SEDATIVE-HYPNOTICS: Benzodiazepines (p.1)

1. Introduction
   of all the sed-hyp drugs used to treat anxiety, the BZDs have been until very recently the major drugs of choice
   historically, ethanol and even opiates were used until the early 1960s when BZDs were initially marketed
   “anxiolytics” – anti-anxiety medications
   much safer than the barbs (which were marketed prior to 1960s)
   like other sed-hyp drugs, BZDs have a marked potential for abuse
   more recently, multiple transmitter system antidepressants have been shown to have good anxiolytic effects without any significant abuse potential,…may gradually replace use of BZDs…

   “ancient history” tranquilizing drugs: the propanediols
   e.g. meprobamate (Miltown, Equanil)
   synthesized in 1951, marketed in 1955

   seems to be an AChE agonist = cholinergic antagonist

   SEs: drowsiness, slower reflexes, ataxia, impaired learn/mem, reduced REM sleep
   does show tolerance, liver enzyme induction, dependence at higher dose levels (2-5x normal dose)

2. Development of the BZDs
   were first synthesized in 1933, but not developed as a saleable drug until 1957
   first BZD for sale in USA: chlordiazepoxide (Librium)
   in 1963 diazepam (Valium) was first marketed

   in 1970 flurazepam (Dalmane) was introduced as a sleeping pill (because it had a very long ½ life), and it displaced the use of barbs for this use

   BZD use peaked in 1973-75, and since then use has steadily declined
SEDATIVE-HYPNOTICS: BZDs (p.2)

2. Development of BZDs (cont.)
but the use has not declined to “none”, BZDs remain moderately frequently used esp. for tx of anxiety, muscle relaxation

3. Mechanism of Action
bind to a “BZD” subunit on the GABA RS complex
which then facilitates the binding of GABA to another part of the RS
which then allows more Cl- to enter post-synaptic membrane --- IPSPs

bind to GABA RSs in limbic system (amygdala, insula, orbitofrontal ctx)

esp. to hippocampus (where they may affect the NMDA RSs)

note: Ss prone to PAs/anxiety seem to be deficient in GABA RSs

3. Pharmacokinetics
like the barbs, the BZDs are all very similar to each other in their effects, but they vary in their lipid solubility and thus, they show a range of redistribution, absorption rates, and metabolism…all of which means that they vary as to their…?

can be classified as short-, medium-, or long-acting BZDs
short: 2 to 12 hours
e.g. Xanax (alpraxolam), Restoril (temazepam)
medium: 15 to 30 hours
e.g. Klonopin (clonazepam), Ativan (lorazepam)
SEDATIVE-HYPNOTICS: BZDs (p.3)

3. Pharmacokinetics (cont.)

*long: 30 to 80 hours*

  e.g. Valium (diazepam), Dalmane (flurazepam)

  *often the result of…

  implications for the “rules of 5”…

Routes of administration:

  usually PO, but sometimes injected

  e.g. w/ pt. in status epilepticus or to induce anesthesia

  might use Versed (midazolam) (2 l/2 hour ½ life)

  can also inject Valium & Ativan

Absorption from gut is fairly rapid, although antiacids decrease absorption

  peak absorption into plasma usually within 1-8 hours

Distribute easily within body tissues, although are *highly protein bound*

Metabolized by several liver microsomal enzymes, but do not significantly act as inducers to these enzymes

  several BZDs have *active metabolites* --- act to extend drug ½ lives

  Librium (chlordiazepoxide)

  Valium (diazepam)*

  Centrax (praxepam)

  Tranxene (chloraxepate)

  Dalmane (fluraxepam)

  *has several active metabolites besides oxazepam

Elimination is by kidneys, as inactive metabolites
SEDATIVE-HYPNOTICS: BZDs (p.4)

3. Pharmacokinetics (cont.)
   drug interactions
   BZD action is prolonged and potentiated by use of any other sed-hyp
e.g. ETOH, barbs.
   also by disulfiram (Antabuse), by certain drugs used to tx TB
   and by oral contraceptives

4. Miscel. Interesting Information
   drug Ambien (zolpidem) is structurally unrelated to the BZD molecule
   but it binds to the GABA 1a RS and has a hypnotic effect, but no
   anxiolytic effects
   used to tx. insomnia, does not have a high abuse risk

   GABA RSs found in ventral tegmentum & nucleus Accumbens
   these are likely to influence DA neurons, are part of “reward” pathway
   responsible for increasing the abuse potential of BZDs?

   GABA B RSs do not seem to be affected by BZDs (only the A RSs)

   # of BZD RSs correlates negatively with S’s general level of anxiety
   e.g. Maudsley “reactive rat” (selectively inbred strain) is highly
   behaviorally fearful (“anxious”), has very low #s of BZD RSs

   exposure to high environmental stressors --- changes in # BZD RSs…
   but some Ss show increase, while others show decrease…

   rats that are less fearful/less “anxious” (e.g. lots of handling) have more
   BZD RSs

   exposure to ETOH --- decrease in # BZD RS

   as S ages --- fewer BZD RSs (basis of increased fear/anx in older Ss?)
SEDATIVE-HYPNOTICS: BZDs (p.5)

5. Clinical Uses for BZDs
   a. anxiolytic (for anxiety, for PAs)
   b. muscle relaxant
   c. hypnotic effects
   d. anti-convulsant
   e. amnestic effects (e.g. before/during surgical procedure)
   f. acute ETOH withdrawal (includes uses a and d above)

note: in use for tx of insomnia
   must match reason for use (SOI vs. SMI) with drug’s ½ life
   do not use for chronic insomnia (tolerance, abuse potential)
   consider using Ambien (zolpidem), Sonata (zaleplon), zopiclone
   instead for more chronic use…no/little tolerance seen so far

   these are all non-BZDs molecules that bind to the same RS as BZDs
   tolerance develops to hypnotic effects of BZDs usually w/i a few
   days to several weeks if used chronically

note: BZDs have little effect on medullary respiratory control centers,
   thus are almost “suicide proof” if used alone…at least are much safer
   in overdose than are barbs or ETOH

note: chronic users of ETOH may become less sensitive to BZDs…why?

note: re. amnestic effects of BZDs (ref. to effects on NMDA RS in
   hippocampus)
   Rohypnol (flunitrazepam) is structurally very similar to Halcion
   (triazolam)
   Xyrem (gamma-hydroxybuterate or GHB) is also similar to BZD
   basic molecule but does not affect BZD GABA RS
   but is sed-hypnotic in effect
   all of these drugs when combined with ETOH really increase amnesia
SEDATIVE-HYPNOTICS: BZDs (p.6)

6. Side Effects (& Toxicity)

- sedation, drowsiness, ataxia, lethargy, mental confusion, exacerbation of dementia, sleepiness, motor impairments, cognitive impairments, disorientation, slurred speech, amnesia

- “paradoxical agitation” = increased anxiety, aggressiveness, hostility, behavioral disinhibition, hallucinations (with amnesia for all the prior), can look “manic”
- may be worse if pt. took both BZD and ETOH
- thought to be related to cortical inhibition, which then leads to subcortical disinhibition…

- changes in sleep architecture – esp. decreased stages 3/4 NREM sleep, and increased stage 2 sleep; REM fairly unchanged
- when D/C BZD use after chronic use --- rebound insomnia, agitation

- if have used a very short ½ life drug (e.g. Halcion), may get EMA due to rebound insomnia
- if have used a very long ½ life will get next day “hangover” EDS

7. Tolerance & Dependence

- tolerance can occur both to hypnotic and to anxiolytic effects
- dependence can occur
- withdrawal Sxs: increased anxiety, rebound insomnia, restlessness, agitation, some dream anxiety attacks (but not as bad as with barbs)
- rare Sxs: hallucinations, seizures, psychotic Sxs
- w/d Sxs usually gone in 7-30 days (read I am Dancing as Fast as I Can)

8. Effects in Pregnancy

- if taken in 1st trimester, can cause teratogenic effects
- if taken perinatal, can cause “floppy-infant syndrome”
- neonatal will go through w/d…
SEDATIVE-HYPNOTICS: BZDs (p.7)

9. Romazicon, Anexate (flumazenil)
drug has a high affinity for the GABA A RS, blocks this RS
so...completely reverses the BZD effects
but has such a short ½ life (about 1 hour), that BZD effects return

has been shown to improve memory in NCs...implications

can trigger PAs in sensitive pts.

10. Non-BZD Drugs Used as Anxiolytics
a variety of non-BZD drugs have been shown to be effective in treating
anxiety, esp. those that are 5HT 1a & 5HT 3 RS agonists
find these 5HT RSs esp. in hippocampus, septum, amygdala, & dorsal
Raphe nucleus, where 5HT 1a agonists are all anxiolytic

e.g. BuSpar (buspirone)
a weak 5HT 1a agonist
is not sedating, is not an hypnotic
does not produce amnesia, confusion, or ataxia
has no synergistic effect with other sed-hyps, incl. ETOH
has no cross-tolerance with other BZDs
has no drug dependence or abuse potential
does have also an antidepressant effect
shows very gradual onset of its anxiolytic (& antidepressant) effect
implications...
in children, may decrease irritability, aggression, & temper outbursts
in developmental disorders, oppositional defiant Dxs

e.g. Prozac (fluoxetine)
an SSRI (selective serotonin reuptake inhibitor)
is as effective as a BZD in decreasing anxiety, but takes 3-6 weeks
also with no drug dependency/abuse potential