Substance Use Disorder Series

MODULE 7

Managing Substance-Related Withdrawal

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Disclosures

- Authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation

Objectives

1. Recognize signs and symptoms of withdrawal
2. Utilize scales and/or protocols for various substance-related withdrawal states
3. Develop a management plan for patients experiencing withdrawal including both pharmacologic and non-pharmacologic treatment options

Definitions

- Center for Substance Abuse Treatment, 2006
  - “Withdrawal: the development of a substance-specific maladaptive behavioral change, with physiological and cognitive concomitants, that is due to the cessation of, or reduction in, heavy and prolonged substance use”
  - “Detoxification: a set of interventions aimed at managing acute intoxication and withdrawal”
    - Seeks to minimize acute physical symptoms
    - Patients say they are “detoxing” in the beginning stages of withdrawal (usually first few days to weeks)

“Detoxification and Substance Abuse Treatment.” Center for Substance Abuse Treatment And Substance Abuse and Mental Health Services Administration. https://store.samhsa.gov/system/files/sma15-4907.pdf Accessed June 28, 2020.

Withdrawal Overview

- Withdrawal symptoms vary according to the drug of dependence and degree of dependence
  - Greatly influenced by the half-life of a given drug/substance
- Withdrawal can be unpredictable
  - Persons experiencing withdrawal from the same drug/substance may have significantly different experiences
- Medically-assisted detoxification is not always necessary or desirable

Overarching Principles for the Management of Substance-Related Withdrawal

- Managing withdrawal is the first step toward recovery in patients with a substance use disorder (SUD)
- Many patients continue to use due to the fear of withdrawal
- Detoxification services do not offer a “cure” for SUD
  - Detox medications help with the physical symptoms
  - Counseling focuses on the psychological symptoms

“Detoxification and Substance Abuse Treatment.” Center for Substance Abuse Treatment And Substance Abuse and Mental Health Services Administration. https://store.samhsa.gov/system/files/sma15-4907.pdf Accessed June 28, 2020.

Overarching Principles continued

- Showing patients respect and dignity can go a long way in their recovery
  - Using a nonjudgmental and supportive manner improves patient retention and chances of recovery
- SUD is not a sign of moral weakness
  - SUD is a disease and requires management
- SUDs are treatable and recovery is possible

"Detoxification and Substance Abuse Treatment." Center for Substance Abuse Treatment And Substance Abuse and Mental Health Services Administration. https://store.samhsa.gov/system/files/sma15-4907.pdf Accessed June 28, 2020.

Treatment Services

- Depending on a patients needs, preferences, and required level of care
  - Physician's office
  - Urgent care facilities and emergency rooms
  - Outpatient clinics
  - Inpatient mental health facility
  - Inpatient hospital detoxification
- Of note, many patients recover at home without professional help

Opioid Withdrawal

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Opioid Withdrawal Overview

- Can occur after a period of prolonged or heavy opioid use when opioids are discontinued, the dose is reduced, or after the administration of an opioid antagonist (naloxone or naltrexone)
- Signs and symptoms may include:
  - Agitation/anxiety
  - Depression
  - Nausea or vomiting
  - Generalized pain (especially muscle aches)
  - Lacrimation (secretion of tears)
  - Runny nose
  - Fever
  - Pupillary dilation
  - Piloerection (goosebumps)
  - Sweating
  - Diarrhea
  - Yawning
  - Insomnia
  - Cravings
  - Elevated heart rate and/or blood pressure

"Clinical Guidelines for Withdrawal Management and Treatment of Drug Dependence in Closed Settings." National Center for Biotechnology Information website. https://www.ncbi.nlm.nih.gov/books/NBK310652 Accessed June 28, 2020.

Opioid Withdrawal Overview continued

- Opioid withdrawal is typically not life-threatening but is often very difficult for patients
- Comparable to a severe influenza infection
- Patient's may describe it as "severely uncomfortable" and/or "feeling like the worst sensation of their lives"

"Clinical Guidelines for Withdrawal Management and Treatment of Drug Dependence in Closed Settings." National Center for Biotechnology Information website. https://www.ncbi.nlm.nih.gov/books/NBK310652 Accessed June 28, 2020.

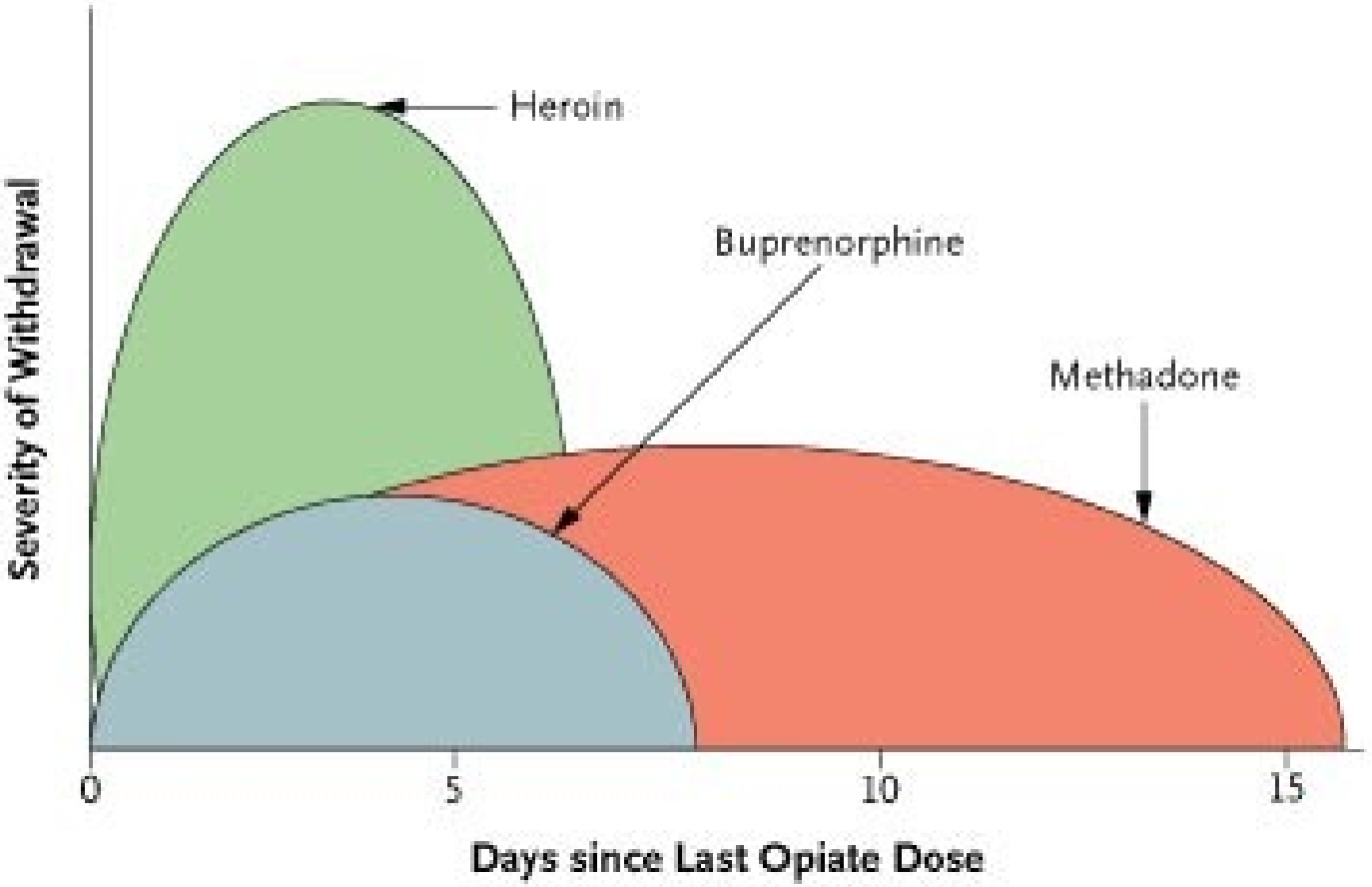
Typical Withdrawal Characteristics of Various Opioids

Opioid	Half-Life (Adults)	Onset of Withdrawal Symptoms After Exposure	Typical Duration of Withdrawal
Heroin	2-6 min[a]	6 h	8-10 days
Methadone	8-150 h (mean 35 h)	24-96 h	10-14 days, secondary withdrawal as long as 6 mo
Buprenorphine	Mean 37 h	6-24 h	Milder withdrawal than other opioids. Usually resolves within 7 days, but may be prolonged in neonates
Morphine	1.5-7 h	8-12 h	7-10 days
Oxycodone	3-5 h	6-12 h	7-14 days, secondary withdrawal as long as 6 mo
Hydrocodone	7-9 h	8-12 h	5-14 days, secondary withdrawal as long as 6 mo
Fentanyl	11-36 h (mean 21 h)	3-5 h	4-5 days

[a] Heroin is metabolized to morphine-6-glucuronide and morphine.

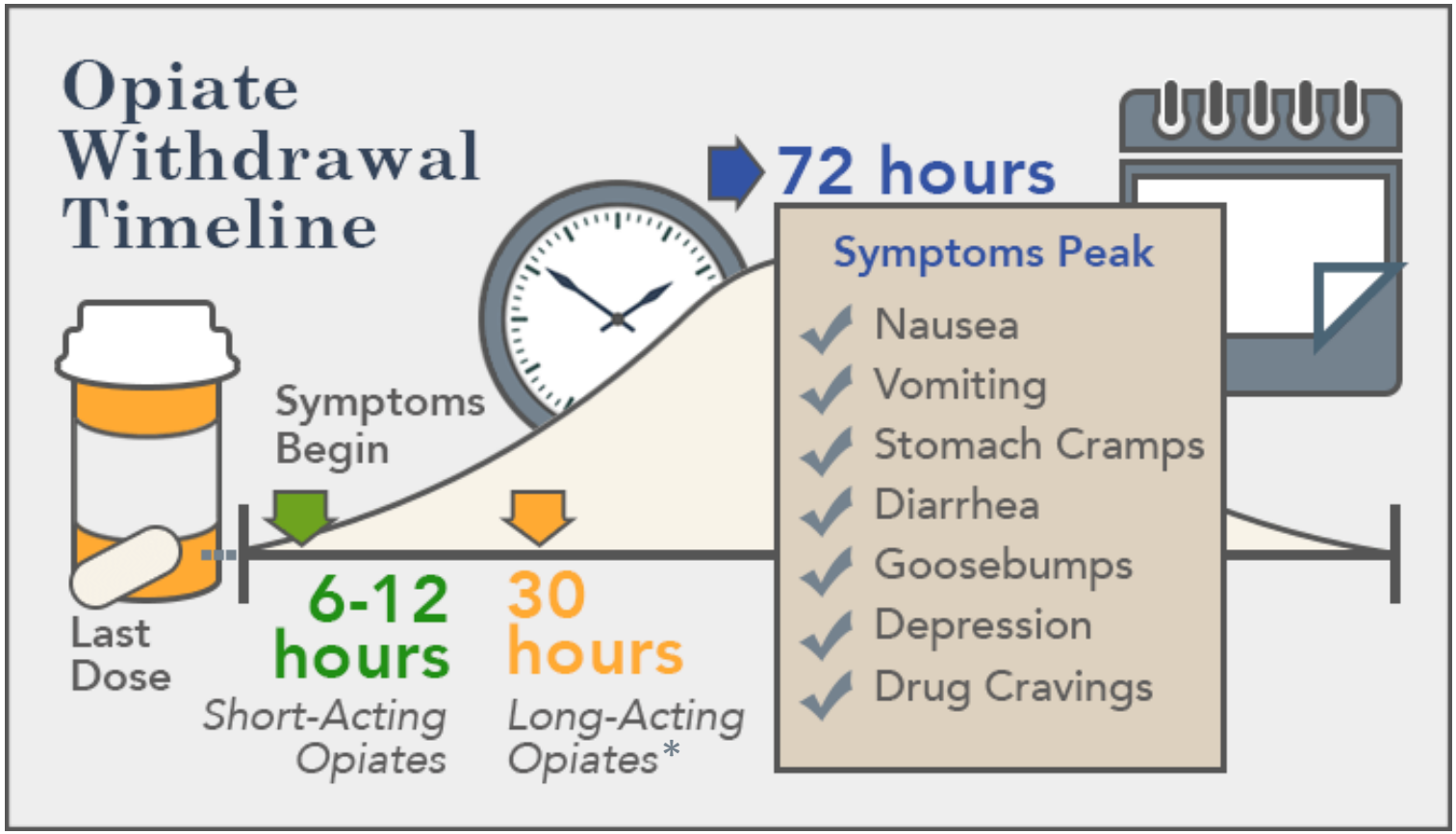
Prunty LM, Prunty JJ. *US Pharm.* 2016;41(11):HS2-HS6.

Comparison of Opioid-Withdrawal Severity of Heroin, Buprenorphine, and Methadone



Kosten KR, O'Connor PG. *N Engl J Med*. 2003;348:1786-95.

Opioid Withdrawal Timeline



*Long-acting opiates include buprenorphine and methadone

"Opiate Withdrawal Timeline, Symptoms, and Treatment." American Addiction Centers. https://americanaddictioncenters.org/withdrawal-timelines-treatments/opiate Accessed June 28, 2020.

Monitoring

- Frequent monitoring is an important part of managing withdrawal
- Allows for the assessment of:
  - General progress
  - Drug use
  - Response to withdrawal medications
  - Severity of withdrawal (can be facilitated by withdrawal scales)
  - Complications or difficulties
  - Ongoing motivation levels
- Several opioid withdrawal scales available

National Guidelines for Medication-Assisted Treatment of Opioid Dependence. 2014. https://www.health.gov.au/sites/default/files/national-guidelines-for-medication-assisted-treatment-of-opioid-dependence.pdf. Accessed June 28, 2020.

Opioid Withdrawal Scales

- Can be used to assess the stage or severity of a patient's opioid withdrawal
- May guide practitioners regarding the level of care required to care for patients
- Scales include:
  - **Clinical Opiate Withdrawal Scale (COWS)**
  - Short Opioid Withdrawal Scale-Gossop (SOWS-Gossop)
  - Subjective Opiate Withdrawal Scale (SOWS)
  - Clinical Institute Narcotic Assessment (CINA)

Prunty LM, Prunty JJ. *US Pharm.* 2016;41(11):HS2-HS6.

Clinical Opiate Withdrawal Scale (COWS)

- A clinician-administered 11-item scale consisting of observed, clinician-rated, and patient-rated items
  - Subjective and most reliable if performed by same physician for a given patient
- Most utilized opioid withdrawal scale in adults
- Scores range from 0-48 and a higher COWS score reflects a greater number of withdrawal symptoms
  - >36 = Severe withdrawal

Wesson Dr, Ling W. *J Psychoactive Drugs*. 2003;34(2):253-259

COWS Example

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset:** *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour 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	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
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	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient 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/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

Non-Pharmacologic Interventions

- Provide a quiet, protective, and welcoming environment
  - Patients need to rest
  - Hot showers help with many symptoms
- Educating patients regarding:
  - Nature/duration of withdrawal symptoms
  - Role(s) of medication, if used
- Complementary Alternative Medicine
  - Examples
    - Meditation, exercise, practicing mindfulness, and pet therapy
    - Aerobic exercise and/or yoga can be very beneficial if patient can tolerate
- Counseling
  - Strategies to avoid high-risk situations and/or triggers and to help patients maintain sobriety
- Physical therapy
  - Can provide some relief to underlying chronic pain

Pharmacologic Treatment Options

- Long-acting (LA) oral opioids
  - Buprenorphine (partial agonist/antagonist)
  - Methadone (pure agonist)
- Opioid-free options
  - Centers around the use of α_2-adrenergic agonists to ameliorate withdrawal signs and symptoms
    - May help around 30% of patients
  - Often includes adjunctive symptom-specific pharmacotherapy

Schuckit MA. *N Engl J Med*. 2016;375:357-368

Long-Acting Opioids

- The use of a long-acting opioid (methadone or buprenorphine) is the most effective approach to relieve withdrawal symptoms
- There appears to be no significant difference between buprenorphine and methadone in improving severity of opioid withdrawal
  - Withdrawal symptoms may resolve more quickly with buprenorphine
- The dose may be gradually reduced to allow patient to adjust to the absence of an opioid
  - Tapering schedules vary
- Some patients will require lifelong maintenance

National Guidelines for Medication-Assisted Treatment of Opioid Dependence. 2014. https://www.health.gov.au/sites/default/files/national-guidelines-for-medication-assisted-treatment-of-opioid-dependence.pdf. Accessed June 28, 2020.

Buprenorphine in Detox

- Buprenorphine (partial agonist/antagonist)
  - Has high affinity for μ-opioid receptor and a slow dissociation rate
  - DATA waiver typically needed to prescribe (exceptions exist) but can be prescribed in any setting
  - Can precipitate or worsen withdrawal with recent use of an opioid
    - Patients need to be in withdrawal to start, typically COWS ≥ 8 to prevent precipitated withdrawal
    - Prior to administration, a minimum of 12-24 hours should have elapsed since the last use of a short-acting opioid and 36-72 hours for longer-acting opioids
  - Duration ~ 24 hours
  - Common adverse events include constipation, sweating, headache, and nausea

National Guidelines for Medication-Assisted Treatment of Opioid Dependence. 2014. https://www.health.gov.au/sites/default/files/national-guidelines-for-medication-assisted-treatment-of-opioid-dependence.pdf. Accessed June 28, 2020.

Role of Methadone in Detox

- MOA: full opioid agonist
- No specific level of withdrawal indicated for initiation
  - Will not cause withdrawal itself
  - Not advised to initiate treatment in an intoxicated patient
- Maintenance prescribing must be managed at a methadone treatment facility – cannot be managed by local physician
- Duration ~24 hours
- Common adverse effects include constipation, nausea, headache, and dizziness
- QTc prolongation is a concern with methadone
  - Can cause torsades de pointes
  - Important to screen for drug interactions

Long-Acting Opioids

- Prescribing and/or administration of maintenance long-acting opioids is limited to inpatient hospitals, addiction-treatment programs, or physicians who have completed specific training to treat OUDs
- May involve concomitant use of non-opioid medications to help control symptoms. Common examples include:
  - Clonidine
  - Antidepressants or anxiety medications
  - Anti-spasm medications

Example Detoxification Protocol For Long-Acting Opioids

Step	Methadone Taper	Sublingual Buprenorphine
Initial Dose	If patient is participating in a methadone program, verify dose; start taper 10 mg below that level; if patient is not participating in a methadone program, start at 10–30 mg administered in divided doses	4-8 mg
Stabilization	7-14 days	2-5 days
Taper	Decrease initial dose by 10-20% every 1–2 days over 2–3 weeks or more	Decrease dose by 10–20% every 1–2 days over 2 weeks or more

Schuckit MA. *N Engl J Med*. 2016;375:357-68.

Non-Opioid Pharmacology

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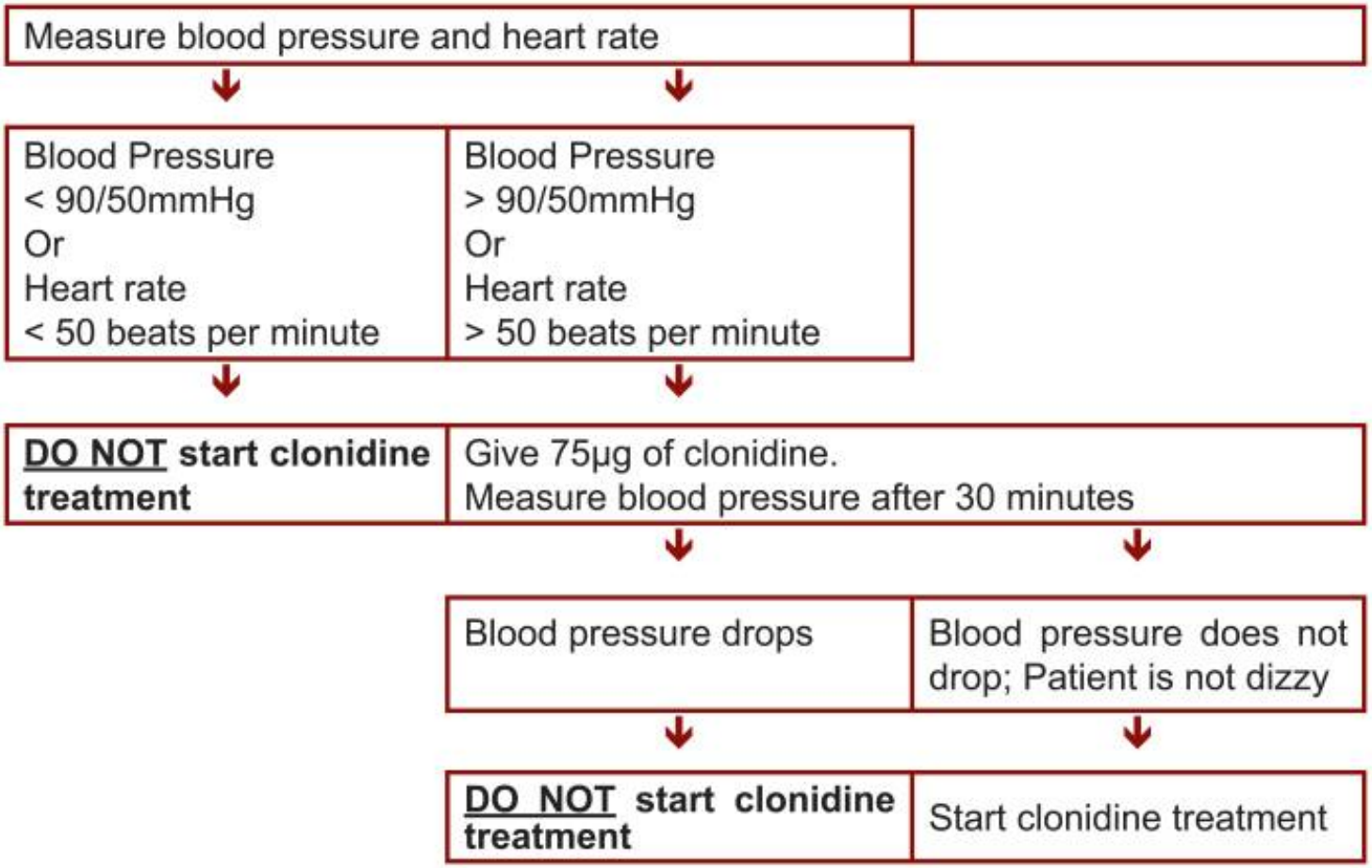
α_2-Adrenergic Agonists

- Not effective for all patients
- Most used agent is clonidine
  - Others include lofexidine and tizanidine
- Decreases signs and symptoms associated with autonomic overactivity by lessening sympathetic outflow
  - Effective in decreasing anxiety, piloerection, insomnia, increased pulse rate and blood pressure among other signs and symptoms
- Adverse effects include hypotension, bradycardia, somnolence, dry mouth, and CNS depression
  - Monitor blood pressure and heart rate before administering
- Most often used in conjunction with other symptomatic treatment options as needed

WHO Procedure for Initiation of Clonidine for Opioid Withdrawal



Agthe AG, et al. *Pediatrics*. 2009;123(5):e849-56.

Example Symptomatic Medications in Withdrawal Management

Medication	Target Symptoms
Clondine	Increased pulse rate and blood pressure, anxiety, chills, piloerection
Temazepam/Diazepam/Lorazepam	Insomnia, anxiety
Loperamide	Diarrhea
Ibuprofen/Naproxen	Bone, muscle, joint, or other pain
Prochlorperazine	Nausea and vomiting
Ondansetron	Nausea and vomiting
Acetaminophen	Fever, headaches, or other pain
Trazodone	Insomnia
Diphenhydramine	Insomnia
Ropinirole	Restless legs
SSRI/SNRI	Depression

Schuckit MA. *N Engl J Med*. 2016;375:357-368

Alcohol Withdrawal

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Overview

- Most patients experiencing alcohol withdrawal have mild symptoms and can be effectively managed as an outpatient
- About 5% of patients will present with severe alcohol withdrawal which could include seizures and/or delirium tremens (DTs)
  - Can be fatal and should be treated in an inpatient setting
- Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) protocols are often used to treat patients with alcohol withdrawal

Diagnostic Criteria for Alcohol Withdrawal

- Cessation of (or reduction in) heavy and prolonged alcohol use
- Two or more of the following, developing within several hours to a few days after the cessation of (or reduction in) alcohol used:
  - Autonomic hyperactivity (e.g., sweating or pulse > 100 bpm)
  - Increased hand tremor
  - Insomnia
  - Nausea/vomiting
  - Transient visual, tactile, or auditory hallucinations or illusions
  - Psychomotor agitation
  - Anxiety
  - Generalized tonic-clonic seizures

"Diagnostic and Statistical Manual of Mental Disorders (DSM-5)." American Psychiatric Association. https://www.psychiatry.org/psychiatrists/practice/dsm Accessed May 29, 2020.

Diagnostic Criteria for Alcohol Withdrawal continued

- The signs or symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder

"Diagnostic and Statistical Manual of Mental Disorders (DSM-5)." American Psychiatric Association. https://www.psychiatry.org/psychiatrists/practice/dsm Accessed May 29, 2020.

Stages of Alcohol Withdrawal

Stage	Onset	Symptoms
1	6-12 hours	Mild tremors, irritability, mild agitation, restlessness, tachycardia, nausea, sweating
2	12-24 hours	Marked tremors, hyperactivity, hyper-alertness, increased startle response, pronounced tachycardia, insomnia, nightmares, illusions, hallucinations, alcohol cravings
3	24-48 hours	**Withdrawal seizures**: generalized tonic-clonic seizures
4	2-4 days	**Delirium tremens (DTs)**: Confusion, agitation, tremor, insomnia, tachycardia, sweating, hyperpyrexia

Miller NS, Gold MS. Am Fam Physician. 1998;58(1):139-46.
Bayard M, McIntyre J, Hill KR, Woodside J. "Alcohol Withdrawal Syndrome." American Family Physician. http://www.aafp.org/afp/2004/0315/p1443.html Accessed June 28, 2020.

Clinical Institute Withdrawal Assessment for Alcohol, Revised

- Also known as CIWA-Ar
- Symptom-driven protocol used for the assessment and management of alcohol withdrawal
- Frequency of administration for a given patient is based on the severity of withdrawal
- Consists of ten items and has a range of 0–67
  - The higher the score, the more severe the symptoms
- Scores of 8-10 indicate minimal to mild withdrawal; 10 to 15 moderate; >15 severe
  - Patients are typically treated if the score is greater than 8–10 (depending on protocol)
- The protocol has been shown to be efficacious and results in lower total benzodiazepine use
- Calculator available: https://www.mdcalc.com/ciwa-ar-alcohol-withdrawal

Sullivan JT, et al. *Br J Addict*. 1989;84(11):1353-1357.

Predictors of Severe Alcohol Withdrawal

Older age
Comorbid medical or surgical illness
Past history of DT or alcohol withdrawal seizure
Severe withdrawal symptoms at initial assessment, despite having significant blood alcohol levels
Presence of dehydration
History of having had withdrawal seizure during this current withdrawal state before the assessment
Presence of hyponatremia or hypokalemia
Elevated AST or GGT levels
Low platelet count
The presence of structural brain lesions
Duration of alcohol use and average daily quantity of alcohol consumed are not consistent predictors of severe alcohol withdrawal

AST – Aspartate aminotransferase; GGT – Gamma glutamyl transferase;
DT – Delirium tremens

Kattimani S, Bharadwaj B. *Ind Psychiatry J*. 2003;22(2):100-108.

Treatment Options

- Non-pharmacologic Treatment
  - General supportive care
    - Quiet/protective environment
    - Nutritional support
    - Electrolyte support
- Pharmacological Treatment
  - Control psychomotor agitation/withdrawal
  - Prevent seizures
  - Prevent hallucinations
  - Prevent delirium tremens

General Supportive Care

- Orient patient to time, place, and date
- Provide patients a quiet room with low lighting and minimal stimulation
- Frequent monitoring of vital signs
- Assess for adequate hydration
  - Volume depletion commonly seen in these patients

Addressing Nutrition

- Patients with alcoholism tend to have poor nutrition, are malnourished, and have several vitamin deficiencies
  - Most of their daily caloric intake is obtained from alcohol consumption
- Non-ICU patients
  - Providing daily meals will help to address many deficiencies
  - Thiamine (vitamin B1) should be given to all patients to prevent Wernicke-Korsakoff Syndrome (WKS)
    - 100 mg IV/IM/PO daily 3-5 days
  - Folic acid (vitamin B9) – 1 mg daily for 3-5 days
  - Multivitamin daily – continue until patient eating balanced diet
- ICU patients
  - Patients presenting to the ICU for the management of alcohol-associated vitamin and electrolyte deficiencies will likely require "**banana bags**"
    - IV solution consisting of thiamine, folic acid, and multivitamins

Electrolyte Deficiencies

- Individualized based on patient's serum chemistry
- Monitor potassium, phosphate, magnesium and calcium
  - Can replace orally or intravenously depending on specific patient symptom(s) and deficit(s)

Pharmacotherapy for "Typical" Alcohol Withdrawal

- Targeted therapy
  - Psychomotor agitation: seizures, anxiety, restlessness, tremor, and bothered by light/sounds
    - Gamma-aminobutyric acid (GABA) receptor agonists
      - **Gold standard = benzodiazepines** for moderate to severe withdrawal
  - Adrenergic symptoms: tremor, sweating, hypertension, and tachycardia
    - Clonidine
  - Delirium/Hallucinations
    - Benzodiazepines
    - Antipsychotic agents

Table 1. Medication Treatment for Alcohol Withdrawal.

Class	Examples	Effects
Benzodiazepines (preferably long-acting)*	Chlordiazepoxide, diazepam, oxazepam, lorazepam	Decreased severity of withdrawal symptoms; reduced risk of seizures and delirium tremens
Anticonvulsants	Carbamazepine	Decreased severity of withdrawal symptoms
Adjunctive agents		
Beta-blockers	Atenolol, propranolol	Improvement in vital signs; reduction in craving
Alpha-agonists	Clonidine	Decreased severity of withdrawal symptoms

* Dosing follows one of three strategies. With fixed-dose therapy, a set amount of medication is given at regular intervals (e.g., 50 to 100 mg of chlordiazepoxide four times daily), with the dose tapered from day 4 to day 7. With a loading-dose strategy, a moderate-to-high dose of a long-acting benzodiazepine (e.g., 20 mg of diazepam) is given initially to provide sedation; the level is allowed to decrease through metabolism. With symptom-triggered therapy, the first dose of 5 mg of diazepam is given when the score for symptoms is at least 8 on the Clinical Institute Withdrawal Assessment for Alcohol scale. The severity of symptoms is measured one hour after this and each subsequent dose of diazepam and then at least every eight hours, with the frequency of monitoring increased if symptoms worsen. The dose is adjusted (e.g., from 5 mg of diazepam to 10 mg three times daily) according to the severity of the symptoms.

Kosten KR, O'Connor PG. *N Engl J Med*. 2003;348:1786-95.

Psychomotor Agitation and Withdrawal

- Includes: tremor, anxiety, diaphoresis, tachypnea, and dysphoria
- Benzodiazepines are drugs of choice:

Drug	Comments
Lorazepam (Ativan®)	Preferred medication for liver disease; no active metabolites
Diazepam (Valium®)	Decrease dose for liver disease
Chlordiazepoxide (Librium®)	Long acting; decrease dose for liver disease

- Oxazepam, barbiturates, gabapentin, and carbamazepine are less commonly used

Comparison of Commonly used Benzodiazepines in Treatment of Alcohol Withdrawal

	Diazepam	Chlordiazepoxide	Lorazepam	Oxazepam
Equivalent doses (to 10 g alcohol)	5 mg	25 mg	1 mg	15 mg
Onset of action	Rapid	Intermediate	Intermediate	Slow
Half-life	Long	Long	Short	Short
Active metabolites	Yes	Yes	No	No
Hepatic metabolism	Yes	Yes	No	No
Routes of administration	• Oral • Intravenous	Oral	• Oral • Sublingual • Intravenous • Intramuscular	Oral

Kattimani S, Bharadwaj B. *Ind Psychiatry J*. 2003;22(2):100-108.

Treatment Regimens

- Symptom-triggered dosing regimen
  - Only medicate when score is above a certain threshold on CIWA-Ar
- Tapered-dosing regimen
  - Give tapering doses of medication at scheduled intervals

"The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management." ASAM. https://www.asam.org/docs/default-source/quality-science/awg-3-20-20.pdf?sfvrsn=d87852c2_2 Accessed June 28, 2020.

Treatment Regimens continued

- Fixed-dose regimen
  - Fixed daily dose is calculated based the amount of alcohol consumption daily and administered in four divided doses
  - After 2-3 days of stabilization, the benzodiazepine is gradually tapered over 7-10 days
- Loading-dose regimen
  - The use of long-acting benzodiazepines to serve as a self-tapering strategy

Alcoholic Hallucinations

- Generally, develops **12 – 24** hours after no alcohol
- Usually resolves in 24-48 hours
- Symptoms:
  - Hallucinations – usually visual, but can be auditory or tactile
  - Vital signs usually normal
- Treatment:
  - Benzodiazepines will usually manage hallucinations effectively
  - Can add an antipsychotic such as:
    - Haloperidol (Haldol®)
    - Quetiapine (Seroquel®)
    - Aripiprazole (Abilify®)

Delirium Tremens (DTs)

- A medical emergency that occurs from severe alcohol withdrawal that can be life threatening
- Occurs typically **two to four** days after last use of alcohol
- Typically lasts up to 7 days
  - Hallucinations, disorientation, agitation (benzodiazepines, antipsychotics)
  - Tachycardia, Hypertension, hyperventilation (β-blockers, clonidine)
  - Fever, diaphoresis (acetaminophen, NSAIDs)
- Hyperventilation and consequent respiratory alkalosis in this setting result in a significant decrease in cerebral blood flow
- Mortality rate ~ 5%
  - Death usually is due to arrhythmia, complicating illnesses (pneumonia)

Wernicke-Korsakoff Syndrome

- A type of brain disorder that can be found in patients with chronic alcoholism
- Combined presence of acute Wernicke encephalopathy (confusion/delirium) followed by chronic Korsakoff psychosis (form of amnesia)
- Brain disorder – lack of vitamin B1 (thiamine)
  - Thiamine plays a crucial role in cerebral energy utilization
  - Deficiencies can initiate neuronal injury by inhibiting metabolism in brain regions with high metabolic requirements and high thiamine turnover
- WKS can also occur in other malabsorptive conditions
  - Chronic illness (AIDs and Cancer), inflammatory bowel disease, bariatric surgery, etc.

Schmidt JK, et al. *Ann Pharmacoth*. 2016;50(5):389-401.

Wernicke Encephalopathy

- Acute, can be reversible if treated
  - Results from a severe acute deficiency of thiamine
  - If left untreated, many patients progress to coma or death
- Classic triad of symptoms
  - Ocular disturbances due to opthalmoplegia: Nystagmus, sometimes eye paralysis
  - Changes in mental state (confusion) – typically a global confusion state
  - Unsteady stance and gait (ataxia) – can hinder walking or standing without support
- Other symptoms:
  - Stupor, hypotension, tachycardia, hypothermia, epileptic seizures, and progressive loss of hearing
- Treatment/Prevention = Vitamin B1 (thiamine)

Schmidt JK, et al. *Ann Pharmacoth*. 2016;50(5):389-401.

Korsakoff Syndrome

- A mental disorder in which retentive memory is significantly impaired
  - A chronic neurologic sequela of Wernicke encephalopathy
- Usually irreversible (results from chronic brain damage)
- Clinical features
  - Marked by deficits in both anterograde (cannot form new memories) and retrograde memory (cannot remember old memories)
  - Apathy
  - Intact sensorium
- Patients are often unaware of their illness

Schmidt JK, et al. *Ann Pharmacoth*. 2016;50(5):389-401.

Sedative, Hypnotic, or Anxiolytic Withdrawal

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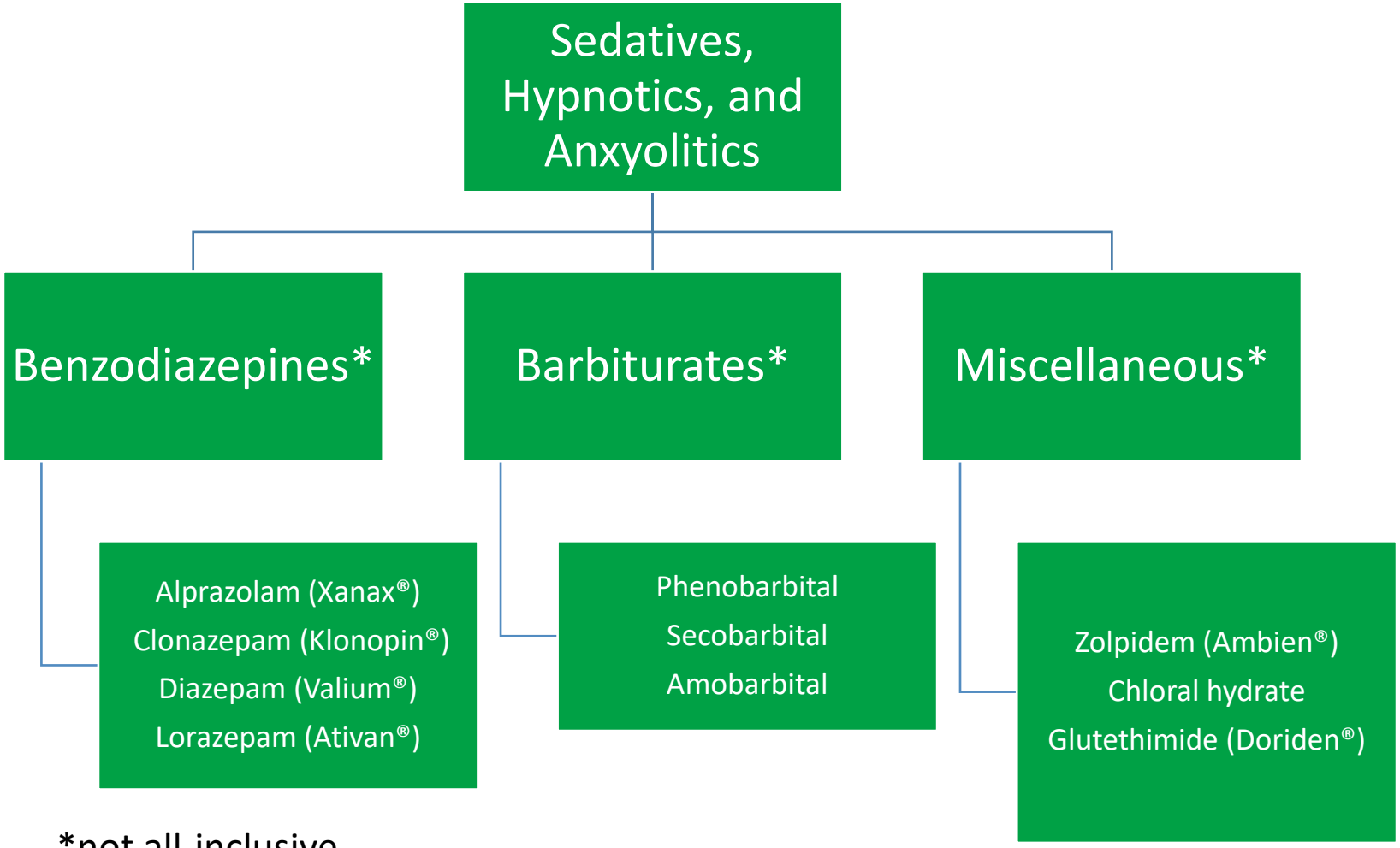
Sedatives, Hypnotics, and Anxiolytics



*not all-inclusive

Sedative, Hypnotic, or Anxiolytic Withdrawal Overview

- Can be a result of cessation of (or reduction in) sedative, hypnotic or anxiolytic that has been prolonged
- Depends on the dose, duration of use, and duration of drug action

Sedative, Hypnotic, or Anxiolytic Withdrawal Overview continued

- Common signs and symptoms include:
  - Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 beats per minute)
  - Hand tremor
  - Insomnia
  - Auditory/visual hallucinations
  - Psychomotor agitation
  - Anxiety
  - Seizures

Management of Withdrawal

- Goals of treatment include:
  - Aid the patient through detoxification safely
  - Develop a treatment plan to help reduce cravings for the drug
  - Address underlying issue(s) that led to addiction such as anxiety, depression or stressful situations

Benzodiazepine Withdrawal

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Common Benzodiazepines

High Potency	
Short half-life	**half-life (h)**
Alprazolam (Xanax®)	12-15
Lorazepam (Ativan®)	10-20
Long half-life	
Clonazepam (Klonopin®)	19-60
Low Potency	
Short half-life	**half-life (h)**
Oxazepam (Serax®	5-10
Temazepam (Restoril®)	3-13
Long half-life	
Chlordiazepoxide (Librium®)	10-30
Diazepam (Valium®)	20-70

Singh S, Sarkar S. *J Geriatr Ment Health*. 2016;3:123-130.

Benzodiazepine Withdrawal

- Symptoms are quite similar to those of alcohol withdrawal including delirium, seizures, and hallucinations
- Most likely to occur after discontinuation of:
  - A therapeutic daily dose used for four to six months
  - A dose exceeding two to three times the upper limit of a therapeutic dose used for two to three months
- Typically begins 12-48 hours after last use (can vary based on benzodiazepine used)
- Withdrawal scales can be extremely helpful
  - CIWA-B
  - Benzodiazepine Withdrawal Symptom Questionnaire

"The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management." ASAM. https://www.asam.org/docs/default-source/quality-science/awg-3-20-20.pdf?sfvrsn=d87852c2_2 Accessed June 28, 2020.

Benzodiazepine Detoxification

- May take place either outpatient or inpatient depending on severity
- Usually involves gradually reducing the dose of the drug
  - May substitute for an alternative benzodiazepine or a barbiturate (although not common)
- Adjunctive medications may be used for anxiety, depression, insomnia, and/or delirium

Inpatient Detoxification Options

- Medication regimens
  - Fixed-dose regimen
    - A fixed daily dose is calculated based on a patients use history and administered in four divided doses
    - After 2-3 days of stabilization, the benzodiazepine is gradually tapered off over 7-10 days
  - Tapered-dosing regimen
    - Give tapering doses of benzodiazepine at scheduled intervals
    - Can use CIWA in between dosing intervals
  - Symptom-triggered treatment
    - Only medicate when CIWA score is above certain threshold

"The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management." ASAM. https://www.asam.org/docs/default-source/quality-science/awg-3-20-20.pdf?sfvrsn=d87852c2_2 Accessed June 28, 2020.

Outpatient Detoxification

- Convert to a low potency benzodiazepine with a long-half life such as chlordiazepoxide or diazepam
- Gradually reduce dose over several weeks (e.g., 8-12 weeks) to >1 year – depends on patient
  - Can decrease dose by greater percent at beginning (e.g., 25%)
    - After reducing initial dose by 50%, for further dosing reductions, may need to decrease dose by 10% for patient comfort

"The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management." ASAM. https://www.asam.org/docs/default-source/quality-science/awg-3-20-20.pdf?sfvrsn=d87852c2_2 Accessed June 28, 2020.

Stimulant Withdrawal

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Stimulant Withdrawal Overview

- Stimulants are also referred to as “uppers”
- Commonly involves both physical and psychological symptoms
  - Psychological symptoms often have a greater impact than physical symptoms

Lautieri A. “Cocaine Withdrawal Symptoms, Timeline and Treatment.” American Addiction Centers. https://americanaddictioncenters.org/cocaine-treatment/withdrawal June 28, 2020.

Symptoms of Stimulant Withdrawal

Physical	Psychological
• Chills • Tremors • Muscle aches • Nerve pain	• Depression/anxiety • Suicidal thoughts • Increased cravings for stimulant

- Physical symptoms tend to subside after 7-10 days, but psychological symptoms may last months to years

Lautieri A. “Cocaine Withdrawal Symptoms, Timeline and Treatment.” American Addiction Centers. https://americanaddictioncenters.org/cocaine-treatment/withdrawal June 28, 2020.

Managing Stimulant Withdrawal

- There are no guidelines or FDA-approved medications for treating stimulant withdrawal
  - Many medications have been studied with little to no success including amphetamines, buprenorphine, naltrexone and methadone
- Treatment typically involves supportive measures to keep patients comfortable
- Symptomatic medications should be offered as needed for aches, chills, and other symptoms
- Medications to treat depression and anxiety can be useful to stabilize moods and reduce depressive symptoms

Table 3. Medication Treatment for Stimulant Withdrawal.

Class	Examples	Effects and Comments
Indirect dopamine agonists	Methylphenidate, amantadine	Treatment retention was improved in one study of each agent; data are very limited.
Adrenergic antagonists	Propranolol	Treatment retention was improved and cocaine use was reduced in patients with severe withdrawal symptoms in one study.
Antidepressants	Desipramine, bupropion	Medications are well tolerated but do not appear to be effective during stimulant withdrawal.

Kosten TR, O'Connor PG. *N Engl J Med* 2003; 348:1786-1795.

Hallucinogens

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Hallucinogen Withdrawal Overview

- Traditional withdrawal symptoms are rarely seen with hallucinogens
  - DSM-V does not recognize hallucinogen withdrawal
- There are no FDA-approved medications for hallucinogen withdrawal
- Reported withdrawal symptoms may include delusions, increased appetite, irritability, and anxiety
- If withdrawal symptoms occur, supportive measures and symptom-specific medications can be used

Cannabis Withdrawal

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Cannabis Withdrawal Overview

- Commonly believed that cannabis is not physically addictive, but this is not necessarily true
- Tetrahydrocannabinol (THC) is a fat-soluble molecule that stays in the central nervous system for an extended time before levels decrease enough to cause withdrawal
  - Average: 7-21 days for symptoms to begin
- When symptoms occur, many individuals think that the cannabis was really helping so they begin using again
  - Using quickly stops the symptoms
  - The pattern continues

Crane M. “Marijuana Withdrawal – Is It Real?” American Addiction Centers. https://americanaddictioncenters.org/marijuana-rehab/withdrawal Accessed July 23, 2019.

Symptoms of Cannabis Withdrawal

- Symptoms may include:
  - Anxiety, nervousness, and/or restlessness
  - Depression
  - Anger, irritability, and/or aggressiveness
  - Malaise, insomnia, and/or disturbing dreams
  - Abdominal pain, chills, sweating, headache, and/or shakes

Cannabis Withdrawal Treatment

- There are no FDA-approved medications to treat cannabis withdrawal
- Symptomatic medications should be offered as needed
  - 6.25 mg of quetiapine has been used with some success

Haroutunian H. 2013. Being Sober: A Step-by-Step Guide to Getting to, Getting Through, and Living in Recovery. New York, USA: Rodale, Inc.

Nicotine Withdrawal

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Overview

- Nicotine withdrawal is different for every person
  - Some patients may require no treatment at all
- Most common symptoms include:
  - Irritability
  - Cravings for tobacco
  - Restless
  - Difficulty sleeping
  - Depressed mood
  - Hunger/increased appetite
- Although nicotine withdrawal is uncomfortable, it is not life-threatening

Pharmacological Approaches

- Nicotine withdrawal and nicotine dependence are managed jointly with the same agents (see module 5 for dosing, side effects, etc.)
  - First line
    - Nicotine replacement therapy (NRT)
    - Sustained release (SR) bupropion
    - Varenicline
  - Second line
    - Clonidine and nortriptyline
- For patients who are experiencing acute moderate to severe symptoms (e.g., experiencing high anxiety), NRT is most effective due to the fast-acting delivery of nicotine

Commonalities Among Withdrawal Syndromes

- Several symptoms that are apparent regardless of the substance
  - Agitation with severe anxiety
  - Depression
  - Difficulty sleeping
  - Nausea/vomiting/pain
- Patients commonly need medical help to overcome these symptoms of withdrawal that can last much longer than detox
- All healthcare providers should know how to refer patients for help

QUESTIONS?

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