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Benzodiazepine Withdrawal

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Short Acting

Uptodate.com

Generic name	Trade name	Usual single adult dose (oral)	Oral peak (hours)	Half-life (hours) parent	Metabolite activity*	CYP3A4 interactions [¶]
Short-acting (<12 ho	urs)					
Midazolam	Versed	0.25 to 0.5 mg/kg; maximum 20 mg (oral formulation not used in adults; dosing is for pediatric sedation)	<1 to 2.5	1.5 to 3	Active	Yes
Triazolam	Halcion	0.125 to 0.25 mg	0.7 to 2	2 to 3	Inactive	Yes



Intermediate Acting

Uptodate.com

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Generic name	Trade name	Usual single adult dose (oral)	Oral peak (hours)	Half-life (hours) parent	Metabolite activity*	CYP3A4 interactions [¶]
Intermediate-acting	(12 to 24 hours)					
Alprazolam	Xanax	0.25 to 0.5 mg	1 to 2	6 to 27	Inactive	Yes
Bromazepam∆	Lexotan, Lexotanil	2 to 6 mg	1 to 2	8 to 20	Inactive	Limited
Estazolam	Prosom	0.5 to 2 mg	0.5 to 6	10 to 24	Inactive	Limited
Etizolam∆♦	Depas, Etilaam, Etizola	0.5 to 1 mg	0.5 to 3	3 to 6	Active (half-life 8 hours)	Yes
Lorazepam	Ativan	0.5 to 3 mg	2 to 4	10 to 20	Inactive	No
Oxazepam	Serax	10 to 30 mg	2 to 4	5 to 20	Inactive	No
Temazepam	Restoril	7.5 to 30 mg	1 to 2	3 to 19	Inactive	No



Long Acting

Uptodate.com

MENTORING, EDUCATION, AND PARTNERS IN HEALTH CLINICAL TOOLS FOR ADDICTION IN TEGRATION

Generic name	Trade name	Usual single adult dose (oral)	Oral peak (hours)	Half-life (hours) parent	Metabolite activity*	CYP3A4 interactions [¶]
Long-acting (>24 hou	ırs)					
Chlordiazepoxide	Librium	5 to 25 mg	0.5 to 4	5 to 30	Active	Yes (CYP3A4 inhibitors); limited (CYP3A4 inducers)
Clobazam	Onfi	10 to 20 mg	0.5 to 4	36 to 42	Active (half-life 71 to 82 hours)	Limited (interacts via CYP2C19)
Clonazepam	Klonopin	0.25 to 0.5 mg	1 to 2	18 to 50	Inactive	Limited
Clorazepate	Tranxene	7.5 to 15 mg	1 to 2	Prodrug	Active (half-life 20 to 160 hours)	Limited
Diazepam	Valium	2 to 10 mg	0.5 to 1	20 to 50	Active	Yes (also interacts via CYP2C19)
Flunitrazepam∆	Rohypnol	0.5 to 2 mg	1 to 2	16 to 35	Active	Limited
Flurazepam	Dalmane	15 to 30 mg	0.5 to 1	2 to 4	Active	Limited

Non benzo hypnotics

Uptodate.com

Generic name	Trade name	Usual single adult dose (oral)	Oral peak (hours)	Half-life (hours) parent	Metabolite activity*	CYP3A4 interactions [¶]
Nonbenzodiazepine h	nypnotics					
Eszopiclone	Lunesta	1 to 3 mg	1	6 to 9	Active (less than parent)	Yes
Zaleplon	Sonata	5 to 15 mg	1	1	Inactive	Yes (CYP3A4 inducers); limited (CYP3A4 inhibitors)
Zolpidem	Ambien, Edluar, Zolpimist	5 to 10 mg	1 to 2	1.5 to 8.4	Inactive	Yes
Zopiclone∆	Imovane	3.75 to 7.5 mg	5 to 7	<2	Active (less than parent)	Yes



Uptodate.com

Duration of action of compounds having active metabolite(s) is significantly greater than predicted by half-life of parent.

- Half-life of active metabolite(s) may exceed 50-100 hours.
- ¶ A list of strong and moderate CYP3A inhibitors and inducers is provided in a separate table within UpToDate. When initiating or altering drug therapy, use of a drug interactions database such as Lexicomp drug interactions is advised.

Δ Not available in United States.

♦ Etizolam is a thienodiazepine derivative and benzodiazepine receptor agonist; its pharmacologic effects are similar to those of classical benzodiazepines (eg, diazepam).^[1]



Cytochrome P450 3A (including 3A4) inhibitors and inducers



WMS Manual: Benzodiazepines

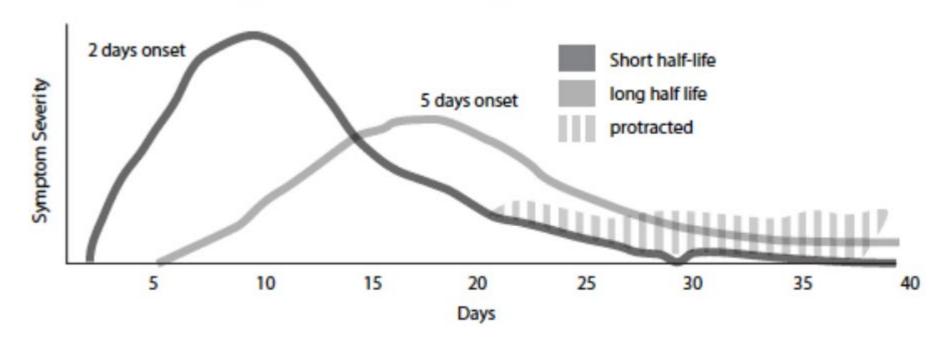
Benzodiazepine withdrawal

Anxiety, panic, insomnia, emotional lability, abdominal cramping, diarrhea, nausea, decreased appetite, tinnitus, diaphoresis, tremor 50+mg DE: Tachycardia, hypertension, confusion, disorientation, seizures, delirium, psychosis *Slower onset & predominance of psychological symptoms compared to alcohol withdrawal



Benzodiazepine withdrawal timeline

The benzodiazepine withdrawal syndrome



Pharmacist Toolkit: Benzodiazepine Taper, 2018



WMS Manual: Benzodiazepines

Benzodiazepine withdrawal

Anxiety, panic, insomnia, emotional lability, abdominal cramping, diarrhea, nausea, decreased appetite, tinnitus, diaphoresis, tremor 50+mg DE: Tachycardia, hypertension, confusion, disorientation, seizures, delirium, psychosis *Slower onset & predominance of psychological symptoms compared to alcohol withdrawal



WMS Manual: Benzodiazepines

TIMELINE

Acute withdrawal

Occurs with abrupt cessation after daily use for 4 wks. or more; onset is within 8–96 hrs. of last use. Risk increases with higher doses, longer use, and shorteracting agents.



Benzodiazepine use >= 3 weeks

Confirmed dosing

Maintain Dose

+/- conversion to long acting benzo

Taper

Deprescribing:

Ashton Manual like approach.

Unconfirmed dosing

Convert to longer acting benzodiazepine

Higher Reported Doses

Reduce DE by 25% to 50%

Start at DE 10mg TID to QID

Follow daily if possible until stable.

Titrate dose as required

Instruct to attend ER for severe /progressive Sx

Consider anti-epileptics

Use tight dispensing intervals / blister packs

Send to ER:

- -Severe Sx
- -Sig medical / psych comorbidities
- -Unreliable patient
- -Homeless
- -Seizure history





Confirmed vs Unconfirmed Benzo Use

Confirmed Dosing

- ⇒Prescribed
 - ⇒Pharmacy Records
 - ⇒Prescription Bottles
 - ⇒Discussion with primary treatment provider
 - ⇒ Instinct / Clinical Judgment
- ⇒ Compliant with medications as prescribed

Approach: "De-Prescribing" utilizing an Ashton Manual like approach

Unconfirmed dosing

- ⇒Street Sources
- ⇒Suspect Diversion
- ⇒Urine toxicology does not align with reported use
- ⇒ Non-compliant with medications as prescribed
- ⇒Benzodiazepine Use Disorder

Approach: Withdrawal Management (Requires modifications of the Ashton Manual like approach)



Benzodiazepine equivalence table may differ.

https://www.hopkinsguides.com/hopkins/view/Johns Hopkins Psychiatry Guide/787140/all/Benzodiazepines

<u>benzo.org.uk</u>: <u>Benzodiazepine Equivalence Table</u>

Agent	Relative Potency (mg)		
Alprazolam (Xanax XR®; Xanax®)	0.5		
Chlordiazepoxide (Librium®)	10		
Clonazepam (Klonopin®)	0.25-0.5		
Diazepam (Diastat®, Valium®)	5		
Lorazepam (Ativan®)	1		
Oxazepam (Serax®)	15-30		

Diazepam (Valium)	10mg
Clonazepam (Klonopin, Rivotril) ⁵	0.5mg
Lorazepam (Ativan, <u>Temesta</u> , <u>Tavor</u>)	1mg
Alprazolam (Xanax, <u>Xanor</u> , <u>Tafil</u>)	0.5 mg



Confirmed Dosing

- Refer to Ashton Manual or Similar Reference
- Utilize benzodiazepine equivalence tables
- Keep in mind that there are some variations between published equivalence tables.
- Lack of firm, evidence-based literature supporting specific conversion ratios
- There may be significant variations between patients
- Principle: Physical Dependence may occur with between 3-4 weeks of use.
- The longer the duration of the use the slower the taper.



Case 1:

- 65 year old female on 1mg of lorazepam BID x 5 year.
- Confirmed dosing, prescribed by FD
- Drinking a bottle of wine per day
- Wants help to stop drinking
- No hx of complicated withdrawal
- Has good family supports amd can be her if managed on an outpatient basis

Which of the following are options?

- Stop lorazepam and provide guidance for tapering her alcohol use.
- 2) Rapidly taper lorazepam and add gabapentin.
- 3) Continue lorazepam 1mg bid + gabapentin.
- 4) Increase her lorazepam to 1-2mg TID with or without adding gabapentin and taper over several days to lorazepam 1mg BID.
- 5) CIWA protocol with lorazepam or Diazepam while maintaining baseline lorazepam 1 mg BID as a minimum dosing regimen.



Case 2:

- 20 yo male
- Childhood hx of abuse
- Uses opioids to manage nightmares, flashbacks, anxiety
- Using smoking 3 pts of fentanyl per day x 2 years
- Prescribed clonazepam 0.5mg TID
- Confirmed dosing
- Does engage in some misuse, twice per week takes 0.5mg QID

- Which of the following are not options?
- 1) Induce suboxone when appropriate but hold clonazepam for at least several days
- 2) Induce Suboxone as above but reduce clonazepam to 0.5mg BID.
- 3) Induce Suboxone but increase clonazepam dose to better manage opioid withdrawal symptoms.
- 4) Induce suboxone and maintain clonazepam at 0.5mg TID with tight dispensing interval



Benzodiazepine use >= 3 weeks

Confirmed dosing

Maintain Dose
Taper (when the time right)

Deprescribing:

Ashton Manual like approach.

Unconfirmed dosing

Convert to longer acting benzodiazepine

Higher Reported Doses

Consider reducing converted equivalent DE by 25% to 50%

Start at DE mg of 10mg TID to QID

Follow daily if possible until stable.

Titrate dose as required

Instruct to attend ER for severe /progressive Sx Consider anti-epileptics

Send to ER:

- -Severe Sx
- -Sig medical / psych comorbidities
- -Unreliable patient
- -Homeless
- -Seizure history



Case 3: Xanax Withdrawal

19-year-old male:

Using street Xanax, up to 10 -15 tabs per day. Thinks that they are 2mg tabs.

Last used Xanax 3 tabs the am before coming to see you. No withdrawal symptoms at this time

Client states they are high quality Xanax and he gets them from a reliable street source

He wants to come off them but is afraid to stop

Walk in clinic declined to prescribe replacement benzodiazepines

- Urine tox is + for benzo, amphetamines and fentanyl
- Client denies amphetamine or opioid use. He wants to know if urine test kits are accurate or if you are misreading the test results.

MDCalc.com







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N.W.T.'s top doc warns fake Xanax laced with fentanyl may be in Yellowknife











RCMP says it has not seized any of the pills in the N.W.T. so far







RCMP: Counterfeit Xanax is not "Xanax"

Increase in the consumption of counterfeit drugs | Royal Canadian Mounted Police (rcmp-grc.gc.ca)

- "Would you be able to tell the difference between counterfeit drugs and real drugs? Probably not! Most of the time, counterfeit pills are almost identical to real ones."
- "Often, these pills don't contain any alprazolam, the active ingredient in Xanax®"



Annual Report, PHILTRE, 2017 to 2018

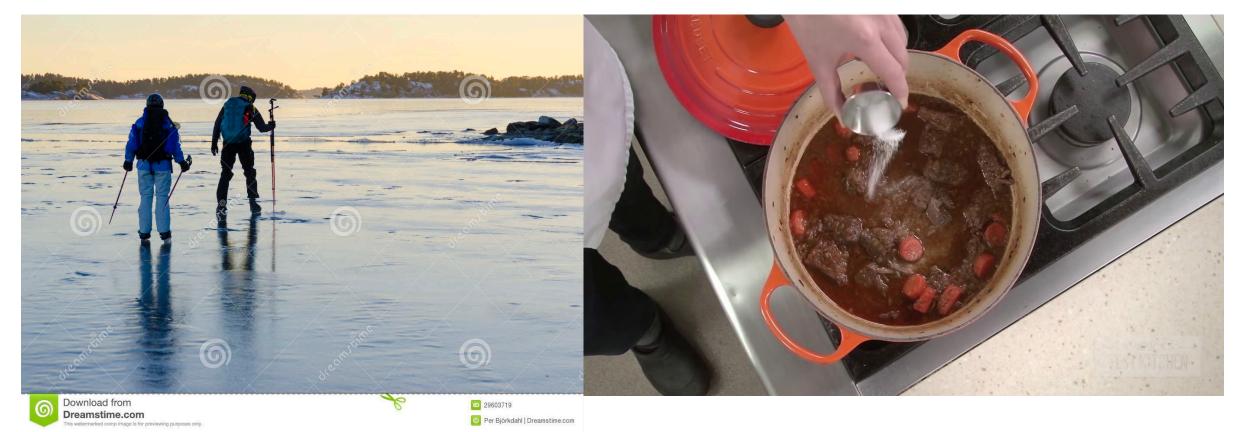
Philtre Annual Report 2018 FINAL.pdf (wales.nhs.uk)

108 samples submitted in the belief that they were diazepam, 45 per cent (n=49) were found upon analysis to contain a different substance or no active compound.

Purchase intent	Substance upon analysis	Number
Diazepam	Etizolam	30
Alprazolam	Etizolam	5
Diazepam	Alprazolam	4
Diazepam	Chlorpheniramine	4
Alprazolam	Caffeine	3
Diazepam	Zolpidem	3
Alprazolam	Diclazepam	2
Diazepam	Zopiclone	2
Diazepam	Phenazepam	2
Alprazolam	Lorazepam	2
Diazepam	Lorazepam	1
Diazepam	Nitrazepam	1
Alprazolam	Clonazolam	1
Diazepam	Clonazolam	1
Diazepam	Tadalafil	1
Diazepam	Diclazepam	1
Alprazolam	Zopiclone	1
Alprazolam	Diazepam	1



What to do when you don't know?





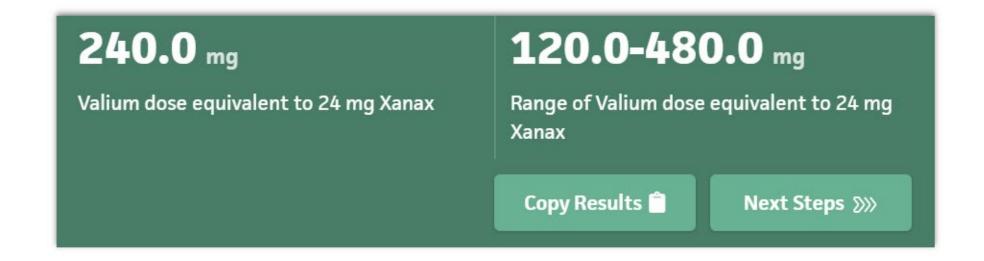
Metaphi Stabilization Guidelines

Convert to a longer-acting BZD:

- a) **Choose the agent:** Consider switching from a shorter-acting agent (alprazolam, lorazepam) to a longer-acting agent (diazepam, clonazepam) during BZD taper. This step is not mandatory, but a longacting agent provides slower onset of withdrawal symptoms, and therefore a smoother taper.
- b) **Calculate equivalency:** Calculate the client's usual BZD dose equivalency in the chosen long-acting agent (TIP: use a table or conversion calculator) and start at 50-75% of this dose, in divided doses, to prevent oversedation. Titrate to the patient's comfort, not exceeding the original dose. Because of differences in potency and drug profiles, consider converting prescription BZD users gradually, substituting one dose at a time.



MDCalc.com



120mg @ 50% = 60mg 120mg @ 75% = 90mg



Is there a dose of benzodiazepine replacement that will prevent seizures?

No good research but there are some expert guidelines that have addressed the question.

• 2013 (reviewed 2016) NHS FIFE guideline for "Benzodiazepine Prescribing in Benzodiazepine Dependence":

"Management of dependence in illicit and recreational users"

"Doses greater than 30mg diazepam are rarely necessary as this is sufficient to prevent withdrawal seizures even in very high-dose benzodiazepine users."

"Starting dose should not exceed 30mg to 40mg."



British Association for Psychopharmacology updated guidelines... for management of substance abuse.

Journal of Psychopharmacology 26(7) 899–952 © The Author(s) 2012

"Management of benzodiazepine dependence in high-dose and/or illicit drug users

"There is little evidence to guide practitioners in the management of this often difficult-to-treat population."

"Doses greater than 30 mg diazepam are rarely necessary, and this is sufficient to prevent benzodiazepine withdrawal symptoms including withdrawal seizures in very high dose benzodiazepine users (D)"



Stabilizing By Titration

- Start with diazepam 10mg TID /QID or lorazepam 1mg TID /QID
- Monitor withdrawal symptoms
- Consider using a CIWA-A or CIWA-B to monitor
- Evaluate tolerance
- Titrate the dose to stabilize







Tapering

- Plan a taper rate: There are many approaches for tapering BZD, such as percentage (taper 10% q1–2 weeks) and milligrams (taper 5–10mg DE q1–2 weeks).
- When the dose has reached **20% of the original dose or 20mg DE**, slow the taper to 5% or 1–2mg q2–4 weeks.
- Set a schedule: Use scheduled doses and avoid PRN dosing. The taper will take longer than the WMS stay. Prescribers should develop and share the taper schedule with the patient's care team.
- Determine dispensing: Use client-centered strategies. Consider daily, every 2–3 days, or weekly dispensing as needed to avoid overuse.



GENERAL PRINCIPLES FOR A BENZODIAZEPINE TAPER

The goal of a benzodiazepine taper is not always discontinuation but reaching a safe and effective therapeutic dose. These are general principles only; the taper should be customized to the client.

- 1) Address underlying mental health concerns: Underlying mental health concerns for which BZD may have been originally prescribed (anxiety disorders, mood disorders, post-traumatic stress disorder) should be considered and addressed with psychological therapies and appropriate medications (e.g., SSRIs, SNRIs) throughout a BZD taper.
- 2) Convert to a longer-acting BZD:
 - a) Choose the agent: Consider switching from a shorter-acting agent (alprazolam, lorazepam) to a longer-acting agent (diazepam, clonazepam) during BZD taper. This step is not mandatory, but a long-acting agent provides slower onset of withdrawal symptoms, and therefore a smoother taper.
 - b) Calculate equivalency: Calculate the client's usual BZD dose equivalency in the chosen long-acting agent (TIP: use a table or conversion calculator) and start at 50-75% of this dose, in divided doses, to prevent oversedation. Titrate to the patient's comfort, not exceeding the original dose. Because of differences in potency and drug profiles, consider converting prescription BZD users gradually, substituting one dose at a time.
- 3) Plan a taper rate: There are many approaches for tapering BZD, such as percentage (taper 10% q1-2 weeks) and milligrams (taper 5-10mg DE q1-2 weeks). When the dose has reached 20% of the original dose or 20mg DE, slow the taper to 5% or 1-2mg q2-4 weeks.
- 4) Set a schedule: Use scheduled doses and avoid PRN-dosing. The taper will take longer than the WMS stay. Prescribers should develop and share the taper schedule with the patient's care team.
- 5) Determine dispensing: Use client-centered strategies. Consider daily, every 2–3 days, or weekly dispensing as needed to avoid overuse.

Long-acting agents

Equivalence Tables

10% q1-2 weeks

Avoid prn dosing

Short dispensing intervals

TIPS

Clonazepam is less likely to cause prolonged sedation (consider it in the elderly and those with liver impairment), while diazepam is available in low-dose formulations (e.g., 2mg) for a smooth taper.

Use a table or conversion calculator to find equivalency.

Conversion and titration can take days or weeks to complete.

Hold the taper for a few weeks if the client experiences negative impacts on function, withdrawal, rebound anxiety, or markedly decreased mood.

A slower taper is required in the elderly.

Use a template or spreadsheet for easy tracking, sharing, or adjusting the taper as needed.

Long-acting BZDs are only required 1–2 times/day. Try to move clients away from frequent dosing when converting from short- to long-acting BZD, e.g., TID to BID.



Benzodiazepines: Tapering and Prescribing

2019 Presbyterian Healthcare Services

"To determine the duration of a taper, consider the duration of prior BZRA use.

If duration of BZRA use was: Then taper over:

< 3month → one week

3 months to one year → 4 weeks

>1 year → 12 weeks (to 12months)

If the patient is deemed to be at high risk of overdose, such as current alcohol abuse or continued use of opioids, it may be in the patient's best interest to attempt a more rapid taper"

These likely represent the minimum length of taper duration.

This is only one organizations published guideline.

Research on rate of taper is poor, so rely on your clinical experience, judgement and knowledge of your patient!



Case 4:

- 24-year-old male
- Fentanyl smoking / injecting daily. Amounts used not clearly known
- Denies benzo use
- Urine is positive for benzodiazepines and fentanyl.
- Stabilized on Suboxone 32 mg x 2 days. No cravings for opioids
- Ongoing problematic anxiety with fine tremor in both hands 48 hours after induction.
- No seizure history

- Which of the following are options?
- 1) Give him a top of suboxone
- 2) Consider benzo withdrawal and add lorazepam 1mg BID or TID with close follow up.
- 3) Start and SSRI for possible GAD



Case 5:

- 24-year-old male
- Fentanyl smoking / injecting daily. Amounts used not clearly known
- Denies benzo use
- Urine is negative for benzodiazepines and positive for fentanyl.
- Stabilized on Suboxone 32 mg x 2 days. No cravings for opioids
- Ongoing problematic anxiety with fine tremor in both hands 48 hours after induction.
- No seizure history

- Which of the following are options?
- 1) Rule out Benzo withdrawal as the urine is negative for benzo and top him up with suboxone.
- 2) Ask about alcohol use.
- Consider benzo withdrawal and add lorazepam 1mg BID or TID with close follow up.
- 4) Start an SSRI for possible GAD
- 5) Top up suboxone an reassure client this is likely opioid withdrawal and will resolve.



Case 6:

- 24-year-old male
- Fentanyl smoking / injecting daily. Amounts used not clearly known
- Denies benzo use
- Urine is negative for benzodiazepines and positive for fentanyl.
- Presents in acute opioid withdrawal, last use of an opioid was 36 hours ago.
- Has mild tremor in both hands with fingers outstretched.
- Patient had witnessed seizure 24 hours after last fentanyl use. No prior history of seizures.

- Which of the following are options?
- Induce on suboxone and refer to neurology for seizure workup.
- 2) Induce on suboxone and simultaneously initiate a benzo due to possible benzo withdrawal not picked up on urine testing.
- 3) Induce on suboxone first using a macro dosing approach, and then initiate a benzo with plan to taper.
- 4) Ask about alcohol use.
- 5) Delay Subxone induction while you stabilize possible benzodiazepine withdrawal.



How Quick To Taper

Factors to Consider:

Length of Use

 May tolerate larger dose reductions when starting taper at higher doses.

Reduce dose reductions towards the end of a taper



Use of Anti-epileptics

- Literature is quite varied
- Data best for carbamazepine
- Carbamazepine: Start 200 mg twice daily, adjust dose weekly up to 400 mg twice daily. Continue for 2-4 weeks after stopping benzodiazepines and then taper anticonvulsant.
- Valproic acid, or Divalproex sodium EC: Start 500 mg twice daily, adjust dose weekly up to 2,000 mg daily. Continue for 2-4 weeks after stopping benzodiazepines and then taper anticonvulsant. (Monitor levels)
- Pregabalin 75mg BID and titrate upwards
- Anti-epileptics are adjunctive treatment and not monotherapy
- May be helpful in difficult or challenging cases



CIWA - B

Objective physiological assessment

For each of the following items, please circle the number which best describes the severity of each symptom or sign.

L							
	1	Observe behaviour for restlessness and agitation	0 None, normal activity	1	2 Restless	3	4 Paces back and forth, unable to sit still
	2	Ask patient to extend arms with fingers apart, observe tremor	0 No tremor	1 Not visible, can be felt in fingers	2 Visible but mild	3 Moderate, with arms extended	4 Severe, with arms not extended
	3	Observe for sweating, feel palms	0 No sweating visible	1 Barely perceptible sweating, palms moist	2 Palms and forehead moist, reports armpit sweating	3 Beads of sweat on forehead	4 Severe drenching sweats



CIWA B

4	Do you feel irritable?	0 Not at all	1	2	3	4 Very much so
5	Do you feel fatigued (tired)?	0 Not at all	1	2	3	4 Unable to function due to fatigue
6	Do you feel tense?	0 Not at all	1	2	3	4 Very much so
7	Do you have difficulties concentrating?	0 No difficulty	1	2	3	4 Unable to concentrate
8	Do you have any loss of appetite?	0 No loss	1	2	3	4 No appetite, unable to eat
9	Have you any numbness or burning in your face, hands or feet?	0 No numbness	1	2	3	4 Intense burning or numbness
10	Do you feel your heart racing (palpitations)?	0 No disturbance	1	2	3	4 Constant racing
11	Does your head feel full or achy?	0 Not at all	1	2	3	4 Severe headache
12	Do you feel muscle aches or stiffness?	0 Not at all	1	2	3	4 Severe stiffness or pain



1:	Do you feel anxious, nervous or jittery?	0 Not at all	1	2	3	4 Very much so
114	Do you feel upset?	0 Not at all	1	2	3	4 Very much so
1!	How restful was your sleep last night?	0 Very restful	1	2	3	4 Not at all
10	Do you feel weak?	0 Not at all	1	2	3	4 Very much so
17	Do you think you had enough sleep last night?	0 Yes, very much so	1	2	3	4 Not at all
18	Do you have any visual disturbances? (sensitivity to light, blurred vision)	0 Not at all	1	2	3	4 Very sensitivity to light, blurred vision
19	Are you fearful?	0 Not at all	1	2	3	4 Very much so
20	Have you been worrying about possible misfortunes lately?	0 Not at all	1	2	3	4 Very much so
2	How many hours of sleep do you think you ha		Total CIWA-B			

How many minutes do you think it took you to fall asleep last night?



Score:

CIWA B

Interpretation of scores: Sum of items 1-20

1–20 = mild withdrawal

21-40 = moderate withdrawal

41-60 = severe withdrawal

61–80 = very severe withdrawal

Source: Busto UE, Sykora K, Sellers EM. A clinical scale to assess benzodiazepine withdrawal. Journal of Clinical Psychopharmacology. 1989;9(6):412-6. doi: 10.1097/00004714-198912000-00005



Withdrawal scales were developed to assist the monitoring and management of withdrawal



A client on methadone + illicit Xanax Use

If the previous client was on 70mg of methadone daily, how might this change your management of the case?





Thank You

....& please complete the feedback form

