Benzodiazepines:
The Ultimate Frenemy

Dr. Rashmi Chadha
MBChB MScCH CCFP MRCGP(Dist.) ABAM (Cert) DCH DRCOG

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Presenter Disclosure

- **Faculty: Rashmi Chadha**
- Relationship with commercial interests: None (no pharmaceutical, medical device or communications company) – no bias to mitigate
- Teaching: Medical Consultant to CPSBC Prescription Review Program, Vancouver Coastal Health, CME (no pharma funding)
- Clinical work: Addictions Physician – VCH South Mental Health & Addictions, VGH Complex Pain and Addiction Service

Outline

- Appreciate the historical context of the development of benzodiazepines (BZD)
- Review indications for prescribing BZD
- Develop an appreciation of the risks associated with chronic BZD use
- Understand how to avoid BZD-related harm
- Practical management strategies for discontinuing BZD

BACKGROUND

Condensed History of Sedatives and Anxiolytics

- 16th-19th Centuries: Opium
- 19th Century: Bromides, Chloral hydrate
- 1900's - 1930's – Barbiturates
- 1950's – Phenothiazines, Meprobomate
- Other compounds – Methaqualone, glutethimide, methyprylon, ethylclorvynol

Drug companies sought medication with:

- Effective anxiolytic properties
- Minimal side effects
- No addictive potential……

.....Benzodiazepines

- Discovered in 1954 by Dr. Leo Sternbach
- Chlordiazepoxide launched in 1960
- Diazepam launched in 1963; most prescribed drug in the US between 1969 and 1982
- Pushback by the late 70's due to their potential for addiction and morbidity
- 30 different BZD on the European and North American market by 2005

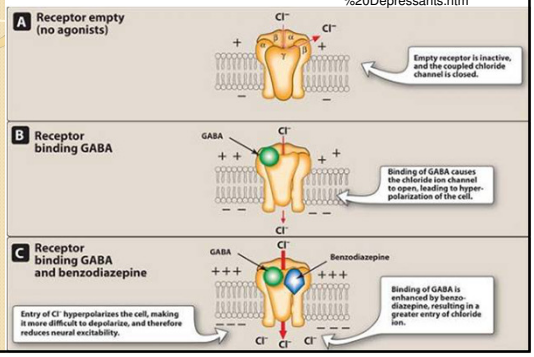
Epidemiology

- In 2006 8.4% of British Columbians used BZD, 3.5% long-term users
- Rate of long-term use decreased from 1996 - 2006 for those >70y, but **increased in middle-aged populations**
- BZD in 40-80% of methadone-related deaths
- BZD in 80% of buprenorphine-related deaths
- 35% of seniors taking BZD meet DSM-IV criteria for dependence/addiction

MECHANISM OF ACTION AND INDICATIONS

Mechanism of Action

http://intranet.tdmu.edu.ua/data/kafedra/internal/pharmakologia/classes_stud/en/nurse/bsn/ptn/Pharmacology/4r/03%20Central%20Nervous%20Sysytem%20Depressants.htm



Indications

- Anxiolytic
- Adjunct when commencing antidepressants
- Sedative
- Anticonvulsant
- Alcohol detoxification agent
- Terminal agitation
- Muscle relaxant
- Depression
- Schizophrenia
- Delirium
- Catatonia
- Aggression, agitation
- Tardive dyskinesia
- Breathlessness in cancer or COPD
- Acute psychosis

Indications

- Anxiolytic ✓
- Adjunct when commencing antidepressants ✓ / ✗
- Sedative ✓
- Anticonvulsant ✓
- Alcohol detoxification agent ✓
- Terminal agitation ✓
- Muscle relaxant ✗
- Depression ✗
- Schizophrenia ✗
- Delirium ✗ ✗
- Catatonia ✗
- Aggression, agitation ✗
- Tardive dyskinesia ✗
- Breathlessness in cancer or COPD ✗
- Acute psychosis ✗

BZD as Anxiolytics

- **GAD** – Short-term benefit (2/52) but effect lost thereafter. Not validated for long-term use (no large studies examining efficacy after years of use, no long-term RCTs comparing long-term BZD with non-BZD alternatives)
- **Panic Disorder** – Robust evidence of BZD efficacy in short-term. No evidence for long-term efficacy.
- **Social anxiety** – Useful in context of episodic performance related anxiety but not for chronic long-term use
- OCD – No value
- PTSD – Ineffective and may worsen PTSD symptoms

BZD as adjunct in early treatment of depression

- Large study initiation of SSRI without BZD VS with BZD showed comparable treatment uptake (39% VS 42%)
- 14% went on to use the BZD for at least a year
- 1% developed abuse/dependence on the BZD
- Authors concluded that when antianxiety medication or CBT has probably started to work, the patient may believe that the BZD is the effective agent and consequently have difficulty discontinuing it
- Patients lose motivation to carry out behavioral treatment (i.e. passivity in treatment – relying on the BZD)

BZD as adjunct in early treatment of depression

- Recent Canadian CANMAT and US (APA) treatment guidelines recommend to limit the use of BZDs in patients with primary major depression to those with pronounced anxiety or persistent insomnia not adequately relieved by an SSRI or SNRI
- Summary: be very cautious in using BZD to assist early anti-depressant treatment in primary care. Potentially use in first 1-2 weeks of antidepressant treatment if *really* needed, but be sure to have a plan to discontinue and warn of s/e of rebound insomnia/anxiety on discontinuation

BZD as Sedatives

- Efficacious for short-term and/or intermittent use (loss of efficacy demonstrated after 2/52 continuous use)
- Daily use causes rapid development of tolerance to sedative effects
- Increased risk of rebound insomnia on discontinuation (even after short-term use)
- Short half-life BZD preferred because of less hangover effect BUT these also have greater abuse liability

Sleep Quality

Belgian 1-year longitudinal study of 131 BZD/Z-drug users vs 95 non-users

- BZD/Z-users sleep quality significantly decreased over 1 year and was significantly worse than in non-users
- Concluded that using BZD/Z's chronically does not maintain or improve sleep quality

Indications

- Anxiolytic (short-term/intermittent)
- Sedative (intermittent)
- Anticonvulsant
- Alcohol detoxification agent
- Terminal agitation
- Acute psychotic agitation

RISKS ASSOCIATED WITH LONG-TERM BZD USE

Mortality

(Courtesy of Dr. A. Mead)

- Effects of anxiolytic /hypnotic drug Rx on mortality hazards
  - Retrospective cohort study: 34,727 pts. vs 69,418 controls
  - HR for mortality = 3.32 (Weich et al, BMJ Mar 2014)
- Hypnotics' Association with Mortality or Cancer
  - Matched cohort study: 10,529 pts vs 23,676 controls
  - Dose dependent elevated hazards of dying
    - Low dose HR = 3.6
    - Med dose HR = 4.43
    - High dose HR = 5.32 (Kripke et al, BMJ Feb 2012)

What most benzodiazepines are prescribed for:

Development of a Vicious Cycle

"The risk–benefit ratio of the benzodiazepines remains positive in most patients in the short term (2–4 weeks) but is unestablished beyond that time, due mainly to the difficulty in preventing short-term use from extending indefinitely with the risk of dependence."

Adverse Effects

Cognitive Decline

- Prospective French study: 969 subjects ≥ 65yrs taking BZD for 2,4, or 7 consecutive yrs vs 4226 never-BZD user controls
- Chronic use significantly associated with lower latent cognitive level and poorer cognitive performance (p=<0.001)

Dementia

1796 cases with Alzheimer's diagnosis (7184 controls)

- Any time use of BZD associated with increased risk (OR 1.5)
- Risk increased with cumulative exposure (OR 1.3 for 3-6/12; OR 1.8 for >6/12)
- Association stronger for long-acting BZD (OR 1.4 for SA; 1.7 for LA)

Etiology of BZD Addiction

- External factors:
  - Lax prescribing
  - Unawareness re: iatrogenic addiction and s/e
  - Lack of other treatments
  - Adverse life events
  - Female
  - Elderly
  - Low income
- Internal factors:
  - Mood disorders
  - Alcohol/substance abuse
  - Personality traits
    - Higher neuroticism
    - Introversion
    - Less effective coping mechanism
  - Somatic dysfunction

RISKS ASSOCIATED WITH BZD TAKEN IN COMBINATION WITH OTHER PHARMACOTHERAPIES

BZD + Opioids

- 40-60% of chronic pain patients concurrently use BZD
- Concurrent BZD use is high in patients on opioid maintenance treatment (~50%)
- Co-administration of BDZ with an opioid increases subjective ratings of "strength", drug "liking", and "high" from the opioid
- BZD implicated in 40-80% of methadone-related deaths and 80% of buprenorphine-related deaths

BZD + Opioids = Risk

- Respiratory depression ——> **Overdose** (BDZ are implicated in as many as 80% of unintentional overdoses involving opioids)
- CNS depression
- Increased psychiatric comorbidity
- Increased risky behaviours
- Daytime somnolence ——> Increased risk MVA
- Cognitive disturbance
- Balance disorder
- Addiction

BZD + Opioids + Alcohol = **Risk**

- Respiratory depression ——> **Overdose** (BDZ are implicated in as many as 80% of unintentional overdoses involving opioids)
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- Increased psychiatric comorbidity
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- Cognitive disturbance
- Balance disorder
- Addiction

SUBSTANCE ABUSE TREATMENT ADMISSIONS DUE TO CO-ABUSE OF PRESCRIPTION OPIOIDS AND BZD **INCREASED BY 570%** BETWEEN 2000-2010.

ADMISSIONS RELATED TO ALL OTHER SUBSTANCE ABUSE DECREASED BY 10% IN THE SAME TIME PERIOD.

AVOIDING BZD-RELATED HARM TO PATIENTS

Primum non nocere

- Comprehensive substance use history
- Avoid prescribing in those with a history of SUD, aggression, violent forensic history, psychiatric disorder that include poor impulse control
- Extreme caution in those with poor coping skills, poor social support, high neuroticism, personality disorder/traits
- Non-pharmacological options – sleep hygeine, CBT, relaxation techniques
- **Intermittent use, short time period, lowest dose possible – provide small quantities**
- Treatment agreement (one doctor, one pharmacy, frequent follow-up)
- Objective monitoring: UDS, pill counts, psychiatric re-evaluation

Primum non nocere : Avoid abrupt discontinuation

Abrupt cessation of ≥50 mg/d diazepam equivalent leads to risk of:

- Seizure
- Psychosis
- Delirium

Therefore….taper

Tapering: Advantages

- Increased energy and improved alertness
  "like a veil has been lifted"
- Improved balance (less accidents and falls)
- Improved cognitive function
  - Psychomotor tasks
  - Working and episodic memory
- Mood stabilization
- Lower risk of adverse drug reactions
- Improved sleep quality and sleep architecture
- Disappearance of personality traits

Potential outcomes of tapering

Vikander B, Koechling UM, Borg S, Tönne U, Hiltunen AJ. Benzodiazepine tapering: A prospective study. Nord J Psychiatry 2010;64:273–282.

1. A gradual decrease in symptoms over the 50-week time-period
2. An increase in the severity of symptoms at the onset of tapering and a decrease in severity post-tapering
3. An increase in the severity of symptoms 4 weeks after the cessation of BZD tapering
4. No change over the 50-week time-period

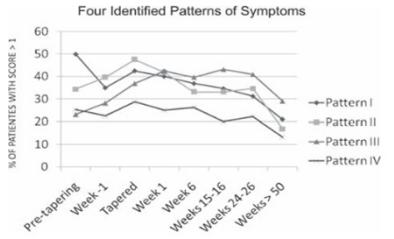

Fig. 2. Four different patterns of symptoms presented as the percentage of patients who obtained ratings of signi cant (>1.0) clinical symptoms, when comparing mean values taken at pre-tapering, during tapering and 4 weeks following cessation of tapering.

2/3 of patients able to completely cessate BZD

BZD tapering: outcomes from different tapering strategies

2014 Systematic Review

- 28 studies of older outpatients tapering chronic BZD
- Indications for LT BZD prescriptions were insomnia, depression, anxiety
- Taper (32%) **vs** Taper + CBT (32%) **vs** Taper + medication substitution (36%)
- Mean success rate for all modalities was 60%; independent of duration/dose
- Conclusion: Patient-centred approach with close monitoring and support leads to successful outcomes

Addiction
REVIEW
doi:10.1111/j.1360-0443.2008.02364.x

Effectiveness of current treatment approaches for benzodiazepine discontinuation: a meta-analysis

Jannette M. Parr[1], David J. Kavanagh[2], Lareina Cahill[3], Geoffrey Mitchell[1] & Ross McD. Young[2]
School of Medicine, University of Queensland, Herston, Queensland, Australia,[1] Institute of Health and Biomedical Innovation, Queensland University of Technology, Queensland, Australia[2] and Far North Queensland Rural Division of General Practice, Innisfail, Queensland, Australia[3]

- Systematic review of 24 studies in GP/outpatient settings
- Routine care VS 1) Brief intervention; 2) Gradual dose reduction (GDR); 3) GDR+psychological intervention or substitution pharmacotherapy
- Conclusion: **Providing an intervention was more effective than routine care. Psychological interventions may improve discontinuation above GDR alone.** While some substitutive pharmacotherapies may have promise, current evidence is insufficient to support their use.

Tapering: Disadvantages

- Time intensive
- Withdrawal-mediated symptoms
- Potential for resurgence of mental health issues

- Misperceptions: perceived as challenging or unecessary by physicians and patients alike
  - "If it ain't broken why fix it?"
  - "Don't take away my sleeping pill"

Withdrawal Symptoms

- Autonomic symptoms
- Vasomotor fluctuations
- Myalgias/spasms
- Numbness/tingling
- Psychological
  - **Anxiety**
  - Impaired concentration
  - **Irritability**
  - Mood swings
  - Nightmares
  - Agitation
  - Dysphoria
  - **Insomnia**
  - Paranoia
- GI Problems
- Chest Pain
- Headache
- Dizziness
- Nausea, vomiting
- Postural hypotension
- Perceptual symptoms
  - Tinnitus
  - Photophobia
  - Derealisation
  - Hyperacusis

Patient Buy-in

Easy
- If patient requests taper
- If obvious morbidities associated with long-term use
- If concurrent opioids

Hard
- If no obvious side effects
- If concurrent disorder
- If overvaluation of benefit
- Previous taper failure
- Ongoing SUD

How to convince the die-hard benzodiazepine users

- Highlight physical health risks (balance disorder, falls, MVA)
- Discuss mental health risks (dementia, behavioral disinhibition)
- Highlight rebound symptoms
- Remind patients about loss of efficacy and sleep quality disturbance
- Remind them again about mortality and dementia/cognitive decline; that 1 lorazepam at night is a frenemy

TAPERING STRATEGIES

Initial Visit

- Discuss options – outpatient preferable to inpatient
- Discuss symptoms to expect:
  - Anxiety symptoms (mood swings, insomnia, decreased concentration)
  - Neurological symptoms (tinnitus, distorted perception, headaches, derealization)
- Discuss medication management parameters (UDS, frequent dispensing)
- Ask to keep diary of BZD use

Choice of BZD to taper with

- Long-acting
- Insufficient evidence to support the use of one long-acting BZD over another
- Consider switching from BZD of choice for taper
  - Diazepam if young and healthy
  - Lorazepam if liver dysfunction or elderly
  - Clonazepam may be good alternative for w/d from alprazolam/triazolam
  - Lorazepam more anxiolytic; diazepam more sedating

Conversion

- Consult equivalence table
- Individual variation in reactions to different BZD – therefore caution about sedation, driving etc
- Direct conversion risks side effects and loss of confidence from patient
- Stepwise conversion

Benzodiazepine equivalences

- Source: Adapted from The Ashton Manual and The Clinical Handbook of Psychotropic Drugs (19th Ed.)

Benzodiazepine	Comparative Dose (mg)
Alprazolam	0.25-0.5
Clonazepam	0.25
Lorazepam	0.5-1
Diazepam	5
Oxazepam	10-15
Temazepam	10

Conversion

- Consult equivalence table
- Individual variation in reactions to different benzodiazepines
- Direct conversion risks side effects and loss of confidence from patient
- Stepwise conversion
- 2 considerations:
  - Rate of taper
  - Size of dose reductions

Rate of taper

- Tailored according to individual patient needs
- Consideration of psychosocial stressors
- Generally aim for dose reductions every 2-3 weeks
- Better results if patient-guided; but monitor for slow-down/stagnation in taper

Size of dose reduction

- General rule of thumb for any taper:
  - 10% q 2/52 (some studies have demonstrated success with faster tapers of 25%q 2/52)
  - Slower dose decrements near end of taper (final third of original dose)
  - Be guided by patient report, otherwise risk failure
- Never regress with reductions
- End of taper is **not** usually challenging

Example 1: Slow and cautious withdrawal from 3 mg lorazepam (1 mg TID): Conversion stage

Stage	Morning	Afternoon	Evening	Diaz. Equiv.
Stage 1 (1/52)	Loraz. 1 mg	Loraz. 1 mg	Loraz. 0.5 mg **Diaz. 5 mg**	30 mg
Stage 2 (3-7/7)	Loraz. 0.5 mg **Diaz. 5 mg**	Loraz. 1 mg	Loraz. 0.5 mg **Diaz. 5 mg**	30 mg
Stage 3 (3-7/7)	Loraz. 0.5 mg **Diaz. 5 mg**	Loraz. 0.5 mg **Diaz. 5 mg**	Loraz. 0.5 mg **Diaz. 5 mg**	30 mg
Stage 4 (3-7/7)	Loraz. 0.5 mg **Diaz. 5 mg**	Loraz. 0.5 mg **Diaz. 5 mg**	(Stop Loraz.) **Diaz. 10 mg**	30 mg
Stage 5	(Stop	Loraz. 0.5	**Diaz. 10 mg**	30 mg

Conversion weeks

- Homework Journal
  - Health issues – balance, memory, "wellness", sleep
  - Psychological issues – emotional dysregulation, anxiety
  - Social issues – relationships
- Be prepared for an over-detailed initial few weeks
- Identify and recognise concerns and fears; reassure and develop therapeutic alliance

Example 1 : Slow and cautious withdrawal from 3 mg lorazepam: Tapering (Insomniac)

Stage	Morning	Afternoon	Evening	Diaz. Equiv.
Stage 6 (1/52)	Diaz. 10 mg	Diaz. 10 mg	Diaz. 10mg	30 mg
Stage 7 (1-2/52)	Diaz. 10 mg	**Diaz. 7 mg**	Diaz. 10 mg	27 mg
Stage 8 (1-2/52)	**Diaz. 7 mg**	Diaz. 7 mg	Diaz. 10mg	24 mg
Stage 9 (1-2/52)	Diaz. 7 mg	**Diaz. 4 mg**	Diaz. 10 mg	21 mg
Stage 10 (1-2/52)	**Diaz. 5 mg**	Diaz. 4mg	Diaz. 10 mg	19 mg
Stage 11 (1-2/52)	Diaz. 5 mg	**Diaz. 2 mg**	Diaz. 10mg	17 mg

Example 2: Alternative withdrawal from 3 mg lorazepam (1 mg TID): Conversion and taper (with incorporated dose decrease for incomplete cross tolerance)

Stage	Morning	Afternoon	Evening
Stage 1 * (1/52)	Diaz. 7 mg	Diaz. 7 mg	Diaz. 7 mg
Stage 2 (1-2/52)	**Diaz. 6 mg**	**Diaz. 6 mg**	Diaz. 7 mg
Stage 3 (1-2/52)	**Diaz. 5 mg**	**Diaz. 5 mg**	Diaz. 7 mg
Stage 4 (1-2/52)	Diaz. 5 mg	**Diaz. 3 mg**	Diaz. 7 mg

(*Provide breakthrough doses of 1-2 mg up to BID prn for Stage 1)

Longitudinal review during taper

- More frequent visits at start, decreasing frequency over time.
- Periodic review of diary; monitor for rebound symptoms
- Avoid making psychiatric diagnoses during taper
- Strategies:
  - Grounding techniques
  - Encourage exercise
  - Encourage use of social supports
  - Refer for counseling if not already done
  - Consider support group
- If pt destabilizes (physical/mental health) consider residential detox

Adjunct medication for PRN use

- Trazodone 25-50 mg HS for insomnia
- Propranolol 10 - 20 mg up to TID for palpitations, sweats, anxiety; caution needed WRT blood pressure (therefore avoid if elderly living alone); ideally BP in clinic *before* test dose and monitor for 1 hour with repeat BP
- TCA for insomnia – not validated in research
- Melatonin for insomnia – not validated in research
- Gabapentin/Pregabalin– current research suggests role in facilitating faster taper due to gaba-ergic properties

Courtesy of Dr. L. Rieb

Example 1: Slow and cautious withdrawal from 3 mg lorazepam: Completion

Stage	Morning	Afternoon	Evening	Diaz. Equiv.
Stage 12 (1-2/52)	**Diaz. 3 mg**	Diaz. 2 mg	Diaz. 10 mg	15 mg
Stage 13 (1-2/52)	Diaz. 3 mg	**(Stop afternoon dose)**	Diaz. 10mg	13 mg
Stage 14 (1-2/52)	**Diaz. 2 mg**	----------	Diaz. 10 mg	12 mg
Stage 15 (1-2/52)	**(Stop morning dose)**	----------	Diaz. 10 mg	10 mg
Stage 16- Completion	----------	----------	**Reduce by 1 mg every 2/52**	Diaz. 9 mg – 0mg ☺

Example 2: Alternative withdrawal from 3 mg lorazepam (1 mg TID): Tapering

Stage	Morning	Afternoon	Evening
Stage 5 (1-2/52)	Diaz. 5 mg	**Diaz. 1 mg**	Diaz. 7 mg
Stage 6 (1-2/52)	**Diaz. 4 mg**	**(Stop afternoon dose)**	Diaz. 7 mg
Stage 7 (1-2/52)	**Diaz. 3 mg**	----------	Diaz. 7 mg
Stage 8 (1-2/52)	**Diaz. 2 mg**	----------	Diaz. 7 mg

Example 2: Alternative withdrawal from 3 mg lorazepam (1 mg TID): Completion

Stage	Morning	Afternoon	Evening
Stage 9 (1-2/52)	**Diaz. 1 mg**	----------	Diaz. 7 mg
Stage 10 (1-2/52)	**(Stop morning dose)**	----------	**Diaz. 6 mg**
Stage 11 (1-2/52)	----------	----------	**Diaz. 5 mg**
Stage 12 - Completion	----------	**Reduce by 1 mg every 1-2/52**	Diaz. 4 mg – 0 mg ☻

Follow-up

- Continue to encourage self-efficacy
- Can take up to 6-12/12 for full "normality"
- Re-assess for any residual/underlying mental health issues
- Reinforce sleep hygiene
- Resist requests for other GABA-A agonists – especially in the first year after discontinuation
- Thereafter reserve for short-term and intermittent use only – reinforce by providing small infrequent dispenses with close follow-up

Z-drugs – Not quite as problematic….?

- Increasing use as physicians and patients perceive it as more safe and less dependency causing c.f. BZD
- Useful for short-term/intermittent management of insomnia (Health Canada advisory recently advised 3.75 mg dosing d/t hangover effect)
- Common side-effects: hangover, difficulty concentrating, headaches
- Chronic zopiclone users have decreased sleep efficiency, increased wake time, increased sleep onset latency, decreased short-wave sleep
- Studies have demonstrated cognitive problems and psychomotor impairment with long-term use. May also increase the risk of depression
- Case reports of abuse (increased risk in those with SUD or psychiatric illness)
- Risk of respiratory and CNS depression if taken in combination with other CNS depressants

Other treatments for withdrawal management

- Inpatient: Phenobarbital, IV/SC flumazenil infusion
- Inpatient/outpatient: gabapentin, pregabalin

Resources

The Ashton Manual
Professor C Heather Ashton DM, FRCP
Information for Physicians
Information for Patients
Stories from Patients
Taper schedules
Website: benzo.org.uk

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