Management of Withdrawal: Alcohol, Benzodiazepines, Opioids

Julie Kmiec, DO
kmiecj@upmc.edu

University of Pittsburgh

AOAAM 2018
Objectives

• Name common signs and symptoms of alcohol, benzodiazepine, and opioid withdrawal
• Discuss evidence-based treatment of alcohol, benzodiazepine, and opioid withdrawal
ALCOHOL
Alcohol Tolerance

• Ordinarily, excitatory (glutamate) and inhibitory (GABA) neurotransmitters are in homeostasis
• Alcohol facilitates GABA$_A$ neurotransmission
• Over time, repeated use of alcohol causes a decrease in the number of GABA receptors (down regulation) and more alcohol is needed to produce effect
Attempt to Regain Homeostasis

- Alcohol acts as an NMDA receptor antagonist, which decreases excitatory tone
- Chronic alcohol use leads to upregulation of NMDA receptors and more glutamate production
Withdrawal

• If alcohol is stopped suddenly, the inhibition from alcohol is reduced, and the glutamate related excitation is unopposed
• This results in symptoms of alcohol withdrawal
• During alcohol use and withdrawal there is an increase in dopamine which contributes to autonomic hyperarousal and hallucinations
Alcohol Withdrawal

• Onset of particular symptoms
  • Withdrawal
    • 6-24 hrs after last drink, peaks 24-36 hrs
  • Seizures
    • 6-48 hrs after last drink, peak at 24 hrs
  • Withdrawal Delirium (aka delirium tremens, DTs)
    • 48-96 hrs after last drink
Signs & Symptoms of Withdrawal

**Signs**
- Elevated BP, HR, temp
- Sweating
- Tremor
- Diaphoresis
- Dilated pupils
- Disoriented
- Seizure
- Hyperactive reflexes

**Symptoms**
- Anxiety
- Insomnia
- Vivid dreams
- Headache
- Loss of appetite
- Nausea
- Irritability
- Insomnia
- Illusions/Hallucinations
### Table 4

Predictors of severe alcohol withdrawal (withdrawal seizure or DT)\[^{6,11,13}\]

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

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

Kattimani & Bharadwaj, 2013
Alcohol Withdrawal Seizures

- Withdrawal seizures begin 6-48 hrs after last drink, peak at 24 hrs
  - May occur before BAL is zero
  - Most are generalized seizures
  - Partly genetic
  - Increased in those with a history of withdrawal seizures
  - Kindling effect – more episodes of alcohol withdrawal, higher risk
  - May occur in 10% of withdrawal patients
  - About 30% with withdrawal seizure progress to delirium

Rogawski, 2005; Tovar, 2011
Alcohol Withdrawal Hallucinosis

- Visual, auditory, tactile hallucinations
- Intact orientation
- Normal vital signs
- Hallucinations can last 24 hours to 6 days
- May occur in up to 25% of those who drink alcohol heavily

Tovar, 2011
Alcohol Withdrawal Delirium

- May begin 48 hours after last drink, last up to 2 weeks
- Tachycardia, hypertension, fever
- Tremor
- Diaphoresis
- Fever
- Confusion, disorientation
- Hallucinations
- Agitation
- Disruption of sleep-wake cycle
- Death

Tovar, 2011
CIWA-AR  
(Sullivan et al., 1989)

- Study found P and BP did not correlate with severity of withdrawal.
- Determined other signs and symptoms are more reliable in assessing severity of withdrawal.
- Score range 0-67
- Score <10 pharmacologic treatment not needed

<table>
<thead>
<tr>
<th>Appendix: Addiction Research Foundation Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulse or heart rate, taken for one minute:</strong></td>
</tr>
<tr>
<td><strong>MATURITy ANU: VOMITING</strong> — Ask “Do you feel sick to your stomach? Have you vomited?” Observation: 6 no nausea and no vomiting 1 mild nausea with no vomiting 2 moderate nausea with dry heaves 3 severe nausea, frequent dry heaves and vomiting</td>
</tr>
<tr>
<td><strong>TREMBLINGS</strong> — Ask “Did you shiver or tremble?” Observation: 6 no trembles, but can be felt by fingerprint 2 3 moderate trembles, with patient’s arms extended 5 severe, even with arms not extended</td>
</tr>
<tr>
<td><strong>PAROXYSMAL SWEATS</strong> — Observation: 6 no sweat visible 2 barely perceptible sweating, patient moist 5 moderately severe sweating</td>
</tr>
<tr>
<td><strong>ANXIETY</strong> — Ask “Do you feel anxious?” Observation: 6 no anxiety, at ease 2 mobility anxiety 5 moderate anxiety 7 extremely severe anxiety</td>
</tr>
<tr>
<td><strong>AGITATION</strong> — Observation: 6 normal activity 2 somewhat more than normal activity 4 moderately agitated and restless 5 very restless 7 panics back and forth during most of the interview, or constantly disorders above</td>
</tr>
</tbody>
</table>

**TACTILE DISTURBANCES** — Ask “Have you any itching, pins and needles sensations, any burning, any sensations of or do you feel bugs crawling on or under your skin?” Observation: 6 none 1 very mild itching, pins and needles, burning or sensations 2 mild itching, pins and needles, burning or sensations 3 moderate itching, pins and needles, burning or sensations 4 constantly severe hallucinations |

**AUDITORY DISTURBANCES** — Ask “Are you more aware of sounds around you? Are they harsh? Do they hurt?” Observation: 6 not present 1 very mild hallucinations or ability to hear 2 mild hallucinations or ability to hear 3 moderate hallucinations or ability to hear 4 constantly severe hallucinations |

**VISUAL DISTURBANCES** — Ask “Does the light appear to be too bright? Is it too dark?” Observation: 6 not present 1 very mild hallucinations or ability to see 2 mild hallucinations or ability to see 3 moderate hallucinations or ability to see 4 constantly severe hallucinations |

**HEADACHE, PULLINESS IN HEAD** — Ask “Does your head feel different? Does it feel like there is a band around your head?” Observation: 6 not present 1 very mild 2 mild 3 moderate 4 extremely severe 5 severe 6 very severe 7 extremely severe |

**ORIENTATION AND CLOTHING OF SENSORY** — Ask “What day is this? What are you? Who are you?” Observation: 6 accurate and can do mental calculations 1 cannot do mental calculations or is uncertain about date 2 disoriented for days 3 disoriented for days by more than 2 calendar days 4 disoriented for hours and/or person

**Total CIWA-A Score**  
Ranger's tachy  
**Maximum Possible Score** 67

This scale is not copyrighted and may be used freely.
Alcohol Withdrawal Treatment

• Benzodiazepines – still gold-standard for moderate to severe withdrawal
• Anticonvulsants – gabapentin and carbamazepine have evidence for treating mild withdrawal (Minozzi et al., 2010)
• Phenobarbital – similar effectiveness to lorazepam (Hendey et al., 2011)
Alcohol Withdrawal Treatment: Adjuncts

- Haloperidol – for agitation, confusion
- Thiamine
- Multivitamin
- Folic acid
# Medications Typically Used for Alcohol Withdrawal

<table>
<thead>
<tr>
<th>Medication</th>
<th>Typical Route of Admin.</th>
<th>Onset of Action</th>
<th>Half-Life</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>Oral</td>
<td>15-30 mins</td>
<td>5-30 hrs, 200 hrs</td>
<td>Phase I &amp; II 3A4</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Oral, IV</td>
<td>&lt;15 mins (IV)</td>
<td>12-18 hrs</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15-30 mins (PO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Oral, IV</td>
<td>&lt;15 mins</td>
<td>30-60 hrs, 100 hrs</td>
<td>Phase I &amp; II 2C19, 3A4</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Oral</td>
<td>30-60 mins</td>
<td>8-14 hrs</td>
<td>Phase II</td>
</tr>
</tbody>
</table>
Considerations

• Active metabolites
  • If several active metabolites drug has longer duration and withdrawal may be delayed
  • Active metabolites may accumulate and cause confusion and falls, especially in
    • Elderly
    • People with liver disease
  • May interact with other medications
Medication Regimens

- Taper
  - Give tapering dose of medication at scheduled intervals
    - Chlordiazepoxide 50 mg q6h x4 doses, then 25 mg q6h x8 doses
    - Diazepam 10 mg q6h x4 doses, then 5 mg q6h x8 doses
    - Lorazepam 2 mg q6h x4 doses, then 1 mg q6h x8 doses
  - Monitor between dosing intervals on CIWA and provide additional medication if score >8-10

Mayo-Smith et al., 1997
Medication Regimens

• Symptom triggered treatment
  • Only medicate when score above a certain threshold on Clinical Institute Withdrawal Assessment (CIWA)
Symptom Triggered Dosing

- CIWA-Ar Score
  - If score > 10 give lorazepam 1 mg or chlordiazepoxide 25 mg
  - If score > 20 give lorazepam 2 mg or chlordiazepoxide 50 mg
- Monitor patient every 4-8 hrs with CIWA-Ar until score has been < 8-10 for 24 hours
- Withdrawal scales are not a substitute for clinical judgment
Examples when taper may be treatment of choice

• Busy unit where patient will not be monitored closely to ensure he/she is given medication for withdrawal regularly
• Patient has a history of complicated withdrawal
• If symptoms triggered dosing is not adequate (i.e., continuing high scores on CIWA)
Evidence for Medication Regimens

- In alcohol withdrawal, those receiving symptom triggered treatment
  - received less medication
  - had shorter length of treatment
  - shorter hospital stay
- compared to those receiving medications on fixed schedule


Outpatient Detoxification Selection

• Patient is
  • reliable and motivated to stop using alcohol and other substances
  • medically and psychiatrically stable
  • has social support
    • transportation to appointments or ED if needed
Stability

• No medical problems that alone require hospitalization
• No medical problems that can be worsened by withdrawal
• No history of complicated withdrawal
  • No history of withdrawal seizures, delirium, +/-hallucinosis
• Not suicidal or homicidal
• Vital signs stable or able to be stabilized
• Not pregnant
Pharmacotherapy

- Anti-cravings
  - Acamprosate
  - Naltrexone
- Deterrent
  - Disulfiram
- Meds to treat comorbid disorders (depression, anxiety, insomnia)
BENZODIAZEPINES
Benzodiazepine Withdrawal

- Withdrawal depends on the
  - Dose
  - Duration of use
  - Duration of drug action
- Most likely to occur after discontinuation of
  - A therapeutic daily dose used for 4-6 months
  - A dose exceeding 2-3x the upper limit of therapeutic dose used for 2-3 months
- Withdrawal begins 12-48 hours after last use, depending on drug used
Signs and Symptoms of Benzo Withdrawal

- Tachycardia, hypertension, fever, diaphoresis
- Agitation, anxiety, irritability
- Delirium, seizures
- Hallucinations (tactile, visual, auditory)
- Insomnia, nightmares
- Tremor, hyperreflexia
- Tinnitus, mydriasis, photosensitivity, hyperacusis
- Anorexia, nausea, diarrhea
- Death
Benzodiazepines

• Onset of Action
  • Rapid (within 15 mins)
    • Diazepam
    • Lorazepam (IV, IM, SL)
  • Intermediate (15-30 mins)
    • Alprazolam
    • Lorazepam (PO)
    • Chlordiazepoxide
    • Clonazepam
  • Slow (30-60 mins)
    • Oxazepam

• Drugs with a quicker off-set have higher potential for dependence due to need for repeated dosing
Relative High

- When asked to rate the high from BZD in people who abuse BZDs
  - Diazepam = #1
  - Lorazepam and alprazolam slightly, but not significantly, lower than diazepam
  - Relative high was significantly less for
    - oxazepam and chlordiazepoxide compared to diazepam, lorazepam, and alprazolam
- Preferred BZD in patients with BZD dependence
  - Diazepam (43%), alprazolam (14%), chlordiazepoxide (4%), lorazepam (4%)

Benzodiazepine Withdrawal

- Withdrawal severity depends on the
  - Dose
  - Duration of drug action (half-life)
  - Individual's characteristics
    - Baseline depression and anxiety
    - Personality traits (e.g., dependent)
    - Lower education level
    - Alcohol use
    - Female

Withdrawal By Half-life

Benzodiazepine Withdrawal

• Successful outcome depends predicted by
  • Dose
    • Lower dose
  • Duration of drug use
    • Shorter period of use
  • Individual's characteristics
    • Lower baseline anxiety

Medications for Benzo Withdrawal

• Benzodiazepines
• Barbiturates
• Adjunctive medications for anxiety, depression, or insomnia
• Antipsychotic in cases of delirium
Medication Regimens

• Taper
  • Give tapering dose of medication at scheduled intervals
  • Also monitor between dosing intervals on CIWA

• Symptom triggered treatment
  • Only medicate when score above a certain threshold on CIWA
**Appendix Addiction Research Foundation Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)**

<table>
<thead>
<tr>
<th>Pulse or heart rate, taken for one minute:</th>
<th>Blood pressure:</th>
</tr>
</thead>
</table>

**NAUSEA AND VOMITING**—Ask: “Do you feel sick to your stomach? Have you vomited?” Observation:
- 0 no nausea and no vomiting
- 1 mild nausea with no vomiting
- 2 moderate nausea with mild vomiting
- 3 severe nausea with moderate vomiting
- 4 intermittent nausea with dry heaves
- 5 constant nausea, frequent dry heaves and vomiting

**TREMOR**—Ask extended and fingers spread apart. Observation:
- 0 no tremor
- 1 not visible, but can be felt by fingering to fingers
- 2 present, without patient's hands extended
- 3 present, with patient's arms extended
- 4 severe, even with arms not extended

**PAROXYSMAL SWEATS**—Observation:
- 0 no sweat visible
- 1 barely perceptible sweating, pants moist
- 2 moist, clothing slightly wet
- 3 moist, clothing soaked
- 4 beads of sweat obvious on forehead
- 5 extremely profuse sweating

**ANXIETY**—Ask: “Do you feel nervous?” Observation:
- 0 no anxiety or unease
- 1 mild unease
- 2 moderate unease
- 3 severely uneased, or paralysed, no anxiety is inferred
- 4 equivalent to severe panic states as seen in severe delirium or acute schizophrenic reactions

**AGITATION**—Observation:
- 0 normal activity
- 1 somewhat more than normal activity
- 2 moderate dizziness and restlessness
- 3 severe restlessness
- 4 pace back and forth during most of the interview, or constantly brood about

**TACTILE DISTURBANCES**—Ask: “Have you any itching, pins and needles sensations, any burning, any numbness or do you feel bugs crawling on or under your skin?” Observation:
- 0 none
- 1 very mild itching, pins and needles burning or numbness
- 2 mild itching, pins and needles burning or numbness
- 3 moderate itching, pins and needles burning or numbness
- 4 moderately severe hallucinations
- 5 severe hallucinations
- 6 extremely severe hallucinations

**AUDITORY DISTURBANCES**—Ask: “Are you aware of sounds aloud?” Observation:
- 0 none
- 1 very mild hearing or ability to hear
- 2 mild hearing or ability to hear
- 3 moderate hearing or ability to hear
- 4 moderately severe hallucinations
- 5 severe hallucinations
- 6 extremely severe hallucinations

**VISUAL DISTURBANCES**—Ask: “Does the light appear or seem bright?” Observation:
- 0 none
- 1 very mild hallucinations
- 2 mild hallucinations
- 3 moderate hallucinations
- 4 moderately severe hallucinations
- 5 severe hallucinations
- 6 extremely severe hallucinations

**HEADACHE, FULLNESS IN HEAD**—Ask: “Does your head feel different? Does it feel like there is a band around your head?” Observation:
- 0 none
- 1 very mild
- 2 mild
- 3 moderate
- 4 moderately severe
- 5 severe
- 6 very severe
- 7 extremely severe

**ORIENTATION AND CLOUDING OF SENSES**—Ask: “What time is it? Where are you? Who am I?” Observation:
- 0 oriented and can do serial additions
- 1 cannot do serial additions or is uncertain about time
- 2 disoriented for date by no more than 2 calendar days
- 3 disoriented for date by more than 2 calendar days
- 4 disoriented for place and/or person

**Total CIWA-Ar Score**

**Rate's Intake: Maximum Possible Score 87**

Withdrawal Scales

• Benzodiazepine Withdrawal Symptom Questionnaire
  • 20 items, scored 0-2
  • Self-report

• CIWA-B
  • 22 items, scored 0-4
  • 17 self-report, 3 observation
  • Mild (1-20), moderate (21-40), severe (41-60), very severe (61-80)

Evidence for Medication Regimens

- In study of BZD withdrawal, no significant differences in
  - withdrawal severity
  - duration of treatment
  - amount of diazepam administered
  - treatment drop-out
  - BZD use at follow-up
- between those receiving fixed-taper vs. symptom triggered diazepam

McGregor et al., 2003
Figure 1. Withdrawal symptoms and prescribed benzodiazepine dosage during inpatient treatment. (A) Benzodiazepine withdrawal score. (B) Prescribed benzodiazepine dosage (▲ symptom triggered, □ gradual taper).
Outpatient Detoxification Selection

• Patient is
  • reliable and motivated to stop using
  • medically and psychiatrically stable
  • has social support
    • transportation to appointments or ED if needed
  • taking BZD as prescribed
  • taking nonprescribed BZD in low dose
Stability

- No medical problems that alone require hospitalization
- No medical problems that can be worsened by withdrawal
- No history of complicated withdrawal
  - No history of withdrawal seizures, delirium, hallucinosis
- Not suicidal or homicidal
- Vital signs stable or able to be stabilized
- Not pregnant
Overview: Outpatient Taper

- Convert to a BZD with long half-life
- Gradually reduce dose of benzodiazepine
  - Various recommendations: 8-12 weeks, 3-6 months, >1 year
  - Long tapers risk becoming the focus of the person's life and poor adherence
- May be able to reduce dose by higher percentage at beginning of taper than at end


## Medications Typically Used for Withdrawal

<table>
<thead>
<tr>
<th>Medication</th>
<th>Typical Route of Admin.</th>
<th>Onset of Action</th>
<th>Half-Life</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>Oral</td>
<td>15-30 mins</td>
<td>5-30 hrs, 200 hrs</td>
<td>Phase I &amp; II 3A4</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Oral, IV</td>
<td>&lt;15 mins (IV) 15-30 mins (PO)</td>
<td>12-18 hrs</td>
<td>Phase II</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Oral, IV</td>
<td>&lt;15 mins</td>
<td>30-60 hrs, 100 hrs</td>
<td>Phase I &amp; II 2C19, 3A4</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Oral</td>
<td>30-60 mins</td>
<td>8-14 hrs</td>
<td>Phase II</td>
</tr>
</tbody>
</table>
Converting Benzodiazepines

• Conventional wisdom is to convert from short to long half-life medication
  • Evidence for this is scarce
• Convert from several to one BZD if patient is taking multiple

Percent Reduction in Dose

• Can decrease dose by greater percentage in the beginning of withdrawal (e.g., 25%)
• After reducing initial dose by 50%, may need to decrease dose deductions by 10% for patient comfort
Phenobarbital Taper

• 310 admissions
• Age range: 19-61 years; median age 36 years
• 78 (25.2%) on MMT; 177 (56.1%) on buprenorphine taper
• 3-day taper
  • 200 mg x1, followed by 100 mg q4 hours x5 doses
  • 60 mg q4 hours x4 doses
  • 60 mg q8 hours x3 doses.
• 25.8% had at least 1 dose held due to sedation
• 11.6% received at least 1 extra dose of phenobarbital

Phenobarbital Taper

• No evidence of induction of opioid withdrawal in MMT patients
• No seizures, falls, transfers to another unit
• 1% developed delirium
• 27.1% had sedation
• 17.1% left AMA
• Within 30 days of discharge
  • 6.1% were readmitted
    • 3 patients (1%) for withdrawal symptoms
  • 7.1% had an ED visit

# Adjunctive Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect of Medication</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyzine</td>
<td>Patients taking 25-50 mg had a decrease in anxiety during a benzodiazepine taper compared to placebo.</td>
<td>Lemoine et al., 1997</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>When given 200-800 mg/day during and after a benzodiazepine taper, it reduced withdrawal symptoms and promoted abstinence compared to placebo.</td>
<td>Schweizer et al., 1991</td>
</tr>
<tr>
<td>Trazodone</td>
<td>A significantly higher percentage of patients taking trazodone during a benzodiazepine taper were abstinent from benzodiazepines at 5 weeks post-taper compared to patients taking placebo, but there was no difference at 12 weeks post-taper.</td>
<td>Rickels et al., 1999</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>A significantly higher percentage of patients taking sodium valproate during a benzodiazepine taper were abstinent from benzodiazepines at 5 weeks post-taper compared to patients taking placebo, but there was no difference at 12 weeks post-taper.</td>
<td>Rickels et al., 1999</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Pretreatment and use of imipramine during benzodiazepine taper increased taper success rate; a significantly higher percentage of patients taking imipramine were abstinent from benzodiazepines at 12 weeks post-taper compared to those taking placebo.</td>
<td>Rickels et al., 2000</td>
</tr>
</tbody>
</table>
## Adjunctive Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect of Medication</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td>Patients treated with pregabalin (150-600 mg/day) had significantly lower withdrawal symptoms compared to placebo, both during taper and 6 weeks after. Group treated with pregabalin had lower anxiety during taper.</td>
<td>Hadley et al. (2012)</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Subjects given buspirone during BZD withdrawal had lower levels of anxiety than subjects given placebo.</td>
<td>Morton &amp; Lader (1995), Udelman &amp; Udelman (1990)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>In MMT patients taking doses up to 1200 mg TID, there were no significant differences between gabapentin and placebo on amount of BZD use per day (both groups reduced use), days abstinent per week, and CIWA-A scale.</td>
<td>Mariani et al. (2016)</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>Randomized, placebo-controlled study found subjects given flumazenil infusion plus oxazepam significantly reduced withdrawal symptoms and cravings compared to oxazepam and placebo. Subjects given flumazenil infusion had lower relapse rates up to 30 days later.</td>
<td>Gerra et al. (2002)</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Cross-over study, compared melatonin to placebo in MMT patients using BZD. Sleep quality improved with cessation of BZD, regardless of group. In each group, ~30% stopped using BZD.</td>
<td>Peles et al. (2007)</td>
</tr>
</tbody>
</table>
CBT

• In subjects tapering off of BZD
  • Addition of group CBT did not increase the percentage who discontinued BZD
  • Of subjects who were unable to discontinue BZD, those receiving group CBT reduced BZD dosage significantly more than controls

• Meta-analysis found psychological intervention plus taper was superior to taper (OR=1.82) and routine care (OR=3.38)

Protracted Withdrawal

• Prolonged neuropsychiatric symptoms after cessation of benzodiazepines
  • anxiety, insomnia, depression, paresthesia, tinnitus, perceptual and motor symptoms
• May contribute to restarting benzodiazepines
• Address symptoms with adjunctive medications, SSRIs/SNRIs, supportive therapy

Anticipated Withdrawal

• Psychological or subjective withdrawal that occurs due to a patient’s anticipation of or apprehension about discontinuing benzodiazepines

• Case report of patient who complained of withdrawal even though taking regular dose of diazepam

Address Comorbidities

- Nonaddictive medications for anxiety
  - SSRI
  - SNRI
  - TCA
  - Hydroxyzine pamoate
  - CBT

- Nonaddictive medications for sleep
  - Trazodone
  - Melatonin
  - TCA
  - Anticonvulsants
  - CBT
OPIOIDS
Opioid Withdrawal

• May begin 4-6 hrs after last heroin use versus 36 hours after last methadone use
• Tachycardia
• Dilated pupils, rhinorrhea, tearing, yawning
• Piloerection, tremor
• GI upset (nausea, vomiting, diarrhea)
• Insomnia
• Muscle and joint pain
• Anxiety, irritability, restlessness
• Chills
# Opioid Withdrawal Timeline

<table>
<thead>
<tr>
<th>Grade</th>
<th>S/S</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td><strong>1</strong> Lacrimation, Rhinorrhea, Diaphoresis, Yawning, Restlessness, Insomnia</td>
<td>8-24 hours after short-acting; up to 36 hours after long-acting opioid</td>
</tr>
<tr>
<td></td>
<td><strong>2</strong> Dilated pupils, Piloerection, Muscle twitching, Myalgia, Arthralgia, Abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Full</td>
<td><strong>3</strong> Tachycardia, Hypertension, Tachypnea, Fever, Anorexia, Nausea, Extreme restlessness</td>
<td>1–3 days after short-acting; 72–96 hours after long-acting</td>
</tr>
<tr>
<td></td>
<td><strong>4</strong> Diarrhea, Vomiting, Dehydration, Hyperglycemia, Hypotension, Curled-up position</td>
<td></td>
</tr>
</tbody>
</table>

Duration of withdrawal:
- Short-acting 7-10 days
- Long-acting 14+ days

TIP 63; SAMHSA
Figure 1. Severity of Opioid-Withdrawal Symptoms after Abrupt Discontinuation of Equivalent Doses of Heroin, Buprenorphine, and Methadone.

Peak withdrawal symptoms are most severe after discontinuation of heroin. Such symptoms last longest with methadone, which has a somewhat later peak of severity. Buprenorphine has milder peak withdrawal symptoms than does methadone; the duration of symptoms is intermediate between those for methadone and those for heroin.
## COWS

<table>
<thead>
<tr>
<th>Reason for this assessment:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient’s Name:</strong></td>
</tr>
<tr>
<td><strong>GI Upset:</strong> Over last 1/2 hour</td>
</tr>
<tr>
<td>No GI symptoms</td>
</tr>
<tr>
<td>1. Stomach cramps</td>
</tr>
<tr>
<td>2. Nausea or loose stool</td>
</tr>
<tr>
<td>3. Vomiting or diarrhea</td>
</tr>
<tr>
<td>5. Multiple episodes of diarrhea or vomiting</td>
</tr>
<tr>
<td><strong>Sweating:</strong> Over past 1/2 hour not accounted for by room temperature or patient activity</td>
</tr>
<tr>
<td>No report of chills or flushing</td>
</tr>
<tr>
<td>1. Subjective report of chills or flushing</td>
</tr>
<tr>
<td>2. Flush or observable moisture on face</td>
</tr>
<tr>
<td>3. Beads of sweat on brow or face</td>
</tr>
<tr>
<td>4. Sweat streaming off face</td>
</tr>
<tr>
<td><strong>Redness:</strong> Observation during assessment</td>
</tr>
<tr>
<td>0 able to sit still</td>
</tr>
<tr>
<td>1. Reports difficulty sitting still, but is able to do so</td>
</tr>
<tr>
<td>2. Frequent shifting or extraneous movements of legs/arms</td>
</tr>
<tr>
<td>5. Unable to sit still for more than a few seconds</td>
</tr>
<tr>
<td><strong>Pupil Size:</strong></td>
</tr>
<tr>
<td>0. Pupils pinned or normal size for room light</td>
</tr>
<tr>
<td>1. Pupils possibly larger than normal for room light</td>
</tr>
<tr>
<td>2. Pupils moderately dilated</td>
</tr>
<tr>
<td>5. Pupils so dilated that only the rim of the iris is visible</td>
</tr>
<tr>
<td><strong>Bone or Joint Aches:</strong></td>
</tr>
<tr>
<td>0. Patient was having pain previously, only the additional component attributed to opiate withdrawal is scored</td>
</tr>
<tr>
<td>0. Not present</td>
</tr>
<tr>
<td>1. Mild diffuse discomfort</td>
</tr>
<tr>
<td>2. Patient reports severe diffuse aching of joints/muscles</td>
</tr>
<tr>
<td>4. Patient is rubbing joints or muscles and is unable to sit still because of discomfort</td>
</tr>
<tr>
<td><strong>Gooseflesh Skin:</strong></td>
</tr>
<tr>
<td>0. Skin is smooth</td>
</tr>
<tr>
<td>3. Piloerection of skin can be felt or hairs standing up on arms</td>
</tr>
<tr>
<td>5. Prominent piloerection</td>
</tr>
<tr>
<td><strong>Runny Nose or Tearing:</strong> Not accounted for by cold symptoms or allergies</td>
</tr>
<tr>
<td>0. Not present</td>
</tr>
<tr>
<td>1. Nasal stuffiness or unusually moist eyes</td>
</tr>
<tr>
<td>2. Nose running or tearing</td>
</tr>
<tr>
<td>4. Nose constantly running or tears streaming down check</td>
</tr>
</tbody>
</table>

**Total Score:**

The total score is the sum of all 11 items.

**Score:**

5-12 = mild, 13-24 = moderate, 25-30 = moderately severe, more than 30 = severe withdrawal

**Initials of person completing assessment:**
Treatment of Opioid Withdrawal

- Clonidine, Lofexidine
  - Alpha-2-adrenergic agonists
- Buprenorphine
  - Mu-opioid receptor partial agonist
- Methadone
  - Mu-opioid receptor full agonist
Withdrawal vs. Maintenance

- Due to high risk of accidental overdose and death after withdrawal from opioids or from continued opioid use, pharmacotherapy is the standard of care for OUD
  - Buprenorphine
  - Methadone
  - Naltrexone-XR
Alpha-2-Agonists

• Opioids are mu-receptor agonists, and inhibit cyclic AMP; when chronic opioids are discontinued, cyclic AMP system in noradrenergic system become overactive

• Alpha-2-agonists suppress noradrenergic hyperactivity in locus coeruleus associated with opioid withdrawal
  • Aches
  • Rhinorrhea
  • Lacrimation
  • Temperature dysregulation
  • Diaphoresis

Kosten & O’Connor, 2003
Dosing of Alpha-2-Agonists

• Clonidine
  • Off-label use since 1970s
  • 0.1 mg to 0.2 mg every 4 hours, up to 1.2 mg per day
  • Start tapering dose after day 3
  • Typically use for up to 10 days
  • Dosing may be limited by hypotension, bradycardia
  • Adverse effects of dry mouth, somnolence, fatigue
Dosing of Alpha-2-Agonists

- Lofexidine
  - FDA approval in 2018, used in Europe for years
  - Three 0.18 mg tabs 4 times daily
  - Dosing guided by symptoms
  - Total daily dosage should not exceed 2.88 mg (16 tablets) and no single dose should exceed 0.72 mg (4 tablets)
  - Gradual dose reduction (1 tab per dose) over 2-4 days
  - Indication for up to 14 days
  - Was shown to produce more rapid resolution in symptoms, less hypotension, and retain people longer than clonidine

Kosten & O’Connor, 2003; FDA Prescribing Information, 2018
Lofexidine

- Possible adverse effects & warnings
  - Hypotension, bradycardia, syncope
  - Somnolence
  - Dry mouth
  - QT prolongation
  - CNS depression when used with other CNS depressants
  - Increased risk of opioid overdose if resume using after withdrawal
- CYP2D6 inhibitors may increase plasma levels (e.g., paroxetine)
- Poor CYP2D6 metabolizers may have more adverse effects
Meds for Associated Symptoms

- Anxiety – Hydroxyzine Pamoate
- Diarrhea – Loperamide, sometimes may need to switch to Diphenoxylate/Atropine
  - Increase in self-treatment with loperamide – QT prolongation, TdP
- Nausea – ondansetron, other antiemetics
- Insomnia – Trazodone, Melatonin, Mirtazapine

Acute Withdrawal

• 3-day rule (Title 21, Code of Federal Regulations, Part 1306.07(b)) allows a practitioner who is not separately registered as a narcotic treatment program or a certified DATA waiver provider, to administer narcotic drugs to a patient for the purpose of relieving acute withdrawal symptoms while arranging for the patient’s referral for treatment
  • Not more than 1 day's medication may be administered at one time
  • Treatment may not be carried out for more than 72 hours
  • The 72-hour period cannot be renewed or extended

https://www.deadiversion.usdoj.gov/pubs/advisories/emerg_treat.htm
Hospitalized Patients

- A physician or other authorized hospital staff may maintain or detoxify a person with buprenorphine or methadone as an incidental adjunct to medical or surgical conditions other than opioid use disorder (OUD).
- A patient who is admitted to a hospital for a primary medical problem other than OUD, such as endocarditis, may be administered opioid agonist medications, methadone and buprenorphine, to prevent opioid withdrawal that would complicate the primary medical problem.
- A DATA 2000 waiver is not required for practitioners to administer or dispense buprenorphine or methadone in this circumstance.

https://www.samhsa.gov/programs-campaigns/medication-assisted-treatment/legislation-regulations-guidelines/special
Buprenorphine

• Mu-partial agonist
• High affinity for mu receptor, slow dissociation
• Usually combined with naloxone to prevent misuse of medication; do not recommend use of mono-product
• Typically DATA waiver to prescribe, with previous exceptions
• Pt needs to be in withdrawal to start medication, typically COWS ≥8 to prevent precipitated withdrawal
• Well tolerated usually, most common adverse effects sweating, constipation, headache, nausea
### Examples of Buprenorphine Tapers

**Suboxone® taper regimen for two study taper groups.**

<table>
<thead>
<tr>
<th>Suboxone® dose (expressed as amount of buprenorphine)</th>
<th>7-day</th>
<th>28-day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stabilization dose</td>
<td>8 mg</td>
<td>16 mg</td>
</tr>
<tr>
<td>Study day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9–11</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>12–14</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>15–16</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>17–19</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>20–22</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>23–25</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>26–28</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Ling et al., 2009
Buprenorphine vs. Clonidrine

• Prospective, randomized, open-label study of buprenorphine and clonidine
• 344 men and women with OUD
• 13-day medically supervised withdrawal study
• Either inpatient or outpatient withdrawal setting

• Adjusting for level of care (IP vs OP), those who received buprenorphine were
  • nine times more likely to have achieved treatment success (attended appointment and negative urine tox) than those receiving clonidine (OR = 9.503, 95% CI: 4.604 – 19.614, p < .001)
  • 22 times more likely to complete treatment (OR = 22, 95% CI: 11 – 46, p<.001)
  • 69.1% receiving clonidine dropped out by day four versus 12% of patients receiving buprenorphine-naloxone, χ² (1, N = 344) = 115.765, p < .001

Ziedonis et al., 2009
Methadone

- Methadone is full mu-opioid agonist
- No need to have specific level of withdrawal to start, however, not wise to start when intoxicated
- Starting dose 20-30 mg, may need to increase slightly to alleviate withdrawal symptoms, then start decreasing the dose
- Reduction of 3% of dose vs. 10% of dose per week have higher retention, less withdrawal, less illicit opioid use
  - Only 40% achieve abstinence in either group
- Starting at methadone 35 mg daily and reducing over 21 days did not offer advantage in alleviating withdrawal or achieving abstinence compared to abrupt cessation and use of clonidine

Kosten & O'Connor, 2003


Antagonist Assisted Withdrawal

- 150 participants randomized
- Open-label
- Participants with naltrexone-assisted detoxification were significantly more likely to
  - be successfully inducted to naltrexone-XR (56.1% compared with 32.7%)
  - receive the second naltrexone injection at week 5 (50% vs. 26.9%)

### TABLE 1. Outpatient Opioid Detoxification Regimen, by Treatment Arm, in a Study of Oral Naltrexone Versus Buprenorphine as Detoxification Strategies for Extended-Release Injectable Naltrexone Induction in Opioid Dependence

<table>
<thead>
<tr>
<th>Protocol Day</th>
<th>Naltrexone-Assisted Detoxification</th>
<th>Buprenorphine-Assisted Detoxification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ancillary medications&lt;sup&gt;a&lt;/sup&gt; to support abstinence</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Buprenorphine, 2 mg sublingually every 1–2 hours, up to 8 mg</td>
<td>Buprenorphine, 6 mg</td>
</tr>
<tr>
<td>3</td>
<td>(Washout)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Naltrexone, 1 mg</td>
<td>Buprenorphine, 4 mg</td>
</tr>
<tr>
<td>5</td>
<td>Naltrexone, 3 mg</td>
<td>Buprenorphine, 4 mg</td>
</tr>
<tr>
<td>6</td>
<td>Naltrexone, 12 mg</td>
<td>Buprenorphine, 2 mg</td>
</tr>
<tr>
<td>7</td>
<td>Naltrexone, 25 mg</td>
<td>Buprenorphine, 1 mg</td>
</tr>
<tr>
<td>8</td>
<td>Extended-release injectable naltrexone, 380 mg i.m.</td>
<td>Extended-release injectable naltrexone, 380 mg i.m.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ancillary medications offered included clonidine (0.1 mg q.i.d., plus every 4 hours as needed; maximum daily dose, 1.2 mg), clonazepam (0.5 mg q.i.d.; maximum daily dose, 2.0 mg), prochlorperazine (10 mg t.i.d.), trazodone (100 mg h.s.), and zolpidem (10 mg h.s.).
Severity of Withdrawal by Treatment

Bisaga, 2014
QUESTIONS/COMMENTS
References


