Benzodiazepines and Other Anxiolytics

Psychology 472
Pharmacology of Psychoactive Drugs
Listen to the audio lecture while viewing these slides

Treatment for Anxiety Disorders
- Ethanol
- Barbiturates and related sedative-hypnotics
- Chloral hydrate,
- Meprobamate and Friends
- Methaqualone (Quaalude) = "love drug"

Problems
- Were dangerous
- Combined with alcohol were deadly
- Lots of sedation
- Etc.

Then in 1960
The Benzodiazepines
- Click on the following hyperlink and listen to the lyrics
- http://www.youtube.com/watch?v=tfGYSHy1jQs

Commentary
- Released in 1966
- Most people believe the drug discussed is Valium
  - May be Nembutal
- Lyrics are still as relevant today as they were when the song was written

History
- Introduced in 1960’s
- Became one of the most popular drugs on the market
  - Work quickly
    - Don’t take weeks or months for reduction of symptoms
- Still widely used – 1 in 5 prescriptions
  - Mostly by GPs and not Psychiatrists
  - Are still frequently abused
Characteristics of users vs. abusers

- Users = older females
- Abusers = young male drug users
- Abusers escalate become dependent

Uses
Severe Anxiety Relief – Primary Use
- Psychological relief leads to physiological relief
Panic Attacks and Phobias (controversial)
- SSRI’s better
  - Anxiety relief, minimal side effects, patient compatibility

Ultimately, term “anxiolytic” becomes synonymous with Benzodiazepines

Uses Continued
Sedative – hypnotic effect for insomnia
- fast-acting = no daytime sedation
- long-acting = some daytime sedation
Anticonvulsant - secondary medication
- Effective at raising seizure threshold
For Anterograde Amnesia - Used before or during surgery
  - Also increases potency of other CNS depressants during surgery

Relaxants - Helps mellow you out
As a Muscle Relaxant - Get direct physiological relief or indirect with psychological relief
Alcoholism Treatment - Used in treating withdrawal

Differences from Barbiturates
- Get less respiratory depression
  - Safer than barbiturates
- Will increase the effects of barbiturates
  - Synergistic effects
  - Work on different binding sites
- Do not usually give as great of sedation
  - Better for daytime use
- Don’t see as great of tolerance effects and takes longer too

In General
- Both Barbiturates and Benzodiazepines tend to slow the system down
- Work on the GABAa receptor (and others as well)
- When used correctly are very effective for what they do.
- Both develop tolerance
- Both have opposite withdrawal effects
Examples of Available Benzodiazepines

- Diazepam (Valium)
- Chlordiazepoxide (Librium)
- Flurazepam (Dalmane)
- Flurazepam (Dalmane)
- Lorazepam (Ativan)
- Quazepam (Dormalin)
- Clonazepam (Klonopin)
- Oxazepam (Serax)
- Temazepam (Restoril)
- Triazolam (Halcion)
- Alprazolam (Xanax)
- Estazolam (ProSom)
- Halazepam (Paxipam)
- Midazolam (Versed)

Pharmacokinetics

- 15 BDZ derivatives used in U.S.
- Differ in pharmacokinetics parameters
  - a. Metabolism rates
    - Move from initial drug to active intermediates
  - Plasma half-life of initial drug + active metabolite determines if they are classified as long- or short-acting

Classification of BZs

- Groups
  - Short-acting
  - Intermediate-acting
  - Long term duration
- Differ based on
  - How fast they take effect
  - Duration of action

Short Acting

- Rapid onset, short duration
- Are metabolized quickly to inactive compounds
- Not used to treat long term anxiety

Short Term BZs

- Midazolam (Versed)
- Used for anesthetic and amnesic properties
- Colonoscopies
- Triazolam (Halcion)
- Used to treat insomnia
- Short term anxiety
  - Alprazolam (Xanax, Niravam)
  - Oxazepam (Serax)
  - Temazepam (Restoril)

Intermediate Type BZs

- Lorazepam (Ativan)
- Clonazepam (Klonopin)
  - Also used for the treatment of seizure disorders
- Quazepam (Dormalin)
  - Estazolam (ProSom)
Long Term BZs
- Primarily used to treat general anxiety.
- Can also be used for:
  - Muscle relaxation
  - Adjunct to Anesthesia
  - Chlordiazepoxide (Librium)
  - Diazepam (Valium)
  - Flurazepam (Dalmane)
  - Halazepam (Paxipam)
  - Prazerpam (Centrax)
  - Clorazepate (Tranzene)

Partial Agonists
- Block only particular types of receptors
  - Reduces anxiety
  - Doesn’t give you the high
  - Where new research is going

Flunitrazepam (Rohypnol)
- Is technically a Benzodiazepine
- Commercially marketed outside the US
- Is similar to Halcion
- Reduces anxiety
- Causes sedation
- Causes amnesia

Combined with Alcohol
- Acts like Chloral Hydrate
- Acts like GHB
- Also called a date-rape drug

Side Effects
- Similar to Barbiturates
  - Sedation
  - Motor impairments
  - Drowsiness
  - Mental confusion
  - Amnesia (especially when taken with alcohol)
  - Others
- Generally is dose related
Characteristics

- GABA receptors are axo-axonic receptors
- BZs are full or partial agonists of GABAa BZ receptors
  - Nonselective BZs" (diazepam, etc.)
  - Partial agonists (bretazenil, abecarnil).
Change affinity for GABA
Causes hyperpolarization of stimulatory neurons

Some BZ have higher affinity for $\alpha_1$ receptors

- Zolpidem (Ambien)
- Zaleplon (Sonata)
- Eszopiclone (Lunesta)

GABA Receptor

Specific Sites and Actions

- Cerebral cortex and hippocampus
  - Mental confusion and amnesia
- Amygdala, orbitofrontal cortex & insula
  - Alleviation of anxiety, agitation and fear
- Spinal cord, cerebellum & brain stem
  - Muscle relaxation (also anxiolytic)
- Cerebellum and hippocampus
  - Antiepileptic action
- Ventral tegmentum / nucleus accumbens
  - Rewarding effects (depend/abuse)
Absorption and Excretion

- BDZs taken orally well absorbed
  - Peak plasma concentration - 1 hour
- Most psychoactive drugs metabolized to inactive, water-soluble product
- Exceptions for some BDZs
  - Some long-acting ones transformed to long-acting metabolites
    - nordiazepam 60 hrs.

Advantages

- Relatively safe
  - Have very low toxicity
  - Minimal respiratory suppression
  - Unlike barbiturates or alcohol.
  - Even at high doses suicides are rare
- Do not induce metabolic enzymes
  - Do not accelerate their own metabolism.
- Act primarily on CNS and peripheral organs
  - Others (e.g., liver) are not impaired.

Problems with Benzodiazepines

- Can cause dementia
- Can impair cognitive performance (especially memory)
  - Decreases academic performance
- Effects can occur for long periods after the drugs are discontinued
- Impairments decrease over time (usually)
- Rebound increases in anxiety and insomnia complicate withdrawal.

More Problems

- Sleep pattern disturbances
  - Daytime sedation or night time rebound
  - Insomnia
- Irrational self-assessment about effects

Addiction Issues with BZs

- Can be problematic in patients with alcohol and substance-abuse problems.
- Can be lethal when combined with alcohol or opioids.

Medical Issues with Benzodiazepines

- Can make chronic pain worse.
- Not truly anxiolytic (poorly relieve stress)
- Limited use as anticonvulsants
- CNS toxicity in chronic use or high doses
  - Headaches irritability, confusion, impaired memory, depression
- Can complicate cognitive-behavioral therapies
  - Memory / cognition issues
Motor Problems with Benzodiazepines

- Get impaired psychomotor and alertness
- BZs at low doses impair driving performance.
  - Slows down stimulatory neurons
  - Women were more affected than were men.
- Combined with cognitive slowing issues makes a dangerous combination

Elderly

- Metabolize BZs more slowly
  - Can take up to 1 month to eliminate single dose
- BDZs can easily cause dementia
  - Often overlooked in elderly
- Slows down motor systems
  - Increase rates of falls and hip fractures.

BZ and Pregnancy

- BZ and metabolites freely cross placenta
  - Small but possible risk of fetal damage
- With use near delivery in high-dose mothers
  - Get BZ dependence / withdrawal in infant
    - "floppy infant syndrome"

Tolerance-Dependence-Withdrawal

- Extended use can develop dependence
  - Withdrawal symptoms – rebound and intensified – anxiety, insomnia, restlessness, agitation, irritability
  - Rare symptoms - hallucinations, psychosis, seizures
Most abuse patterns are similar to drugs

Antagonist

- Flumazenil (Romazicon) – high-affinity binding to GABA\(_A\) complex – but shows no activity!
- Blocks access of active BDZs to produce reverse effect
- Used as antidote for BDZ overdose
  - Short ½ life an advantage
  - Does not work on alcohol overdoses

Conclusions

- Good drug group for treatment of anxiety
- Good drug for treating alcohol withdrawal
- Has abuse potential
  - Not used as much as other downers but are safer
- Problems often occur when used with other drugs