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Opioid Use Disorder: Pathophysiology, Assessment, and Effective Interventions

An evidence-based approach to helping patients with this chronic, relapsing disease.

ABSTRACT: Opioid use disorder (OUD) is a chronic, relapsing disease. Genetic variability, dysregulated stress system response, and history of opioid experimentation or escalating exposure all contribute to the likelihood of developing OUD, which produces complex brain changes that make it difficult to stop opioid use. Understanding the neurobiology of OUD helps nurses anticipate the behaviors of patients with OUD and approach them with empathy. Here, the authors discuss the pathophysiology of OUD, available screening tools, medical treatments, and behavioral interventions that have demonstrated efficacy in reducing substance use.

Keywords: addiction, medication-assisted treatment, motivational interviewing, opioid-related disorders, opioids, opioid use disorder

Opioid use disorder (OUD) has reached epidemic proportions in the United States, with related deaths, health care costs, and economic burden escalating at a rapid pace (see *The Magnitude of the Growing U.S. Opioid Epidemic*[1-3]). In addition to the adverse physical and emotional effects experienced by those who have the disorder, the negative societal effects of OUD are substantial as well. People with OUD often find themselves unable to maintain steady employment or take care of themselves or their families.

The Centers for Disease Control and Prevention (CDC) describes the rise in opioid use and overdose deaths as having occurred in three phases[4]:

- In the 1990s, an increase in prescriptions of opioids for chronic pain coincided with a rise in overdose deaths from prescribed opioids.
- 2010 saw a rapid increase in overdose deaths from heroin.
- 2013 marked the start of a significant rise in overdose deaths involving synthetic opioids, particularly illicit fentanyl.

The rate of opioid overdose deaths in the United States continues to rise, challenging health care providers. In response to this alarming escalation, in 2016 the CDC introduced the *CDC Guideline for Prescribing Opioids for Chronic Pain*, which sought to clarify evidence-based recommendations for using opioids to manage pain in adults ages 18 and older who are receiving treatment outside of a palliative or end-of-life care setting.[5] By mid-2017, 23 states had limited opioid prescribing in some way, with most setting a maximum number of days (ranging from three to 14) for first-time opioid prescriptions and many requiring prescribers to review

their state's prescription drug monitoring program (PDMP) before prescribing to determine whether patients were receiving opioids from other prescribers, thereby increasing their risk of overdose or of developing OUD.[6] In April 2018, the National Institutes of Health launched the Helping to End Addiction Long-Term (HEAL) Initiative, which supports research into strategies that prevent and treat OUD and improve pain management.[7] This article discusses OUD pathophysiology and medical treatments, as well as the screening tools and behavioral interventions that can help nurses support patients in overcoming OUD.

PATHOPHYSIOLOGY OF OUD

OUD is a chronic relapsing disease influenced by such factors as genetics, stress system response, and prior opioid experimentation or increasing exposure.[8] In the United States, nearly 80% of current heroin users report they previously used an opioid medication for nonmedical reasons.[9,10] Prolonged or increasing exposure to opioids is associated with tolerance, dependence, and addiction (see *Drug Use Terminology*[11]).

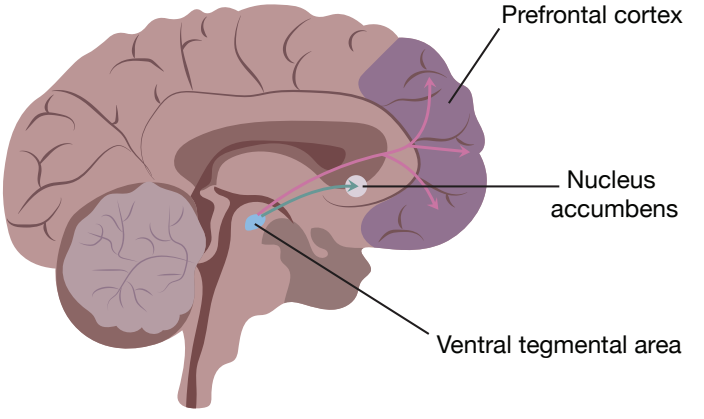
Development of OUD. Current research emphasizes the roles pleasure seeking and pain avoidance play in the development of OUD. Piazza and Deroche-Gamonet point out that humans invest a great deal of time and money in recreational activities, such as sports, music-related activities, visual entertainment, and gourmet food, which are designed specifically to produce feelings of pleasure by altering brain activity, typically through the five senses.[12] They suggest that using drugs, such as opioids, can be seen as another form of recreation in which brain activity is similarly altered, though the alteration occurs as a direct result of the pharmacological substance rather than through the sensory system.

From usage to addiction. Piazza and Deroche-Gamonet posit that the transition to addiction occurs in three stages[12]:

- *recreational drug use*, in which drug intake is moderate and sporadic and only one among many recreational activities the person engages in
- *intensified drug use*, in which drug intake escalates and becomes a primary recreational activity; while social and personal functioning are diminished, behavior remains generally under control
- *addiction*, in which control over drug use is lost and behavior is largely focused on drug seeking and drug taking

The first phase occurs in most people who use psychoactive drugs for nonmedical purposes, as these drugs stimulate a release of rewarding neurotransmitters. The second phase occurs in a portion of those people whose brains have a hyperactive dopaminergic (reward) system and an impaired prefrontal cortex (suggestive of increased impulsivity). The third and final phase is associated with impaired neuronal structure and signaling in the brain's reward-related areas that create such an intense need for the drug that its absence causes intense suffering.

Figure 1. Effect of Opioids on the Brain



Opioids attach to mu receptors in the ventral tegmental area, which releases dopamine into the nucleus accumbens, producing feelings of pleasure that reward the person's drug-taking behavior.

The Magnitude of the Growing U.S. Opioid Epidemic

- In 2013, according to the Centers for Disease Control and Prevention, the U.S. economic burden of prescription opioid overdose, abuse, and dependence was estimated to be greater than $78.5 billion in terms of lost productivity, health care expenses, and criminal justice costs.[1]
- In 2014, deaths from drug overdose in the United States totaled 47,055, triple the number recorded in 1999, and nearly 61% (28,647) of these deaths involved opioids.[2]
- In 2016, the National Survey on Drug Use and Health reported that 948,000 Americans had used heroin in the past year, nearly twice as many as in 2006, with the greatest increase in use occurring among young adults ages 18 through 25.[3]

NEUROBIOLOGY OF OPIOID USE

Under normal circumstances, the prefrontal cortex of the brain, which mediates cognitive, emotional, and behavioral functioning, stops us from pursuing pleasure from behaviors that may be overly risky. Prefrontal cortex feedback, however, may be compromised in people with OUD.[13, 14]

The action of opioids on neuronal receptors. Opioids stimulate the brain's mesolimbic dopaminergic system, as well as other systems, by attaching to neuronal opioid receptors. There are three opioid receptor subtypes: mu, kappa, and delta, in addition to the nociceptin opioid receptor, formerly known as opioid receptor like-1.[15, 16]

Opioids attach to mu receptors in the brain's ventral tegmental area, increasing the release of the neurotransmitter dopamine into the brain's nucleus accumbens, which is involved with reward, dopamine release, and stimulant action (see Figure 1).[14] The release of dopamine into the nucleus accumbens creates pleasurable feelings, thereby rewarding the drug-taking behavior, which may explain why opioids are often taken frequently in the initial stages of opioid use.[14] Opioids also elevate dynorphin neuropeptide levels, which activate the kappa receptors, reducing dopamine transmission and creating feelings of dysphoria (unease or dissatisfaction). This may explain why opioid users often take additional opioids in an attempt to reverse the unpleasant psychological feelings brought on by kappa receptor activation.[17]

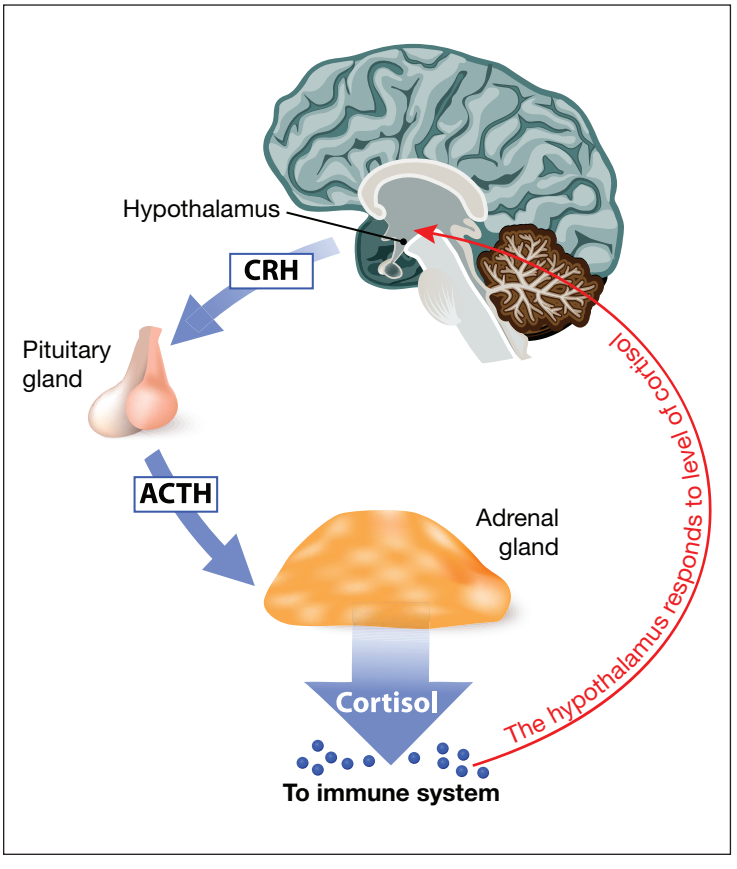
Endogenous versus exogenous opioids. Normally, in response to behaviors that promote healthy living, such as exercise, eating, and sexual activity, the brain produces endorphins, which stimulate the release of endogenous opioids, such as dopamine, in order to reward those healthy behaviors. Exogenous opioids, such as heroin, stimulate the brain to release more dopamine than is released as a natural reward, causing the brain to make adaptations to neuronal structure and signaling. It's been suggested that, eventually, these adaptations raise the "set point" at which dopamine is released so that normally pleasurable activities are no longer enjoyable in the absence of exogenous opioids.[14] The negative physical and psychological effects of drug withdrawal are felt to be so intolerable that drug use often continues despite immense negative consequences, and chronic relapse may occur even long after acute withdrawal.[13]

The hypothalamic–pituitary–adrenal (HPA) axis. Opioids can substantially disrupt the HPA axis, which controls the body's response to stress (see Figure 2[18-20]). The combined effects of HPA axis disruption; the development of tolerance, dependence, and addiction; and the adaptations that the brain

Drug Use Terminology[11]

- Tolerance: the need for a higher dose of a substance to achieve the desired effect
- Dependence: a state in which unpleasant symptoms emerge when a substance to which the body has adapted is withdrawn
- Addiction: a chronic disorder in which a substance is sought and used compulsively despite harmful physical effects or detrimental life consequences

Figure 2. Effects of Opioids on the Stress Response



The hypothalamic–pituitary–adrenal (HPA) axis is the neuroendocrine pathway that controls the body's response to stress. Under normal conditions, the hypothalamus receives input from the brain, autonomic system, environment, and peripheral endocrine glands. When this input signals stress, the hypothalamus releases corticotropin-releasing hormone (CRH), causing the anterior pituitary gland to release adrenocorticotropic hormone (ACTH), which in turn directs the adrenal glands to secrete cortisol, thereby producing the body's stress response.[18, 19] While opioid administration dampens the HPA axis, opioid withdrawal stimulates it.[20] Over time, a continuous pattern of opioid intoxication and withdrawal causes the HPA axis to become hyperresponsive and stress can trigger cravings, putting people at risk for relapse even after months of abstinence.[19, 20]

makes to cope with a massive influx of exogenous opioids make it extremely challenging for people with OUD to remain drug free. Recognizing these challenges can help nurses better understand the behavior of patients with OUD and empathize with their struggle to overcome this disorder.

Patients with signs or symptoms of acute opioid use or withdrawal and those presenting with conditions or adverse events associated with chronic opioid use should raise nurses' index of suspicion for OUD (see *Recognizing Opioid Use and Withdrawal*[21]).

SCREENING FOR OPIOID USE

Several screening tools are available to help nurses assess patients for OUD. These include

- the Kreek-McHugh-Schluger-Kellogg (KMSK) questionnaire, available at http://lab.rockefeller.edu/kreek/assets/file/KMSKquestionnaire.pdf.
- the Drug Abuse Screening Test (DAST-10), available at https://cde.drugabuse.gov/sites/nida_cde/files/DrugAbuseScreeningTest_2014Mar24.pdf.
- the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, OUD Diagnostic Criteria, available at www.aoaam.org/resources/Documents/Clinical%20Tools/DSM-V%20Criteria%20for%20opioid%20use%20disorder%20.pdf.

BEHAVIORAL INTERVENTIONS

The following behavioral and counseling techniques have demonstrated efficacy in reducing substance use and, when combined with pharmacotherapy, often provide enormous positive outcomes:

- Motivational interviewing–a counseling technique that helps patients with OUD work through ambivalence about their drug use and develop motivation to change their behavior.[22]

Patients presenting with conditions or adverse events associated with chronic opioid use should raise nurses' index of suspicion for OUD.

Recognizing Opioid Use and Withdrawal[21]

Signs and symptoms of acute opioid use:

- slurred speech
- sedated appearance
- impaired concentration
- analgesia
- cough suppression
- pinpoint pupils
- "track marks," a pattern of healed or acute puncture wounds from IV injections, usually found along a vein on the nondominant arm

Conditions and adverse events associated with chronic opioid use:

- constipation
- infections of the skin, pericardium, and bones
- HIV
- hepatitis B and C
- pneumonia
- tuberculosis
- hyperalgesia
- accidents
- trauma
- overdose

Signs and symptoms associated with opioid withdrawal:

- runny nose
- tearing
- yawning
- sweating
- tremors
- piloerection
- pupillary dilation
- abdominal cramps
- diarrhea
- nausea and vomiting
- bone and muscle pain
- dysphoria
- skin crawling
- craving for opioids

Table 1. Using Motivational Interviewing to Support Patients with OUD[22, 26]

Objective Behavior	Current Stage of Change	Internal Processes	Motivational Interviewing Goals	Questions to Ask/Actions to Take
Patient defends opioid use, doesn't acknowledge having a problem, and isn't motivated to stop using illicit opioids.	Precontemplation: Not ready to stop using illicit opioids.	Patient may feel changing behaviors will be too difficult or unpleasant (because of withdrawal symptoms, for example). Previous failed attempts may spark feelings of hopelessness or a lack of confidence.	• Help patients identify negative consequences of illicit opioid use and benefits of stopping use. • Help patients identify personal qualities they like in themselves and build self-confidence. • Teach patients about the addiction disease process, provide educational materials, and refer them to reputable online sources.	*Questions:* • How has your life changed since you started using illicit opioids? • Do you ever feel illicit opioid use gets in the way of relationships, work, school, or taking care of yourself or your family? • How do you imagine your life would change if you weren't using illicit opioids? • Can you tell me about an important life accomplishment, or five things about yourself that make you proud? *Action:* • Refer patients to resources that explain the negative consequences of using illicit opioids.
Patient is aware of negative personal consequences of illicit opioid use, but is still ambivalent about stopping and is weighing the pros and cons.	Contemplation: Considering stopping use of illicit opioids, possibly preparing to stop use.	To move forward, a sense of urgency or motivation to change is crucial.	• Help patients explore possible barriers to giving up illicit opioid use and find solutions. • Help patients identify role models who have successfully given up illicit opioid use.	*Questions:* • What are the three best reasons to quit using illicit opioids? • Why might you want to quit using illicit opioids? • How would you quit, if you decided to do that? • Can you think of anyone or anything that would help you quit using illicit opioids? • Would anyone or anything prevent you from quitting? • Has anyone in your life successfully quit drug use? *Action:* • If patients are unable to identify someone who has successfully quit, help them identify a role model.
Patient has committed to stop using illicit opioids and has made such statements as, "I can't do this anymore."	Preparation: Ready to stop using illicit opioids.	Fear of failure is a primary concern.	• Assist patients in developing a plan to stop illicit opioid use; refer them to treatment centers and support groups. • Help patients set a realistic quit date. • Explain that relapses are common but success can be achieved even after relapse.	*Question:* • What do you think is a realistic date to quit using illicit opioids? *Action:* • Refer patients to treatment centers.

Table 1. Continued

Objective Behavior	Current Stage of Change	Internal Processes	Motivational Interviewing Goals	Questions to Ask/Actions to Take
Patient makes and executes a plan to stop using illicit opioids.	Action: Stopping use of illicit opioids.	Patient may continue to experience fear of failure and resistance to change, lack social support, have unrealistic expectations, and be at increased risk for relapse.	• Encourage positive behavioral changes by celebrating small successes. • Explain that recovery can take a while to achieve. • Help patients identify and establish support systems in giving up illicit opioid use.	*Actions:* • Express encouragement by congratulating patients. Let them know if you've noticed signs they haven't been using illicit opioids, such as a change in their appearance or attitude. • Ask how patients are feeling and whether they've made any connections with others in recovery. • If they haven't, ask if they would like help finding support. • If they're feeling negative about a perceived lack of progress in relationships they neglected while using, explain that change takes time and that people process emotions at different rates.
Patient is committed to not using illicit opioids and has been successful in coping with temptations and avoiding triggers.	Maintenance: Not using illicit opioids for at least six months.	Stressful life events or an encounter with a friend who uses illicit opioids may precipitate relapse.	• Encourage patients to establish new friendships; avoid people, places, and things that trigger illicit opioid cravings; and develop positive, healthy coping mechanisms, such as exercise, volunteering, or psychotherapy. • Continue to celebrate patients' successes.	*Actions:* • Let patients know you're happy to hear they've decided to take positive actions, such as joining a support group, seeing a therapist, or starting an exercise routine. • Continue to express encouragement and to congratulate patients on achievements, such as not using illicit opioids, acquiring stable housing or a job, returning to school, or reestablishing a relationship.
Patient has changed behavior, lifestyle, and attitude toward use of illicit opioids.	Termination: Not using illicit opioids for two years.	Patient projects an observable confidence in avoiding relapse.	• Congratulate patients on their success and continue to encourage positive health behaviors.	*Action:* • Remind patients of their accomplishments and of all the positive life changes they have made.

- Cognitive behavioral therapy–a technique that helps patients with OUD identify triggers for relapse by helping them focus on their current situation and learn relaxation exercises and social techniques that support their recovery efforts.[23]
- Contingency management–the use of tangible rewards, such as cash prizes or vouchers to foster positive behaviors.[24]

MOTIVATIONAL INTERVIEWING

Motivational interviewing is a patient-centered, directive method of counseling that helps patients strengthen their motivations to change by exploring and resolving their ambivalence to change.[25] This technique provides practitioners with a guideline for assessing patients' readiness to change as well as suggestions for encouraging

Table 2. Medication-Assisted Treatment for OUD[21, 28]

Medication	Action at Receptor	Potential Adverse Effects	Implications for Practice
Methadone (Dolophine, Methadose)	Full mu-opioid agonist	Constipation, nausea, drowsiness, sweating, sexual dysfunction, weight gain, edema, amenorrhea, overdose, and prolonged QT interval (the latter more commonly associated with doses > 200 mg/day in patients treated for pain)	• Initially, patients need to attend a licensed treatment center daily, which can interfere with lifestyle flexibility • Good option for moderate-to-severe OUD or if buprenorphine–naloxone treatment has failed • Higher risk of overdose than buprenorphine–naloxone
Buprenorphine–naloxone (Suboxone and others)	Partial mu-opioid agonist/antagonist	Constipation, vomiting, insomnia, sweating, blurred vision, oral hypoesthesia (oral numbness), glossodynia (tongue pain), oral mucosal erythema, palpitations, poor attention span	• Patients can receive prescriptions from a physician, NP, or PA. • Providers must complete and maintain certification to prescribe. • Sublingual and buccal formulations are available for buprenorphine–naloxone. Sublingual and buccal, as well as extended-release injectable and long-term implant formulations are available for buprenorphine monotherapy. • Good option for patients with moderate-to-severe OUD who are motivated to quit and can tolerate a reduced opioid effect. • Overall lower risk of overdose than methadone, except if taken with benzodiazepines or alcohol.
Naltrexone (Vivitrol, Revia)	Mu-opioid antagonist	Insomnia, hepatic dysfunction, nasopharyngitis, injection site pain	• Patients can receive prescriptions from a physician, NP, or PA. • Available as a daily oral tablet or monthly IM injection, though the oral form is not widely used to treat OUD owing to low rates of adherence. • May interfere with pain medications given for acute illnesses or trauma. • Good option for those with mild OUD and a high motivation to quit all forms of opioids. • Does not alleviate withdrawal symptoms.

OUD = opioid use disorder; PA = physician assistant.

positive health choices. Motivational interviewing is used to identify the stage of change a patient with OUD is experiencing. Its basic principles are as follows[22]:

- Resist the "righting reflex," that is, avoid the tendency to tell patients with OUD that they should stop using opioids and instead initiate a conversation that will allow them to verbalize reasons they should stop using.
- Understand patients' motivations and show interest in their concerns, as this will motivate them to stop using.
- Listen to patients and empathize; their ability to stop using opioids starts with their decision to do so.
- Empower patients by helping them identify a plan to stop using.

Motivational interviewing can enable nurses to use patients' objective behavior to determine their stage in the disease process, their readiness to change, the internal processes they may be experiencing, appropriate goals, and questions that can prompt them to take positive actions (see Table 1[22, 26]). Although motivational interviewing can be learned from a book, proper training and practice produce better results.[25]

Online Resources for Nurses

Treatment Locators

Substance Abuse and Mental Health Services Administration
Directory of inpatient treatment providers: http://findtreatment.samhsa.gov

U.S. Department of Veterans Affairs
Locations of programs for veterans with substance use disorders: www.va.gov/directory/guide/SUD.asp

Information and Research Initiatives

National Institutes of Health
The Helping to End Addiction Long-Term (HEAL) Initiative: https://heal.nih.gov

National Institutes of Health/National Institute on Drug Abuse
Understanding Drug Use and Addiction: www.drugabuse.gov/publications/drugfacts/understanding-drug-use-addiction

MEDICATION-ASSISTED TREATMENT

People with OUD need access to a variety of treatment modalities to remain free from opioid use. Medication, mental health services, medical care, addiction counseling, and recovery support services work together to provide a holistic approach.[21] Unfortunately, medication-assisted treatment is greatly underused and there are still providers who encourage an abstinence-only approach. For instance, according to the Substance Abuse and Mental Health Services Administration's Treatment Episode Data Set 2002–2012, the proportion of heroin admissions with treatment plans that included receiving medication-assisted opioid therapy fell from 35.2% in 2002 to 27.6% in 2012.[27] The slow adoption of these evidence-based treatment options for opioid dependence is partly due to misconceptions about substituting one drug for another.[21] The goal of medication maintenance therapy for opioid addiction is to help patients with OUD avoid withdrawal symptoms and minimize cravings, allowing them to achieve their rehabilitation goals, reconnect with family and friends, and return to a productive lifestyle. Medications prescribed for opioid addiction fall into three classes: full mu-opioid agonists, partial mu-opioid agonists, and mu-opioid antagonists (see Table 2[21, 28]).

The full mu-opioid agonist methadone occupies the opioid receptor in the same way morphine does but has a much longer duration of action, with a half-life of eight to 59 hours (approximately 55 hours in opioid-naive patients and 24 hours in opioid-tolerant patients) versus morphine's half-life of one to five hours.[29] Methadone's longer duration of action normalizes the HPA axis, minimizes opioid withdrawal symptoms and cravings, inhibits the effect of illicit opioids, and reduces the risks associated with compulsive opioid use. The partial mu-opioid agonist buprenorphine, often prescribed in a combination formulation with the opioid antagonist naloxone, provides similar advantages to those of methadone, but as a partial agonist, it's less likely than a full agonist to cause respiratory depression. The mu-opioid antagonist naltrexone attaches to the opioid receptor but causes no opioid effects, essentially blocking the effect of opioids and, thereby, preventing patients with OUD from experiencing the "high" of opioid administration.[21]

Several studies have shown that substance use disorders are more stigmatized than other chronic diseases and that health care providers often have negative attitudes toward patients with such disorders.[30-32] Providing health care providers with information on the pathophysiology of opioid addiction, treatment options and programs, and the importance of empathic listening is key to breaking the cycle of shame and blame associated with OUD (see *Online Resources for Nurses*). Nurses can play a pivotal role in advocating the use of OUD screening tools, motivational interviewing, and appropriate treatment for patients with this chronic, relapsing disorder. ▼

For three additional continuing nursing education activities on the topic of opioid use disorder, go to www.nursingcenter.com.

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