Identification and Management of Benzodiazepine and Z-drug abuse

Presentation provided by
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CSAM-SCAM Fundamentals
### Disclosures

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Objectives

1) Why can Benzodiazepine use be harmful?
2) When is Benzodiazepine use harmful?
3) What can we do about harmful Benzodiazepine use?
4) How and when to taper Benzodiazepines if required.
Benzos – more than just a prescription
Joanne

- 46 yr old woman
- Complex comorbidities
  - Fatigue, lassitude, depression, obesity, metabolic syndrome, fibromyalgia, chronic LBP
- Laid off 4 yrs ago
- Meds:
  - HM Contin, + Percocet 12/day for BTP
  - Valium 10 mg qid prescribed (but multiple BZD’s, multiple MD’s)
  - Celexa, Mirtazapine, quetiapine,
  - Gabapentin
Sedatives, Hypnotics, Anxiolytics

- Benzodiazepines
- Zopiclone
- Barbiturates (not used much)
- Antihistamines (diphenhydramine, hydroxyzine) – usually non-addicting
- Beta-blockers – non-addicting
- Buspirone – non-addicting
- Dimenhydrinate
Definitions

**Sedative**
- Calm down, treat agitation

**Hypnotic**
- Induce sleep go to sleep fast, feel refreshed tomorrow !!!

**Anxiolytic**
- Reduce anxiety (physical, emotional, cognitive)
Hard Facts about BZD

- Most people will become dependent after > 6 weeks continuous use
- Only 30% of benzodiazepine dependent people ever get off them completely
- Methadone patients at high risk of benzodiazepine abuse (25 - 65%)
- Methadone maintenance patients using non-prescribed benzodiazepines on higher doses and more risk-taking behaviour
Why do patients love them?

Most loved Addiction. 99(2):165-173, February 2004 Jaffe et al

1. Anxiety and Insomnia
2. Because of their effects of intoxication / pleasure
3. As a primary drug
4. To enhance a drug, such as methadone
5. Self medication to help mood, coping skills and / or reduce voices
6. To help come down from amphetamines, ecstasy, crack cocaine or cocaine
7. As a substitute for alcohol
How addictive are BZD?

- Depends on population being considered
  - Ordinary populations: Risk very low
  - Psychiatric patients: Intermediate risk
  - Addictive populations: Risk very high but little firm data

- Pharmacological factors (Rickels et al 1990)

- Non-drug factors
  - patient factors such as personality, gender, vulnerabilities, health, anxiety trait and depressive diagnosis (Rickels et al 1990)
How addictive are BZD?

- The more you do it
- The more you will end up doing it
- The more problems you will have from it (physical, psychological & social health problems, tolerance)
- And the more difficulty you will have stopping it (physical & psychological dependence)

The Benzo Trap!
Therapeutic Uses - Medical

- Anticonvulsant
- Muscle Relaxant
  - Cerebral palsy, dystonia
- Amnesia with Sedation
  - Peri-operative or medical procedures
- Alcohol withdrawal
- Insomnia
- Acute Agitation
- Effects: Anticonvulsant, Muscle-relaxant
Therapeutic Uses - Psychiatric

- Severe acute anxiety
  - Not first line treatment for any chronic anxiety disorder
- Severe generalized anxiety disorder unresponsive to other treatments
- Panic disorder, social phobias
- Adjunctive treatment of depression, bipolar affective disorder and schizophrenia
- Effects: Sedative, hypnotic, anxiolytic!
BZD Patterns of Use

- 45% of Use < 30 days
- 80% of Use < 4 months
- 15% of Use >12 months
- Women, twice the rate as men
BZD Patterns of Abuse

Two patterns of abuse
- Recreational (non-medical use to get high)
- Quasi-therapeutic use
  - long-term drug-taking, inconsistent with accepted medical practice

Substance Use Disorder
- DSM V Criteria (11)
  - 2-3 criteria = mild substance use disorder
  - 4-5 = moderate
  - 6-7 = severe
Continuum of Substance Use

- **Experimental**
  - Motivated by curiosity or desire to experience new feelings or moods

- **Social**
  - Use on specific social occasions

- **Situational**
  - Pattern associated with specific situations

- **Intense**
  - Higher doses and increased frequency

- **Compulsive**
  - Persistent and frequent high doses producing psychological or physiological dependence
Why can Benzodiazepines be abused?

- GABA is the major inhibitory neurotransmitter of the CNS, it decreases neuronal excitation
- Benzodiazepines act by potentiating the effects of GABA
- Many BZD have active metabolites
Benzodiazepines – Adverse Effects

**Acute:**
- Sedation
- Decreased respiratory drive
- Overdose (with other drugs, esp alcohol and opioids)
- Disinhibition

**Chronic:**
- Decreased Neurocognition (esp elderly)
- Physiologic dependency (Tolerance, Withdrawal)
- Addiction (Intoxication, 4 C’s)
Benzodiazepines – Adverse Effects

- Overdose
  - Rare fatalities if BZD alone
- Severe CNS & Respiratory Depression if combined with:
  - alcohol
  - barbiturates
  - narcotics
  - tricyclic antidepressants

Benzodiazepines – Adverse Effects

- Motor Impairment (reaction time)
- Cognitive dysfunction (sedation, amnesia)
- Impairments in
  - visuospatial ability,
  - verbal learning and
  - Memory
- Associated with decreased functional status
- Increased risk
  - Age >65
  - Alcohol
  - Using > 1 BZD
  - Fast acting, short half life, highly lipid soluble (Alprazolam)

# Half Lives

<table>
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<tr>
<th>BDZ (Duration Action)</th>
<th>Onset of effect</th>
<th>Equivalence to 5mg diazepam</th>
<th>Elimination ( t_{1/2} )</th>
<th>Active Metabolites</th>
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<tr>
<td><strong>Short &lt;12h</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Alprazolam (Xanax)</td>
<td>fast</td>
<td>0.25-0.5</td>
<td>6-14</td>
<td>Yes</td>
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<tr>
<td>Triazolam (Halcion)</td>
<td>fast</td>
<td>0.125-0.25</td>
<td>1.5-5.5h</td>
<td>No</td>
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<tr>
<td>Oxazepam (Serax)</td>
<td>slow</td>
<td>8-12</td>
<td>6-12h</td>
<td>No</td>
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<tr>
<td><strong>Medium (10-15h)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Lorazepam (Ativan)</td>
<td>fast</td>
<td>0.5-1</td>
<td>10-20h</td>
<td>No</td>
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<tr>
<td>Temazepam (Restoril)</td>
<td>intermediate</td>
<td>5-17</td>
<td>6-24</td>
<td>Yes</td>
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<tr>
<td><strong>Long &gt;24h</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Flurazepam (Dalmane)</td>
<td>fast</td>
<td>7.5-15</td>
<td>50-100h</td>
<td>Yes</td>
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<tr>
<td>Diazepam (Lorazepam)</td>
<td>fast</td>
<td>5mg</td>
<td>20-100h</td>
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<tr>
<td>Clonazepam (Rivotril)</td>
<td>intermediate</td>
<td>0.5-1</td>
<td>17-50h</td>
<td>No</td>
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<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>intermediate</td>
<td>10-25</td>
<td>7-25h</td>
<td>Yes</td>
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Benzodiazepines – Adverse Effects

1) SuboxoneCME.com
When is BZD use problematic?

Risk Factors for BZD abuse

1. Comorbid substance use disorders
   - 80% of BZD abuse part of polydrug abuse (Gold et al. Psych Annals, 1995)
   - 40% of alcohol abuse

2. Psychiatric comorbidities:
   - PD
   - chemical coping

3. Genetic vulnerability (tolerance)

4. Environmental factors

5. Pharmacodynamics of BZD (reinforcing properties)
Are Z Drugs Addictive?

- **Z drugs**
  - Zopiclone (Imovane)
  - Zolpidem (Ambien)
  - Zaleplon (Sonata) - US
- **Non-BZD**
- Onset (1 H to 2.5 h), T1/2 (short)
- Abuse potential
  - lower than BZD
  - **Potentiate ETOH impairment**
  - **Reinforcing, abusable, and performance-impairing**
  - increased risk in SUD & Psych

Addressing Problematic BZD Use

**IMPLEMENT SAFE PRESCRIBING GUIDELINES**

- Other sedating drugs
- COPD, sleep disorders
- Elderly (esp long acting)
- Liver dysfunction
- Comorbidities are the rule, not the exception
- If prescribing: careful assessment, care plan, Rx goals, short course
- Medical monitoring
  - manage complications quickly
- Should clearly state intended short term nature and dependence potential
Management of BZD Addiction

1. Recognize abuse, misuse, overuse & abuse cycles
2. Recognize withdrawal syndrome
3. Implement safer alternatives to BZD
4. Motivational interviewing (Stages of Change)
5. Benzodiazepine withdrawal management
   • Inpatient vs outpatient
Why taper?

- Often not because patient “addicted” although depends on your setting
- Possible benefits of tapering:
  - more alert, energetic
  - better able to make positive life changes
  - not need drug anymore
  - avoid future adverse effects
- High risk if concomitant use of other depressants
- Most actually feel better after coming off BZD
- Need to be aware of comorbid medical conditions
  - consider physiological stress to patients of tapering
  - patients with chronic medical conditions experience w/d more severely
Why is it so hard to stop?

- **Withdrawal!**
  - Reducing causes increased excitation throughout the brain which causes the symptoms of withdrawal, including agitation, anxiety, and insomnia.
- **The number of GABA receptors is slowly restored to pre-BZD levels in response to benzodiazepine cessation or dose reduction.**
- The rate of withdrawal of treatment needs to allow time for GABA receptors to regenerate if withdrawal symptoms are to be minimized.
BZD Withdrawal

- **Symptoms**
  - Anxiety-related
    - irritability, insomnia, panic attacks, hypersensitivity (photo/phono, touch)
  - Neurologic
    - tinnitus, distorted vision, dysperceptions, tremor
  - Muscle twitching, insomnia, irritability, decreased concentration

- **Signs**
  - Autonomic hyperactivity
    - diaphoresis, tremor, tachycardia, HTN
  - Hyperreflexia
  - Mydriasis

- **Complications** (Abrupt cessation of high dose BZD)
  - Seizures, Arrhythmias
  - Psychosis, Delirium
  - Suicidal Ideation
BDZ Withdrawal - Anxiety

Common to all anxiety
- Agitation
- Panic attacks
- Agoraphobia
- Insomnia
- Nightmares
- Depression
- Poor memory,
- Loss of concentration

Specific to W/D anxiety
- Perceptual distortions, depersonalization
- Hallucinations (visual and auditory)
- Tingling and loss of sensation, formication (a feeling of ants crawling over the skin)
- Sensory hypersensitivity
- Muscle twitches and fasciculations
- Psychotic symptoms, confusion, convulsions (rare)
BZD Withdrawal - depends on speed of Taper

- **Most people only experience mild withdrawal symptoms** when withdrawal is slow and tapered to their needs [Ashton, 2002d].

- **Severe withdrawal symptoms are associated with the following** [Kan et al, 2004]:
  - Rapid withdrawal
  - Prolonged use of benzodiazepines
  - High-dose use
  - Short-acting, potent benzodiazepines
  - People with a history of anxiety problems

- **Withdrawal symptoms characteristically vary** in severity and type from day to day and from week to week. As some symptoms resolve, others may take their place. These symptoms gradually become less severe and less frequent with time [Ashton, 2002d].
How long do symptoms last?

- **Up to 15% of people develop protracted withdrawal symptoms** (months or years)
  - **Anxiety**: Gradually diminishes over 1 year
  - **Insomnia**: Gradually diminishes over 6–2 months
  - **Depression**: Few months responds to antidepressants

**Cognitive impairment**
- Gradually improves, but may last for >1 year

**Gastrointestinal symptoms**
- Gradually recede, but may last for at least 1 year and occasionally persist indefinitely

**Perceptual symptoms**
- (e.g. tinnitus, paraesthesia, pain (usually in limbs))
- Gradually recedes, but may last for at least 1 year and occasionally persist indefinitely

**Motor symptoms**
- (e.g. muscle pain, weakness, tension, painful tremor, jerks)
- Usually gradually recede, but may last for >1 year
Tapering General Principles

- Written Treatment & management plan
- Rx plan
  - Clear, Continuous, Comprehensive, CMS
- Alternative treatment strategies for insomnia and anxiety (both pharmacologic and non-pharma)
- Implement behavioural therapies
  - MI, CBT
- Regular Monitoring, Support & Reassessment
  - Single prescriber
  - Contingency Management System (CMS)
Tapering

- Ashton Manuel (benzo.org.uk)
- Switch to equivalent dose of diazepam or clordiazepoxide
- Use scheduled fixed dose and interval taper schedule (not PRN),
- Taper over 6 weeks to many months (2-5 mg or 10 % of dose / 1-2wk)
- Decrease rate of taper at doses < 20mg diazepam equivalent (or last 25% of of taper)
Why use Diazepam?

Withdrawal is most easily managed from diazepam because:

• Diazepam and its metabolites (desmethyldiazepam and nordiazepam) have long half-lives (between 20 hours and 200 hours)

• Ensures a gradual fall in blood concentrations.

• The blood level of its longest active metabolite for each dose falls by a half in about 8 days
Tapering

- Consider Adjuncts
  - Gabapentin (start at 300 mg tid and go up)
  - carbamazepine (200mg TID)
  - valproic acid (250mg TID)
  - Propanolol (20-30mg TID-QID)
  - SSRI’s or trazodone\(^1,2\)
- Consider inpatient taper to start if patient is taking unknown or high dose (>60-80mg diazepam/day)

Key Points on BZD

- Safe if used alone, but high OD risk if used with other depressants especially alcohol or opioids
- Appropriate and effective for short-term use only
- Rarely appropriate for chronic use
- Many subtle negative side effects
- Taper should usually be proposed/attempted in any chronic users, especially if elderly or those abusing other substance
Key Points on BDZ

- Daily use of benzodiazepines (BZs) = risky
- Certain situations ↑ risk
  - Prescribing practices/med characteristics
  - Patient characteristics
- Taper BZs slowly if daily use ~2+ weeks
Tapering

- It is possible
- It is worth doing
- It needs the right time, the right support and the right regimen
- Relapse happens but should not be a reason not to try and keep trying!
Summary

1. Why can BZD use be problematic?
   • Similar addiction risks as other prescribed Rx
   • 3 Dz Risk Factors: Host, Environment, Agent

2. When is BZD use problematic?
   • Close Monitoring reveals worsening Disorders
   • Worsening Complications
   • Declining Functional status & Cognition
   • Obvious addiction

3. What can we do about problematic BZD use?
   • Know the Science (Outcome-based EBM)
   • Taper gently
Case Review

• Joanne
  • Complex comorbidities
• What to do:
  • 1.
  • 2.
  • 3.
  • 4.
Joanne

- 46 yr old woman
- Complex comorbidities
  - Fatigue, Lassitude, depression, obesity, metabolic syndrome, fibromyalgia, chronic LBP
- Laid off 4 yrs ago
- Meds:
  - HM Contin, + Percocet 12/day for BTP
  - Valium 10 mg qid prescribed (but multiple BZD’s, multiple MD’s)
  - Celexa, mirtazepine, quetiapine,
  - Gabapentin
Taper Regimen for Joanne

For people taking 40 mg per day of diazepam or less, a typical withdrawal schedule:

- Reduce by 2.5 mg to 5 mg every 1–2 weeks to 20 mg per day
- Reduce by 1 mg to 2 mg every 1–2 weeks to 10 mg per day
- Reduce by 1 mg every 1–2 weeks to 5 mg per day
- Reduce by 0.5 mg to 1 mg every 1–2 weeks until completely stopped.

Total withdrawal time from diazepam 40 mg per day might be 5-6 months or longer.

Stopping the last few milligrams is often seen by patients as being particularly difficult but this is usually an unfounded fear derived from long-term psychological dependence on benzodiazepines.
Thank You!