

TERMINOLOGY

CLINICAL CLARIFICATION

- Opioid use disorder is a pattern of opioid use that is problematic and leads to significant distress or impairment
 - The term *opioid use disorder* has replaced the terms *opioid abuse* and *opioid dependence* in the diagnostic lexicon¹
 - Defined as occurrence of at least 2 out of 11 specific criteria related to opioid use, over a 1 year time period¹
- A chronic, relapsing medical condition associated with compulsive drug-seeking behavior, physical dependence, and tolerance
- Associated with increased morbidity and death
 - Opioids accounted for 66.4% of drug overdose deaths (13.3 per 100,000 population) in 2016, with increases across age groups, racial/ethnic groups, urbanization levels, and multiple states²
 - The U.S. Department of Health and Human Services declared the opioid crisis a nationwide public health emergency in 2017³

CLASSIFICATION

- Based on severity of diagnostic criteria symptoms:¹
 - Mild: presence of 2 to 3 symptoms
 - Moderate: presence of 4 to 5 symptoms
 - Severe: presence of 6 or more symptoms
- Based on time frame of opioid misuse¹
 - Opioid use disorder (no modifier): currently meets, or has met, opioid use disorder criteria within the past 3 months
 - Opioid use disorder in early remission: not currently meeting opioid use disorder criteria, but met criteria between 3 and 12 months ago
 - Opioid use disorder in sustained remission: has not met criteria for greater than 1 year

DIAGNOSIS

CLINICAL PRESENTATION

- History
 - Signs and symptoms reflect compulsive, prolonged self-administration of opioids for no legitimate medical purpose or, if a medical condition is present requiring opioid treatment, opioids are used in doses greatly exceeding amount needed¹
 - A comprehensive medical assessment is imperative
 - Obtaining information from other sources such as family members (with appropriate patient consent) can also provide important information about drug use⁴
 - Particular attention should be paid to the following:^{5,6,7}
 - Concomitant medical conditions including infectious diseases (eg, hepatitis, HIV, tuberculosis), acute trauma, and pregnancy
 - Evaluation of past and current alcohol and substance use; opioid use often co-occurs with other substance use disorders
 - For opioids, include type and amount used recently, route of administration, last use, and problems resulting from drug use
 - Review prescription drug monitoring program, if available; data may identify patients receiving opioid prescriptions from multiple sources⁶
 - Electronic databases that track controlled substance prescriptions within a state allow health care authorities to obtain timely information regarding prescribing and patient behaviors⁸
 - Sharing between states can be facilitated in most cases⁹
 - Do not capture data from patients receiving prescription drugs written for others
 - State laws vary regarding prescription drug monitoring programs; clinicians should be familiar with associated legal requirements⁶
 - Concomitant use of alcohol and sedatives, hypnotics, or anxiolytics with opioids can lead to respiratory depression
 - Addiction treatment history
 - Includes previous pharmacotherapy and assessment of withdrawal potential
 - Psychiatric history to evaluate for possible co-occurring psychiatric disorders
 - Assessment of mental health status and possible psychiatric disorders should be completed
 - Social and environmental factors
 - Can identify facilitators and barriers to addiction treatment, specifically pharmacotherapy and best environment for treatment
 - Addictive behaviors (eg, gambling, exercise)

Opioid use disorder

- Family history of substance use and addiction treatment, addictive behavior, or psychiatric illness
 - Family history of opioid use disorder or other substance use disorders is common
- Symptoms of opioid use disorder can be grouped into 4 general categories^{1, 10}
 - Impaired control
 - Taking opioids in larger amounts or over longer period than intended
 - Persistent desire or unsuccessful attempts to stop or reduce use
 - Spending significant time obtaining, using, or recovering from use of opioids
 - Craving opioids
 - Social impairment
 - Failure to fulfill home, work, or school obligations as a result of repeated opioid use
 - Continued opioid use despite experiencing social or interpersonal problems
 - Giving up or reducing important social, recreational, or occupational activities
 - Risky use
 - Recurrent opioid use in hazardous situations (eg, driving)
 - Continued opioid use despite knowledge of physical or psychological problems related to use
 - Use of illegal drugs, especially when unknown contents such as diluents (eg, talc) or addition of unknown drugs (eg, fentanyl) may be present
 - Pharmacologic criteria
 - Tolerance: needing increased amounts of opioids to achieve same effect
 - Tolerance typically develops fairly rapidly for analgesic, respiratory-depressant, and euphoria-producing properties; relatively little tolerance occurs to constipation or pupillary constriction¹⁰
 - Physical dependence: a physiologic state of adaptation to a substance, without which, symptoms and signs of withdrawal occur¹¹
 - Note that these pharmacologic criteria are not considered to be met for those taking opioids solely under appropriate medical supervision¹
 - Note that presence of these criteria reflect physiologic changes and do not alone indicate opioid use disorder
- Associated features of opioid use disorder¹²
 - History of drug-related crime may be present (eg, possession or distribution of controlled substances, larceny, robbery, forgery, receiving stolen goods)
 - Social difficulties related to drug use may occur at all socioeconomic levels; includes divorce or other marital difficulties, irregular employment, unemployment
 - Health professionals and those with ready access to legal opioids may have a pattern that involves problems with professional hospital staff, state licensing boards, or other administrative authorities, and is also reflective of illegal activities
 - High-risk sexual behavior and history of sexually transmitted infections is frequently present, particularly in younger patients¹³
 - Women with opioid use disorder often report amenorrhea, which is secondary to the dopaminergic effects of opioids¹³
- Symptoms of opioid withdrawal may be identified and are a consideration in treatment options
 - May be spontaneous (discontinuation or abrupt reduction of opioid dose) or precipitated (administration of opioid agonist [eg, naloxone, naltrexone] or partial agonist [eg, buprenorphine])⁶
 - Precipitated withdrawal occurs faster and may be much more severe, occasionally requiring hospitalization
 - Onset of withdrawal following opioid discontinuation varies with half-life of particular opioid¹³
 - Short-acting opioids (eg, morphine, heroin): symptoms may appear within 8 to 12 hours of last dose, peak at 48 to 72 hours, and clear after 7 to 10 days⁵
 - Longer-acting opioids (eg, methadone): symptoms may take 1 to 3 days to appear after last dose; peak between 3 and 8 days, and do not clear for several weeks⁵
 - Symptoms may be milder than those following equivalent doses of short-acting opioids
 - Initial symptoms include anxiety, restlessness, agitation, and drug craving
 - Symptoms of progressive withdrawal include muscle/joint aches, abdominal cramping, nausea, loose stools, and insomnia
- Physical examination
 - Patients with opioid use disorder often present with no physical signs; may present with signs of opioid intoxication or withdrawal or signs of IV drug use
 - Intoxication
 - Sedation, often with periodic loss of consciousness or brief sleep (head nodding)
 - Decreased respiratory rate (rate of 12 or lower consistent with opioid intoxication¹⁴); may be accompanied by bradycardia, hypotension, and hypothermia

Opioid use disorder

- Constricted pupils (pupil diameter less than 2 mm with decreased reactivity; may not be present if other drugs used concurrently)¹⁵
- Drooping eyelids
- Scratching (to relieve itching caused by histamine release)
- Acute withdrawal
 - Mydriasis (dilated pupils)
 - Diaphoresis
 - Vomiting and diarrhea
 - Tachycardia and hypertension
 - Piloerection (gooseflesh)
 - Rhinorrhea and lacrimation
 - Yawning
 - Observed restlessness
- May be fentanyl patches on the skin or evidence of their use¹⁶
- Injection drug users may have:
 - Recent injection site marks (small red, inflamed puncture wounds with slight bruising surrounding the marks)
 - Old injection sites show pigmentation change and atrophied skin
 - Thrombosed veins
 - Skin abscesses or cellulitis

CAUSES AND RISK FACTORS

- Causes
 - Most opioids bind as agonists to the μ -receptor and typically produce the effects commonly associated with opioids (eg, miosis, respiratory depression, analgesia, euphoria, drowsiness)¹⁰
 - Classes of opioids¹⁷
 - Naturally derived (from opium): morphine, opium, codeine, and thebaine
 - Semisynthetic: buprenorphine, dihydrocodeine, hydrocodone, hydromorphone, oxycodone, oxymorphone, levorphanol, and heroin
 - Synthetic: fentanyl, methadone, meperidine, and tramadol
 - Highly addictive and can cause rapid progression to physiologic tolerance and withdrawal
 - Addiction is a complex disease that affects brain function and behavior
 - Involves alteration of brain structure and function; affects multiple brain circuits, including those involved in reward and motivation, learning and memory, and inhibitory control over behavior¹⁸
 - Effects of prolonged drug exposure compromise the ability to choose; drug seeking and use become compulsive, bypassing individual's self-control or willpower⁵
 - These alterations remain after drug use has stopped
 - May explain why patients with opioid use disorder remain at risk for relapse even after long periods of abstinence despite potentially adverse consequences¹⁸
 - Exact process of opioid addiction has not been clearly defined; contributing factors include the reinforcing properties and availability of opioids, social and environmental factors, genetic vulnerability, personality, and existing psychiatric disorders
 - Opioids all have highly reinforcing pharmacologic properties¹³
 - Positive reinforcement
 - Intrinsic property of opioids is the activation of dopamine receptors, a final common pathway of reward (eg, euphoria, analgesia)
 - Drives early stages of opioid use disorder to achieve positive effects of the drug
 - Negative reinforcement
 - Produced by opioid withdrawal, after physiologic dependence has occurred
 - Opioid withdrawal activates region of brain (locus caeruleus) resulting in increased systemic sympathetic tone and high intensity cravings¹³
 - Increased sympathetic tone leads to some characteristic features of withdrawal (eg, chills, diarrhea, nausea, cramps, anxiety)
 - Later stages of opioid use to avoid negative effects of abstinence
 - Substance use disorder and dependence are heritable disorders
 - Approximately 40% to 60% of susceptibility to substance use disorders is associated with genetic factors¹⁹
 - Environmental and social factors are believed to affect such factors as drug availability and likelihood of initial use¹³
 - Exposure to opioid drug class, both for medical and nonmedical use
 - Use of or permissive attitudes toward opioids by peers, family members, or role models

Opioid use disorder

- Ease of access to opioids, both prescription and illicit (eg, heroin)
 - Use in family and/or friends
 - Physician opioid prescribing patterns may be a factor in opioid use disorder, dependence, and overdose²⁰
- Individual temperaments (eg, impulsivity, novelty seeking) have propensity to develop a substance use disorder¹
- Psychiatric diseases commonly co-occurring with opioid addiction include:
 - Other substance use disorders²¹
 - Strong associations exist between alcohol and cocaine abuse and subsequent development of an opioid use disorder²¹
 - Depression
 - Anxiety
 - Posttraumatic stress disorder
 - Conduct disorder in childhood and adolescence
- Progression of use often follows trend to maximize drug bioavailability and effect; limited access to prescription opioids may also influence progression to IV use¹³
 - Use may start with oral prescription opioids, which can lead to inhaled prescription opioids, to inhaled heroin, and ultimately to injection of heroin (most potent and bioavailable method)
 - Inhalation may involve smoking (heating heroin in foil and inhaling smoke) or nasal snorting (of powdered heroin)
- Risk factors and/or associations
 - Age
 - Can begin at any age but more commonly observed in late teens or early 20s¹
 - Young adults (aged 18-25 years) have highest prevalence of both prescription opioid and heroin use¹³
 - Use of opioids at earlier age associated with higher prevalence of dependence, increased clinical severity, and worse consequences¹³
 - Sex
 - Men are more likely to use most types of illicit drugs (eg, heroin, misuse of prescription drugs)²²
 - Both sexes are equally likely to develop a substance use disorder
 - Gender differences are variable regarding opioid use severity, craving, medical conditions, and associated social and functional impairment²³
 - In general, women progress from use to dependence more quickly than men²³
 - Women have greater likelihood of psychiatric comorbidity (eg, anxiety, depression), medical problems, employment problems, and family/social impairment²³
 - Women may be more susceptible to craving and relapse²²
 - Genetics¹⁹
 - Characterized by genetic heterogeneity, much of which remains unknown
 - Can raise individual risk of addiction to a specific type of drug
 - Genetically determined differences noted in drug metabolism, response to drug administration, and temperamental factors (eg, impulsivity, novelty-seeking)
 - Variations in the μ -receptor (*OPRM1*) gene have been studied, but association with rates of opioid dependence is not clearly established¹³
 - Ethnicity/race
 - White people represent majority of persons with opioid use disorder²⁴
 - Other risk factors/associations
 - Chronic pain conditions (eg, spinal pain, joint pain, general chronic pain, osteoarthritis, migraines)
 - Common in people with opioid use disorder and often present before first diagnosis of opioid use disorder²⁵
 - Long-term opioid therapy is commonly prescribed as treatment for severe chronic pain; opioid treatment for chronic noncancer pain remains controversial owing to its questionable efficacy and association with opioid misuse and use disorders in some individuals²⁵
 - Misuse of prescription opioids is risk factor for heroin use
 - 80% of heroin users report misuse of prescription opioids in the past²⁶

DIAGNOSTIC PROCEDURES

- Primary diagnostic tools
 - Opioid use disorder is primarily diagnosed based on patient history and comprehensive assessment, including a physical examination⁵
 - Diagnose opioid use disorder when patient meets at least 2 out of 11 of the revised diagnostic criteria (*DSM-5*)¹
 - Problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least 2 of the following, occurring within a 12-month period:¹
 - Opioids are often taken in larger amounts or over a longer period than was intended
 - Persistent desire or unsuccessful efforts to cut down or control opioid use

Opioid use disorder

- Significant time spent in activities necessary to obtain, use, or recover from opioid's effects
- Craving, or a strong desire or urge to use opioids
- Recurrent opioid use resulting in failure to fulfill major role obligations at work, school, or home
- Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids
- Important social, occupational, or recreational activities are given up or reduced because of opioid use
- Recurrent opioid use in situations in which it is physically hazardous
- Continued opioid use 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, defined by either:
 - A need for markedly increased amounts of opioids to achieve intoxication or desired effect
 - A markedly diminished effect with continued use of the same amount of an opioid
 - *Note: this criterion is not considered to be met for those taking opioids solely under appropriate medical supervision*
- Withdrawal, as manifested by either:¹
 - Characteristic opioid withdrawal syndrome
 - Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms
 - *Note: this criterion is not considered to be met for those taking opioids solely under appropriate medical supervision*
- Specify if:
 - In early remission: after full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met for at least 3 months but for less than 12 months (with exception that "craving, or a strong desire or urge to use opioids" may be met)
 - In sustained remission: after full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met at any time during a period of 12 months or longer (with exception that "craving, or a strong desire or urge to use opioids" may be met)
- Specify if:¹
 - On maintenance therapy: additional specifier used if individual is taking prescribed agonist medication (ie, methadone or buprenorphine) and none of the criteria for opioid use disorder have been met for that class of medication (except tolerance to, or withdrawal from, the agonist)
 - Also applies to those individuals being maintained on a partial agonist/antagonist, or a full antagonist (ie, oral or depot naltrexone)
 - In a controlled environment: additional specifier used if individual is in an environment where access to opioids is restricted (eg, closely supervised and substance-free jails, therapeutic units, and locked hospital units)
- Specify current severity level:
 - Mild: presence of 2 to 3 symptoms
 - Moderate: presence of 4 to 5 symptoms
 - Severe: presence of 6 or more symptoms
- Comparing old terminology, the term *opioid dependence* most closely compares to the threshold for *moderate use disorder*⁶
- Various withdrawal scales are available to assist in identifying and quantifying severity of opioid withdrawal symptoms, including:⁶
 - COWS (Clinical Opioid Withdrawal Scale): uses both signs and symptoms (objective and subjective)²⁷
- Initial laboratory work-up includes CBC, liver function, hepatitis C, and HIV testing; test women of childbearing age for pregnancy⁵
 - Consider testing for sexually transmitted infections including syphilis and tuberculosis; test for hepatitis A and B if appropriate⁶
 - Hepatitis serology is recommended⁶
- Urine drug testing during the comprehensive assessment process is recommended⁶
 - Objective means to verify patient-reported history of use, to show discrepancy between self-reported drug use and substances detected, and to help determine proper treatment²⁸
 - Results should be used in combination with patient history, psychosocial assessment, and physical examination
 - Can provide information about recent drug use, however:^{6,4}
 - Positive drug test is not diagnostic of physical dependence, opioid use disorder, or its severity
 - Negative urine test does not rule out opioid use, disorder, or physical dependence
 - Many tests available, with variable reliability and validity⁶
 - Interpretation requires thorough knowledge of methodology and reliability
 - Other sample matrices are available (eg, blood, saliva); use individualized according to patient's needs²⁸

Opioid use disorder

- Be aware of potential mandatory reporting requirements²⁹
- Be aware of limitations of various testing matrices
- Laboratory
 - Urine drug testing^{17,4}
 - Understand limitations of tests used, including detection limits and what substances can be detected
 - Used clinically to identify drug use, misuse, diversion, or a suspected substance use disorder or relapse⁴
 - 2 types:
 - Urine drug screen¹⁷
 - Qualitative test performed at point of care (eg, office setting) or by laboratory; provides relatively rapid results
 - Consists of immunoassays that use antibodies to detect drug or drug-class metabolites in urine; interpreted by visual analysis of the test result
 - Standard drug screening panels screen for amphetamines, cocaine, marijuana, opiates, phencyclidine, and often benzodiazepines
 - Screens for opioids metabolized to morphine (eg, codeine, morphine), but not other opioids like oxycodone, hydrocodone, buprenorphine, and methadone
 - Intended for workplace drug testing; substances targeted and their associated cutoff levels are not appropriate in clinical care of patients with addiction²⁸
 - Other commercial immunoassays available include semisynthetic opioids (eg, buprenorphine, hydrocodone, oxycodone) and synthetic opioids (eg, meperidine, methadone, fentanyl)
 - If heroin use is suspected, test for 6-monoacetylmorphine, a metabolite specific only to heroin; however, 6-MAM has an extremely short half-life and is detected in urine for only up to 8 hours after heroin use¹⁷
 - Heroin is rapidly converted to 6-monoacetylmorphine and subsequently to morphine
 - Base drug testing panels on the patient's drug of choice, prescribed medications, and drugs common within patient's geographic location and peer group²⁸
 - May also detect substances with similar characteristics (cross reactivity) leading to false-positive test results
 - Nonopioids with potential for false-positive test results for opiates include quinolones, rifampin, poppy seeds, and dextromethorphan, especially at low cutoff thresholds¹⁷
 - Use as screening test; results are presumptive and prone to false-positive and false-negative outcomes
 - Incorrect interpretation can lead to legal consequences, unemployment, and unnecessary medications
 - Apply clinical judgment, patient history, and other collaborative information to determine if confirmatory testing is warranted
 - Confirmatory testing of positive drug screen results¹⁷
 - Methods include gas chromatography/mass spectrometry and liquid chromatography/tandem mass spectrometry
 - Able to identify specific molecular structures and quantify amount of drug or substance present
 - Requires highly trained personnel and is time consuming
 - Requires understanding of what substances can be detected
 - Generally, positive immunoassay results only require definitive testing when they conflict with patient's account of drug use or to detect specific substances not identified, quantify levels present, or refine accuracy of the results^{28,4}
 - Can help inform decisions with major clinical or nonclinical patient implications (eg, treatment transition, changes in medication therapies, changes in legal status)²⁸
 - A definitive test should be done if patient disputes findings of presumptive test²⁸
 - Confirmatory testing of negative point-of-care drug screen results
 - Not done on all negative point-of-care urine test results but done randomly on some
 - Methods include gas chromatography/mass spectrometry and liquid chromatography/tandem mass spectrometry
 - May show substances not tested for on point-of-care testing that inform decisions with major clinical or nonclinical patient implications
 - Interpretation
 - Cutoff levels
 - Specify concentrations required to produce positive results for immunoassays and confirmation testing; established to help minimize false-positive results, especially in workplace drug testing¹⁷
 - Results lower than established cutoff value are reported as negative; does not indicate the substance is not present, rather that concentration did not meet the cutoff level
 - Be aware of cutoff levels used when interpreting urine drug testing in clinical decision making; use of lower cutoff values may be indicated, such as when testing for medication adherence¹⁷

Opioid use disorder

- Detection times¹⁷
 - Vary with drug characteristics (eg, half-life, dosing intervals and strength, metabolites, drug interactions) and patient factors (eg, body mass, urine concentration and pH, renal or liver impairment)
 - Approximate drug detection time in urine
 - Codeine and heroin (morphine): 48 hours
 - Morphine: 48 to 72 hours
 - Oxycodone and hydromorphone: 2 to 4 days
 - Methadone: 3 days
- CBC and liver function test results may show infection or other medical conditions and liver dysfunction⁶
 - Abnormal results may require further evaluation
 - Baseline testing may be required before initiation of pharmacotherapy

DIFFERENTIAL DIAGNOSIS

- Most common
 - Other substance intoxication¹
 - Alcohol and sedative-hypnotic intoxication can clinically resemble opioid intoxication
 - May be differentiated by absence of pupillary constriction
 - Diagnosis aided by lack of response to naloxone challenge
 - If coingestion exists, naloxone will not reverse all of the sedative effects
 - Clinically appropriate use of opioid medications
 - People may take opioid medications as physician prescribed for legitimate medical indications for long periods of time
 - May develop physiologic signs and symptoms of tolerance and withdrawal also observed in patients with opioid use disorder
 - However, does not result in symptoms of impaired control, social impairment, and risky use
 - Differentiated by applying diagnostic criteria for opioid use disorder
 - Other substance use disorders (ie, alcohol, sedative, hypnotic, or anxiolytic use disorders)
 - May co-occur with opioid use disorder
 - Signs and symptoms may clinically resemble opioid use disorder
 - Similarly associated with impaired control, social impairment, risky use, and pharmacologic criteria of tolerance and withdrawal
 - Differentiated based on thorough history, psychosocial assessment, and physical examination; drug testing can add objective evidence to corroborate information but is not diagnostic

TREATMENT

GOALS

- General treatment goals
 - Stop illicit drug use
 - Prevent or reduce frequency and intensity of relapses
 - Sustain periods of remission
 - Optimize level of functioning during periods of remission
 - Being productive in family, work, and society
- Goals of pharmacotherapy⁶
 - Suppress opioid withdrawal (eg, with methadone or buprenorphine) or prevent relapse after detoxification (eg, with naltrexone)
 - Block effects of illicit opioids
 - Reduce craving; stop or reduce illicit opioid use
 - Promote/facilitate patient engagement in activities related to recovery, including psychosocial therapies

DISPOSITION

- Admission criteria
 - In some cases of mild opioid use disorder, management can be by primary care with medication and referral for intensive outpatient treatment³⁰
 - For moderate and severe opioid use disorder, determination of the most appropriate American Society of Addiction Medicine criteria to assign is best performed by a specialist in addiction medicine³⁰
 - American Society of Addiction Medicine provides criteria for service planning and placement³⁰
 - Inpatient/medically supervised residential treatment may be indicated for withdrawal management in patients with severe withdrawal symptoms, need for significant psychosocial support, or management of medical comorbidities
 - American Society of Addiction Medicine provides criteria for levels of care for withdrawal management for adults³¹

Opioid use disorder

- For pregnant women, some obstetricians initiate opioid agonist therapy in inpatient setting; not always necessary or available, but allows close monitoring of medication response²⁹
- Patients with significant co-occurring substance use disorders, especially severe alcohol or sedative, hypnotic, or anxiolytic use, may require higher level of care; withdrawal may result in seizures, hallucinosis, or delirium⁶
- Patients with severe or unstable psychiatric symptoms may require hospitalization⁶
- Patients with significant medical comorbidities may benefit from admission
- Criteria for ICU admission
 - Precipitated withdrawal from administration of naltrexone may be severe enough to warrant ICU admission⁶
- Recommendations for specialist referral
 - While patients can be treated by primary care providers, patients with moderate to severe opioid use disorder are often referred to an addiction specialist physician who holds subspecialty board certification in addiction medicine or addiction psychiatry
 - State laws vary regarding specific referral requirements (eg, if going over specific daily doses of buprenorphine)
 - Refer to behavioral health care provider to determine optimal type and intensity of psychosocial treatment⁵
 - Consider referring women of childbearing age to gynecologist to discuss contraception
 - Fertility increases as treatment becomes effective

TREATMENT OPTIONS

- Patients often have concomitant medical or psychiatric conditions requiring immediate attention⁵
 - Treat or appropriately refer any urgent or emergent medical or psychiatric problems, including drug-related impairment or overdose⁵
 - Resuscitate volume-depleted patients with IV crystalloid fluids; monitor electrolytes
 - Treatment of opioid overdose³²
 - Support respiration with bag valve mask (or intubation, if necessary)
 - Give naloxone for opioid overdose
 - Provide prescription for naloxone and training on proper use to patients and their families/significant others⁶
 - Administer naloxone to treat opioid overdose
 - Opportunity to refer or initiate treatment for addiction
- Treatment of opioid use disorder
 - Treatment settings, interventions, and services needed vary based on type of drug used and individual patient characteristics (eg, severity of episode, response to treatments, interventions required, comorbidities, complication risks)³³
 - Effective treatment addresses patient's multiple needs, not just his or her drug use disorder¹⁸
 - Includes associated medical, psychological, social, vocational, and legal problems; should also be appropriate to individual's age, sex, ethnicity, and culture
 - Should be a shared decision that accommodates patient preference^{34,6}
 - Consider patient's openness to and understanding of pharmacologic treatment, preferred treatment setting, past treatment experiences, as well as the potential efficacy and safety of treatments
 - Treatment needs to be readily available; longer delays between first contact, initial screening, and treatment result in fewer patients actually entering treatment^{35,33}
 - Treatment does not need to be voluntary to be effective¹⁸
 - Sanctions or enticements from family, work, or criminal justice system can increase treatment entry, retention, and potential success
 - Emergency/inpatient settings
 - To allow initiation of treatment of opioid use disorder as soon as possible, patients may be started on pharmacotherapy in emergency department and inpatient settings by providers without additional Drug Enforcement Agency waiver, under certain conditions
 - Federal guideline on emergency narcotic addiction treatment (Title 21 CFR 1306.07 [b]) allows practitioners not specifically registered as narcotic treatment provider to administer (but not prescribe) narcotic drugs to relieve acute withdrawal symptoms while arranging for referral for treatment³⁶
 - May not be carried out for more than 3 days (also referred to as *the 72-hour rule*); may not be renewed or extended
 - Provider may administer (but not prescribe) buprenorphine or methadone without a waiver, as an induction or bridge medication for up to 3 consecutive days while arranging for referral for treatment²⁰
 - Buprenorphine is most often used, rather than methadone, in this setting
 - Doses may not be prescribed for home use and patient must return daily
 - Provide plan for prompt follow-up in outpatient clinic or addiction treatment facility to continue medication-assisted therapy induction, stabilization, and long-term maintenance²⁰

Opioid use disorder

- Different treatment programs/settings provide variety of intensity of clinical and environmental support services⁶
 - Offer various settings, staffing, support systems, therapies, assessments, documentation, and treatment plans
 - Level of care is determined after determining priority dimensions (by comprehensive assessment), diagnoses, and dose and intensities required³¹
 - American Society of Addiction Medicine established 6 dimensions of multidimensional assessment:³¹
 - 1. Acute intoxication or withdrawal potential: past and current experiences of substance use and withdrawal
 - 2. Biomedical conditions and complications: health history and current physical condition
 - 3. Emotional, behavioral, or cognitive conditions and complications: thoughts, emotions, and mental health issues
 - 4. Readiness to change
 - 5. Relapse, continued use, or continued problem potential
 - 6. Recovery/living environment: individual's recovery or living situation and surrounding people, places, and things
 - Settings include:
 - General outpatient location (eg, clinician's office or practice site)
 - Provide regularly scheduled sessions, usually fewer than 9 contact hours per week for adults³¹
 - When determining whether opioid treatment program or office-based opioid treatment is preferable, consider individual's psychosocial situation, co-occurring disorders, and chance for treatment retention versus risks of diversion
 - Information for locating physicians authorized to treat opioid use disorder or opioid treatment programs can be found on the Substance Abuse and Mental Health Services Administration's website³⁷
 - Intensive outpatient program or partial hospitalization program
 - Typically located in specialty addiction-treatment facility, community mental health center, or similar setting
 - Intensive outpatient programs typically provide 9 to 19 hours of structured programming per week for adults³¹
 - Partial hospitalization programs (day treatment) generally provide 20 or more hours of clinically intensive programming per week³¹
 - Residential addiction treatment facility or hospital
 - Organized treatment services featuring planned and structured care regimen in 24-hour residential setting³¹
- Opioid treatment programs
 - Federally approved programs certified by the Substance Abuse and Mental Health Services Administration in conformance with Title 42 of the Code of Federal Regulations (Part 8)³⁵
 - Also referred to as methadone clinics; opioid medications administered or dispensed include methadone, a Schedule II drug, as well as buprenorphine and naltrexone
 - Can also exist in other settings such as residential and hospital settings
 - Patients with co-occurring alcohol or other substance use disorders (eg, sedatives, hypnotics, anxiolytics) may best be treated in more supervised opioid treatment program setting to reduce risk of adverse events⁶
 - Provide comprehensive, individually tailored program of medication therapy integrated with psychosocial and medical treatment and support services³⁵
 - While proven to decrease opioid use and related sequelae, capacity of opioid treatment programs has been unable to meet demands of increasing opioid addiction¹¹
- Office-based opioid treatment
 - The Drug Addiction Treatment Act of 2000³⁸ allows qualified practitioners who obtain waivers to use buprenorphine to treat opioid use disorder or withdrawal management in an office-based or other health care setting^{35,6}
 - Information on buprenorphine waiver management can be obtained through the Substance Abuse and Mental Health Services Administration³⁹
 - Advantages over specialized opioid treatment programs include greater accessibility and reduced stigma associated with obtaining treatment⁴⁰
 - May not be suitable for patients with active alcohol, sedative, hypnotic, or anxiolytic use disorder or heavy use of these substances⁶
 - Various models exist for providing medication-assisted treatment in primary care settings in the United States. Key components include:⁴¹
 - Pharmacotherapy with buprenorphine or naltrexone
 - Integration of care
 - Psychosocial services
 - Education and outreach
 - A directory of providers authorized to prescribe buprenorphine is published by the Substance Abuse and Mental Health Services Administration⁴²

Opioid use disorder

- Treatment modalities include
 - Pharmacotherapy (ie, methadone, buprenorphine, or naltrexone) combined with psychosocial treatment
 - Use of medications, combined with counseling and other behavioral therapies, is effective in helping patients stabilize their lives and reduce their illicit drug use³³
 - Typically superior to withdrawal management and preferred treatment in most cases
 - Withdrawal management in conjunction with psychosocial treatment
 - Involves medically supervised, controlled tapering of treatment medication (ie, methadone or buprenorphine with or without naloxone) for patients who want to remain abstinent from opioids without medication assistance³⁵
 - Does little alone to change long-term drug abuse; abrupt cessation of opioids can lead to strong cravings and continued drug use^{18, 5}
 - Using opioid withdrawal management as sole treatment for opioid use disorder increases risk of relapse and associated safety concerns⁶
- Pharmacotherapy (medication-assisted treatment), in conjunction with psychosocial interventions, is the cornerstone of treatment
 - Consider patient preference, past treatment, and treatment setting when determining medication
 - Recommended for patients with opioid use disorder who are able to give informed consent and who have no specific contraindication to medication chosen⁶
 - FDA-approved pharmacotherapy for treatment of opioid use disorder includes:⁴⁰
 - Methadone
 - Full opioid agonist; long acting (24-30 hours)
 - Occupies μ -receptors, relieving withdrawal symptoms and reducing or eliminating cravings for opioids⁶
 - Taken orally; reaches brain slowly and dampens euphoric effects
 - Can only be dispensed through federal- and state-approved opioid treatment programs; generally requires daily supervised dosing to help prevent misuse and diversion⁵
 - Regulations require monitored administration of methadone until patient's clinical response and behavior show that unmonitored prescribed dosing is appropriate
 - Recommended for patients that may need daily doses and supervision or who are unsuccessful with buprenorphine treatment⁶
 - Has substantial QT-prolonging effects; can increase risk of ventricular arrhythmia (torsades de pointes), especially at higher doses³⁴
 - Other adverse effects include constipation, sweating, insomnia, decreased libido/sexual performance³⁵
 - Buprenorphine (with or without naloxone, an opioid antagonist)
 - Partial opioid agonists
 - Relieve drug cravings without euphoria or dangerous adverse effects of other opioids⁶
 - Maximal effect is less than full opioids; reaches ceiling where additional doses do not increase effect; limited effect on pain control
 - Safer than full agonists, as respiratory depression is limited by ceiling effect
 - High affinity for μ -receptor; will displace full agonists (eg, morphine, methadone) and reduce their effects⁶
 - Can cause precipitated withdrawal if insufficient time has passed since last opioid dose
 - Full agonists cannot displace buprenorphine
 - Can be prescribed in office-based settings by physicians certified through DATA-2000 (the Drug Addiction Treatment Act of 2000), in addition to opioid treatment programs³⁸
 - Initiated when patients are in mild to moderate withdrawal to reduce risk of precipitated withdrawal⁵
 - Generally at least 6 to 12 hours after last use of heroin/short-acting opioids or 24 to 72 hours after last use of long-acting opioids (eg, methadone)
 - COWS (Clinical Opiate Withdrawal Scale) of at least 11 to 12 (mild to moderate withdrawal) is indicative of sufficient level of withdrawal to initiate treatment (induction) with buprenorphine
 - Available forms include buprenorphine sublingual, buprenorphine-naloxone sublingual or buccal, and implantable buprenorphine
 - Combined buprenorphine/naloxone
 - Preferred over buprenorphine monotherapy in most patients (except if allergic or in pregnant or lactating women)
 - Less likely to be misused or diverted; oral naloxone has poor bioavailability, but becomes bioeffective if taken by IV and can precipitate withdrawal¹³
 - Generally well tolerated; adverse effects can include headache, anxiety, sweating, constipation, fluid retention in lower extremities, and sleep disturbance⁶

Opioid use disorder

- Discontinuation and tapering is a slow process (indefinite duration) and should be closely monitored; typically takes several months⁵
- Naltrexone and extended-release naltrexone
 - Opioid antagonists; long acting; naltrexone (24-30 hours) and extended release (up to 30 days)
 - Block physiologic and subjective effects of exogenous opioids; produce no opioidlike effect and no physiologic dependence⁴³
 - Indicated for the prevention of opioid relapse following detoxification⁶
 - Cannot be initiated until patients are fully detoxified without risking precipitated withdrawal
 - In general, requires about 6 days for short-acting opioids and 7 to 10 days for long-acting opioids (eg, methadone, buprenorphine) after last use⁶
 - A naloxone challenge (administration of short-acting or low-dose naltrexone followed by observation for signs or symptoms of withdrawal) can be used to ascertain patient is no longer physically opioid-dependent
 - Can be prescribed in any setting by any clinician; requires no special regulations for facilities or prescribers⁶
 - Consider for patients with mild opioid use disorder who have occupations not permitting opioid agonist treatment, or when medication administration cannot be supervised⁴⁰
 - Oral formula may be useful when adherence can be supervised or patient is highly motivated; extended-release injectable form may be preferred when issues with adherence are present⁵
 - Outcomes often adversely affected by poor medication compliance⁶
 - Patients must remain abstinent from opioids for 7 to 10 days before initiation of extended-release naltrexone, and therefore this treatment can be difficult to initiate, resulting in increased risk of relapse; once initiated, extended release naltrexone and buprenorphine with or without naloxone have been shown to be equally effective⁴³
 - Adverse effects may include headache, insomnia, decreased energy/sedation, anxiety, nausea/vomiting, abdominal cramping/pain, cold symptoms, and joint/muscle pain
- Maintenance therapy
 - Evidence suggests use of maintenance agonist pharmacotherapy for pharmaceutical opioid dependence⁴⁴
 - Methadone or buprenorphine appear equally effective
 - Ongoing maintenance treatment with buprenorphine appears more effective in maintaining abstinence from opioids than tapering or discontinuation of buprenorphine therapy⁴⁵
 - Factors associated with successful buprenorphine maintenance program include:⁴⁶
 - Stable or controlled psychiatric or medical comorbidities
 - An environment that is safe and substance free
- Length of treatment
 - No predetermined time frame⁵
 - Remaining in treatment for an adequate period is critical³³
 - Individuals progress at various rates; depends on the type and degree of the patient's problems and needs
 - Optimally determined as collaboration between patient and clinicians
 - Best outcomes occur with longer durations of treatment
 - However, research indicates that generally:¹⁸
 - For residential/outpatient setting, less than 90 days is of limited effectiveness and significantly longer times are recommended
 - For methadone maintenance, 12 months is considered minimum, with some individuals benefiting from years
- Relapses
 - Recovery from drug addiction often requires multiple episodes of treatment³³
 - Relapses to drug abuse can occur and treatment should be reinstated or adjusted³³
 - Inform patients of increased risk of overdose/potential death owing to decreased opioid tolerance if patient discontinues agonist (methadone or buprenorphine) or antagonist (naloxone) therapy and resumes opioid use⁶
- Prescribe or supply naloxone rescue kit with counseling on proper use to patients with opioid use disorder and their family members^{6,20}

Opioid use disorder

- Drug therapy
 - For opioid agonist pharmacotherapy (medication-assisted treatment)
 - Buprenorphine
 - For the prevention of undue symptoms of opiate agonist withdrawal during induction of opiate agonist dependence treatment
 - Buprenorphine Hydrochloride Sublingual tablet; Adults: Administer first dose when early signs of opioid withdrawal appear and at least 4 hours after the last used short-acting opioid or 24 hours after last used long-acting opioid. Rapidly titrate dose, in 2 mg to 4 mg increments, until clinical effect is achieved. Use as part of a complete treatment program. Initiate treatment with supervised administration. Single-agent buprenorphine is preferred over buprenorphine; naloxone for induction. Physicians must meet and maintain the requirements of the Drug Addiction Treatment Act in order to provide medication-assisted treatment (MAT) to opioid-dependent patients.
 - Dose up to 12 mg for induction, but 16 mg/day is common maintenance dose
 - Buprenorphine/naloxone
 - For induction treatment in patients dependent on heroin or other short-acting opioid products who are in opioid withdrawal
 - Sublingual film (ie, Suboxone)
 - Buprenorphine Hydrochloride, Naloxone Hydrochloride Oral dissolving film; Adults and Adolescents 16 years and older: ONLY the sublingual route should be used during induction therapy due to higher systemic exposure of naloxone during buccal administration and an increased risk of precipitating withdrawal; the buccal or sublingual route may be used during maintenance therapy. DAY 1 DOSING: First induction dose buprenorphine; naloxone 2 mg/0.5 mg or 4 mg/1 mg SL film; may titrate in 2 or 4 mg increments of buprenorphine, at approximately 2-hour increments, under supervision, up to a total dose of buprenorphine; naloxone 8 mg/2 mg SL film. DAY 2 DOSING: A single daily dose of buprenorphine; naloxone up to 16 mg/4 mg SL film is recommended. DAY 3 DOSING AND BEYOND: Progressively adjust dose in increments or decrements of 2 mg/0.5 mg or 4 mg/1 mg to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms. An adequate maintenance dose should be attained as quickly as possible. To avoid precipitating withdrawal, only initiate the first induction dose when objective signs of moderate withdrawal appear and not less than 6 hours after the patient last used an opioid. Not indicated for induction in patients dependent on methadone or long-acting opioids because these patients may be more susceptible to precipitated and prolonged withdrawal during induction than patients on short-acting agents. Prior to induction therapy, consider the type of opioid dependence (i.e., short- or long-acting opioids), the time since last opioid use, and the severity of opioid dependence. Physicians must meet and maintain the requirements of the Drug Addiction Treatment Act in order to provide medication-assisted treatment (MAT) to opioid-dependent patients.
 - Sublingual tablet (ie, Zubsolv)
 - Buprenorphine Hydrochloride, Naloxone Hydrochloride Sublingual tablet; Adults and Adolescents 16 years and older: Consider type of opioid dependence (i.e., short- or long-acting opioids). Not indicated for induction in patients dependent on long-acting opioids. For short-acting opioid dependence, initiate 1st induction dose only when signs of withdrawal appear and not less than 6 hours after last used opioid. Induction dosing is as follows: DAY 1 DOSING: Initial dose is 1.4 mg/0.36 mg SL. During the remainder of Day 1, may administer 1 to 2 SL tablets of buprenorphine; naloxone 1.4 mg/0.36 mg SL at 1.5 to 2 hour intervals up to a total of 5.7 mg/1.4 mg. Some patients may tolerate up to 3 tablets (1.4 mg/0.36 mg per tablet) as a single, second SL dose. DAY 2 DOSING: A single daily dose of up to 11.4 mg/2.9 mg SL is recommended. Base dosage on clinical need to control acute withdrawal symptoms and administer under supervision. DAY 3 DOSING AND BEYOND: Maintenance target dose is 11.4 mg/2.9 mg SL as a single daily dose. See maintenance treatment section. Physicians must meet and maintain the requirements of the Drug Addiction Treatment Act in order to provide medication-assisted treatment (MAT) to opioid-dependent patients.
 - Methadone
 - NOTE: For the treatment of narcotic addiction in detoxification programs, methadone may be dispensed only by pharmacies and clinics approved by the FDA and state authorities according to treatment requirements stipulated in the federal methadone regulations. However, in a hospital setting, a physician or authorized hospital staff personnel may administer or dispense narcotic drugs to maintain or detoxify a person as an incidental adjunct to medical or surgical treatment of conditions other than addiction

Opioid use disorder

- For the treatment of opiate agonist withdrawal during detoxification treatment
 - Methadone Hydrochloride Oral solution; Adults, including pregnant women: 20 to 30 mg PO initially unless low opioid tolerance is expected; use a lower initial dose for these patients. May give an additional 5 to 10 mg 2 to 4 hours after initial dose if withdrawal symptoms have not been suppressed or if symptoms reappear. Max total dose on day 1: 40 mg. Base subsequent days dosing on withdrawal control at the time of expected peak methadone activity (2 to 4 hours after dosing). May take up to 5 days to achieve steady-state dose. Prior to achieving steady state, adequate total daily doses may not hold patients for a full 24 hours. Continue stabilizing dose for 2 to 3 days.
 - Patients need to show withdrawal symptoms but no signs of sedation or intoxication. Deaths caused by the cumulative effects of methadone have occurred in early treatment
 - Monitor patients with a QTc interval of 451 to 499 milliseconds more frequently and discuss the potential risks versus benefits of treatment; patients with a QTc interval of 500 milliseconds or greater should receive intervention to lower cardiac risk either by discontinuing or lowering the methadone dose or by eliminating contributing factors⁴⁷
- For relapse prevention
 - Naltrexone
 - Oral tablet
 - Naltrexone Hydrochloride Oral tablet; Adults: 25 mg PO with food initially. If no withdrawal signs occur, give 50 mg PO once daily thereafter. NOTE: Naltrexone should be used as part of a comprehensive treatment plan that includes psychosocial support and medication compliance techniques. Patients must be opioid-free for a minimum of 7–10 days before starting naltrexone to avoid precipitation of opioid withdrawal.
 - Intramuscular injection
 - Naltrexone Suspension for injection, Extended Release; Adults: 380 mg IM by gluteal injection every 4 weeks or once monthly.
- For opioid overdose
 - Naloxone
 - Effective dose is empiric³²
 - Goal is to reverse respiratory depression while avoiding precipitous withdrawal
 - Has short half-life; patient should be observed for 4 to 6 hours after respiratory rate has improved
 - Naloxone Hydrochloride Solution for injection; Adults, Adolescents, and Children: 0.4 mg or 2 mg IM or subcutaneously into the anterolateral aspect of the thigh. Seek immediate medical attention after injection. May repeat dose every 2 to 3 minutes as needed if additional doses are available; each device contains a single dose.
 - Naloxone Hydrochloride Solution for injection; Neonates and Infants: 0.4 mg or 2 mg IM or subcutaneously into anterolateral aspect of thigh; pinch thigh muscle during administration. Seek immediate medical attention after injection. May repeat dose every 2 to 3 minutes as needed; each device contains a single dose.
- Nondrug and supportive care
 - Psychosocial interventions
 - Recommended in conjunction with any pharmacologic treatment of opioid use disorder⁵
 - Minimum recommended requirements include psychosocial needs assessment, supportive counseling, links to existing family supports, and referrals to community services⁵
 - Help engage patient in treatment, provide incentive to remain abstinent, modify attitudes and behavior surrounding drug use, manage cravings, and increase skills to cope with emotional/social challenges and environmental cues which may trigger relapse^{6,18}
 - Selecting psychosocial therapy appropriately targeted and individualized to suit patient needs is important
 - Research on optimal interventions to use with medications in opioid addiction is limited⁴⁸
 - Variety of formats available, including:^{6,48}
 - Cognitive-behavioral therapy
 - Learning to recognize and stop negative patterns of thinking and behaving
 - Contingency management
 - Providing incentives to encourage/reinforce positive behaviors
 - Individual, group, and couples counseling
 - Includes behavioral therapy, commonly for substance use disorder treatment¹⁸
 - Behavioral therapies vary in focus
 - May include addressing a patient's motivation to change, providing incentives for abstinence, building skills to resist drug use, replacing drug-using activities with constructive and rewarding activities, improving problem-solving skills, and facilitating better interpersonal relationships¹⁸
 - Participation in group therapy and other peer-support programs during and following treatment can help maintain abstinence

Opioid use disorder

- Mutual help programs
 - Includes 12-step programs such as Narcotics Anonymous, Alcoholics Anonymous, and Methadone Anonymous
 - Other groups include Self-Management and Recovery Therapy, Women for Sobriety, and Secular Organization for Sobriety groups, among many others
 - Not considered a form of treatment on their own, but may provide positive reinforcement and motivation and social support from other members during and after active treatment³⁵
- Motivational interviewing
 - Building motivation/commitment to engaging in treatment and recovery process
- Social skills training
- Family therapy
- Relapse-prevention strategies are an important part of an addiction-treatment plan; opioid use disorder is a chronic, relapsing disease⁵
 - May involve drug counseling and/or other psychosocial treatments; involvement of patient's social network (eg, family, friends, clergy, employers) may provide strong support systems⁷
- Psychiatric treatment may be needed to manage psychiatric comorbidities that complicate addictive disorder or act as trigger³³
- Education/harm reduction
 - Provide targeted risk-reduction counseling for infectious diseases (eg, HIV/AIDS, HBV, HCV, tuberculosis) and link patients to treatment if necessary³³
 - Offer contraceptive counseling to age-appropriate women in treatment for substance use disorder to minimize risk of unplanned pregnancy²⁹
 - Unplanned pregnancy rates are about 80% in women with substance use disorders²⁹
 - Safe injection information to help reduce hazards of injection and can include:
 - Self-administering small test dose to test potency before administering entire dose of drug of unknown potency⁴⁹
 - Proper skin cleaning before injection⁴⁹
 - Using clean/new needles and avoiding reuse of needles or sharing needles⁴⁹
 - Refer to syringe exchange program if available⁵⁰
 - Medication interactions⁴⁰
 - Concurrent use of alcohol, benzodiazepines, or gabapentin with buprenorphine can increase risk of sedation, respiratory depression, and death
 - Naltrexone should not be used concurrently with opioids
- Offer HAV and HBV vaccination, if appropriate⁵
- Comorbidities
 - Viral (eg, HIV, HCV) and bacterial infections¹
 - Most common with opioid injection
 - Other substance use disorders (eg, tobacco, alcohol, cannabis, benzodiazepines, stimulants)¹
 - May be taken to manage symptoms of withdrawal and craving or enhance opioid effects
 - Concomitant use of alcohol, sedatives, hypnotics, or anxiolytics with opioids may contribute to respiratory depression
 - Coexisting psychiatric disorders, including:^{1,6}
 - Depression
 - May be opioid-induced or exacerbate pre-existing primary depressive disorder
 - Anxiety
 - Post-traumatic stress disorder
 - Personality disorders
 - Conduct disorder in childhood or adolescence¹
- Special populations
 - Pregnant women
 - Rise of opioid use in pregnancy has increased parallel to the epidemic in the general population²⁹
 - Pregnant women with opioid use disorder are more likely to seek prenatal care late in pregnancy, miss appointments, and experience poor weight gain⁵

Opioid use disorder

- Complications of untreated opioid use disorder specific to pregnancy include: miscarriage, preterm labor and delivery, intrauterine growth restriction, and neonatal abstinence syndrome⁵¹
 - Neonatal abstinence syndrome is an expected and treatable drug withdrawal syndrome experienced by neonates shortly after birth resulting from chronic maternal opioid use during pregnancy; occurs in 30% to 80% of infants born to women taking opioid agonist therapies^{29, 52}
 - Characterized by disturbances in newborn's gastrointestinal, autonomic, and central nervous systems (eg, irritability, high-pitched cry, tremors, poor feeding, regurgitation, loose stools, sweating, yawning, sneezing)⁵²
 - The term *NOWS (neonatal opioid withdrawal syndrome)* is sometimes used to reflect associated constellation of symptoms⁵¹
 - Dosage of methadone or buprenorphine does not have consistent effect on incidence and severity of neonatal abstinence syndrome⁵¹
- Universal *SBIRT (screening, brief intervention, and referral to treatment)* is essential in early obstetric care to improve maternal and infant outcomes^{53, 29}
 - Validated screening tools include: 4Ps, NIDA (National Institute on Drug Abuse) Quick Screen, and CRAFFT (for women aged 26 years or younger)⁵⁴
 - Providers should be aware of state laws surrounding substance use screening and reporting^{55, 56}
 - Policies that dissuade women from seeking prenatal care are contrary to the welfare of the mother and fetus⁵⁵
- Some elements of prenatal care may require modification (eg, increased testing for sexually transmitted diseases, additional ultrasonography examinations) based on patient's particular clinical needs²⁹
- Care should be comanaged by an obstetrician and an addiction medicine specialist physician⁵
 - Other specialty consults may be required according to individual patient's needs (eg, anesthesiology, pediatrics, pain management, maternal-fetal medicine, nutrition, behavioral health, social services)
 - By federal law, to coordinate care among health care providers, written patient consent regarding addiction treatment must be obtained⁵⁷
- Treatment with opioid agonist pharmacotherapy (medication-assisted treatment) is recommended for pregnant women with opioid use disorder, in addition to counseling and behavioral therapy²⁹
 - Medications include methadone and buprenorphine; benefits and disadvantages exist for both and choice should be individualized⁵¹
 - Methadone²⁹
 - Associated with higher retention rate⁵¹
 - Managed by addiction treatment specialists within registered opioid treatment program in communication with obstetric team
 - With advancing gestation, often requires increased or split dosing to maintain adequate levels⁵
 - Buprenorphine
 - Buprenorphine monotherapy is currently recommended in pregnancy^{51, 29}
 - Use of buprenorphine/naloxone combination therapy appears to have no maternal, fetal, or neonatal adverse effects and may be additional option during pregnancy; however, the FDA only recommends monotherapy in pregnancy⁵¹
 - Compared to methadone, evidence suggests lower risk of preterm birth, greater birth weight, and larger head circumference with buprenorphine treatment; neonatal abstinence syndrome may be less severe and require shorter hospital stays^{58 59}
 - Typically requires fewer dosing adjustments during pregnancy than methadone⁵
 - Hospitalization during initiation of methadone or buprenorphine may be advisable, especially in third trimester⁵
 - Data on safety and efficacy of naltrexone in pregnancy are limited^{29, 51}
 - Infants born to women using opioids during pregnancy should be monitored in hospital for neonatal abstinence syndrome by a pediatric care provider, typically for 4 to 7 days^{51 29}
 - Opioids are recommended as first line drug for newborns with neonatal abstinence syndrome⁵²
 - Encourage breastfeeding for mothers who are stable on opioid agonists, are not using illicit drugs, and have no other contraindications (eg, HIV infection)²⁹
 - Associated with less severe neonatal abstinence syndrome, less need for pharmacotherapy, and shorter infant hospital stay
 - Consider providing prescription for naloxone for emergency administration in case of life-threatening opioid overdose^{29, 5}
 - Not recommended for use in pregnant women as it may precipitate preterm labor or fetal distress, however risk of maternal death from overdose outweighs fetal risks⁶
 - Vaccination for HAV and HBV are recommended if serology is negative⁵

Opioid use disorder

- Adolescents
 - During adolescence (about age 12 into early 20s), neurodevelopmental molding and maturation confer greater vulnerability to addictions; in addition, risk-taking behaviors are generally more prevalent⁶⁰
 - Age at first substance use is inversely correlated with the lifetime incidence of developing a substance use disorder
 - Progression of use from oral opioids to injection of heroin is more prominent in adolescents than adult opioid users; accelerates faster with earlier age of first opioid use¹³
 - Tolerance to opioids happens rapidly in adolescents; heroin's lower cost and higher potency make it appealing as addiction increases
 - Signs of opioid use disorder in younger patients may manifest as failing grades, breaking curfew, and legal involvement
 - Other associated features may include changing peer groups, isolation from family/friends, decreased social and leisure activities, mood changes (eg, depression, irritability, anger), and problematic behaviors (eg, truancy, running away, stealing, lying)¹³
 - Treatment in specialized facilities providing multidimensional services may be beneficial for adolescents⁵
 - Many unique medical, legal, and ethical dilemmas may complicate treatment
 - Full range of treatment options (including methadone, buprenorphine, and naltrexone) can be considered in treatment of opioid use disorder in adolescents; most efficacy studies have been conducted on adults⁵
 - Methadone is not easily available for patients under age 18 years¹³
 - Buprenorphine is FDA approved for adolescents aged 16 years and older⁵
 - Naltrexone may be considered for young adults aged 18 years or older⁶
- Individuals with co-occurring psychiatric disorders
 - Common among individuals with opioid use disorder⁶
 - Higher prevalence of substance use in those with psychiatric disorders than in general population
 - Evaluation for presence of commonly associated disorders, including depression, anxiety, personality disorders, and posttraumatic stress disorder, should be obtained at onset of treatment
 - Patients with psychiatric disorders should be asked about suicidal ideation and behavior⁶
 - Management of patients with suicide risk includes immediate risk reduction, managing underlying factors associated with suicidal intent, and careful monitoring and follow-up
 - Pharmacotherapy in conjunction with psychosocial treatment should be considered for patients with opioid use disorder and a co-occurring psychiatric disorder⁶
 - Providers should have knowledge of potential interactions between medications used to treat opioid use disorder and co-occurring psychiatric disorders
 - Reassessment using a detailed mental status examination should be obtained after stabilization with methadone, buprenorphine, or naltrexone
- Individuals with pain
 - Acute and chronic pain are common among patients with opioid use disorder⁶
 - Accurate diagnosis of cause of pain is important so choice of suitable treatment can be made⁶
 - Nonpharmacologic treatments may be effective (eg, physical therapy)
 - Pharmacologic treatments to consider include:⁶
 - Nonnarcotic medications (eg, NSAIDs, acetaminophen) should be tried initially
 - Adjunctive medications may include anticonvulsants, tricyclic antidepressants, or combined norepinephrine-serotonin reuptake inhibitors
 - Pain management is variable depending on whether patient is in treatment for opioid use disorder⁶
 - Patients with untreated and active opioid use disorder⁶
 - Both methadone and buprenorphine have analgesic effects and may be considered; transition to opioid agonist treatment can help manage both pain and opioid use disorder
 - Patients in treatment for opioid use disorder with opioid agonists⁶
 - Patients on methadone with severe, acute pain will require doses of opioids in addition to their regular daily dose of methadone
 - Those on methadone with chronic pain should be managed in coordination with pain specialist
 - Patients on buprenorphine
 - For mild acute pain: may require temporarily increasing buprenorphine dosing
 - For severe acute pain: discontinuing buprenorphine and starting high potency opioid (eg, fentanyl) with close monitoring is suggested
 - Buprenorphine is often adequate for chronic pain control in patients with opioid use disorder; consider splitting doses

Opioid use disorder

- Patients in treatment for opioid use disorder with opioid antagonist (naltrexone)⁶
 - Will not respond to opioid analgesics in usual manner
 - Mild pain may be treated with NSAIDs and more severe pain with short-term ketorolac
 - Emergency pain control options include: regional anesthesia, conscious sedation with benzodiazepines or ketamine, and general anesthesia using nonopioids
- Individuals in criminal justice system
 - Substantial proportion of people in the criminal justice system (eg, prisons, jails, drug courts, probation, parole) have opioid use disorder and associated problems⁶
 - Screening for opioid use disorder and consideration for initiation or continuation of medication for opioid use disorder is recommended⁶
 - Pharmacotherapy (methadone, buprenorphine, or naltrexone), in addition to psychosocial treatment, may be considered⁶
 - Insufficient evidence to recommend any one treatment superior for prisoners or parolees
 - Pharmacotherapy should be initiated 30 days before release from prison and aftercare established in advance⁶
 - Discharge from prison is often associated with opioid overdose and death

MONITORING

- Drug use during treatment must be monitored continuously, as lapses during treatment do occur¹⁸
 - May provide incentive to maintain abstinence, as well as early indications of relapse and allow for individual treatment plan modification
 - Methadone treatment is monitored through certified opioid treatment programs and involves:⁶
 - Frequent testing for alcohol and other relevant substances in monitoring for relapse
 - Testing for methadone to ensure adherence and detect potential diversion
 - Buprenorphine and naltrexone treatment requires frequent monitoring in early treatment⁶
 - Weekly (at least) office visits recommended until patients are stable
 - Stable patients can be seen less often but at least monthly⁶
 - Stability can be determined by factors such as:⁶
 - Participation in psychosocial treatment and other recovery-associated activities
 - Good occupational and social functioning
 - Abstinence from illicit drugs
 - Typically involves urine drug testing for buprenorphine/metabolites and other substances; other reliable test for presence of drugs may be used⁶
 - Reviewing state Prescription Drug Monitoring Program for other prescribed medication may be useful
- Frequency of urine drug testing is determined by various factors including the stability of patient, type of treatment, and treatment setting^{6,5}
 - More frequent testing is typically required in early treatment or during episodes of relapse
 - Testing at each office visit is common for patients in office-based practice with buprenorphine; federal law mandates at least 8 drug tests per year for patients in opioid treatment programs⁶
 - Periodic definitive/confirmatory testing of negative immunoassay test results for specific drugs or metabolites is warranted⁴
- Treatment and service plans must be continually assessed and modified as necessary to ensure individual needs are met³³
 - In addition to counseling or psychotherapy, an individual may require medication, medical services, family therapy, parenting instruction, vocational rehabilitation, and/or social and legal services
- Diversion potential exists for both buprenorphine and buprenorphine/naloxone. Strategies to reduce diversion include:⁶
 - Frequent office visits
 - Observed dosing
 - Urine drug testing for buprenorphine and metabolites
 - Recall visits for medication counting

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS

- Social/family disruption and lost productivity⁶¹
 - Criminal justice involvement, school dropout, unemployment¹³
- Depression¹
 - Common during chronic intoxication or in association with physical or psychosocial stressors related to opioid use
- Insomnia, especially during withdrawal¹
- Injected opioid complications^{10,1}
 - Hepatitis and HIV infection (HCV can occur in up to 90% of people with opioid use disorder)¹
 - Cellulitis, abscesses from injection directly into subcutaneous tissues (skin popping)

Opioid use disorder

- Bacterial endocarditis
- Tuberculosis
- Peripheral edema secondary to sclerosed veins
- Tetanus and *Clostridium botulinum* infections (rare, but serious)
- Talc granulomatosis
- Risky behaviors (eg, unprotected sexual contact) can lead to contracting infectious diseases such as HIV/AIDS and hepatitis⁶
- Sniffing heroin or opioids can result in irritation of nasal mucosa, potentially resulting in perforation of nasal septum
- Constipation from slowing of gastrointestinal activity and gut motility¹
- Sexual dysfunction¹
 - Erectile dysfunction in men
 - Altered reproductive function and irregular menses in women
- Hyperalgesia⁶²
 - Some evidence suggests chronic opioid use may lead to hyperalgesia, a state of nociceptive sensitization caused by opioid exposure
 - A paradoxical response; patient taking opioids for treatment of pain could become more sensitive to certain painful stimuli

PROGNOSIS

- Opioid use disorder typically continues over many years once established, though brief periods of abstinence are common¹
 - Patients generally require long-term or repeated episodes of care to achieve sustained abstinence and recovery¹⁸
 - Short-term treatment programs focused on abstinence are associated with high relapse rates²⁹
 - Longer treatment is associated with a greater likelihood of abstinence⁶³
- Stable long-term remission is possible with appropriate treatment and follow-up
 - Prevalence of long-term abstinence from opioid use is low (less than 30% after 10-30 years of observation)⁶³
 - Many continue to use alcohol and other drugs after cessation of opioid use
 - Maintaining opioid abstinence for at least 5 years substantially increases the likelihood of future stable abstinence⁶³
- In treated individuals, relapse following abstinence is not uncommon¹
 - Factors that contribute to relapse include:
 - Development of conditioned responses to drug-related stimuli (eg, craving on seeing any powdery substance that look like heroin)¹
 - Occurs with most drugs that elicit intense psychological changes and often persists long after detoxification
 - Comorbid psychiatric disorders and history of abuse (physical or sexual) are associated with persistent opioid use; social/ family support and employment facilitate recovery⁶³
 - Patients who are actively using other substances (eg, marijuana, stimulants) during treatment for opioid use disorder have a poorer prognosis⁶
 - Associated with increased risk of accidental overdose from loss of tolerance
- Acute opioid withdrawal is not typically life-threatening, however:²⁰
 - Patients with comorbid conditions (eg, type 1 diabetes, congestive heart failure, coronary artery disease, liver failure, epilepsy) have increased risk of death
 - Symptoms of withdrawal may lead to behaviors (eg, crime, foregoing needed medical treatments) that increase risk of morbidity and mortality
- Mortality⁶¹
 - Opioid use is associated with increased mortality⁶
 - Long term, the mortality rate of people addicted to opioids is about 6 to 20 times greater than that of the general population⁶³
 - Leading causes of death in people using opioids for nonmedical purposes are overdose and trauma⁶¹
 - Overdose
 - Number of overdose deaths involving opioids (including prescription opioids and illegal opioids such as heroin and illicitly manufactured fentanyl) was 5 times higher in 2016 than in 1999⁶⁴
 - Significant increases in overdose deaths were related to synthetic opioids, particularly illicitly manufactured fentanyl
 - 40% of all opioid overdose deaths involved a prescription opioid⁶⁵
 - Opioid overdose may be accidental or deliberate (clinically distinctive problems)
 - Associated with increased risk for completed suicides and suicide attempts¹
 - Mortality rate owing to infection (eg, cellulitis, HIV, hepatitis, endocarditis) up to 1.5% to 2% per year¹

SCREENING AND PREVENTION

SCREENING

- At-risk populations
 - Screening for drug use remains controversial
 - In 2015, the US Preventive Services Task Force concluded that evidence was insufficient to assess the balance of benefits and harms of screening adolescents, adults, and pregnant women for illicit drug use; this topic is currently in update process⁶⁶
 - However, the Substance Abuse and Mental Health Services Administration recommends SBIRT (substance use screening, brief intervention, and referral to treatment) as part of routine health care⁶⁰
 - The American College of Obstetricians and Gynecologists recommends universal screening of pregnant women for substance use; maternal and infant outcomes are improved with universal screening, intervention, and treatment referral²⁹
 - Pregnancy provides an opportunity to identify and treat women with substance use disorders
 - Screening should be done, in partnership with the pregnant woman, at the first prenatal visit²⁹
 - Screening tools for prenatal substance abuse include: NIDA (National Institute on Drug Abuse) Quick Screen, CRAFFT (for women age 26 or younger), and 4Ps²⁹
 - American Academy of Pediatrics recommends that pediatricians incorporate universal SBIRT (substance use screening, brief intervention, and referral to treatment) practices into the medical care standards for adolescents⁶⁰
 - Providers should educate themselves on state and federal laws surrounding substance use screening and reporting before applying universal screening protocols⁵¹
 - Mandatory reporting of substance use may be required in some states
- Screening tests
 - Screening is not a full assessment; patients with problem identified on screening or through discussion with patient require referral for full assessment³³
 - SBIRT (screening, brief intervention, and referral to treatment):
 - An evidence-based practice used to identify, reduce, and prevent problematic use, abuse, and dependence on alcohol and illicit drugs; useful in any health care setting (eg, emergency departments, primary care centers, office/clinic practices, other community settings)⁵³
 - Screening: use standardized screening tools to assess patient for risky substance use behaviors
 - Brief Intervention: engage patient in short conversation, providing feedback and advice
 - Referral to treatment: provide referral for brief therapy or additional treatment if needed
 - Many screening tools are available, for example:²⁰
 - SOAPP-R (Revised Screener and Opioid Assessment for Patients with Pain)⁶⁷
 - Devised as screening tool for chronic pain patients before initiation of opioid therapy; found to correlate well with opioid use disorder in emergency department setting²⁰
 - NIDA (National Institute on Drug Abuse) Quick Screen:³³
 - First, inquires about patient's (aged 18 or older) drug use during the past year⁶⁸
 - If patient affirms use of illegal or prescription drugs for nonmedical reasons, begin NIDA (National Institute on Drug Abuse)-Modified ASSIST; determine risk level
 - CRAFFT
 - Screening tool validated for adolescents aged 12 through 18 years; 2 or more positive responses indicate need for further assessment⁶⁹
 - Have you ever ridden in a CAR driven by someone (including yourself) who was high or had been using alcohol or drugs?
 - Do you ever use alcohol or drugs to RELAX, feel better about yourself, or fit in?
 - Do you ever use alcohol or drugs while you are by yourself, or ALONE
 - Do you ever FORGET things you did while using alcohol or drugs?
 - Do your FAMILY or FRIENDS ever tell you that you should cut down on your drinking or drug use?
 - Have you ever gotten into TROUBLE while you were using alcohol or drugs?
 - 4Ps²⁹
 - A screening tool for pregnant women; any affirmative answer should prompt further questions
 - Parents: did any of your parents have a problem with alcohol or other drug use?
 - Partner: does your partner have a problem with alcohol or drug use?
 - Past: in the past, have you had difficulties in your life because of alcohol or other drugs, including prescription medications?
 - Present: in the past month have you drunk any alcohol or used other drugs?

Opioid use disorder

- In combination with self-reported data, review of state prescription drug monitoring program may provide objective data for consideration; used alone, does not assess risk for opioid use disorder²⁰

PREVENTION

- Encourage use of nonopioid analgesics to treat pain when appropriate²⁰
 - Physician prescribing may be important driver of opioid abuse, dependence, and overdose
- Guidelines are available for prescribing opioids for chronic pain (defined as pain for 3 months or longer, excluding cancer, palliative, and end-of-life care)
 - CDC guideline provides recommendations for primary care clinicians prescribing opioids for chronic pain (outside of active cancer treatment, palliative care, and end-of-life care)^{70, 71}
 - ASIPP (American Society of Interventional Pain Physicians) has developed guidelines to improve pain and function in chronic noncancer pain on a long-term basis⁷²
- Prescription drug monitoring programs⁸
 - State-level intervention intended to improve opioid prescribing, inform clinical practice, and protect patients at risk
- Education
 - An Opioid Overdose Prevention Toolkit is available from the Substance Abuse and Mental Health Services Administration⁷³
 - Provides strategies to health care providers, communities, and local governments for developing practices and policies to help prevent opioid-related overdoses and deaths
 - Provide adolescents with clear and consistent education about abstaining from substance use, as this is a critical period⁶⁰

SYNOPSIS

KEY POINTS

- Opioid use disorder is a pattern of opioid use that is problematic and leads to significant distress or impairment
 - A chronic, relapsing, complex disease that affects brain function and behavior
- Signs and symptoms reflect compulsive, prolonged self-administration of opioids for no legitimate medical purpose or, if a medical condition is present requiring opioid treatment, are used in doses greatly exceeding amount needed¹
- Primarily diagnosed based on patient history and comprehensive assessment, including a physical examination
 - A comprehensive patient assessment is imperative and includes: concomitant medical conditions, past and current substance use, addiction treatment history, psychiatric history, social and environmental factors, addictive behaviors, and family history for substance use and addiction
- Diagnosis, outlined in *DSM-5*, is based on occurrence of at least 2 out of 11 specific criteria related to opioid use, over a 1-year period; specified as mild, moderate, or severe according to number of symptoms present¹
 - Criteria reflect impaired control, social impairment, risky use, tolerance and withdrawal
- Treatment settings, interventions, and services needed vary based on the type of drug used and individual patient characteristics (eg, severity, response to treatments, interventions required, comorbidities, complication risks)³³
 - Can be treated effectively with a combination of medication (eg, methadone, buprenorphine, naltrexone) and psychosocial services
 - Office-based opioid treatment has increased treatment accessibility by allowing qualified practitioners (with DATA-2000 [Drug Addiction Treatment Act of 2000] waiver) to treat suitable patients with opioid use disorder with buprenorphine
 - Federal guideline on emergency narcotic addiction treatment allows providers without a waiver to administer (but not prescribe) buprenorphine (or methadone) as an induction or bridge medication for up to 3 consecutive days while arranging for referral for treatment
 - Monitoring, continuing care, and maintenance pharmacotherapy for extended time frames recommended to help maintain abstinence, as relapse is common
- Complications include social impairment (family, work relations), depression, constipation, infectious diseases (especially from injected drug use), sexual dysfunction, and hyperalgesia
- Stable long-term remission is possible with appropriate treatment, although prevalence is low (less than 30% after 10-30 years of observation)⁶³
- Opioid use is associated with increased mortality; mortality rate of people with opioid use disorder is about 6 to 20 times greater than that of the general population⁶³

URGENT ACTION

- Identify and treat or appropriately refer any urgent or emergent medical or psychiatric problems, including drug-related impairment or overdose

PITFALLS

- Tolerance and withdrawal are not considered in the diagnosis of patients who are taking opioids under appropriate medical supervision only (eg, significant injury requiring prolonged opioid administration for pain control)¹

Opioid use disorder

- Urine drug tests can provide information about recent drug use but do not identify substance use disorders or physical dependence⁴
- Owing to the relapsing nature of opioid use disorder, clinicians should be vigilant for evidence of relapse or drug seeking in patients with a history of this disease¹²
- Patients are at increased risk of overdose/potential death owing to decreased opioid tolerance if patient discontinues agonist (methadone or buprenorphine) or antagonist (naloxone) therapy and resumes opioid use⁶

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