Sedative Hypnotics and Their Use and Misuse

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January 24, 2015

Prevalance of Abuse

2.9 Million Initiates of I illicit Drugs
NIH 2011 - 2014

• 12th graders – 68.2% alcohol
  38.1% cigarettes
  17.2% smokeless tobacco
  50.4% illicit drugs
  4.5% cocaine
  7.6% hallucinogens
  7.7% tranquilizers
  11.1% opioids

Barbiturates

• Synthesized originally in 1864 by von Bayer
• 1903 Barbital was synthesized (Veronal)
• 1912 Phenobarbital was synthesized
• These were the drug of choice during days leading up to the development of Benzodiazepines
• Benzodiazepines were developed in the 1950’s
• 1954 Dr. Leo Sternbach found chlordiazepoxide
Barbiturates

Types of Barbiturates

- Ultrashort: Generic methohexital, Therapy General anesthesia
- Short acting: Generic thiopental, Therapy Sedation
- Generic pentobarbital, Therapy Seizures
- Generic secobarbital, Therapy Hypnotic
- Generic amobarbital
Types of Barbiturates

• Intermediate
  butabarbital        Hypnotic,
  butalbital                seizures, HA's

Long Acting
  phenobarbital        Sedation, and
  mephobarbital        seizures

Barbiturates

• Are highly lipid soluble
• Are excreted through hepatic metabolism and then renal excretion
• Favored through alkalinization of the urine
• Half-lives are increased in pregnancy and in patients with chronic liver disease
• Depresses respiratory drive
• Hepatic metabolism is responsible for tolerance by induction
Benzodiazepines

• Next in 1963 diazepam was developed (Valium)
• Thereby leading to the Age of Anxiety – 20th Century
• These were used for many uses – sedative, hypnotic, anxiolytic, amnesic.

How Do They work?

• Both the benzodiazepines, barbiturates and the new non-benzodiazepines are modulated at the GABAa receptor.
• GABAa is a ligand-gated Cl- channel
• When stimulated it gives a fast inhibitory post-synaptic potential- therefore is allosterically activated by benzodiazepines; it reduces the probability of generation of an active potential
GABA beta

- This is a G protein coupled receptor that acts as a dimer- Increases permeability to K+ and decreases Ca++ conductance
- For barbiturates there is a positive modification of GABAa via allosteric mechanism that increases its effect; in other words, it is a direct GABAa agonist and prolongs the opening of the Cl- channel, esp. at B2 and B3 subunits
GABAa Receptor

[Diagram of GABAa Receptor with labels for benzodiazepine (BDZ) binding site, gamma subunit, and chloride (Cl^-)]

GABAa Receptor

[Diagram showing GABAa receptor with GABA binding sites and chloride ions]
How Benzos Work

Non-benzodiazepines

- Zolpidem (Ambien)
- Zalepom (Sonata)
- Zopidone (Lunesta)
- These may act through overlapping binding sites at alpha and beta subunits
- These drugs inhibit flumitrazepam
Benzodiazepines

• Rx. peaked in 1975 – 10% of all prescriptions
• They are prescribed mainly for anxiety and insomnia now
• They are relatively safe with rare OD’s
• Are addicting
• Are taken with other drugs

Clinical Uses of Benzodiazepines

• Anxiety disorders
  – Acute anxiety
  – Generalized anxiety disorder
  – Panic disorder
  – Phobias (social, simple)
  – PTSD
  – Obsessive-compulsive Disorder
Clinical Uses of Benzodiazepines

- Insomnia
- Anxiety associated with medical illness
  - Cardiovascular
  - Gastrointestinal
  - Somatoform disorder

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Clinical Uses of Benzodiazepines

- Convulsive Disorders
- Acute status epilepticus
- Neonatal seizure disorders
- Preeclampsia
- Tetanus
- Adjunct to other anticonvulsants
- Amnestic (before surgery or procedure)
Clinical Uses of Benzodiazepines

• Spastic disorders and other types of acute muscle spasm – cerebral palsy, multiple sclerosis, paraplegia secondary to spinal trauma
• Involuntary movement disorders – restless leg syndrome, akathisia associated with neuroleptic use, choreiform disorders and myoclonus

Clinical Uses of Benzodiazepines

• Detoxification from alcohol and other substances
• Agitation or anxiety associated with other psychiatric conditions – acute mania, psychosis, anxiety with depression, impulse control disorder, catatonia or mutism
• Other adjunctive uses- surgery, dentistry, diagnostic procedures, cardioversion, chemotherapy
Toxicity and Side Effects

• With the introduction of chlordiazepoxide (Librium) in 1960, these agents replaced barbiturates as sedative-hypnotics.
• They cause significantly less respiratory depression and are rarely lethal by themselves in an overdose.

Toxicity and Side Effects

• Drowsiness, lethargy
• Ataxia, muscle incoordination
• Seizures, if abruptly discontinued
• Hypotonia, dysarthria, dizziness, and even hyperactivity
Characteristics of Benzodiazepines

• High Potency
  – Alprazolam (Xanax)
  – Lorazepam (Ativan)
  – Trizolam (Halcion)

• Drugs with a long half life
  – Clonazepam (Klonopin)
  – Chloradiazepoxide (Librium)
  – Chorazepate (Tranxene)
  – Diazepam (Valium)
  – Flurazepam (Dalmane)
Characteristics of benzodiazepines

- Drugs with a short half-life
  - Oxazepam (Serax)
  - Temazepam (Restoril)

Mechanisms of Abuse

- Hedonic uses
- Tolerance
- Withdrawal syndrome
- Benzodiazepines with rapid onset have the greatest risk for this type of abuse
- Tolerance causes patients to escalate the dose
- Withdrawal syndrome appears on decreasing dosage or discontinuation
Mechanisms of Abuse

- Tolerance develops as decreased responsiveness to GABAa receptors to Benzos
- Some evidence too that mRNA involved with the synthesis of alpha1 part of the GABAa site are reduced during long exposure to Benzos
- Glutamatergic system may also play a role in the withdrawal syndrome

Abuse Liability

- Benzodiazepines occupy a intermediate position of abuse liability
- Barbiturates and methaqualone had a greater risk of liability
Toxicity

- When used alone – low risk
- However when used with other types of medications, they act synergistically with other CNS depressants, sedating antidepressants, neuroleptics, anticonvulsants, antihistamines and alcohol, with and without opiates

Toxicity and Drug Interactions

- Psychomotor retardation – drowsiness, poor concentration, ataxia, dysarthria, motor incoordination, muscle weakness, vertigo and mental confusion.
- Memory impairment – Benzos induce anterograde amnesia. This appears separate from sedation as an effect.
Toxicity and Drug Interactions

- Paradoxical Disinhibition – Increased excitement, irritability, aggression, hostility, and impulsivity may occur.
- This paradoxical disinhibition may in rare cases result in attacks of rage or violence or other antisocial behaviors. They are more common in children and the elderly.

- Depression and emotional blunting – there is an association between Benzos use and depressive symptoms, and in some cases the emergence of suicidal ideation.
- Dependence – may appear as early withdrawal or protracted withdrawal in patients.
Abuse of benzodiazepines

- Approximately 80% is polydrug abuse
- Rarely alone
- Usually with opioids
- 3-41% abuse with ethanol

Abuse of Benzodiazepines

- Increased risk of abuse
  - High potency
  - Short duration of action
  - High purity
  - Water solubility
  - High volatility
Benzodiazepine Overdose

- Dizziness
- Confusion
- Drowsiness
- Blurred vision
- Unresponsiveness
- Anxiety
- Agitation

Trends in Drug Use
Physical Exam Findings

• Nystagmus
• Hallucinations
• Sturred speech
• Ataxia
• Coma
• Hypotonia
• Weakness
• Amnesia
• Paradoxical excitation
• Respiratory depression
• Hypotension

Diagnosis

• Immunoassay screening
• Get ABG’s, CXR, Pregnancy test
• Serum electrolytes
• Glucose
• Bun
• O2
• Ethanol level
• Acetaminophen level
Pearls

- Benzodiazepine risk increases with age
- Women are as twice as likely to receive a benzodiazepine Rx.
- ¼ of all Rx. for benzodiazepines are for long acting
- Men are more likely to abuse with opioids

Withdrawal Symptoms

- Insomnia
- Gastric problems
- Tremors
- Agitation
- Fearfulness
- Muscle Spasms
Withdrawal Symptoms

- Less likely
  - Irritable
  - Depersonalization
  - Derealization
  - Hypersensitive to stimuli
  - Suicidal behavior
  - Depression
  - Psychosis
  - DT’s
  - Seizures

Contraindications to Use

- Respiratory depression
- Myasthenia gravis
- Sleep apnea
- Bronchitis
- COPD
- Caution: Personality disorders, depression, pregnancy, elderly
## Pharmacokinetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>½ Life (hrs)</th>
<th>Speed of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>12-15</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>10-30</td>
<td>Intermediate</td>
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<tr>
<td>Clonazepam</td>
<td>18-50</td>
<td>Slow</td>
</tr>
<tr>
<td>Diazepam</td>
<td>20-80</td>
<td>Fast</td>
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<tr>
<td>Lorazepam</td>
<td>10-20</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>5-10</td>
<td>Slow</td>
</tr>
<tr>
<td>Prazepam</td>
<td>50-200</td>
<td>Slow</td>
</tr>
</tbody>
</table>

## Drug Interactions

- With drugs metabolized by cytochrome P450 enzymes
- With drugs metabolized through glucuronidation
- Oral contraceptives, some antibiotics, antidepressants, antifungal agents inhibit the cytochrome enzymes in the liver
- Carbamazepine and phenytoin accelerate may benzodiazepines.
Drug Interactions

- Common
  - Ketoconazole
  - Itremazole
  - Macrolide antibiotics
  - Fluoxetine
  - Nefozodone
  - Cimetidine

Benzodiazepine Use and Risk of Alzheimer’s Disease

- On Sept 9, 2014 published in the BMJ by Sophie Billioti de Gage et al

- Conclusion – Benzodiazepine use is associated with an increased risk of Alzheimer’s Disease. The stronger the association observed for long term exposures reinforces the suspicion of a possible direct association, even if benzodiazepine use might also be an early marker of a condition associated with an increased risk of dementia. Unwarranted long term use of these drugs should be considered as a public health concern.
Benzodiazepine Use and Risk of Alzheimer’s Disease

• Use of benzos significantly associated with an increased risk of Alzheimer’s Disease.
• 1.52 odds ratio for any use
• 1.85 odds ratio for long term use (6 months or more)
• 1.72 for use of benzos with a long half life.
• This was a case-control study; not a randomized, controlled trial.

Guidelines for the use of benzodiazepines in Office Practice

• Contra-indications:
  – Pregnancy and risk for pregnancy
  – Active substance abuse, including alcohol
  – Medical and mental health problems that may be aggravated by Benzos...including fibromyalgia, chronic fatigue syndrome, bipolar disorder, ADHD, kleptomania and other impulse control disorders. Sleep apnea, COPD, CHF.
  – Pt.s being treated with opioids for chronic pain or replacement therapy for narcotic addiction.
  – Grief reactions.
Indications for short-term treatment with Benzos

• Short term treatment of anxiety disorders – 2-6 weeks.
• Insomnia- short term 1-2 weeks.
• Muscle relaxant- short term 1-2 weeks.
• Urgent treatment of acute psychosis and agitation.
• Treating alcohol detoxication
• Seizures
• Sedation

Indications for long term use of Benzodiazepines

• May be used longer in the terminally ill
• Certain neurological disorders
• Severely handicapped
Tapering Benzodiazepines

• A long term project
• Start slow, starting with $\frac{1}{2}$ of a tablet every 2 weeks (or 10% of the daily dose of the BZD)
• May switch to an equivalent dose of a long acting BZD or phenobarbital and then taper off
• Counseling should be available
• Carbamazepine, valporate, and gabapentin can be used to facilitate more rapid withdrawal.

Special Considerations

• Care to not taper alprazolam too quickly...more prone to withdrawal seizures
• Patients with other addiction problems or on high doses or taking other opiates will be more difficult to withdraw. Consider consult.
• As patients age, they become more sensitive to the same dose of BZD.
• There is risk to operating machinery even with stable doses of BZD's.
### Equivalence Table

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Equivalent</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax)</td>
<td>.5 mg.</td>
<td></td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>25 mg.</td>
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</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>0.5 mg.</td>
<td></td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>10 mg.</td>
<td></td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>1 mg.</td>
<td></td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>20 mg.</td>
<td></td>
</tr>
<tr>
<td>Zolpidem (Ambien)</td>
<td>20 mg.</td>
<td></td>
</tr>
<tr>
<td>Zaleplon (Sonata)</td>
<td>20 mg.</td>
<td></td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>3 mg.</td>
<td></td>
</tr>
</tbody>
</table>

### Bibliography

- Substance Abuse – Fourth Edition
- Principles of Addiction – Fifth Edition
- The Pharmacological Basis of Therapeutics- Goodman and Gilman
- Drug Information Service – University of Texas Health Center at San Antonio and the College of Pharmacy at Austin