Opioid withdrawal: Clinical features, assessment, and diagnosis

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INTRODUCTION

Spontaneous opioid withdrawal occurs when a patient who is physiologically dependent upon opioids reduces or stops opioid use abruptly. Precipitated opioid withdrawal can occur when a patient who is physiologically dependent upon opioids and who has or recently had opioids in their system is administered an opioid antagonist (naloxone, naltrexone, or nalmefene) or an opioid partial agonist (buprenorphine). Signs and symptoms of opioid withdrawal include drug craving, anxiety, restlessness, gastrointestinal distress, diaphoresis, and tachycardia. Untreated opioid withdrawal frequently results in return to opioid use.

Patients in opioid withdrawal or seeking to stop an opioid to which they are physiologically dependent can undergo medically supervised opioid withdrawal (also known as detoxification), in which medication is used to reduce the severity of withdrawal symptoms [1].

This topic describes the clinical manifestations, course, assessment and diagnosis of opioid withdrawal. Medically supervised opioid withdrawal as the first step in treatment of opioid use disorder is described separately. Pharmacotherapy and psychosocial interventions for opioid use disorder are also discussed separately. The management of unplanned withdrawal in the emergency department and opioid withdrawal in adolescents are discussed separately. (See "Opioid withdrawal: Medically supervised withdrawal during treatment for opioid use disorder" and "Opioid withdrawal in the emergency setting" and "Opioid withdrawal in adolescents" and

"Opioid use disorder: Pharmacologic management" and "Opioid use disorder: Psychosocial management".)

OVERVIEW

Patients presenting for opioid withdrawal management include those with untreated opioid use disorders, those on methadone or buprenorphine maintenance who are ending this treatment voluntarily or not, those currently using opioids who are to be initiated on extended-release naltrexone, and those ending chronic opioid treatment for pain management. Supervised opioid withdrawal uses medication to reduce the severity of withdrawal symptoms.

Supervised withdrawal alone is unlikely to result in sustained abstinence from opioids [2], nor does it address reasons the patient became dependent on opioids or the damage that the addiction has done to relationships, employment, finances, and the mental, physical, and spiritual health of the patient. Without successful transition to follow-up treatment, medications for opioid use disorder (buprenorphine, methadone, extended-release naltrexone), or supervised withdrawal alone is associated with many harms, including elevated rates of death, incarceration, and infectious disease transmission [3,4].

CLINICAL MANIFESTATIONS

The signs and symptoms of unmedicated opioid withdrawal include [5-7]:

- **Gastrointestinal distress** – Abdominal cramps, diarrhea, nausea, and/or vomiting
- **Flu-like symptoms** – Lacrimation, rhinorrhea, diaphoresis, shivering, and piloerection (goosebumps)
- **Sympathetic nerve and central nervous system arousal** – Mydriasis, mild hypertension, and tachycardia, anxiety and irritability, insomnia, agitation, restless leg syndrome, general restlessness, tremor, and, less frequently, low-grade temperature and tactile sensitivity
- **Other** – Yawning, sneezing, anorexia, dizziness, myalgias/arthralgias, leg cramps and dysthymia

There can be significant individual differences in the expression of opioid withdrawal, especially in those experiencing milder symptoms [8].

Co-occurring conditions — Patients with opioid use disorders have elevated rates of other substance use disorders, especially nicotine (up to 85 percent), and elevated rates of mental disorders (up to 70 percent), especially major depression, panic disorder, generalized anxiety disorder, posttraumatic stress disorder, and antisocial personality disorder [9-11].

Elevated rates of mental disorders and other substance use disorders are also seen in patients exhibiting nonmedical use of prescribed opioids [12,13] and those with chronic pain treated with opioids [14,15]. A systematic review of 11 studies of patients with nonmedical use of prescription opioids found a pooled prevalence of co-occurring anxiety disorders to be 29 percent and depressive disorders 27 percent, both two to three times the rate found in the general population [12]. The direction of causality for these comorbidities is unknown and likely is a combination of shared vulnerability [13,16], opioid exposure leading to development of comorbid symptoms and diagnoses [17], and comorbid diagnoses elevating the risk to develop physiologic dependence with or without addiction [18,19].

While it should be expected that the presence of comorbid conditions will make treatment of symptoms in opioid withdrawal more difficult [20], there are few studies that directly address the effect of the comorbidities on the course or severity of opioid withdrawal. An exception is comorbid tobacco use disorder, which has been associated with worse opioid withdrawal symptoms in inpatients treated with clonidine and methadone taper [21]. High rates (40 percent) of benzodiazepine use in the prior month were reported in those seeking opioid detoxification, with the most commonly cited reason being to control anxiety [22].

Other co-occurrences that may complicate supervised opioid withdrawal include:

- Comorbid alcohol and benzodiazepine withdrawal (see "Management of moderate and severe alcohol withdrawal syndromes")
- Expressed suicidal ideation with comorbid cocaine and methamphetamine withdrawal (see "Suicidal ideation and behavior in adults" and "Methamphetamine use disorder: Epidemiology, clinical features, and diagnosis", section on 'Abstinence syndrome' and "Cocaine use disorder: Epidemiology, clinical features, and diagnosis")
- Personality disorders (see "Overview of personality disorders" and "Approaches to the therapeutic relationship in patients with personality disorders")

Those who report high levels of pain during opioid withdrawal (58 percent of 814 people who inject drugs) showed increased risk of subsequent nonfatal overdose [23]. In studies of patients with current and prior misuse of prescription opioids, suicidal ideation has been found to be elevated even in patients who do not have active opioid withdrawal [24]. The FDA issued a

warning that those who have prescribed opioids for pain suddenly discontinued may experience serious harms including marked withdrawal, uncontrolled pain, psychological stress, and suicide.

COURSE

An opioid typically must be consumed daily for three weeks or more for physiologic dependence to develop and for the patient to require medically supervised withdrawal. However, in those previously tolerant to opioids, briefer periods of recurrence of use may trigger withdrawal after shorter periods of use followed by cessation. Withdrawal will only occur in those who have developed tolerance to the opioid.

Following cessation of opioid use, the precise onset and completion of withdrawal, the order of symptoms, and which symptoms are most prominent can vary prominently among individuals and across opioid drugs [25]. As examples, the duration of the syndrome can range from four to five days for short-term intravenous fentanyl to two to three weeks for methadone. A rough rule of thumb is that onset of symptoms occurs after two to three times the half-life of the withdrawn opioid. A table provides onset, peak and duration of opioid withdrawal for select opioids (table 1). The proliferation of fentanyl dependence in individuals not only knowingly using fentanyl, but those using contaminated heroin, oxycodone-pills, methamphetamine, etc has led to the lore that fentanyl withdrawal occurs earlier, is more severe, and is more enduring than from heroin [26]. The lipophilicity of fentanyl leads to distribution into adipose tissue so that later release leads to extended duration of effect, and hence duration of withdrawal. High body mass index (BMI) status appears to correlate with more severe withdrawal scores than an individual's use status.

Unmedicated opioid withdrawal can be quite uncomfortable but rarely life threatening, though Takotsubo (stress-induced) cardiomyopathy may be underappreciated [27] and seizures are reported at the case report level [28]. Withdrawal precipitated by medications (eg, antagonists, partial agonists, inverse agonists) is more rapid in onset and often with more severe symptoms, with reports of life-threatening delirium and severe autonomic instability [29,30]. Risks associated with overdose during supervised withdrawal are described separately. (See "Opioid withdrawal: Medically supervised withdrawal during treatment for opioid use disorder".)

ASSESSMENT

Initial evaluation — Our initial evaluation of patients at risk of opioid withdrawal includes a substance use history, psychiatric assessment and history, mental status examination, medical history and physical examination, laboratory testing, level of care determination, and, if physiologic dependence is in doubt, a naloxone challenge test.

Substance use history — A thorough substance use history of a potentially opioid-dependent patient should include:

- For each substance used, the amount used, frequency, route, duration, and time of last use. Duration of use influences the likelihood of physiologic dependence and withdrawal symptoms. The use of other substances along with opioids can influence the level of care needed and choice of subsequent maintenance medications. As an example, high risk for continued alcohol or benzodiazepine use may preclude the option to safely use buprenorphine/naloxone for outpatient detoxification. (See 'Course' above and 'Level of care determination' below and "Opioid withdrawal: Medically supervised withdrawal during treatment for opioid use disorder".)

- History of prior medically supervised withdrawal, medication used, complications, and response.

- Prior medication for opioid use disorder or other substance use disorder treatment: what worked and what did not. This will aid in determining initial planning for the postdetoxification period.

Psychiatric status, history, mental status examination — Unless the subject is already in the throes of marked withdrawal when immediate action is needed, it is important to ascertain the patient's current mental status, as well as the patient's history and current status of mental disorders, in particular, suicidality, anxiety, mood, psychotic, and trauma-related disorders, past treatment and response. Co-occurring mental disorders can be exacerbated by opioid withdrawal and may require symptomatic management with benzodiazepine, antipsychotic or other medications, or influence the needed level of care. (See 'Co-occurring conditions' above and 'Level of care determination' below.)

If the withdrawal is not managed by a psychiatrist, one should be consulted if active mental disorders are known or suspected. If the patient is on psychiatric medications, it is important to determine how these might impact supervised withdrawal. Noteworthy examples include:

- Lithium levels can vary markedly with dehydration and must be monitored closely.

- Carbamazepine may increase methadone dosing needs.

- Psychotropics strongly interacting with the CYP2D6 and 3A4 systems, such as fluoxetine, paroxetine, haloperidol, and amitriptyline, can affect levels of methadone and, to a lesser extent, buprenorphine. One might reduce starting doses of methadone by 50 percent and then follow symptom-guided dosing (balancing symptom control with side effects). For buprenorphine/naloxone, following symptom control/side effects alone is adequate to control for any needed dose adjustments.

Medical history and physical examination — Clinical priorities in taking a medical history and conducting a physical examination include:

- Patient history or physical examination finding symptoms/signs of cardiovascular disease (eg, congestive heart failure, hypertension or hypotension, and arrhythmias).

- Autonomic instability might reveal undisclosed alcohol or benzodiazepine dependence or infection.

- History consistent with esophageal varices, blackouts, or falls due to vomiting should be elicited.

- Dehydration can commonly result from the gastrointestinal symptoms of opioid withdrawal, so if there are such signs prior to initiating the supervised withdrawal, or a history of frequent vomiting or severe diarrhea during supervised withdrawal, aggressive hydration (beyond encouraging oral intake) may be needed.

- Diabetes can be complicated by poor oral intake during withdrawal.

- Both liver and renal failure must be taken into account when choosing adjunctive medications targeting specific withdrawal symptoms. A table on adjunctive medications for opioid withdrawal symptoms indicates those to be avoided in the presence of renal or liver failure (table 2).

- Older patients are at elevated risk of dementia and/or delirium. Risk for delirium, in particular, is elevated in older adults with dementia; risk is also elevated in older adults with prior traumatic brain injury, medical illness, especially concurrent infection and hepatic insufficiency, dehydration/malnutrition, and current substance use disorders [31].

- Cognitive impairment may increase the risk of agitation during supervised withdrawal. (See 'Level of care determination' below.)

- Some HIV medications affect levels of methadone and, much less so, buprenorphine [32]. Medication dosing in supervised withdrawal that is based on the severity of withdrawal

symptoms and medication side effects, such as sedation and respiratory suppression, will control for these alterations. A brief summary is provided below:

- All of the nonnucleoside reverse transcriptase inhibitors are metabolized by the liver and usually are CYP3A4 inducers. Abacavir, nevirapine, and efavirenz may necessitate increased methadone dosing.
- The protease inhibitors are metabolized by the liver. While typically these are CYP3A4 inhibitors, some increase methadone renal clearance, necessitating increased dosing needs. Ritonavir, most ritonavir combinations, and nelfinavir might require higher dosing of methadone.
- Most of the nucleoside reverse transcriptase inhibitors undergo renal excretion, so they do not interact with methadone. An exception is abacavir, which may require methadone dosing increase.

The physical examination is an opportunity to engage the patient in medical care that in many cases has been ignored and to address potential physical consequences of opioid use, such as the presence of antecubital or other subcutaneous abscesses, cardiac murmur suggesting the presence of valve vegetation, signs of malnutrition, or signs of liver decompensation seen in hepatitis B/C infection or alcohol use disorder.

If withdrawal is not managed by an internist or primary care clinician, one should be consulted if clinically significant findings or potential complications are detected by medical history and physical examination.

Laboratory and other testing — Laboratory studies should include a complete blood count, a comprehensive metabolic profile including electrolytes, calcium and magnesium, glucose, liver and renal function tests; prothrombin time/partial thromboplastin time, HIV and hepatitis B/C screens, a urinalysis to rule out infection; and a urine drug screen, including ethyl glucuronide/ethyl sulfate and when not included in standard screening panels, specified tests for oxycodone, buprenorphine, tramadol, high-potency opioids such as fentanyl, and methadone. An electrocardiogram will assess QT/QTc, cardiac rhythm, and evidence of cardiac ischemia. Opioid-dependent women should be tested for pregnancy (with a negative result) prior to supervised withdrawal. (See "Opioid withdrawal: Medically supervised withdrawal during treatment for opioid use disorder".)

Withdrawal symptoms — A baseline assessment of the presence and severity of opioid withdrawal symptoms and signs is made upon the patient's presentation using a standardized

rating tool. Instrument selection is discussed separately. (See "Opioid withdrawal: Medically supervised withdrawal during treatment for opioid use disorder".)

Naloxone challenge test — History and clinical evaluation using rating scales are usually sufficient to determine physiologic dependence. If dependence is uncertain, one can perform a naloxone challenge test provided that pregnancy has been ruled out. A 0.2 mg dose of naloxone is administered intravenously or intramuscularly, or 0.8 mg subcutaneously. Withdrawal signs should appear 1 to 5 minutes after naloxone administration in an opioid-dependent patient. If no withdrawal is elicited after 5 minutes, administer 0.8 mg naloxone intravenously or intramuscularly or 3.2 mg subcutaneously, and observe for signs of withdrawal for another 20 minutes. The patient should be warned that withdrawal may occur quickly. They should also be reassured that the dose is sufficiently low and half-life is sufficiently short that resulting distress is typically minimal, especially if follow-up treatment for withdrawal symptoms is initiated quickly. (See "Opioid withdrawal: Medically supervised withdrawal during treatment for opioid use disorder".)

Precipitated withdrawal by this test can be serious and require more intensive medical management. For this reason, extended-release formulations or high doses of naloxone are never used in the test [33].

Level of care determination — Patients withdrawing from opioids should be assessed for the level of care needed for medically supervised withdrawal. Treatment can be provided at several levels of care, including outpatient, intensive outpatient, partial hospital, residential (medically supervised) programs, or inpatient (medically managed) services. The best established system for assisting the clinician in determining the appropriate level of care is the American Society of Addiction Medicine (ASAM)'s Treatment Criteria [34]. In general, higher (or more intensive) levels of care are provided to patients with more severe and/or complex conditions, such as those with co-occurring medical disease or mental disorders. (See "Substance use disorders: Determining appropriate level of care for treatment".)

The appropriate level of care for managing medically supervised withdrawal for a patient can be determined by applying the findings from the areas of assessment above to the first three dimensions of the ASAM criteria:

- Withdrawal potential
- Biomedical conditions and complications
- Emotional, behavioral, and cognitive conditions and complications

Examples of opioid-dependent patients requiring a higher level of care for medically supervised withdrawal include patients with:

- A co-occurring mood, anxiety, or psychotic disorder; in contrast, patients with a trauma-related disorder, such as posttraumatic stress disorder, may have greater difficulty tolerating residential or inpatient care.
- A patient with withdrawal-associated suicidality, confusion, or other cognitive impairment will often need inpatient care.
- A need for dual supervised withdrawal from benzodiazepines, barbiturates, or alcohol as well as opioids, typically requiring close medical observation on a residential or inpatient unit.
- A history of congestive heart failure, hypertension or hypotension, or arrhythmia.
- Patients needing higher doses of an opioid agonist, for example, more than 12 mg/day of buprenorphine on day 1 or the maximum 40 mg/day 1 of methadone, generally require inpatient or residential care.
- A patient with a recent history of recurrence of use at the prior, lower level of care.

DIAGNOSIS

The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) diagnostic criteria for opioid withdrawal are as follows [35]:

- A. Presence of either of the following:
  - 1. Cessation of (or reduction in) opioid use that has been heavy and prolonged (ie, several weeks or longer).
  - 2. Administration of an opioid antagonist after a period of opioid use.
- B. Three (or more) of the following developing within minutes to several days after Criterion A:
  - Dysphoric mood
  - Nausea or vomiting
  - Muscle aches
  - Lacrimation or rhinorrhea
  - Pupillary dilation, piloerection, or sweating
  - Diarrhea

- Yawning
- Fever
- Insomnia

- C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

- D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Opioid use disorder and withdrawal".)

SUMMARY

- **Precipitants** – Opioid withdrawal occurs when a patient with physiologic dependence on opioids reduces or stops using an opioid abruptly, or when an antagonist or partial agonist is administered to a patient with physiologic dependence. Untreated opioid withdrawal frequently results in recurrence of opioid use. (See 'Introduction' above.)

- **Clinical manifestations** – Symptoms and signs of unmedicated opioid withdrawal include (see 'Clinical manifestations' above):

  - Gastrointestinal distress – Abdominal cramps, diarrhea, nausea, and/or vomiting

  - Flu-like symptoms – Lacrimation, rhinorrhea, diaphoresis, shivering, piloerection, and goose bumps

  - Sympathetic nerve and central nervous system arousal – Mydriasis, mild hypertension, and tachycardia, anxiety and irritability, insomnia, agitation, restless leg syndrome, general restlessness, tremor, and, less frequently, low-grade temperature and tactile sensitivity

  - Other – Yawning, sneezing, anorexia, dizziness, myalgias/arthralgias, leg cramps and dysthymia

- **Co-occurring conditions** – Panic disorder and other anxiety disorders, mood disorders, suicidality, acute and posttraumatic stress disorder, and other substance use disorders are seen in greater frequency in patients with physiologic dependence on opioids. (See 'Co-occurring conditions' above.)

- **Course** – Following cessation of opioid use, the precise onset and completion of withdrawal, the order of symptoms, and their severity, varies among individuals and across opioid drugs [36]. Unmedicated opioid withdrawal can be quite uncomfortable but is rarely life threatening (see 'Course' above). A table describes times to onset and peak withdrawal, and duration of withdrawal for various opioids (table 1).

- **Assessment** – We include an evaluation of each of the following in our assessment of individuals with opioid withdrawal (see 'Initial evaluation' above):

  - **Substance use history** – We review substance use history thoroughly. The use of other substances along with opioids can influence the level of care needed and the choice of subsequent medication. Additionally, the duration of use can influence the likelihood of physiologic dependence and withdrawal symptoms. (See 'Substance use history' above.)

  - **Psychiatry history and mental status** – Unless the subject is already in marked withdrawal and needs immediate attention, we assess the individual's current mental status with attention to suicidality, anxiety, psychosis, mood, and trauma-related disorders. (See 'Psychiatric status, history, mental status examination' above.)

  - **Medical history, physical examination, and laboratory testing** – These are opportunities to engage the patient in medical care that in many cases has been ignored and to address potential physical consequences of opioid use. (See 'Medical history and physical examination' above.)

  - **Withdrawal symptoms** – A baseline assessment of the presence and severity of opioid withdrawal symptoms and signs is made upon the patient's presentation using a standardized rating tool. (See 'Withdrawal symptoms' above.)

  - **Naloxone challenge test** – History and clinical evaluation using rating scales are usually sufficient to determine physiologic dependence. If dependence is uncertain, one can perform a naloxone challenge test provided that pregnancy has been ruled out. (See 'Naloxone challenge test' above.)

- **Subsequent treatment** – As part of treatment planning, we include plans for transition to a maintenance treatment program for all individuals who have undergone medically supervised withdrawal. Supervised withdrawal alone does not generally result in sustained abstinence from opioids, and increases the risk of serious harms, including death. (See "Opioid withdrawal: Medically supervised withdrawal during treatment for opioid use disorder".)

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