Benzodiazepines: Pharmacology to Co-Prescribing Risks and Concerns

Issues in Benzodiazepine Pharmacology

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Jointly Provided By

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There are no prerequisites for participation.

Method of Participation and How to Receive CME Credit.
There are no fees for participating in and receiving credit for this activity.

- Review the activity objectives, faculty information, and CME information prior to participating in the activity.
- View the CME presentations
- Complete the CME activity evaluation and post-test at the conclusion of the activity. A passing score of 75% must be achieved in order to receive a credit certificate.

Resources available under the Resources Tab (bottom right of screen).

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Disclaimer
This educational program is designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation.
Learning Objectives
At the conclusion of this session, attendees should be able to:
• Describe pharmacology of older and newer benzodiazepines
• Describe the side effects of benzodiazepines
• Discuss combinations of benzodiazepines and opioids

Target Audience
Physicians, physician assistants, advanced practice pharmacists, APRNs, residents, & fellows who prescribe controlled substances.

CME Accreditation
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Warren Alpert Medical School of Brown University and the Rhode Island Department of Health Academic Center. The Warren Alpert Medical School is accredited by the ACCME to provide continuing medical education for physicians.

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The Warren Alpert Medical School of Brown University designates this live activity for a maximum of 1.5 AMA PRA Category 1 Credits™.

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Faculty Disclosure/Conflict of Interest
The following Speakers and Planning Committee members have indicated that they have no relevant financial relationships to disclose:

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**Issues in Benzodiazepine Pharmacology: Basis for Use and Abuse/Misuse**

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**Key Issues of Benzodiazepine Use & Abuse**

- What are the pharmacological effects of benzodiazepines (BZ)?
- How do these make them prone to misuse or abuse?
- How do BZ compare in their actions to other treatments of anxiety and sleep disorders?
- What are the ramifications of BZ use in “at risk” disorders and their co-use with other agents such as opiates?

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**National Overdose Deaths**

**Number of Deaths from Prescription Drugs**

![Graph showing national overdose deaths from prescription drugs]

Source: National Center for Health Statistics, CDC Wonder
National Overdose Deaths
Number of Deaths from Heroin

Source: National Center for Health Statistics, CDC Wonder

Inhibitory GABA Synapse

VGAT: Vesicular GABA transporter
GAT: GABA transporter pumps GABA out of synaptic cleft and into glia and presynaptic terminals (helps in signal termination)
GABA-T: GABA-transaminase (aminotransferase) inactivates GABA (helps in signal termination)
GABA Receptors

**Ionotropic Receptor (GABA-A Receptor)**
These are chloride ion channels that open upon binding to GABA.

**Metabotropic Receptors (GABA-B Receptor)**
Bind to GABA & may modulate ion channels indirectly.
Coupled to G proteins and mediate slow & prolonged inhibition.

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Mechanism of Action

- **Benzodiazepines** are active on the benzodiazepine-GABA-CL receptor complex and increase GABAergic activity on the GABA-A receptor which exist as multi-subunit, ligand-gated chloride channels.
- This enhances the GABA-induced ionic currents through these channels and is therefore inhibitory.
  - G- channels open→ hyperpolarization (↑ -ve), ↓ excitable
- Activities can differ between agents to a small degree in effects in humans due to their differential effects on the multi-subunit GABA-A receptor (i.e. Z-drugs).

**Benzodiazepines (BZ) Initial Use**

- The initial discovery of the first benzodiazepine chlordiazepoxide in the early 60’s was revolutionary in that these agents had a much safer therapeutic profile as compared to the agents they replaced as anxiolytics and hypnotics such as the barbiturates and meprobamate.
- An explosion in the use of the agents was a cultural phenomena as there was a “honeymoon” panacea period of use, overuse, and misuse.
- Challenge still remains: balancing the promise of using these agents with the pitfalls of abuse and misuse.

**Discussion points:**
- What are the long deleterious effects of benzodiazepines compared to many commonly used pharmacotherapy options?
- How do they compare in terms of danger upon abuse to typically abused substances like alcohol and nicotine?

**Pharmacological Properties**

- All benzodiazepines (BZ) are associated with abuse, dependence, withdrawal, and tolerance. The withdrawal syndrome can appear similar to the severe exacerbation of the original anxiety/sleep disorder and is associated with an increased risk of tonic-clonic seizures as well-so we withdraw BZ gradually when we attempt to discontinue.
- Tolerance develops to the sedative, muscle relaxant, and anticonvulsant effects as well as to those on punished responding in animals.
- Persistence of the anti-anxiety effect is controversial.
- BZ work quickly, but do patients stay on them just due to the negative reinforcement effect?
  - Is it a persistent anti-anxiety effect, or is it avoidance of withdrawal?
  - So easy to start them, so hard to taper off!

**Interaction issues**

- There are potent drug-drug interactions with other CNS depressants such as opiates, alcohol, barbiturates, carisoprodol (& others) that can lead to both increased toxicity as well as for an increase in brain reward and abusability.
- We take advantage of cross tolerance between benzodiazepines and ethanol but when they are used in combination the effect can be lethal.
- Drug-disease interactions are also critical, such as the effect of these agents along or in combination on Obstructive Sleep Apnea (OSA).
- Combined effects can also prove initially deleterious to operating dangerous machinery or driving.
**Key Effects in Animal Models of Anxiety**

- Benzodiazepines increase punished responding.
- They increase locomotor, feeding, or drinking behavior that has been suppressed by novel or aversive stimuli.
- Similar to ethanol effects in the Geller Conflict Model.
- Generally, they increase punished responding at dosages less than that which impairs motor function.
- Differences between these drugs in animal models does not reliably predict differences in their activity in humans (i.e. sedation).


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**Benzodiazepine Clinical Uses**

- Anxiety Disorders
  - Used in GAD, Panic disorder- and sometimes in PTSD
- Insomnia
  - BZ are widely used and some indicated for insomnia
  - Are “Z-drugs” better than BZ and more specific as sedatives?
- Agitation
- Alcohol withdrawal (CIWA protocols)
- “Indirect” Skeletal Muscle Relaxers
- Seizure disorders: especially in status epileptic; there is rapid tolerance to their anti-seizure efficacy
- Akathisia and various movement disorders
- Conscious anesthesia, pre-op anxiety, nausea & vomiting, others.


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**Benzodiazepines & Sleep**

- Like many psychotropic medications, BZ’s affect sleep architecture and the literature is complex.
- BZ decrease sleep latency, especially when first used.
- There is a decrease in the number of awakenings and the time spent in stage 0–wakefulness- and stage 1 sleep.
- Prominent decrease in the time spent in slow-wave sleep (stages 3 and 4).
- Most BZ increase the time to and shorten the time spent in REM sleep, discontinuation can have the opposite effect.
- Zolpidem and zaleplon suppress REM sleep to a lesser extent than do benzodiazepines and thus may be superior to benzodiazepines for use as hypnotics.

Z-Drugs & Hypnotic Specificity

Selective hypnotic activity may be due to action of one subtype of GABA-A complex that includes the subunit involved in BDZ binding but is only expressed in arousal circuits.

- The GABA-A receptor is a pentamer that consists of at least one alpha, beta and gamma subunit (see schematic) of different varieties.
- So numerous different GABA-A receptors can be formed from the different alpha, beta and gamma subunits. (e.g. α1,α2,β3,γ1 γ2 or α2,α3, β2,β3,γ2 or α3,α4, β3,β3,γ1 etc.)
- It is proposed that Z-drugs specifically activates the GABA-A receptors expressed in the CNS circuits controlling arousal.


The GABA-A receptor is a pentameric complex formed from various combination of α, β and γ subunits. Multiple forms of α, β & γ subunits exist that might act in different neural systems.
BZ Specificity of Action?

<table>
<thead>
<tr>
<th>GABAa, α1/β2/δ Subtype and Relative Activity of Selected GABA Agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha Receptor Subtype</strong></td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Chlorzepate</td>
</tr>
<tr>
<td>Chloride</td>
</tr>
<tr>
<td>Diazepam</td>
</tr>
<tr>
<td>Flunitrazepam</td>
</tr>
<tr>
<td>Meprobamate</td>
</tr>
<tr>
<td>Oxazepam</td>
</tr>
<tr>
<td>Triazolam</td>
</tr>
</tbody>
</table>

Activity: ++ = high, + = moderate, 0 = none, – = low.

Benzodiazepines do not bind to α1 in α2-δ receptors and this in turn blocks the γ-aminobutyric acid (GABA) receptor.

Benzodiazepines are potent GABA agonists and are used to enhance the activity of GABA receptors.

Benzodiazepine Adverse Effects

- Especially upon initiation they can cause:
  - Sedation
  - Paradoxical release of anxiety and/or hostility
  - Psychomotor impairment
  - Memory disruption
  - Increased risks of accidents (initially greater)
  - Vertigo
  - Ataxia with falls (especially in the elderly)
  - Dystonia

Lader, M. H. (1999). Limitations on the use of benzodiazepines in anxiety and insomnia: are they justified? European Neuropsychopharmacology 9 (Suppl. 6), S399-S405.

BZ Use Associated with Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Risk of Alzheimer’s disease associated with benzodiazepine use (metabolites assessed five to 15 years before diagnosis in people with Alzheimer’s disease (cases) and controls</th>
<th>Benzodiazepine use ever use</th>
<th>5-Arylpyrazole 3-Arylpyrazole 5-Arylpyrazole3-Arylpyrazole (OR 95% CI)</th>
<th>Multivariable odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevented</td>
<td>1000 (20.5)</td>
<td>450 (85.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Prevalent</td>
<td>1000 (20.5)</td>
<td>500 (95.5)</td>
<td></td>
</tr>
<tr>
<td>Multivariable odds ratio</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Age 65</td>
<td>970 (19.4)</td>
<td>427 (85.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt; 95</td>
<td>970 (19.4)</td>
<td>427 (85.4)</td>
<td>1.00</td>
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<tr>
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<td>1.00 (1.00 to 1.00)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

Benzodiazepine metabolites

<table>
<thead>
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<th>Risk of Alzheimer’s disease associated with benzodiazepine use (metabolites assessed five to 15 years before diagnosis in people with Alzheimer’s disease (cases) and controls</th>
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<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Not age, sex, or other factors included.

**Indicated to high levels of benzodiazepines or treatments, especially in elderly patients on or near end-stage treatment with risk of malnutrition, comorbidity and treatment, or other cognitive decline, dementia or treatment, or other cognitive decline, dementia or treatment, comorbidity diagnosis.

Zolpidem & Suicide Association

Nationwide case control study

Case group comprising 2199 people who committed suicide between January 1, 2002, and December 31, 2011 compared to matched controls.

After adjustment for potential confounders and comorbidities zolpidem exposure significantly (P<.05) increased the risk of suicide with an OR =2.06 (95% CI 1.82-2.34) as compared to controls.

The risk increased significantly with the level of zolpidem use.

Subgroup analyses showed the exposure to zolpidem consistently increased OR for suicide in different groups of age, sex, urbanization level, occupation, mental disorders, CCI levels, and in groups of people with or without the presence of insomnia.


Benzodiazepines Pharmacokinetics

- Drug abusers prefer more lipophilic quick in compounds (i.e. diazepam, alprazolam).
- Shorter acting agents are more prone to abuse and dependence.
- Quick in and out BZ are often useful as hypnotics.
- Lorazepam, oxazepam, and alprazolam are not metabolized to active compounds and are short acting.
- Some other benzodiazepines (see table) used in anxiety are metabolized to active metabolites (principally N-desmethyldiazepam) with very long half-lives so these drugs are very long lasting.
- Long acting BZ can take weeks to reach steady state levels of the active metabolites and can take weeks to be eliminated.

**Table 3. Distribution of New Jersey Medicaid Enrollees & Person-Years by Benzodiazepine (BZD) Exposure, Number of Hip Fracture Cases, and Incidence Rates and Incidence Rate Ratios Comparing BZD Exposed to Unexposed Person-Time**

<table>
<thead>
<tr>
<th>BZD Exposure Category</th>
<th>No. of Enrollees* (n = 19,326)</th>
<th>No. of PY (n = 186,577)</th>
<th>No. of Hip Cases</th>
<th>Incidence Rate (PER 1000 PY)</th>
<th>Incidence Rate Ratio</th>
<th>95% CI</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any BZD</td>
<td>8,137</td>
<td>81,296</td>
<td>347</td>
<td>17.28</td>
<td>1.90 (1.86-1.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting BZD</td>
<td>12,434</td>
<td>9,101</td>
<td>29</td>
<td>12.82</td>
<td>1.03 (0.99-1.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting BZD</td>
<td>8,137</td>
<td>81,296</td>
<td>347</td>
<td>17.28</td>
<td>1.90 (1.86-1.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting high-potency BZD</td>
<td>7,200</td>
<td>7,200</td>
<td>168</td>
<td>15.85</td>
<td>1.00 (0.95-1.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting high-potency BZD</td>
<td>7,200</td>
<td>7,200</td>
<td>168</td>
<td>15.85</td>
<td>1.00 (0.95-1.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New BZD (115 mg)</td>
<td>15,144</td>
<td>15,144</td>
<td>23</td>
<td>16.27</td>
<td>1.04 (0.98-1.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New BZD (45 mg)</td>
<td>12,962</td>
<td>12,962</td>
<td>29</td>
<td>17.14</td>
<td>1.17 (1.12-1.23)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The total number of persons exposed to the number of enrollees because each person may contribute time to more than one time-varying predictor category. **Statistically significant (P<.05) association with included variables.

Benzodiazepines Points

- Metabolite duration of action can be the longest and most variable in the elderly.
- Zolpidem dose should be reduced by half in women.
- Long acting BZD can be given all at HS; this is especially useful in patient with GAD and insomnia.
- Dosing and monitoring: Serum levels not useful. Titrate until efficacy occurs or adverse effects (usually sedation) become intolerable.
- These agents tend to be studied for short term use as hypnotics with (often ignored) recommendations for not using them chronically.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak Level (hrs)</th>
<th>Half-Life (hrs)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>2-4</td>
<td>10 ± 3-4</td>
<td>Many long acting metabolites</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>1-2</td>
<td>2-6.3 produg 48-100+ minlab.</td>
<td>Produg of deoxymethylclonazepam long half life can be &gt;100 hours</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1-2</td>
<td>43 ± 13</td>
<td>Rapid oral absorption Biphasic deoxymethyl Diazepam metabolite erratic bioavailability from IM injection</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1-6</td>
<td>14 ± 5</td>
<td>Higher dosages in seizures &amp; panic. Better anticonvulsant &amp; hypnotic (SMR)</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>2-4</td>
<td>8 ± 2.4</td>
<td>No active metabolites</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>1-2</td>
<td>12 ± 2</td>
<td>Rapid oral absorption; wears off faster than half-life suggests. Dosed higher in panic disorder.</td>
</tr>
</tbody>
</table>

*Including half-lives of major active metabolites below initial agent.*
### Pharmacokinetic Properties of Select Benzodiazepines & Z-drug Hypnotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak Level (hrs)</th>
<th>Half-Life (hrs)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flurazepam</td>
<td>1-2</td>
<td>74 ± 24</td>
<td>To n-desalkyl-flurazepam, half-life.</td>
</tr>
<tr>
<td>Temazepam</td>
<td>2-3</td>
<td>11 ± 6</td>
<td>Slow oral absorption.</td>
</tr>
<tr>
<td>Triazolam</td>
<td>1</td>
<td>2.9 ± 1.0</td>
<td>Rapid onset, short duration of action.</td>
</tr>
<tr>
<td>Quazepam</td>
<td>2</td>
<td>8 ± 2.4</td>
<td>Prototype but non-selective metabolite.</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>&lt;1</td>
<td>1-2</td>
<td>Very short acting. Metabolized: aldehyde dehydrogenase.</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>1-3</td>
<td>1.5-3.5</td>
<td>Has the slow dose of 10-15mg for 1-2 hours. No active metabolites: dose form available for middle of the night use.</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>1</td>
<td>6</td>
<td>Minor active metabolites; studied for longer term use.</td>
</tr>
</tbody>
</table>


### A Plethora of Anxiety Disorder Treatment Options

- **SSRI**: GAD, Panic Disorder, Social Anxiety Disorder, PTSD, OCD
- **SNRI**: GAD, Panic Disorder, Social Anxiety Disorder
- **Buspirone / Geprone ER**: GAD
- **Tricyclic Antidepressants**: Panic Disorder
- **MAOI’s**: (Interaction problem, patch useful)
- **Pregabalin**: GAD (indication in Europe)
- **CBT and related treatments**
- **Benzodiazepines; GAD & Panic Disorder**
  - Advantage is quick acting

### SSRI Pharmacology

<table>
<thead>
<tr>
<th>SSRI</th>
<th></th>
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<tbody>
<tr>
<td>Fluoxetine (Prozac®)</td>
<td></td>
</tr>
<tr>
<td>Sertraline (Zoloft®)</td>
<td></td>
</tr>
<tr>
<td>Paroxetine (Paxil®)</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine (Luvox®)</td>
<td></td>
</tr>
<tr>
<td>Citalopram (Celexa®)</td>
<td></td>
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<tr>
<td>Escitalopram (Lexapro®)</td>
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</tbody>
</table>
SNRI Pharmacology

Venlafaxine (Effexor®)
Duloxetine (Cymbalta®)
Desvenlafaxine (Pristiq®)

Buspirone Pharmacology

Treatment Response Comparison

Need time for sufficient symptom control.

- **SSRIs/SNRIs/Buspirone**
  - Response may take several weeks in anxiety disorders and even up to twelve weeks for OCD.
  - Interactions can be an issue with SSRI/SNRI
  -QTc issues, delayed orgasm, & GI ulceration (combined with NSAID’s) can be a concern with some drugs in some cases but lower doses minimizes this.

Need to start with low dosages due to possible anxiogenesis with SSRIs/SNRIs !

**Benzodiazepines:**
For GAD/Panic D/O, BZ have been shown to work quicker than the SSRIs/SNRIs
Non–Pharmacologic Treatments

Cognitive Behavioral Therapy (CBT)
- Training individuals to detect internal and external anxiety cues, and to apply newly learned coping skills which target both psychic and somatic symptoms
  - Self monitoring
  - Relaxation
  - Cognitive therapy
  - Imagery rehearsal of coping skills
Also do not minimize the benefit of exercise!
Don’t forget sleep hygiene and CBT re: sleep issues.

Benzodiazepine Abuse & Dependence

- BZ are CIV drugs denoting a potential for abuse and dependence.
  - What is the mechanism for their abuse?
  - How do they potentiate the abuse and toxicity of other agents?
- When can we say there is abuse and dependence involved in our patients?
- Which patients should not receive BZ?
- Is there a BZ primer effect for alcoholics?
- BZ and issues with difficult patients.

Issues with Other Sedatives

Additional problems with co-use of other agents
- The “indirect” skeletal muscle relaxers
  - i.e. carisoprodal and mebrobamate
- Barbiturates - i.e. in Fioricet® and Fiorinal®
- Alcohol
- Opiates
- Other drugs of abuse
- Various
Reward Pathways: Role of Opioids


Alcohol & Reward


BZ, Alpha-1 GABA-A Receptors, & DA Release

**Behaviorism of Addiction**

Positive reinforcement

Reward (i.e. increase of DA in Nucleus Accumbens) increases the frequency of the behavior preceding it - drug taking.

Negative reinforcement

Taking away a withdrawal syndrome (aversive) increases/maintains drug seeking.

Quicker into the brain (more lipophilic) drug is a more immediate and powerful positive reinforcer and a quicker out one is a more immediate aversive and can increase the power of negative reinforcement from drug reuse.

**Reward & Benzodiazepines**

**Intracranial Self Stimulation (ICSS): “Threshold” model**

(Kornetsky & Associates)

- Procedure in which electrodes are implanted in medial forebrain bundle of rat and “reward threshold” is determined
- Drugs of abuse (i.e. morphine, barbiturates) will decrease the amount of current needed for animal to experience reward.
  - Note: Haloperidol INCREASES the current needed for reward while morphine DECREASES it.

*This model predicts which drugs are likely to be abused.*
Benodiazepines Lower Reward Threshold in the ICSS Model

Key Aspects of Dependence

Tolerance: The phenomenon of decreased effect with prolonged exposure to a drug
- Acute tolerance: soon after exposure to a drug
- Chronic tolerance: over repeated use of drug
- Reverse tolerance: need less of drug for effect

Withdrawal syndrome: The onset of a constellation of signs and symptoms typically the opposite of the drug’s effect.
- Can be due to abrupt discontinuation of drug or intake of an antagonist
- BZ withdrawal has a delayed onset with longer acting drugs but is more severe the shorter acting ones.

When is it Addiction?

ADDICTION is a chronic relapsing disorder.

COMPULSIVE drug seeking and drug taking behavior persists despite serious consequences in drug addicted individuals.

ADDICTIONS exist to other non-drug related behaviors with positive and negative reinforcement properties (i.e. gambling, sex, even video games!) and some commonalities in brain chemistry are involved.
DSM-IV-TR Criteria for Drug Dependence

1. Tolerance
2. Withdrawal
3. Larger amounts/longer period than intended
4. Inability to, or persistent desire to, cut down or control
5. A great deal of time spent obtaining, using, or recovering
6. Important activities given up or reduced
7. Use despite problems caused or exacerbated by use


DSM-5 Criteria Substance Abuse Disorders

The DSM-5 details various substance abuse disorder degrees of severity and criteria for specific drugs as:

“The term ‘dependence’ has been easily confused with the term ‘addiction’ when, in fact, the tolerance and withdrawal that previously defined dependence are actually very normal responses to prescribed medications that affect the central nervous system and do not necessarily indicate the presence of an addiction.”


“The Difficult Patient” & Prescribing

Difficult patients can present that can split providers and put us "on tilt".

Dependent Clingers
Entitled Demanders
Manipulative Help-Rejecters
Self-Destructive Deniers

Often we inherit patients who get started on BZ (or other controlled drugs) “out of desperation” and will not tolerate the withdrawal discomfort.

Personality Disorder Issues Can Complicate Treatment

Cluster B: Dramatic or erratic
- Antisocial
  - Disregard for and violation of the rights of others
- Borderline
  - Instability in interpersonal relationships, self image, and affects, and emotional impulsivity
- Histrionic
  - Excessive emotion and attention seeking
- Narcissistic
  - Grandiosity, need for admiration, and lack of empathy


“Dramatic Triangle” of Cluster B PD

Savior/Rescuer

Abuser

Victim

https://www.karpmandramatriangle.com/

Practice Notes
- Try not to use benzodiazepines in a patient with a history of drug abuse and dependence.
- Beware of the priming effects of BZ.
- Discuss the risks of abuse and dependence up front with your patients.
- Review interactions with current medications and lifestyle.
- Discuss alternative treatments for their condition.
  - Compare benefits as well as adverse effects and risks.
  - Caution high risks groups to their unique risks (i.e. the elderly).
Practice Notes

- Try to use BZ over the short term and at the lower dosages when possible. Make a contract with your patient if possible.
- Try to slowly taper the dosage down in patients receiving them chronically.
- Stress via your therapeutic alliance with the patient that you understand the reason they want these medications, but that you have concerns.
- Be balanced in your considerations as despite their short-comings, BZ are still quite safe and useful.

Select References


Baur, N., de la Torre, G., Hass, M. H. (1999). "Limitations on the use of benzodiazepines in anxiety and insomnia: are they justified?" European Neuropsychopharmacology, 9(Suppl. 6), S399-S405.

Select References continued

Begaud, B., et al. (2013). "Practice guidelines on the use of benzodiazepines in anxiety and insomnia: are they justified?" European Neuropsychopharmacology, 9 (Suppl. 6), S399-S405.


Mihic, M. H. (1999). "Limitations on the use of benzodiazepines in anxiety and insomnia: are they justified?" European Neuropsychopharmacology, 9 (Suppl. 6), S399-S405.
Benzodiazepine safety: concerns with co-prescribing and co-morbid conditions

May 12, 2016

Jessica Hawthorne, PharmD
PGY2 Psychiatric Pharmacy Resident
Providence VA Medical Center

Benzodiazepine use and overdose deaths are increasing!

[Graph showing increase in overdose deaths over years]

Petition for FDA black box warning on BZD + opioid co-prescribing

[Table showing petitioned labeling for opioids and benzodiazepines]

Petitioned labeling for all opioid class medications:

WARNING: CONCURRENT USE WITH BENZODIAZEPINES REDUCES THE MARGIN OF SAFETY FOR RESPIRATORY DEPRESSION AND CONTRIBUTES TO THE RISK OF FATAL OVERDOSE, PARTICULARLY IN THE SETTING OF MISUSE.

Petitioned labeling for all BZD class medications:

WARNING: CONCURRENT USE WITH OPIOIDS REDUCES THE MARGIN OF SAFETY FOR RESPIRATORY DEPRESSION AND CONTRIBUTES TO THE RISK OF FATAL OVERDOSE, PARTICULARLY IN THE SETTING OF MISUSE.

[Links to petition and news articles]

CDC Guideline for Prescribing Opioids for Chronic Pain, 2016

“Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible”

Recommendation category: A

Evidence type: 3

CNS depressant induced respiratory failure

- CNS depression most common cause of death in BZD overdose
- Respiratory muscle failure
  - Through direct suppression of medullary respiratory center; dose dependent
  - CO₂ retention, hypoventilation, atelectasis leading to hypoxemia
- Airway/parenchymal pulmonary pathology
  - Bronchospasm, pneumonitis/pneumonia, pulmonary edema

Benzodiazepine respiratory effects

- GABA-A receptors highly concentrated in medulla respiratory center
- Hypnotic doses of BZDs without effect on respiration in normal subjects in absence of other CNS depressant drugs
- Severe intoxication: require respiratory assistance when taken concomitantly with another CNS depressant
- Alprazolam relatively more toxic in overdose
  - Retrospective study using database of poisoning admissions to toxicology service found longer hospitalizations, more ICU admissions and mechanical ventilation
Benzodiazepine respiratory effects

- Pulmonary muscle relaxation
  - Inhibit voltage-gated calcium channels in tracheal smooth muscle cells
- Airway obstruction during sleep
  - Inhibit hypoglossal nerve and recurrent laryngeal nerve that control upper airway muscles

*May worsen hypoxia/hypoventilation in cardiopulmonary disorders, including: OSA, COPD, asthma, and CHF*


- Higher doses (pre-anesthetic) marginally depress alveolar ventilation, decrease hypoxic drive
  - Can result in respiratory acidosis
  - Exaggerated in COPD: alveolar hypoxia, CO2 narcosis
  - Apnea during anesthesia
  - Midazolam associated with ↑ V₉ and RR


Benzodiazepines and OSA

- Increased risk of OSA and worsened severity of pre-existing OSA
  - Decreased oropharyngeal muscle tone
  - Decreased ventilatory drive in response to CO2
  - Blunt arousal response to hypoxia and hypercapnia during sleep
  - Exaggerated impact of apneic episodes on alveolar hypoxia, pulmonary hypertension, and cardiac ventricular load
  - Should consider as a relative contraindication to BZD use

Benzodiazepines in COPD

- COPD associated with nocturnal wheezing and oxygen desaturation
- BZD use worsens hyperventilation and hypoxemia in COPD
- Decreased ventilatory drive in response to CO₂
- Reduction in respiratory muscle functional parameters including diaphragm endurance
- Risk factor for respiratory failure in COPD
- “Overlap syndrome” (+ OSA) exacerbates hypoxia and hypercapnea during sleep


Benzodiazepines in COPD

- Chen et al. retrospective nationwide matched case-control study in Taiwan
- Case group: 2,434 COPD patients with respiratory failure
- Control group: 2,434 COPD patients without respiratory failure
- Outcome: exposure to BZD and non-BZD BZRAs during 180 days preceding index date
- Results: use of BZRAs associated with increased risk of respiratory failure aOR 1.56 (95% CI 1.14-2.13)
- BZDs: aOR 1.58 (95% CI 1.14-2.20)
- Non-BZDs: aOR 0.85 (95% CI 0.51-1.44)
- >2X increase in risk in patients who received ≥2 BZRAs (aOR 2.33, 95% CI 1.61-3.34) and those using a combination of BZD + non-BZD (aOR 2.25, 95% CI 1.48-3.43)


Benzodiazepines in COPD

<table>
<thead>
<tr>
<th></th>
<th>Non-users [reference]</th>
<th>Users</th>
<th>Adjusted aOR [95% CI]</th>
<th>Adjusted aOR [95% CI]</th>
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<td></td>
<td></td>
</tr>
<tr>
<td>Number of BZRAs used</td>
<td>1 level of BZRAs</td>
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<td>5.00 (2.02-12.30)</td>
<td>1.30 (0.38-4.56)</td>
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<tr>
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<td>2 levels of BZRAs</td>
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<td>non-BZD only</td>
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<td>4.00 (1.20-14.06)</td>
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<tr>
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<td>BZD &amp; non-BZD</td>
<td>196</td>
<td>2.50 (1.48-4.24)</td>
<td>2.50 (1.48-4.24)</td>
</tr>
</tbody>
</table>

Figure 1: Benzodiazepines in COPD

Benzodiazepines in other special populations

- Increased risk of respiratory depression and overdose in:
  - Children
  - Elderly
  - Liver dysfunction
  - Alcoholics
Opioids respiratory effects

- Mu and delta opioid receptors in medulla linked to sedation and respiratory depression
- Effects lead to reduced glutamate activity
- Mu opioid inhibition of chemoreceptors → diminished sensitivity to \(O_2\) and \(CO_2\) changes
- Changes in tidal volume and respiratory frequency
- Non-tolerant individuals at greater risk

Benzodiazepines and opioids

- Animal and human data show synergistic effects on sedation and respiratory depression
- National Center for Health Statistics 2010 data on pharmaceutical OD deaths
  - After opioids, BZD most commonly involved: opioids 75.2% and BZD 29.4%
  - BZD class most commonly involved in an opioid-related death (30.1%)

Benzodiazepines and opioids

- A VHA case-cohort study of US veterans who received opioids 2004-2009 looked at the association between BZD prescribing patterns and risk of drug OD death
  - In the study population 12,069 veterans (27%) were prescribed BZDs during the study period
  - 49% of Veterans who died of opioid OD (n=1,185) were co-prescribed BZDs during the period in which they died
Benzodiazepines and opioids

- Period of current BZD receipt and former BZD receipt associated with increased risk of OD death
- Greater risk associated with higher BZD doses
- Lorazepam and temazepam associated with lower rates of OD death than other BZDs
- Study cannot determine direct causal link, may be a marker of risk

Background

- The VHA has an Opioid Safety Initiative (OSI) to promote safe prescribing of opioids
- Goals pertaining to BZD and opioid co-prescribing include:
  - Develop new models of mental health and primary care collaboration
  - Establish safe and effective tapering programs
  - Increase use of UDS and SPDMP databases
- OSI measures: Veterans on opioids are also on a BZD
  - Q3 2015: PVAMC: 15.6%; VISN: 13.8%; National: 11%
  - Q1 2016: PVAMC: 16.2%; VISN: 13%; National: 10.1%

This study was approved by the PVAMC institutional review board in October 2015. Data was collected from November 2015 to March 2016. Research authors have nothing to disclose concerning possible financial or personal relationship with commercial entities that may have direct or indirect interest in the research subject matter.

Objectives

- Identify whether patients co-prescribed BZDs and opioids have additional safety concerns for their concomitant use
- Determine whether providers at the PVAMC are taking additional safety measures when BZDs and opioids are co-prescribed compared to when opioids are prescribed alone
- Describe characteristics of patients co-prescribed BZDs and opioids and prescribing habits of providers

Study Design

- Retrospective cross sectional review of medical records
- Data collected includes patient characteristics, prescribing habits, and safety measures
Inclusion Criteria

- **BZD + opioid cohort**: Veterans with active prescriptions for both BZDs and opioids issued for >90 days
- **Opioid cohort**: Veterans with an active prescription for an opioid issued for >90 days

Exclusion Criteria

- Hospice/palliative care patients
- Opioids prescribed for cancer pain

Statistical analysis

- Categorical safety measures were tested using Chi-square for statistical significance, with critical alpha-level set at <0.05

Identified additional safety concerns include:

- Elderly
- OSA/BMI>35 without sleep study
- COPD/asthma
- AUD/SUD
- Concomitant skeletal muscle relaxants, Z drugs, and other CNS depressants

Appropriate safety measures

- Prescribers were more likely to document opioid indication in the BZD + opioid group (Chi-square 12.83, df=1, p<0.001)
- For all other safety measures, there were no significant differences between groups
Prescriber habits

- Results suggest a need to increase:
  - Prescriber communication (including communication between PC and MH)
  - Documentation of acknowledgement of co-prescribing and patient education

**Benzodiazepines prescribed**

- Alprazolam 28%
- Clonazepam 23%
- Lorazepam 20%
- Oxazepam 1%
- Oxetazolam 1%
- Temazepam 1%

**Opioids prescribed**

- Fentanyl 3%
- Hydrocodone 39%
- Hydromorphone 1%
- Methadone 4%
- Morphine 6%
- Oxycodone 39%
- Tramadol 8%

**Co-prescribing Information**

| Acknowledgement in pain control (%) | 0 |
| Prescriber communication (including communication between PC and MH) (%) | 0 |
| Documentation of acknowledgement of co-prescribing and patient education (%) | 0 |
| Prescriber communication documented (%) | 0 |

**Prescribing Habits**

<table>
<thead>
<tr>
<th>BZD + Opioid Group</th>
<th>Opioid Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>BZD prescribed (%)</td>
<td>43</td>
</tr>
<tr>
<td>Opioid prescribed (%)</td>
<td>43</td>
</tr>
<tr>
<td>Time between BZD and Opioid (%)</td>
<td>22</td>
</tr>
<tr>
<td>Time between Opioid and BZD (%)</td>
<td>28</td>
</tr>
</tbody>
</table>

**PTSD and Anxiety Diagnosis**

- More patients with PTSD and anxiety in BZD + Opioid group
- Are these patients prescribed first line treatments?
- PTSD diagnosis not on SSRI/SNRI:
  - BZD + opioid group: 18/30 (60%)
  - Opioid group: 4/8 (50%)
- Anxiety diagnosis not on any antidepressant:
  - BZD + opioid group: 21/30 (42%)
  - Opioid group: 6/11 (55%)
Next steps

- Educate providers and patients to increase awareness of co-prescribing safety risk and to promote safe prescribing
- Addition of FDA black box warning on all opioids and BZDs would increase prescriber and patient awareness of safety risk
- Increase provider adherence to opioid safety measures recommended in the OSI, especially for patients in this high risk group (UDS, SPDMP, pain consent, naloxone kits)
- Encourage communication between primary care and mental health for patients co-prescribed opioids and BZDs and before co-prescribing is considered

Next steps

- Encourage use of first line treatments for conditions such as PTSD, anxiety disorders, and insomnia for patients on opioids before consideration for BZDs
- Develop safe and effective tapering programs for patients co-prescribed with significant safety concerns or lack of therapeutic benefit
- In patients who are not candidates for tapering programs, examine and address comorbid conditions (i.e., OSA) and concomitant medications (i.e., Z drugs) to reduce risk of respiratory depression and overdose

STOP BANG: screening for OSA

Screening for Obstructive Sleep Apnea

Ask your patient to answer the following questions to determine if he or she is at risk for obstructive sleep apnea:

1. Snore - Have you been told that you snore? (Yes) (No)
2. Tired - Are you often tired during the day? (Yes) (No)
3. Obstructed - Do you have trouble breathing, or does anyone notice you stop breathing during your sleep? (Yes) (No)
4. Gasping - Do you have high blood pressure or are you overweight to control high blood pressure? (Yes) (No)

If the patient answers yes to two or more questions on the STOP portion, he or she is at risk for obstructive sleep apnea. To find out if the patient is at risk for severe risk of obstructive sleep apnea, he or she should complete the BANG questions below.

B - BMI - Is your body mass index greater than 25? (Yes) (No)
A - Age - Are you 50 years old or older? (Yes) (No)
N - Neck - Are you a male with a neck circumference greater than 17 inches or a female with a neck circumference greater than 16 inches? (Yes) (No)
G - Gender - Are you a male? (Yes) (No)

Score 3-4: Most likely to have OSA
Score 5-10: Likely to have OSA
Score 11 or more: Possible existence of OSA

New VA order checks

Upon entry of an opioid or benzodiazepine order, the order check will display if any of the following conditions are met:
- A beta is ordered for a patient receiving an opioid
- An opioid is ordered for a patient receiving a benzodiazepine
* FTA at least one of the following:
  - Age > 65
  - Sleep Apnea ds. w/ 1 year
  - Admission above ds. w/ 1 year
  - High Risk for Suicide
  - Audit C > 7
  - Suicide risk ds. w/ 1 year

Providers can Accept or Cancel the order.

Example: Lorazepam ordered for patient on an opioid

Benzodiazepine taper considerations

- Tapering reduces risk of relapse or rebound of treated condition and reduces withdrawal symptoms
  - Sweating, tachycardia, muscle cramps, tremor, insomnia, anxiety, agitation, N/V, hallucinations, seizures
- Risk factors for withdrawal include: long term use, high dose, short half-life BZD (triazolam, alprazolam)
- Anticipate and treat rebound anxiety and insomnia with alternative non-pharmacologic/pharmacologic treatments
- Therapeutic alliance, patient education, and patient inclusion in treatment plan is critical during this process

CIWA-Br

Patient report

Clinical observations

Scores:
- 20 Items, Scored 0-4
  - 1-20: mild
  - 21-40: moderate
  - 41-60: severe
  - 61-80: very severe


Benzodiazepine taper strategies

- Tapering schedules vary widely; unknown which method is best
- Taper with scheduled, not PRN dosing
- Inpatient taper may be needed with: SUD history, history of BZD overdose, seizure disorder, unstable psychiatric disorder, high BZD doses, etc.
- Individualize tapers based on patient factors and initial response
  - Direct taper example
    - Reduce original dose by 25% every 1-2 weeks until on 50% of dose, then by 10% per week
  - Switch to long-acting for taper
    - Consider if patient intolerant of direct taper and for patients on short half-acting BZ
  - Consider stabilizing on 50% dose for weeks-months before continuing taper
  - Last 25% of taper is hardest
  - May not be able to taper off entirely (harm reduction)

Select references


Select references

Obtain Credits/Certificate

Please complete the Post-Test and Survey upon conclusion. A passing score of 75% is required for credit.

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