Management of Withdrawal: Alcohol, Benzodiazepines, Opioids

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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

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Table 4

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

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 & 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,

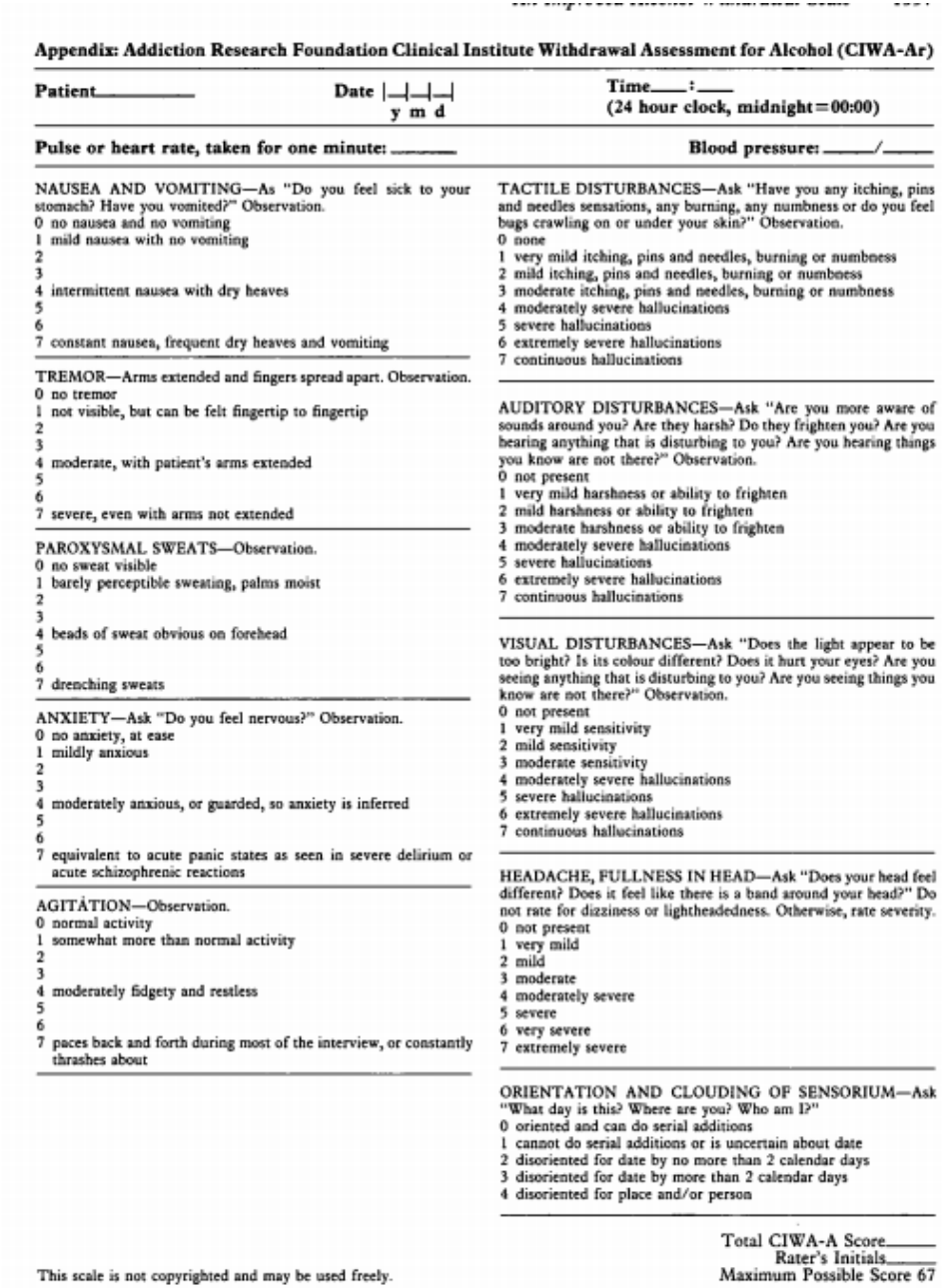
Alcohol Withdrawal Delirium

- 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



Appendix: Addiction Research Foundation Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)

Patient_____ **Date** |__|__|__| (y m d) **Time**___:___ **(24 hour clock, midnight = 00:00)**

Pulse or heart rate, taken for one minute: _____ **Blood pressure:** _____/_____

NAUSEA AND VOMITING—As "Do you feel sick to your stomach? Have you vomited?" Observation.
0 no nausea and no vomiting
1 mild nausea with no vomiting
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3
4 intermittent nausea with dry heaves
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7 constant nausea, frequent dry heaves and vomiting

TREMOR—Arms extended and fingers spread apart. Observation.
0 no tremor
1 not visible, but can be felt fingertip to fingertip
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4 moderate, with patient's arms extended
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6
7 severe, even with arms not extended

PAROXYSMAL SWEATS—Observation.
0 no sweat visible
1 barely perceptible sweating, palms moist
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3
4 beads of sweat obvious on forehead
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6
7 drenching sweats

ANXIETY—Ask "Do you feel nervous?" Observation.
0 no anxiety, at ease
1 mildly anxious
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3
4 moderately anxious, or guarded, so anxiety is inferred
5
6
7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

AGITATION—Observation.
0 normal activity
1 somewhat more than normal activity
2
3
4 moderately fidgety and restless
5
6
7 paces back and forth during most of the interview, or constantly thrashes 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
7 continuous hallucinations

AUDITORY DISTURBANCES—Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation.
0 not present
1 very mild harshness or ability to frighten
2 mild harshness or ability to frighten
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VISUAL DISTURBANCES—Ask "Does the light appear to be too bright? Is its colour different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation.
0 not present
1 very mild sensitivity
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HEADACHE, FULLNESS IN HEAD—Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.
0 not present
1 very mild
2 mild
3 moderate
4 moderately severe
5 severe
6 very severe
7 extremely severe

ORIENTATION AND CLOUDING OF SENSORIUM—Ask "What day is this? Where are you? Who am I?"
0 oriented and can do serial additions
1 cannot do serial additions or is uncertain about date
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-A Score_____
Rater's Initials_____
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

Medication	Typical Route of Admin.	Onset of Action	Half-Life	Metabolism
Chlordiazepoxide	Oral	15-30 mins	5-30 hrs, 200 hrs	Phase I & II 3A4
Lorazepam	Oral, IV	<15 mins (IV) 15-30 mins (PO)	12-18 hrs	Phase II
Diazepam	Oral, IV	<15 mins	30-60 hrs, 100 hrs	Phase I & II 2C19, 3A4
Oxazepam	Oral	30-60 mins	8-14 hrs	Phase II

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

Daeppen JB, Gache P, Landry U, Sekera E, Schweizer V, Gloor S, Yersin B. Symptom-triggered vs fixed-schedule doses of benzodiazepine for alcohol withdrawal: a randomized treatment trial. *Arch Intern Med*. 2002 May 27;162(10):1117-21.
Saitz R, Mayo-Smith MF, Roberts MS, Redmond HA, Bernard DR, Calkins DR. Individualized treatment for alcohol withdrawal. A randomized double-blind controlled trial. *JAMA*. 1994 Aug 17;272(7):519-23. PubMed PMID: 8046805.

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%)

Griffiths RR, Wolf B. Relative abuse liability of different benzodiazepines in drug abusers. *J Clin Psychopharmacol*. 1990 Aug;10(4):237-43.
Malcolm R, Brady KT, Johnston AL, Cunningham M. Types of benzodiazepines abused by chemically dependent inpatients. *J Psychoactive Drugs*. 1993 Oct-Dec;25(4):315-9.

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

Murphy SM, Tyrer P. A double-blind comparison of the effects of gradual withdrawal of lorazepam, diazepam and bromazepam in benzodiazepine dependence. Br J Psychiatry. 1991 Apr;158:511-6.
Rickels K, Schweizer E, Case WG, Greenblatt DJ. Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. Arch Gen Psychiatry. 1990 Oct;47(10):899-907.
Schweizer E, Rickels K, Case WG, Greenblatt DJ. Long-term therapeutic use of benzodiazepines. II. Effects of gradual taper. Arch Gen Psychiatry. 1990 Oct;47(10):908-15.

Withdrawal By Half-life

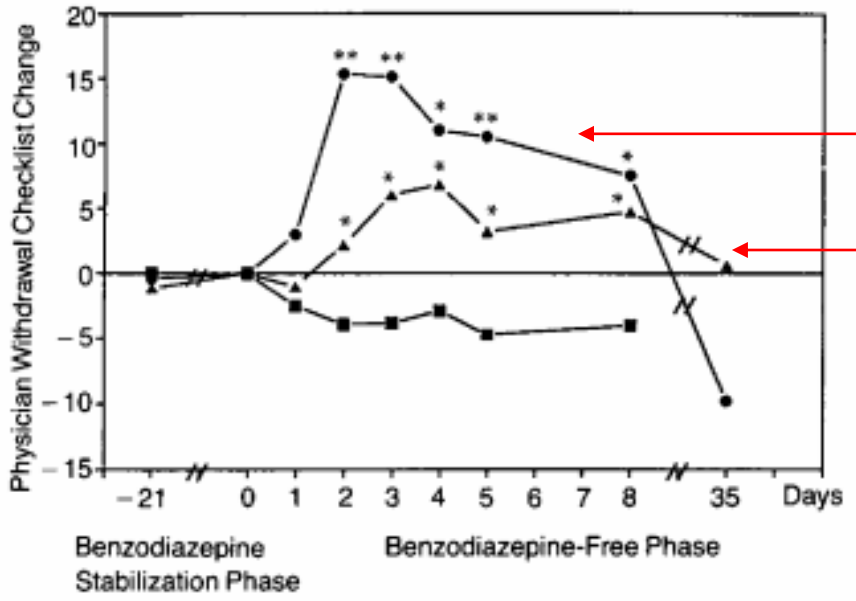

Fig 2.—Physician Withdrawal Checklist total score. Decreasing sample size (solid line with triangles indicates long half-life, n = 26; solid line with circles, short half-life, n = 21; and solid line with squares, controls n = 10). Asterisks indicate significant differences between short half-life and control and long half-life and control benzodiazepine–treated groups (one asterisk indicates $P<.05$; two asterisks, $P<.01$). Differences between short half-life and long half-life benzodiazepine–treated groups were significant at day 2 ($P<.001$) and day 3 ($P<.02$). Base – 35-day benzodiazepine-free differences were significant for the short half-life benzodiazepine–treated group (n = 8, $t = 2.61$, $P<.04$).

Short Half-Life Benzos

Long Half-Life Benzos

Rickels K, Schweizer E, Case WG, Greenblatt DJ. Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. *Arch Gen Psychiatry*. 1990 Oct;47(10):899-907.

Benzodiazepine Withdrawal

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

Rickels K, DeMartinis N, García-España F, Greenblatt DJ, Mandos LA, Rynn M. Imipramine and buspirone in treatment of patients with generalized anxiety disorder who are discontinuing long-term benzodiazepine therapy. *Am J Psychiatry*. 2000 Dec;157(12):1973-9.

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
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Total CIWA-A Score_____
Rater's Initials_____
Maximum Possible Score 67

Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict. 1989 Nov;84(11):1353-7.

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)

Tyrer P, Murphy S, Riley P. The Benzodiazepine Withdrawal Symptom Questionnaire. *J Affect Disord*. 1990 May;19(1):53-61.
Busto, U.E., Sykora, K. & Sellers, E.M. (1989). A clinical scale to assess benzodiazepine withdrawal. *Journal of Clinical Psychopharmacology*, 9 (6), 412–416.

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

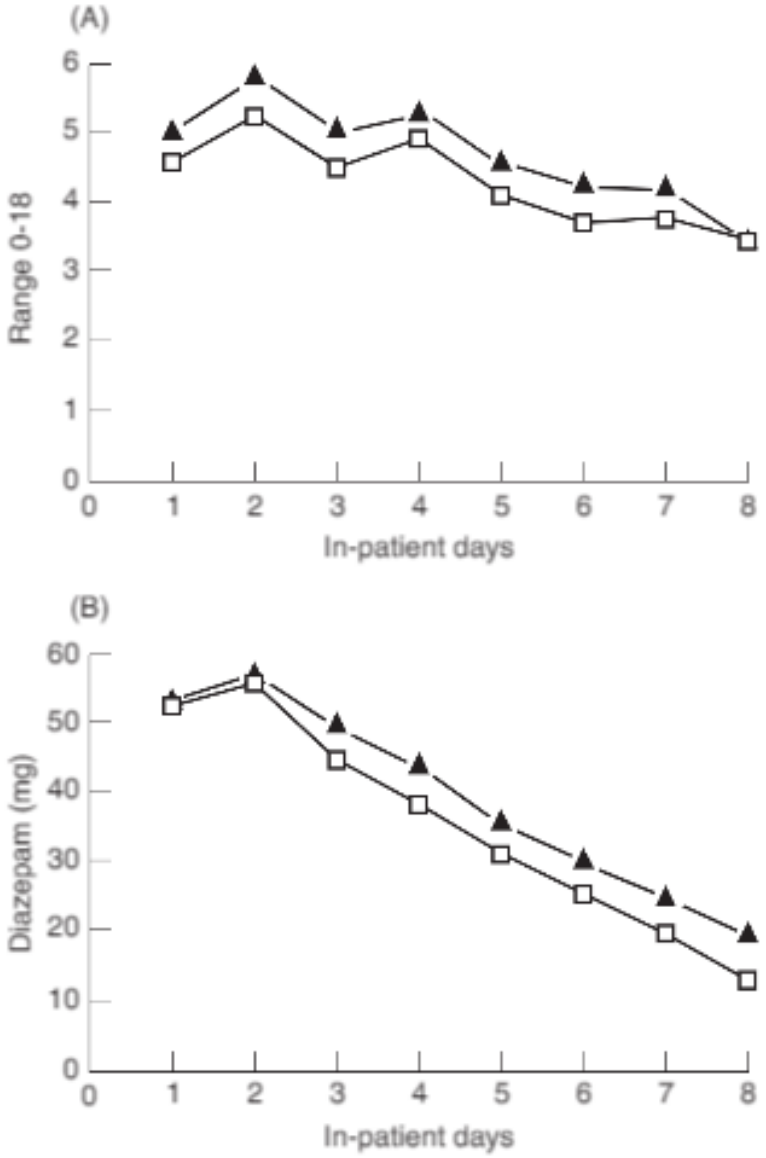

Figure 1. *Withdrawal symptoms and prescribed benzodiazepine dosage during inpatient treatment. (A) Benzodiazepine withdrawal score. (B) Prescribed benzodiazepine dosage (▲ symptom triggered, □ gradual taper).*

McGregor et al., 2003

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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

Lader M, Kyriacou A. Withdrawing Benzodiazepines in Patients With Anxiety Disorders. *Curr Psychiatry Rep*. 2016 Jan;18(1):8.
Denis C, Fatséas M, Lavie E, Auriacombe M. Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. *Cochrane Database Syst Rev*. 2006 Jul 19;(3):CD005194.
Rickels K, Schweizer E, Case WG, Greenblatt DJ. Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. *Arch Gen Psychiatry*. 1990 Oct;47(10):899-907.

Medications Typically Used for Withdrawal

Medication	Typical Route of Admin.	Onset of Action	Half-Life	Metabolism
Chlordiazepoxide	Oral	15-30 mins	5-30 hrs, 200 hrs	Phase I & II 3A4
Lorazepam	Oral, IV	<15 mins (IV) 15-30 mins (PO)	12-18 hrs	Phase II
Diazepam	Oral, IV	<15 mins	30-60 hrs, 100 hrs	Phase I & II 2C19, 3A4
Oxazepam	Oral	30-60 mins	8-14 hrs	Phase II

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

Denis C, Fatséas M, Lavie E, Auriacombe M. Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. *Cochrane Database Syst Rev*. 2006 Jul 19;(3):CD005194.
Murphy SM, Tyrer P. A double-blind comparison of the effects of gradual withdrawal of lorazepam, diazepam and bromazepam in benzodiazepine dependence. *Br J Psychiatry*. 1991 Apr;158:511-6. PubMed PMID: 1675901.

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

Schweizer E, Rickels K, Case WG, Greenblatt DJ. Long-term therapeutic use of benzodiazepines. II. Effects of gradual taper. *Arch Gen Psychiatry*. 1990 Oct;47(10):908-15.

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

Kawasaki SS, Jacapraro JS, Rastegar DA. Safety and effectiveness of a fixed-dose phenobarbital protocol for inpatient benzodiazepine detoxification. *J Subst Abuse Treat*. 2012 Oct;43(3):331-4.

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

Kawasaki SS, Jacapraro JS, Rastegar DA. Safety and effectiveness of a fixed-dose phenobarbital protocol for inpatient benzodiazepine detoxification. *J Subst Abuse Treat*. 2012 Oct;43(3):331-4.

Adjunctive Medications

Medication	Effect of Medication	Study
Hydroxyzine	Patients taking 25-50 mg had a decrease in anxiety during a benzodiazepine taper compared to placebo.	Lemoine et al., 1997
Carbamazepine	When given 200-800 mg/day during and after a benzodiazepine taper, it reduced withdrawal symptoms and promoted abstinence compared to placebo.	Schweizer et al., 1991
Trazodone	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.	Rickels et al., 1999
Sodium valproate	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.	Rickels et al., 1999
Imipramine	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.	Rickels et al., 2000

Adjunctive Medications

Medication	Effect of Medication	Study
Pregabalin	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.	Hadley et al. (2012)
Buspirone	Subjects given buspirone during BZD withdrawal had lower levels of anxiety than subjects given placebo.	Morton & Lader (1995) Udelman & Udelman (1990)
Gabapentin	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-B scale.	Mariani et al. (2016)
Flumazenil	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.	Gerra et al. (2002)
Melatonin	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.	Peles et al. (2007)

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)

Voshaar RC, Gorgels WJ, Mol AJ, van Balkom AJ, van de Lisdonk EH, Breteler MH, van den Hoogen HJ, Zitman FG. Tapering off long-term benzodiazepine use with or without group cognitive-behavioural therapy: three-condition, randomised controlled trial. *Br J Psychiatry*. 2003 Jun;182:498-504.
Parr JM, Kavanagh DJ, Cahill L, Mitchell G, McD Young R. Effectiveness of current treatment approaches for benzodiazepine discontinuation: a meta-analysis. *Addiction*. 2009 Jan;104(1):13-24.

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

Ashton H. Protracted withdrawal syndromes from benzodiazepines. *J Subst Abuse Treat*. 1991;8(1-2):19-28.

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

Winokur A, Rickels K. Withdrawal and pseudowithdrawal from diazepam therapy. *J Clin Psychiatry*. 1981 Nov;42(11):442-4.

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

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

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

TIP 63; SAMHSA

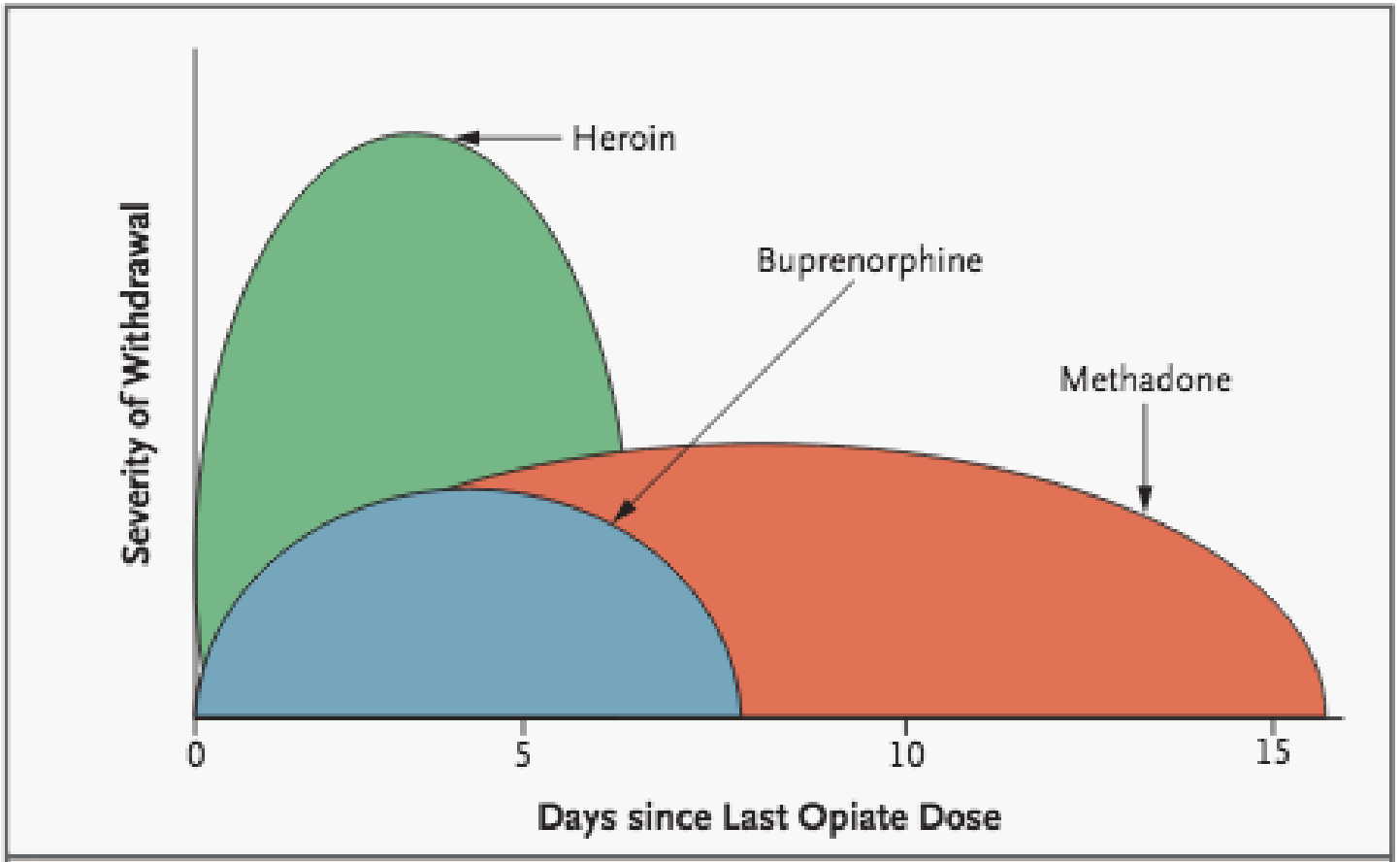


Figure 1. Severity of Opioid-Withdrawal Symptoms after Abrupt Discontinuation of Equivalent Doses of Heroin, Buprenorphine, and Methadone.

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.

Kosten & O'Connor, 2003

COWS

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

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

This version may be copied and used clinically.

Journal of Psychoactive Drugs Volume 35 (2), April - June 2003

Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35(2), 253–9.

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 coerleus 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

Eggleston W, Clark KH, Marraffa JM. Loperamide Abuse Associated With Cardiac Dysrhythmia and Death. Ann Emerg Med. 2016 Apr 26. pii: S0196-0644(16)30052-X. doi: 10.1016/j.annemergmed.2016.03.047. PubMed PMID: 27140747.

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.

	Suboxone® dose (expressed as amount of buprenorphine)					
	7-day			28-day		
Stabilization dose	8 mg	16 mg	24 mg	8 mg	16 mg	24 mg
Study day						
1	8	16	24	8	16	24
2	6	12	20	8	16	24
3	6	10	16	6	12	20
4	4	8	12	6	12	20
5	4	4	8	6	12	20
6	2	2	4	6	10	16
7	2	2	2	6	10	16
8	–	–	–	6	10	16
9–11	–	–	–	6	8	12
12–14	–	–	–	4	8	10
15–16	–	–	–	4	6	8
17–19	–	–	–	4	4	6
20–22	–	–	–	2	4	4
23–25	–	–	–	2	2	2
26–28	–	–	–	2	2	2

Ling et al., 2009

Buprenorphine vs. Clonidine

- 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, $\chi 2$ (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

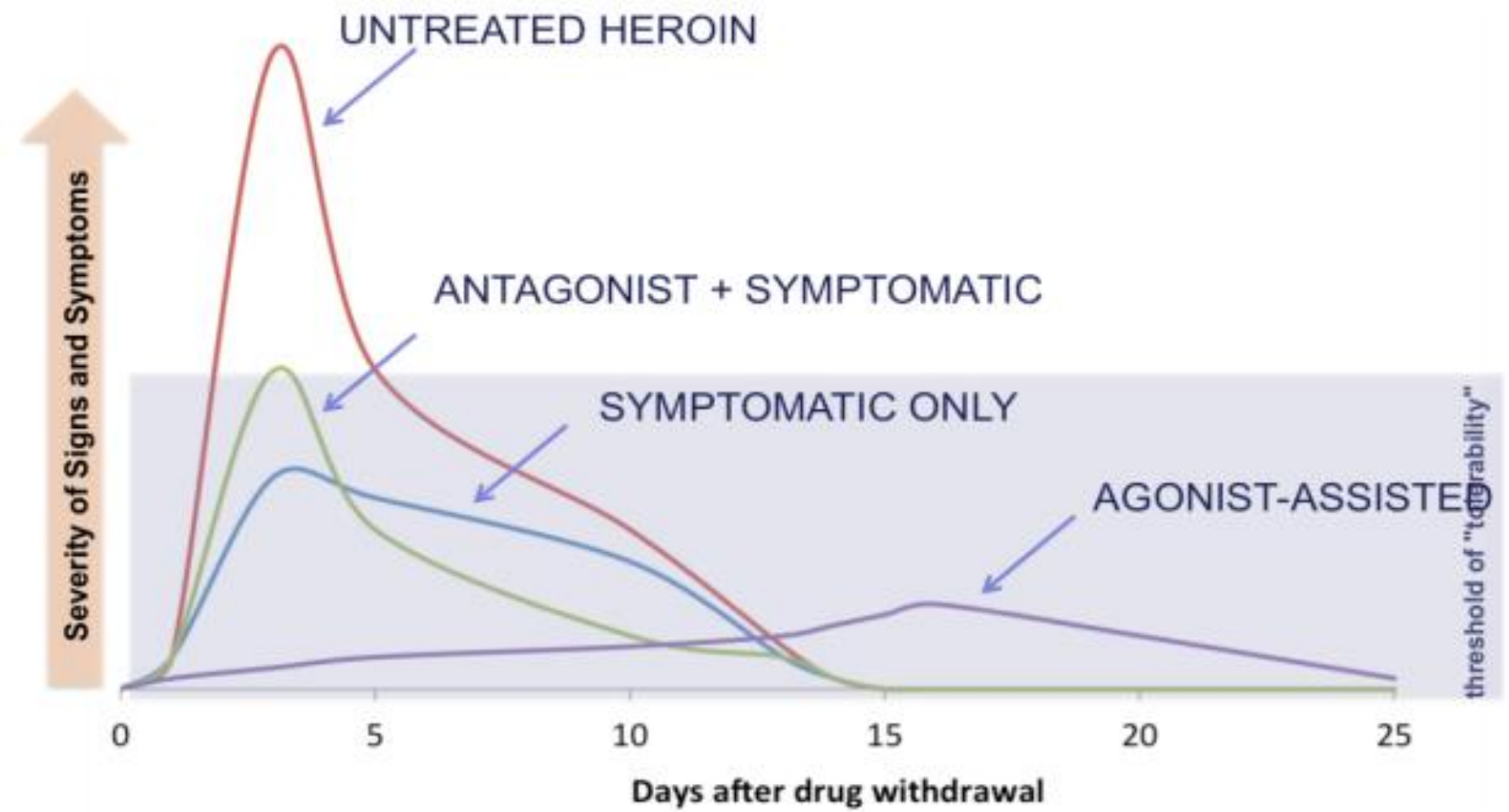
TABLE 1. Outpatient Opioid Detoxification Regimen, by Treatment Arm, in a Study of Oral Naltrexone Versus Buprenorphine as Detoxification Strategies for Extended-Release Injectable Naltrexone Induction in Opioid Dependence

Protocol Day	Naltrexone-Assisted Detoxification	Buprenorphine-Assisted Detoxification
1	Ancillary medications[a] to support abstinence	
2	Buprenorphine, 2 mg sublingually every 1–2 hours, up to 8 mg	
3	(Washout)	Buprenorphine, 6 mg
4	Naltrexone, 1 mg	Buprenorphine, 4 mg
5	Naltrexone, 3 mg	Buprenorphine, 4 mg
6	Naltrexone, 12 mg	Buprenorphine, 2 mg
7	Naltrexone, 25 mg	Buprenorphine, 1 mg
8	Extended-release injectable naltrexone, 380 mg i.m.	
15		Extended-release injectable naltrexone, 380 mg i.m.

[a] 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.).

- 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%)

Severity of Withdrawal by Treatment



Bisaga, 2014

QUESTIONS/COMMENTS

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