Sublingual and Transmucosal Buprenorphine for Opioid Use Disorder: Review and Update

This Advisory reviews current information on the use of sublingual and transmucosal buprenorphine for the medication-assisted treatment of opioid use disorder. The intended audiences are prescribing physicians, other healthcare professionals, and healthcare policymakers. Topics include new formulations of buprenorphine, the effectiveness and safety of buprenorphine treatment, contraindications and cautions (including medication interactions), informed consent and treatment agreements, treatment monitoring, and indications of diversion and misuse.

Opioid misuse remains a significant problem in the United States. According to the 2014 National Survey on Drug Use and Health (NSDUH), 914,000 people ages 12 or older used heroin in the past year; 586,000 had heroin use disorder.¹ Nonmedical use of prescription pain relievers continues to be more widespread than heroin use—the NSDUH estimates that 4.3 million people currently engage in nonmedical use of pain relievers and that 1.9 million people have a pain reliever use disorder.¹

Mortality and morbidity are significant concerns. Hospitalizations involving opioid overdose among adults increased more than 150 percent between 1993 and 2012.² The National Center for Health Statistics reports that although deaths from opioid analgesics have leveled off in recent years, 16,235 people died of an opioid analgesic-related overdose in 2013.³ Heroin deaths nearly tripled between 2010 and 2013, increasing to 8,257 deaths in 2013.³

Medication-assisted treatment (MAT) is an important part of an effective response to opioid use disorder.⁴ MAT, “including opioid treatment programs, combines behavioral therapy and medications to treat substance use disorders.”⁵ Products approved by the Food and Drug Administration (FDA) for use in treating opioid use disorder include methadone, buprenorphine (or buprenorphine with naloxone), and naltrexone.* These medications have been shown to be effective, safe, and cost-effective treatments when used and monitored properly.⁷

MAT, particularly with opioid agonist medications, has been found to reduce morbidity and mortality, decrease overdose deaths, reduce transmission of infectious disease, increase treatment retention, improve social functioning, and reduce criminal activity.³ National and international health organizations, such as the American Society of Addiction Medicine (ASAM)⁸ and the World Health Organization,⁹ consider MAT an evidence-based best practice for treating opioid use disorder. A study¹⁰ involving needle exchange program participants suggests that those who misuse opioids are both aware of and interested in buprenorphine therapy. However, despite governmental and professional endorsement of MAT, and potential patients’ apparent interest in it, there remains a significant gap between the need for and the availability of this treatment.¹⁰,¹¹

Is MAT “Recovery?”

Recovery status is best defined by factors other than medication status. Neither medication-assisted treatment of opioid addiction nor the cessation of such treatment by itself constitutes recovery. Recovery status instead hinges on broader achievements in health and social functioning—with or without medication support.

—Recovery experts A. Thomas McLellan and William White⁶

* More specifically, methadone and buprenorphine (or buprenorphine/ naloxone) are approved to treat opioid dependence; extended-release injectable naltrexone is approved for prevention of relapse to opioid use.
Online DATA 2000 Waiver-Qualifying Training Resource

www.samhsa.gov/medication-assisted-treatment/training-resources/buprenorphine-physician-training

The Drug Addiction Treatment Act of 2000 (DATA 2000) enables qualifying physicians to receive a waiver from the special registration requirements in the Controlled Substances Act in order to prescribe an opioid agonist for the medication-assisted treatment of opioid use disorder. The waiver applies to Schedule III, IV, or V medications specifically approved by FDA for the treatment of opioid use disorder. Buprenorphine-containing products are currently the only pharmacotherapy covered by DATA 2000. To obtain a waiver, a physician must submit to the Substance Abuse and Mental Health Services Administration (SAMHSA) a notice of intent to prescribe buprenorphine. Detailed information on physician waiver qualifications can be found through SAMHSA’s Buprenorphine Waiver Management Web page (www.samhsa.gov/medication-assisted-treatment/buprenorphine-waiver-management). To qualify, a physician must hold a valid medical license, be registered with the Drug Enforcement Administration, be capable of referring patients to counseling and other services, and meet at least one of the following criteria:

- Hold a subspecialty board certification in addiction medicine or addiction psychiatry
- Have completed not less than 8 hours of approved training
- Have participated as an investigator in one or more clinical trials leading to the approval of a narcotic drug in Schedules III, IV, or V for maintenance or detoxification treatment
- Have experience or training deemed by his or her state medical licensing board or the U.S. Department of Health and Human Services to demonstrate the ability to treat and manage opioid dependence

Buprenorphine Products

Buprenorphine is available either alone (the mono-product) or in combination with naloxone (the combination product). Naloxone is an opioid antagonist with low bioavailability when taken orally or sublingually; when the combination product is taken as directed, naloxone has little effect on the action and efficacy of buprenorphine.13 However, if the combination product is injected, the naloxone produces significant attenuation of buprenorphine’s effects and may precipitate acute withdrawal.14 The combination product is designed to be less subject to diversion and injection misuse than the mono-product. For this reason, the combination product is the preferred formulation for all patients, with the exception of pregnant women15 and those with a demonstrated allergy to naloxone.

Buprenorphine, both as a mono- and as a combination product, has long been available in sublingual tablet form. Newer formulations include a soluble buprenorphine/naloxone film for sublingual or buccal use. The films dissolve more quickly than tablets, an advantage when monitored dose ingestion is indicated.16

Two new formulations (Zubsolv sublingual tablets and Bunavail buccal film) provide higher bioavailability of buprenorphine than other formulations. Higher bioavailability means that more buprenorphine enters the bloodstream, allowing for lower doses. For example, one Bunavail 4.2 mg/0.7 mg buccal film provides buprenorphine exposure equivalent to one Suboxone 8 mg/2 mg sublingual tablet,17 one Zubsolv 5.7 mg/1.4 mg sublingual tablet provides buprenorphine exposure equivalent to one Suboxone 8 mg/2 mg sublingual tablet.18

Exhibit 1 provides a list of available buprenorphine products. As the safety and efficacy of each of these products are considered equivalent, practitioners should use the most cost-effective formulation that is most appropriate for the patient. Medicare Part D and many state Medicaid programs cover buprenorphine products.

Review: Effectiveness and Safety of Buprenorphine

Research has shown buprenorphine to be an effective pharmacotherapy for treating opioid use disorder. Clinical trials have demonstrated the efficacy of buprenorphine through patient retention and reductions in opioid-positive drug test results. For example, a Cochrane review19 evaluated the effectiveness of buprenorphine maintenance with various formulations of buprenorphine and buprenorphine/naloxone compared with placebo and with methadone maintenance treatment. The authors examined 31 randomized clinical trials (involving 5,430 participants). They found that, compared with placebo, buprenorphine was effective at retaining patients in treatment at any dose above 2 mg, and was effective at...
Suppressing illicit opioid use at doses equivalent to 16 mg or greater. However, buprenorphine was not as effective as methadone at retaining patients in treatment.

Maintenance treatment with buprenorphine is more effective than short-term buprenorphine treatment followed by medication tapering. A recent study examined use of buprenorphine to treat patients dependent on prescription opioids. The study compared use of a buprenorphine taper (6 weeks stabilization plus a 3-week taper) with ongoing buprenorphine maintenance and found that maintenance was superior to tapering in both patient retention and rate of relapse to opioid use. Earlier, Weiss et al. found that patients being treated for prescription opioid dependence were most successful at reducing opioid use while receiving buprenorphine (with naloxone) treatment. Even after 12 weeks of medication treatment with concurrent counseling, tapering was associated with very high relapse rates (higher than 90 percent, 8 weeks post-taper).

Studies have also assessed the efficacy of treatment with buprenorphine products in primary care settings and have found that buprenorphine can be safely and effectively used in these settings.

One characteristic of buprenorphine, a partial mu opioid agonist, is that it is safer than full agonists (e.g., methadone) because of its relatively poor bioavailability and its ceiling effect. The ceiling effect means that as the buprenorphine dose increases, its effects (including respiratory depression) increase but only to a point. A plateau is reached at moderate doses, meaning the effects no longer increase even as the dose is increased. This ceiling effect also means that buprenorphine carries a lower risk of misuse, dependence, and side effects than full agonists. However, there is still some risk of overdose, particularly if the patient concurrently uses another opioid, benzodiazepines, alcohol, sedatives, or certain medications that interact with buprenorphine (see Exhibits 2–4).

Overdose prevention education and a prescription for naloxone (in case of overdose) should be considered for all patients considering or receiving buprenorphine; these should be provided again prior to discontinuation of MAT.
### Exhibit 2. Buprenorphine and Buprenorphine/Naloxone Contraindications and Cautions

<table>
<thead>
<tr>
<th>Contraindication/Caution</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demonstrated allergy/hypersensitivity to buprenorphine (or naloxone)</td>
<td>Do not prescribe. (^{22})</td>
</tr>
<tr>
<td>Compromised respiratory function (e.g., chronic obstructive pulmonary disease, decreased respiratory reserve, hypoxia, hypercapnia [abnormally elevated carbon dioxide levels in the blood], preexisting respiratory depression)</td>
<td>Prescribe with caution; monitor closely. Warn patients about the risk of using benzodiazepines or other depressants while taking buprenorphine. (^{22})</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td><strong>Mild impairment (Child-Pugh score of 5–6):</strong> (^{30}) No dose adjustment needed. <strong>Moderate impairment (Child-Pugh score of 7–9):</strong> (^{30}) Combination products are not recommended for induction with patients with moderate hepatic impairment as they may precipitate withdrawal. (^*) However, combination products may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have been inducted with a mono-product; (^{23,29}) patients should be carefully monitored for signs and symptoms of buprenorphine toxicity or overdose. (^{22}) Also consider the possibility of naloxone interfering with buprenorphine’s efficacy. (^{23,26}) <strong>Severe impairment (Child-Pugh score of 10–15):</strong> (^{30}) Do not use the combination product. With a mono-product, consider reducing the starting and titration doses by half compared with patients with normal liver function; monitor for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. (^{22})</td>
</tr>
</tbody>
</table>

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* Moderate to severe hepatic impairment results in reduced clearance of naloxone much greater than clearance of buprenorphine. Nasser et al. \(^{29}\) found that moderate hepatic impairment led to 2 to 3 times the exposure (compared with subjects with no or mild impairment) for both naloxone and buprenorphine. In subjects with severe hepatic impairment, buprenorphine exposure was also 2 to 3 times higher; however, naloxone exposure increased more than tenfold.

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Exhibit 2 provides contraindications and cautions for use of buprenorphine.

Patients dependent on opioids frequently have co-occurring medical conditions. Rates of HIV infection and hepatitis C virus (HCV) infection are particularly high in people who inject drugs. There appear to be fewer potential interactions between buprenorphine and antiretrovirals (ARVs) than between methadone and ARVs. One explanation is that because buprenorphine is absorbed sublingually (or buccally in newer formulations), it is less competitive with ARVs for absorption in the gastrointestinal tract. \(^{31}\)

There appear to be no significant interactions between buprenorphine and most HCV medications. In particular, most direct-acting antivirals approved for the treatment of HCV do not have clinically significant interactions with buprenorphine. \(^{32}\) Exhibit 3 lists potential interactions between buprenorphine and HIV medications, specifically ARVs. Exhibit 4 lists potential interactions between buprenorphine and medications in several drug classes.

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Patients should be closely monitored for cognitive effects and sedation when therapies are initiated or discontinued or dosage is changed. For the most current product-specific information, review the product label (Section 7, Drug Interactions) through Drugs@FDA—www.accessdata.fda.gov/scripts/cder/drugsatfda.
Bruce et al.³⁴ note some caveats to relying on the current research regarding interactions between buprenorphine and other medications:

- Many studies have small numbers of patients and may not be generalizable to all populations.
- Studies typically exclude patients with many of the disorders that people with HIV, HCV, or both commonly experience (e.g., hepatic and renal impairments).
- Most studies focus on single drug–drug interactions; however, a patient is frequently taking several medications concurrently, the combination of which may not have been studied.
- The need for and level of dose adjustments may vary widely between patients.
- The practitioner must remain alert to the possibility of a medication interaction even when existing data do not support such an interaction.
- When an interaction is likely (e.g., with atazanavir, central nervous system depressants, CYP3A4 inhibitors), the patient should be clinically monitored daily; practitioners should keep in mind that the timing of symptom development is variable and depends on a variety of factors.

### Exhibit 3. Potential Interactions Between Buprenorphine and HIV Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Type</th>
<th>Potential Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>Protease inhibitor (PI)</td>
<td>Increased buprenorphine concentrations. Some patients may experience cognitive impairment²²,³³ or oversedation,³³,³⁴ Slower titration or dose reduction of buprenorphine may be warranted.²²,³⁴</td>
</tr>
<tr>
<td>Darunavir-ritonavir</td>
<td>PI</td>
<td>Some pharmacokinetic (PK) effect; dose adjustments unlikely to be needed but clinical monitoring is recommended.³⁵</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Nonnucleoside reverse transcriptase inhibitor (NNRTI)</td>
<td>Increased buprenorphine concentrations, but no clinically significant effect. Dose adjustments unlikely to be needed. However, use with caution, as long-term effects (more than 7 days) are unknown.³⁴,³⁶</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>NNRTI</td>
<td>Some PK effect; dose adjustments unlikely to be needed.³⁶</td>
</tr>
<tr>
<td>Elvitegravir (with cobicistat)</td>
<td>Integrase inhibitor</td>
<td>Some PK effect; no dose adjustments needed.³⁷</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>NNRTI</td>
<td>Some PK effect; no dose adjustments needed.³⁸</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>PI</td>
<td>Some PK effect; no dose adjustments needed.³⁹</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>PI</td>
<td>Some PK effect; no dose adjustments needed.⁴⁰</td>
</tr>
</tbody>
</table>

### Buprenorphine Induction and Stabilization/Maintenance

“The goal of induction and stabilization is to find the lowest dose of buprenorphine at which the patient discontinues or markedly reduces the use of other opioids without experiencing withdrawal symptoms, significant side effects, or uncontrollable craving for the [opioid] of abuse.”⁴¹


Following treatment induction and stabilization is the maintenance phase. The maintenance dose of Suboxone sublingual film is generally in the range of 4 mg/1 mg buprenorphine/naloxone to 24 mg/6 mg buprenorphine/naloxone per day, with a target of 16 mg/4 mg as a single daily dose²³ (see Exhibit 1 for the recommended maintenance target dosages and ranges for other formulations). The optimal maintenance dose of
buprenorphine products will vary from patient to patient. Doses should be incrementally adjusted to a level that holds the patient in treatment and suppresses opioid withdrawal effects. Dosages higher than 24 mg/6 mg daily of buprenorphine/naloxone have not been demonstrated to provide a clinical advantage.23

### Informed Consent and Treatment Agreements

Informed consent and treatment agreements can clarify expectations of both practitioner and patient and provide a structure for effective monitoring.

### Informed Consent

Practitioners need to discuss the risks and benefits of the treatments available (including other MAT and non-MAT options) for opioid use disorder and should also explain:41
- The difference between addiction and physical dependence and why MAT is not simply “switching one addiction for another.”
- The patient’s risk of relapse with and without MAT.
- The estimated duration of treatment with buprenorphine.
- Reasonable expectations for treatment results.
- The importance of counseling and peer support.

A written informed consent should be reviewed and signed by both the practitioner and the patient.
Treatment Agreements

Treatment agreements should also be written and signed, and updated periodically as treatment progresses. Typical provisions of treatment agreements include:41

- Acknowledgment by the patient of the potential benefits and risks of treatment and the goals of treatment.
- Identification of one physician and one pharmacy to provide the patient’s opioid prescriptions (for MAT or for other conditions).
- Authorization for the physician and staff to communicate with other named providers of care and, as needed, with significant others.†
- Agreement to participate in other treatments or consultations, including counseling, as directed.
- Acknowledgment that the physician will be using the state’s prescription drug monitoring program (PDMP; see Monitoring Strategies section, below).
- Agreement to avoid all illicit use of substances.
- Agreement to undergo toxicology screens and pill/film counts upon request.
- Procedures to obtain prescriptions and refills, including exclusion of early refills.
- Expected frequency of office visits.

Patients should be warned of the significant risk all forms of buprenorphine pose to children. Even very brief exposure to buprenorphine formulations can lead to sedation, respiratory depression, cerebral anoxia, and death.45 Because buprenorphine is absorbed through the lining of the mouth, a child does not need to swallow or chew the medication to have significant exposure, even if the medication is quickly taken out of the child’s mouth. A child exposed to buprenorphine in any way, even for a few seconds, requires immediate medical attention and hospital observation for 24 hours.45 Practitioners should include child-safety recommendations in treatment agreements, such as:45

- Keep medications in a location inaccessible to children (e.g., a locked or otherwise secure cabinet).
- Never store buprenorphine in anything other than a child-resistant container.
- If a child is exposed, or is thought to have been exposed, to buprenorphine, call 911 immediately.

- Remember that sharing your medication with others could put someone else’s household members at risk.

Behavioral Treatment

Concurrent behavioral treatment is a critical element of MAT. The ASAM National Practice Guideline recommends that prescribers offer patients behavioral treatment early in their buprenorphine treatment.8 The guideline recommends that behavioral treatment should include, at minimum:8

- Assessment of psychosocial needs.
- Supportive individual or group counseling (or both).
- Linkages to existing family support systems.
- Referrals to community-based services.
- Cognitive–behavioral therapies.
- Contingency management.
- Relapse prevention.
- Motivational interviewing.

Mutual-help programs may also benefit patients but are not a substitute for behavioral therapy.

Research shows that when treating SUDs [substance use disorders], a combination of medication and behavioral therapies is the most effective. Behavioral therapies help patients engage in the treatment process, modify their attitudes and behaviors related to drug and alcohol abuse, and increase healthy life skills. These treatments can also enhance the effectiveness of medications and help people stay in treatment longer.46
Information about incorporating behavioral treatment can be found at:
www.pcssmat.org/new-online-module-counseling-mat-better-outcomes-with-integrated-care

Monitoring of Adherence and Response to Treatment

Effective monitoring of adherence and response to treatment can increase the likelihood of positive clinical outcomes and reduce the possibility of diversion.

Monitoring Strategies

Monitoring medication adherence in office-based settings should include unannounced urine toxicology screening, pill/film counts, and observed ingestion. State PDMPs should also be used.

Urine toxicology

Urine testing can be used to determine whether the patient is taking the prescribed buprenorphine and to test for illicit substance use. Point-of-service dipstick tests and laboratory testing may both be useful. The Providers’ Clinical Support System for Medication Assisted Treatment suggests these strategies to minimize patients’ ability to tamper with urine samples:

- Don’t allow patients to take purses, backpacks, and so on into the bathroom.
- Turn off running water and color the toilet water to eliminate possible dilution.
- Monitor the bathroom door so that only the patient can go in.
- Test the temperature, specific gravity, and creatinine of the urine immediately after it has been voided.

It is important to remember that urine toxicology is only a tool and should not be relied upon exclusively for clinical decision making.

Pill/film counts

The practitioner should have the patient bring his or her medication container to each appointment to show that the medication is being taken as directed. Unannounced inventories can help ensure that medication is not being diverted.

Observed ingestion

Observed ingestion (having the patient take the medication in front of the practitioner or a trained monitor) at the beginning of buprenorphine therapy can help the practitioner ensure that the patient knows how to take the medication. Later in therapy, observing ingestion periodically can help patients adhere to therapy.

See SAMHSA’s Technical Assistance Publication (TAP) 32, Clinical Drug Testing in Primary Care, for additional information about drug testing.

Prescription drug monitoring programs

PDMPs are state-operated electronic databases that collect data on controlled substances (and, in some cases, over-the-counter medications) dispensed in the state. PDMPs help physicians monitor whether patients are obtaining the prescribed medication, obtaining prescriptions for controlled substances from other prescribers, or refilling prescriptions early. Where available, prescribers should register with and check the PDMP for each patient before buprenorphine induction and prior to writing prescriptions. So that there is clear communication and transparency, patients should be informed up front that the PDMP will be accessed to monitor their controlled prescription drug use. PDMP information can also help practitioners educate patients about the risk of overdose and potential drug–drug interactions, particularly related to benzodiazepines and other sedative-hypnotics.

The PDMP Training and Technical Assistance Center Web site provides current information about PDMPs at www.pdmpassist.org.
Responding to Patient Behaviors

Practitioners should verbally acknowledge and reinforce a patient’s adherence to treatment, reduction of illicit drug use, and positive life changes. Practitioners may also concretely reinforce progress by reducing the frequency of office visits and/or increasing the patient’s responsibility for his or her medication. Some patients will continue to illicitly use opioids and/or other substances or relapse to opioid use after a period of abstinence. Other patients may have trouble adhering to the treatment plan (e.g., not taking buprenorphine as directed, missing appointments). Diversion or misuse of buprenorphine may also occur. Signs and behaviors suggestive of diversion and misuse of buprenorphine products include:

- Unsupported claims of intolerance or allergy to naloxone to obtain the mono-product, which is more subject to misuse.
- Early requests for refills for unsubstantiated reasons (e.g., prescription was “lost” or “stolen”).
- Difficulty keeping appointments or providing payment.
- A sudden request for a dose increase by a previously stabilized patient.
- Positive toxicology screens for illicit substance use or negative toxicology screens for buprenorphine.
- Ongoing close ties to individuals (e.g., spouse, partner, significant others, friends) who sell opioids or have opioid use disorder but are not in treatment.

Relapse or continued substance use are not reasons for automatically discontinuing MAT. Instead, either situation should prompt discussion with the patient and evaluation of the treatment plan. If the situation is handled well, a stronger patient–physician alliance can be formed. Changes to treatment should be made on an individual basis and could include any combination of the following: adjusting the patient’s buprenorphine dosage, increasing the frequency of office visits, requiring supervised administration, intensifying counseling, or encouraging the patient to engage in more intensive peer support programs. Some patients may require more structured treatment, such as that offered in a residential program or an opioid treatment program. See the Resources section of this publication for treatment locators.

Duration and Discontinuation of Treatment

The optimal duration of office-based buprenorphine treatment remains unclear. A decision to discontinue buprenorphine therapy should be made based on clinical judgment and upon mutual agreement by the practitioner and patient. ASAM suggests that certain factors may be associated with successful discontinuation of buprenorphine treatment:

- Employment, engagement in mutual-help programs, or involvement in other meaningful activities
- Sustained abstinence from opioids and other substances during treatment
- Positive changes in the psychosocial environment
- Evidence of additional psychosocial supports
- Persistent engagement in treatment for ongoing monitoring past the point of medication discontinuation

Discontinuation of buprenorphine therapy requires a tapering regimen. ASAM recommends a slow taper (usually over several months) with close monitoring. A patient who relapses to illicit use of opioids should resume MAT.

Resources

Relevant Publications From SAMHSA
(see back page for electronic access and ordering information)

Technical Assistance Publication (TAP) 30: Buprenorphine: A Guide for Nurses

TAP 32: Clinical Drug Testing in Primary Care

Treatment Improvement Protocol (TIP) 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction

TIP 43: Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs

Other Resources

Behavioral Health Treatment Services Locator
http://findtreatment.samhsa.gov

Buprenorphine Treatment Physician Locator
www.samhsa.gov/medication-assisted-treatment/physician-program-data/treatment-physician-locator
Medication-Assisted Treatment Web Site
www.samhsa.gov/medication-assisted-treatment

Opioid Treatment Program Directory
http://dpt2.samhsa.gov/treatment/directory.aspx

National Alliance for Model State Drug Laws
www.namsdl.org/prescription-monitoring-programs.cfm

Poison Help Line
1-800-222-1222 (24 hours a day, 7 days a week)
www.aapcc.org

Prescription Drug Monitoring Program Center of Excellence
www.pdmpexcellence.org

Prescription Drug Monitoring Program Training and Technical Assistance Center
www.pdmpassist.org

Providers’ Clinical Support System for Medication Assisted Treatment
www.pcssmat.org

Notes


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