



**Benzodiazepines and
Other Anxiolytics**

Psychology 472
Pharmacology of Psychoactive
Drugs

Listen to the audio lecture while viewing these slides

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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

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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 Today = 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

Continued

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 GABA_A 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)
- Chlorazepate (Tranxene)
- 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

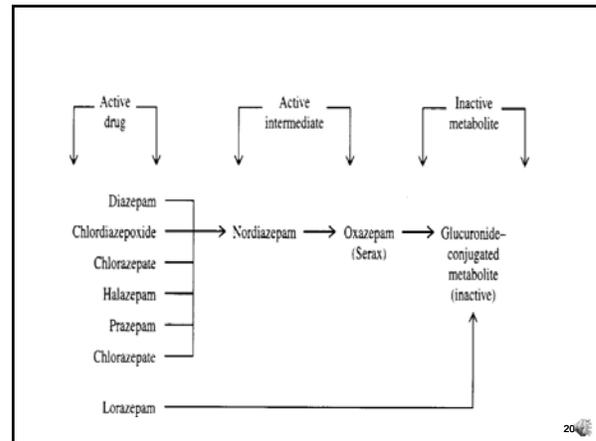
- Loroazepam (Ativan)
- Clonazepam (Klonopin)
 - Also used for the treatment of seizure disorders
- Quazepam (Dormalin)
 - Estazolam (ProSom)



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)
 - Prazepam (Centrax)
 - Clorazepate (Tranzene)

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Partial Agonists

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

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Flunitrazepam (Rohypnol)

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

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Combined with Alcohol

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

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Side Effects

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

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Characteristics

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

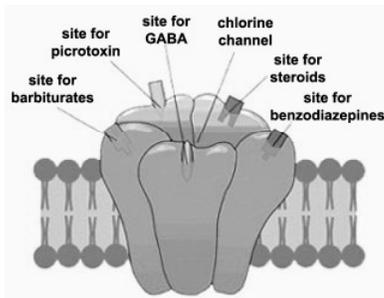
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Some BZ have higher affinity for α_1 receptors

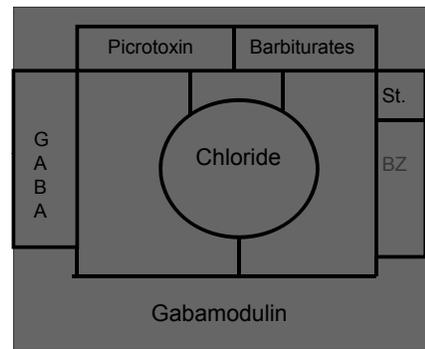
- Zolpidem (Ambien)
- Zaleplon (Sonata)
- Eszopiclone (Lunesta)

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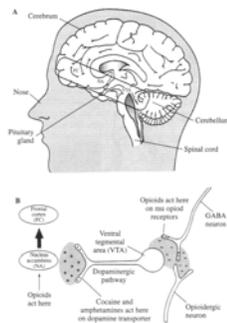
GABA Receptor



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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)

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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.

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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.

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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.

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More Problems

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

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Addiction Issues with BZs

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

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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

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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