

# Opioid withdrawal

## TERMINOLOGY

### CLINICAL CLARIFICATION

- Opioid withdrawal is a syndrome of physical and psychological symptoms that occurs after abrupt cessation, therapeutic discontinuation, or dosage reduction of opioids (ie,  $\mu$ -receptor agonists), or after administration of an opioid antagonist or partial opioid agonist to a person who is physically dependent upon opioids as a result of persistent, regular opioid use
- Acute withdrawal symptoms may develop upon abrupt discontinuation of opioids after as few as 5 days of regular and uninterrupted opioid use<sup>1</sup>
- For short-acting opioids (eg, heroin, morphine immediate-release, oxycodone immediate-release), acute withdrawal symptoms usually begin 6 to 12 hours after the last dose, peak in 24 to 48 hours, and diminish over the next 3 to 5 days<sup>2</sup>
- For longer-acting opioids (eg, methadone) or opioid formulations (eg, oxycodone extended-release, morphine extended-release), acute symptoms occur 30<sup>3</sup> to 72 hours after last dose (although anxiety may occur before this) and resolve over the next 10 days or so<sup>2</sup>
- Antagonist-precipitated withdrawal can begin within 1 minute of an IV-administered dose of naloxone and last 30 to 60 minutes. Buprenorphine-induced withdrawal occurs within 90 minutes of sublingual dosage, with most discomfort resolving within hours<sup>4</sup>
- Subacute symptoms of opioid withdrawal (eg, protracted abstinence syndrome, postacute withdrawal syndrome) follow the acute withdrawal period and may persist for weeks, often leading to a return to active use

### CLASSIFICATION

- *Spontaneous withdrawal*: follows abrupt cessation of or dramatic reduction in opioid use
- *Precipitated withdrawal*: follows administration of an antagonist (eg, naloxone, naltrexone) or partial opioid agonist (eg, buprenorphine) to a patient who is physically dependent; symptoms may be more severe than experienced during spontaneous withdrawal but are shorter lived
  - Symptoms caused by use of an antagonist are likely to be more severe than those induced by a partial opioid agonist

## DIAGNOSIS

### CLINICAL PRESENTATION

- History
  - Acute symptoms of opioid withdrawal are highly variable and may include some or all of the following:
    - Myalgia and arthralgia
    - Hyperalgesia
    - Gastrointestinal distress (eg, stomach cramping, nausea, loose stools)
    - Anxiety
    - Moodiness
    - Dysphoria
    - Irritability
    - Insomnia
    - Hot or cold flashes
    - Poor concentration
    - Increased drug craving
  - Subacute symptoms of opioid withdrawal (eg, postacute withdrawal syndrome, protracted abstinence syndrome) include:
    - Depression
    - Anhedonia
    - Insomnia
    - Fatigue
    - Anorexia
    - Drug craving
    - Impaired concentration
    - Sleep disturbances
- Physical examination
  - Acute signs of opioid withdrawal include:
    - Tachycardia
    - Hypertension
    - Diaphoresis
    - Rhinorrhea
    - Oscitation (ie, yawning)
    - Increased lacrimation

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- Muscle twitching
- Restlessness
- Vomiting
- Diarrhea
- Piloerection (ie, gooseflesh)
- Tremor
- Mydriasis

## CAUSES AND RISK FACTORS

- Causes
  - Locus caeruleus is a nucleus contained in the pons, with a high density of noradrenergic neurons that possess  $\mu$ -opioid receptors; it is involved in the stimulation of wakefulness, blood pressure, and breathing, and in overall general alertness<sup>5</sup>
    - Linking of opioid molecules with  $\mu$ -receptors in the locus caeruleus causes suppression of cyclic adenosine monophosphate production and the subsequent reduction in neuronal norepinephrine release; typical symptoms of opioid intoxication occur, including slowed respiration, drowsiness, and decreased blood pressure
    - Repeated exposure to opioids results in heightened neuronal activity of the nucleus cells due to progressive tolerance to the opioid-induced inhibition of norepinephrine release; approximate normal amounts of norepinephrine are released, and the patient feels and appears fairly normal
    - If opioids are not present to suppress the increased activity of locus caeruleus cells, increased amounts of norepinephrine are released and withdrawal symptoms appear (eg, jitters, anxiety, muscle cramps, diarrhea)
  - Mesolimbic reward system also contributes to withdrawal
    - Dopaminergic cells within ventral tegmental area produce dopamine, which is released into the nucleus accumbens upon stimulation of  $\mu$ -opioid receptors, producing the euphoria and reward mechanism that helps drive repeated use of opioid
    - With repeat opioid exposure,  $\mu$ -opioid receptors in the ventral tegmental area neurons become less responsive to opioid binding and less dopamine is released, requiring the patient to increase opioid intake to obtain the desired effect
    - When the opioid is removed, dopamine levels markedly decrease, causing dysphoria and depressed mood and contributing to drug craving
- Risk factors and/or associations
  - Genetics
    - Some evidence supports a genetic component to severity of withdrawal, particularly involving *OPRM1*, a gene that encodes the  $\mu$ -opioid receptor:<sup>6</sup>
      - Presence of the allele *OPRM1* rs6848893 has been associated with worse withdrawal, especially abstinence-induced withdrawal
      - Presence of the allele *OPRM1* rs6473797 has been associated with worse antagonist-induced withdrawal
  - Other risk factors/associations
    - Avoid opioid withdrawal in pregnant women (whenever possible) because it poses potential risks to the fetus; preferably, give pregnant women medication-assisted therapy (eg, methadone, buprenorphine)<sup>7</sup>

## DIAGNOSTIC PROCEDURES

- Primary diagnostic tools
  - Diagnosed through focused history and physical examination consistent with physical dependence on opioids, which reveals repetitive exposure to opioids and uncomfortable and distressing symptoms upon interruption or reduction of opioid or opioid antagonist consumption<sup>8</sup>
  - Drug screening (eg, urine screen for drugs of abuse) can identify or confirm opioid use; however, screening *does not* confirm physical dependence before withdrawal signs are observed<sup>9</sup>
    - Use caution when interpreting urine drug screens, as 1 dose could cause a positive test result; patient history and/or clinician observation of withdrawal signs are required to confirm physical dependence on opioids
    - Some commonly abused drugs, including opioids (eg, fentanyl, buprenorphine, tramadol), are not detected on typical drug screens and require specific testing<sup>10</sup>
    - Many of the more common screens for drugs of abuse do not detect methadone and oxycodone; these drugs require specific assays, which often are routinely added to the main assay
  - Test all women of childbearing age for pregnancy<sup>7</sup>
    - Providing medication-assisted therapy for opioid-dependent pregnant women is generally preferred over introducing the physiologic stress of withdrawal to the fetus or risking maternal relapse, which threatens the well-being of both mother and fetus<sup>11</sup>

# Opioid withdrawal

- Regularly assess (eg, every 2 hours) patients who are at risk for withdrawal from known or suspected prolonged opioid use for withdrawal signs and symptoms. Several validated withdrawal scoring systems are available to help identify and determine the severity of opioid withdrawal: Opiate Withdrawal Scale, Clinical Opioid Withdrawal Scale, Subjective Opiate Withdrawal Scale, and Objective Opiate Withdrawal Scale<sup>12</sup>
  - Outpatient<sup>4</sup>
    - May observe patient in physician's office, in emergency department, or during outpatient therapy (eg, intensive outpatient, partial hospitalization program)
    - Choose treatment based on severity of withdrawal and level of psychosocial support available
  - Inpatient<sup>4</sup>
    - Residential programs allow for observation and treatment of withdrawal
    - Hospital admission is preferred for those with significant comorbidities that cannot be medically managed by a residential program
- Other diagnostic tools
  - Clinical Opiate Withdrawal Scale<sup>12</sup>
    - Each item is scored for severity, and scores are totaled to reflect overall severity of the withdrawal syndrome:
      - Severe: higher than 36
      - Moderately severe: 25 to 36
      - Moderate: 13 to 24
      - Mild: 5 to 12
    - Piloerection
      - 5: prominent piloerection
      - 3: can feel piloerection on patient's forearm
      - 0: smooth skin
    - Anxiety or irritability
      - 4: irritable or anxious to the point of difficulty participating in evaluation
      - 2: obviously anxious or irritable
      - 1: reports anxiety or irritability
      - 0: none
    - Yawning
      - 4: yawns several times per minute
      - 2: yawns 3 or more times during assessment
      - 1: yawns 1 or 2 times during assessment
      - 0: no yawns
    - Tremor (observation of outstretched hands)
      - 4: gross tremor present or muscle twitches
      - 2: mild tremor observed
      - 1: tremor felt but not observed
      - 0: no tremor
    - Gastrointestinal distress (over previous 30 minutes)
      - 5: multiple episodes of vomiting or diarrhea
      - 3: vomiting or diarrhea
      - 2: nausea or loose stools
      - 1: stomach cramps
      - 0: no gastrointestinal symptoms
    - Rhinorrhea or lacrimation (not counting cold or allergy symptoms)
      - 4: nose constantly running or tears streaming down face
      - 2: obvious rhinorrhea or lacrimation
      - 1: nasal congestion or unusually moist eyes
      - 0: not present
    - Arthralgia/myalgia (if pain was previously present, consider only additional component attributed to opiate withdrawal)
      - 4: observed rubbing muscles or joints and unable to remain still due to discomfort
      - 2: reports severe diffuse joint or muscle aches
      - 1: mild diffuse discomfort
      - 0: no pain or discomfort
    - Pupil size (observation)
      - 5: dilated to degree that only iris rim is visible

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- 2: moderately dilated
- 1: possibly larger than normal for room light
- 0: pinned pupils or normal size for room light
- Restlessness (observation)
  - 5: cannot sit still for more than a few seconds
  - 3: frequent extraneous movements of legs and/or arms or shifting
  - 1: reports difficulty sitting still but is able to do so
  - 0: able to sit still
- Sweating (over previous 30 minutes without being accounted for by room temperature or activity)
  - 4: sweat streaming off face
  - 3: beads of sweat on face
  - 2: flushed or has observable facial moisture
  - 1: subjective report of chills or flushing
  - 0: no chills or flushing reported by patient
- Resting pulse rate (after patient has been lying or sitting down for 1 minute)
  - 4: more than 120 beats per minute
  - 2: 101 to 120 beats per minute
  - 1: 81 to 100 beats per minute
  - 0: fewer than 80 beats per minute

## Clinical Opiate Withdrawal Scale (COWS).

Score	Criteria
Resting pulse rate in beats per minute (after sitting or lying for 1 minute)	
0	Pulse rate 80 or below
1	Pulse rate 81 to 100
2	Pulse rate 101 to 120
4	Pulse rate greater than 120
Sweating (over previous 30 minutes, not accounted for by room temperature or patient activity)	
0	No report of chills or flushing
1	Subjective report of chills or flushing
2	Flushed or observable moistness on face
3	Beads of sweat on brow or face
4	Sweat streaming off face
Restlessness (observation during assessment)	
0	Able to sit still
1	Reports difficulty sitting still, but is able to do so
3	Frequent shifting or extraneous movements of legs/arms
5	Unable to sit still for more than a few seconds
Pupil size	
0	Pin size or normal size for room light
1	Possibly larger than normal for room light
2	Moderately dilated
5	So dilated that only rim of iris is visible
Bone or joint aches (if patients was having pain previously, only the additional component attributed to opiates withdrawal is scored)	
0	Not present
1	Mild diffuse discomfort
2	Patient reports severe diffuse aching of joints and muscles
4	Patient is rubbing joints or muscles and is unable to sit still because of discomfort
Runny nose or tearing (not accounted for by cold symptoms or allergies)	
0	Not present
1	Nasal stuffiness or unusually moist eyes

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2	Nose running or tearing present
4	Nose constantly running or tears streaming down cheeks
Gastrointestinal upset (over the past 30 minutes)	
0	No gastrointestinal symptoms
1	Stomach cramps
2	Nausea or loose stool
3	Vomiting or diarrhea
5	Multiple episodes of diarrhea or vomiting
Tremor (observation of outstretched hands)	
0	No tremor
1	Tremor felt by examiner but not observed
2	Slight observable tremor
4	Gross tremor or muscle twitching
Yawning (observation during assessment)	
0	No yawning
1	Yawning 1 or 2 times during assessment (approximately 2 minutes)
2	Yawning 3 or more times during assessment
4	Yawning several times per minute
Anxiety or irritability	
0	None
1	Reports increasing irritability or anxiousness
2	Obviously irritable or anxious
4	Participation in assessment is difficult due to irritability or anxiety
Gooseflesh skin (piloerection)	
0	Skin is smooth
3	Piloerection of skin can be felt or hairs standing up on arms
5	Prominent piloerection
Score: 5-12, mild; 13-24, moderate; 25-36, moderately severe; more than 36, severe withdrawal.	

## DIFFERENTIAL DIAGNOSIS

- Most common
  - Sedative-hypnotic withdrawal
    - Early sedative-hypnotic withdrawal symptoms are similar to opioid withdrawal: agitation, anxiety, increased vital signs, tremors, and gastrointestinal distress
      - As withdrawal develops further, symptoms of untreated or undertreated sedative-hypnotic withdrawal are more severe and may be life-threatening (eg, seizures, cardiovascular instability and collapse, coma) compared with opioid withdrawal
    - History of sustained sedative-hypnotic use (eg, alcohol, benzodiazepines, barbiturates) and/or urine drug screening that supports use of sedative-hypnotics helps to differentiate from opioid withdrawal; additionally, benzodiazepines will suppress withdrawal from sedative-hypnotics, whereas opioids will not
      - Do not use a single positive urine drug screen alone to support the diagnosis of sedative-hypnotic (or other drug) withdrawal because a screen could be positive after single use of a drug; watch for withdrawal symptoms as well
  - Panic disorder
    - Features similar to opioid withdrawal are present during a panic attack: physical signs and symptoms of anxiety (eg, sweating, palpitations, dizziness, tachycardia)
    - Differentiated from opioid withdrawal by relatively fast resolution of symptoms of panic, reaching a peak within minutes of onset
    - Responds to benzodiazepines
    - In most situations, urine drug screen will not show opioids
  - Gastroenteritis
    - Has features similar to opioid withdrawal: nausea and vomiting, diarrhea, and abdominal discomfort
    - Is differentiated by history of exposure to someone with similar symptoms and difference in clinical course
    - Urine drug screen for opioids is typically negative in patients with gastroenteritis

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- Stool studies may be diagnostic, particularly if gastroenteritis is due to bacterial infection
- Influenza
  - Very similar presentation to opioid withdrawal but often with history of exposure to someone with influenza and marked fever
  - In influenza, gastrointestinal symptoms are more rare in adults
  - Urine drug screen for opioids is typically negative in patients with influenza
- Systemic infection
  - Generalized symptoms and signs are similar to opioid withdrawal: anxiety, chills, nausea, vomiting, tachycardia, agitation, and diaphoresis
  - Differentiated by findings of end-organ dysfunction (eg, acute renal dysfunction, delirium) and cardiovascular instability (eg, hypotension) with an infection source (eg, pneumonia, urinary tract) in septic patients
- Thyrotoxicosis
  - Similar presentation to opioid withdrawal: restlessness, anxiety, and irritability, accompanied by tachycardia
  - Thyromegaly and exophthalmos may be present in patients with thyroid excess
  - Differentiated by marked suppression of TSH level in thyrotoxicosis and negative urine drug screen is likely
- Pheochromocytoma
  - Similar presentation to opioid withdrawal: anxiety, diaphoresis, and tachycardia; hypertension and palpitations are also common
  - Differentiated by elevated metanephrine and catecholamine levels in serum and urine, and presence of adrenal tumor on CT or MRI. Also, urine drug screen result is usually negative for opioids

## TREATMENT

### GOALS

- Medical stabilization and management of opioid withdrawal
- Foster patient readiness for effective long-term treatment of opioid use disorder

### DISPOSITION

- Admission criteria
  - Opioid withdrawal does not specifically require inpatient or medically supervised management; however, some patients benefit from inpatient/supervised residential treatment, in which adjunct medical therapies and significant psychosocial assistance can be provided in a supportive environment<sup>13</sup>
  - Inpatient or medically supervised management is also appropriate for patients with medical comorbidities that may require management, which is provided in a residential treatment facility, free-standing detoxification center, or hospital setting<sup>13</sup>
  - American Society of Addiction Medicine criteria help place patients in the appropriate setting, with the necessary degree of medical supervision and intervention<sup>13</sup>
    - Determined by severity of withdrawal symptoms, existence of co-occurring disorders (and need for concurrent medical management), and level of psychosocial support available to the patient
      - Level 4: severe, unstable withdrawal with need for 24-hour nursing care and daily physician visits to modify regimen and manage instability
        - Typical patient has severe withdrawal that requires monitoring or intervention more often than hourly, or may be pregnant, requiring obstetric intervention for a complication (eg, bleeding, leaking amniotic fluid)
        - Treatment is provided in a permanent inpatient facility
      - Level 3.7: severe withdrawal with need for 24-hour nursing care and physician availability. Medically monitored inpatient (or residential) treatment for patients who are unlikely to complete withdrawal without medical and nursing monitoring
        - Typical patient has marked withdrawal requiring close medical monitoring or has a comorbid condition that complicates or worsens the withdrawal process (eg, chronic pain exacerbated by withdrawal, post-traumatic stress disorder with dissociative episodes)
        - Treatment is provided in a permanent inpatient facility (often in a specialty or step-down unit) or in a freestanding withdrawal management/treatment facility
      - Level 3.2: moderate withdrawal with need for 24-hour support to increase likelihood of completing withdrawal management. Clinically managed residential withdrawal management (so-called social detox), emphasizing peer and social support
        - Typical patient has moderate withdrawal when he or she does not have a safe, supportive environment in which to withdraw
        - Treatment is delivered in an office setting, general medical or mental health facility, or addiction treatment facility (eg, day hospital program)

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- Level 2: Moderate withdrawal with need for daytime supervision and support
  - Typical patient is motivated to complete program and has supportive family or nighttime living arrangements
    - Treatment is delivered in office setting, in general medical or mental health facility, or in addiction treatment facility (eg, day hospital program)
- Level 1: mild withdrawal with daily or less than daily outpatient supervision. Ambulatory (outpatient) withdrawal management not requiring extended onsite monitoring
  - Typical patient would not have used high-potency opioids (eg, injectable or smokable forms) daily for more than 2 weeks before admission or use of opioids is close to therapeutic level
    - Treatment is delivered in an office setting, in a medical health care or mental health facility, or in an addiction treatment center
- For patients unable to complete withdrawal management at a lower level of service (eg, experiencing intense cravings, increasing suicidal ideation) after a time of observation, increased intensity of supportive services (ie, increasing the level of management) is indicated

## Admission criteria: American Society of Addiction Medicine.

Level	Definition	Management	Typical patient	Treatment delivery
1	Mild withdrawal with daily or less than daily outpatient supervision	Ambulatory (outpatient) withdrawal management not requiring extended onsite monitoring	Has not used high-potency opioids (eg, injectable or smokable forms) daily for more than 2 weeks before admission, or opioid use is close to therapeutic level	Office setting, general medical or mental health facility, or addiction treatment facility (eg, day hospital program)
2	Moderate withdrawal with all day withdrawal management and supportive living arrangement or family for nighttime support	Ambulatory withdrawal management with extended onsite monitoring	Has moderate withdrawal symptoms, can be managed well during the day, and is motivated to obtain further therapy	Office setting, general medical or mental health facility, or addiction treatment facility (eg, day hospital program)
3.2	Moderate withdrawal with need for 24-hour support to increase likelihood of completing withdrawal management	Clinically managed residential withdrawal management (ie, "social detox"), emphasizing peer and social support	Is in moderate withdrawal and does not have a safe, supportive environment in which to withdraw	Typically, nonmedical facility with medical care available locally
3.7	Severe withdrawal with need for 24-hour nursing care and physician availability	Medically monitored inpatient (or residential) treatment for patients unlikely to complete withdrawal without medical and nursing monitoring	Is in marked withdrawal, requiring close medical monitoring, or has a comorbid condition that complicates or worsens withdrawal process (eg, chronic pain exacerbated by withdrawal, posttraumatic stress disorder with dissociative episodes)	Permanent inpatient facility (often in a specialty or step-down unit) or a freestanding withdrawal management/treatment facility
4	Severe, unstable withdrawal with need for 24-hour nursing care and daily physician visits to modify regimen and manage instability	Intensive medical management and counseling	Is in severe withdrawal, requiring monitoring or intervention more often than hourly, or is pregnant, requiring obstetric intervention for a complication (eg, bleeding, leaking amniotic fluid)	Permanent inpatient facility

Data from Mee-Lee D et al: The ASAM Criteria. Treatment Criteria for Addictive, Substance-Related, and Co-Occurring Conditions. 3rd ed. Carson City, NV: The Change Companies; 2013

- Recommendations for specialist referral
  - Refer to an addiction medicine physician, addiction psychiatrist, or medical toxicologist with addiction experience for evaluation, treatment recommendation, and ongoing management; look for subspecialty board certification in addiction medicine or addiction psychiatry when choosing a referral
    - Properly trained clinicians (eg, licensed alcohol/drug counselors, social workers) can assess patient and recommend appropriate level and location of care after withdrawal is completed or after patient is placed on methadone or buprenorphine

# Opioid withdrawal

## TREATMENT OPTIONS

- Managing opioid withdrawal alone (generally referred to as *detoxification*) without initiating a plan for ongoing disease management is not considered a treatment strategy for the patient with opioid use disorder because there is a high risk of relapse<sup>4</sup>
  - Medication-assisted therapy (eg, methadone or buprenorphine maintenance) is recommended for most patients owing to superior patient retention, greater periods of abstinence from abused opioids, and marked reduction in morbidity and mortality
- Many situations exist in which managed opioid withdrawal *without* ongoing medication-assisted therapy is appropriate, including:<sup>4</sup>
  - Patient prefers to regain a drug-free state and maintain abstinence from opioid use without medication assistance. These are typically highly motivated patients (often due to threatened work restrictions) with solid psychosocial support (eg, health professionals, airline pilots)
  - Withdrawal management (ie, detoxification) is the only treatment available in the area
  - Mild opioid dependence (eg, regular use of relatively low amounts of an opioid and/or history of mild withdrawal symptoms)
  - Iatrogenic physical dependence following prolonged controlled use of opioids in outpatients (often managed by gradual dose taper)
  - Iatrogenic physical dependence in inpatients who had extended hospitalization for a critical illness and who required prolonged use of opioids (eg, sustained sedation for ventilator tolerance in an ICU patient)
    - Weaning protocols are usually in place at institutions and generally support a 5% to 10% daily reduction in the opioid to avoid significant withdrawal discomfort
- Preferably, patients presenting in opioid withdrawal are evaluated by a clinician skilled in the assessment of opioid use disorders who recommends an appropriate initial treatment based on diagnosis as supported by *DSM-5*<sup>14</sup>
  - Information required includes reported type of opioid and amounts used, frequency and route of administration, treatment history, last use of opioids, and problems related to their use
- Withdrawal risk is determined by amount of drug used and patient-reported severity of withdrawal symptoms, which occur in all opioid-dependent patients<sup>2</sup>
  - Mild risk: 1 to 2 bags of heroin daily or less than 50 mg oxycodone or equivalent daily (less than 75 morphine mg equivalents)
  - Moderate risk: 3 to 6 bags of heroin daily or 50 to 100 mg oxycodone or equivalent daily (75-150 morphine mg equivalents)
  - Severe risk: more than 6 bags of heroin daily or more than 100 mg oxycodone or equivalent daily (more than 150 morphine mg equivalents)
    - Opioid equivalency data are available, such as that provided by the CDC<sup>15</sup>
- When withdrawal from opioids without medication-assisted therapy is considered appropriate, medical management (ie, detoxification) rather than abrupt discontinuation is recommended; life-threatening complications are not a usual component of opioid withdrawal, but medical management is strongly recommended because:<sup>16</sup>
  - Patients may exit therapy against medical advice and return to active opioid use because they are experiencing marked discomfort and strong drug cravings
  - There is a potential for complication of medical and surgical conditions
  - The clinician-patient relationship is strained significantly when withdrawal discomfort is not adequately managed
    - A poor clinician-patient relationship affects patient trust and makes it difficult to engage the patient and provide direction into effective therapy beyond withdrawal management
- Inpatients who develop withdrawal and those experiencing withdrawal who require admission are moved to a quiet area with subdued lighting, where they can rest or ambulate as needed; restraints are not used.<sup>4</sup> According to WHO, physical exercise is not recommended while withdrawal symptoms are present as this may prolong withdrawal and worsen symptom severity<sup>8</sup>
  - Reassure patients that symptoms are taken seriously and efforts are being made to reduce their severity
- Clinical Opiate Withdrawal Scale is useful to determine presence of withdrawal, severity of withdrawal, and patient response to therapies<sup>12</sup>
  - For patients with mild (Clinical Opiate Withdrawal Scale score of less than 13) withdrawal symptoms, symptomatic management may be adequate (eg, loperamide for diarrhea, ondansetron for nausea/vomiting), although  $\alpha_2$ -agonist therapy (clonidine or lofexidine) is also strongly recommended to diminish symptom severity<sup>4</sup>
  - Manage patients with moderate (Clinical Opiate Withdrawal Scale score of 13-36) to severe (Clinical Opiate Withdrawal Scale score of greater than 36) withdrawal symptoms with  $\alpha_2$ -agonist therapy or (preferably) a tapering schedule of methadone or buprenorphine (if not proceeding to medication-assisted therapy), rather than abruptly discontinuing all opioids



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- $\alpha_2$ -adrenergic agonists (eg, clonidine, lofexidine) and symptomatic management or as a supplement to other medication<sup>4</sup>
  - Owing to the noradrenergic basis of withdrawal symptoms,  $\alpha_2$ -adrenergic agonists have been employed off-label for many years to treat opioid withdrawal<sup>17</sup>
  - Hypotension often limits their use, particularly clonidine, so it is generally not used alone any more<sup>17</sup>
  - Lofexidine is not used alone in the United States, but it is used alone in the United Kingdom<sup>18</sup>
- Methadone taper<sup>4</sup>
  - Outpatient methadone detoxification, using a gradually tapering dose, is appropriate when patients are otherwise medically fit and stable
    - Methadone tapering for acute withdrawal management usually lasts from 6 to 10 days, decreasing methadone dose by 10% to 20% per day
    - In the United States, outpatient methadone detoxification must be provided through a licensed opioid treatment program
    - Although buprenorphine is, for the most part, clinically equal to methadone, methadone may be the better choice for patients with any or all of the following:<sup>19</sup>
      - Lack stable lifestyle (eg, homeless)
      - Lack ability to pay for buprenorphine
      - Require a broader range of services as may be provided through a comprehensive methadone program (ie, opioid treatment program)
    - A complete listing of US methadone treatment providers (ie, opioid treatment programs) by state is available<sup>20,21</sup>
  - Inpatient hospital setting: methadone may be prescribed by any clinician (including physician assistant and nurse practitioner in some states) with full prescriptive authority (including Drug Enforcement Administration Schedule II through V drugs) to maintain or detoxify an opioid-dependent patient as an *adjunct to the management of conditions other than the dependency* (eg, myocardial infarction, surgical management) so that opioid withdrawal does not complicate a primary medical problem<sup>22</sup>
    - It is recommended that the admitting physician be in contact with the patient's opioid use disorder treatment provider to obtain history, including confirmation of the patient's daily dose requirement, and to maintain treatment continuity
  - Also, the law allows prescribing clinicians to administer (but not prescribe for outpatient use) methadone for the treatment of opioid withdrawal alone for a nonrenewable 72-hour period while arranging the patient's referral for treatment (known as the *72-hour rule*). This allows flexibility for clinicians when confronted with a patient in opioid withdrawal<sup>22</sup>
    - No more than 1 day's dose of methadone may be administered or given to the patient at a time
- Buprenorphine taper<sup>4</sup>
  - In the United States (as a result of the Drug Addiction Treatment Act), buprenorphine, a partial  $\mu$ -opioid agonist with a very high affinity for the  $\mu$ -receptor, may be used for opioid detoxification in an outpatient (ie, office-based) setting, provided the prescribing clinician has received appropriate training in use of buprenorphine and Drug Enforcement Administration certification to prescribe from an office or clinic setting<sup>23</sup>
    - Listing of US buprenorphine providers by state is available<sup>24</sup>
  - Appears to be equal to methadone in efficacy, but its legal status, allowing prescription and dispensing in an outpatient setting (ie, *x-waiver*), increases its availability. It can also be dispensed or prescribed from opioid (ie, methadone) treatment programs<sup>25</sup>
    - Eliminates need for daily visits to obtain medication
    - Safer than full agonists (eg, methadone) owing to its *ceiling effect* (ie, increase in dose reaches a plateau, with higher doses having no further effect), with less risk of overdose and lower bioavailability<sup>25</sup>
      - Combination of a sedative-hypnotic (eg, ethanol, benzodiazepines) or another opioid with buprenorphine appears to mitigate the ceiling effect
    - Safe for use in primary care setting<sup>25</sup>
  - As with methadone, buprenorphine may be ordered in the inpatient hospital setting by any clinician with full prescribing authority (Drug Enforcement Administration certification) in order to maintain or detoxify an opioid-dependent patient as an *adjunct to the management of conditions other than the dependency*<sup>23</sup>
    - 72-hour rule also applies, which allows buprenorphine to be administered, when it is not required as an adjunct to the management of other conditions, for a nonrenewable 72-hour period while arranging the patient's referral for treatment; limited to 1 day's dose administered or given to the patient at a time<sup>23</sup>
      - Does not allow prescribing for take away dosing without a Drug Enforcement Administration waiver (ie, x-waiver)
  - Buprenorphine taper may be as brief as 3 to 5 days (rare) or as long as 30 or more days; it often takes several months.<sup>3</sup> Optimum taper duration is determined by patient response. Comparative efficacy between short and long tapers has not been determined, but longer tapers may be better tolerated<sup>3</sup>

# Opioid withdrawal

- Do not initiate buprenorphine until the patient is in mild to moderate withdrawal (ie, Clinical Opiate Withdrawal Scale score of 13 or greater) to avoid precipitated withdrawal; some clinicians hold initial dose until patient has a Clinical Opiate Withdrawal Scale score of 25 or higher, particularly a patient with more severe dependence<sup>12,26</sup>
- Buprenorphine is usually provided as a combination sublingual film or tablet containing both buprenorphine and the antagonist naloxone; naloxone is not effective orally or sublingually, but it is effective if improperly used intravenously, decreasing the opioid effect and lowering potential for abuse
- Ultrarapid (anesthesia-assisted) detoxification is **no longer recommended**
  - Life-threatening adverse events may occur, including pulmonary edema, aspiration pneumonia, and diabetic ketoacidosis, which may lead to cardiac arrest and sudden death.<sup>4</sup> Ultrarapid detoxification is no more efficacious in reducing withdrawal severity than more standard methods of withdrawal management<sup>27</sup>
  - Not recommended by American Society of Addiction Medicine,<sup>4</sup> and in 2013 the CDC published a warning of possible death with this method<sup>28</sup>
- Drug therapy
  - Opioid agonist therapy<sup>4</sup>
    - Methadone
      - If provided for outpatient management, patient must ensure that medication is kept in a secure location that children cannot access
      - For treatment of opioid agonist withdrawal during detoxification treatment
        - Short-term therapy: stabilize opioid agonist withdrawal with methadone (low- and slow-dose initiation due to prolonged half-life of methadone and risk of inadvertent iatrogenic overdose)
        - 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.
        - NOTE: Prescribing clinicians may use methadone to manage withdrawal in an inpatient setting when the patient is admitted for a primary medical problem **other than addiction**; clinicians do not require government registration to administer or order methadone in this setting<sup>22</sup>
        - 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
        - Patients with a QTc interval of 451 to 499 milliseconds should receive more frequent monitoring 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 factors<sup>29</sup>
      - After acute stabilization, discontinue methadone
        - Methadone Hydrochloride Oral tablet; Pregnant women: Medical withdrawal of methadone maintenance is generally not recommended during pregnancy. If required, slow decrements of 2 to 2.5 mg q7 to q10 days. OB needs to monitor the effects on the fetus.
        - Methadone Hydrochloride Oral tablet; Adults: Dose decrements as tolerated by patient on a daily basis or at 2-day intervals. Dose sufficient to keep withdrawal symptoms tolerable. Many hospitalized patients may tolerate daily dosage reductions of 20%. In ambulatory patients, a slower downward schedule may be required.
    - For medical management (ie, maintenance treatment) of opiate agonist dependence in conjunction with appropriate social and medical services
      - Long-term therapy: initiate methadone maintenance therapy in an opioid treatment program
        - Methadone Hydrochloride Oral tablet; Adults: Following induction therapy and detoxification, titrate patients to a dose that prevents opioid withdrawal symptoms for a full 24 hours, reduces drug craving, and blocks/attenuates the euphoric effects of self-administered opioids, ensuring that the patient is tolerant to the sedative effects of methadone. Usual dose: 80 to 120 mg/day PO. Pregnant women may require dose adjustments during pregnancy to provide effective dosing. MAINTENANCE: In the U.S., administer under the Code of Federal Regulations (CFR), Title 42, Section 8.12. Continue as long as patient compliant and continued benefit derived. DISCONTINUATION: Avoid abrupt discontinuation due to risk for opioid withdrawal symptoms and relapse of addiction. Individualize rate of taper; generally reduce dose by less than 10% of the established maintenance dose, with 10 to 14-day intervals between dose reductions.

# Opioid withdrawal

- After maintenance treatment, discontinue methadone
  - Methadone Hydrochloride Oral tablet; Adults: Dose decrements as tolerated by patient on a daily basis or at 2-day intervals. Dose sufficient to keep withdrawal symptoms tolerable. Many hospitalized patients may tolerate daily dosage reductions of 20%. In ambulatory patients, a slower downward schedule may be required.
- Buprenorphine<sup>4</sup>
  - If prescribed or dispensed for outpatient management, patient must ensure that medication is kept in a secure location that children cannot access
  - Buprenorphine induction
    - NOTE: Physicians must meet and maintain the requirements of the Drug Addiction Treatment Act to provide medication-assisted treatment to opioid-dependent patients on an outpatient basis
    - NOTE: Prescribing clinicians may use buprenorphine to manage withdrawal in an inpatient setting when the patient is admitted for a primary medical problem *other than addiction*; clinicians do not require a Drug Addiction Treatment Act waiver to administer or order in this setting<sup>22</sup>
    - 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.
  - Subsequent gradual buprenorphine dose reduction<sup>26</sup>
    - Reducing buprenorphine to eventually discontinue it can occur over a short (ie, 3-7 days), moderate (10-14 days or longer, with 2 mg [or 10%-20%] sublingual dose reduction every 2-3 days), or longer period
    - Reducing buprenorphine over longer periods is believed to be more effective in reducing recurrent use than discontinuing it over shorter periods<sup>26</sup>
- $\alpha_2$ -adrenergic agonists<sup>4</sup>
  - Clonidine
    - Clonidine Hydrochloride Oral tablet; Adults: The usual initial dose is 0.1 mg to 0.2 mg PO, with titration to a maximum total dose of 1 mg/day PO, administered in two to four divided doses, according to response and tolerability (e.g., blood pressure). Maximal doses are generally administered for two to four days after cessation of the opiate during the time of maximal withdrawal. Clonidine doses are then tapered, and the drug is discontinued 7 to 10 days after cessation of the opiate. American Psychiatric Association (APA) guidelines state that an initial dose of clonidine 0.1 mg PO three times (total 0.3 mg per 24 hours) is usually sufficient to suppress signs of opiate withdrawal. Use of higher doses may be acceptable during inpatient detoxification - monitor for hypotension and sedation. Adjust subsequent dosing until withdrawal symptoms are reduced. Hold the dose if blood pressure falls below 90/60 mmHg, and resume when BP returns to normal. Elderly patients may be more sensitive to the effects (sedation and hypotension) of the usual dosage and may require lower dosages. Clonidine may be a useful alternative to buprenorphine for targeting noradrenergic-mediated withdrawal symptoms such as nausea, vomiting, diarrhea, cramps, and sweating.
  - Lofexidine
    - Lofexidine Oral tablet; Adults: Initially, 0.54 mg (3 x 0.18 mg tablets) PO 4 times daily (given every 5 to 6 hours) is usual dose during peak withdrawal symptoms (e.g., first 5 to 7 days following the last opioid use) ; base dose upon opiate withdrawal symptoms. May use for up to 14 days. Max: 2.88 mg/day (16 tablets/day). Do not exceed 0.72 mg/dose (4 tablets/dose) PO. GERIATRIC PATIENTS: No studies have been performed to determine safety and effectiveness; consider dosage adjustments similar to those recommended in patients with renal dysfunction. DISCONTINUATION: Gradually taper the dose over 2 to 4 days to reduce drug withdrawal symptoms (e.g., reduce by 1 tablet/dose every 1 to 2 days).
- Nondrug and supportive care
  - Procedures
  - For patients in a closed environment (eg, inpatient or residential care), provide a calm, quiet setting<sup>8</sup>
    - Allow rest or moderate activities as desired
    - Offer opportunities to meditate or perform other calming activities
    - Do not force patients to engage in exercise until withdrawal is complete as exercise may prolong and worsen withdrawal symptoms
    - Patients are often anxious and afraid and may respond well to accurate information regarding drugs and withdrawal
    - Patients may be confused and vulnerable; do not provide counseling or psychotherapy during moderate to severe acute withdrawal

# Opioid withdrawal

- Management advice for difficult behavior<sup>8</sup>
  - Anxious, agitated, or panicking
    - Approach in a confident and calm manner
    - Limit number of people attending to patient
    - Explain any interventions carefully
  - Confusion or disorientation
    - Maintain close supervision
    - Provide reality orientation by explaining to patient where he or she is and what is happening
  - Angry or aggressive
    - Ensure that staff is protected and safe
    - Maintain calm, reassuring attitude when interacting with patient
    - Listen carefully
    - Use patient's name and keep interactions personal
    - Use calm, open-ended questions
    - Maintain a consistent and even voice tone, even if patient is shouting and hostile
    - Acknowledge patient's feelings
    - Do not challenge patient
    - If possible, remove any source of anger
- Maintain hydration. Oral intake of sport drinks is usually adequate, and IV hydration is rarely necessary<sup>2</sup>
  - Patients are advised to drink 2 to 3 L of fluid daily; hydration is sometimes provided by electrolyte replacement solutions
- Acupuncture has been shown to reduce withdrawal symptoms but has little effect on drug cravings<sup>30</sup>
- Providers who administer antagonists must be prepared for possible violent behavior created by precipitated withdrawal
  - In controlled settings, titrating to effect using smaller initial doses may reverse respiratory depression while preventing precipitation of full withdrawal
- Comorbidities
  - Prolonged QT interval or arrhythmia history may preempt use of methadone because it tends to increase QT prolongation<sup>31</sup>
    - Treating with methadone doses of 100 mg or less is not associated with QT prolongation<sup>32</sup>
    - Prolonging the QT interval to more than 500 milliseconds confers risk of arrhythmia<sup>29</sup>
    - In the United States, the following has been recommended by an expert Substance Abuse and Mental Health Services Administration panel:<sup>29</sup>
      - Obtain a baseline ECG at time of admission and again within 30 days of the first test for the following patients, with annual monitoring ECG:
        - Patients with significant risk factors for QT prolongation, including symptoms suggestive of arrhythmia (eg, episodes of syncope, dizzy spells, palpitations, seizure), history of cardiac arrhythmia, or prolonged baseline QT interval
        - Patients receiving other medication that may prolong QT interval
        - Patients with family history of premature death
        - Patients who have history suggestive of a possible cardiac arrhythmia
      - Obtain an ECG when methadone dose exceeds 120 mg/day and for any patient who experiences unexplained syncope or generalized seizures
  - Severe asthma or chronic hypercapnic respiratory failure also may preempt the choice of methadone in an unmonitored (eg, outpatient) setting beyond the inpatient unit<sup>31</sup>
- Special populations
  - Opioid-dependent pregnant women typically are not withdrawn from opioid drugs owing to the physiologic stress that withdrawal has on the developing fetus and the additional risk of maternal relapse, which threatens the well-being of both mother and fetus<sup>7</sup>
    - Both buprenorphine (in a single component sublingual tablet or film without naloxone) and methadone are used during pregnancy and while breastfeeding; the relative infant dose of buprenorphine<sup>33</sup> and methadone<sup>34</sup> is less than 1% of the maternal dose, adjusted for weight; therefore, maternal treatment alone is not sufficient to suppress neonatal abstinence syndrome<sup>25</sup>
    - Newborns of mothers who use opioids regularly or who are maintained on opioids (eg, methadone maintenance) are monitored and treated for emergence of opioid withdrawal (ie, neonatal abstinence syndrome)
    - Use caution to avoid precipitated withdrawal when initiating buprenorphine in pregnant women; that is, confirm mild to moderate withdrawal before initiating buprenorphine

# Opioid withdrawal

- Opioid withdrawal also may occur in breastfed infants of opioid-using mothers when maternal use of opioids is reduced or abruptly discontinued<sup>7</sup>
  - Opioid-dependent women who are breastfeeding but wish to stop are advised to gradually reduce breastfeeding to lessen withdrawal symptoms in their nursing children

## MONITORING

- Closely monitor (every 1-2 hours) patients who potentially may begin experiencing withdrawal; use a validated clinical scale (eg, Clinical Opiate Withdrawal Scale)<sup>4</sup>
- When treating with  $\alpha_2$ -adrenergic agonist (eg, clonidine, lofexidine) in a monitored setting (eg, inpatient unit, residential treatment), take vital signs every 1.5 to 2 hours with patient both sitting and standing to monitor for hypotension<sup>2</sup>
- If methadone dose required to suppress withdrawal exceeds 120 mg daily, if patient has a history of prolonged QT interval, or if patient is taking other medications that may prolong the QT interval (as seen with methadone) and increase the risk of arrhythmia, consider using ECG to assess the QT interval<sup>20</sup>

## COMPLICATIONS AND PROGNOSIS

### COMPLICATIONS

- Sustained tachycardia<sup>4</sup>
- Electrolyte imbalance<sup>4</sup>
- Hypovolemia<sup>4</sup>
- Increased risk of overdose if patient resumes opioid use owing to decreased tolerance<sup>4</sup>
- Physical trauma to providers and self-inflicted trauma when withdrawal is rapidly precipitated by administering an antagonist

### PROGNOSIS

- Opioid withdrawal is highly uncomfortable, but it is not life-threatening for most patients
- If withdrawal management is not quickly followed by patient admission into a treatment program, especially a medication-assisted program (eg, buprenorphine or methadone maintenance), withdrawal is associated with a high relapse rate into active opioid use (up to 88% after 1-3 years<sup>35</sup><sup>36</sup>)

## SCREENING AND PREVENTION

### SCREENING

- At-risk populations
  - Patients who experience acute withdrawal symptoms, which may develop upon abrupt discontinuation of opioids after as few as 5 days of regular and uninterrupted opioid use

### PREVENTION

## SYNOPSIS

### KEY POINTS

- Opioid withdrawal is a syndrome of physical and psychological symptoms that occurs after abrupt cessation of or significant dosage reduction of opioids or administration of an antagonist
- Typical symptoms are basically the reverse of signs and symptoms of opioid intoxication (eg, tachycardia, hypertension, mydriasis, diaphoresis, gastric distress, piloerection, arthralgia/myalgia), reflecting increased noradrenergic activity
- Although not life-threatening for most patients, opioid withdrawal is extremely uncomfortable and is associated with increased cravings and recurrent drug use; inpatient or residential management may be necessary, where adjunct medical therapies and significant psychosocial assistance can be provided in a supportive environment
- Using validated clinical scales (eg, Clinical Opiate Withdrawal Scale) helps establish the severity of withdrawal and response to therapy
- Inpatients with an iatrogenic physical dependence from extended hospitalization for a critical illness requiring treatment with prolonged use of opioids for pain or sedation (eg, long-term opioid infusion in the ICU) are weaned off the medication by a daily reduction of 5% to 10%<sup>4</sup>
- Mild (ie, Clinical Opiate Withdrawal Scale score below 13) withdrawal may be managed by use of  $\alpha_2$ -adrenergic agonists (clonidine or lofexidine) to decrease withdrawal severity in combination with symptomatic treatments (eg, loperamide for diarrhea)<sup>12</sup>
- Moderate (ie, Clinical Opiate Withdrawal Scale score 13-36) and severe (ie, Clinical Opiate Withdrawal Scale score higher than 36) withdrawal are best managed with opioid agonist replacement (eg, methadone, buprenorphine) and subsequent slow weaning; these drugs require special Drug Enforcement Administration licensure to use for outpatient, long-term management, but the drugs may be prescribed by any prescribing practitioner in the inpatient hospital setting<sup>12</sup>

# Opioid withdrawal

- Medical management alone of opioid withdrawal is not considered appropriate treatment of opioid use disorder; all patients are referred to an appropriate methadone or buprenorphine provider or at least evaluated by a clinician with expertise in treating opioid use disorder

## PITFALLS

- It is imperative to educate all patients who have been withdrawn from opioids regarding the high risk of relapse without additional treatment and about their current diminished opioid tolerance, which places them at high risk for overdose (ie, patient cannot tolerate predetoxification doses)<sup>4</sup>
- Be prepared to manage an agitated and possibly combative patient if a full dose of an antagonist (eg, naloxone) is given to a patient who has overdosed, as the patient may be thrust into full opioid withdrawal<sup>4</sup>
  - o Ideal treatment is titration to effect, starting with a low dose, in a controlled setting

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