, compounded formulations of buprenorphine cannot be used to treat opioid dependence and are not subject to the DATA 2000 waiver.\textsuperscript{24}

**Literature review**

A MEDLINE search of English-language journals was conducted using the terms buprenorphine, methadone, and maintenance treatment. Results were limited to clinical trials with adults older than 19 years. Key articles with similar primary efficacy endpoints were reviewed in chronological order.

A randomized, double-blind, double-dummy parallel study was conducted with 162 outpatients seeking treatment for opioid dependence.\textsuperscript{25} Patients were stratified by age, sex, and Clinical Institute Narcotic Assessment scores and then randomized to receive either buprenorphine or methadone. Outcomes measures included retention time in treatment, urine samples negative for opioids, and failure to abstain from opioid use. The first 120 days were considered the induction or maintenance phase, followed by 49 days of gradual dosage reduction and 11 days of placebo administration. Patients were offered 30–60 minutes of optional counseling. Buprenorphine was compounded as a tincture (30% ethanol) and administered sublingually in an 8-mg dose held under the tongue for 10 minutes. After 17 weeks, the retention time in treatment for the buprenorphine-treated group was similar to that of the group receiving methadone 60 mg/day (42% versus 32%, respectively). Retention time in treatment in both groups was superior to the group receiving methadone 20 mg/day (20%, \( p < 0.01 \)). Retention rates at week 25 were also significantly different, with 30% of buprenorphine patients remaining in treatment compared with 20% in the methadone 60-mg/day group (\( p < 0.05 \)) and 6% of patients in the methadone 20-mg/day group (\( p < 0.01 \) versus buprenorphine). Only four patients needed treatment with buprenorphine 8 mg per day versus methadone 20 mg per day to observe a difference in one patient who remains in treatment for 25 weeks. Adverse effects associated with both drugs included difficulty urinating, anxiety, sedation, drowsiness, and constipation.

Ling et al.\textsuperscript{26} conducted a multi-center, randomized, double-blind, dose-ranging study of buprenorphine for the treatment of opioid dependence. Patients from 12 outpatient treatment centers were randomized (\( n = 736 \)) to receive buprenorphine 1, 4, 8, or 16 mg daily. All patients received one hour of counseling per week. Retention time in treatment, illicit opioid use (determined by urine analysis), and opioid craving were determined. Patients were also monitored for adverse drug events. The percentages of patients completing 16 weeks of treatment (\( n = 375 \)) were compared by dosage group. In the 16-mg buprenorphine group, 61% of patients completed the 16-week study, compared with 40% in the 1-mg group (\( p = 0.001 \)), 51% in the 4-mg group, and 52% in the 8-mg group (\( p = 0.019 \) compared with the 1-mg group). More patients in the 16-mg buprenorphine group contributed 13 or more consecutive negative urine samples compared with the 1-mg group (26.8% versus 8.6%, respectively) (\( p < 0.001 \)). Patients in the 8- and 16-mg groups had significantly fewer cravings at weeks 4 (\( p < 0.01 \)), 8 (\( p < 0.01 \)), and 12 (\( p = 0.04 \)) but not at week 16 (\( p = 0.15 \)). Negative results at week 16 could be attributable to a lack of statistical power, since only patients who completed the study were included in the analysis. These results suggest a positive dose–response curve for buprenorphine as measured by the percentage of patients who completed the study and the number of participants contributing 13 or more negative urine samples. While this study provides evidence for short-term treatment, it does not establish treatment efficacy for longer than 12 weeks.

A single-center, randomized, double-blind, triple-dummy trial (\( n = 220 \)) with opioid-dependent patients compared levomethadyl acetate 75–115 mg three times per week, buprenorphine 16–32 mg three times per week, methadone 60–100 mg daily, and methadone 20 mg daily.\textsuperscript{27} Buprenorphine was dispensed as a tincture for sublingual administration. There was a 2-week induction period, a maintenance period of 3–17 weeks, and a disposition period from week 18 to week 28. During dose induction (weeks 1 through 2), patients received gradually increasing doses of medication at daily clinic visits. Starting at week 3, patients were evaluated in the clinic three times per week. Patients were also provided with their study medications during these visits. Patients received three oral solutions in three different colored bottles to maintain blinding. A total of four blinded dose increases were permitted during maintenance; however, dose increases could only occur every two weeks. Primary outcome measures included patient retention, percentage of positive urine specimens, and the degree of continuous abstinence as measured by the number of consecutive opioid-free urine specimens. Buprenorphine three times per week, levomethadyl acetate three times per week, and high-dose methadone daily all led to a greater decrease
in illicit opioid use compared with low daily doses of methadone. This was measured by the percentage of patients with at least 12 consecutive negative urine samples ($p = 0.005$) and the percentage of opioid-positive urinalyses over 17 weeks ($p = 0.002$). There were significant differences in patient retention among the groups, with more patients completing the trial in the buprenorphine, levomethadyl acetate, and high-dose methadone groups versus the low-dose methadone group at week 17 ($p < 0.001$). One limitation of this study was the lack of detail about the disposition phase (weeks 18 to 28) in the methods and results sections.

Not all of the clinical trial results favored buprenorphine over methadone. A multicenter, double-blind, prospective, randomized controlled clinical trial was conducted in Switzerland with opioid-dependent patients from three outpatient clinics ($n = 58$). In this six-week study, patients were randomized to receive either methadone 30–120 mg daily or buprenorphine 4–16 mg daily. Patients were required to attend the clinic daily to receive medication. Patients that missed three or more consecutive clinic visits were excluded from the study. Dosage adjustments were made by increasing the doses of methadone by 30 mg per day and buprenorphine by 4 mg per day. Additional instructions on the frequency of dosage increases were not provided to the researchers. Patients were started on methadone 30 mg daily and buprenorphine 4 mg daily. By the end of the six-week study, the mean ± S.D. daily buprenorphine dose was 10.5 ± 3.4 mg, and the mean ± S.D. daily methadone dose was 69.8 ± 29.8 mg. Ninety percent of patients in the methadone group completed the study, compared with 56% of the buprenorphine-treated group ($p = 0.002$). The percentages of opioid-positive urinalysis results were similar between groups (62% in the buprenorphine group versus 59.5% in the methadone group) ($p = 0.759$).

A multicenter, randomized, double-blind, double-dummy trial compared the effectiveness of methadone and buprenorphine for opioid maintenance treatment over 13 weeks. Patients ($n = 405$) received either buprenorphine tablets or methadone syrup daily for the first 6 weeks and then twice the daily dose on alternate days for the duration of treatment. The maximum daily doses were 32 mg for buprenorphine and 150 mg for methadone. Patient retention, as measured by the number of patients completing the study, the time to termination of opioid use, and urinalysis results were considered primary endpoints. The number of patients who completed the study was similar between groups (59.4% for the methadone group and 50% for the buprenorphine group) ($p = 0.061$). Similarly, there was no significant difference in the percentage of opioid-positive urine samples between groups ($p = 0.262$). Time to termination of opioid use was greater for patients treated with methadone versus buprenorphine ($p = 0.037$).

Office-based treatment with the sublingual formulation of buprenorphine and buprenorphine–naloxone was studied in a randomized, double-blind, placebo-controlled trial. Patients ($n = 326$) received buprenorphine, buprenorphine–naloxone, or placebo daily in the office-based clinic. Efficacy was measured by the percentage of negative urinalysis results and the percentage of patients with self-reported cravings. For the first 4 weeks of the study, primary efficacy parameters were evaluated in a double-blind fashion. A 48-week, open-label phase study for safety followed. The percentage of negative urinalysis results increased significantly with both buprenorphine alone and buprenorphine–naloxone (17.8% and 20.7%, respectively) compared with placebo (5.8%) ($p < 0.001$ for both comparisons). Similarly, both buprenorphine formulations decreased craving for opiates when compared with placebo ($p < 0.001$ for both comparisons). The buprenorphine- and buprenorphine–naloxone-treated groups were compared with placebo, not with each other, using inferential statistics. However, when opiate-craving scores were graphed over time using descriptive statistics, the scores in both treatment groups were nearly superimposable. The percentage of negative urine samples ranged from 35.2% to 67.4% in the open-label phase.

The effects of counseling and attendance frequency at an outpatient clinic for opioid abuse were studied in 166 patients during a 24-week randomized, controlled clinical trial. Patients received either once- or thrice-weekly dispensing of buprenorphine–naloxone plus standard medical management (i.e., brief, manual-guided, medically focused counseling) or enhanced medical management (similar to standard management, but sessions were longer) plus once-weekly dispensing of buprenorphine–naloxone. This study did not detect a difference in the number of opioid-negative urine specimens ($p = 0.82$) or mean number of consecutive weeks of abstinence ($p = 0.54$) among the three groups. All three treatments resulted in decreased self-reported frequency of opioid use from baseline ($p < 0.001$).

Based on the available literature, it appears that buprenorphine, buprenorphine–naloxone, and methadone are similarly efficacious for the treatment of opioid-dependent patients. Buprenorphine–naloxone has less potential for abuse and diversion. The adverse-effect profiles for buprenorphine, buprenorphine–naloxone, and methadone are similar. Once-weekly office visits for patient evaluation and dispensing of buprenorphine seem feasible and convenient for both practitioners and patients.
Dosing and administration

The three phases of opioid maintenance treatment are induction (up to one week of treatment), stabilization (up to two months of treatment), and maintenance (two months or greater).32 Before initiating buprenorphine induction therapy for opioid dependence, patients should be in acute withdrawal or already detoxified from full opioid-agonist therapy to prevent the precipitation of opioid withdrawal symptoms.3 At treatment initiation, patients should wait at least four hours after the last dose of short-acting full opioid agonist or until early signs of opioid withdrawal ensue (i.e., yawning, sweating, lacrimation, rhinorrhea, anxiety, restlessness, insomnia, dilated pupils). Patients receiving methadone (>30 mg daily) or other extended-release opioids (e.g., morphine sulfate, oxycodone hydrochloride) may experience acute withdrawal symptoms when the first dose of buprenorphine is administered.8 Buprenorphine monotherapy is given for the first day of treatment. On the first day, the minimum dosage of buprenorphine should be used. This allows the patient to stop using other opioids without developing withdrawal symptoms, cravings, or adverse effects. On day 2, if the patient is not pregnant, a switch to buprenorphine–naloxone can be made. The patient should be evaluated for withdrawal symptoms. If the patient is experiencing such symptoms, a maximum day 2 dose of 12 mg of buprenorphine and 3 mg of naloxone should be administered. The patient should then be observed for two hours. If the withdrawal symptoms are relieved, the new daily dose of buprenorphine–naloxone has been established. If not, another 4 mg of buprenorphine and 1 mg of naloxone in tablet form should be administered up to a maximum of 16 mg of buprenorphine and 4 mg of naloxone on day 2. On subsequent days, dose increases can be continued if necessary up to 32 mg of buprenorphine–8 mg of naloxone. The recommended target dose for buprenorphine is 16 mg daily, with a range of 4–24 mg daily. This dosing regimen is based on results from three pivotal clinical trials.25-27 Dosage reductions can occur over as little as three days or a longer period, depending on the circumstances.32 Buprenorphine–naloxone is the preferred treatment for opioid maintenance therapy, since the presence of naloxone, a pure narcotic antagonist, deters patients from dissolving the tablet and injecting the drug. Clinicians can refer to the federal clinical guidelines for using buprenorphine to treat opioid addiction for detailed information on special populations, such as adolescents, the elderly, and patients with concurrent mental disorders or pain.32

Policy and procedure

DATA 2000 enables qualifying physicians to receive a waiver from the special registration requirements in the Narcotic Addict Treatment Act (NATA) of 1974 (and its enabling regulations that govern opioid treatment programs) to prescribe or dispense Schedule III, IV, and V narcotics for the treatment of opioid addiction in office-based and other clinical settings if those medications have been approved by FDA for use in addiction treatment.32 Taken literally, this can pose problems for health-system pharmacists. How does a pharmacist verify that a physician meets “qualifying requirements”? According to the Substance Abuse and Mental Health Services Administration (SAMHSA), neither the Controlled Substances Act (as amended in DATA 2000) nor Drug Enforcement Administration (DEA) implementing regulations (21 CFR 1306.07(c)) impose limitations on a physician treating patients with a drug like buprenorphine as an incidental adjunct to medical or surgical conditions other than opioid addiction. Thus, a patient with opioid addiction who is admitted to a hospital for a primary medical problem other than opioid addiction (e.g., childbirth, myocardial infarction) may be administered opioid agonists (e.g., methadone, buprenorphine) to prevent opioid withdrawal that would complicate the primary medical problem. The physician does not have to work in a methadone clinic, and a DATA 2000 waiver is not required to prescribe or dispense either buprenorphine or methadone for hospitalized patients receiving treatment for an acute medical condition. In this instance, a pharmacist does not need to routinely verify the physician’s intent for writing the inpatient order for methadone or buprenorphine. Both methadone and buprenorphine may be ordered for any legitimate medical reason, such as for the treatment of pain.23 It is good practice for the admitting physician to consult with the patient’s addiction treatment provider, when possible, to obtain the patient’s treatment history.

The procedure for dispensing buprenorphine differs in the outpatient setting. A physician must be qualified under DATA 2000 to prescribe sublingual buprenorphine and buprenorphine–naloxone. Any prescription for buprenorphine or buprenorphine–naloxone must contain the physician’s DEA number, which qualifies the physician to prescribe these medications. If the prescription does not contain a unique DEA number, the pharmacist must verify that the prescribing physician has a valid waiver to prescribe the aforementioned medications by (1) checking the SAMHSA physician locator (buprenorphine.samhsa.gov/bwns_locator/index.html), (2) calling SAMHSA (1-866-287-2728), or (3) contacting the prescribing physician directly and asking the physician to fax his or her DEA registration certificate. If the physician is not registered, the pharmacist must contact the prescribing physician and
ask if he or she has notified SAMHSA about his or her desire to prescribe buprenorphine and buprenorphine–naloxone. The prescription can be dispensed if the physician has submitted, in good faith, a written notification to SAMHSA for permission to dispense controlled narcotics for maintenance or detoxification treatment.

**Conclusion**

Buprenorphine is an attractive option for the pharmacologic treatment of opioid dependence. Compliance and adherence to buprenorphine therapy for opioid-dependent patients remain clinical issues. Future research efforts should focus on improving compliance and adherence to buprenorphine therapy.

**References**