Benzodiazepines Overuse

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Pharmacist Objectives

✔ Participants will review the pharmacology of benzodiazepines and be able to identify how various benzodiazepines differ.
✔ Participants will review how benzodiazepines are used clinically, including risks and benefits.
✔ Participants will learn the patterns of use of benzodiazepines.
✔ Participants will develop an understanding of the risks around prescribing benzodiazepines and opioids, including recent and relevant recommendations from the CDC around pain management.

Technician Objectives

✔ Participants will review the mechanism of action of the benzodiazepine class and understand difference between drugs in this class.
✔ Participants will review how and when benzodiazepines are used in specific disease states.
✔ Participants will learn the patterns of use of benzodiazepines.
✔ Participants will develop an understanding of the risks and benefits of benzodiazepines.

A Bit of History

Prior to discovery of benzodiazepines, included alcohol, opium derivatives, paraldehyde, chloral hydrate, bromides and especially, barbiturates. All had limited effectiveness and high lethality.

In 1950, meprobamate (Miltown) was discovered with the hope that it might be a safer alternative, but it was found not to be an anxiolytic, but caused sedation, tolerance, abuse and still could be highly lethal. The first benzodiazepine, chlordiazepoxide (Librium) was discovered in 1955, shortly followed by the development of diazepam (Valium). Benzodiazepines were found to not only be effective as anxiolytics, but were significantly safer than barbiturates and meprobamate.

A Bit More History

Once hitting the market, benzodiazepines became the most widely prescribed drugs in the world, and became known in the press as “happy pills”, and as “mother’s little helper” by the Rolling Stones.

In the 1980’s it was recommended that BZD’s be considered controlled substances, and the “triplicate prescription program” in New York State was started.

Benzodiazepines: Mechanism of Action

BZDs act at the level of the limbic, thalamic and hypothalamic regions of the CNS, although there are BZD receptors throughout the CNS.

- BZDs act by enhancing the actions of GABA, the brain’s primary inhibitory neurotransmitter, at the GABA-BZD receptor complex.
- There are two BZD receptor subtypes on the GABA-A receptor that mediate either sedation/sleep (type 1) or muscle relaxation, anticonvulsant activity, motor coordination and memory (type 2).
- Essentially, BZDs have sedative, anti-anxiety, anticonvulsant and muscle relaxant properties

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Currently Available Benzodiazepines

**Anxiolytics**
- Alprazolam (Xanax)
- Chlordiazepoxide (Librium)
- Clonazepam (Klonopin)
- Clorazepate (Tranxene)
- Diazepam (Valium)
- Lorazepam (Ativan)
- Oxazepam (Serax)

**Hypnotics**
- Estazolam (ProSom)
- Flurazepam (Dalmane)
- Midazolam (Versed)*
- Temazepam (Restoril)
- Triazolam (Halcion)

How to Tell One BZD From Another?

Why so many forms when all BZDs do essentially the same thing in the brain, i.e., enhance GABA transmission?

Pharmacokinetics

BZDs are differentiated by their pharmacokinetic profiles, based on lipophilicity and metabolism:

- **Half-life** (short, intermediate, slow)
- **Onset-of-action** (rapid, intermediate, slow)
- **Metabolic pathways** (with or without active metabolites, with or without P450 involvement)

**LONGER ACTING**
- Chlordiazepoxide (Librium)
- Diazepam (Valium)
- Clonazepam (Klonopin)

**MEDIUM ACTING**
- Lorazepam (Ativan)
- Oxazepam (Serax)
- Temazepam (Restoril)

**SHORT ACTING**
- Alprazolam (Xanax)
- Triazolam (Halcion)
- Midazolam (Versed)

Pharmacokinetics

- Long the half-life: more hang-over and delayed/attenuated withdrawal (Clonazepam)
- Shorter half-life: greater withdrawal with interdose rebound (Alprazolam)
- Hepatic impairment and elderly: shorter half-life, 3-hydroxy forms safer (Lorazepam, Oxazepam and Temazepam)
- More lipophilic: rapid onset, produce euphoria, wears off quickly (Alprazolam)
- Less lipophilic: slower onset, longer lasting, less euphoric (Clonazepam)
- Diazepam is lipophilic but long half-life, so quick onset, short acting in single dose, but will provide steady state coverage with chronic, multiple dosing.

Benzodiazepines Are Used for:

1. Generalized anxiety disorder (and generic anxiety)
2. Alcohol withdrawal
3. Panic disorder
4. Muscle spasms, restless legs
5. Seizures/epilepsy
6. Social phobia
7. Insomnia (“hypnotics”)
8. Catatonia
9. Sedation (procedures)
10. Akathisia
11. Manic agitation

Schatzberg AF, DeBattist C 2015
Drug Interactions

Potentiates sedative effects of narcotics and alcohol, some P450 inhibitors could increase levels of BZDs metabolized by that system (e.g., CYP3A4 inhibitors and alprazolam).

BZDs alone are generally safe in overdose, but combined with other CNS depressants, will cause death.

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Side Effects

Tolerance to sedation occurs in 5-10 days, while anxiolytic effects can continue indefinitely.

Physical dependence occurs more quickly if used well above normal dose, but also can occur over months with normal dosing.

Additional Side Effects:
- Memory impairment: anterograde amnesia with shorter acting, higher doses, IV use (e.g., midazolam)
- Cognitive impairment with long-term use: controversial; study showing 50% increase of dementia

Abuse and Withdrawal

If discontinued suddenly:
- Hyperpyrexia
- Seizures
- Cognitive impairment
- Hypertension
- Muscle cramps
- Anxiety, panic attacks
- Insomnia
- Perceptual disturbances (hallucinations, derealization)
- Death

Bisaga and Marioni 2015

First Line Treatment of Anxiety Disorders

- Panic Disorder – SSRI/BZD, exposure therapy
- Agoraphobia – exposure therapy
- Specific Phobia – exposure therapy
- Social Phobia – exposure/CBT therapy, SSRIs/beta blockers
- Obsessive-Compulsive Disorder – SSRIs
- Posttraumatic Stress Disorder (PTSD) – SSRIs/CBT, exposure therapy
- Acute Stress Disorder – supportive therapy
- Generalized Anxiety Disorder (GAD) – SSRIs/Effexor/Buspar, psychotherapy
- Anxiety Disorder Due to Medical Condition – optimal treatment of medical condition
- Substance-induced Anxiety Disorder – substance abuse treatment

Benzodiazepine Overuse and Consequences

1. Excessive and/or inappropriate prescribing?
2. Substance abuse?
3. Polysubstance abuse?
4. Polypharmacy?
5. Resulting in what seems to be a contribution to ED utilization and death rates

Schatzberg AF, DelBattist, C 2015
Top US Psychiatric Prescriptions for 2013

1. Alprazolam: 48,465,000
2. Sertraline: 41,416,000
3. Citalopram: 39,445,000
4. Fluoxetine: 28,258,000
5. Lorazepam: 27,920,000
6. Trazodone: 26,242,000
7. Escitalopram: 24,920,000
8. Duloxetine: 18,573,000
9. Bupropion XL: 16,053,000
10. Venlafaxine ER: 15,796,000
11. Diazepam: 14,335,000

BZD Overuse and Consequences

- Between 1996 and 2013, the percentage of adults receiving BZD prescriptions increased from 4.1% to 5.6%.
- Lorazepam equivalents went from 1.1 kg/100,000 adults to 3.6 kg/100,000 adults.
- Annual increase of 2.5% in prescriptions but a 9%/yr increase in quantity.
- Overall death rate increased from 0.58/100,000 to 3.07/100,000.

Emergency Department Visits

From 2005 to 2011, over 940,000 ED visits involved BZDs, with visits increasing from nearly 90,000 in 2005 to over 175,000 in 2011 (an increase of 94%).

<table>
<thead>
<tr>
<th></th>
<th>BZDs Alone</th>
<th>BZDs + Opioids</th>
<th>BZDs + Alcohol</th>
<th>BZDs + Opioids + Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>46,966</td>
<td>22,682</td>
<td>16,473</td>
<td>3,727</td>
</tr>
<tr>
<td>2011</td>
<td>89,310</td>
<td>50,561</td>
<td>27,452</td>
<td>8,229</td>
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</tbody>
</table>

ED Visits: Risk of Serious Outcomes

<table>
<thead>
<tr>
<th></th>
<th>12-34 yo</th>
<th>35-44 yo</th>
<th>45-64 yo</th>
<th>65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>BZD alone</td>
<td>28%</td>
<td>30%</td>
<td>37%</td>
<td>39%</td>
</tr>
<tr>
<td>BZD + opioids</td>
<td>37%</td>
<td>43%</td>
<td>47%</td>
<td>59%</td>
</tr>
<tr>
<td>BZD + alcohol</td>
<td>35%</td>
<td>43%</td>
<td>51%</td>
<td>55%</td>
</tr>
<tr>
<td>BZD + opioids + alcohol</td>
<td>39%</td>
<td>47%</td>
<td>57%</td>
<td>70%</td>
</tr>
</tbody>
</table>

SUMMARY:
1. Combining benzodiazepines with opioids or alcohol significantly increases the risks of a serious outcome.
2. The number of patients prescribed BZDs (as well as opioids) have been increasing.
3. Not all visits involving BZDs are the result of prescribing practices. Non-prescribed use or use of amounts beyond what is prescribed can be due to patient efforts to control symptoms or for “enjoyment,” including to enhance the high from opioids.
### Benzodiazepine Use by Age

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Use Rate</th>
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<tbody>
<tr>
<td>18-35</td>
<td>2.6%</td>
</tr>
<tr>
<td>36-50</td>
<td>5.4%</td>
</tr>
<tr>
<td>51-64</td>
<td>7.4%</td>
</tr>
<tr>
<td>65-89</td>
<td>8.7%</td>
</tr>
</tbody>
</table>

Female:Male ratio: 2:1

Lower % when managed by psychiatrists

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### Study of 300 Unintentional Drug Deaths in NM, 2006-2008

**INCREASE RISK OF DEATH**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>2.4</td>
</tr>
<tr>
<td>One or more sedatives</td>
<td>3.0</td>
</tr>
<tr>
<td>Increased age</td>
<td>1.3</td>
</tr>
<tr>
<td># of prescriptions</td>
<td>1.1 for each added Rx</td>
</tr>
</tbody>
</table>

**Female:Male ratio:** 2:1

Lower % when managed by psychiatrists

**Study of 300 Unintentional Drug Deaths in NM, 2006-2008**

In 2012, 478,000 with sedative SUD (> heroin or methamphetamine)

**Primary Benzodiazepine Abuse**

- Having at least one prescription for a sedative/hypnotic was a stronger risk factor than having an opioid prescription. Overlapping opioid or sedative/hypnotic prescriptions were strongly associated with risk.

- Risk factors for sedative SUD include:
  - Participation in SUD self-help groups
  - Younger age
  - Longer duration of BZD use
  - Higher dosages
  - Lower level of education
  - Non-native cultural origin
  - Outpatient treatment of SUD.

**Primary Benzodiazepine Abuse**

- Having another BH disorder increases risk: 50% have another psychiatric disorder.
- BZD abuse is a common secondary drug of abuse in individual with opioid or alcohol SUDs.
- 40-50% of those in methadone or buprenorphine treatment will test positive for BZDs.
- BZDs may enhance an opioid high, are used when withdrawing, can cause a high used alone, or may be used to “self-medicate” a comorbid psychiatric disorder, so the causes of misuse can be complicated.

**FDA Requires Black Box Warning for Benzodiazepines - 2016**

Concomitant benzodiazepine use with opioids may result in profound sedation, respiratory depression, coma, and death: reserve concomitant use for patients with inadequate alternative treatment options:

- Limit to minimum required dosage and duration; monitor patients for signs and symptoms of respiratory depression and sedation.
**CDC Guidelines for Opioid Use 2016**

- Give preference to nonpharmacologic therapy and nonopioid therapy for chronic pain.
- Establish realistic goals for treatment of pain and improvement of functioning.
- Opioid risks and benefits, provider and patient responsibilities should be discussed.
- Initial treatment should be with immediate-release opioids.
- Lowest effective doses should be used, extra care if prescribing > 50 MME/day, and avoiding using >90MME/day.
- For acute pain, use the lowest dose and shortest duration of opioids.
- For chronic pain, opioid usage should be regularly evaluated for effectiveness.
- Prescribing the combination of opioid pain medication and benzodiazepines should be avoided.
- Substance abuse treatment (including MATs) should be offered for patients with opioid use disorder.

**Summary**

- BZDs are useful treatment for a variety of illnesses, but may be over prescribed
- BZDs generally are considered safe when not combined with other sedatives, but there are worrisome side effects especially with long-term use and in the elderly
- BZDs misuse mostly a risk for patients with SUDs
- BZDs appear to significantly increase mortality when combined with opiates

**References**


SAMHSA, Center for Behavioral Health Statistics and Quality. (December 18, 2014) The DAWN Report: benzodiazepines in combination with opioid pain relievers or alcohol: greater risk of more serious ED visit outcomes. Rockville, MA.

**References**


