Benzodiazepines

CRIT program
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Learning objectives

At the end of this session, you should:

1. Understand why people use benzodiazepines
2. Know the characteristics of benzodiazepine intoxication and withdrawal syndromes
3. Understand the consequences of these drugs
4. Know the current options for treatment of benzodiazepine dependence
Roadmap

1. Case and controversies
2. History and Epidemiology
3. Benzo effects
4. Treatment
Case

• 29 yo man presents for follow-up at methadone clinic after inpatient admission for femur fracture from falling onto subway track from platform.
• Treated with clonazepam since age 16 for panic disorder. Takes 6mg in divided doses daily. Missed his afternoon dose, the day of the accident
• Started using heroin at age 23
• On methadone maintenance for 1 year, doing well, about to get his first take home
Thoughts

• Did BZDs cause his fall?
  – or did not taking BZDs cause his fall?
• Should he get take homes?
• Is it possible for him to come off of BZDs? How?
• Did teenage BZD treatment cause his heroin addiction?
History and Epidemiology
History

• First discovered in 1954 by a Austrian scientist, Leo Sternbach → Librium

• 1963 → Valium

• Used for anxiety, seizures, withdrawal, insomnia, drug-associated agitation
History

- Widely available starting in the 1960s
- 1973 – 87 million prescriptions
- 1980s – high potency benzodiazepines found to be more effective for panic and anxiety than other drugs
  - Advantages: rapid onset and less risk of dependence
- 2007 – 74 millions prescriptions
Widespread Use

• Due to their significant margin of safety and effectiveness
  – BZDs are among the most prescribed psychotropic medications worldwide
  – On WHO essential drug list that should be available in all countries
Nonmedical use – “not prescribed for the respondent or that the respondent took only for the experience or feeling that the drug caused”

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Past Month Use: 2002-2008

- Pain Pills
- Cocaine
- Tranquilizers
- Stimulants
- Heroin

CRIT 2010  NSDUH 2008
DEA NFLIS 2006 Report

- Prescription drugs seized by law enforcement and analyzed forensics labs

Figure 1. Distribution of benzodiazepines within region, 2001–2005.
DEA NFLIS 2006 Report

- Prescription drugs seized by law enforcement and analyzed forensics labs: 2001-2005

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rx Dispensed</th>
<th>Items seized per 10k Rx Dispensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>65M</td>
<td>6.06</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>169M</td>
<td>5.96</td>
</tr>
<tr>
<td>Morphine</td>
<td>23M</td>
<td>5.80</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>161M</td>
<td>5.29</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>82M</td>
<td>3.55</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>550M</td>
<td>1.63</td>
</tr>
<tr>
<td>Codeine</td>
<td>165M</td>
<td>1.06</td>
</tr>
</tbody>
</table>
Benzodiazepine Effects
Why benzos?

• Indications for a prescription:
  – Anxiety, insomnia, nausea, seizure, agitation, procedural sedation
• Advantages:
  – Immediate anxiolysis vs. buspirone and SSRI
• Other reasons:
  – Started for acute indication, yet not discontinued
  – Boosting other sedating medications (opioids)
  – Euphoria seeking
  – Opioid or alcohol withdrawal or cocaine toxicity
Mechanism of Action

- Organic bases with BENZene ring + DIAZEPENE moiety
- Modulates the gamma-aminobutyric acid A (GABA-A) receptor boosting affinity of GABA for the receptor
  - GABA - chief inhibitory neurotransmitter
- BZDs slow the brain down
- GABA receptor density low in respiratory brainstem > limiting the incidence of respiratory depression
Classes of Benzos

- Side chains determine potency, duration of action, and elimination
  - Short-acting – Oxazepam
    - few active metabolites, clearance unaffected by age or liver disease
  - Intermediate-acting – Lorazepam
  - Long-acting – Diazepam and chlordiazepoxide
    - active metabolites, tissue accumulation, impaired clearance with age and liver disease
Tolerance

- To sedative and euphoric effects in days
- To anti-epileptic effects limits use for chronic seizure control
- Incomplete tolerance to cognitive impairment
- To the anxiolytic effects “is practically nonexistent”

Up To Date. Sedatives and hypnotics: Pharmacology and epidemiology

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Adverse Effects

- Sedation
- Lethargy
- Respiratory Depression
- Impaired motor skills
- Impaired judgment
- Cognitive dysfunction
- Delirium
- Short-term memory impairment
- Anterograde amnesia
- Ataxia
- Hypotonia
- Depressed mood
- Exacerbation of COPD, sleep apnea

*Patients often do not recognize their own impairment*

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BZDs in elderly

• Among Medicare enrollees, hip fracture linked to BZDs, regardless of half-life
  – First 2wks is highest risk time

• Beers Criteria 2002 for potentially inappropriate medication use in elderly
  – Medium/high doses of short acting BZDs and all long-acting BZDs
Does the cognitive function of long-term benzo users improve following withdrawal?

Are they still impaired compared to controls or normative data?

Overdose

• Without concomitant sedating medications, benzos rarely cause life-threatening overdose
  – Sedated with normal vital signs

• Flumazenil – competitive antagonist of the GABA-A receptor that can reverse BZD actions
  – Risks of reversal (seizures and agitation) usually outweigh the benefits outside of precedural sedation

Principles of Addiction Medicine, 4th edition, chapter 47.
Up To Date. Benzodiazepine poisoning and withdrawal
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Poisoning hospitalizations 1999-2006

Overdose deaths in NYC 2006-2008

Unintentional overdose deaths in NYC

NYC Vital Signs. NYC DPMH. 2010
Opioid overdose deaths in WV 2006

Benzos in Methadone Patients

Upon MMT entry in Israel
- 47% of patients abusing benzos ceased after 1 year
- 27% of patients not abusing benzos had started by 1 year
- Reasons for abuse included:
  - 87% to improve emotional state
  - 41% to boost other drugs
  - 40% for sleep
  - 24% to get high on benzos alone
  - 23% for withdrawal
  - 19% to reduce the effects of stimulants

Acute to chronic opioid use

- Euphoria
- Normal
- Withdrawal

- Tolerance and Physical Dependence

Acute use  CRIT 2010  Chronic use
Methadone Maintenance

Euphoria

Chronic use

Maintenance

Withdrawal

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Boosting methadone with benzodiazepines
Overdose and oversedation

Among 250 opioid dependent subjects with previous methadone or buprenorphine prescriptions, reported the following symptoms when also taking benzos:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Methadone</th>
<th>BPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme drowsiness</td>
<td>42%</td>
<td>24%</td>
</tr>
<tr>
<td>Unconsciousness</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Overdose</td>
<td>7%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Withdrawal Syndrome

• Symptoms? > Similar to alcohol withdrawal
  – Tremors, anxiety, perceptual disturbances, dysphoria, psychosis, seizures

• Onset of symptoms?
  – Varies by how long BZD has been used and half-life
    • can occur within hours for short-acting or weeks for long-acting
Treatment
Prescribers are ambivalent

On the one hand
- Rarely the abuse drug of choice
- Given the amounts prescribed, benzo abuse is “remarkably low”
- Benzos work fast with few side effects
- Benefit maintained over time

On the other hand
- Non-medical use very common
- Concerning subgroups
  - Other sedating meds
  - Elderly
  - Other addictions
- Hard to discontinue
- Does not improve long-term course of PTSD
- Co-morbid depression may worsen


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Which hand?

Consider when prescribing benzos

• Intent –
  – Are you treating a diagnosed medical problem?
• Effect –
  – Does the medication improve the patient’s functional status or worsen it?
• Monitoring –
  – Are you assessing the patient at the peak or trough effect of the medication?
Withdrawing benzodiazepines

Don’t stop BZDs abruptly due to risk of withdrawal seizures

**Strategy 1** - Taper over weeks to months

- Taper 10% starting dose every 1-2 wks
- Decrease taper amount and lengthen interval for final 25-35% of taper.

_Consider cognitive behavioral therapy/SSRI during and after for breakthrough symptoms_


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Withdrawing benzodiazepines

Don’t stop BZDs abruptly due to risk of withdrawal seizures

**Strategy 2 - Substitute and taper**

1. Stabilize on phenobarbital using hx and symptoms
2. Dose TID
3. Taper 30mg per day or slower

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phenobarbital 30mg equiv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>0.5-1mg</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>1-2mg</td>
</tr>
<tr>
<td>Diazepam</td>
<td>10mg</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2mg</td>
</tr>
</tbody>
</table>

Consider cognitive behavioral therapy/SSRI during and after for breakthrough symptoms

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Withdrawing benzodiazepines

Don’t stop BZDs abruptly due to risk of withdrawal seizures

**Strategy 3 – Taper with adjunct**

- Short BZD taper (3 days?) and treat with anti-convulsant for 2-3 weeks
  - carbamazepine 200 TID or
  - valproic acid 250TID

*Consider cognitive behavioral therapy/SSRI during and after for breakthrough symptoms*

Harris et al. Alcohol Alcohol 2000:35; 319-325.
BZD treatment – Cochrane Review

Cochrane review authors conclusions:
1. Gradual taper is preferable to abrupt discontinuation
2. Carbamazepine appears to be a helpful adjunct to gradual taper
3. Confirming the benefit of switching from short to long-acting at beginning of taper requires further study

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Patient’s perspective on chronic benzo use

• Purpose of benzos
  – Means of coping with stress/anxiety and insomnia
    “Sometimes my life gets so up in the air that I say to my children, right now I wish I had a wafer-sized Valium.”
  – Lifeline or life-transforming properties
    “It makes me want to go on living.”
    “I think if it weren’t for the chemicals I wouldn’t be chugging along.”
    “I don’t mentally think I would have survived without it and that’s the truth.”
  – Lack of awareness, underestimation, disregard for side effects
    “He wouldn’t have given it to me if he thought it was gonna hurt me.”
    “It’s just a small, little, tiny white pill.”
    “It’s the lowest dose that they make.”
    “My head always feels foggy.”

Cook et al. JGIM 2007: 22; 1094-1100.
Patient’s perspective on chronic benzo use

• Attitudes toward taper/ discontinuation
  – Resistance to taper
    “I see no reason why I should put myself through hell… We don’t have that long to live and we might as well enjoy ourselves while we’re here.”
    “On numerous occasions I’ve tried to go off of it. And the reaction is I can’t sleep and I’m totally wired. I’m up all night.”
  – Rejection of psychological interventions
    “I just don’t want to. I’m not one of those people who can sit around and talk about my problems with strangers.”
  – The physician-patient relationship
    “I have complete faith in Dr. ________. I mean we go back a lot of years. Whatever he says, goes.”

Cook et al. JGIM 2007: 22; 1094-1100.
Case

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  – Or did not taking BZDs cause his fall?
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• Is it possible for him to come off of BZDs? How?
• Did teenage BZD treatment cause his heroin addiction?
What should be done about benzos?

• Prescribe with caution
• Educate patients
  – Safety first – Teens, mixing meds
  – Function over feelings
  – Risk of tolerance to benefits and withdrawal
  – Communication among prescribers
• Discontinue if risks outweigh the benefits
Thanks!

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Benzos in Methadone Patients

Among 361 cocaine/heroin users enrolled in a contingency management trial, benzodiazepine use was associated with

– Increased cocaine use during treatment
– Blunted response to CM

Prescription Drug Misuse

• Higher doses than prescribed
• More frequently than prescribed
• Without a prescription
• Reasons other than intended by the prescriber
Self-medication

• One physician survey reported that:
  – 26% of psychiatrists
  – 11% of other physicians

Used unsupervised benzodiazepines in the past year

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<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Usual dose (oral)</th>
<th>Oral peak (hr)</th>
<th>Half-life (hr) parent</th>
<th>Metabolite activity*</th>
<th>CYP3A4 interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>Xanax</td>
<td>0.25-0.5 mg</td>
<td>1-2</td>
<td>6-27</td>
<td>Inactive</td>
<td>Yes</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Klonopin</td>
<td>0.25-0.5mg</td>
<td>1-2</td>
<td>18-50</td>
<td>Inactive</td>
<td>Limited</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Librium</td>
<td>5-25 mg</td>
<td>0.5-4</td>
<td>5-30</td>
<td>Active</td>
<td>Yes</td>
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<tr>
<td>Clorazepate</td>
<td>Tranxene</td>
<td>7.5-15 mg</td>
<td>1-2</td>
<td>Prodrug</td>
<td>Active</td>
<td>No</td>
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<tr>
<td>Diazepam</td>
<td>Valium</td>
<td>2-10 mg</td>
<td>0.5-1</td>
<td>20-50</td>
<td>Active</td>
<td>Limited</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Ativan</td>
<td>0.5-3 mg</td>
<td>2-4</td>
<td>10-20</td>
<td>Inactive</td>
<td>No</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Dalmane</td>
<td>15-30 mg</td>
<td>0.5-1</td>
<td>2-4</td>
<td>Active</td>
<td>Limited</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>Rohypnol</td>
<td>0.5-2 mg</td>
<td>1-2</td>
<td>16-35</td>
<td>Active</td>
<td>Limited</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Versed</td>
<td>0.025-0.1 mg</td>
<td>1-2</td>
<td>1.5-3</td>
<td>Active</td>
<td>Yes</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Serax</td>
<td>10-30 mg</td>
<td>2-4</td>
<td>5-20</td>
<td>Inactive</td>
<td>No</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Restoril</td>
<td>7.5-30 mg</td>
<td>1-2</td>
<td>3-19</td>
<td>Inactive</td>
<td>No</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Halcion</td>
<td>0.125-0.25 mg</td>
<td>0.7-2</td>
<td>2-3</td>
<td>Inactive</td>
<td>Yes</td>
</tr>
<tr>
<td>Zolpidem*</td>
<td>Ambien</td>
<td>5-10 mg</td>
<td>1-2</td>
<td>1.5-4.5</td>
<td>Inactive</td>
<td>Limited</td>
</tr>
</tbody>
</table>

Duration of action of compounds having active metabolite(s) is significantly greater than predicted by half-life of parent.

* Half-life of active metabolite(s) may exceed 50-100 hours.
* Nonbenzodiazepine hypnotic.
DEA NFLIS 2006 Report

Prescriptions dispensed (in 1000s) 2001-2005

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Pharmacology & Kinetics

• Acts on GABA receptors by potentiating its inhibitory effects on the CNS
• Kinetics divided into three groups:
  – Short acting
    • Triazolam (Halcion), Oxazepam (Serax), Alprazolam (Xanax)
    • Midazolam (Versed) → but has more active metabolites
  – Intermediate acting
    • Lorazepam (Ativan), Temazepam (Restoril)
  – Long acting
    • Diazepam (Valium), Chlordiazepoxide (Librium), Clonazepam (Klonopin)
• Rapidly absorbed in GI tract, metabolized in liver
Withdrawal syndrome

Marked decrease or cessation of benzodiazepines after several weeks of regular use and 2 or more …

• Autonomic hyperreactivity
• Increased hand tremor
• Insomnia
• Nausea or vomiting
• Hallucinations
• Psychomotor agitation
• Anxiety
• Tonic-clonic seizures
Poisoning hospitalizations
1999-2006

Benzos for panic disorder
Anxiolysis maintained – dose decreased

Nagy et al. Arch Gen Psychiatry 1989: 46; 993. N=60 – Natural history observation cohort
Mean Age at First Use 2008 NSDUH

Age in Years

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Z drugs

- Zolpidem (ambien), esopiclone (lunesta) and zaleplon (sonata)
- Same GABA target
- Case reports of withdrawal and abuse
- Post-marketing surveillance indicates low abuse potential considering the amount prescribed
Urine testing

- Urine specimens contain little parent BZD
- Many immunoassays detect oxazepam: less likely clonazepam, lorazepam or triazolam unless present in high doses
- Chlorazepate, chlordiazepoxide, diazepam, and temazepam are metabolized to oxazepam
Cognitive Function

- Many studies find no cognitive impairment with long-term BZD
- Others find impaired psychomotor, learning, concentration and visuospatial function
- Improvement when discontinued, though function still worse at 6 months
- Most patients do not recognize impairment
Metabolism

- Primarily hepatic, typically by CYP2C19 and/or CYP3A4
- Oxazepam, temazepam, and lorazepam are not metabolized by the liver, and excreted by the kidney

Up To Date. Benzodiazepine poisoning and withdrawal
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