



## Prescribing Controlled Drugs Benzodiazepines & stimulants: *Balancing SAFE Practice Principals*

Ted Parran MD FACP  
Isabel and Carter Wang Professor and Chair in Medical Education  
CWRU School of Medicine

[typ@cwru.edu](mailto:typ@cwru.edu)

1

---

---

---

---

---

---

---

---



## Disclosures

None

2

---

---

---

---

---

---

---

---



## 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)

3

---

---

---

---

---

---

---

---

Overview of Benzodiazepine Pharmacology

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

4

---

---

---

---

---

---

---

---

4

Benzodiazepines  
Chemical  
Classification

Source: Katzung B.G. Basic Clinical Pharmacology, 10th Edition.  
http://www.accessmedicine.com  
Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

5

---

---

---

---

---

---

---

---

5

NON-Benzodiazepine Selective Agonists at  $\alpha_1$  BZ receptors

Source: Katzung B.G. Basic Clinical Pharmacology, 10th Edition.  
http://www.accessmedicine.com  
Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

6

---

---

---

---

---

---

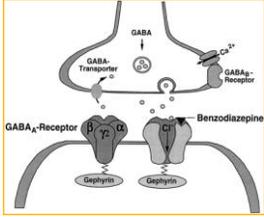
---

---

6

**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)

---

---

---

---

---

---

---

---

---

---

7

**Pediatric Conception of the Gaba-Glutamate "balance"**

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




---

---

---

---

---

---

---

---

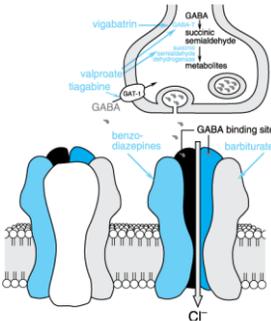
---

---

8

**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>  
 Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

---

---

---

---

---

---

---

---

---

---

9

### Receptors

- GABA-A & GABA-B
- BZ receptors are located on GABA-A
  - $\alpha_1$ -GABA-A: sedative and amnestic effects; most abundant
  - $\alpha_2$ -GABA-A: anxiolytic effects
  - $\alpha_3$ -GABA-A: noradrenergic, serotonergic and cholinergic neurons produce depressant effects
- Currently available BZ have no specificity for BZ receptor subtypes
- Investigational compounds selective for  $\alpha_2$  and  $\alpha_3$  (**potentially** anxiolytic)
- Selective  $\alpha_1$ -GABA-A receptor agonists: zolpidem etc

10

---

---

---

---

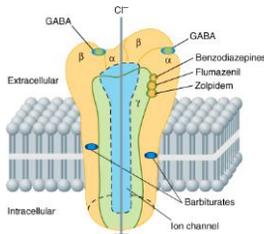
---

---

---

---

### Pentameric structure of the GABA<sub>A</sub> receptor



- Benzodiazepines
- Zolpidem will only bind GABA<sub>A</sub> receptors containing an  $\alpha_1$  subunit
- Propofol only binds to GABA<sub>A</sub> receptors containing  $\beta_2$  and  $\beta_3$  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

Source: Katzung BG, Masters SB, Trevor AJ: Basic & Clinical Pharmacology, 22th Edition. <http://www.accessmedicine.com>  
Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

11

---

---

---

---

---

---

---

---

### 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

12

---

---

---

---

---

---

---

---

### 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 aspiration at high dose

13

13

---

---

---

---

---

---

---

---

### 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

14

14

---

---

---

---

---

---

---

---

### 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  $T_{1/2}$  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%)

15

15

---

---

---

---

---

---

---

---

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

16

---

---

---

---

---

---

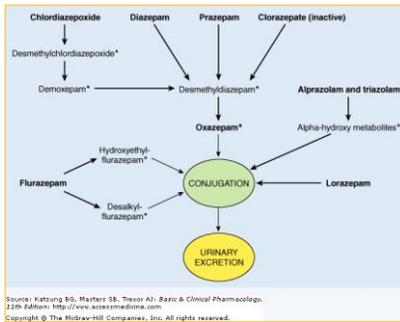
---

---

---

---

Metabolic Pathways of Benzodiazepines



17

---

---

---

---

---

---

---

---

---

---

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	<b>Most potent</b> of benzodiazepines, 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

18

---

---

---

---

---

---

---

---

---

---

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

---

---

---

---

---

---

---

---

19

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

---

---

---

---

---

---

---

---

20

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

---

---

---

---

---

---

---

---

21

### 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.

22

---

---

---

---

---

---

---

---

### Tolerance



- Result of down-regulation of brain BZ receptors
- Tolerance most pronounced at the  $\alpha_1$ -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!

23

---

---

---

---

---

---

---

---

### 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

24

---

---

---

---

---

---

---

---

**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

25

---

---

---

---

---

---

---

---

**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

26

---

---

---

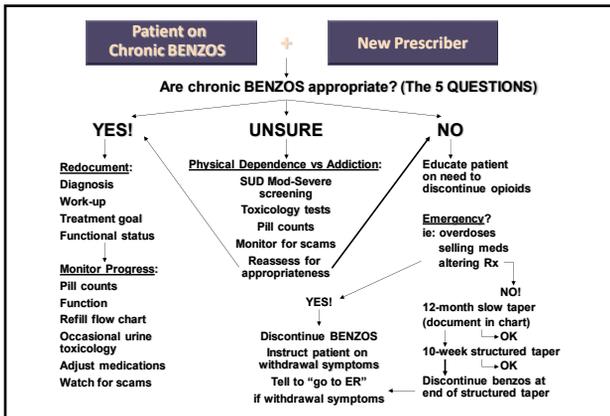
---

---

---

---

---



27

---

---

---

---

---

---

---

---

**TAPERING** off of Sedative-Hypnotics 

- To Taper Off the benzodiazepine
  - Switch to intermediate onset, long T<sub>1/2</sub> 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)



28

---

---

---

---

---

---

---

---

**Benzodiazepine W/D: OPT options** 

- Short T<sub>1/2</sub> drug – see daily, Long T<sub>1/2</sub> drug – see QOD
- Short T<sub>1/2</sub> = 7 days, Long T<sub>1/2</sub> = 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.



29

---

---

---

---

---

---

---

---



**More on Psychostimulants**

30

---

---

---

---

---

---

---

---

**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.

31

---

---

---

---

---

---

---

---

**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.

32

---

---

---

---

---

---

---

---

**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

33

---

---

---

---

---

---

---

---

## 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

34

---

---

---

---

---

---

---

---

## 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 30<sup>th</sup> and April 2<sup>nd</sup>, 2014
- 2,087 Respondents of whom 110 (5.3%) had ever used methylphenidate nonmedically
- 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

35

---

---

---

---

---

---

---

---

## 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

36

---

---

---

---

---

---

---

---



### 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 topiramate)
- Tamper resistant: Concerta (gel-like matrix)
- Pro-drugs: *lis*-dexamfetamine (Vyvanse)
- There is ***no low abuse potential*** CRX stimulant

37

---

---

---

---

---

---

---

---



### 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)

38

---

---

---

---

---

---

---

---



### 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)

39

---

---

---

---

---

---

---

---



### 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

40

---

---

---

---

---

---

---

---



### 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"**

41

---

---

---

---

---

---

---

---



### 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>

42

---

---

---

---

---

---

---

---



## 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

43

---

---

---

---

---

---

---

---



## 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*

44

---

---

---

---

---

---

---

---



## 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!

45

---

---

---

---

---

---

---

---