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Psychiatry and Addictions Case Conference

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BENZODIAZEPINES

CONTINUE OR TAPER?

MARK DUNCAN MD
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SPEAKER DISCLOSURES

✓ None

OBJECTIVES

- Highlight concerning issues around benzodiazepine use
- Describe the utility of benzodiazepine use in psychiatric conditions
- Walk through the assessment of someone on benzodiazepines
- Describe different benzodiazepine tapering options

47YO M WITH H/O ANXIETY AND CHRONIC PAIN

Presents to establish care for chronic pain management and anxiety treatment. Previous provider has decided to move his practice to Texas abruptly. Looking for someone to take over the following meds.

- Oxycodone 10mg q6hr prn x 6 months
- Clonazepam 2mg TID x 10 months.

PMH: HTN on HCTZ

Substances

- **Alcohol:** 2 standard drinks/week; **Drugs:** none

Question: What should you do with the clonazepam?

BENZODIAZEPINES HAVE MANY RISKS

- Use disorders
- Overdose
- Withdrawal and seizures
- Sedation
- Falls
- Medication interactions
- Cognitive problems
- Dementia
 - Mixed evidence base
 - Cumulative Risk?

Risks Increase with Age

In study using benzos for insomnia in pts ≥ 60 yo

- **2x's** more likely to have adverse event vs improved sleep
- **3x's** more likely to have dizziness, loss of balance, falls
- **4x's** more likely to have morning sedation
- **5x's** more likely to have memory loss, confusion, and disorientation

https://www.pbm.va.gov/PBM/AcademicDetailingService/Documents/Benzodiazepine_Provider_AD_Educational_Guide.pdf

<https://www.psychiatrytimes.com/view/benzodiazepine-use-risk-dementia>

Glass, J., et al., Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ, 2005. 331(7526): p. 1169.

BENZODIAZEPINES AS TREATMENT

- Benzodiazepines **are an evidence-based treatment** for anxiety disorders, **but not first line.**
 - Best for panic disorder
 - Good or better vs SSRIs/SNRIs for GAD and Social Anxiety Disorder
 - Useful short term adjunct + antidepressants
 - PTSD: in rare cases and short term
 - Many patients being treated for anxiety disorders **do not grow tolerant to anxiolytic effect**

Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. *Lancet*. 2019 Feb 23;393(10173):768-777. doi: 10.1016/S0140-6736(18)31793-8. Epub 2019 Jan 31. Erratum in: *Lancet*. 2019 Apr 27;393(10182):1698. doi: 10.1016/S0140-6736(19)30857-8. PMID: 30712879.

Offidani E, Guidi J, Tomba E, Fava GA. Efficacy and tolerability of benzodiazepines versus antidepressants in anxiety disorders: a systematic review and meta-analysis. *Psychother Psychosom*. 2013;82(6):355-62. doi: 10.1159/000353198. Epub 2013 Sep 20. PMID: 24061211.

Gomez AF, Barthel AL, Hofmann SG. Comparing the efficacy of benzodiazepines and serotonergic anti-depressants for adults with generalized anxiety disorder: a meta-analytic review. *Expert Opin Pharmacother*. 2018 Jun;19(8):883-894. doi: 10.1080/14656566.2018.1472767. Epub 2018 May 28. PMID: 29806492; PMCID: PMC6097846.

Starcevic V. Benzodiazepines for anxiety disorders: maximising the benefits and minimising the risks. *Advances in Psychiatric Treatment*. 2012;18(4):250-258. doi:10.1192/apt.bp.110.008631

BENZODIAZEPINES AND ADDICTION

- **Most who use benzodiazepines do NOT have a use disorder**
 - 2015-2016 National Survey on Drug Use and Health
 - **Estimated 30.6 million adults used benzodiazepines (12.6%)**
 - 10.6% used as prescribed
 - 2.2% misused benzodiazepines
 - Highest among 18-25yo's
 - Lowest if >65yo (0.6%)
 - 70% got from a friend or relative
 - Alprazolam most commonly misused benzodiazepine
 - **0.2% have a benzo use disorder**

2022-2023 Drug Combo Deaths, WA State

- Benzo + synthetic Opioid: 4.49%
- Meth + Opioids : 35.4%

SUD Risk

- OUD and Benzodiazepines
 - Up to 30% of those on MOUD also on benzos and 1/3 of that sample will misuse them
- AUD and Benzodiazepines
 - Up to 30% in some samples of people in AUD treatment also have benzo misuse

Maust DT, Lin LA, Blow FC. Benzodiazepine Use and Misuse Among Adults in the United States. *Psychiatr Serv*. 2019 Feb 1;70(2):97-106. doi: 10.1176/appi.ps.201800321. Epub 2018 Dec 17. PMID: 30554562; PMCID: PMC6358464.
Blanco C, Han B, Jones CM, Johnson K, Compton WM. Prevalence and Correlates of Benzodiazepine Use, Misuse, and Use Disorders Among Adults in the United States. *J Clin Psychiatry*. 2018 Oct 16;79(6):18m12174. doi: 10.4088/JCP.18m12174. PMID: 30403446; PMCID: PMC10309967.
McHugh RK, Votaw VR, Taghian NR, Griffin ML, Weiss RD. Benzodiazepine misuse in adults with alcohol use disorder: Prevalence, motives and patterns of use. *J Subst Abuse Treat*. 2020 Oct;117:108061. doi: 10.1016/j.jsat.2020.108061. Epub 2020 Jun 22. PMID: 32811622; PMCID: PMC7438601.

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Substances

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Question: How do you assess this pts use/need for clonazepam?

BENZODIAZEPINE ASSESSMENT

SHOULD I CONTINUE OR TAPER?

- **Why are they taking it?**
 - Clear indication?
- **How long have they been taking it?**
 - When is it safe to abruptly stop benzodiazepines?
- **Is it an appropriate dose?**
 - Too high → reduce dose
- **Have they tried other forms of treatment?**
 - Other medications
 - Psychotherapy
- **Has there been any aberrant behavior?**
 - PMP shows multiple providers
 - Regular early refills
 - Missed appointments
- **Do the risks outweigh the benefits?**

WHEN IS IT WITHDRAWAL SYMPTOMS?

Benzodiazepine Discontinuation

– Rebound

- Within hours to days, transiently more intense: insomnia and anxiety
- Short duration, time-limited

– Symptom recurrence

- Days to months, 60-80% for anxiety and insomnia disorders
- Plan ahead!

– Pseudowithdrawal

- Expectations of withdrawal
- “Anxious state”, personality structure, worry about alliance

WHEN DO YOU NEED TO WORRY ABOUT WITHDRAWAL SYMPTOMS?

Withdrawal Phases

– Physiologic Withdrawal

Therapeutic daily doses

- Mild symptoms after 4-6 weeks of use
- **Clinically significant after 4-6 months**
 - Lasts 10-14 days
- Protracted withdrawal after long-term use (1+ year)
 - Duration: weeks to months/waxing and waning

High daily doses (4-5x's of high dose range)

- Moderate to severe withdrawal in all patients after 6 to 12 weeks
 - i.e. Clonazepam 24mg or Diazepam 160mg

Psychopathologic symptoms
Increased anxiety
Nervousness
Sleep disorders
Inner restlessness
Depressive symptoms
Irritability
Psychosis-like conditions, delirium
Depersonalization and derealization
Confusion
Vegetative symptoms
Trembling
Sweating
Nausea and vomiting
Motor agitation
Dyspnea
Increased heart rate
Elevated blood pressure
Headaches
Muscle tension
Neurologic and physical complications
Increased risk of seizures
Impairment of voluntary movements
Cognitive impairments
Impairment of memory
Pronounced perceptual impairments
Hyperacusis
Photophobia
Hypersomnia
Dysesthesia, kinesthetic disorders, muscle twitching and fasciculations

* Data are from Soyka,⁶ Ashton,⁴⁵ Lader and Kyriacou,⁴⁷ and Soyka and Batra.⁴⁹

WHEN DO YOU NEED TO WORRY ABOUT WITHDRAWAL SYMPTOMS?

Factors affecting withdrawal

- Pharmacokinetic
 - Short-acting: w/in 24 hours, peaks 1-5 days
 - Long-acting: w/in 5 days, peaks 1-9 days
- Higher dose and longer use → inc risk more severe
- Increase in psychopathology → more severe
- Other substances
- Older patients → more severe

WHEN SHOULD YOU WORRY ABOUT SEIZURES?

- Risks
 - High dose benzodiazepine
 - Short half-life of drugs
 - Abrupt discontinuation
 - Meds that lower seizure threshold
- Are rare: 2.5%- 8%
- Within 1-3 days after cessation, or longer
- Generalized and repetitive focal nonconvulsive
- If doing a benzo taper → no seizure prophylaxis needed
- If doing a quick taper for several days → seizure prophylaxis needed for 4 weeks

Exceptions

1987 48 case reports

- Dose: 5-20mg
- 6 cases sz's occurred 15 days to 1 month after stopping med
- Multiple co-morbid problems
 - Insomnia
 - Alcohol
 - h/o seizures's

Martinez-Cano, H, et al 1995; Albiero, A, et al 2012; Fialip, J, et al 1987; Schatzberg, A, et al Manual of Clin Psychopharm 2010

PATIENT EXPERIENCE-TAPERING AND DISCONTINUATION

- 19 question internet Survey, N=1207; 1190 took benzos
- 2018-2019
- 71% female; 26% male, >30 but <50 38.8%
- Indications
 - Situational anxiety: 43%
 - Insomnia: 40%
 - Panic attacks: 40%
 - Depression: 33%
 - GAD: 24%

PATIENT EXPERIENCE-TAPERING AND DISCONTINUATION

- 63% had discontinued benzodiazepines
- 24% were in the process of tapering
- Of those who discontinued
 - 10% took over 1 year or longer to taper
 - 4.4% took over 2 years to taper
 - 5.2% stopped abruptly without problem
 - 17% stopped abruptly with consequences

Informed Consent?

- 76% said health care provider 'definitely did not' tell them and stopping them would be difficult.
- 6% said they were 'clearly warned' or 'warned but not sufficiently'

PATIENT EXPERIENCE-TAPERING AND DISCONTINUATION

- Worst Experience they Ever Had
 - “If I could think of the one worst possible thing you could do to a person, it would be benzo withdrawal. If I could make it go away by chopping my arms and legs off, I would!”
- Health care professionals did not treat them well
 - “My doctor cut me off without warning. I believe doctors who do this should lose their license ... I went to the emergency room within days of being discontinued and was “locked down” in mental health unit for 9 days”
- Limited tapering options
 - “This is my third taper ... much better because I am going at a slow pace, but the first two were just horrible”.
- Misrepresentation of risks
 - “The doctor who prescribed the benzo said it was “medically impossible” to overdose or become addicted to benzos. That is plainly false”.
- Symptoms were numerous, severe, and long lasting
 - “Benzos ruined my life. I have been benzo-free for two years and still in protracted withdrawal”.
- Successful taper and minimal complaints
 - “Got 80% of my health back when quit!” (after stopping 20 yeas of benzos and TCA)

PATIENT EXPERIENCE-TAPERING AND DISCONTINUATION

- Severity of Benzodiazepine Discontinuation Symptoms

Domain	Not at all	Mild problem	Moderate problem	Severe problem	Quite severe problem	Enormous problem
Work life	16.2%	4.5%	9.9%	9.9%	9.4%	49.1%
Fun, recreation, hobbies	10.3%	5.9%	9.4%	12.3%	13.3%	48.0%
Social interaction, friendships	12.8%	7.5%	11.2%	11.4%	14.5%	41.7%
Ability to take care of home, others	13.7%	7.8%	13.6%	12.3%	13.3%	38.4%
Relationship with spouse, family	14.3%	8.4%	14.7%	11.2%	12.8%	37.7%
Ability to drive or walk	22.8%	13.8%	15.2%	9.1%	9.0%	29.2%

BENZODIAZEPINES DISCONTINUATION AND MORTALITY

- Comparative effectiveness study using data from US commercial insurance from 2013-2017.
- Long term use: ≥ 90 of days during 1 year baseline and stable dose

Results

- Small absolute increase (2.1 percentage points) in mortality among those whose benzos were discontinued.
- Discontinuation associated with absolute increases in nonfatal overdose, SI, and ED use
- Confounders
 - Patients tapered off benzos were higher risk for problems due to comorbidities vs those not tapered off

STRATEGIES FOR TAKING A PT OFF BENZODIAZEPINES

- Education: letter vs in office visit
 - Letter or office visit counseling patients about harms with recommendations to stop
 - The content of the educational interview was structured and included four key points:
 1. information on benzodiazepine dependence, abstinence and withdrawal symptoms
 2. the risks of long-term use, memory and cognitive impairment, accidents and falls
 3. reassurance about reducing medication
 4. a self-help leaflet to improve sleep quality if patients were taking benzodiazepines for insomnia
 - Results
 - 45% in written instructions and planned taper discontinued benzos
 - 45% in interview with f/u visits discontinued benzos

Vicens C, Bejarano F, Sempere E, Mateu C, Fiol F, Socias I, Aragonès E, Palop V, Beltran JL, Piñol JL, Lera G, Folch S, Mengual M, Basora J, Esteva M, Llobera J, Roca M, Gili M, Leiva A. Comparative efficacy of two interventions to discontinue long-term benzodiazepine use: cluster randomised controlled trial in primary care. *Br J Psychiatry*. 2014 Jun;204(6):471-9. doi: 10.1192/bjp.bp.113.134650. Epub 2014 Feb 13. PMID: 24526745.

STRATEGIES FOR BENZODIAZEPINE TAPERS

- Ashton Method-slow substitution tapers
 - <https://www.benzo.org.uk/manual/bzsched.htm>
 - Can take 10months or longer
 - Patients dictate the rate and pace

Schedule 1. Withdrawal from high dose (6mg) alprazolam (Xanax daily with diazepam (Valium) substitution. (6mg alprazolam is approximately equivalent to 120mg diazepam)

	Morning	Midday/Afternoon	Evening/Night	Daily Diazepam Equivalent
Starting dosage	alprazolam 2mg	alprazolam 2mg	alprazolam 2mg	120mg
Stage 1 (one week)	alprazolam 2mg	alprazolam 2mg	alprazolam 1.5mg diazepam 10mg	120mg
Stage 2 (one week)	alprazolam 2mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 3 (one week)	alprazolam 1.5mg diazepam 10mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 4 (one week)	alprazolam 1mg diazepam 20mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 5 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	alprazolam 1mg diazepam 20mg	110mg
Stage 6 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	alprazolam 0.5mg diazepam 20mg	100mg
Stage 7 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	Stop alprazolam diazepam 20mg	90mg
Stage 8 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	alprazolam 1mg diazepam 10mg	diazepam 20mg	80mg
Stage 9 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	alprazolam 0.5mg diazepam 10mg	diazepam 20mg	80mg
Stage 10 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	Stop alprazolam diazepam 10mg	diazepam 20mg	60mg
Stage 11 (1-2 weeks)	Stop alprazolam diazepam 20mg	diazepam 10mg	diazepam 20mg	50mg
Stage 12 (1-2 weeks)	diazepam 25mg	Stop midday dose; divert 5mg each to morning and night doses	diazepam 25mg	50mg
Stage 13 (1-2 weeks)	diazepam 20mg	--	diazepam 25mg	45mg
Stage 14 (1-2 weeks)	diazepam 20mg	--	diazepam 20mg	40mg

STRATEGIES FOR BENZODIAZEPINE TAPERS

- VA Benzo Taper

Milestone Suggestions		Example: Alprazolam 2 mg bid Convert to 40 mg diazepam daily
Week 1		35 mg/day
Week 2	Total dose decrease by 25%	30 mg/day (25%)
Week 3		25 mg/day
Week 4	Total dose decrease by 50%	20 mg/day (50%)
Week 5-8	Hold dose	Continue at 20 mg/day for 1 month
Week 9-10	Current dose reduction of 25% every two weeks	15 mg/day
Week 11-12		10 mg/day
Week 13-14		5 mg/day
Week 15		discontinue

Perry PJ et al. Psychotropic Drug Handbook Philadelphia PA.2007

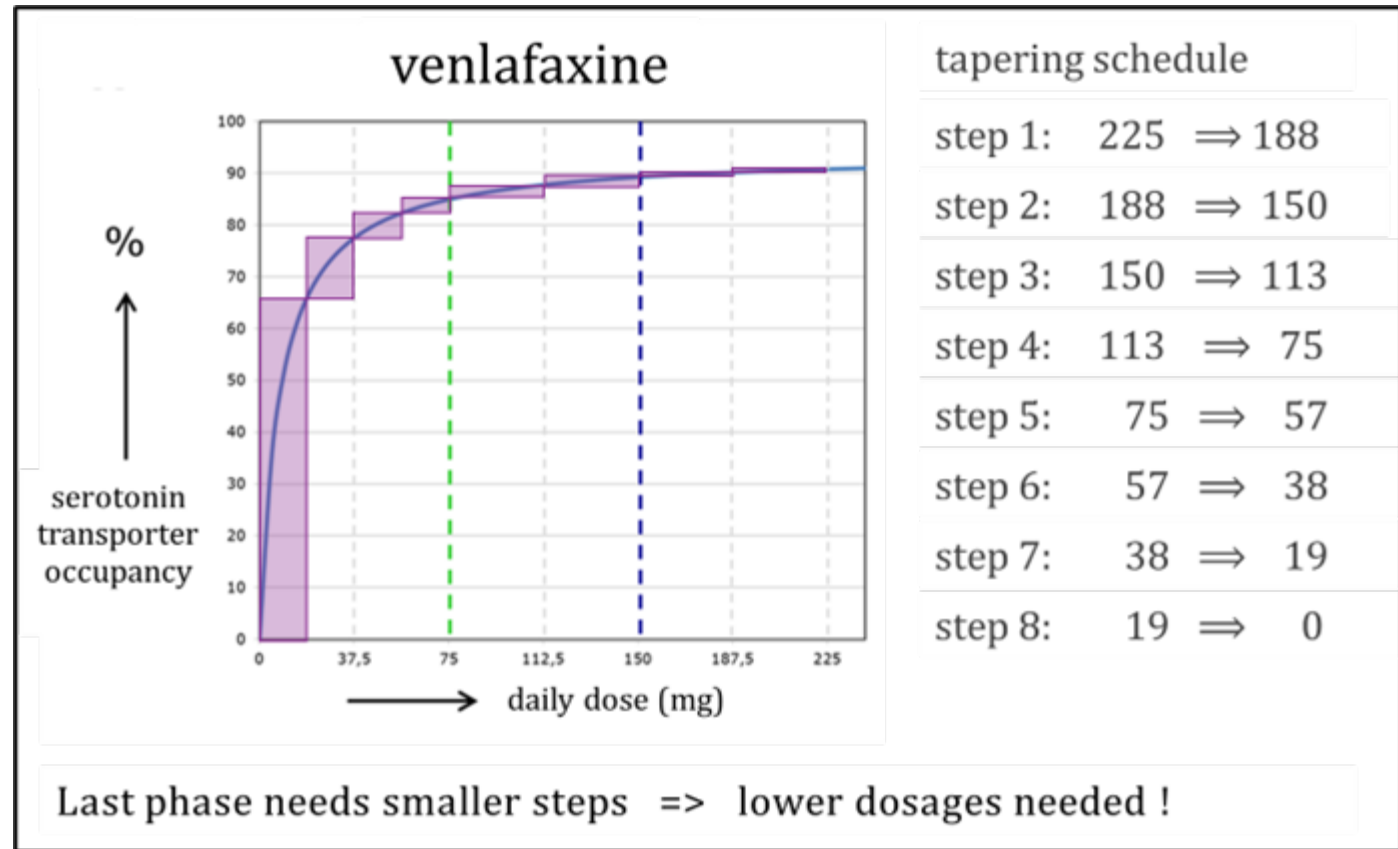
Lader M et al. CNS Drugs 2009 ; 23:19-31.

STRATEGIES FOR TAKING A PT OFF BENZODIAZEPINES: SLOW DOWN

- Cut-and-Hold: A % of the current dose (in mgs/fraction of mg) is reduced, then held until symptoms subside.
 - Pro: may be accomplished with existing forms of drug (e.g. $\frac{1}{4}$ or $\frac{1}{2}$ of scored 2 mg diazepam tablet).
 - Con: symptoms from larger dose reductions at once may be more intense.
 - Example: 20mg diazepam dose reduced 5% (1 mg) and held until withdrawal symptoms subside.
- Microtaper: Daily micro-reductions (μg in size), with % dose reduction (from current dose) calculated monthly.
 - Pro: may allow for finer adjustment and symptom control, since commercially available BZRA doses can be too large to taper comfortably. Many report better symptom tolerability with this method.
 - Con: off-label method that can be subject to accuracy issues.
 - Example: 20mg diazepam dose, 0.07 mg cut daily (~10% reduction over 1 month).

STRATEGIES FOR TAKING A PT OFF BENZODIAZEPINES: SLOW DOWN

- Hyperbolic approach
- Liquid doses
- Tapering strips
 - Not available outside of Netherlands



BENZODIAZEPINE TAPER ADJUNCTIVE MEDS

- Carbamazepine 200mg tid on own or with 3 day benzo taper x 2-3 weeks
- Propranolol 60-120mg/day, divided 3-4 times as adjunct to benzo taper
- Trazodone 25mg-150mg qhs
- Mirtazapine 7.5mg-45mg qhs – I like if also trying to treat depression, anxiety, or in elderly patients
- Gabapentin: pilot for tx of benzo misuse in methadone patients. Mean dose: 2666mg total daily dose. N=19, 50% retention

Dickinson WE, 2014 Principles of Addiction Medicine; Schatzberg, A, et al Manual of Clin Psychopharm 2010; Soyka, M, et al 2017; Oude Voshaar, R, et al 2003; Mariani, J, et al 2016

OTHER CONSIDERATIONS

- Duration: will work with patient on setting a patient-centered goal
- Actively address pre-withdrawal symptoms
- CBT: for underlying symptoms. If anxiety → CBT for Anxiety
- Benzo w/d can mimic other symptoms that seem atypical: depersonalization/derealization, agoraphobia, intrusive thoughts, nerve pain, irritable bowel.
- If misusing other substances
 - Recommend inpt detox

BENZODIAZEPINES AND COLLABORATIVE CARE?

- CoCM could provide support for a benzo taper
 - CBT can be useful for benzo tapering
 - Support prescribed medication taper plan
 - Allow psychiatric assessment and new med recommendation

CASE 2

- 58yo F with severe OUD on methadone and clonazepam 1mg BID. Her psychiatrist retired and she needs someone to continue her clonazepam for Generalized Anxiety Disorder. The patient has used both illicit and prescribed benzos in the past, but states that she has been consistent with her benzo dose the past few years. PMP is in line with this.
- Current medications
 1. Methadone 140mg qday
 2. Clonazepam 2mg TID

Question: Should the Clonazepam be continued?

- A. **Yes**-she is stable right now
- B. **Yes**-the combination of Methadone and Benzo's are not that dangerous
- C. **Yes**-but lower the dose
- D. **No**-the combination of Bup and Benzo's are dangerous
- E. You have it all wrong

BENZOS 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

DETOX VS MAINTENANCE

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

Success: no benzos/no additional benzos

Mean maintenance dose: 2.64mg total daily dose

Co-occurring psych disorder: 64% (38%-mood, 32%-anxiety, 70% had personality disorder-antisocial most common)

Clonazepam
Detox

Clonazepam
Maintenance

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****

WHEN WOULD I TAPER SOMEONE'S BENZODIAZEPINES?

- Risks outweigh the benefits
 - Risk: problems with current meds-sedation, falls cognitive problems, ongoing substance use, misuse of benzos
- When a patient asks
 - Provide patient education and reassurance that a taper can be success. They may voluntarily agree to a taper.

SUMMARY

- Benzodiazepines can be an effective treatment for anxiety disorders
- Benzodiazepines have a long list of problems that get worse as people age
- Most people on benzodiazepines are not addicted, but some are
- Long term use of benzodiazepines should be considered from a risk/benefit perspective
- Outpatient tapering of benzodiazepines is doable in many situations. Taking it slow and being flexible is a good strategy.
- In some cases ongoing benzodiazepine prescribing may be the best option.