**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

"a*nxiolytics*" – 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

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**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)

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**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)* Serax (oxazepam)

Centrax (praxepam)

Tranxene (chloraxepate)

Dalmane (fluraxepam)

*has several active metabolites besides oxazepam

Elimination is by kidneys, as inactive metabolites

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**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?)

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**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

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**6. Side Effects (& Toxicity)**

sedation, drowsiness, ataxia, lethargy, mental confusion, exacerbation of dementia, sleepiness, motor implairments, 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…

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**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