# Benzodiazepine use disorder

A Pragmatic Approach

#### Disclosures

None

# Learning Objectives

- 1. Review the pharmacology of benzodiazepines including benzodiazepine analogues
- 2. Describe an approach to managing the signs and symptoms of benzodiazepine withdrawal
- 3. Discuss approaches to benzodiazepine tapering

#### Introduction

- Benzodiazepines are CNS depressants that depress or slow down brain activity
- First benzodiazepine was chlordiazepoxide in 1960 (1,2)
- Today about 35 benzodiazepine derivatives exist, 21 approved internationally
- Anxiolytic, hypnotic, anti-convulsive and muscle relaxing properties
- Associated with physical dependance and addiction
- Associated with increased morbidity and mortality in some studies
- Difficult to distinguish from untreated anxiety or insomnia

#### Medicinal Use of Prescription Sedatives in Canada

- General Population (age 15+): 2019 10.7% (unchanged from 2017 11.7%)
   (2019 Canadian Alcohol and Drugs Survey)
- Youth and Young Adults 15-24) Lowest prevalence of prescriptions. 7.8% in 2019, (increase from 6.4% in 2017)
- Adults (25+): 11.1% (12.6% in 2017)
- Older Dults (65+): Highest rate of prescriptions. 13.2% in 2019 (16.5% in 2017)
- Sex: Significantly higher in female 13.9% compared to males 7.3%

# Non-Medicinal Use of Prescription Sedative Self Reported use in the past year (2019)

- General Population (age 15+): 2.6% reported using sedatives to get high. M>F (5.3% and 1.2%)
- Student (Grades 7-12): 1.1% of students in grades 7-9 (an increase from 0.6%). M=F (2.2% and 2.0%). Grades 10-12: 4.8%.
- Post-secondary Students: 17-25y/o 8.6% (5.2% M and 12.0% F). Among those, 23.8% reported problematic use. M>F. 31.4% and 20.4%

# Pharmacology of Benzodiazepine

#### Mechanism of Action (3)

- Binds to Gamma-aminobutyric acid (GABA) Type A receptors
  - Responsible for Inhibitory neurotransmission in CNS
  - Ligand-gated choline ion channels.
  - When GABA is bound to these receptors -Increase the amount to chloride current generated by the receptors
  - Benzo's augment GABA's inhibitory effect by increasing the frequency of channel opening
  - Inhibitory effect leads to anxiolytic, hypnotic, anti-convulsive and muscle-relaxing properties

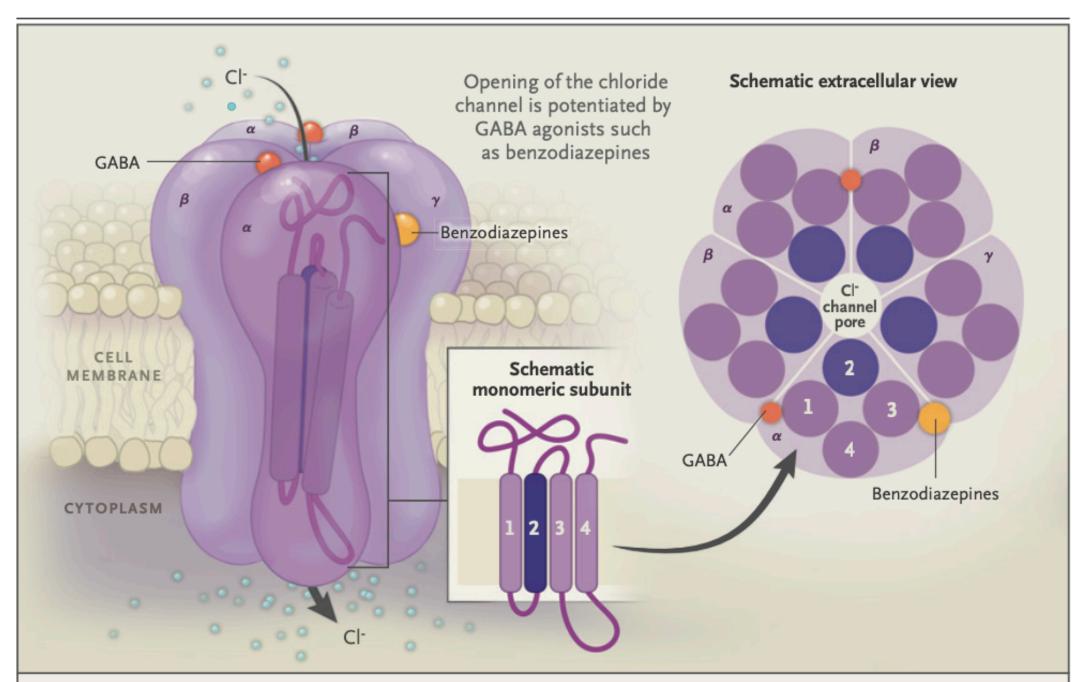


Figure 1. Pharmacologic Characteristics of  $\gamma$ -Aminobutyric Acid Type A (GABA<sub>A</sub>) Receptors.

The GABA<sub>A</sub> receptor consists of five transmembrane glycoprotein subunits arranged around the central chloride channel. Each subunit is composed of four domains (domains 1 through 4); domain 2 (dark purple) is the part of the monomeric subunit that lines the chloride channel. Benzodiazepines increase the affinity of the GABA<sub>A</sub> receptor for GABA and the likelihood that the receptor will open for chloride ions (light blue).

3. Soyka, M et al. Treatment of Benzodiazepines Dependence. N Engl J Med 2017;376:1147-57.

DOI: 10.1056/NEJMra1611832

# Pharmacology of non-benzodiazepine receptor agonists Zolpidem, eszopiclone, and zaleplon

- Modulation of the GABA-a receptor chloride channel complex
- Main site of drug action is located within the GABA-A receptor complex on the alpha-subunit

### Pharmacology

#### **Pharmacokinetics**

- Categories
  - Short Acting Agents (midazolam)- 15-30minutes
  - Intermediate (lorazepam, oxazepam, temazepam) 30-60 minutes
  - Long Acting Agents (choldiazepoxide, clonazepam, diazepam) 60 minutes +

#### Rick Factors

- 1. Longer duration of benzodiazepine use (4)
- 2. High benzodiazepine doses
- 3. Lower level of education
- 4. High rates of misuse of benzodiazepines have also been found among people who use injection drugs (5) and those receiving methadone maintenance treatment (6,7)

- 4. 4. Dependence develops in half the patients who use benzodiazepines for longer than 1 month (7) 11. de las Cuevas C, Sanz E, de la Fuente J. Benzodiazepines: more "behavioural" ad-diction than dependence. Psychopharmacology (Berl) 2003;167:297-303.
- 5. Benzodiazepine use among injecting drug users: problems and implications. Darke S. Addiction. 1994;89(4):379.
- 6 Characteristics of benzodiazepine abuse in methadone maintenance treatment patients: a 1 year prospective study in an Israeli clinic. Gelkopf M, Bleich A, Hayward R, Bodner G, Adelson M. Drug Alcohol Depend. 999;55(1-2):63.
- 7. Determination of the main risk factors for benzodiazepine dependence using a multivariate and multidimensional approach. Kan CC, Hilberink SR, Breteler MH. Compr Psychiatry. 2004;45(2):88.

## Physical Dependence

- Chronic exposure to benzodiazepines causes reduced GABA-A receptor response and changes to the GABA-A receptor sub style expression
- Leads to reduced inhibitory response
- Increase of excitatory glutamatergic receptors during withdrawal which could result in the observed withdrawal syndrome

#### Table 2. Behavioral Correlates of Benzodiazepine Dependence.\*

People who have become dependent on therapeutic doses of benzodiazepines usually have several of the following characteristics:

They have taken benzodiazepines in prescribed "therapeutic" (usually low) doses for months or years.

They have gradually come to "need" benzodiazepines to carry out normal, day-to-day activities.

They have continued to take benzodiazepines even though the original indication for the prescription has disappeared.

Because of withdrawal symptoms, they have difficulty stopping use of the drug or reducing the dose.

Those taking short-acting benzodiazepines have anxiety between doses or a craving for the next dose.

They contact their doctor regularly to obtain repeat prescriptions.

They become anxious if the next prescription is not readily available; they may carry their tablets around with them and may take an extra dose before an event that is anticipated to be stressful or before spending the night in a strange bed.

They may have increased the dosage since the original prescription.

They may have anxiety symptoms, panic attacks, agoraphobia, insomnia, depression, or increasing physical symptoms, despite continuing to take benzodiazepines.

Doctor-shopping, emergency visits, and lost prescriptions are common.

They use private prescriptions rather than those for which the cost would be reimbursed by health insurance.

They take hypnotic agents during the day.

<sup>\*</sup> Data are from Soyka,6 Ashton,45 and Soyka et al.46

#### Prevention

- Any patient who has taken benzo for longer than 3-4 weeks is likely to have a withdrawal if abruptly discontinued
- Reducing the risk of dependance by issuing prescriptions limited to 1-2 weeks

# Benzodiazepine Use Disorder DSM-5 Criteria

- A problematic pattern of sedative, hypnotic, or anxiolytic use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
  - 1. Sedatives, hypnotics, or anxiolytics are often taken in larger amounts or over a longer period than was intended.
  - 2. A persistent desire or unsuccessful efforts to cut down or control sedative, hypnotic, or anxiolytic use.
  - 3. A great deal of time is spent in activities necessary to obtain the sedative, hypnotic, or anxiolytic; use the sedative, hypnotic, or anxiolytic; or recover from its effects.
  - 4. Craving, or a strong desire or urge to use the sedative, hypnotic, or anxiolytic.
  - 5. Recurrent sedative, hypnotic, or anxiolytic use resulting in a failure to fulfill major role obligations at work, school, or home.
  - 6. Continued sedative, hypnotic, or anxiolytic use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of sedatives, hypnotics, or anxiolytics.
  - 7. Important social, occupational, or recreational activities are given up or reduced because of sedative, hypnotic, or anxiolytic use.
  - 8. Recurrent sedative, hypnotic, or anxiolytic use in situations in which it is physically hazardous.

#### DSM-5 Criteria

- 9. Continued sedative, hypnotic, or anxiolytic use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the sedative, hypnotic, or anxiolytic.
- 10. Tolerance.\*
- 11. Withdrawal.\*
- Specifier Mild (2-3), Moderate (4-5), Severe (6+)

#### Pharmacology of benzodiazepines used to treat anxiety symptoms/disorders

Drug	Adult oral total daily dose (mg)*	Comparative potency (mg)¶	Onset after oral dose (hours)	Metabolism	Elimination half-life (hours) <sup>Δ</sup>
Alprazolam	0.5 to 6	0.5	1	CYP3A4 to minimally active metabolites.	11 to 15 16 (older adults)
Alprazolam extended release	0.5 to 6 once daily	0.5	1		20 (hepatic impairment) 22 (obesity)
Bromazepam * §	6 to 30	7.5	1	CYP1A2. No active metabolite.	8 to 20
Chlordiazepoxide§	5 to 100	10	1	CYP3A4 to active metabolites.	30 to 100  Prolonged in older adults and hepatic impairment
Clonazepam	0.5 to 4	0.25 to 0.5	0.5 to 1	CYP3A4. No active metabolite.	18 to 50
Clorazepate	15 to 60	7.5	0.5 to 1	CYP3A4 to active metabolite.	36 to 200
Diazepam	4 to 40	5	0.25 to 0.5	CYP2C19 and 3A4 to active metabolites.	50 to 100  Prolonged in older adults and renal or hepatic impairment

Lorazepam immediate release	0.5 to 6 0.5 to 4 (hypnotic)	1	0.5 to 1	Non-CYP glucuronidation in liver. No active metabolite.	10 to 14
Lorazepam extended release	1 to 6 mg¥	1	0.5 to 1	Non-CYP glucuronidation in liver. No active metabolite.	13 to 27
Oxazepam	30 to 120 15 to 30 (hypnotic)	15 to 30	1 to 2	Non-CYP glucuronidation in liver. No active metabolite.	5 to 15
Prazepam * §	15 to 60	15	2 to 3	CYP3A4 to active metabolites.	30 to 200 Prolonged in older adults

Data on drug metabolism and activity of metabolite(s) are for assessment of potential for CYP drug interactions and risk of accumulation. Risk of accumulation is greater, and dose reduction necessary, for older or debilitated adults and for patients with renal or hepatic insufficiency.

- Not available in the United States.
- § Use only when other preferred agents are unavailable or not tolerated.
- ¥ To be used only when converting from immediate release lorazepam. Total daily dose is equal to the current total daily dose of immediate release lorazepam. Dose is given once daily in the morning after discontinuing immediate dose lorazepam tablets the night before.

<sup>\*</sup> Range of usual **total** daily dose for treatment of adults with anxiety or panic disorder typically given in divided doses two to four times daily.

<sup>¶</sup> Important: Data shown are approximate equal potencies relative to lorazepam 1 mg orally and are NOT recommendations for initiation of therapy or for conversion between agents.

Δ Half-life of parent drug and pharmacologically active metabolite, if any.

# Benzodiazepine Abstinence Syndrome

- Ranges from anxiety/insomnia to seizures/psychosis
- Potentially fatal
- Influenced by 3 factors
- Dose
- Duration of use
- Duration of half life

# Sedative, hypnotic, anxiolytic withdrawal DSM-5 Criteria

- 1. Cessation of (or reduction in) sedative, hypnotic, or anxiolytic use that has been prolonged.
- 2. At least 2 of the following, developing within several hours to a few days after the cessation of (or reduction in) sedative, hypnotic, or anxiolytic use described in Criterion A:
  - A. Autonomic hyperactivity (e.g. sweating or pulse rate greater than 100 beats per minute)
  - B. Hand tremor
  - C. Insomnia
  - D. Nausea or vomiting
  - E. Transient visual, tactile, or auditory hallucinations or illusions
  - F. Psychomotor agitation
  - G. Anxiety
  - H. Grand mal seizures cc
- 3. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- 4. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.ccc

### Benzodiazepine Withdrawal Timeline

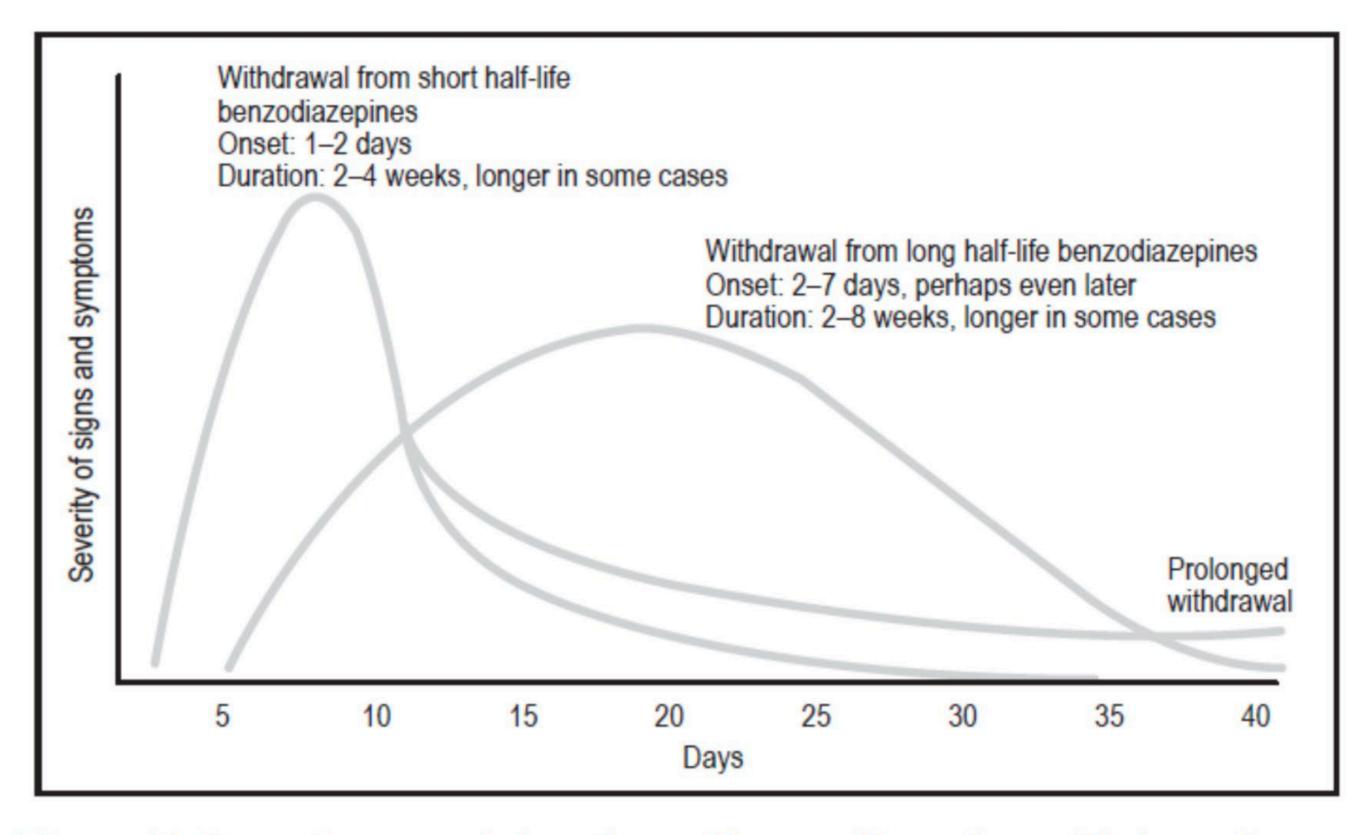


Figure 5: Symptoms and duration of benzodiazepine withdrawal

Source: NSW Health (2008, p.30)

## Three main indicators for tapering

- 1. Patients on therapeutic doses who demonstrate lack of clinical efficacy or emergence of unacceptable side effects
- 2. Patients on supratherapeutic doses
- 3. Patients with benzodiazepine use disorder and/or co-morbid SUD

#### Consensus for treatment of withdrawal

- Benzodiazepines should be gradually reduced over a period of several weeks (eg 4 to 6 weeks or more for diazepam > 30mg per day) to prevent seizures and avoid severe withdrawal (1-3)
- Recommendations range from
  - Reducing initial dose by 50% every week or so (4) TO
  - Reducing the daily dose by 10% and 25% every 2 weeks (5)
  - Duration of 4-6 weeks or 4-8 weeks is suitable for withdrawal for most patients
  - If possible, avoiding prolonged withdrawal treatment from becoming the patients "morbid focus" (6)
- 1. Darker CD, Sweeney BP, Barry JM, Farrell MF, Donnelly-Swift E. Psychosocial interventions for benzodiazepine harm-ful udependence. Cochrane Database Syst Rev 2015;5:CD009652.

### Interestingly...

- Whether switching to a long acting agent (eg diazepam) has fundamental advantages is unclear (1)
- Withdrawal from short acting benzo's are associated with higher dropout rates than withdrawal from longer acting agents (2,3) but switching from a drug with a short half life to one with a longer half life is not associated with better outcomes (2,3)

#### Confirmed vs Unconfirmed Benzo Use

Confirmed dosing	Unconfirmed
Pharmacy records	Street sources
Collateral from Primary Care provider	Diversion
Compliant with medications as prescribed	Urine toxicology does not alight with reported use

### Three main indicators for tapering

- 1. Patients on therapeutic doses who demonstrate lack of clinical efficacy or emergence of unacceptable side effects (confirmed)
- 2. Patients on supratherapeutic doses (confirmed)
- 3. Patients with benzodiazepine use disorder and/or co-morbid SUD (unconfirmed)

# 1. Patients on therapeutic doses from whom a trial off benzodiazepines is warrants

- These are patients that have been prescribed benzodiazepines
- Preparation:
  - Patient should be involved in planning the taper schedule
  - Educate around rebound anxiety/insomnia and re-currance of initial symptoms
  - Plan for additional psychosocial skills

# 1. Patients on therapeutic doses from whom a trial off benzodiazepines is warrants

- General Tapering tips
  - Initial 10-25% dose reduction
  - Reductions of 10-25% every 1-2 weeks, slowing down the taper once reaching diazepam equivalent 5mg
  - For long term benzo use (>1yr), rate should be even slower, ~5-10% or diazepam 2-5mg equivalents per 1-2 weeks
  - Use scheduled dosing (NOT prn)
  - Reduce the dose, not the frequency
  - Pause the taper if needed
  - Using the same benzodiazepine is usually adequate
  - Only dispense enough to last until the next appointment

#### Designing and following the withdrawal schedule

- Design the schedule around symptoms. Eg if insomnia is a major problem, continue QHS dosing, or if getting out of bed is the difficulty, continue AM dosing.
- Diazepam is very slowly eliminated, and needs only at most twice a day dosing to achieve smooth blood concentrations
- Hold dosing schedule when requested, try not to increase the dose again\*
- Avoid PRN dosing
- Monitor for increases of other substances eg alcohol, cannabis, etc
- In some cases after discontinuation, some will like to carry a few tablets "just in case"

#### Case 1

- 64 y/o F
- H/o hypertension, diabetes, and anxiety
- Medications: metoformin, enalapril, and lorazepam 2mg PO BID
- Lorazepam x 30 years. Stable. No risk of diversion or misuse

# Case 1 (Continued)

- Patient centred approach
- Understand how the patient uses the medication and when they are most concerned about anxiety eg before bedtime, or in the morning
- Connect with counselling CBT
- Taper summary
  - Week 1-2: 1mg in AM and 0.5mg QHS\*\*
  - Week 3-7: 0.5mg BID\*\*
  - Week 8-12: 0.5mg OD
  - Week 12: Discontinue

## 2. Patients on supratherapeutic doses

- Greater risk of seizures, psychosis, delirium
- Can be done on an outpatient basis if:
  - Good therapeutic alliance
  - Frequent contact
  - Slow taper 5% reduction per week
  - Use diazepam or other longer-acting agent to promote smoother taper
  - Consider an anti-convulsant Carbamazepine, valproic acid

# What is a supra-therapeutic dose?

Benzodiazepine	Max Recommended Daily dose
Alprazolam	6-10mg
Clonazepam	4mg
Lorazepam	6-10mg
Oxazepam	120mg
Diazepam	40mg

#### Benzodiazepine Substituion

- Always switch to a longer acting agent
- Start with half the equivalent dose
- Increase until the patient denies withdrawal symptoms, but do not prescribe above the full equivalent dose

# Benzodiazepine Equivalency

John Hopkins Guide (https://www.hopkinsguides.com/hopkins/view/Johns\_Hopkins\_Psychiatry\_Guide/787140/all/Benzodiazepines )Vs Ashton Manual (benzo.org.uk)

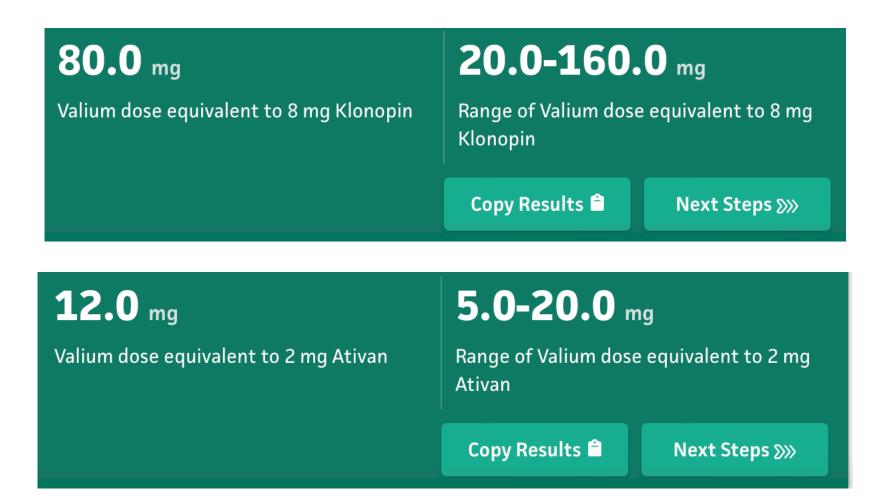
Agent	Relative Potency	Benzo	Half-life(hrs)[active metabolite]	Approximate Equivalent oral dose
Alprazolam	0.5mg	Alprazolam	6-12	0.5
Chlordiapoxide	10	Clonazepam	18-50	0.5
		Diazepam	20-100 [36-200]	10
Clonazepam	0.25-0.5	Lorazepam,	10-20	1
Lorazepam	1	Nitrazepam	15-38	10
Oxazepam	15-30	Oxazepam	4-15	20
Diazepam	5	Temazepam	2	0.5

#### Case 2

- 38 y/r M. Longstanding history of migraines, GAD, MDD, OCD. 15+ years.
- Psychosocial issues on STD, pending ODSP, financial issues, housing issues.
- Tried CBT, individual counselling
- Seen by multiple specialists psychiatrists, neurologist. Primary care has retired.
- Previous medication trials: Multiple SSRI, SNRI, TCA medications.
- Medications: Sertraline 200mg, Valproic Acid (1500mg for migraines), clonazepam 2mg QID, and lorazepam 1mg BID.
- Utox: benzo +
- Frequently requesting dose increases of benzo's due to reports for worsening anxiety. "It's the only thing that helps"

# Case 2 (Continued)

- Convert clonazepam and lorazepam to diazepam equivalent
- Diazepam Equivalents: ~ 25mg-180mg
- 25mg x 75% = 18.75mg diazepam ~ 18mg
- Rate of Decrease:
- Reduce by 1mg/week from 18mg to 4mg (~5% reduction per week)
- Reduce by 1mg Q2weeks until discontinued
- Duration: ~ 21 weeks



# Adjuctive Medications

- Alpha 2 Receptor agonists clonidine
- Anti-convulsants carbamazepine, pregabalin, gabapentin
- Insomnia trazodone, mirtazapine
- B-blockers propranolol

#### 3. Patients with benzodiazepine use disorder and/or comorbid SUD

Confirmed dosing	Unconfirmed
Pharmacy records	Street sources
Collateral from Primary Care provider	Diversion
Compliant with medications as prescribed	Urine toxicology does not alight with reported use

### Internal Questions

- Are they ready? Yes, (hopefully) because they are here today.
- Are they known to me, and have they been consistent with regular follow up? Yes/no
- Is this patient forthcoming with their reported quantities of benzo use? Hopefully
- Is the patient forthcoming with their other substance use? Hopefully.
- Is the illicit benzo they are taking actually the benzo that they believe they are taking? Likely not.
- Do they have a seizure history? Yes/no
- Inpatient or outpatient? Depends on seizure history?
- Are there other concurrent substance use that I should be worried about? OPiates, alcohol...
- Is there a dose of benzodiazepine replacement that will prevent seizures?



'Fake Xana enforceme fentanyl; a

Story by Jamie Duff

has been on the rise in Quebec. Take Xanax<sup>®</sup> as an example. It's mainly consumed by youth, and fatal Xanax<sup>®</sup> overdoses have been reported in the news a number of times recently. In light of this trend, the Drug and Organized Crime Awareness Service (DOCAS) would like to tell you about this phenomenon.

#### **Counterfeit drugs**

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. When police conly way to find out what the drugs actually contain is to have them analyses.

Halifax

Fake Xanax pills containing fentanyl circulating in



**Nova Scotia** 

Frontline addictions workers are seeing more contaminated drugs in the Halifax area

Mairin Prentiss · CBC News · Posted: Apr 09, 2019 1:18 PM EDT | Last Updated: April 10, 2019



FORT WAYNE, Ind. (WANE) — A new illegal drug suspected in cases of drug overdose is on the streets of Fort Wayne.

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Unlike opioids, overdoses from Bromazolam can't be reversed with Narcan.

#### 3. Patients with benzodiazepine use disorder and/or comorbid SUD

- General Tapering tips
  - Calculate diazepam equivalents
  - Start at 50-75% of this dose
  - For long term benzo use (>1yr), rate should be even slower, ~10% or diazepam equivalents 5mg per 1-2 weeks
  - When the dose has reached 20% of the original dose or 20mg diazepam equivalent, slow the taper to 5% or 1–2mg every 2-4 weeks
  - Use scheduled dosing (NOT prn)
  - Reduce the dose, not the frequency
  - Pause the taper if needed
  - No early refills
  - Involve pharmacy Daily dosing, observed dosing
  - Monitoring options Urine drug screens, Connecting Ontario, Pill count
  - Only dispense enough to last until the next appointment

- 22 y/o M
- Using illicit Xanax approximately 20mg/day x 4 years
- Initially reported Xanax use to help with anxiety. Use gradually increased over the years
- No other illicit drug use
- UDS: Benzo +
- No reported withdrawal seizure



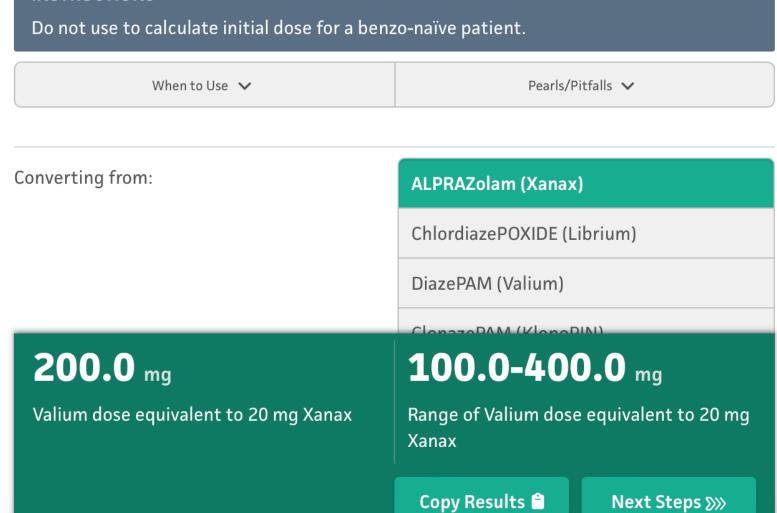
#### Benzodiazepine Conversion Calculator 🖈

Provides equivalents between different benzodiazepines.

#### **IMPORTANT**

This calculator should be used as a reference for oral benzodiazepine conversions. Equipotent benzodiazepine doses are reported as ranges due to paucity of literature supporting exact conversions, thus reported ranges are based on expert opinion and clinical experience published in psychiatric literature.

#### **INSTRUCTIONS**



- $100 \times 75\% = 75$ mg
- $100 \times 50\% = 50$ mg

- Using the equalivancy table (JH vs Ashton)
- 20/0.5 = 40 doses x 5 = 200 mg x 50% = 100 mg
- 20/0.5 = 40 doses x 10 = 400mg x 50% = 200mg

### Is there a dose that is adequate to prevent seizures?

- No Clear research.
- Consensus opinion suggests
  - "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)."

# Stabilize by titration

- Consider starting diazepam 10mg PO TID/QID
- Monitor withdrawal symptoms using scales eg CIWA
- Evaluate tolerance and withdrawal symptoms
- Titrate accordingly

- 22 y/o M
- Using illicit fentanyl 4 years
- Denied illicit benzo use
- Last opiate was 24 hours ago
- COWS 14
- UDS: Benzo + Fentanyl +
- No reported withdrawal seizure
- What would you do?

- 22 y/o M
- Using illicit fentanyl 4 years
- Reporting illicit alprazolam use ~ 4-8mg/day.
- UDS: Benzo + Fentanyl +
- No reported withdrawal seizure
- What would you do?

- 22 y/o M
- Using illicit fentanyl 4 years
- you have start and titrated methadone, on 110mg OD.
- UDS: Benzo + EDDP+
- No reported withdrawal seizure
- CIWA 8
- What would you do?

- 22 y/o M
- Reports illicit benzo use.
- Diazepam equalavent ~ 50-100mg
- UDS: Benzo +
- Reports h/o withdrawal seizure
- What would you do?

## Group discussion

- Street fentanyl sometimes contains benzodiazepine contaminants
- Initiate OAT treatment, frequent follow up. Consider BZD taper. Document.
- For overlaping symptoms consider CIWA B vs COWS to determine which toxidrome withdrawal symptoms are most likely from and treat accordingly
- These are complex cases! Discuss with colleagues and document!

# Questions?

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