ABSTRACT

As a result of the approval of sublingual buprenorphine and buprenorphine/naloxone tablets, as well as the congressional approval of the Drug Addiction Treatment Act (DATA 2000), scheduled agents may now be prescribed by private physicians and dispensed at pharmacies for the treatment of opiate dependence. Prior to this, pharmacologic treatment was generally limited to methadone, which can only be distributed in specialized, limited clinics as a result of its Schedule II status. Buprenorphine, a Schedule III partial opioid agonist, decreases opioid craving and withdrawal, but differs from full µ-opioid agonists (eg, methadone and morphine) in that it generally causes less sedation, has a “ceiling effect” on analgesia and respiratory depression, and has a lower potential for abuse and diversion (especially when combined with the opioid antagonist naloxone). This article includes a therapeutic profile of buprenorphine-based therapy and the specific requirements from the Substance Abuse and Mental Health Services Administration for prescribing and dispensing buprenorphine products for opiate dependence. Physicians must meet certain DATA 2000 requirements to receive formal permission to prescribe buprenorphine for opiate dependence and pharmacists, while not required to have any special credentials, are responsible for complying with several associated federal regulations and verifying that buprenorphine prescriptions are written by physicians who are in compliance with DATA 2000.

(REVIEW MEDICATION-ASSISTED TREATMENT FOR OPIOID DEPENDENCE: ADHERING TO REQUIREMENTS FOR BUPRENORPHINE DISPENSING

Walter L. Fitzgerald, Jr, MS, JD, DPh*

The 2002 approval of sublingual buprenorphine and buprenorphine/naloxone tablets for the treatment of opiate dependence represents the first time that a Schedule III, IV, or V agent became available for physician office-based treatment of opiate dependence. Prior to that, treatment for opiate dependence could only be dispensed under the Schedule II designation and in a very limited number of clinics that specialized in opiate dependence (eg, methadone clinics). Because buprenorphine is subject to less restrictive controls than Schedule II controlled substances, patients have greater access to needed treatment; however, pharmacists now face the challenges of dispensing controlled substances for opiate dependence treatment.

As a partial agonist at the µ receptor and an antagonist at the κ receptor, buprenorphine decreases opioid craving and withdrawal, but differs from full µ-opioid agonists (eg, methadone and morphine) in that it generally causes less sedation, has a “ceiling effect” on analgesia and respiratory depression, and has a lower potential for abuse and diversion (especially when combined with the opioid antagonist naloxone). The implications of buprenorphine’s κ receptor antagonism are not well understood, but may be attributed to the agent’s mild antidepressant effects.

In the treatment of the opioid-dependent patient, buprenorphine-based therapy involves 3 phases: induction, stabilization, and maintenance. Induction is the first stage and is focused on helping patients begin the process of switching from the opioid of abuse to buprenorphine. According to consensus guidelines on the use of buprenorphine in the treatment of opioid dependency, the goal of the induction phase is to find the minimum dose of buprenorphine at which the patient discontinues or minimizes use of other opioids, without experiencing withdrawal symptoms, significant side effects, and craving for the drug of abuse. The buprenorphine/naloxone combination

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is recommended for induction treatment (and for stabilization and maintenance), with initial doses being administered as observed treatment (in the physician’s presence) and further doses provided via prescription. To minimize risks of precipitated withdrawal, patients who are transferring from long-acting opioids (eg, methadone and sustained-release morphine or oxycodone) to buprenorphine should be inducted using sublingual buprenorphine, but switched to buprenorphine/naloxone tablets when feasibly possible. Pregnant women should be inducted and maintained on buprenorphine monotherapy, because naloxone may precipitate opioid withdrawal in the mother and fetus. The stabilization phase begins when a patient is experiencing no withdrawal symptoms, minimal or no side effects, and no longer has uncontrollable cravings for opioids. The maintenance phase is the longest period that a patient is on buprenorphine, and involves indefinite treatment and a focus on issues that may have contributed to the patient’s addiction.

The value of buprenorphine in pharmacologic management of opioid dependence is largely based on its comparison to methadone, the current gold standard for this condition. Trials comparing buprenorphine to placebo and methadone found that although buprenorphine is effective in the treatment of heroin dependence, it appears to be inferior to methadone in retaining patients in treatment and suppressing heroin use. Buprenorphine is safer than methadone in overdose situations due to its ceiling effect, but it may still cause significant respiratory depression, particularly when administered intravenously. In fact, several deaths have been associated with intentional misuse of buprenorphine intravenously, usually in combination with other depressants, such as benzodiazepines, alcohol, and other opioids. Although chronic administration of buprenorphine may still result in dependence, the withdrawal syndrome is milder and may have a delayed onset, compared to that seen with full opioid agonists. The buprenorphine/naloxone combination product is highly likely to produce marked and intense withdrawal if it is misused parenterally by opioid-dependent patients.

The most notable advantage of using buprenorphine is its relative accessibility. Buprenorphine may be prescribed by private physicians and dispensed at pharmacies, whereas methadone can only be distributed through specialized clinics, limiting its use to less than 15% of individuals with opioid dependence. The wider accessibility of buprenorphine is due to its Schedule III designation and the congressional approval of the Drug Addiction Treatment Act of 2000 (DATA 2000).

**Certification Requirements from SAMHSA**

The DATA 2000 enables qualifying physicians to receive a waiver from the special registration requirements in the Controlled Substances Act for the provision of medication-assisted treatment for opioid dependency. This waiver allows physicians to provide medication-assisted treatment with US Food and Drug Administration-approved Schedule III, IV, or V opioid medications, but they must meet specific criteria to qualify for this waiver and they must notify the Center for Substance Abuse Treatment (CSAT, a component of the Substance Abuse and Mental Health Services Administration [SAMHSA]) of their intent to begin dispensing or prescribing this treatment. An official Notification of Intent must be submitted, which contains information on the physician’s qualifying credentials, additional addiction medicine-related certifications, and an agreement that the physician will not have more than 30 patients on opioid dependency therapy at any one time during the first year. One year after the date on which a physician submitted the initial notification, the physician may submit a second notification of the need and intent to treat up to 100 patients. Once all the criteria for waiver are verified, the US Drug Enforcement Administration (DEA) assigns the physician a special identification (ID) number (DATA 2000 waiver ID number, sometimes referred to as the “X” number), which must be included on all buprenorphine prescriptions for opioid dependency therapy, together with the physician’s regular DEA registration number. Physician assistants and nurse practitioners are not permitted to prescribe buprenorphine for treatment of opioid dependency, even in states that allow them to prescribe Schedule II, III, IV, or V medications.

In dispensing buprenorphine or buprenorphine/naloxone for opioid dependence, pharmacists are not required to have any special credentials; however, they must be aware of regulations pertaining to both DATA 2000 and the dispensing of controlled substances within their state. Pharmacists are responsible for verifying that buprenorphine prescriptions are written by physicians who are in compliance with the aforementioned
provisions of DATA 2000 and therefore, they must ensure that both the DEA number and the DATA 2000 waiver ID number are included on the prescription. If the prescription is telephoned to the pharmacy, the pharmacist must obtain both of these numbers for the prescription record. In cases in which a written prescription for buprenorphine is missing the DATA 2000 waiver ID number, the pharmacist is required to clarify whether the prescribing physician has made the appropriate notification to SAMHSA. A physician may write a prescription before the waiver ID number has been issued, provided that the physician has notified SAMHSA of his or her intention to immediately begin treating a patient. Pharmacists who need to verify whether physicians have valid waivers may call 1-866-BUP-CSAT or e-mail info@buprenorphine.samhsa.gov.

Induction doses of buprenorphine and buprenorphine/naloxone should be given in the physician’s office, and although most physicians maintain an office supply of medication, some who lack a supply will write prescriptions for a patient’s induction doses and may call or fax ahead to a pharmacy to ensure that the medication will be ready in advance of the patient’s arrival. Pharmacists may dispense these prescriptions, but they should make certain that the patient understands that he or she must return to the physician’s office for supervised administration of medication. Because it may take several days to complete the induction process, patients may be returning to the pharmacy repeatedly at the very beginning of treatment. Patients may present with a coupon covering the first day’s dose, which should be submitted for reimbursement.

Federal regulations concerning confidentiality of substance abuse treatment records and the privacy of health records may have an impact on the dispensing of buprenorphine therapy. Physicians who elect to phone or fax in prescriptions are technically disclosing patient information; therefore, it is particularly important that they ask patients to sign a release-of-information form. When prescriptions are transmitted by the physician, there are also prohibitions on further redisclosure of patient identifying information by the pharmacist, unless a signed patient consent is obtained by the pharmacy. For patients who directly deliver a prescription to a pharmacist (without com-

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<th>Table 1. Physician Requirements for DATA 2000 Waiver</th>
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<td>To qualify for a waiver under DATA 2000 a licensed physician (MD or DO) must meet any 1 or more of the following criteria:</td>
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<td>• The physician holds a subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties.</td>
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<tr>
<td>• The physician holds an addiction certification from the American Society of Addiction Medicine.</td>
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<tr>
<td>• The physician holds a subspecialty board certification in addiction medicine from the American Osteopathic Association.</td>
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<td>• The physician has, with respect to the treatment and management of opioid-addicted patients, completed not &gt;8 hours of training (through classroom situations, seminars at professional society meetings, electronic communications, or otherwise) that is provided by the American Society of Addiction Medicine, the American Academy of Addiction Psychiatry, the American Medical Association, the American Osteopathic Association, the American Psychiatric Association, or any other organization that the Secretary determines is appropriate for purposes of this subclause.</td>
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<td>• The physician has participated as an investigator in 1 or more clinical trials leading to the approval of a narcotic drug in Schedule III, IV, or V for maintenance or detoxification treatment, as demonstrated by a statement submitted to the Secretary by the sponsor of such approved drug.</td>
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<td>• The physician has such other training or experience as the State medical licensing board (of the State in which the physician will provide maintenance or detoxification treatment) considers to demonstrate the ability of the physician to treat and manage opioid-addicted patients.</td>
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<td>• The physician has such other training or experience as the Secretary considers to demonstrate the ability of the physician to treat and manage opioid-addicted patients. Any criteria of the Secretary under this subclause shall be established by regulation. Any such criteria are effective only for 3 years after the date on which the criteria are promulgated, but may be extended for such additional discrete 3-year periods as the Secretary considers appropriate for purposes of this subclause. Such an extension of criteria may only be effectuated through a statement published in the Federal Register by the Secretary during the 30-day period preceding the end of the 3-year period involved.</td>
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munication between pharmacist and physician), confidentiality of substance abuse treatment records does not apply.

Although buprenorphine has a lower potential for abuse and diversion than other opioids, there have been reports of buprenorphine products being diverted, misused (rarely resulting in death), and injected. In general, rates of buprenorphine abuse/diversion appear to have stabilized or decreased since 2006; however, recent reports describe increasing levels of diversion/abuse in Baltimore, Maryland, Massachusetts, and other parts of the United States. The effects of parenteral abuse of buprenorphine or buprenorphine/naloxone tablets differ, depending on the clinical scenario. In individuals who are physically dependent on illicit opioids (eg, heroin) or in those taking therapeutic full agonist opioids (eg, oxycodone and methadone), parenteral use of buprenorphine/naloxone (more so than buprenorphine alone) could result in precipitated withdrawal. Those receiving prescription buprenorphine or buprenorphine/naloxone tablets who dissolve and inject their own medication could experience an agonist effect from buprenorphine, but no antagonist effect from naloxone, because large doses of opioid antagonists are required to precipitate withdrawal in buprenorphine-maintained patients. In those who abuse opioids but who are not physically dependent on them, sublingual or injected use of either buprenorphine product could produce opioid agonist effects (but mild euphoria), with no precipitated withdrawal.

Both pharmacists and physicians share legal responsibility for the legitimacy of a prescription. But even if a pharmacist determines that an individual prescription is legal, there are other ways by which patients may attempt to divert prescriptions. An opioid user, for example, may be treated by 2 or more qualified physicians and may present to a pharmacy with multiple prescriptions for buprenorphine. Pharmacists should refuse to dispense the second prescription and must notify both prescribing physicians. Keeping in mind the limitation on the number of buprenorphine-treated patients per physician, pharmacists who notice an abnormally high number of new prescriptions from a single physician should suspect the possibility of fraudulent prescriptions.

**RECORDKEEPING AND STORAGE REQUIREMENTS**

As Schedule III controlled substances, both buprenorphine and buprenorphine/naloxone are subject to federal regulations regarding recordkeeping, inventory, proper dispensing, and disposal. Every pharmacy is required to maintain complete and accurate records on a current basis for every controlled substance purchased, received, distributed, dispensed, or otherwise disposed of. Unless state law prescribes a longer period, all records of controlled substances must be maintained for 2 years, pursuant to federal law. Records (Table 2) and inventories of Schedule III, IV, and V controlled substances must be maintained either separately from all other records or in another way that allows the required information to be readily retrieved (Table 3). Pharmacists should check with their individual state authorities for any additional state-specific requirements regarding dispensing and recordkeeping of controlled substances.

**PHARMACY COUNSELING ON BUPRENORPHINE THERAPY**

Overcoming any negative views of opiate-dependent patients is critical to providing effective and objec-

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**Table 2. Records of Controlled Substances that Must Be Maintained**

| 1. Official Order Forms (DEA Form-222) * |
| 2. Power of Attorney authorization to sign Order Forms |
| 3. Receipts and invoices for Schedule II, III, IV, and V controlled substances, as well as “threshold quantities”† of List I chemicals |
| 4. All inventory records of controlled substances, including the initial and biennial inventories |
| 5. Records of controlled substances distributed or dispensed (ie, prescriptions) and threshold amounts of List I chemicals distributed |
| 6. Report of Theft or Loss (DEA Form-106) |
| 7. Inventory of Drugs Surrendered for Disposal (DEA Form-41) |
| 8. Records of transfers of controlled substances between pharmacies |
| 9. DEA registration certificate |

* DEA’s Official Order Forms are the required records of receipt and sale for Schedule II controlled substances.

† The quantity of a particular chemical, above which recordkeeping and other control provisions of the CSA apply. 

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The changing profile of heroin users and the phenomenon of abuse of oxycodone hydrochloride controlled-release have demonstrated that just about anyone can suffer from opioid dependency, and thus, the stereotypical view of the addicted patient should be re-evaluated. Because drug dependency is a sensitive topic, pharmacists should have access to a private area when counseling patients about buprenorphine therapy and should be aware that patients may appear irritable, because they may be undergoing withdrawal (depending on the phase of their treatment). Patients should be cautioned that a serious overdose may occur if benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol are taken concurrently with buprenorphine or buprenorphine/naloxone. They should also be informed about buprenorphine-related side effects, which include headache (most common), withdrawal syndrome, pain, nausea, insomnia, abdominal and back pain, constipation, infection, asthenia, rhinitis, anxiety, and depression. Patients should be told to abstain from performing any potentially dangerous tasks that require alertness (eg, driving or operating machinery) because buprenorphine may impair mental or physical abilities. When possible, the patient’s family members should be informed that, in the event of an emergency, medical staff should be made aware that the patient is physically dependent on opioids and is treated with buprenorphine or buprenorphine/naloxone.

CONCLUSIONS

The availability of buprenorphine-based treatment for opioid dependence has provided the medical community, including community pharmacists, with the opportunity to reach more opioid-dependent patients. Opioid dependence treatment is no longer confined to the limited number of patients seen in specialized clinics, but to a significantly larger percentage of patients who may be treated in private practice. In 2007 alone, over 2 million buprenorphine prescriptions were issued to 300,000 patients and almost 14,000 physicians have been authorized to prescribe buprenorphine for opioid dependence treatment. But in order to ensure proper use and continued accessibility of buprenorphine, it is essential for both prescribers and pharmacists to be fully aware of, and comply with, the regulations governing the distribution of this controlled substance.

REFERENCES

3. Wesson DR. Buprenorphine in the treatment of opiate depen-