# 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.

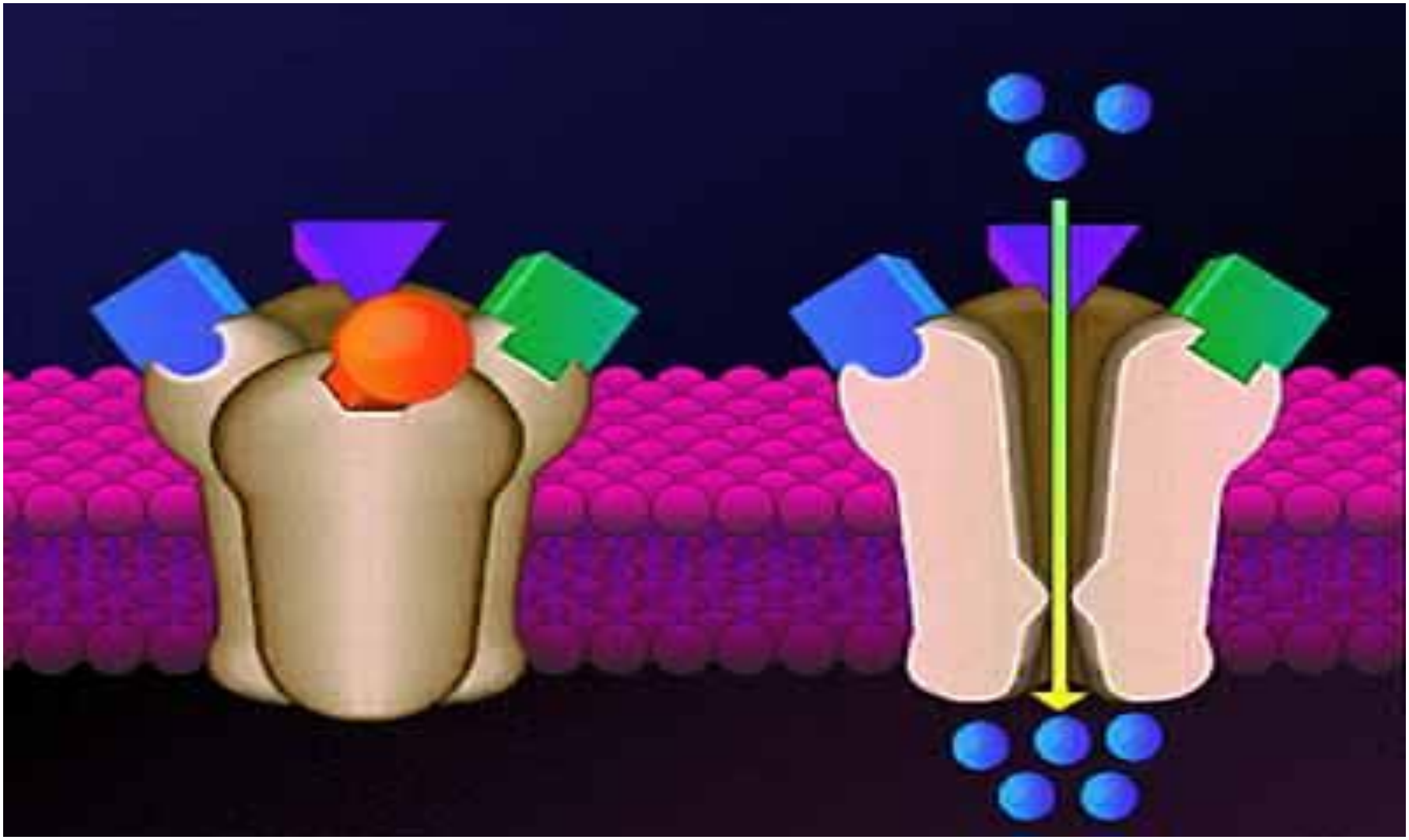
# Clinical Uses of BZDs

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

# Pharmacodynamics: How BZDS work

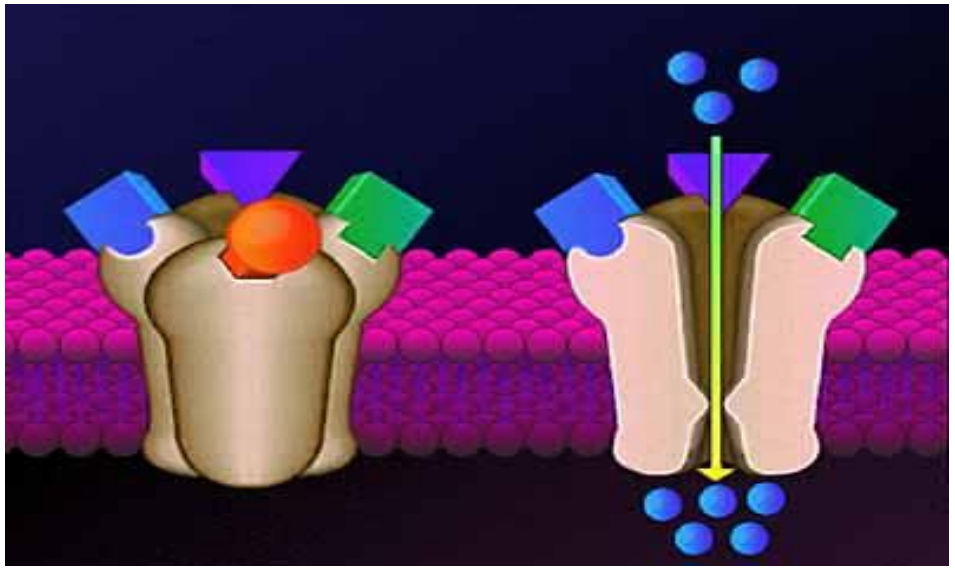
- Where in the brain? BZD receptor binding highest in:
  - Cerebral cortex
  - Hippocampus (& perhaps other limbic system structures)
  - Cerebellum
  - More moderate (but significant) binding in
    - Hypothalamus, thalamus
    - Basal ganglia (movement)

# The GABA-a receptor complex



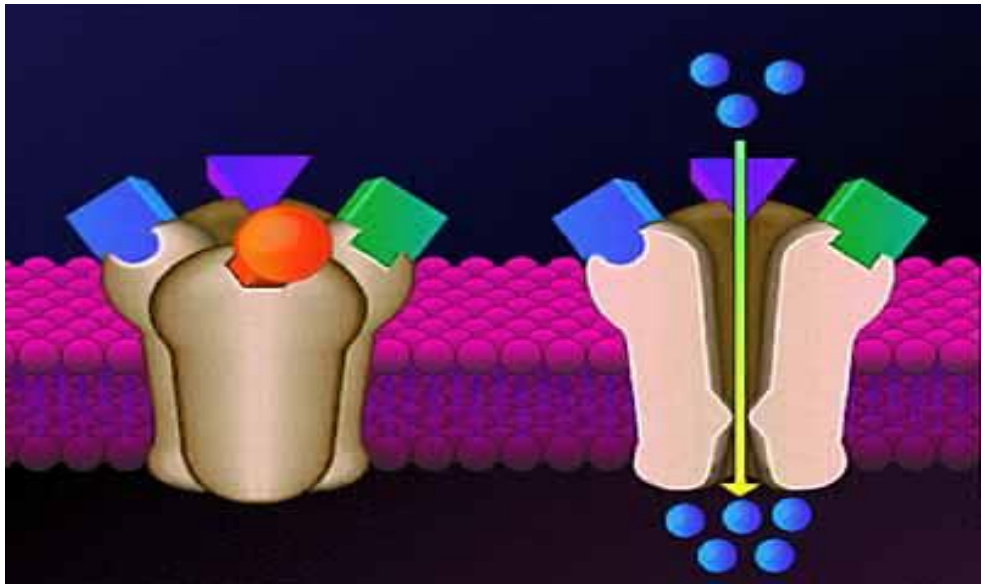
# Pharmacodynamics: How BZDS work

- 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



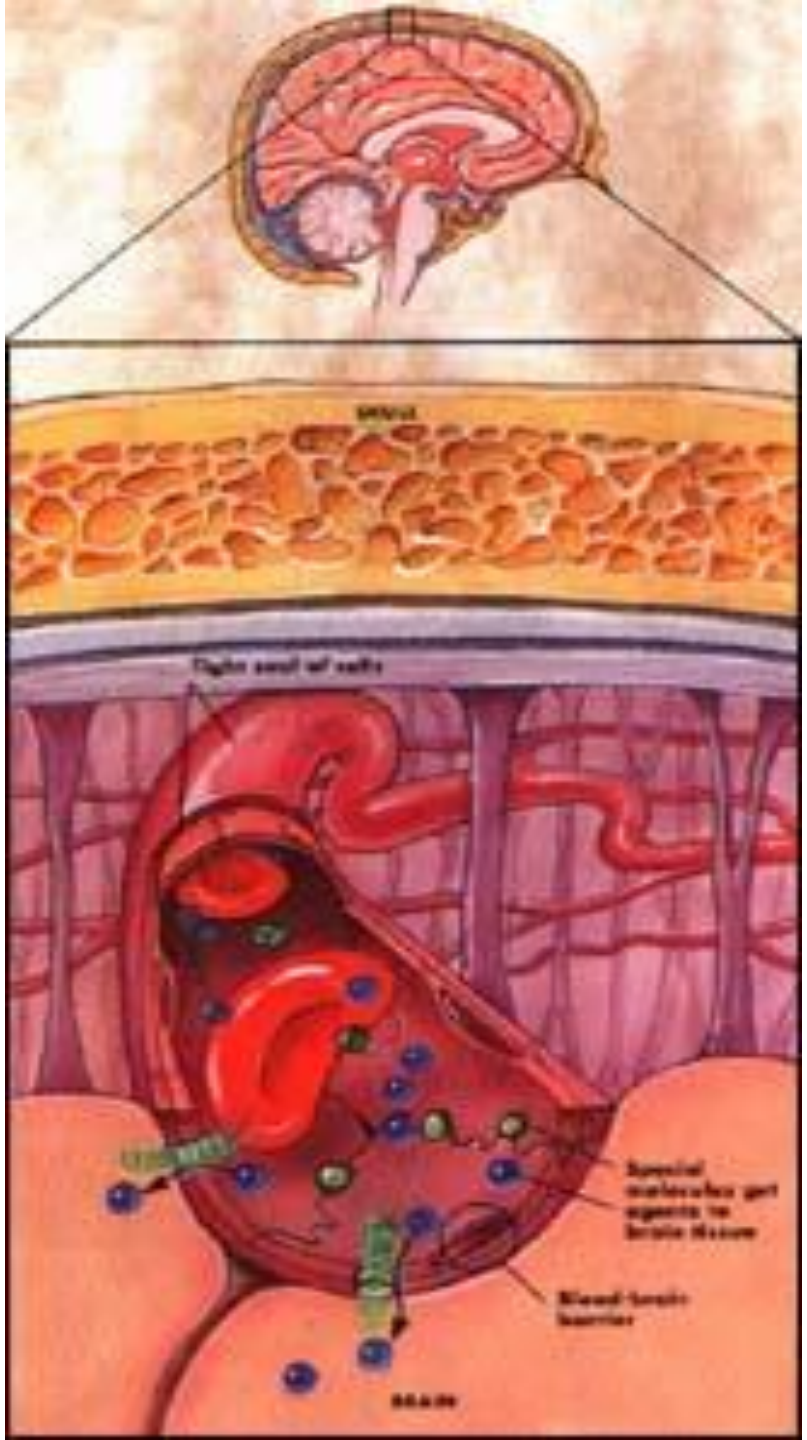
# Pharmacodynamics: How BZDS work (cont.)

- 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

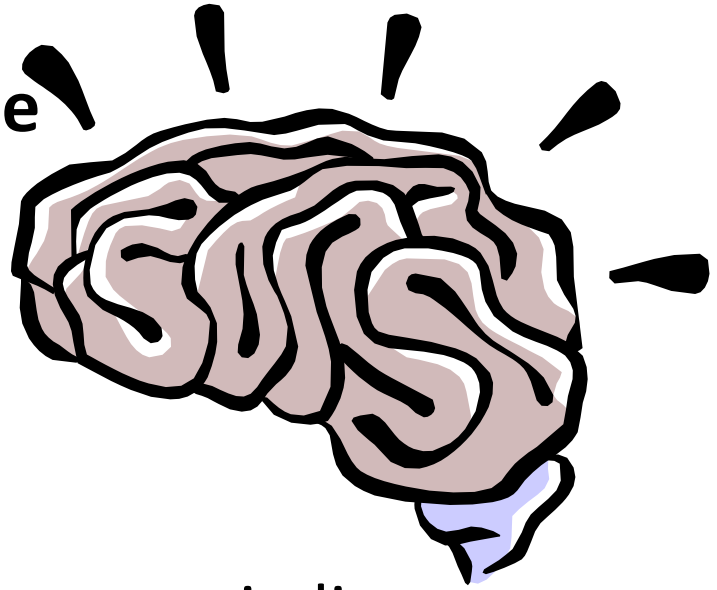
- Blood-brain barrier
  - Example: Imodium
- BZDs cross barriers easily
  - Blood brain barrier (BBB)
  - Placental barrier
  - These effects similar to other CNS depressants as well as psychostimulants
- Variable half-lives



# BZD Pharmacokinetics

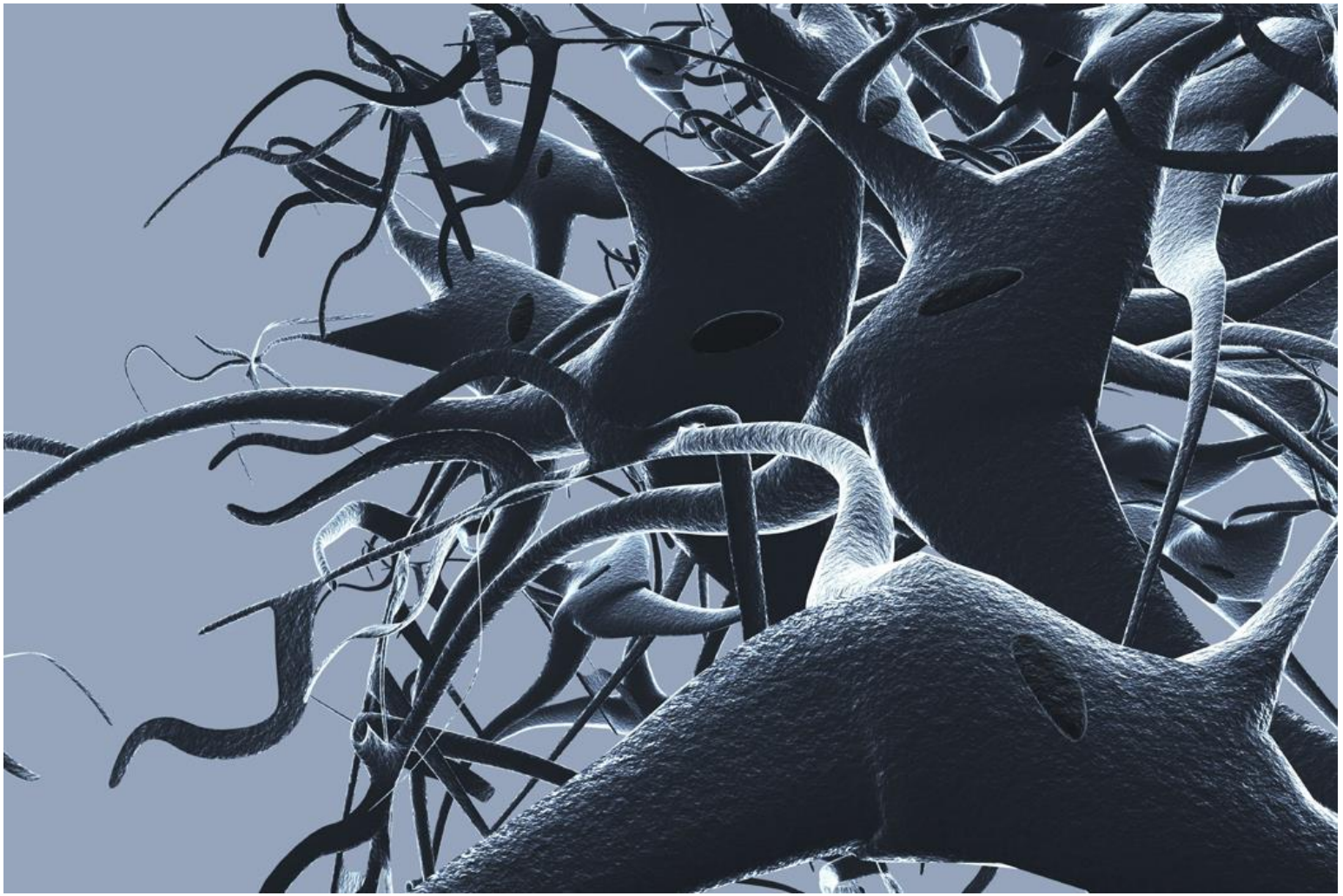
| Generic Name | Trade Name | Rapidity | ½ Life | Dose (mg) |
|---|---|---|---|---|
| alprazolam | Xanax | Intermediate | Short | 0.75-4 |
| chlordiaze-poxide | Librium | Intermediate | Long | 15-100 |
| clonazepam | Klonopin | Intermediate | Long | 0.5-4 |
| diazepam | Valium | Rapid | Long | 4-40 |
| 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

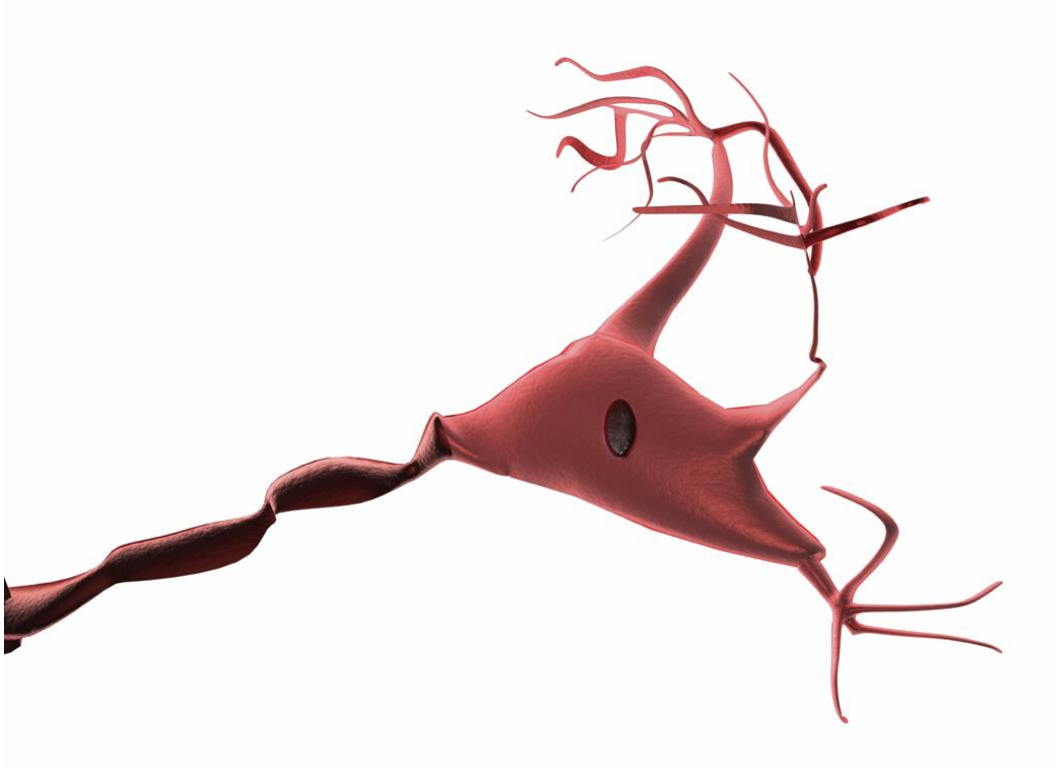
# Low Dose BZD Withdrawal (Perry, et. al., 2003)

- 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

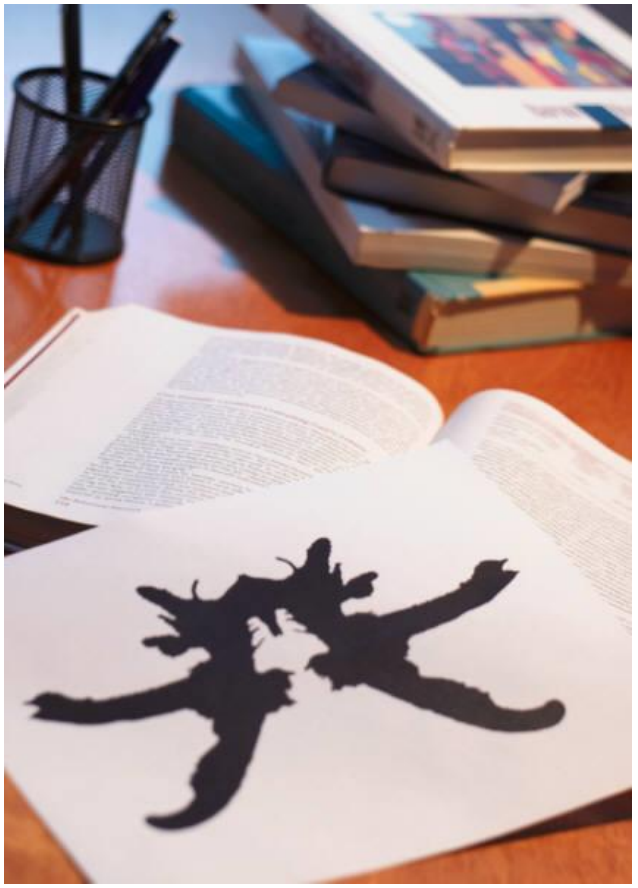
WITHDRAWAL

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

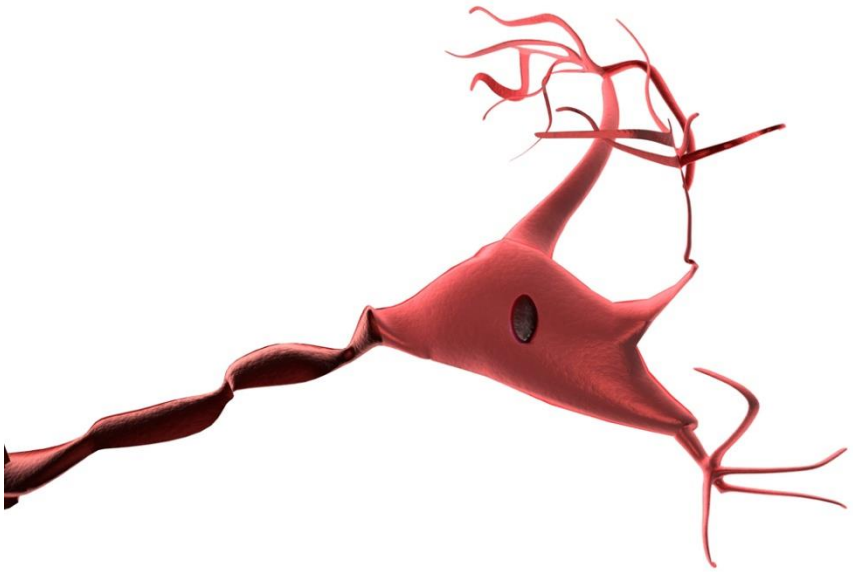
- Statistics somewhat more elusive than with low dose withdrawal given the ethical considerations of studying abrupt discontinuation of high BZD doses
  - Significant risk of more severe withdrawal symptoms
    - Symptoms occur sooner than with low dose d/c
    - Symptoms are more intense
    - Duration: 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!