Prescribing Controlled Drugs Benzodiazepines & stimulants:
Balancing SAFE Practice Principles

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Disclosures

None

The Sed Hypnotic Family

- Benzos
- Non-benzo hypnotics (e.g. zolpidem)
- Barbiturates (e.g. butalbital)
- Barbiturate-like (e.g. Soma)
- Gabapentinoids (e.g. gabapentin & pregabalin)

Overview of Benzodiazepine Pharmacology

- Mechanism of action
- Receptor activity
- Pharmacokinetics
- Adverse effects
- Drug interactions
- Use in clinical practice

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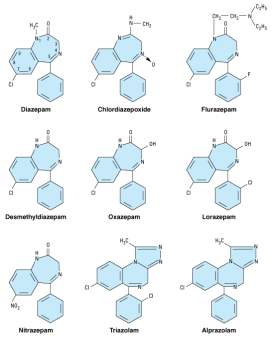
Benzodiazepines Chemical Classification



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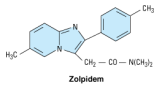
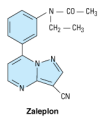
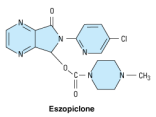
NON-Benzodiazepine Selective Agonists at α_1 BZ receptors







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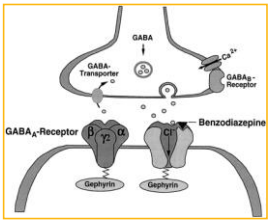
Mechanism of Action

- BZ receptors on the postsynaptic GABA neuron
- Enhance the inhibitory effect of GABA on neuronal excitability by increasing neuronal membrane permeability to Chloride ions



BZ (benzodiazepines)

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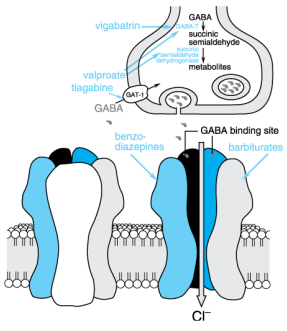
Mechanism of Action

- Benzodiazepines and Barbiturates and Alcohol ***multiply*** each other's effects.



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

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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, serotonergic and cholinergic neurons produce depressant effects
- 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 etc

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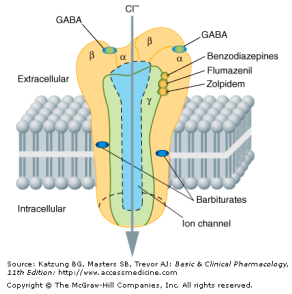
Pentameric structure of the $GABA_A$ receptor



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

- Benzo area of action
- Zolpidem will only bind $GABA_A$ receptors containing an α1 subunit
- Propofol only binds to $GABA_A$ receptors containing β_2 and β_3 subunits
- Barbiturates – more of a direct effect to open the Cl ion channel, thus a narrower toxic/therapeutic ratio.
- BZ antagonist: flumazenil blocks actions of BZ and zolpidem ***BUT NOT*** barbiturates or ethanol

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Organ level effects

- Sedation
  - Calming effect with concomitant reduction of anxiety and some depressed effects on psychomotor and cognitive functions (disinhibition)
  - Dose dependent anterograde amnesia
- Hypnosis
  - Effects of BZ on normal sleep: TOTALLY DISRUPTIVE
    - 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 (some psychomotor function might be impaired) *Primarily if IV or IM (lorazepam)*
    - Ex: clonazepam, nitrazepam, 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 at HIGH DOSE*
- Effects on Respiration and Cardiovascular Function
  - Some respiratory depression (esp. pts with pulmonary disease or OSA)
  - Dose related effects
  - May affect the medullary vasomotor center → cardiovascular depression

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Pharmacokinetics: Absorption

- Readily absorbed following oral administration
- Diazepam is the most rapidly absorbed orally
- Temazepam is slowly absorbed
- Chlordiazepoxide and Diazepam are poorly and erratically absorbed after IM administration
- Lorazepam and Midazolam are rapidly and completely absorbed after IM administration

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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, cross the placenta and are 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 and is relatively unstable in urea

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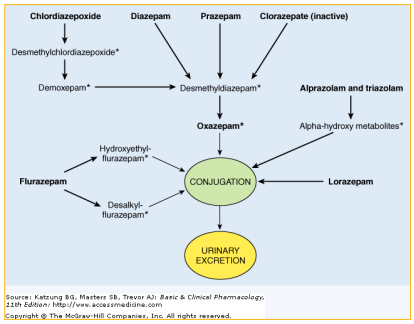
Metabolic Pathways of Benzodiazepines



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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	Second most potent, 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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Adverse Effects-CNS

- Sedation & Drowsiness
- Amnesia
- Psychomotor impairment
- Ataxia
- Disorientation
- Depression/confusion
- Aggression, irritability and excitement
- Cognitive impairment (memory)
- Paradoxical disinhibition

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Drug-drug interactions

- Pharmacodynamic
  - **Other CNS depressants (EtOH, barbiturates, opioids)**
- Pharmacokinetic
  - CYP P 450 3A4 metabolism

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Generic Name	Brand Name	Approximate Equivalent Dosages (mg)	Approved Dosage Range (mg/day)
Alprazolam	Xanax	**0.5 – 1.0**	0.75-4; 1.5-8
Chlordiazepoxide	Librium	25	25-100
Clonazepam	Klonopin	**0.5**	1-4
Clorazepate	Tranxene	15	7.5-60
Estazolam	ProSom	4	0.5-1
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
Quazepam	Doral	30	7.5-15
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 → characteristic withdrawal symptoms and worsening of underlying anxiety / insomnia symptoms.

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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!

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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 > 4-6 months

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BENZODIAZEPINE CONTRAINDICATIONS #1

- Current of Past SUD Moderate-Severe
- History of Diversion
- SUD Mild (binge type behavior)
- If they don't take them (legitimate medical purpose)
- The ELDERLY
- Obst. Sleep Apnea
- Severe COPD
- Non-adherence

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BENZODIAZEPINE CONTRAINDICATIONS #2

- Opioid prescriptions
- METHADONE OR BUPRENORPHINE CLINIC
  - DOUBLE contraindication
- Continued low risk “social” alcohol use
- Barbiturate prescriptions
- Specific diagnosis to try to avoid chronic daily benzos:
  - Fibromyalgia
  - Most anxiety disorders … especially PTSD
  - Chronic insomnia

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LONG TERM BENZODIAZEPINE PRESCRIBING:
Commonly done, not well supported by data

- Benzodiazepines are very “STICKY” drugs
  - Short term prescribing commonly becomes long term
- Problems with chronic (daily) benzo exposure:
  - TACHYPHYLAXIS (INSOMNIA)
  - PHYSICAL DEPENDENCE AND WITHDRAWAL (W/D sx are identical to indications)
  - LIKELY IMPAIR HELP SEEKING BEHAVIOR
  - FDA INDICATION ARE ALL FOR SHORT TERM USE
  - EFFICACY STUDIES ARE ALMOST ALL SHORT DURATION

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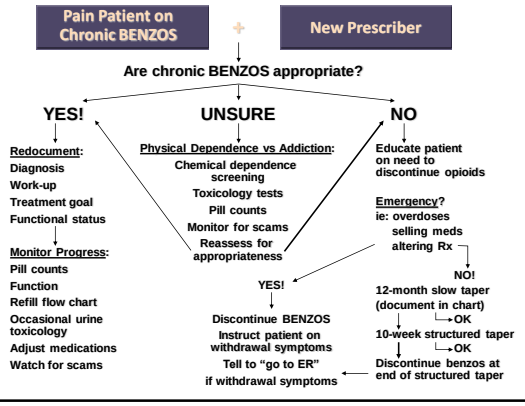


TAPERING off of Sedative-Hypnotics

- To Taper Off the benzodiazepine
  - **Short** – switch to intermediate onset, long T1/2 agent administered **nightly** and taper.
  - **Long** – switch to intermediate onset, long T1/2 **nightly** and taper.
  - Start NON-benzo TX Plan for mental health issues
- The Taper (Outpatient setting)
  - 10% / month = NON - urgent taper
  - 10% / week = Urgent taper
  - Avoid PRN benzos entirely

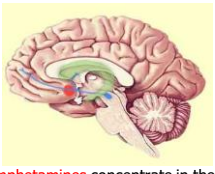
Benzodiazepine W/D: Adjuncts (6-12 mos)

- Tegretal 400-600mg / day
- Valproic acid 500 – 1500 mg/day
- Gabepentin 300 – 2400 mg / day
- Topirimate 50-200 mg/d
- Give for 6-12 months
- Improves abstinence rates over time
- Also give SSRI's / high dose buspirone / prn hydroxyzine / clonidine-prazocin / beta blockers / etc for TX of underlying anxiety sx.

More on Psychostimulants

The Pleasure Centers Affected by Drugs

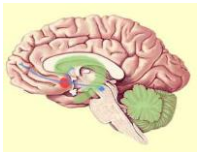
Cocaine and stimulants – methamphetamine / ecstasy / bath-salts / **ALL prescribed stimulants (ADD/ADHD/Obesity/Narcolepsy)**



- Cocaine and amphetamines concentrate in the central link of the reward circuit (the ventral tegmental area and the nucleus accumbens). These areas contain especially high concentrations of dopaminergic synapses, which are the preferred target of these drugs.

The Pleasure Centers Affected by Drugs

Cannabinoids / marijuana / "medical" marijuana / THC / Marinol / synthetic cannabinoids ("spice", "K2", etc)



- The active ingredient in cannabis is THC, which concentrates chiefly in the ventral tegmental area and the nucleus accumbens, but also in the hippocampus, the caudate nucleus, and the cerebellum.
- THC's effects on the hippocampus might explain the memory problems that can develop with the use of cannabis, while its effects on the cerebellum might explain the loss of coordination and balance experienced by people who indulge in this drug.

A Brief Diversion: **clinical implications of THC & Stimulant RX**

- THC produces the opposite effect of psychostimulants with regards to the "therapeutic actions" (sorry but THC antagonizes their "legitimate medical purpose") … so stimulants should not be Rxed in THC users
- THC use mimics the SX of ADD and ADHD … so in a THC user the DX of ADD / ADHD is problematic
- THC INTENSIFIES the "high" from stimulants (not a legitimate medical purpose)
- Patients receiving RX stimulants should be regularly screened for THC use

Stimulant Use, Abuse, Addiction: The US History

- Opioids – stimulants – opioids – stimulants … … …
- 1865 – O, 1880 – C, 1900 – O, 1920 – C, 1930 – O, 1950s-1960s – S*, 1970s – O, 1988-1994 – C, 1995-2013 – O
- Today (decreasing opioids, increasing stimulants)
- Increasing stimulants: cocaine, crack, RX stimulants, methamphetamine

- * 1950s & 60s stimulant addiction epidemic = CII for most RX Stimulants

The Harris Interactive Study

- A self-administered, anonymous online questionnaire of subjects between the ages of 18 and 24 currently enrolled in a 2 or 4 year college.
- Administered between March 30th and April 2nd, 2014
- 2,087 Respondents of whom 110 ***(5.3%)*** **had ever used methylphenidate nonmendically**
- 30% of RX stimulants were used intermittently (i.e. during parties and exam weeks) and these students were in the bottom third of class GPA

So what are the family members of the STIMULANT Family?

- Cocaine HCL, cocaine HCO3 (Crack)
- RX Stimulants: Ritalin, Adderall, Vivanse, Cylert, phentermine, Dexedrine, Concerta
- Ecstasy (MDMA)
- Methamphetamine
- Bath salts
- Caffeine

The prescribed stimulants

- Mixed amphetamine salts (Adderall)
- Methylphenidate
- Phentermine (Adipex etc)
- Others (Belviq or lorcaserin / Bontril or phendimetrazine / Didrex or benzphetamine / Qsymia or phentermine and topirimate)
- Tamper resistant: Concerta (gel-like matrix)
- Pro-drugs: lis-dexamfetamine (Vyvanse)
- There is no low abuse potential CRX stimulant

Psychostimulant Pharmacology: 2 ***ACTIONS***

1. Systemic effect - block the re-uptake of nor-epinephrine.
2. Central nervous system effect - block the re-uptake of dopamine.

Stimulants - acute pharmacologic ***effects***

- Local anesthetic (ONLY COCAINE)
- Stimulant (PRIMARY MEDICAL EFFECT)
  - increase in heart rate, blood pressure, reflexes, concentration, energy, smooth muscle spasm
  - decrease in appetite, need for sleep
- Euphoriant (UNWANTED SIDE-EFFECT) -
  - increase in mood, excitement, disinhibition

Stimulants - more pharmacologic ***effects***

- RAPID tolerance to the Euphoric effect
  - The "High" disappears after several days / few weeks
- SLOW PARTIAL TOLERANCE re: Stimulant effect
  - The same dose maintains its efficacy over long periods of time = low dose long-term use less concerning
- Little if any need for dose increases – ever
- "Rapid escalators" are a REALLY bad sign – high risk for a SUD

Mechanism of Stimulant Psychoactive Effect: **Basic Science** RESEARCH

- **Binding** to dopamine transporter correlates best with behavioral potency in animals ⟶ ↑ **Dopamine Levels** in nucleus accumbens
- **Lesions** of mesolimbic dopamine circuit ("reward" circuit) abolish cocaine self-administration

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So … who should get long term Benzos / Stimulants?

- Who **TO** prescribe them to?
  - **Presence** of **Indications** – patient specific and disease specific
    AND
  - **Lack** of **Contraindications**
- Who **NOT TO** prescribe to?
  - Lack of **indications**
    OR
  - Presence of **contraindications** **(even if indications exist)**
- "DON'T RX long term controlled drugs to patients with current or past SUD" … say *I'm so sorry but no*

So … what are the alternatives?

- Non-controlled drugs and therapy (of course)
  - Benzodiazepines: ("none of that #@!& works" = SUD HRB)
    - SSRIs / buspirone / anti-seizure meds (if gabapentin use LOW DOSE) / alpha agonists / beta blockers / CBT / meditation / aerobic exercise / stretching
  - Psychostimulants: ("none of that #@!& works" = SUD HRB)
    - SNRIs / Strattera / alpha agonists / behavioral therapy
- Remember … when CRX it is essential to maintain boundaries!