

Benzodiazepines: A Model for Central Nervous System (CNS) Depressants



Objectives

- Summarize the basic mechanism by which benzodiazepines work in the brain.
- Describe two strategies for reducing and/or eliminating benzodiazepine use.
- List at least three medication alternatives to benzodiazepine therapy.

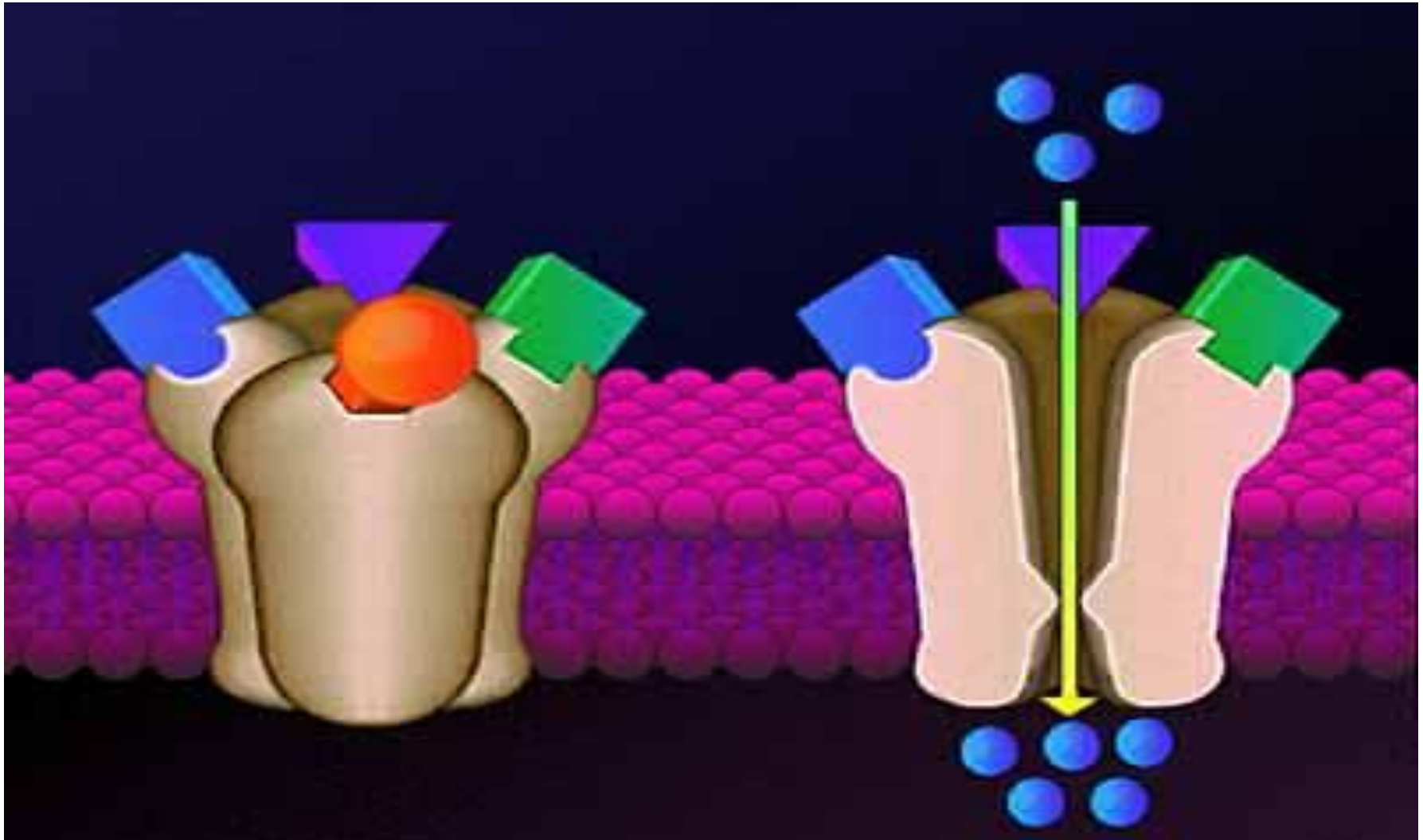
Clinical Uses of BZDs

- Treat a variety of anxiety disorders
- Hypnotics
- Muscle relaxants
- To produce anterograde amnesia
- Alcohol & other CNS depressant withdrawal
- Anti-convulsants

Pharmacodynamics: How BZDS work

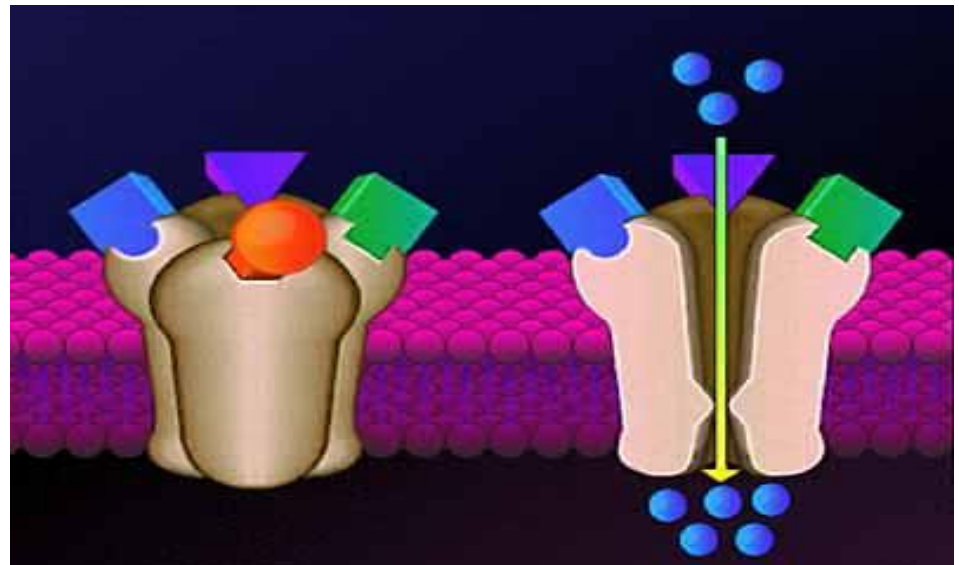
- Where in the brain? BZD receptor binding highest in:
 - Cerebral cortex
 - Hippocampus (& perhaps other limbic system structures)
 - Cerebellum
 - More moderate (but significant) binding in
 - Hypothalamus, thalamus
 - Basal ganglia (movement)

The GABA-a receptor complex



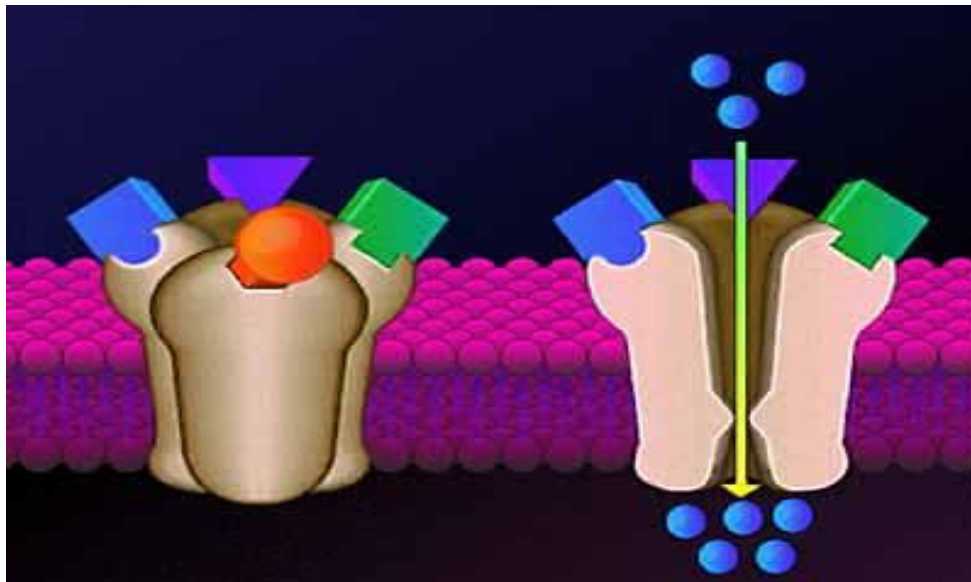
Pharmacodynamics: How BZDS work

- BZDs bind to sub-receptor on the GABA(a) receptor complex in the brain (GABA: gamma amino-butryic acid)
 - This BZD binding causes GABA to more readily bind to it's own sub-receptor
 - In turn, GABA binding causes the chloride (Cl^-) channel to open, allowing chloride to enter the intracellular environment



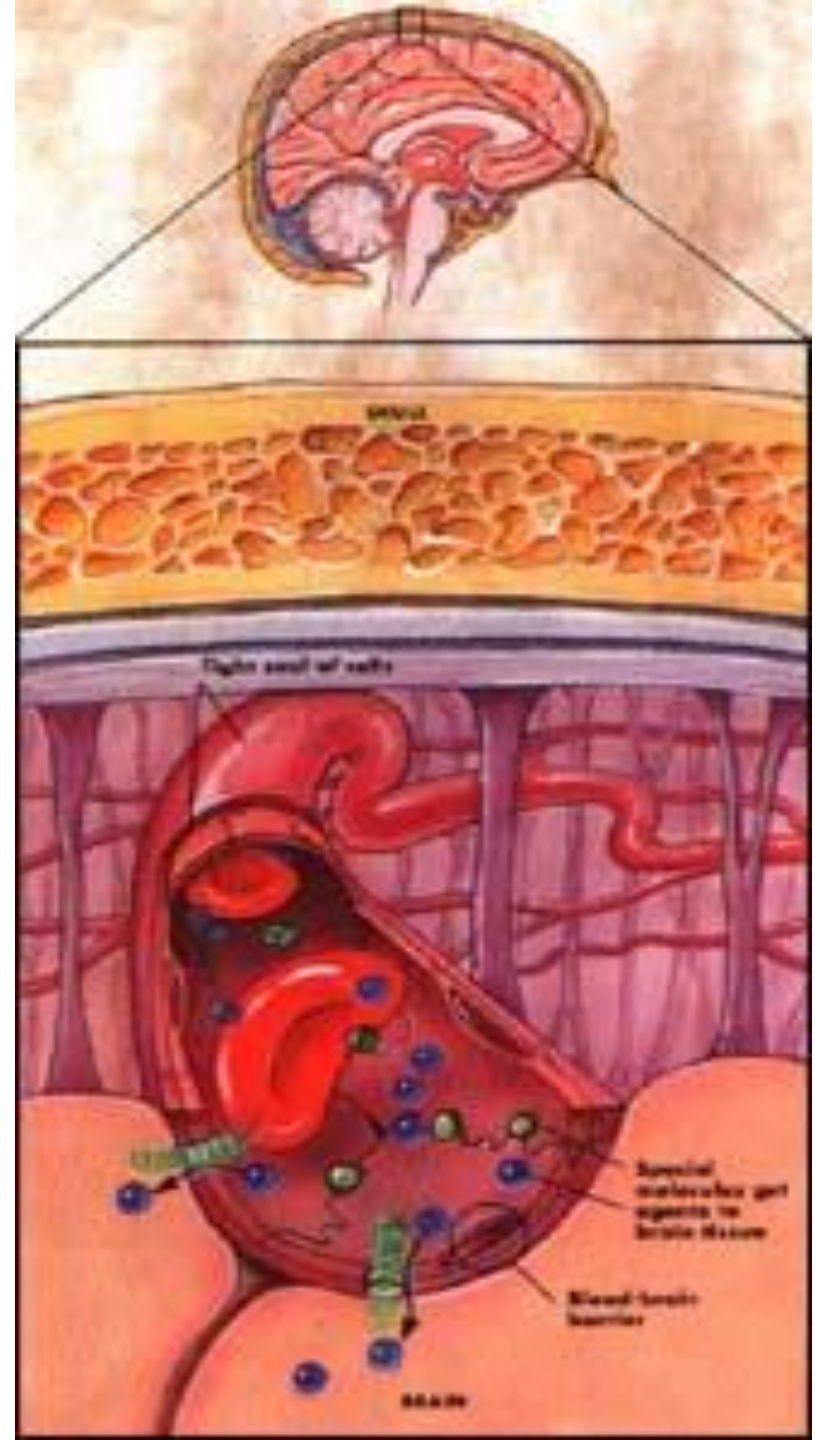
Pharmacodynamics: How BZDS work (cont.)

- Influx of Cl^- causes central nervous system (CNS) depressant effect (inhibitory)
- Similar areas of the brain affected by barbiturates & alcohol in a similar manner



BZD Pharmacokinetics

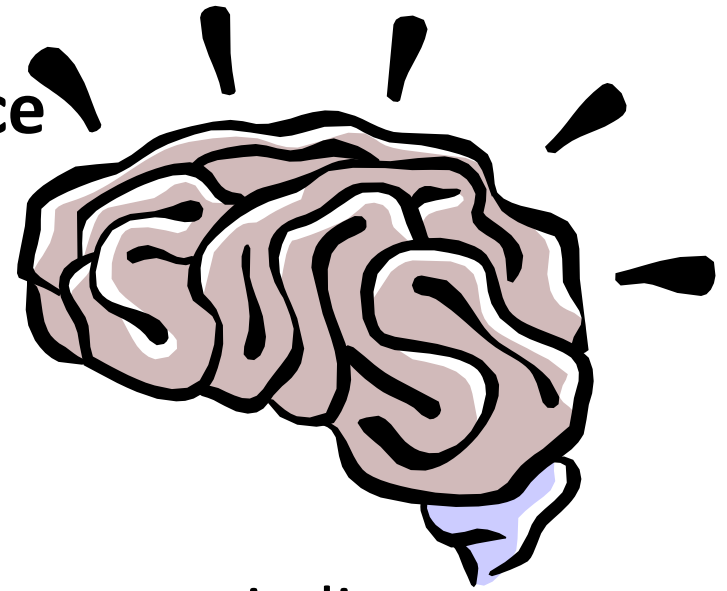
- Blood-brain barrier
 - Example: Imodium
- BZDs cross barriers easily
 - Blood brain barrier (BBB)
 - Placental barrier
 - These effects similar to other CNS depressants as well as psychostimulants
- Variable half-lives



BZD Pharmacokinetics

Generic Name	Trade Name	Rapidity	½ Life	Dose (mg)
alprazolam	Xanax	Intermediate	Short	0.75-4
chlordiazepoxide	Librium	Intermediate	Long	15-100
clonazepam	Klonopin	Intermediate	Long	0.5-4
diazepam	Valium	Rapid	Long	4-40
triazolam	Halcion	Intermediate	Very short	0.125-0.5
temazepam	Restoril	Short	Short	7.5-30

BZD: Tolerance



- Tolerance
 - “Down regulation” and/or increase in liver enzymes
 - Occurs even at therapeutic doses
 - Does not occur as readily for the anti-anxiety effects as much as with the sedative and/or muscle relaxant properties of BZDs
 - Cross-tolerance with BZDs, alcohol and the barbiturates

Discontinuing BZDs



BZD Withdrawal

- The duration, severity, frequency and subsequent treatment of symptoms during BZD withdrawal depends on several factors:
 - BZD half-life (short versus long-acting)
 - Duration of BZD use/abuse
 - Dosing (High vs. low doses)

BZD withdrawal as a function of dose/half-life (leaving out abuse duration)

High Dose/Short acting (1)	High Dose/Long acting (2/3)
Low Dose/Short acting (2/3)	Low dose/Long acting (4)

Low Dose versus High Dose BZD Withdrawal: Occurrence & Symptoms

LOW DOSE BZD WITHDRAWAL



Low Dose BZD Withdrawal (Perry, et. al., 2003)

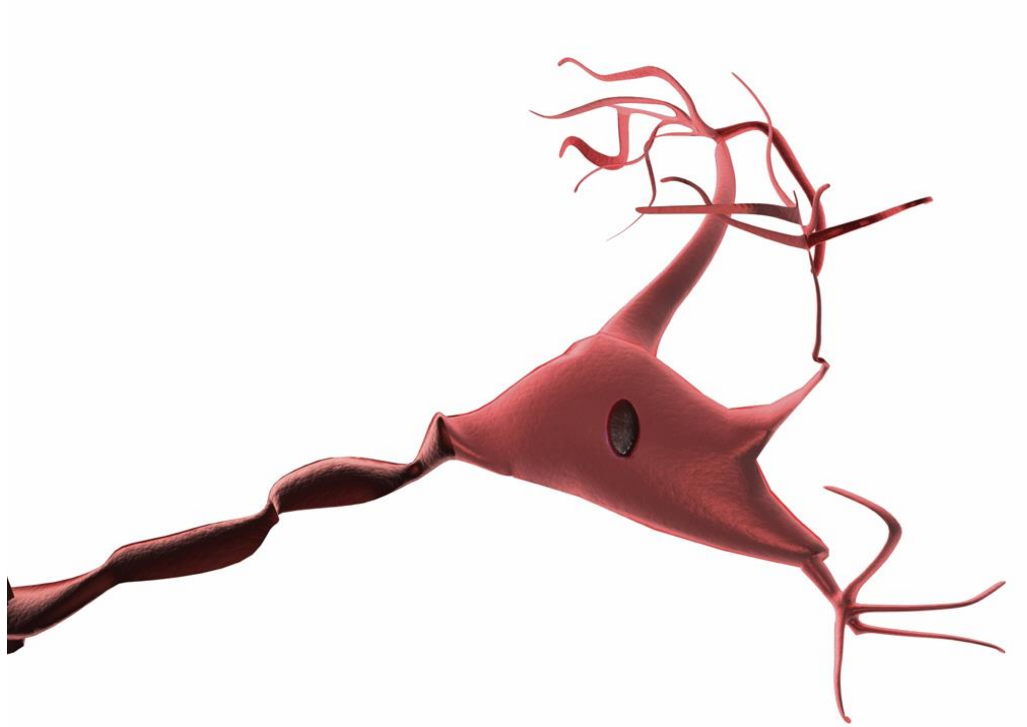
- Incidence and Duration:
 - Low dose BZDs, taken <8 months: small risk of producing withdrawal symptoms but may produce rebound symptoms
 - Low dose BZD used 3 years (average) or more, 50% experience mild to moderate withdrawal
 - With short-acting BZD, minor withdrawal symptoms begin within 1 day of d/c
 - With long-acting BZD, minor withdrawal symptoms begin within 5 days of d/c
 - Symptoms gradually disappear within 2-4 weeks
 - Rate of severe withdrawal: 2-5%

Low Dose BZD Withdrawal Symptoms

(see any problems here re: differential dx?)

- Nausea
- Vomiting
- Anorexia
- Heightened sensory perception (esp. light & sound)
- Illusions
- Blurred vision
- Insomnia
- Sweating
- Tremor
- Decreased coordination
- Weakness
- Irritability
- Restlessness
- Depersonalization
- Anxiety

Low Dose BZD Withdrawal Management



Low Dose BZD discontinuation

- “Simple” tapering
 - May not be needed at all for long-acting/short duration BZD use
 - Can be done outpatient with long-acting and/or low dose BZDs
 - Severe withdrawal symptoms not expected
 - Tapering toward end of the protocol may need to be less aggressive than at the beginning of the protocol
 - But tapering especially needed with short-acting BZDs or if person has been taking BZDs for a long time

Low Dose BZD d/c: sample schedule

- If individual is currently taking a long-acting BZD
 - He/she can remain on the same medication during tapering
 - Suggested rate: divide daily dose by 5 and round result to a dose closest to available tablet dosages
 - Each week, reduce dose by tapering the calculated percentage

See example next slide

Low dose/long-acting BZD discontinuation: Example

- Individual taking 20 mg/day of diazepam (Valium)
- 20% of 20mg = 4mg
 - Week 1: dose at 16 mg/day
 - Week 2: dose at 12 mg/day
 - Week 3: dose at 8 mg/day
 - Week 4: dose at 4 mg/day
 - This schedule covers the 4 week period when withdrawal symptoms typically seen
 - Tapering can be slowed during and even after Week 4

Low dose/short-acting BZD discontinuation (e.g. Halcion)

- Consider tapering with same BZD using previously described schedule

Or

- Substitute a cross-tolerant long-acting BZD
 - Long-acting BZDs produce less severe withdrawal symptoms
 - Use approximate equivalent dose for the short-acting BZD

Low Dose versus High Dose BZD Withdrawal: Occurrence & Symptoms

HIGH DOSE BZD

WITHDRAWAL



High Dose BZD Withdrawal (Perry, et. al., 2003)

- Statistics somewhat more elusive than with low dose withdrawal given the ethical considerations of studying abrupt discontinuation of high BZD doses
 - Significant risk of more severe withdrawal symptoms
 - Symptoms occur sooner than with low dose d/c
 - Symptoms are more intense
 - Duration: about 1 week for short-acting BZDs
 - Duration: about 2 weeks for long-acting BZDs

High Dose BZD Withdrawal Symptoms

- Any or some combination of the low dose symptoms previously listed
- More severe symptoms:
 - Seizures
 - Disorientation/delirium
 - Psychosis
 - Depression
 - Panic attacks



High Dose BZD Withdrawal Management



High Dose BZD Discontinuation

- Short-acting BZDs
 - Consider tapering with the same drug
 - Most research involves alprazolam withdrawal
 - Original strategy: taper at a rate of 1mg q 3 days; however, many individuals taking the drug for longer than 12 weeks could not tolerate this strategy
 - More currently, taper at rate of 0.5mg q 3 days; this method may not work in inpatient setting given time constraints
 - Slower taper with alprazolam may be even better

High Dose BZD Discontinuation

- Another method for short-acting BZDs
 - Substitute diazepam at 40% of the reported daily dose being taken (using equivalence chart)
 - Taper diazepam at a rate of 10% per day
 - Advantages of diazepam:
 - Long half-life
 - Active primary metabolite, desmethyldiazepam
 - Diazepam dose is divided and given q 6 hrs

High Dose BZD Discontinuation

- Long-acting BZDs
 - Can also be withdrawn using diazepam substitution at 40% of the total daily dose and tapering at 10%/day
- For all high-dose withdrawal methods, may want to consider concurrent carbamazepine or other anti-convulsant medication use
- May want to consider barbiturate substitution especially for those with BZD/alcohol dependence

Use of Adjunctive Medication to Treat BZD Withdrawal

Some of these strategies
subsequently discussed
may be considered during
withdrawal from other
addictive substances as
well



Treating BZD withdrawal with Medications: Anxiety

- Treating anxiety during withdrawal
 - Reduce NE (Inderal, Clonidine, etc.)
 - May help reduce severity of sympathetic nervous system-related symptoms during withdrawal (e.g. the fight or flight symptoms)
 - Does not prevent seizures nor actual symptoms
 - Mild effect on “subjective” states of anxiety
 - Tricyclic antidepressants (TCAs)
 - Can produce sedative effect (helps with sleeping)
 - Can reduce anxiety/depression for some
 - Could lower seizure threshold i.e. may be safer to use at the end of BZD tapering

Treating BZD withdrawal with Medications: Anxiety

- Treating Anxiety with SSRIs:
 - May help with reduce impulsivity/compulsivity
 - Reduce (pre-existing) depression and anxiety; may need to start well before tapering endpoint (SSRIs may take several weeks to start being effective)
 - “Safer” than TCAs when used with substances of abuse (e.g. TCAs and alcohol)
 - Downside:
 - Can produce transient but immediate anxiety symptoms
 - Can make GI symptoms of withdrawal worse (opiates)

Treating BZD withdrawal with Medications:

Anti-convulsant mood stabilizers

- carbamazepine (Tegretol)
 - Used more in high-dose/short-acting BZD withdrawal or polydrug users
 - Provides anti-convulsant effect
 - Stabilize mood
 - May need to monitor WBC count
 - May decrease blood level of methadone due to hepatic enzyme induction (carbamazepine does not “play well with others”)

Treating BZD withdrawal with Medications:

Anti-convulsant mood stabilizers

- gabapentin (Neurontin)
 - Not approved as mood stabilizer but may have this effect
 - Has a gabaergic mechanism
 - May provide mild anti-anxiety effect
 - May be used in polydrug withdrawal
 - Has anti-convulsant effect
 - Can reduce certain types of pain
 - Not metabolized in the liver
(fewer drug-drug interactions)





to you all in your
professional and personal lives!