Treatments for Anxiety and Sleep Disorders: One Mechanism Does Not Fit All

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Conflicts of Interest

• I have no financial conflicts of interest related to this presentation
• Trade names will be indicated for many of the medications that are described as a means of clarification, not as advertisement
• As a Professor of Pharmacology at the University of Vermont, this presentation is based on my research and ideas and does not necessarily represent the position of the University of Vermont

Anxiolytic Pharmacology Objectives

• Define and characterize the major anxiety disorders
• Consider the patient needs for acute treatment vs. prevention
• Describe the mechanism of action, uses, beneficial and adverse effects, and pharmacokinetics of benzodiazepines and other GABA receptor modulators
• Discuss the adverse effects and drug interactions of GABA receptor modulators
• Describe agents that are useful for prevention of anxiety and describe their molecular targets and clinical use
• Compare and contrast the use of benzodiazepines vs. non-GABA agents in specific patient situations
Pathologies of Anxiety

Generalized anxiety disorder (GAD): People suffering from GAD have general symptoms of motor tension, autonomic hyperactivity, etc. for at least one month.

Phobic anxiety:
- Simple phobias. Agoraphobia, fear of animals, etc.
- Social phobias.

Panic disorders: Characterized by acute attacks of fear as compared to the chronic presentation of GAD.

Obsessive-compulsive behaviors: These patients show repetitive ideas (obsessions) and behaviors (compulsions).

Assess Potential for Medication-Induced Anxiety

- Stimulants
  - Amphetamines, cocaine, caffeine, nicotine
- Nasal Decongestants/Asthma Treatments
  - Ephedrine, epinephrine, pseudoephedrine, phenylpropanolamine
- Dopaminergics
  - Bromocriptine, L-Dopa, carbid/levodopa
  - Buproprion
- Drug Withdrawal
  - Anxiety is a symptom of withdrawal from benzodiazepines, opioids, barbiturates, other sedatives
  - Alcohol withdrawal produces profound anxiety
Definitions

- Anxiolytic drug: reduces anxiety
- Sedative drug: tranquillizes
- Hypnotic drug: facilitates sleep

- Significant overlap among these three categories
- Differences often a matter of context and dose

GABAergic Anxiolytics: Acute Treatment

Benzodiazepines

- Treatment needs to be fast
- Treatment is short-term
  - Treatment while waiting for longer-term preventatives to become fully active
- As an adjunct to preventative treatment when needed
Increasing GABA\(_A\)-Receptor Chloride Channel Provides Rapid Anxiolytic Activity

- Most anxiolytics modulate the GABA\(_A\) receptor by binding allosteric sites
- Benzodiazepines increase frequency of opening
- Barbiturates increase open time—stronger effect
- Increase Cl\(^-\) entry, causing hyperpolarization

Barbiturates

- Use in treatment of anxiety and insomnia largely historical
- Narrow therapeutic index, high abuse potential relative to benzodiazepines
- Used in anesthesia induction
  - PHENOBARBITAL still used for epilepsy
  - Low dose reduces toxicity and tolerance
  - Actions via GABA\(_A\) receptor: can have activity even in the absence of GABA

Benzodiazepines

- First developed in the 1960s by Hoffman-LaRoche chloralose (Librium™), DIAZEPAM (Valium™)
- They became the most prescribed medications for multiple purposes due to their high effectiveness and lower toxicity profile compared with barbiturates
- They remain commonly prescribed agents, however concerns about tolerance, dependence and abuse have led to caution in their long-term use
- The best option for fastest relief of panic attack

1954 Advertisement
Important Benzodiazepines

- **DIAZEPAM** (Valium™, prototypic agent)
- **CLONAZEPAM** (Klonopin™ commonly used)
- **ALPRAZOLAM** (Xanax™ commonly used)
- **LORAZEPAM** (Ativan™ commonly used)
- **TEMAZEPAM** (Restoril™ for sleep induction)

Benzodiazepine Therapeutic Uses

- Treatment of anxiety across contexts
  - Especially effective at acute treatment of panic attack or phobia
- Treatment of insomnia across contexts
  - Only short-term due to tolerance
- Management of agitation
- Management of alcohol withdrawal
- Sedation for a variety of procedures and anesthetic induction
- Treatment of status epilepticus and some epilepsy
- Treatment of post-injury muscle tension

Benzodiazepine Adverse Effects

- Sedation (unless desired!)
- Ataxia / falls (major consideration in elderly)
- Impaired motor performance (driving, etc.)
- Impaired cognition / confusion (not a good choice for test anxiety)
- Anterograde amnesia (particularly short half-life compounds)
- Disinhibition of impulses
  - Relatively safe in overdose
Benzodiazepines are safer than barbiturates

- However, they readily contribute to CNS depression and combination can result in death
  - i.e. mixing with alcohol or other CNS depressants

Toxicity/Overdose with Benzodiazepines

- Benzodiazepine overdose is treated with FLUMAZENIL
  - benzodiazepine receptor antagonist
  - short half-life
  - respiratory function should be adequately supported and carefully monitored

- Flumazenil is not effective against barbiturate overdose.

Benzodiazepine Controversies

- Tolerance: more for sedation than anxiolytic effect
  - Hypnotic use can lead to rebound insomnia and retrograde amnesia
- Withdrawal: more likely and more severe with longer use, higher dose, shorter elimination half-life, rapid discontinuation
  - Abuse & dependence: self-treatment or "recreational" use most likely among those who abuse other substances
  - Overall, benzodiazepines are relatively safe drugs, though caution always in order
  - Short-term use preferred, though not always feasible
Benzodiazepine Kinetics:
Most important factors distinguishing compounds

- Rate of absorption
- Duration of action
- Rate of elimination
- Biotransformation pathway
  - First two highly related to lipophilicity
  - $T_{1/2}$ determines accumulation and whether steady-state is reached
- Some compounds are metabolized by CYP oxidation and others are directly glucuronidated. Those with long half-life induce CYP enzymes more strongly.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rapidity of onset</th>
<th>Elimination half-life</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>fast</td>
<td>~2 days</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>slow</td>
<td>~1-2 days</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>intermed.</td>
<td>~12 hrs</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>intermed.</td>
<td>~10 hrs</td>
<td>Glucuronid.</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Fast</td>
<td>~5 hrs</td>
<td>Glucuronid.</td>
</tr>
</tbody>
</table>

Note: If CYP induction/inhibition is of great concern due to drug interaction, lorazepam is the drug of choice. For short-acting (sleep induction), temazepam is the drug of choice.

Drug-Drug Interactions with benzodiazepines

- Additive effects with other CNS depressants
- Reduce the effect of some antiepileptic drugs.
  - Due to both tolerance and enzyme induction
- Combination of anxiolytic drugs should be avoided.
- Concurrent use with antihistaminic and anticholinergic drugs as well as the consumption of alcohol should be avoided.
- SSRI's, statins, and oral contraceptives may decrease metabolism of benzodiazepines by inhibiting CYP enzymes.
Case Workshop: Acute Anxiety

Non-GABA Anxiolytics: Prevention
Antidepressants

• All major classes of antidepressants have anxiolytic activity
• The effect is not acute, thus they are used for prevention or maintenance
• SSRIs, SNRIs (serotonin/norepinephrine reuptake inhibitors) used for obsessive compulsive disorder and post-traumatic stress
• TCAs (tricyclic antidepressants) and MAOIs (monoamine oxidase inhibitors) useful in prevention of panic attack

Antidepressant Mechanisms: Re-uptake inhibitors

• Raise levels of serotonin (5-HT) or norepinephrine (NE)
• SSRI: Inhibit reuptake by the serotonin transporter (SERT)
  • CITALOPRAM (Celexa™)
• SNRI and TCA inhibit both 5-HT and NE reuptake
  • VENLAFAXINE (Effexor™) SNRI
  • AMITRIPTYLINE (Elavil™) TCA
Antidepressant Mechanisms: Receptor antagonists

- **MIRTAZEPINE** (Remeron™): indirectly increases release of 5-HT by blocking α2 receptors
- **TRAZODONE**: Blocks 5-HT2 receptors

<table>
<thead>
<tr>
<th>Antidepressants: Adverse Effects</th>
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<tr>
<td><strong>Table 1. Mechanisms of therapeutic and adverse effects</strong></td>
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<table>
<thead>
<tr>
<th>Class or drug</th>
<th>↑5HT</th>
<th>↑NE</th>
<th>anti-α</th>
<th>anti-M</th>
<th>anti-H</th>
<th>Others</th>
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<tbody>
<tr>
<td>Tricyclics</td>
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<td>●</td>
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<td>MAOIs</td>
<td>●</td>
<td>●</td>
<td>○</td>
<td>●</td>
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<td>●</td>
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<tr>
<td>SSRI</td>
<td>●</td>
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<td>●</td>
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<tr>
<td>SNRIs</td>
<td>●</td>
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<tr>
<td>Bupropion</td>
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<tr>
<td>Mirtazapine</td>
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- SSRI are the safest, but not always the most effective; some SSRI agents are inhibitors of CYP450 enzymes leading to potential drug interactions
- Bupropion (Wellbutrin™) has anti-depressant activity but may provoke anxiety
- Mirtazapine is more sedating due to anti-histamine effects

Serotonin Syndrome

- Symptoms
  - CNS excitation
  - Mental state: anxiety/agitation
  - Autonomic excitation: hypertension, hyperthermia
  - Differential diagnosis: hyperreflexia
- Treatment:
  - Benzodiazepine sedation
  - Serotonin antagonist (5-HT2 blocker TRAZODONE)
- Rarely seen with a single SSRI, most often from either overdose or drug combinations (i.e. MAOIs+SSRIs)
- Differentiated from other diagnoses through hyperreflexia and clonus
Non-GABA Anxiolytics

**BUSPIRONE (Buspar™)**

- Non-sedating anxiolytic, unrelated to any of the others described in this session
- Effective only with chronic use (not effective for acute panic attack)
- Partial agonist at pre- and post-synaptic 5-HT<sub>1A</sub> receptors
  - Some antagonist activity at D<sub>2</sub> receptors
  - Shows some antidepressant and antipsychotic activities

**Pharmacokinetics and Adverse Effects of BUSPIRONE**

- Rapidly absorbed orally
- Undergoes extensive hepatic metabolism (hydroxylation and dealkylation) to form several active metabolites (e.g., 1-(2-pyrimidyl)piperazine, 1-PP)
- Well tolerated by elderly, but may have slow clearance
- Adverse effects: Dizziness, headache, GI upset sometimes seen
- Combination with MAOIs may result in tachycardia, hypertension
- Lacks abuse potential

Non-GABA Anxiolytics

**PROPRANOLOL**

- β-Adrenoceptor antagonist
- Decreases sympathetic overactivity
- Decreases heart rate and blood pressure
- Used for performance anxiety

- The α<sub>2</sub>-adrenergic receptor agonist clonidine is another option
Summary of Anxiolytic Pharmacology

1. Generalized Anxiety Disorder
   - SSRI (Citalopram), SNRI (Venlafaxine), BUSPIRONE, Benzodiazepine
2. Phobic Anxiety
   - Benzodiazepines (acute)
   - TCA and MAOI (prevention)
3. Panic Disorders
   - Benzodiazepines (acute)
   - TCA and MAOI (prevention)
4. Obsessive-Compulsive Behavior
   - SSRIs
5. Posttraumatic Stress Disorder (?)
   - SSRIs, BUSPIRONE
6. Performance Anxiety
   - PROPRANOLOL
7. Sedation
   - Benzodiazepines, PHENOBARBITAL

Case Workshop: Anxiety Prevention

Sleep Disorder Pharmacology Objectives

- Outline the treatment of insomnia using non-pharmacologic approaches and the limits of pharmacology
- Compare and contrast the use of short-acting benzodiazepines vs. non-benzodiazepine GABA agonists for treatment of acute insomnia
- Discuss endocrine-related treatments for insomnia through melatonin and orexin receptors
• The American College of Physicians (ACP) recommends cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder
• Medications are useful for short-term relief, but have poor long-term efficacy in the treatment of insomnia

Treatment with long-term benefits
• Treat or reduce aggravating factors
  • Medical problems (gastritis, reflux, arthritis)
  • Medications (stimulants, some SSRIs)
  • Exposure to toxins (alcohol)
• Cognitive Behavioral Therapy
  • Sleep Hygiene
  • Relaxation
  • Stimulus Control
  • Sleep Restriction

Insomnia and the Sleep Cycle
• Sleep onset insomnia
• Sleep maintenance insomnia
• Awakening in the middle of the night
Hypnotics: Problem with hangover sedation and tolerance

- Benzodiazepines/Barbiturates both reduce REM sleep and NREM sleep
- Rebound insomnia and nightmares can occur
- Tolerance occurs within 1-2 wks

Benzodiazepines for Sleep: Short-acting

TEMAZEPAM

- Metabolite of Diazepam (Valium™)
- Similar speed of onset (10 min), but much faster elimination
- Used to decrease sleep latency
- SHORT-TERM USE, not a treatment for chronic insomnia

Non-benzodiazepine Hypnotics acting on the benzodiazepine receptor

- ZOLPIDEM (Ambien™), ESZOPLICONE (Lunesta™), ZALEPLON (Sonata™)
- Agonists that bind similar to benzodiazepines, but to only a subset of GABA<sub>A</sub> receptors (alpha-1 sub receptor) that are associated with sleep
- Produce pure sedation
  - Little, if any, muscle-relaxant and anticonvulsant properties of benzodiazepines
  - Too potent to be an anxiolytic
ZOLPIDEM/ESZOLPICONE: Adverse Effects

- Safety: High therapeutic index unless combined with other CNS depressants
- Can cause daytime drowsiness
- Concerns about complex sleep behaviors, including sleep-walking and driving
- Can exaggerate the deleterious hypoxic effects of obstructive sleep apnea
- Abuse potential similar to benzodiazepines

ZOLPIDEM/ESZOLPICONE Pharmacokinetics

- Both are readily absorbed orally
- Short elimination half-lives: best for sleep onset insomnia, fewer carryover effects
  - Sublingual form for waking during the night (faster onset than oral)
  - Controlled release form of zolpidem available for maintenance (longer half-life)
- Although they act at the same site as the benzodiazepines, their chemical structure is very different
- Both metabolized by CYP450 oxidation, thus may have interactions with drugs that use/affect these enzymes.

Endocrine-related Treatments for Insomnia: Correct problems with circadian rhythm

- Ramelteon (Roserem™)
  - Melatonin Receptor Agonist (MT1, MT2 receptors)
  - Short acting (2 hr half-life)
- Suvorexant (Belsomra™)
  - Orexin receptor antagonist
  - Longer acting (10 hr half-life)
Other Drugs with Hypnotic Activity

- Barbiturates: No longer recommended (low therapeutic index)
- Antihistamine hypnotic: DIPHENHYDRAMINE
- Found in over-the-counter sleep aids (ZzzQuil, Tylenol PM)
- Drowsiness side effect (anti-muscarinic?)
- Limited by rapid tolerance, day-time drowsiness, not consistently effective
- Hypnotic Antidepressants: DOXEPIN (TCA), TRAZODONE (5-HT₂ antagonist), MIRTAZAPINE (SNRI with anti-histamine effects)
- Doxepin is the only antidepressant FDA-approved for insomnia
- Antipsychotics: QUETIAPINE (Seroquel™)

Steps in a Pragmatic Approach to the Treatment of Insomnia Disorder

- Step 1: Evaluation
  - Evaluate sleep and daytime symptoms and comorbid conditions.
  - Optimize treatment of comorbid conditions.

- Step 2: Initial Treatment
  - Acute insomnia diagnostic: consider short-acting hypnotic (e.g., temazepam or zolpidem 3-4 nights weekly for 3-5 weeks), then taper and discontinue.
  - Chronic insomnia disorder diagnostic: implement cognitive behavioral interventions.

- Step 3: Evaluate Response and Treatment
  - Evaluate sleep and daytime symptom response.
  - Continued symptoms with cognitive behavioral intervention: consider combined treatment using a drug appropriate for sleep onset or sleep maintenance symptoms.
  - Continued symptoms with pharmacotherapy: consider switching class of hypnotic (e.g., benzoazepine or benzoazepine receptor agonist to doxepin, temazepam, or suvorexant).

- Step 4: Evaluate Response and, if Symptoms Continue, Reevaluate Diagnosis
  - Reevaluate and treat comorbid disorders.
  - Evaluate other contributing factors (e.g., life events, new medical or psychiatric disorder) and address with psychosocial, behavioral, or medical treatment.

- Step 5: Treatment-Resistant Insomnia Disorder Diagnostic
  - Refer to sleep specialist for evaluation of other sleep-wake disorders, including sleep apnea.

- Step 6: Monitor
  - Monitor for long-term treatment response and sequelae such as depressive or anxiety disorder, substance use disorder, or neurodegenerative disorder.

Summary of Pharmacologic Treatment for Insomnia

- Sleep onset insomnia
  - Short-acting medication
    - [e.g., zolpidem]
  - Short-acting benzodiazepine (i.e., temazepam)
  - Melatonin-receptor agonist [rolimelatonin]

- Sleep maintenance insomnia
  - Longer-acting medication
    - Non-benzodiazepine [zolpidem extended release, eszopiclone]
  - Orexin receptor antagonist (levrospine)
  - Risk for hangover sedation

- Awakening in the middle of the night
  - Sublingual tablet form of zolpidem
  - Needs to be at least four hours of time in bed remaining
Case Workshop: Insomnia