Prescribing Controlled Drugs Benzodiazepines & stimulants:

Balancing SAFE Practice Principals

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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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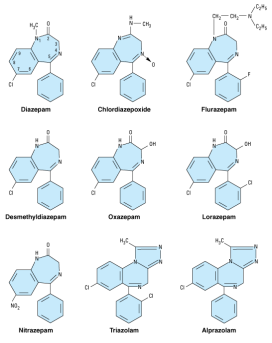
Benzodiazepines Chemical Classification



Source: Katzung BG: *Basic & Clinical Pharmacology*, 10th Edition: http://www.accessmedicine.com

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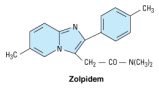
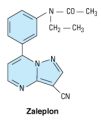
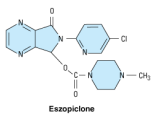
NON-Benzodiazepine Selective Agonists at α_1 BZ receptors







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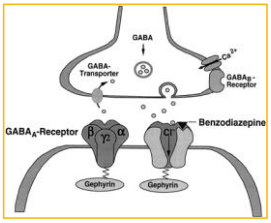
Mechanism of Action

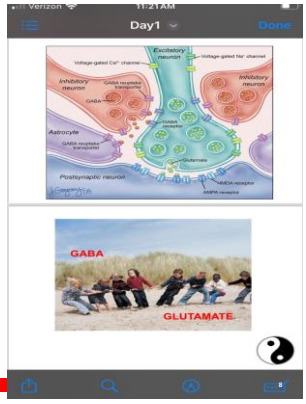
- BZ receptors on the postsynaptic GABA neuron
- Enhance the inhibitory effect of GABA on neuronal excitability by increasing neuronal membrane permeability to Chloride ions



BZ (benzodiazepines)

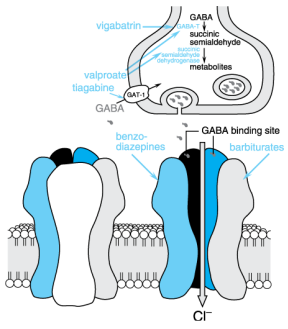
Pediatric Conception of the Gaba-Glutamate "balance"

- GABA: inhibitory
- Glutamate: excitatory
- Brain state: dynamic "balance" (or imbalance) between the two



Mechanism of Action

- Benzodiazepines and Barbiturates and Alcohol and *probably* Gabapentinoids ***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

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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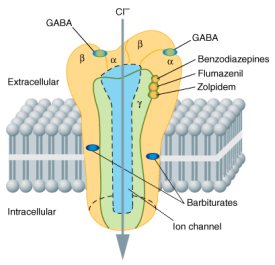
Pentameric structure of the $GABA_A$ receptor



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th 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 (acute NOT chronic)
  - *Primarily if IV or IM (lorazepam)*
  - *NOT for long-term OPT seizure control*
- Muscle Relaxation (Mythical)
  - *ONLY at HIGH DOSE, and SHOULD NO LONGER BE USED*
- Effects on Respiration and Cardiovascular Function (Minimal)
  - Some respiratory depression (esp. pts with pulmonary disease or OSA)
  - Dose related effects
  - May affect the medullary vasomotor center → cardiovascular depression
  - May depress the gag reflex = increased risk of aspitation at high dose

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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 (more frequent dosing until steady state then T ½ life dosing)
- BZ are widely distributed into body tissues, cross the blood-brain-barrier and EASILY cross the placenta
- BZ 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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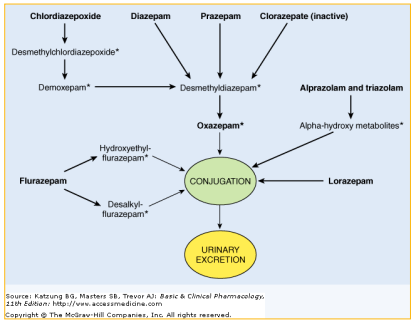
Metabolic Pathways of Benzodiazepines



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Pharmacokinetics of Benzodiazepines & 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: TYPICALLY TRANSIENT*

- Sedation* & Drowsiness*
- Amnesia*
- Psychomotor impairment*
- Ataxia*
- Disorientation* / confusion*
- ***Depression***
- Aggression / Irritability / Excitement*
- Cognitive impairment (memory)*
- Paradoxical disinhibition*

* EXCEPT IN OLDER PATIENTS

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Drug-drug interactions of Benzos

- Pharmacodynamic: please avoid mixing together in the same brain!
  - **Other CNS depressants**
    - ***EtOH***
    - ***Other sedative hypnotics like barbiturates OR gabapentinoids***
    - ***OR non-benzo sleepers,***
    - ***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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Physical Dependence / Withdrawal

- 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
- Tolerance most pronounced at the α_1-GABA-A receptor: sedative and amnestic effects
- *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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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 RX
- METHADONE OR BUPRENORPHINE CLINIC
  - DOUBLE contraindication
- Continued low risk "social" alcohol use
- Other Sedative-Hypnotic RX (Barbs / Benz / Sleepers / ?gabapentinoids)
- 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 RX commonly becomes long term RX
- Problems with chronic (daily) benzo exposure:
  - TACHYPHYLAXIS (increased INSOMNIA)
  - PHYSICAL DEPENDENCE AND WITHDRAWAL (W/D sx are identical to indications)
  - LIKELY IMPAIR HELP SEEKING BEHAVIOR
  - FDA INDICATIONS ARE ALL FOR SHORT TERM USE
  - EFFICACY STUDIES ARE ALMOST ALL SHORT DURATION

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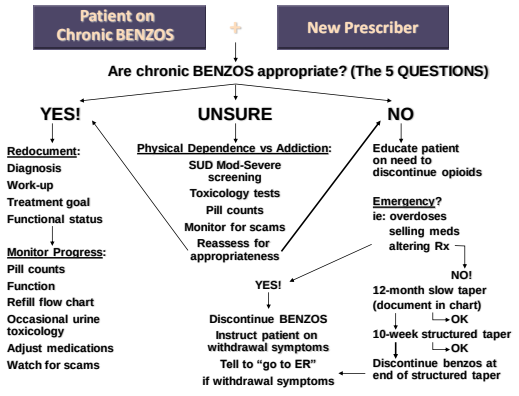


TAPERING off of Sedative-Hypnotics

- To Taper Off the benzodiazepine
  - Switch to intermediate onset, long T1/2 agent administered **nightly** and taper (aka Librium).
  - Start NON-benzo TX Plan for mental health issues
- Two Potential Tapers (Outpatient setting)
  - 5% to 10% / month = ***NON - urgent taper***
  - 10% / week = ***Urgent taper*** (W/D sx in week 4-10)

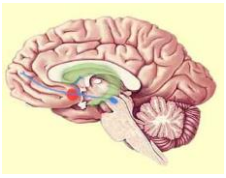
Benzodiazepine W/D: **OPT** options

- Short T ½ drug – see daily, Long T ½ drug – see QOD
- Short T ½ = 7 days, Long T ½ = 14-21 days duration
- START IMMEDIATELY:
  - Tegretol 200 BID up to TID OR Depakote 500 BID up to QID
- Add in if needed:
  - PRN Topiramate 25 BID and titrate as needed up to 50 QID
  - OR Lamictal or Trileptal
- After primary W/D, continue one agent for 6 - 12 months
- Also give SSRI's / high dose buspirone / prn hydroxyzine / clonidine - prazosin / beta blockers / etc for TX of the underlying anxiety sx.

More on Psychostimulants

The Pleasure Centers Affected by Drugs

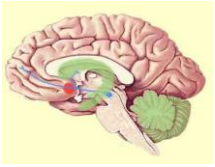
Cocaine and stimulants – methamphetamine / ecstasy / bath-salts / **ALL prescribed stimulants (ADD/ADHD/Obesity/Narcolepsy)**



- 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 even making a DX of ADD / ADHD is problematic
- THC INTENSIFIES the "high" from stimulants (not a legitimate medical purpose)
- ALL 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.

3. (cocaine also blocks the Na-K pump in peripheral nerves)

Stimulants - acute pharmacologic ***effects***

- Local anesthetic (ONLY COCAINE)
- Stimulant (PRIMARY MEDICAL EFFECTS)
  - increase heart rate, blood pressure, reflexes, tremor, concentration, energy, smooth muscle spasm
  - decrease appetite, need for sleep
- Euphoriant (UNWANTED SIDE-EFFECT) -
  - increase in mood, excitement, disinhibition
- SEs/AEs: Anxiety / Tics / SZ / ?Psychosis (& above)

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 over time
- "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 NA**

Lesions of mesolimbic dopamine circuit ("reward" circuit) abolish cocaine self-administration

So … it **is** the dopamine surge causing the psychoactive effect after all!!!

"IV Ritalin Abuse: prototype for RXDA"

Stimulant Prescribing

- Drug-drug interactions:
  - Pharmacologic – very few OTT MAOIs
  - Pharmacodynamic – other controlled drugs
- Contraindications:
  - Current or H/O SUD Mod – Severe
  - Regular THC users (decreased / loss of efficacy)
  - Medical – HTN / hyperthyroid / tachyarrhythmias / ?SZ / unstable angina / closed-angle glaucoma

https://doi.org/10.2165/00003088-200140100-00004

Stimulant Prescribing

- ID an indication: using careful, well documented H&P skills and validated instruments
- Rule out contraindications: using careful, well documented H&P skills and validated tools
- Start with low dose / monitor
- Expect long-term efficacy at stable low doses
- Re-evaluate if transient efficacy & escalating dose

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!