

Benzodiazepines

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Presentation Outline

- ▶ History of Drug Class
- ▶ Historical & Current Controversies
- ▶ Current Benzodiazepines Available
- ▶ Characteristics of Drug Class
- ▶ Applications with Adults and Children
- ▶ Applications for Learning
- ▶ Negative Effects

The History of Benzodiazepines

▶ Before the 1950's

- ▶ Patients' treated with alcohol, alkaloids from opium, narcotic plants, paraldehyde, chloral hydrate, bromides, and barbiturates (the most common).

▶ The 1950's - The "Psychopharmacology Revolution"

- ▶ Anxiolytic drugs are the last group of new psychopharmacological agents to be developed.
- ▶ Anxiety is seen as a manifestation of neuroses.
- ▶ Anxiety symptoms are said to be a positive way to explore external conflict, therefore treatment is avoided.

The History of Benzodiazepines

- ▶ **1952 - Major Shift in Thinking About Anxiety**
 - ▶ Professor Hans Jurgen Eysneck publishes study on the ineffectiveness of psychoanalysis in treatment of anxiety.
 - ▶ DSM-1 published - separates neuroses and anxiety, resulting in increased interest in anxiety.
 - ▶ Discovery of chlorpromazine (a tranquilizer) as an effective treatment for psychotic patients.
- ▶ **1953 - Introduction of Meprobamate (a barbiturate) in Anxiety Treatment**
 - ▶ First major psychopharmacology breakthrough for anxiety.
 - ▶ Major side effects include severe drowsiness, addiction, increased drug tolerance, lethal overdose, and drug abuse.

The History of Benzodiazepines

- ▶ **Late 1950's - First Benzodiazepine Discovered (Methaminodiazepide)**
 - ▶ Failure of Meproamate prompts research for new drug.
 - ▶ Discovered by Polish researcher Leo Hynryk Sternback at Hoffman-LaRoche
- ▶ **1958 -Methaminodiazepide patented and Released Commercially as Chlordiazepoxide**
 - ▶ Several animal trials conducted.
 - ▶ First human clinical trials done with schizophrenia patients and elderly patients.

The History of Benzodiazepines

- ▶ **1960 - First Benzodiazepine Study Published**
 - ▶ Results of 3 comparative clinical trials published in the Journal of the American Medical Association.
 - ▶ This study, combined with other clinical trials, leads to FDA approval of Chlordiazepoxide under the trade name "Librium"
- ▶ **1963 - Development of Diazepam (Valium)**
 - ▶ A chemically simpler but more effective version of Chlordiazepoxide.

The History of Benzodiazepines

▶ 1960's Onward

- ▶ 1000's of benzodiazepines developed.
- ▶ Over 100 marketed in various countries

▶ Late 1970's - Third Generation of Benzodiazepines Released

- ▶ Alparazolam (Xanax) - used mainly as an anxiolytic.
- ▶ Triazolam (Halcion) - used mainly as a hypnotic.

Historical & Current Controversies: The Rise and Fall of Benzodiazepines

- ▶ **1965 - 1975 - The Rise of Benzodiazepines ("Happy Pills")**
 - ▶ Benzodiazepines become the most prescribed medication in the world.
 - ▶ Valium is the most prescribed benzodiazepine.
 - ▶ 10-20% of American adults are regularly using benzodiazepines.
 - ▶ Over 80 million prescriptions worldwide.
 - ▶ Heavily marketed by pharmaceutical companies, particularly Hoffman-LaRoche.
 - ▶ Main messaging - the drug is safe and effective, especially compared to tranquilizers.
 - ▶ Dependency concerns attributed to combining the drug with other drugs/substances.

Historical & Current Controversies: The Rise and Fall of Benzodiazepines

- ▶ **1973 - the "LaRoche Affair" and the Beginning of the Fall**
 - ▶ UK Government sues Hoffman-LaRoche for costs due to mass consumption of the drug.
 - ▶ Hoffman-LaRoche forced to repay the government almost 4 million pounds.
 - ▶ Sparks similar legal action in other European countries.
- ▶ **Mid 1970's**
 - ▶ Rise of media's focus on the mass medicalization of society.
 - ▶ FDA includes benzodiazepines on its list of controlled substances.
 - ▶ Prescriptions fall from 100 million units in 1975 to 70 million in 1979.

Historical & Current Controversies: The Rise and Fall of Benzodiazepines

- ▶ **1980's - Concern Over Addictive Qualities of Benzodiazepines**
 - ▶ 1980 - major study released citing withdrawal symptoms from benzodiazepines.
 - ▶ 1982 - UN Commission declares the drug as a controlled substance after WHO finds that the drug can result in dependency and depression of the nervous system.
- ▶ **1989 - Reduction in Prescriptions**
 - ▶ "Triplicate Prescription Program" implemented in some USA States.
 - ▶ Restriction of benzodiazepines put under the same control measures as opiates, barbiturates, and amphetamines.
 - ▶ Treatment limited to 30 days.
 - ▶ Administrative obstacles result in physicians prescribing older and riskier medications instead, such as barbiturates and meprobamate.
 - ▶ Prescriptions fell by half from 1988 to 1989.

Historical & Current Controversies: The Rise and Fall of Benzodiazepines

- ▶ **Mid 1990's Onward - Period of Scientific and Commercial Stability Begins**
 - ▶ Gradual implementation of guidelines for benzodiazepine usage.
 - ▶ More risks than benefits cited regarding Triplicate Program.
 - ▶ Use of SSRI's over benzodiazepine's in treatment of anxiety.
 - ▶ Benzodiazepine's considered second-line treatment for anxiety.
 - ▶ However, some researchers say that there are no substantial benefits in the use of SSRI's over benzodiazepines.

List of Benzodiazepines

Drug Name	Generic Name
Prosom	Estazolam
Alprazolam Intensol	Alprazolam
Doral	Quazepam
Niravam	Alprazolam
Diazepam Intensol	Diazepam
Tranxene	Clorazepate
Xanax	Alprazolam
Librium	Chlordiazepoxide
Klonopin Wafer	Clonazepam
Serax	Diazepam
Dalman	Flurazepam
Lorazepam Intensol	Lorazepam

Drug Name	Generic Name
Diastat	Diazepam
Halcion	Triazolam
Ativan	Lorazepam
Restoril	Temazepam
Tranxene SD	Clorazepate
Tranxene T-Tab	Clorazepate
Versed	Midazolam
Onfi	Clobazam
Diastat AcuDial	Diazepam
Diastat Pediatric	Diazepam
Serax	Diazepam
Dalman	Flurazepam

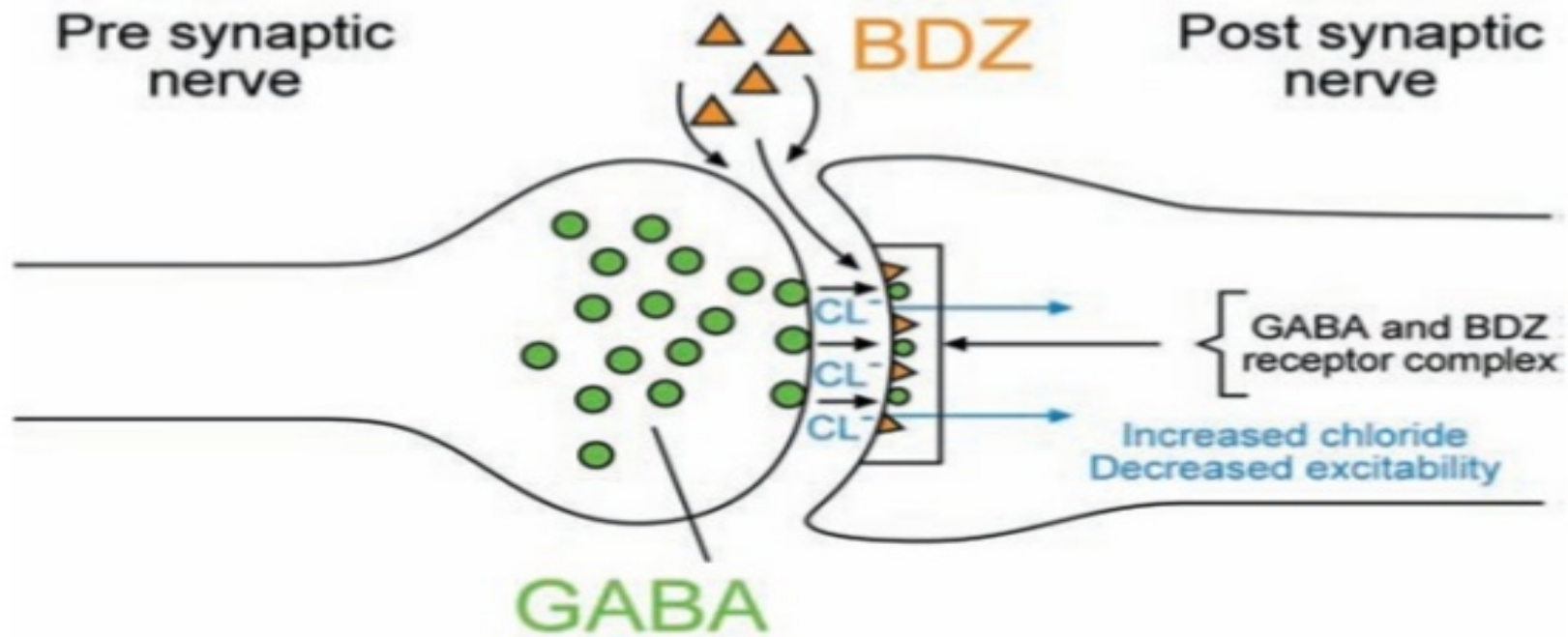
(List of Benzodiazepines, n.d.)

Mechanisms of Action

- ▶ Target central nervous system --> **GABA**
- ▶ **GABA** inhibits or reduces neuron activity
- ▶ Benzodiazepines open **GABA**-activated chloride channels and allow chloride ions to enter post-synaptic neuron
- ▶ Neurons becomes negatively charged and resistant to excitation --> calming, sedative effect

Mechanism of Action

Benzodiazepine Mechanism Of Action



Characteristics of Drug Class

- ▶ Differences in their onset of action, peak action, and half-life
- ▶ Characterized as either short, immediate, or long acting
- ▶ Short- and intermediate-acting benzodiazepines preferred for the treatment of **insomnia** (ex. Alprazolam -Xanax®)
- ▶ Longer-acting benzodiazepines are recommended for the treatment of **anxiety** (ex. Diazepam - Valium®)

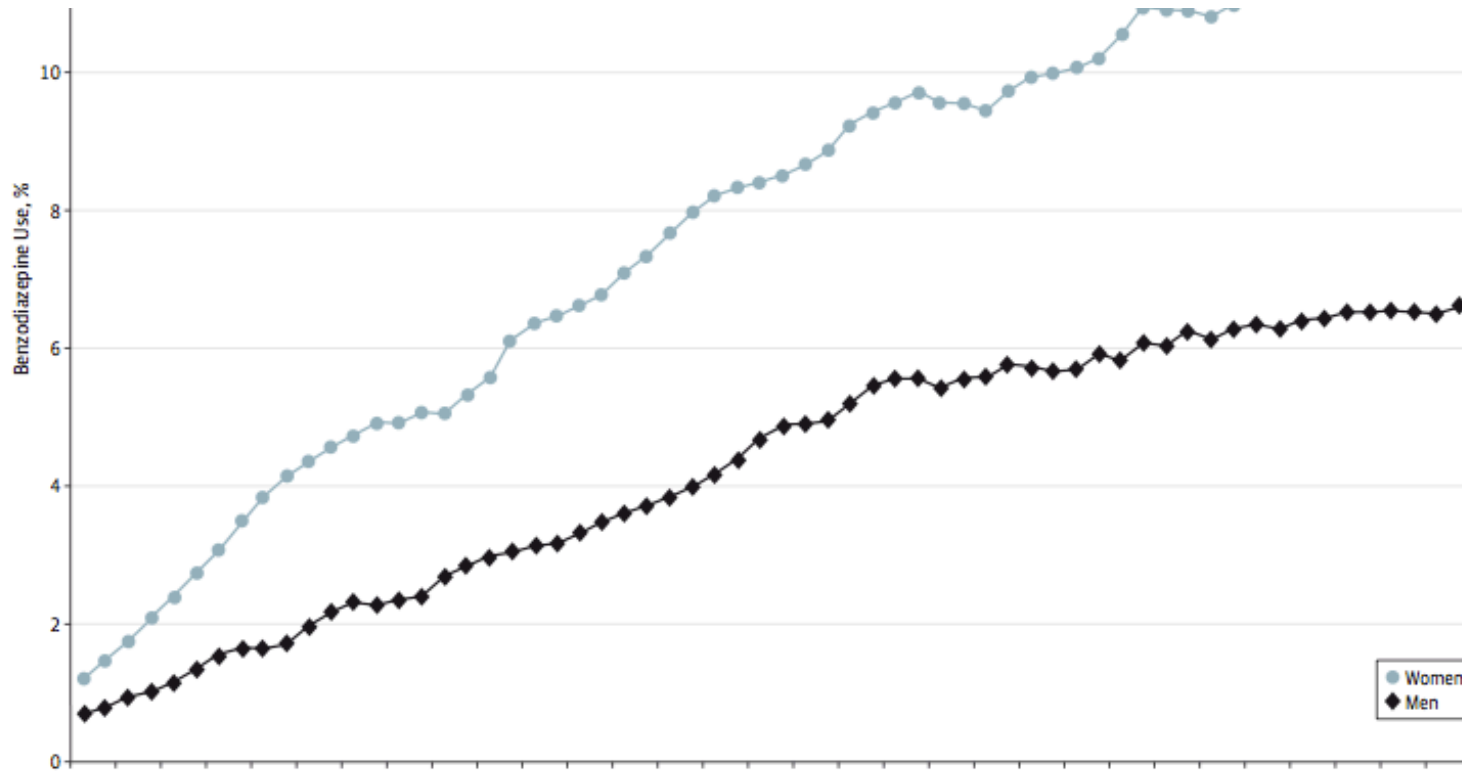
Onset of Action

Commonly Prescribed Benzodiazepines

Generic Name	Brand Name	Onset of Action	Peak Onset	Half Life
Alprazolam	Xanax	15-30 mins	0.7-1.6 hours	6-20 hours
Clonazepam	Klonopin	15-30 mins	1-4 hours	18-39 hours
Diazepam	Valium	Within 15 mins	1 hour by mouth	20-50 hours
Lorazepam	Ativan	15-30 mins by mouth	1-1.5 hours by mouth	10-20 hours

Applications

- ▶ Benzodiazepines are characterized by the following drug actions:
 - ▶ Anxiety relief
 - ▶ Hypnotic
 - ▶ Muscle relaxant
 - ▶ Anti-convulsant
 - ▶ Amnesiac (mild memory-loss inducer)



Percentage of Benzodiazepine use in adults (2008)

Anxiolytic Applications

- ▶ Generalized Anxiety Disorder
- ▶ Panic Disorder
- ▶ Social Anxiety Disorder
- ▶ Used for short term relief of severe or disabling anxiety symptoms
- ▶ BZDs are generally reserved for patients who do not respond to other treatments
- ▶ BZDs do not have an anti-depressive effect when used alone

Hypnotic Applications

- ▶ Induction and maintenance of sleep
- ▶ Reduction of wakefulness
- ▶ Increase sleep duration and efficiency
- ▶ Short term use (2-4 weeks)
- ▶ Best for severe insomnia
- ▶ Part of a holistic treatment
- ▶ Being replaced by Melatonin

Other applications

Muscle relaxant

- ▶ Emergency treatment of seizures
- ▶ Management of muscle spasms
- ▶ Movement disorders related to the use of antipsychotic drugs

Tranquilizer

- ▶ Mixed evidence for the use of acute "rapid tranquilization" in patients with excitement, agitation, or severe psychotic symptoms.
- ▶ Short-term use only
- ▶ Patients should be withdrawn from them in a tapered manner when no longer needed.

Alcohol Withdrawal

- ▶ Helps to prevent epileptic seizures and delirium tremens in patients going through alcohol withdrawal.

Applications in children

- ▶ There is a lack of research in the application of BDZs in children
- ▶ Mixed results in the research in treating children with anxiety disorders
- ▶ Night terrors
- ▶ Behavioral disinhibition is a drawback
- ▶ Pediatric surgeries - preoperative medication
- ▶ Seizures

Applications for Learning

- ▶↓ Controlled trials do not support the use of benzodiazepines in children
- ▶↓ Used in clinical practice for *highly* anxious children to promote participation in therapy and school attendance
- ▶↓ Anterograde Amnesia
- ▶↓ Deficits in learning and memory
- ▶↓ Impairment of visual memory as shown by the Paired Associates Learning (PAL) and Delayed Matching to Sample (DMS) tests for memory

Applications for Learning

▶ ↓ Impaired performance on psychomotor tasks

▶ ↓ Deficits on visuo-spatial learning

▶ ↓ Impaired attentional set-shifting

▶ ↓ Impairment in short-term number recall

Impairment in long-term memory recall: delayed picture recognition tasks

Applications for Learning

Middle-aged patients demonstrate impairment in verbal learning and memory, psychomotor, visuo-motor and visuo-conceptual abilities

Chronic use of BZDs produces cognitive dysfunction that persists after their discontinuation

Older patients dependent on BZDs had more difficulty in learning short term and delayed recall as compared to alcohol-dependent patients

Applications for Learning

- ▶ Comparing the effects of triazolam and diazepam on performance in a water maze task with rats
 - ▶ The drugs did not affect the rats ability to complete the maze that they had previously mastered
 - ▶ When the drugs were given prior to learning the new maze configurations, there was an increase in errors as well as an increase in swim time

The cost of taking Benzodiazepines

- ▶ Weighing the risks and the benefits
 - ▶ Adverse Reactions
 - ▶ Drug Interactions
 - ▶ Prenatal and Neonatal Risks
 - ▶ Risks of use with Aging Population
 - ▶ Dosage Abuse

Adverse reactions

- ▶ IV dosage must be controlled to avoid
 - ▶ Hypotension
 - ▶ Heart problems
 - ▶ Nausea/vomiting
 - ▶ Respiratory problems
 - ▶ Vision problems
 - ▶ Skin reactions
- ▶ Unusual sleep
- ▶ Anterograde Amnesia
- ▶ Persistent drowsiness following a dose
- ▶ Development of tolerance

Drug Interactions

- ▶ Before starting any type of benzodiazepine it is important to complete a drug interaction screen
- ▶ Some prominent interactions include:
 - ▶ Phenothiazines
 - ▶ Opiates
 - ▶ Barbiturates
 - ▶ Alcohol
 - ▶ Illicit Drugs
 - ▶ Herbal medicines
 - ▶ Drugs that affect liver or CNS function

Prenatal and Neonatal Risks

Prenatal

- ▶ Category D FDA class drugs
 - ▶ Evidence for adverse effects but may be used if benefits outweigh risks
- ▶ Risk for malformation
- ▶ Withdrawal in neonate

Postnatal

- ▶ Not recommended except under physician care
- ▶ Drug is passed through breastmilk
- ▶ Recorded cases of sedation and inability to suckle

Risks of use in Elderly Population

- ▶ The use of Benzodiazepines is to be avoided as much as possible
- ▶ Due to increased sensitivity and decreases metabolism ability in older patients the risks are greater for:
 - ▶ Cognitive impairment
 - ▶ Delirium
 - ▶ Falls
 - ▶ Fractures
 - ▶ Car accidents

(American Geriatric Society)

Dosage Abuse

- ▶ Cardiac arrest
- ▶ Respiratory Arrest
- ▶ Dependence
- ▶ Insomnia
- ▶ Sudden stoppage can have severe side effects

References

- American Geriatrics Society 2015 Beers Criteria Update Expert Panel. (2015). American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society*, *63*(11), 2227–2246. <https://doi.org/10.1111/jgs.13702>
- Baldwin, D. S., Aitchison, K., Bateson, A., Curran, H. V., Davies, S., Leonard, B., Nutt, D. J., Stephens, D. N., & Wilson, S. (2013). Benzodiazepines: Risks and benefits. A reconsideration. *Journal of Psychopharmacology*, *27*(11), 967-971. doi: 10.77/0269881113503509
- Benzodiazepines. (n.d.). Retrieved Feb 26, 2017, from <http://www.cesar.umd.edu/cesar/drugs/benzos.asp>
- Coull, J.T., Middleton, H.C., Robbins, T.W. Sahakain, B.J. (1995) Clonidine and diazepam have differential effects on tests of attention and learning. *Psychopharmacology*, *12*(3), 3-22. doi:10.1007/BF02311180
- Kant, J., Wylie, R., Vasilakis, A., Ghosh, S. (1996) Effects of triazolam and diazepam on learning and memory as assessed using a water maze. *Pharmacology Biochemistry and Behavior*, *53*(2), 317–322 doi: 10.1016/0091-3057(95)02028-4
- López-Muñoz, F., Álamo, C., & García-García, P. (2011). The discovery of chlordiazepoxide and the clinical introduction of benzodiazepines: Half a century of anxiolytic drugs. *Journal of Anxiety Disorders*, *25*(4), 554-562. doi:10.1016/j.janxdis.2011.01.002
- List of Benzodiazepines. (n.d.). Retrieved February 22, 2017, from <https://www.drugs.com/drug-class/benzodiazepines.html>

References

- Nakamura-Palacios, E., Roelke, C. (1997) Effects of acute or daily administration of diazepam on spatial learning and working memory. *Drug Alcohol Depend.* 46(3) 181-190. [10.1016/S0376-8716\(97\)00062-8](https://doi.org/10.1016/S0376-8716(97)00062-8)
- Nail, J., Christofferson, J., Ginsburg, G. (2015) Academic impairment and impact of treatments among youth with anxiety disorders. *Child Youth Care* 44, 327. doi:10.1007/s10566-014-9290-x
- Nordqvist, J. (2016, August 25). *Benzodiazepines: Uses, Side Effects, and Risks*. Retrieved from http://www.medicalnewstoday.com/articles/262809.php#benzodiazepines_mechanisms
- Olfson, M., King M., Schoenbaum, M. (2015). Benzodiazepine use in the united states. *Jama Psychiatry*, 72(2): 136-142, doi:10.1001/jamapsychiatry.2014.1763
- Witek, M. W., Rojas, V., Alonso, C., Minami, H., and Silva, R. R. (2005). Review of benzodiazepine use in children and adolescents. *Psychiatric Quarterly*, 76(3): 283-296, doi: 10.1007/s11126-005-2982-5