CME CREDIT ***LEARNING OBJECTIVE:*** Readers will recognize that opioid addiction is a chronic condition that requires ongoing treatment

VANIA MODESTO-LOWE, MD, MPH
Connecticut Valley Hospital, Middletown, CT; Quinnipiac University, Hamden, CT; University of Connecticut School of Medicine, Farmington, CT

KATIE SWIEZBIN, BS
Quinnipiac University, Hamden, CT

MARGARET CHAPLIN, MD
University of Connecticut School of Medicine, Farmington, CT; Community Mental Health Affiliates, New Britain, CT

GABRIELA HOEFER
Samford University, Birmingham, AL

Use and misuse of opioid agonists in opioid addiction

ABSTRACT

Although methadone (an opioid agonist) and buprenorphine (a partial opioid agonist) have evidence to support their use in treating opioid use disorder, they remain misunderstood and underutilized. In this article, we outline the risks and benefits of using these drugs as maintenance therapy in opioid-dependent patients.

KEY POINTS

Opioid use disorder is potentially lethal and has become more prevalent in the United States over the past few decades.

The opioid agonist methadone and the partial agonist buprenorphine are the currently recommended treatments for patients who need opioid maintenance therapy. However, they carry the risk of adverse effects (eg, respiratory depression, QTc interval prolongation, hepatotoxicity), diversion, and overdose.

Patients being considered for opioid agonist therapy need a comprehensive assessment including a thorough medical history and physical examination, psychiatric evaluation, psychosocial appraisal, and determination of readiness to change.

When methadone and buprenorphine are properly prescribed they confer significant benefits, including reduction or elimination of opioid use, reductions in overdose risk, and positive changes in behavior and lifestyle.

doi:10.3949/ccjm.84a.16091

For a patient struggling with opioid addiction, opioid agonist therapy with methadone or buprenorphine can reduce craving and opioid use and may even save his or her life. But many clinicians are unfamiliar with this evidence-based treatment,[1,2] which is best started early in the course of addiction.[3]

See related editorial, page 385

This article outlines the pharmacology of these drugs, their clinical uses, and the challenges of using them to treat opioid addiction.

DIAGNOSTIC CRITERIA

Opioid addiction, formally known as opioid use disorder, is a pattern of opioid misuse leading to clinically significant impairment in multiple areas of life. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, lists 11 diagnostic criteria, but only 2 need to be present within the past year to make the diagnosis[4]:

- Taking opioids longer or in higher doses than was intended
- A persistent desire or unsuccessful efforts to cut down or control opioid use
- Spending a great deal of time obtaining, using, or recovering from using opioids
- Craving opioids
- Repeatedly failing to fulfill obligations at work, school, or home due to opioid use
- Continuing to use opioids even though it causes or exacerbates social or interpersonal problems
- Giving up or curtailing important social, occupational, or recreational activities because of opioid use
- Repeatedly using opioids in situations in which it is physically hazardous

- Continuing to use opioids despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
- Tolerance
- Withdrawal.

Recent estimates indicate that 2.23 million people in the United States have opioid use disorder (426,000 with heroin and 1.8 million with prescription opioids).[5]

Progression from prescription opioids to heroin

We have observed that many patients with opioid use disorder start by misusing prescription opioids. Over time, tolerance can develop, which drives patients to use higher and higher doses.[6]

As the addiction progresses, a subset of prescription opioid users advances to using heroin, which is typically less expensive and easier to obtain.[7] Most patients start with the intranasal route but eventually inject it intravenously.[6,7]

Approximately 2.23 million people in the United States have opioid use disorder

For many addicts, heroin use has medical consequences such as hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infection, psychiatric problems such as depression and anxiety, and illegal activities such as theft and sex work.[8] People who use heroin appear to have more severe addiction and a lower socioeconomic status than prescription opioid users.[9–11] But recently, a growing number of middle class individuals are becoming addicted to heroin.[12]

METHADONE

Methadone is a long-acting synthetic opioid that functions as a full agonist on the mu-opioid receptor. The drug binds, occupies, and stimulates the receptor, preventing withdrawal symptoms and reducing opioid cravings for at least 24 hours.[13]

Adverse effects of methadone

The most common adverse effects include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating.[14] Other adverse effects:

Unintentional overdose. The risk is serious, as a single 30-mg dose can be fatal in people who are opioid-naïve.[13]

QTc prolongation, which can lead to torsade de pointes. This risk, which is dose-related, must be taken into consideration in patients who have any cardiac symptoms (eg, syncope, arrhythmia), pathology (familial QT prolongation), or other risk factors for QTc prolongation (eg, hypokalemia, QTc-prolonging medications).[15]

Respiratory depression, which can be fatal. This dose-related risk is heightened during the first 4 weeks of treatment if titration is too rapid or if methadone is used in combination with other drugs that cause central nervous system or respiratory depression.[13,14]

Starting methadone

To prevent respiratory depression and death related to rapid induction, the general rule is to start methadone at a low daily dose (20–30 mg) depending on the patient's withdrawal symptoms.[14] During this period, patients need to be closely monitored and educated on the perils of concomitant use of central nervous system depressants.[14]

In most patients, the dose is titrated up until their withdrawal symptoms and cravings are eliminated, which generally requires 60 to 120 mg daily.[14] Hepatic and renal impairment, pregnancy, and advanced age can alter methadone pharmacokinetics and may therefore necessitate dose adjustment.

BUPRENORPHINE

Buprenorphine is an alkaloid thebaine opioid derivative that acts as a partial mu-opioid agonist and a kappa antagonist.[16] Like methadone, buprenorphine is used to manage cravings and withdrawal symptoms.[16] Dosages of 4 to 16 mg (up to 32 mg) per day of buprenorphine are usually required to adequately control opioid cravings.[16]

Sublingual and subdermal products

Buprenorphine is currently available in the United States in sublingual and subdermal formulations.[16,17]

Sublingual buprenorphine is usually combined with naloxone in a 4:1 ratio to deter intravenous use. Intravenous injection of the combination product can precipitate withdrawal due to the antagonist action of naloxo-

one. (Taken orally or sublingually, naloxone is poorly absorbed and has little or no clinical effect.) Buprenorphine-naloxone is available in tablets, a sublingual film strip, and a buccal film strip. Buprenorphine is also available by itself in a sublingual formulation.

The US Food and Drug Administration has approved a buprenorphine subdermal implant, Probuphine. Four rods, about 1 inch long, are placed under the skin in the inner aspect of the upper arm and provide the equivalent of 8 mg of buprenorphine daily for 6 months.[17] However, this method is formulated only for maintenance treatment and cannot be used for induction. Additionally, it is recommended that the implants be surgically removed at the end of 6 months, after which another set of implants can be inserted in the other arm or the patient can switch to sublingual therapy, depending on the clinical situation and patient preference.[17]

Generally safer than methadone

Buprenorphine works on the same receptor as methadone and therefore has a similar side effect profile. However, buprenorphine has a ceiling effect, which greatly reduces the risk of fatal respiratory depression.[18] It also does not cause clinically significant QTc prolongation and is preferable in patients who have cardiac risk factors.[18]

Another advantage is that buprenorphine has fewer identified medication interactions than methadone.[18] Further, induction of buprenorphine in patients with opioid use disorder has been shown to be safer than methadone.[19]

Although buprenorphine has been found to be 6 times safer than methadone with regard to overdose among the general population,[20] it can still cause fatal intoxication if used in combination with central nervous system depressants.[21]

Buprenorphine has been also associated with hepatotoxicity, though the risk of new-onset liver disease appears to be low.[22]

NALTREXONE IS LESS EFFECTIVE THAN METHADONE, BUPRENORPHINE

Besides methadone and buprenorphine, the only other approved option for treating opioid use disorder is the opioid antagonist naltrexone.

Naltrexone has significantly less abuse potential, as it provides no euphoria, but patients do not like it. Even with the long-acting formulation (Vivitrol), naltrexone treatment is significantly less effective than methadone or buprenorphine.[23–25] Further, although naltrexone is not a controlled substance and so does not face the same scrutiny as the agonist therapies, there are other significant barriers. Additional information on naltrexone is presented in reviews by Modesto-Lowe and Van Kirk[24] and Woody.[25]

OBSTACLES TO TREATMENT

People hold conflicting views about opioid agonist therapy. Some believe that "trading one drug for another" is not a legitimate therapeutic strategy, and they may feel ashamed of being on maintenance therapy.[26] Similarly, some argue that the answer to establishing stable abstinence does not lie simply in prescribing medications.

The contrary argument is that these medications, if used appropriately, confer many benefits such as reducing the medical and psychosocial sequelae of opioid addiction.[18] In fact, properly treated patients no longer meet the diagnostic criteria of opioid use disorder, and both methadone and buprenorphine are on the World Health Organization's (WHO) list of essential medicines.[27]

Despite endorsement by the WHO, the stigma attached to the opioid agonists has been difficult to overcome. Patients with opioid use disorder may be viewed with distrust by healthcare providers and often do not feel welcome in healthcare settings or in self-help recovery groups.[28]

Heroin is typically less expensive and easier to obtain than prescription opioids

Barriers to methadone therapy

Federal regulations on methadone prescribing and use were established to promote patient safety and decrease diversion, but they may also complicate access to care.[29] They stipulate that to qualify for methadone maintenance, patients need to demonstrate opioid addiction for 1 year, except for pregnant women and those who have been incarcerated in the past 6 months. Patients under the age of 18 must have 2 documented failed treatment episodes as well as approval by a guardian to receive treatment.

Inconvenience. Methadone can be prescribed for opioid dependence only by an accredited treatment program. Patients must therefore travel to the clinic and wait to be evaluated on a daily basis for a minimum of 90 days. Only after they demonstrate consistent responsible behavior and negative results on urine testing do they become eligible to take methadone home.[29] If a patient is to travel out of the area during the initial 90 days of treatment, he or she must make arrangements in advance to find a clinic that will provide a "guest dose."

The inconvenience arising from the regulations may deter some patients from seeking methadone therapy. In spite of this, once patients are started on methadone, more of them continue treatment than with buprenorphine.[18] A proposed reason is that methadone is a potent full opioid agonist and therefore relieves withdrawal symptoms and craving more effectively than buprenorphine, which is a partial agonist.[30] Another possible reason is the higher level of supervision afforded by methadone clinics, which require daily contact for at least 90 days.

Safety concerns arise from methadone diversion, as illicit use may have lethal consequences. In the past decade, deaths from methadone overdose have risen significantly, most of them due to respiratory depression or torsade de pointes.[13] However, most cases of diversion and overdose involve methadone that is prescribed for pain by individual practitioners and not from maintenance programs.[13]

Buprenorphine is safer than methadone but can still kill if used with central nervous system depressants

Advantages of buprenorphine

Together, methadone's lethality, stigma, and inconvenience may contribute to patients preferring buprenorphine.[31]

The regulations governing buprenorphine's use are less restrictive than those with methadone. For example, patients must have a diagnosis of opioid addiction to be prescribed buprenorphine, but they are not required to carry the diagnosis for a year before treatment.[31] Additionally, they do not need to travel to a federally approved opioid treatment center daily and can receive buprenorphine directly from a physician in an outpatient setting.

Under the Drug Abuse Treatment Act (DATA) of 2000, any physician can apply for a waiver to prescribe and dispense buprenorphine in his or her office. To qualify for an initial waiver, physicians must either obtain certification in the fields of addiction medicine or addiction psychiatry or complete an approved 8-hour training session.[32] Each physician starts with a maximum of 30 patients, but can apply to treat up to 100 patients after 1 year and eventually up to 275 patients. Physicians must document every buprenorphine prescription they write and be able to refer patients for counseling.[31]

As of February 2017, nurse practitioners and physician assistants can also apply for a DATA 2000 waiver. All waivered providers are subject to unannounced visits from the Drug Enforcement Administration once every 5 years.[32]

While there are no federal restrictions on the amount of buprenorphine that can be dispensed, some states and some insurance companies have placed restrictions on dose or length of treatment.[33] Buprenorphine patients can fill their prescriptions at any pharmacy and are permitted to bring their medication home, which improves access to care. However, office-based outpatient treatment is not without risk, and preventing buprenorphine diversion remains a challenge.[34]

'Lending' buprenorphine is a felony

Addicts have illegally used buprenorphine to self-treat opioid withdrawal, craving, and dependence.[35] Its misuse has also been coupled with self-treatment of conditions that include depression and pain.[36]

A survey found that 83.7% of patients deem buprenorphine diversion to be appropriate; further, most patients said they consider it unethical to withhold prescribed buprenorphine from individuals showing symptoms of withdrawal.[34] Physicians who prescribe buprenorphine must inform their patients that even "lending" or giving away their medication is a felony.

Prescribing physicians must also be diligent about monitoring for signs of diversion such as inconsistent urine toxicology screens, "lost" medication, and requests for early refills or escalating doses.[37]

EVALUATING PATIENTS FOR OPIOID REPLACEMENT THERAPY

In addition to federal regulations, we propose a 4-step approach to evaluate eligibility for opioid replacement therapy based on existing guidelines.[37–39]

Step 1: History and physical examination

The history should give particular attention to the patient's cardiac, pulmonary, and hepatic status, with consideration of the risks of any medical comorbidities (eg, bacterial endocarditis, HIV and HCV infection) that might influence treatment.[37]

It is also essential to evaluate for any contraindications or drug interactions before prescribing methadone or buprenorphine.[38]

Contraindications to methadone maintenance include[40]:

- Cor pulmonale
- Methadone hypersensitivity
- Pseudomembranous colitis
- Selegiline use (due to risk of serotonin syndrome)
- Ileum paralyticus.

Contraindications to buprenorphine use include:

- Hypersensitivity to naloxone or buprenorphine
- Impaired liver function (due to the risk of inadvertent overdose associated with slowed metabolism).

Concurrent use of alcohol or illicit benzodiazepines is a relative contraindication to both methadone and buprenorphine due to the risk of respiratory depression and overdose.[37] Likewise, avoid coprescribing opioid agonists and benzodiazepines whenever possible. Obtain a complete list of current medications and query a prescription-monitoring database to determine whether any controlled substances are currently prescribed.[37]

During the physical examination, look for stigmata of intravenous drug use such as track marks or abscesses[37] and document any physical findings consistent with intoxication or withdrawal. Patients must be completely detoxed or in withdrawal before beginning buprenorphine induction; premature induction can precipitate withdrawal.[38]

A discussion of pregnant patients with opioid use disorder is beyond the scope of this paper. However, it is incumbent on the prescriber to inquire whether the client is pregnant or intends to become pregnant and what birth control methods are in place.

Step 2: Assess psychiatric status

Assessment of the patient's psychiatric status, including an assessment of alcohol and other drug use, will help determine his or her eligibility for opioid agonists.[37] To prepare for the need to manage patients with psychiatrically complex issues, it is helpful to develop relationships with addiction specialists and psychiatrists who are familiar with opioid replacement therapy in your area. This will make it easier to collaborate on patients' care.

Ask all patients directly about suicidal or homicidal ideation. Any patient with active suicidal or homicidal ideation should be assessed for need of immediate hospitalization by a psychiatrist or another qualified mental health professional. Patients with a history of suicidal ideation should be monitored closely by a mental health professional throughout treatment.[37]

Many if not most patients with opioid use disorder have concurrent psychiatric disorders, and the interplay between these disorders is complex.[40,41] Depression, for example, can precede and even precipitate drug use (an observation supporting the "self-medication theory").[42] If the underlying depressive disorder is not addressed, relapse is nearly inevitable.

Regulations for buprenorphine are less restrictive than those for methadone

It has also been shown that both chronic opioid use and withdrawal can exacerbate aversive emotional states. This escalation of symptoms may result from the pharmacologic effects of opioids or from psychosocial sequelae that can arise from chronic opioid use.[41] In this situation, maintaining abstinence can lead to resolution of depressive symptoms. As depression and opioid use can occur together, successful treatment requires equal attention to both illnesses.

Other common comorbidities in patients with opioid use disorder include posttraumatic stress disorder, attention deficit hyperactivity disorder, antisocial personality disorder, and concurrent substance abuse disorders.[43] The confluence of antisocial personality disorder is particularly important, as patients with an-

tisocial personality disorder display disruptive and maladaptive behaviors.

Identify any psychotropic medication that is prescribed and check carefully for drug interactions. This applies especially to methadone, as many psychiatric medications also prolong the QT interval. Moreover, patients may not be forthcoming about the use of psychiatric medication.

Find out whether the patient is using any other addictive substances, particularly those that affect the central nervous system, as those who use fentanyl, benzodiazepines, or alcohol are at the highest risk of overdose.[31] Often the best option for those with concurrent substance use disorders is inpatient detoxification followed by residential rehabilitation care. Either buprenorphine or methadone can then be initiated upon return to an outpatient setting.

Step 3: Assess psychosocial status

To what extent do the patient's home environment and support systems promote a drug-free lifestyle? Unfortunately, the psychosocial status of many of these patients is fragile, and they may live in areas where illicit drugs are readily available (which can be urban, suburban, or rural), making it difficult to stay substance-free.[38]

Patients with active suicidal or homicidal ideation should be assessed for need of immediate hospitalization

Generally, lifestyle modifications are needed to transform maladaptive behaviors and promote an environment conducive to long-term recovery. Referrals to social services to address housing, vocational needs, and entitlements may be helpful.[39]

Step 4: Assess readiness to change

According to one model, people go through 5 stages when changing a behavior: precontemplation, contemplation, preparation for action, action, and maintenance.[43] In general, the further along the stages a patient is, the more appropriate he or she is for office-based treatment with buprenorphine.[39]

The level of change can be assessed with tools such as Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES). Use of stage-specific strategies may enhance a patient's readiness to cease opioid use.[43]

Precontemplation. Those in the precontemplation stage are not ready to think about changing their behavior.[43] They may be unaware of or unwilling to consider the risks associated with their opioid use and resistant to the idea of quitting. Engagement with opioid agonists for individuals in this stage is low and dropout rates are likely high.

Thus, the proper approach for "precontemplators" is to help them develop some ambivalence about their opioid use. One tactic is to involve the patient in a discussion of the personal benefits and risks of opioid use.

Contemplation. Individuals in the contemplation stage have begun to weigh the costs and benefits of opioid use and express ambivalence about it.[44] Because the patient is willing to explore the risks of ongoing use and consider the benefits of treatment, the goal in this stage is to elicit a commitment from the individual to seek treatment.

Preparation. The person in this stage moves from thinking about treatment to planning what action to take.[45] As the individual prepares to enter treatment, indecision tends to resurface, as well as self-doubt about his or her ability to change. During this stage, it is important for the provider to spell out goals (abstinence) and strategies (eg, counseling, medication) and enhance a sense of self-efficacy.

Action and maintenance. Patients in these stages engage in treatment and employ new strategies to abstain from opioid use. Maintaining these behaviors can be a daily struggle. Expressing confidence in the patient's ability to abstain from use will support his or her progress. Behavioral interventions such as strategic avoidance of triggers and engagement in alternative activities (eg, support groups, exercise, faith-based practices) will help to maintain abstinence.

A CHRONIC CONDITION

Opioid use disorder, like many chronic illnesses, requires long-term attention to attain successful patient outcomes. The opioid agonists methadone and buprenorphine are the mainstay of treatment for it, conferring benefits such as reducing opioid use and preventing relapse.

Candidates for opioid agonist therapy should undergo a multidisciplinary assessment, including an evaluation on the patient's readiness to change his or her opioid use.

Patient education should include a discussion of the risks of methadone (eg, respiratory depression, fatal overdose, and QTc prolongation) and buprenorphine (eg hepatotoxicity) and their benefits (eg, controlling craving, decreasing the risk of relapse). Patients should also be educated about overdose and diversion.

Despite the difficulties inherent in treating patients with opioid use disorder, when used appropriately, opioid agonist therapy can be lifesaving for patients struggling with long-term opioid addiction.

***ACKNOWLEDGMENT**: We thank Katelyn Colosi, BS, and Drs. Susan Wolfe, Dennis Bouffard, and Sinha Shirshendu for their helpful comments.*

REFERENCES

1. **Wakeman SE, Pham-Kanter G, Donelan K**. Attitudes, practices, and preparedness to care for patients with substance use disorder: results from a survey of general internists. Subst Abus 2016; 37:635–641.
2. **Samuels EA, Dwyer K, Mello MJ, Baird J, Kellogg AR, Bernstein E**. Emergency department-based opioid harm reduction: moving physicians from willing to doing. Acad Emerg Med 2016; 23:455–465.
3. **Mohlman MK, Tanzman B, Finison K, Pinette M, Jones C**. Impact of medication-assisted treatment for opioid addiction on Medicaid expenditures and health services utilization rates in Vermont. J Subst Abuse Treat 2016; 67:9–14.
4. **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.
5. **Center for Behavioral Health Statistics and Quality**. Behavioral health trends in the United States: results from the 2014 National Survey on Drug Use and Health. www.samhsa.gov/data/. Accessed April 6, 2017.
6. **Compton WM, Jones CM, Baldwin GT**. Relationship between nonmedical prescription-opioid use and heroin use. N Engl J Med 2016; 374:154–163.
7. **Ruan X, Wyche MQ, Kaye AD**. Analyzing the relationship between nonmedical prescription-opioid use and heroin use. J Opioid Manage 2016; 12:11–14.
8. **Hser YI, Evans E, Grella C, Ling W, Anglin D**. Long-term course of opioid addiction. Harv Rev Psychiatry 2015; 23:76–89.
9. **Nielsen S, Hillhouse M, Mooney L, Ang A, Ling W**. Buprenorphine pharmacotherapy and behavioral treatment: comparison of outcomes among prescription opioid users, heroin users and combination users. J Subst Abuse Treat 2015; 48:70–76.
10. **Moore BA, Fiellin DA, Barry DT, et al**. Primary care office-based buprenorphine treatment: comparison of heroin and prescription opioid dependent patients. J Gen Intern Med 2007; 22:527–530.
11. **Fischer B, Patra J, Cruz MF, Gittins J, Rehm J**. Comparing heroin users and prescription opioid users in a Canadian multi-site population of illicit opioid users. Drug Alcohol Rev 2008; 27:625–632.
12. **Compton WM, Jones CM, Baldwin GT**. Relationship between nonmedical prescription-opioid use and heroin use. N Engl J Med 2016; 374:154–163.
13. **Jones CM, Baldwin GT, Manocchio T, White JO, Mack KA**. Trends in methadone distribution for pain treatment, methadone diversion, and overdose deaths—United States, 2002–2014. MMWR Morb Mortal Wkly Rep 2016; 65:667–671.
14. **Baxter LE Sr, Campbell A, Deshields M, et al**. Safe methadone induction and stabilization: report of an expert panel. J Addict Med 2013; 7:377–386.
15. **Alinejad S, Kazemi T, Zamani N, Hoffman RS, Mehrpour O**. A systematic review of the cardiotoxicity of methadone. EXCLI J 2015; 14:577–600.
16. **Johnson RE, Strain EC, Amass L**. Buprenorphine: how to use it right. Drug Alcohol Depend 2003; 70(suppl 2):S59–S77.
17. **Ling W**. Buprenorphine implant for opioid addiction. Pain Manage 2012; 2:345–350.
18. **Saxon AJ, Hser YI, Woody G, Ling W**. Medication-assisted treatment for opioid addiction: methadone and buprenorphine. J Food Drug Anal 2013; 21:S69–S72.
19. **Kimber J, Larney S, Hickman M, Randall D, Degenhardt L**. Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study. Lancet Psychiatry 2015; 2:901–908.
20. **Marteau D, McDonald R, Patel K**. The relative risk of fatal poisoning by methadone or buprenorphine within the wider population of England and Wales. BMJ Open 2015; 5: e007629.
21. **Kintz P**. Deaths involving buprenorphine: a compendium of French cases. Forensic Sci Int 2001; 121:65–69.
22. **Zuin M, Giorgini A, Selmi C, et al**. Acute liver and renal failure during treatment with buprenorphine at therapeutic dose. Dig Liver Dis 2009; 41:e8–e10.
23. **Klein JW**. Pharmacotherapy for substance use disorders. Med Clin North Am 2016; 100:891–910.
24. **Modesto-Lowe V, Van Kirk J**. Clinical uses of naltrexone: a review of the evidence. Exp Clin Psychopharmocol 2002; 10:213–227.
25. **Woody GE**. Agonist models for treating persons with substance use disorders. Curr Psychiatry Rep 2014; 16:489.
26. **Sanders JJ, Roose RJ, Lubrano MC, Lucan SC**. Meaning and methadone: patient perceptions of methadone dose and a model to promote adherence to maintenance treatment. J Addict Med 2013; 7:307–313.
27. **Herget G**. Methadone and buprenorphine added to the WHO list of essential medicines. HIV/AIDS Policy Law Rev 2005; 10:23–24.
28. **Suzuki J, Dodds T**. Clinical recommendation of 12-step meeting attendance and discussion regarding disclosure of buprenorphine use among patients in office-based opioid treatment. Subst Abus 2016; 37:31–34.
29. **Rettig RA,Yarmolinsky A**. Federal Regulation of Methadone Treatment. Washington, DC: National Academies Press; 1995.
30. **Srivastava A, Kahan M, Nader M**. Primary care management of opioid use disorders: abstinence, methadone, or buprenorphine-naloxone? Can Fam Physician 2017; 63:200–205.
31. **Substance Abuse and Mental Health Services Administration**. Federal Guidelines for Opioid Treatment Programs. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2015.
32. **Substance Abuse and Mental Health Services Administration SAMSHA**. Buprenorphine waiver management. www.samhsa.gov/medication-assisted-treatment/buprenorphine-waiver-management. Accessed April 6, 2017.
33. **Mark TL, Lubran R, McCance-Kats EF, Chalk M, Richardson J**. Medicaid coverage of medications to treat alcohol and opioid dependence. J Subst Abuse Treat 2015; 55:1–5.
34. **Johnson B, Richert T**. Diversion of methadone and buprenorphine from opioid substitution treatment: the importance of patients' attitudes and norms. J Subst Abuse Treat 2015; 54:50–55.
35. **Yokell MA, Zaller ND, Green TC, Rich JD**. Buprenorphine and buprenorphine/naloxone diversion, misuse, and illicit use: an international review. Curr Drug Abuse Rev 2011; 4:28–41.
36. **Schuman-Olivier Z, Albanese M, Nelson SE, et al**. Self-treatment: illicit buprenorphine use by opioid-dependent treatment seekers. J Subst Abuse Treat 2010; 39:41–50.
37. **American Society of Addiction Medicine**. National practice guidelines for the use of medications in the treatment of addiction involving opioid use. www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf. Accessed April 6, 2017.
38. **McNicholas L**. Clinical guidelines for the use of buprenorphine in

the treatment of opioid addiction. Rockville, MD: US Department of Health and Human Services, Substance Abuse and Mental Health Service Administration; 2004.
39. **Center for Substance Abuse Treatment**. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2004. (Treatment Improvement Protocol (TIP) Series, No. 40.) www.ncbi.nlm.nih.gov/books/NBK64245/. Accessed April 6, 2017.
40. **Zippel-Schultz B, Specka M, Cimander K, et al**. Outcomes of patients in long-term opioid maintenance treatment. Subst Use Misuse 2016; 51:1493–1503.
41. **Martins SS, Keyes KM, Storr CL, Zhu H, Chilcoat HD**. Pathways between nonmedical opioid use/dependence and psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depend 2009; 103:16–24.
42. **Khantzian EJ**. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. Am J Psychiatry 1985; 142:1259–1264.
43. **Belding MA, Iguchi MY, Lamb RJ, Lakin M, Terry R**. Stages and processes of change among polydrug users in methadone maintenance treatment. Drug Alcohol Depend 1995; 39:45–53. 44. Peteet JR, Brenner S, Curtiss D, Ferrigno M, Kauffman J. A stage of change approach to addiction in the medical setting. Gen Hosp Psychiatry 1998; 20:267–273.
45. **Vijay A, Bazazi AR, Yee I, Kamarulzaman A, Altice FL**. Treatment readiness, attitudes toward, and experiences with methadone and buprenorphine maintenance therapy among people who inject drugs in Malaysia. J Subst Abuse Treat 2015; 54:29–36.

***ADDRESS**: Vania Modesto-Lowe, MD, MPH, Connecticut Valley Hospital, PO Box 351, Silver Street, Middletown, CT 06457; vania.modesto-lowe@ct.gov*