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Diagnosing and treating opioid dependence

The surge in opioid abuse highlights the importance of questioning patients about their use of prescription analgesics—and knowing when and how to intervene.

PRACTICE RECOMMENDATIONS

› *Ask all patients about the inappropriate use of substances, including prescription opioids.* (A)

› *Recommend pharmacotherapy for patients entering treatment for opioid dependence.* (A)

› *Warn patients who are opioid dependent about the risk of accidental fatal overdose, particularly with relapse.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

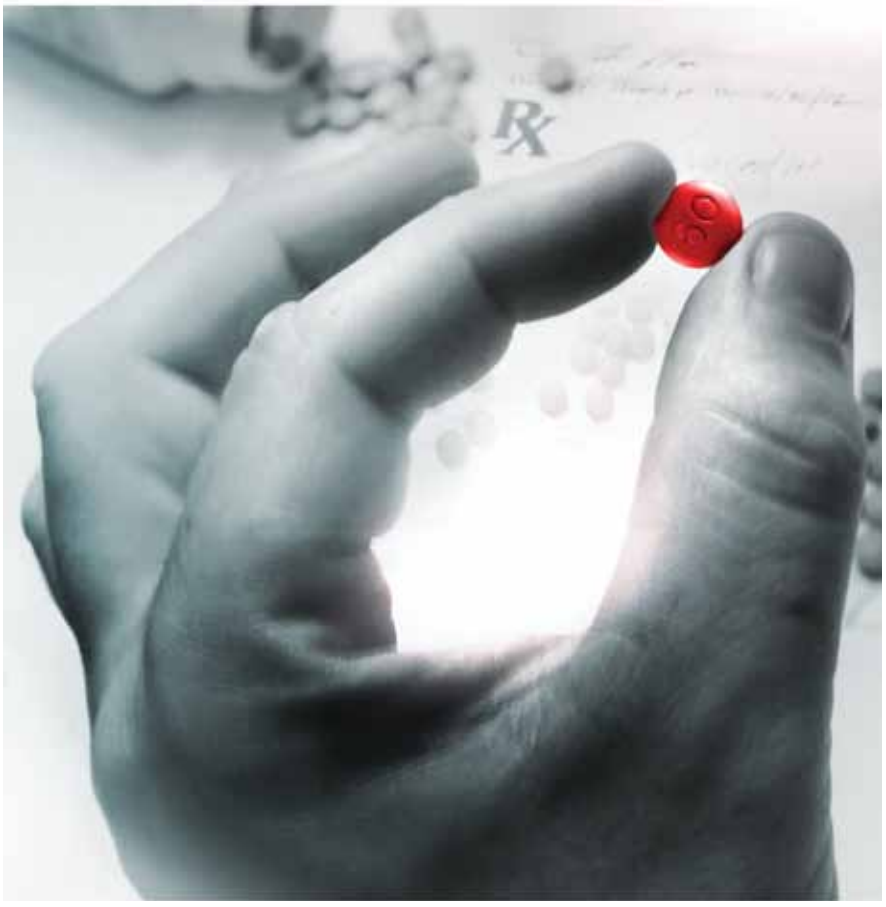
CASE► Sam M, age 48, is in your office for the first time in more than 2 years. He has gained a considerable amount of weight and appears a bit sluggish, and you wonder whether he's depressed. While taking a history, Sam reminds you that he was laid off 16 months ago and had been caring for his wife, who sustained a debilitating back injury. When you saw her recently, she told you she's back to work and pain-free. So you're taken aback when Sam asks you to refill his wife's oxycodone prescription for lingering pain that often keeps her up at night.

If Sam were your patient, would you suspect opioid dependence?

Dependence on opioid analgesics and the adverse consequences associated with it have steadily increased during the past decade. Consider the following:

- Between 2004 and 2008, the number of emergency department visits related to nonmedical prescription opioid use more than doubled, rising by 111%.[1]
- The increasing prevalence of opioid abuse has led to a recent spike in unintentional deaths,[2] with the number of lives lost to opioid analgesic overdose now exceeding that of heroin or cocaine.[3]
- More than 75% of opioids used for nonmedical purposes were prescribed for someone else.[4]

The course of opioid use is highly variable. Some people start with a legitimate medical prescription for an opioid analgesic, then continue taking it after the pain subsides. Others experiment briefly with nonmedical prescription opioids or use them intermittently without adverse effect. Some progress from prescription opioids to heroin, despite its dangers.[5] Still others have a catastrophic outcome, such as an overdose or severe accident, the first time they use opioids.[6] Rapid



To evoke and strengthen motivation for change, ask a patient who denies that opioid use is a problem or is clearly ambivalent about seeking treatment, "How would you like your situation to be different?"

progression from misuse of opioids to dependence is most likely in vulnerable populations, such as those with concurrent mental illness, other substance use disorders, or increased sensitivity to pain.[7]

Understanding the terms. Before we continue, a word about terminology is in order. "Misuse" generally refers to the use of a medication in a manner (ie, purpose, dose, or frequency) other than its intended use, while "drug addiction" is the repeated use of a drug despite resulting harm. Here we will use "opioid dependence" to mean a pattern of increasing use characterized by significant impairment and distress and an inability to stop, and "opioid withdrawal" to reflect a constellation of symptoms, such as insomnia, nausea, diarrhea, and muscle aches, that can follow *physiological* dependence (though not necessarily opioid dependence). Our definitions of these terms are consistent with those of the American Psychiatric Association (APA).[8] Worth noting, however, is the fact that as the APA prepares for the publication of the 5th edition of its *Diagnostic and Statistical Manual of Mental Disorders*, its Substance Disorder Work Group has proposed replacing the term "opioid dependence" with "opioid use disorder" to reduce the confusion associated with these definitions.[9]

Assessing illicit opioid use: Start with a targeted question

Most patients who are opioid dependent do not seek treatment for it,[10] and are typically free of medical sequelae associated with drug addiction when they see family practitioners. The absence of self-reporting and obvious physical signs and symptoms, coupled with the increase in illicit use of prescription opioids, underscores the need for family physicians to identify patients who are abusing opioids and ensure that they get the help they need.

Screening tools. There are a number of screening tools you can use for this purpose—eg, CAGE-Adapted to Include Drugs (CAGE-AID) and Drug Abuse Screening Test (DAST)[11,12]—but they have not been found to be significantly better than a careful substance abuse history.[13]

Straightforward questions. You can start by asking, "Do you take any medications for pain?" If the answer is Yes, get the

Opioid dependence: Red flags to keep in mind[14-16]

Suspect opioid dependence in a patient who:

- describes pain resulting from back or orthopedic injuries without corresponding documentation or imaging
- requests a specific opioid for pain management
- shows little interest in a physical exam, diagnostic testing, or nonpharmacological remedies
- talks about changes in work or relationship status
- ceases to participate in activities or hobbies that previously occupied a considerable amount of his or her time. This may signal social isolation or indicate that the patient is spending a great deal of time in pursuit of opioids.

Rapid progression from misuse of opioids to dependence is most common in vulnerable populations, such as those with concurrent mental illness, another substance use disorder, or increased sensitivity to pain.

name of the drug and inquire about the frequency of use and the route, the amount typically taken, and the duration of the current use pattern. Ask specifically about opioids when taking a substance abuse history. After a question about alcohol use, you can say, "Do you use any other drugs in a serious way? Marijuana? Opioids like Percocet, Vicodin, or Oxycontin?" Although it can be very difficult to detect opioid dependence if the patient is not forthcoming, other likely indicators of drug-seeking behavior should trigger additional questions. (See "Opioid dependence: Red flags to keep in mind" above.[14-16])

"Brief" protocols. Recent studies of Screening, Brief Intervention, and Referral to Treatment (SBIRT) programs have found that the simple, time-limited interventions they offer (visit http://www.samhsa.gov/prevention/sbirt/SBIRTwhitepaper.pdf to learn more) lead to a reduction in self-reported illicit opioid use.[17,18] Family physicians can readily incorporate SBIRT protocols into routine practice, as an evidence-based and often reimbursable approach to substance abuse.[17]

Additional steps before initiating treatment

After screening and diagnostic evaluation provide evidence that a patient is opioid dependent, you can take several steps to guide him or her to the appropriate treatment.

A thorough biopsychosocial assessment covering co-occurring psychiatric illnesses, pain, psychosocial stressors contributing to opioid use, and infectious disease screening is required to gain a clear picture of the patient's situation. In every case, acute emergencies such as suicidal ideation require immediate intervention, which may involve hospitalization.[19]

Assess the patient's desire for help. After the initial assessment, it is often helpful to categorize the patient's "stage of change" (precontemplation, contemplation, preparation, action, or maintenance),[20] and to tailor your next step accordingly. A patient who denies that opioid use is a problem or is clearly ambivalent about seeking treatment may require a conversation that uses principles of motivational interviewing—a collaborative approach that aims to evoke and strengthen personal motivation for change.[21] Consider a question that encourages him or her to express reasons for change, such as: "How would you like your current situation to be different?" As almost everyone abusing opioids has thoughts about stopping, such a question may help the patient focus on specific changes.

CASE ▶ When you question Sam about his interest in oxycodone, he breaks down. He's been unable to find work or to lose the excess weight he gained during the many months he cared for his wife. He tells you that soon after his wife stopped taking the pain pills, he started taking them. At first, he took one occasionally. Then he started taking the opioids every day, and finally, whenever he awakened at night. Now, Sam says, he has no more pills, and he's nauseous, depressed, and unable to sleep—and looking to you for help.

Sam fits the criteria for opioid withdrawal as a result of physiological dependence; further questioning reveals that he also suffers from opioid dependence, and that he is receptive to treatment.

TABLE

Treating opioid dependence: Key clinical recommendations

Recommendation	Evidence (SOR)	Comments
Screen all patients for substance use, including opioids. Brief interventions and referral to treatment when appropriate may reduce opioid use[17,22]	Consistent findings from RCTs; evidence-based guideline (**A**)	SBIRT reduces self-reported opioid use; efforts to replicate such reports with objective evidence (eg, toxicology screens) are underway
Recommend maintenance medication (ie, buprenorphine, naltrexone, methadone) for all patients entering treatment for opioid dependence with physiological dependence; methadone is the safest for pregnant women[23-25]	Consistent findings from RCTs; evidence-based guideline (**A**)	Methadone is the gold standard for pregnant women; further studies are needed to determine the safety of in utero exposure to buprenorphine and naltrexone
Keep patients on maintenance medication for ≥3 months; higher relapse rates are noted when medication is discontinued in <3 months[23,24]	Consistent findings from RCTs (**A**)	Relapse rates are higher when maintenance medication is discontinued in <3 months
Caution patients with opioid dependence of the risk for accidental overdose and death with relapse and take action—eg, offering naloxone rescue kits to patients and families, as appropriate[26]	Consistent findings from RCTs and prospective cohort studies; evidence-based guideline (**A**)	
Take steps to prevent diversion and accidental ingestion of agonist therapies, using tools such as frequent toxicology screens, random pill counts, and designated pharmacies, and monitoring adherence to psychosocial treatment[26,27]	Practice guideline (consensus) (**C**)	

RCTs, randomized clinical trials; SBIRT, Screening, Brief Intervention, and Referral to Treatment; SOR, strength of recommendation.

Recommending treatment and following up

Several options are available for patients who, like Sam, have signs and symptoms of opioid withdrawal as a result of physiological dependence. You can provide a referral to a physician specializing in addiction, recommend detoxification and/or treatment in an inpatient facility, or initiate pharmacological treatment and provide a referral to a behavioral therapist. Whatever the initial approach, most patients will ultimately be treated as outpatients, with a combination of pharmacotherapy and behavioral therapy—often, with monitoring and oversight by a primary care physician. Which approach to pursue should be guided by evidence-based recommendations (**TABLE**)[17,22-27] and jointly decided by physician and patient.

Medication plays a key role in recovery

Recommend medication-assisted treatment, either with an agonist (buprenorphine or methadone) or an antagonist (naltrexone), for every patient with physiological opioid dependence. The goals of pharmacotherapy are to prevent or reduce withdrawal symptoms and craving, avoid relapse, and restore to a normal state any physiological functions (eg, sleep, bowel movements) that have been disrupted by opioid use.[28] When continued for ≥3 months, medication has been shown to improve outcomes.[23,24,29] In one recent study, 49% of opioid-dependent participants who were still taking buprenorphine-naloxone at 12 weeks had successful outcomes (minimal or no opioid use), vs 7% of those undergoing a brief buprenorphine-naloxone taper.[24]

There are risks associated with medication-assisted therapy, however. The ones of greatest concern are a potential increase in drug-drug interactions, the risk of diversion (a concern with both buprenorphine and methadone), and the potential for accidental overdose.[2,30]

Buprenorphine, a partial mu-opioid receptor agonist, is a Schedule III controlled substance and can be dispensed by a pharmacy, making inpatient opioid detoxification unnecessary for many opioid-dependent patients. Physicians who wish to prescribe

Treatment for opioid dependence calls for a combination of pharmacotherapy and behavioral therapy—often with oversight by a primary care physician.

buprenorphine for the treatment of opioid dependence must complete an 8-hour course, offered by the American Medical Association and the APA, among other medical groups, and obtain a Drug Enforcement Administration code ("X") license.[31]

Buprenorphine has a high affinity for, and a slow dissociation from, mu-opioid receptors, resulting in the displacement of other opioids from the mu receptor and less severe withdrawal.[32] As a partial agonist, buprenorphine attenuates opioid withdrawal symptoms with a ceiling, or near maximal, effect at 16 mg, thereby lowering the risk for overdose.[33] A sublingual formulation that combines buprenorphine with naloxone, an opioid antagonist that exerts its full effect when injected but is minimally absorbed sublingually, reduces the potential for abuse of buprenorphine without interfering with its effectiveness.[34]

Compared with methadone, buprenorphine is less likely to interact with antiretroviral medications or to cause QTc prolongation, erectile dysfunction, or cognitive or psychomotor impairment.[31,35-37] Limitations include the ceiling effect, which can be a problem for cases in which more agonist is needed; cost (approximately $12/d), and the lack of approval by the US Food and Drug Administration (FDA) for use during pregnancy.

Buprenorphine maintenance involves 3 phases: induction, stabilization, and maintenance.[38] Induction takes place in a clinician's office at the time the patient experiences opioid withdrawal symptoms, typically 6 to 48 hours after taking the last opioid. Extended treatment improves clinical outcomes,[23,24] and longer-term maintenance (of indefinite duration) is frequently required.

Naltrexone is a mu-receptor antagonist, and therefore does not cause physical dependence or have agonist effects such as euphoria and sedation. As a result, it has no diversion value and may appeal to those who view opioid-agonist pharmacotherapy as simply trading one drug for another.[39] Naltrexone is not a controlled substance and is not subject to the regulatory requirements that buprenorphine and methadone face.

Although agonists can be started in the first day or 2 after a patient decides to stop using opioids, patients must be opioid-free for ≥7 days before starting naltrexone. That's because its antagonist properties will precipitate withdrawal if another opioid is present on the opioid receptors. During the 7-day "washout" period, you can treat opioid withdrawal symptoms with medications such as clonidine and dicyclomine, but such symptoms make patients especially vulnerable to relapse while waiting to start naltrexone.

Oral naltrexone's effectiveness as a treatment for opioid dependence has been limited by poor adherence. But a long-acting intramuscular form of the drug, approved by the FDA in 2010 and requiring once-a-month injection, mitigates this concern.[40,41]

Methadone is a full mu-opioid agonist, administered daily at specialized clinics, as a maintenance therapy for opioid dependence. Although office-based physicians can prescribe methadone for pain, the drug can only be used for opioid dependence under the auspices of state- and federally regulated opioid treatment programs (http://findtreatment.samhsa.gov/TreatmentLocator/faces/quickSearch.jspx; a mobile phone application is also available at http://www.samhsa.gov/mobile/treatmentlocator.aspx).

Methadone, a Schedule III controlled substance with a half-life averaging 24 to 36 hours, requires daily dosing.[42] Its slow metabolism and long half-life increase the risk for overdose.

Methadone is best for patients who are highly dependent on opioids and likely to benefit from a structured treatment environment with daily supervision (although patients who are doing well may earn take-home privileges so they don't have to come to the clinic every day).[43] New patients should receive an initial dose of 30 mg or less, and a maximum first-day dose of 40 mg.[44]

Methadone remains the standard of care for pregnant women being treated for opioid dependence, while studies of the effects of buprenorphine and naltrexone on a developing fetus continue. Although methadone's efficacy, particularly in lower doses, is similar to that of buprenorphine,[45] its adverse effect profile is worse. Adverse effects include drug-drug interactions, the potential for respira-

tory depression (especially when combined with alcohol or sedatives), QTc prolongation (which requires monitoring by electrocardiogram), sedation, and weight gain, and should be considered before selecting methadone as a maintenance pharmacotherapy.[30,37,46] And, because relapse rates within 12 months of tapering off methadone have been reported to exceed 80%,[47] both the clinician and the patient need to consider the likelihood of long-term, even lifelong, maintenance before initiating treatment.

Behavioral interventions are a vital part of the picture

Studies evaluating the extent to which various types and amounts of counseling improve outcomes compared with pharmacotherapy alone have had conflicting results.[24,48] Nonetheless, most clinicians consider counseling to be a critical component of treatment for opioid dependence and recommend, at a minimum, either individual or group counseling (various modalities have been shown to be effective) and regular attendance at a self-help group like Narcotics Anonymous. Contingency management, a type of therapy that uses prizes as incentives for desired behaviors; and family therapy, individual counseling, and community-based programs have all been found to improve outcomes.[6,49]

CASE ▶ You refer Sam to an addiction psychiatrist, who stabilizes him on 16 mg buprenorphine/naloxone daily as part of an outpatient treatment program. Sam is enrolled in a weekly buprenorphine stabilization group, where he gives a urine sample each week. He also begins seeing a social worker weekly for counseling and attends Narcotics Anonymous meetings 2 to 3 times a week. At a follow-up appointment with you 6 months later, he reports that he has been abstinent from oxycodone for 6 months, his sleep is improved, and he feels better about his chances of finding another job.

Your role in safeguarding the patient

With the rising prevalence of opioid overdose, patient education aimed at crisis prevention is crucial, as well. Warn patients of the risk of accidental overdose, often associated with relapse, stressing the importance of continuing treatment and taking their maintenance medication exactly as prescribed.

There are other steps you can take to safeguard patients—eg, providing naloxone rescue kits to patients and their families when appropriate. You can also institute diversion and overdose prevention measures for patients taking buprenorphine or methadone—providing a lock box for take-home medication, implementing treatment contracts, and using a designated pharmacy to dispense buprenorphine, for example.[26,27,50]

Regular monitoring, urine drug screens (see **TABLE W1** at jfponline.com), and random pill counts, in which patients are typically given 24 hours to bring in their prescribed medication so it can be counted, can also help keep patients on track. Treatment for concurrent psychiatric disorders—depression, anxiety, and personality disorders are common among patients with opioid dependence—is likely to improve the outcome of treatment, as well. JFP

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Relapse rates within 12 months of tapering off of methadone maintenance are >80%, so patient and clinician need to consider the likelihood of long-term, even lifelong, use before starting treatment.

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Patients must be opioid-free for at least 7 days before starting naltrexone.

TABLE W1

Pharmacokinetics of common opioids: Time detectable in urine*

Drug (half-life)	Time detectable in urine	Comment
Codeine (2.5-3 h)	48 h	Pharmacogenetic-dependent effects may affect detection
Fentanyl Transdermal (17 h) Submucosal (7 h)	Not usually detected in urine (lack of metabolites)	Excretion of transdermal fentanyl can last days
Hydromorphone IR (2.3 h) ER (18.6 h)	2-4 d	Significant interpatient variability
Methadone (8-59 h)	3 d	
Morphine (1.5-2 h)	48-72 h	90% eliminated within 24 h
Oxycodone IR (3.2 h) ER (4.5 h)	Often not detected in urine	High-fat meals may increase serum concentrations of ER formulation
Propoxyphene Parent drug (6-12 h) Metabolite (30-36 h)	6-48 h	

ER, extended release; IR, immediate release.

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