The Challenges of Benzodiazepines and OUD?

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Disclaimer

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Objectives

- Describe the impact benzos have and don't have on OUD treatment
- Identify when to continue benzodiazepines
- Identify when to taper benzodiazepines and how to approach those tapers.

Case

- 27yo F on Bup-Nal for OUD-severe. He has been in treatment x 1 month and is doing fairly well around her opioid use, but has ongoing Xanax use. At the time of enrollment she had endorsed wanting to stop using them. However, she has continued to use them and every urine drug screen is positive. She reports to having too much social anxiety without them.

- 35yo F on Bup-Nal 12-6mg qday for OUD-severe (heroin), with persistent benzo use for social anxiety.

What would be your next few steps?

A) Cut Bup dose in half to reduce toxicity potential
B) Start a benzo taper
C) Continue prescribing Bup and refer to mental health
D) Ask her for her dose and start prescribing both benzodiazepines and Buprenorphine-Naloxone yourself
E) Other

Do Benzo's have a role for anxiety disorders?

- Yes
  - But…
  - **Benzodiazepines are NOT a first-line treatment for any anxiety disorder, or OCD and related disorders, or for PTSD**
    - FDA Indications: GAD, Panic, Alcohol Withdrawal, Seizure disorders, Insomnia
    - Off-label Use: Catatonia, Agitation, Anesthesia
    - 1st Line Treatment: Inpatient alcohol withdrawal, Catatonia
  - There are many other choices for anxiety disorders

Alternatives

- First-line treatments for anxiety disorders
  - SSRIs (SNRIs)
  - CBT
- Alternative anxiolytics
  - Buspirone
  - Pregabalin
  - Gabapentin
  - Hydroxyzine
  - Beta blockers
  - Atypical antipsychotics
  - Clonidine
  - Prazosin
  - Mindfulness/meditation
  - Other therapies

Courtesy of Deb Cowley

BZs vs Antidepressants

- Meta-analysis of 56 studies for GAD
- 12,655 participants
- Effect sizes:
  - SSRIs: 0.33 (small)
  - SNRIs: 0.36 (small)
  - BZs: 0.50 (medium)

- Gomez A et al., Expert Opin Pharmacother 2018

BZs are rapidly effective with short-term use

Courtesy of Deb Cowley

Long-term treatment

- 8 studies of BZs for anxiety disorders for ≥ 13 weeks

- 4 were of maintenance treatment (20 weeks – 36 months after acute trials)
  - Clorazepate vs. buspirone, alprazolam vs. imipramine vs. placebo, clonazepam vs. paroxetine
  - ***No significant difference in outcomes after 8 weeks***
  - Benzo's: Lowest rate of dropout & side effects with BZs
  - Taper after 3 years -> lower relapse rate after clonazepam vs paroxetine
    - Shinfuku et al., 2019

Courtesy of Deb Cowley

Long-term treatment: take home points

- Little efficacy data to support long-term BZs OR preference for SSRIs (few studies)
- Effects of BZs greatest in first 4 weeks, antidepressants catch up by 8 weeks
- Greater tolerability with BZs
- No evidence for tolerance (need for dose increases) in patients with anxiety disorders over time (up to 3 years)
    - Shinfuku et al., 2019; Willems et al., 2013; Rickels, 2018

Courtesy of Deb Cowley

When would you use a benzodiazepine?

- Need for rapid relief of disabling symptoms, short-term treatment
- Nothing else works (including therapy)
- Patient cannot tolerate side effects of other medications
- Adjunct early in treatment

Courtesy of Deb Cowley

Monitoring

- Regular follow up
- Document refills, timing, expected refill date
- Monitor the PMP
- Urine drug screens
- Warning signs:
  - Lost prescriptions
  - Need for early refills
  - Need for higher doses
  - Missed appointments

- If a patient is being prescribed both benzos and MOUD→consider having one provider prescribe both

Courtesy of Deb Cowley with additions by Mark Duncan

Case

- 42yo M with OUD, confirmed diagnosis of severe Social Anxiety Disorder, and possible GAD. Taking to 2mg of Clonazepam BID x 4 years from illicit benzos, confirmed by wife and PCP. PCP confirms the patient has tried multiple antidepressants over the years the patient has been working with him. He presents for OUD treatment and is now on Buprenorphine-Nal 24mg. He asks if you would prescribe him Clonazepam.

- What would you do?
  A. Take on prescribing of Clonazepam
  B. Start a Clonazepam taper
  C. Send him to detox
  D. Retry an SSRI/SNRI
  E. Refer to therapy for anxiety

Why are we worried about benzo's and OUD?

- 1998 French case series
  - 6 overdose deaths related to bup + benzo's
  - IV Buprenorphine (Not Bup-Nal) or massive oral dosages

- Can occur at therapeutic doses of Buprenorphine in the following contexts
  - Related supra-therapeutic doses of benzodiazepines
    - Removes ceiling effect
  - IV injection of benzos at therapeutic doses
  - Combined with sedatives

Reynaud M et al, 1998; Schuman-Olivier Z et al, 2013

A Note on Benzodiazepines and Buprenorphine.

Patients taking Buprenorphine with a benzodiazepine is **much safer** than allowing a person to continue to use/misuse benzodiazepines with a full agonist opioid that may or may not contain fentanyl or other high potency opioids.

- **Untreated Opioid Use Disorder Mortality: HR 29.04**
  (Dupouy J et al, 2017 https://pubmed.ncbi.nlm.nih.gov/28694272/)

- **Buprenorphine + Benzodiazepine HR 2.92** (56 deaths out of 9263 person years where both a benzodiazepine and Buprenorphine were prescribed)
  (Park TW et al, 2020, https://www.ncbi.nlm.nih.gov/pubmed/31916306)

**See FDA Drug Safety Communication urging caution about withholding MOUD from patients taking benzodiazepines or CNS depressants. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-urges-caution-about-withholding-opioid-addiction-medications

Drug Alcohol Depend. 2013 October 1; 132(3): 580–586. doi:10.1016/j.drugalcdep.2013.04.006.

Benzodiazepine use during buprenorphine treatment for opioid dependence: Clinical and safety outcomes

Zev Schuman-Olivier[a,b,*], Bettina B. Hoeppner[a,b], Roger D. Weiss[a,d], Jacob Borodovsky[c,e], Howard J. Shaffer[a,e], and Mark J. Albanese[a,e]

- N=386, Primary Care-Nurse Care Manager Program
- Benzodiazepine use
  - Prescribed, Ilicit, Misuse, Not misused
- No impact on treatment retention
- No impact on illicit opioid or cocaine use
- Those prescribed benzo's had more ED visits
  - OR 3.75 due to accidental injury
- Prescribed benzo's were continued

2020

ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
RESEARCH REPORT
doi:10.1111/add.14886

Associations between prescribed benzodiazepines, overdose death and buprenorphine discontinuation among people receiving buprenorphine

- N=63,389 Massachusetts residents received Buprenorphine, 18+
- Findings
  - 24% filled at least 1 Benzo prescription
  - 183 deaths opioid OD
    - 31% at least one benzo prescription

Park, TW, Larochelle, MR, Saitz, R, Wang, N, Bernson, D, Wally, AY

2020

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Associations between prescribed benzodiazepines, overdose death and buprenorphine discontinuation among people receiving buprenorphine

- N=63,389, Buprenorphine, 18+
- 183 deaths opioid OD

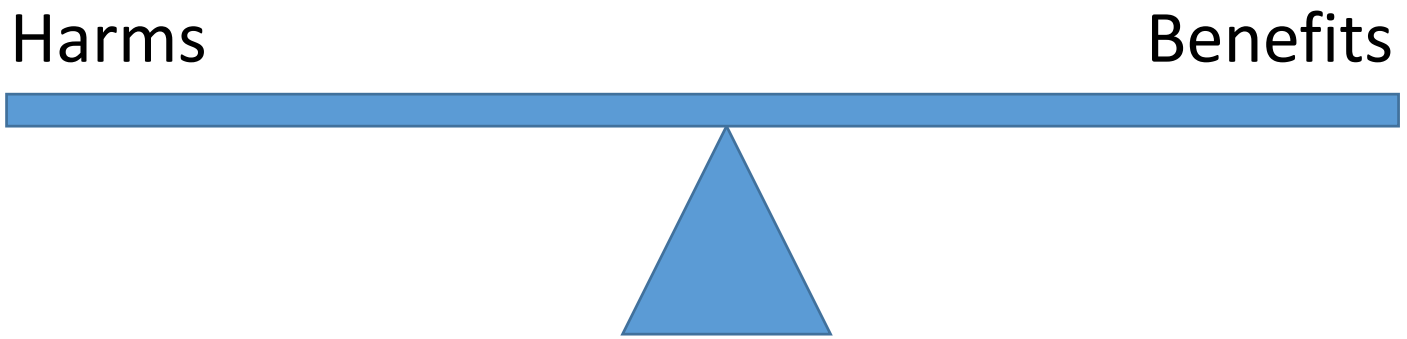
Results	aHR	95% CI
Increased risk of fatal opioid OD	2.92 (unadjusted rate: 60 per 10,000 person years)	2.10-4.06
Increased risk of all-cause mortality	1.90	1.48-2.44
Decreased** risk of Buprenorphine **discontinuation	0.87	0.85-0.89

The Benzodiazepine Bind

- Buprenorphine + Benzo's increase risk for OD and death
- Increase risk of accidents

?

- Buprenorphine +/- Benzo's likely reduce OUD overdose and mortality vs no MOUD
- Benzo's may reduce risk of Bup discontinuation



What options do I have for benzos in OUD?

- Send to detox
- Taper in clinic
- Continue to prescribe
  - Treat anxiety disorder
  - Treat benzo disorder (substitution treatment)

Detox vs Maintenance

- 2003, Israeli Methadone Clinic, N=66
  - All had documented benzo use disorder

- Clonazepam detox vs Clonazepam maintenance
  - Patient's choose which option
  - All started on 6mg total daily dose and then tapered off or down to maintenance dose (4-8 wks for maintenance dose)
  - Clonazepam given under daily supervision
  - Occasional misuse ok

- Failure
  - 2 daily benzo misuses above permitted dose
  - If continue to misuse→change modality of stop

Weizman T, Gelkopf M, Melamed Y, Adelson M, Bleich A. Treatment of Benzodiazepine Dependence in Methadone Maintenance Treatment Patients: A Comparison of Two Therapeutic Modalities and the Role of Psychiatric Comorbidity. Australian & New Zealand Journal of Psychiatry. 2003;37(4):458-463. doi:10.1046/j.1440-1614.2003.01211.x

Detox vs Maintenance

- 2003, Israeli Methadone Clinic, N=66
- Clonazepam detox vs Clonazepam maintenance

Mean maintenance dose: 2.64mg total daily dose
Co-occurring psych disorder: 64% (38%-mood, 32%-anxiety, 70% had personality disorder-antisocial most common)

Table 1. Success and failure rates of clonazepam detoxification (CDTX) and maintenance (CMT) at 2, 4, 6, 8, 10 and 12 months

	2 months	4 months	6 months	8 months	10 months	12 months
CDTX	n = 33	n = 31	n = 30	n = 30	n = 29	n = 29
Success	9 (27.3%)	7 (22.6%)	5 (16.7%)	5 (16.7%)	4 (13.8%)	4 (13.8%)
Failure	24 (72.7%)	24 (77.4%)	25 (83.3%)	25 (83.3%)	25 (86.2%)	25 (86.2%)
CMT	n = 33	n = 33	n = 32	n = 29	n = 28	n = 26
Success	26 (78.8%)	25 (75.8%)	24 (75%)	20 (69%)	19 (65.5%)	17 (65.4%)
Failure	7 (22.2%)	8 (24.2%)	8 (25%)	9 (31%)	9 (34.5%)	9 (34.6%)

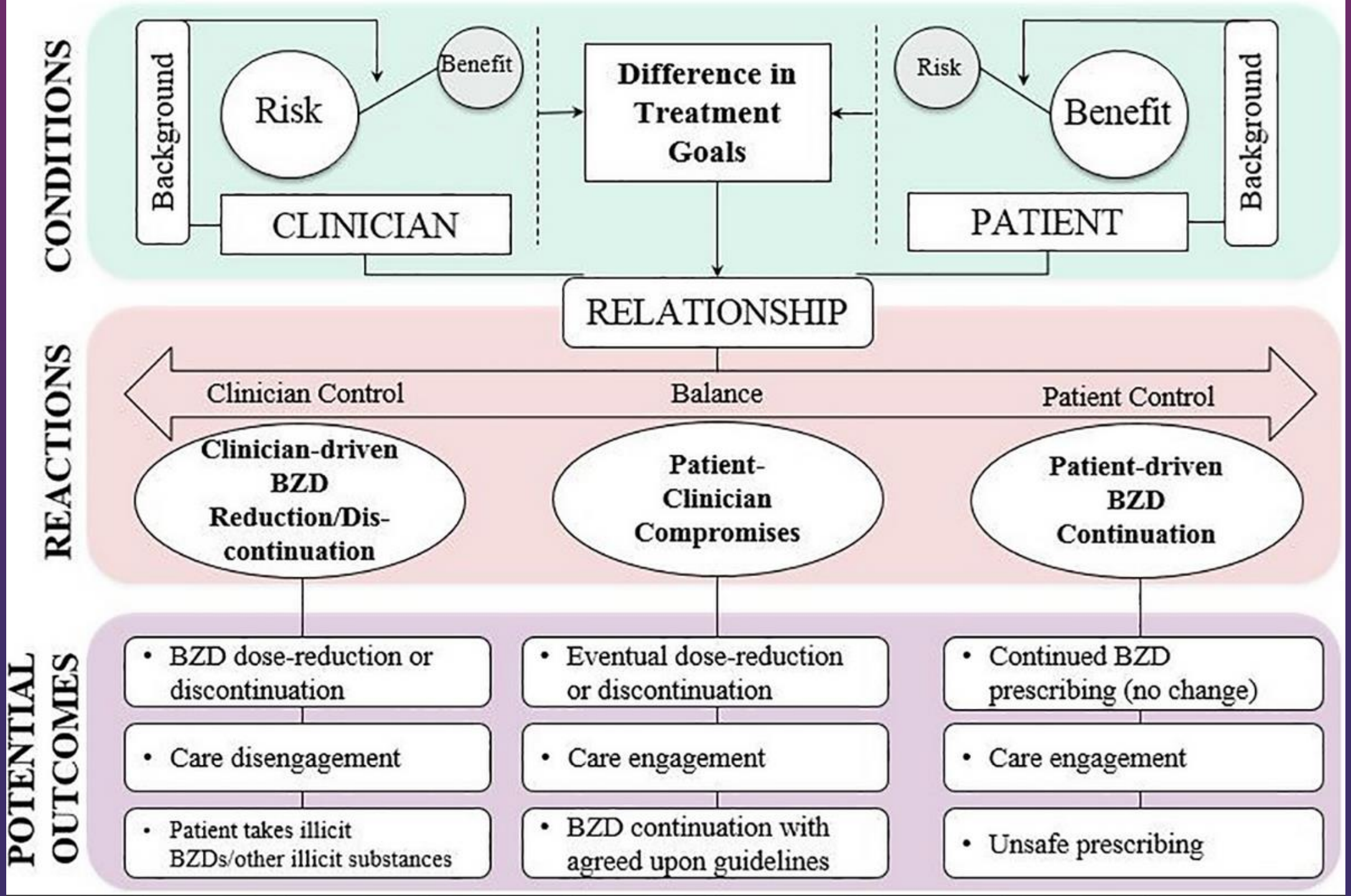
CMT Success groups: had more mood and anxiety disorders
CDTX Success group: higher methadone doses

Weizman T, Gelkopf M, Melamed Y, Adelson M, Bleich A. Treatment of Benzodiazepine Dependence in Methadone Maintenance Treatment Patients: A Comparison of Two Therapeutic Modalities and the Role of Psychiatric Comorbidity. Australian & New Zealand Journal of Psychiatry. 2003;37(4):458-463. doi:10.1046/j.1440-1614.2003.01211.x

“It could be dangerous…”

- 26 semi-structured interviews with 26 MOUD patients and 10 MOUD providers.
  - N=9 Office based buprenorphine clinic; N=17 methadone clinic
  - Patients were using benzos at least 3 times a week
- Results
  - Patients focus on benefits (reduce anxiety) over risks (overuse, loss of control, sleep all day)
  - Patients can learn to use benzos safely (as people stabilize in MOUD they use benzos more safely and appropriately)
  - Clinicians prioritized risks of benzos over benefits→different tx goals/outcomes
    - Compromise can balance differences

Park TW, Sikov J, dellaBitta V, Saitz R, Walley AY, Drainoni ML. "It could potentially be dangerous... but nothing else has seemed to help me.": Patient and clinician perspectives on benzodiazepine use in opioid agonist treatment. J Subst Abuse Treat. 2021 Dec;131:108455. doi: 10.1016/j.jsat.2021.108455. Epub 2021 Apr 30. PMID: 34098286; PMCID: PMC8556389.


CONDITIONS
Background
Risk
Benefit
CLINICIAN
Difference in Treatment Goals
Risk
Benefit
Background
PATIENT
RELATIONSHIP
REACTIONS
Clinician Control
Balance
Patient Control
Clinician-driven BZD Reduction/Dis-continuation
Patient-Clinician Compromises
Patient-driven BZD Continuation
POTENTIAL OUTCOMES
• BZD dose-reduction or discontinuation
• Care disengagement
• Patient takes illicit BZDs/other illicit substances
• Eventual dose-reduction or discontinuation
• Care engagement
• BZD continuation with agreed upon guidelines
• Continued BZD prescribing (no change)
• Care engagement
• Unsafe prescribing

Benzo Case Anecdotes

- 42yo M with OUD, Social Anxiety Disorder, possible GAD. Transitioned to 2mg of Clonazepam BID x 4 years from illicit benzos. 2 years ago he lost his job and got a DUI from benzo intoxication.

- 23yo with OUD and benzo use disorder now on Sublocade, using Xanax of street. Mom asks if you will give him more Librium for a taper.

- 57yo F on methadone for OUD. Presents looking for someone to prescribe her Clonazepam 1mg TID. PMP shows consistent, prescriptions. Previous provider retired.

- 35yo F with OUD-mod on Bup, with multiple ED admissions for prescribed benzo intoxication and w/d.

Benzodiazepine Tapers?

- Do you offer tapers for people using illicit benzodiazepines?

- Do you offer tapers for people using prescribed benzodiazepines?

  - https://www.pbm.va.gov/PBM/AcademicDetailingService/Documents/Academic_Detailing_Educational_Material_Catalog/59_PTSD_NCPTSD_Provider_Helping_Patients_Taper_BZD.pdf

  - https://www.benzo.org.uk/manual/bzsched.htm

Benzodiazepine Summary

- Treat the OUD regardless of benzo use
- Benzodiazepines are effective treatments for anxiety disorders, but not first line.
- Ambulatory tapers can work sometimes, but temper expectations
- Co-prescribing can work, but it may not work. Careful monitoring and support needed.

Psychiatry Consultation Services for Washington State Healthcare Providers

Psychiatry Consultation Line (PCL)

for prescribing providers with adult psychiatry and/or addictions questions

877-WA-PSYCH (877-927-7924) | pclwa@uw.edu

Staffed 24/7

www.pcl.psychiatry.uw.edu

Partnership Access Line (PAL)

for primary care providers with child and adolescent psychiatry questions

866-599-7257 | paladmin@seattlechildrens.org

8am - 5pm, Monday - Friday (excluding holidays)

www.seattlechildrens.org/PAL

PAL for Moms

for providers with behavioral health questions related to pregnancy and postpartum

877-PAL4MOM (877-725-4666) | ppcl@uw.edu

9am - 5pm, Monday - Friday (excluding holidays)

www.mcmh.uw.edu/ppcl

Psychiatry & Addictions Case Conferences (UW PACC-ECHO)

for providers interested in didactic presentations and case-based learning

uwpacc@uw.edu

12:00-1:30 pm, Thursdays

ictp.uw.edu/programs/uw-pacc

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