Benzodiazepine Pharmacology Considerations in Primary Care

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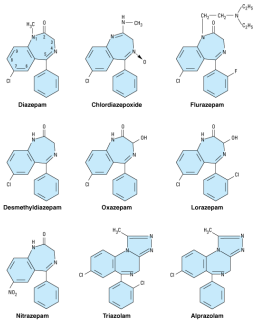
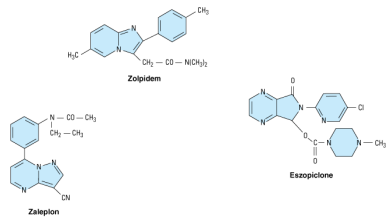
Benzodiazepines Chemical Classification

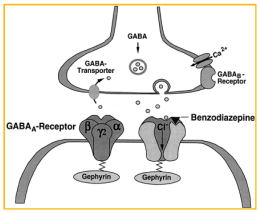


NON-Benzodiazepine Selective Agonists at α_1 BZ receptors



Mechanism of Action

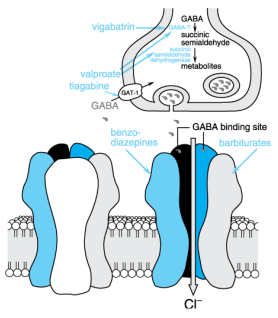
- BZ receptors on the postsynaptic GABA neuron
- ***Enhance*** the ***inhibitory*** effect of GABA on neuronal excitability by increasing neuronal membrane permeability to Chloride ions
- More GABA & less GLUTAMATE = more relaxed and less alert



BZ (benzodiazepines)

Mechanism of Action

- Benzodiazepines and Barbiturates and Alcohol and other sedatives or opioids ***multiply*** each other's effects.
- This certainly includes pregabalin and perhaps gabapentin.



BZD Associated Receptors

- GABA-A & GABA-B
- BZ receptors are located on GABA-A
  - α_1-GABA-A: sedative and amnestic effects; most abundant
  - α_2-GABA-A : anxiolytic effects
  - α_3-GABA-A: noradrenergic, seratonergic and cholinergic neurons
- Currently available BZ have no specificity for BZ receptor subtypes
- Investigational compounds selective for α_2 and α_3 (***potentially*** anxioselective)
- Selective α_1-GABA-A receptor agonists: **zolpidem**,

Flumazenil (Romazicon)

- GABA-A receptor antagonist
  - Competitively occupies the receptor and blocks/reverses binding of other ligands without affecting GABA mediated chloride conduction
  - Not effective against barbiturates, alcohol or tricyclic antidepressants
  - Half life= 0.7-1.3 hours
- Adverse effects: agitation, confusion, dizziness, and nausea.
- May cause a severe precipitated abstinence syndrome (withdrawal) in patients who have developed physiologic BZ dependence
- If co-ingestion of BZ with tricyclic antidepressants, seizures and cardiac arrhythmias may follow flumazenil administration.

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Organ level effects of Benzodiazepines

- Sedation
  - Calming effect with concomitant reduction of anxiety and some depressed effects on psychomotor and cognitive functions (disinhibition)
  - Dose dependent anterograde amnesia, or inability to remember events occurring during the drug's duration of action
- Hypnosis
  - Effects of BZ on normal sleep:
    - Latency of sleep onset is decreased
    - Duration of stage 2 NREM is increased
    - Duration of REM is decreased
    - Duration of stage 4 NREM slow-wave is decreased
  - New hypnotics decrease the latency to persistent sleep
  - ***Use for more than 1-2 weeks leads to some tolerance to their effects on sleep patterns***

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Organ level effects

- Anticonvulsant Effects
  - Some BZ sufficiently selective to exert anticonvulsant effects without marked CNS depression (some psychomotor function might be impaired), but should ***NOT*** typically be used long term for this indication
    - Ex: clonazepam, lorazepam and diazepam
- Muscle Relaxation
  - Inhibitory effects on the polysynaptic reflexes and internucial transmission and at high doses may also depress transmission at the skeletal neuromuscular junction – **only works at *HIGH HIGH* doses**
- Effects on Respiration Function
  - Some respiratory depression (esp. pts with pulmonary disease, OSA)
  - Dose related effects

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Pharmacokinetics: Distribution

- BZ are all relatively lipophilic
  - Lipophilicity is important in determining the duration of clinical effect after single dose administration
  - Diazepam and clorazepate have the highest lipid solubility → quickest onsets of action
- CNS is the central compartment of BZ distribution
- After a single dose, BZ will redistribute rapidly out of the CNS to other lipophilic tissues
- BZ are widely distributed into body tissues, cross the blood-brain-barrier, and highly bound to plasma proteins (70-99%)

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Pharmacokinetics: Elimination

- All BZ are hepatically metabolized and renally excreted
  - Oxidation (P450 3A4)
  - Glucuronide conjugation
- Lorazepam, Oxazepam, & Temazepam are conjugated only
- Clonazepam undergoes nitroreduction

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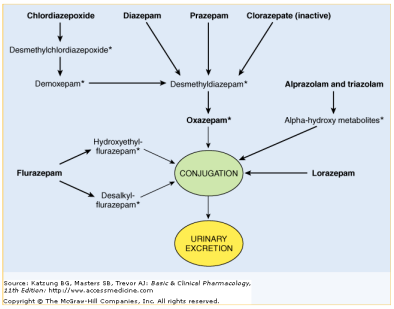
Metabolic Pathways of Benzodiazepines



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

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Pharmacokinetic Properties of Some Benzodiazepines and Newer Hypnotics

Drug	Peak Blood Level (hours)	Elimination Half-Life (hours)	Comments
Alprazolam**	1–2	12–15	Rapid oral absorption
Chlordiazepoxide	2–4	15–40	Active metabolites; erratic bioavailability from IM injection
Clorazepate	1–2 (nordiazepam)	50–100	Prodrug; hydrolyzed to active form in stomach
Clonazepam	2	24-50	Most potent of benzodiazepaines, 0.5 mg ~ equal to at least 5 and prob 10 mg diaz
Diazepam	1–2	20–80	Active metabolites; erratic bioavailability from IM injection
Flurazepam	1–2	40–100	Active metabolites with long half-lives
Lorazepam**	1–6	10–20	No active metabolites
Oxazepam**	2–4	10–20	No active metabolites
Temazepam*	2–3	10–40	Slow oral absorption
Triazolam*	1	2–3	Rapid onset; short duration of action
Zolpidem*	1–3	1.5–3.5	No active metabolites

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Generic Name	Brand Name	***Approximate Equivalent Dosages (mg)***	Approved Dosage Range (mg/day)
Alprazolam	Xanax	1	0.75-4; 1.5-10
Chlordiazepoxide	Librium	25	25-100
Clonazepam	Klonopin	0.5	1-4
Clorazepate	Tranxene	15	7.5-60
Flurazepam	Dalmane	30	15-30
Diazepam	**Valium**	**10**	2-40
Lorazepam	Ativan	2	0.5-10
Midazolam	Versed	4	N/A
Oxazepam	Serax	30	30-120
Phenobarbital		90	
Temazepam	Restoril	30	15-30
Triazolam	Halcion	0.5	0.125-0.5

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More on Receptors

- Benzodiazepine dependence **&** ETOH dependence
  - With long term use of BZ (or/and ethanol) there is a decrease in efficacy of GABA A receptors
    - BZ receptors reduced by 30% in the hippocampus and by 25% in the frontal cortex
  - When high-dose BZ or/and ethanol are abruptly discontinued → "down-regulated" state of inhibitory transmission is unmasked = not enough inhibitory transmission = increased excitatory transmission → **LESS GABA AND MORE GLUTAMATE**
  - characteristic withdrawal symptoms and worsening of underlying anxiety / insomnia symptoms

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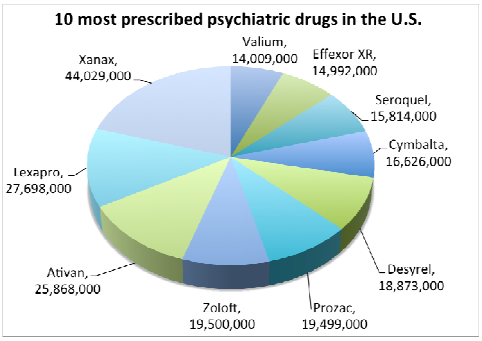

The Use of Medicines in the United States: Review of 2010
Report by the IMS Institute for Healthcare Informatics

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Physiologic Factors Influencing Benzodiazepine Pharmacokinetics

Factor	Phyisiologic and Pharmacokinetic Effect	Clinical Significance/Comments
Aging	•Increased elimination half-life •Decreased clearance (oxidative metabolism) •Decreased plasma proteins→ increased free fraction •Decreased gastric acidity→ icreased BZ absorbtion	•Lower and less frequent dosing in elderly •BZ that undergo glucoronidation preferred in the elderly (lorazepam, oxazepam)
Gender	•Age related changes in oxidative metabolism more pronounced in males •Decreased glucuronidation in women → decreased clearance •Zolpidem	•Elderly males require especially low doses •Longer half life in women of lorazepam, temazepam •Much higher effect

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Physiologic Factors Influencing Benzodiazepine Pharmacokinetics

Factor	Phyisiologic and Pharmacokinetic Effect	Clinical Significance/Comments
Obesity	•Increased BZ elimination half-lives due to increase in Vd	•Increase chance of drug accumulation
Liver Disease	•Decreased clearance and increased elimination half-lives of long acting BZs and alprazolam (cirrhosis and hepatitis); •Increased elimination half-life of lorazepam in cirrhosis but not acute hepatitis	•Avoid long acting BZs or use significantly lower doses
Kidney Disease	•Decreased plasma protein bounding→ increased free fraction	•Decreased doses
Ethnicity	•Decreased oxidative metabolism (CYP 2C19) of diazepam and alprazolam in Asians	•Asians may require lower doses of diazepam, alprazolam and posibly other BZs

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Tolerance

- Result of down-regulation of brain BZ receptors
- Usually develops to the disinhibition, sedation, euphoria and drowsiness seen initially with BZ
  - Problematic when used for insomnia
- ***Tolerance to the anxiolytic effect is rare***
  - SO PATIENTS WHO CONTINUE TO ESCALATE DOSE ARE CONCERNING!

Physical Dependence

- Becomes apparent when withdrawal occurs upon discontinuation of the drug
- Can occur after continued use beyond 6 weeks
- Reported in 50% of patients on treatment for > 3-6 months

References

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Questions?