CNS Depressants

- Includes alcohol & a wide variety of drugs used as sedatives, hypnotics (sleeping pills), anti-anxiety tranquilizers, anesthetics, and anti-convulsants

Cause Dose-Dependent CNS Depression

- Depending on dose, you may experience
  - calming, relief from stress/anxiety
  - disinhibition, intoxication
  - slowing, sedation
  - sleep
  - anesthesia
  - coma
  - death due to respiratory depression

Other General Characteristics of CNS Depressants

- Additive or synergistic interaction with other depressants
- Cross-tolerance & cross-dependence
- Low doses may appear “stimulating” because of depression of inhibitions
- All enhance actions of GABA
- Cognitive inhibition (impair memory, judgment)
- Hyperexcitability rebound afterwards
- Withdrawal can be dangerous

GABA Receptor Complex

Barbiturates

Classic non-selective sedative/hypnotics or “downers” that dominated the market
1903-1960 (still used for select purposes)
Barbiturate History

- Developed in 1860’s by Adolph Bayer
- 1st marketed in 1903
- Superseded by more selective drugs for most uses, but ~ 12 different barbs currently available, most for oral use, 4 for injection

Characteristics of Barbiturates

- Barbs differ in length of action
  - Utrashort (minutes, because of re-distribution)
  - Short < 4 hr
  - Intermediate 4-6 hr
  - Long > 6 hr
- Barb effects almost indistinguishable from those of alcohol
- Barbs have an extra transmitter action (decrease excitatory actions of glutamate throughout brain) which broaden their effects and increase lethality.
- Can’t get anti-anxiety effects without full CNS depressant actions.

Some Well-Known Barbs

- sodium thiopental (Pentothal)(U)
- secobarbital (Seconal)(S)
- pentobarbital (Nembutal)(S)
- amobarbital (Amytal)(I)
- phenobarbital (Luminal)(L)
- mephobarbital (Mebaral) (L)

FYI – Brevital (methohexital) is another ultra-short similar to Pentothal but Diprivan (propofol) (Michael Jackson’s drug of choice) is a “non-barbiturate” hypnotic/anesthetic

Barbiturate Withdrawal

- begins with growing anxiety, agitation, the shakes, GI upset & bodily arousal
- severe withdrawal includes delirium, seizures, uncontrolled HR & possible death, even with medical supervision
- This dose-dependent withdrawal is very similar to alcohol withdrawal & is characterized by hyper-excitability of body and brain.

Problems With Barbs

- Nonselective effects even at low doses
- Low safety margin; easy to overdose & cause lethal depression of breathing; used in suicides
  - Such a good “killer” its used in assisted suicides & lethal injections
  - Used in 27% of geriatric suicides
  - No antidote except life support, activated charcoal & hemodialysis
- Dangerous interaction with other depressants
- Rapid development of tolerance
- Risk of significant dependence – all barbs are “Controlled Substances” (amo, pento and seco are Schedule II)
- Possibly life-threatening withdrawal
- Decreased REM sleep; morning grogginess
- Withdrawal rebound of insomnia & anxiety
- Memory and cognition impaired (like alcohol)
- 2-3 X increase in birth defects (from 1/100 to 2-3/100 births) (still probably better for epileptic women to stay on meds during pregnancy

Reasonable Uses for Barbs Today

- To control seizures (perhaps only good reason for use of oral barbs)
- As an intravenous anesthetic; Wada test
- Sedation in emergencies
- Induced coma to reduce brain activity, swelling, blood flow & release of glutamate after severe head injury or stroke
- In assisted suicides/lethal injections
- Barbs should not be used as anxiolytics or hypnotics
**FYI** – less common, low-dose uses
- Added to some migraine or tension headache meds to relax person
  - (e.g. Fiorinal, Fiorace)
- Added to some bowel-spasm meds to relax person
  - (e.g. Donnatel)
- Sometimes used in psychotherapy particularly for psychogenic conditions (like dissociative amnesia, conversion disorder, psychogenic mutism, catatonia) – the drug-assisted “amytal interview”

“Non-Barbiturate” Sedative-Hypnotics

Several drugs were released claiming to be big improvements over the barbs
- Examples:
  - methaqualone (Quaalude)
  - meprobamate (Miltown)
- Turned out not to be significant improvements & one after another have been removed from the legal market

Finally, in the 1960’s, :

**Benzodiazepines**

- “Minor Tranquilizers” or “Anxiolytics”
- More selective CNS Depressants (doses that relieve anxiety do not produce as much general depressant action as barbs)
- 15 different benzos currently available, differ in half-life/time course
- Act via benzodiazepine receptor on GABA receptor, increasing the calming effects of GABA (they are sometimes called BZRAs)

**Benzos Are Classified by Length of Action**

<table>
<thead>
<tr>
<th>Table 13.5</th>
<th>Kinetic Classification of Benzodiazepines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Half-life (hours)</td>
</tr>
<tr>
<td>Long half-life</td>
<td></td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>75</td>
</tr>
<tr>
<td>*Diazepam (Valium)</td>
<td>50</td>
</tr>
<tr>
<td>Intermediate half-life</td>
<td></td>
</tr>
<tr>
<td>*Alprazolam (Xanax)</td>
<td>15</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>15</td>
</tr>
<tr>
<td>Short half-life</td>
<td></td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>4</td>
</tr>
<tr>
<td>Midazolam (Versed)</td>
<td>1</td>
</tr>
</tbody>
</table>

- As soon as we cover a drug family, DO something to review, summarize, & create a study aid to re-read regularly until our next exam.

http://www.uni.edu/walsh/drugcategory.html
http://www.uni.edu/walsh/drugcategorybarb.html

Long Acting Benzodiazepines

- *Valium – diazepam (1/2 life ~50 hrs)
- *Librium – chlordiazepoxide
- Dalmane – flurazepam
- Paxipam - halazepam
- Centrax - prazepam
- Tranxene - chlorazepate
- Provide sustained effects when needed (anticonvulsant, muscle relaxant; alcohol detoxification; anti-anxiety)
- Should be avoided in the elderly!
Short and Intermediate Acting Benzodiazepines

- *Xanax* - alprazolam (15 hrs)
- Halcion - triazolam (4)
- Restoril - temazepam
- Ativan – lorazepam
- Serax - oxazepam
- Klonopin - clonazepam
- Pro-Som – estazolam
- Versed - midazolam (1)

Used to treat insomnia without producing daytime sedation; also for anxiety disorders. Used as surgical anesthetics.

“Approved” vs “Off-Label” Use of a Drug: An Example

- Brand name drug companies that produce Halcion, Restoril and Dalmane did the years of research necessary to get FDA approval to market their drugs as hypnotics & list this use in their package insert. This is a FDA “approved use” of these drugs.
- If doctors prescribe other benzodiazepines to promote sleep (ones that did not submit such research related to sleep to the FDA), use for that purpose would be “off-label” (those drugs cannot be marketed for that use & can’t list that use on their label or package insert).

*“Off-Label Use”*

- Some off-label use involves drugs very similar to those that have been approved by the FDA for that use, so it is reasonable to expect similar therapeutic benefits
- But some “off-label” use is very experimental (doctor is prescribing drug for a condition despite little or no published research (yet) supporting this use).

Benzodiazepine Benefits

- wide safety margin (high LD) as long as other depressants aren’t used
- 2 antidotes for overdose available:
  - antagonist *flumazenil* (Romazicon) (short half-life, must be re-administered)
  - NEW! narcotic antagonist Narcan (naloxone) can also help in benzo overdose! (but not good if person is opiate dependent)
- less tolerance and dependence than barbs
- less dangerous withdrawal (can be delayed several days due to longer half-life)
- sleep somewhat more normal than with barbs (but still REM suppression)

Problems With Benzodiazepines

- Great for short term use, but dependency & abuse still possible with extended use (Schedule IV drugs)
- Significant cognitive/memory storage impairment
- Driving impairment (2); interaction with alcohol
- (low dose Xanax= impairment like BAC .15)
- May cause birth defects in 1st trimester
- Over-response in elderly common; idiosyncratic responses possible in them, brain-damaged or those with personality or impulse control disorders

* Sometimes used specifically for this purpose – e.g. ultrashort acting midazolam (Versed) for colonoscopy. Benzos primarily produce anterograde amnesia.
Clinical Notes

- Don’t address the source of anxiety; may decrease effectiveness of cog-behav therapy
- Rebound insomnia & anxiety possible when stopped, promoting continued use
- Taper dose slowly over months to stop

Drug Abuse Warning Network (DAWN)

- Network of metropolitan hospitals with ER departments
- From ER medical records glean how many visits are associated with different drugs

Benzo Withdrawal: Rebound Hyperexcitability

Not as dangerous as barb withdrawal because it is naturally more gradual
But rebound insomnia, anxiety, restlessness, agitation & irritability make quitting difficult for dependent users
In rare cases can get DTs & seizures like barbs
Even after withdrawal users are prone to relapse (like alcoholics)

Benzos May Be Following the Barbs Out of Widespread Popular Use

- Benzos are being replaced by safer, more selective drugs for many, if not most, of their therapeutic uses.
- Use for anxiety now being replaced by antidepressants (& sometimes other drugs) – more than a 50% decrease in benzene prescriptions
- Use for insomnia decreasing as well
- BUT: Swing to new drugs may be going too far!
- Benzos still have their place & new drugs have their own problems.

Rohypnol - a “date-rape drug”

- “Roofies” contain a high potency* benzo (flunitrazepam) not marketed in the US, but similar to Halcion.
- Actually any combination of alcohol + sufficient benzo could produce similar effects.
- Impairs consciousness & memory of victim
- DAWN reports about 15,000/yr cases of such “intentional poisonings”, 2/3 in females, ~60% via tainted drinks
- http://www.youtube.com/watch?v=iZ85R1YtgKI

*High-potency benzos only require a low dose (e.g. 6 mg Xanax is equivalent to 60 mg. Valium, a low potency benzo)
GABA –related Club Drug
Gamma-hydroxybutyrate (GHB)
(street name Georgia Home Boy, Grievous Harm to Body, & several inaccurate refs to Ecstasy or Everclear)
- Potent depressant used as a general anesthetic in some countries and as date-rape or club drug in others
- Found in the CNS – some GABA is converted into GHB
- Overdose can be deadly – nausea, vomiting, loss of consciousness, respiratory depression, possible seizures
- DAWN reports ~ 3400-5,000 overdoses per yr, 72 fatal
- Now a Schedule I drug AND a Schedule III drug (Xyrem) for improving nighttime sleep/decreasing daytime sleepiness in narcolepsy
  - http://www.youtube.com/watch?v=-nbO-T4CzIo FDA Alert

The Trend in Drug Development:
The Search for Even More Selective Drugs
- more “selective” drugs affect only a sub-group of receptors
- Non-Benzodiazepine Selective BZRAs
  - zolpidem (Ambien) Primarily sedative/hypnotic effects with little anti-anxiety, anticonvulsant or muscle relaxing effects. More normal sleep, less insomnia rebound. Half-life 2 hrs; short-term use only
  - zaleplon (Sonata) – half-life >1 hr, so can be taken in middle of night (about 4 hr effect).
  - eszopiclone (Lunesta) Half-life ~6 hrs – approved for use up to 6 months
  - http://www.fda.gov/forconsumers/consumerupdates/ucm107757.htm
- Research on Ambien just raised a more general drug issue: lack of attention to sex differences in drug response 

Other Alternatives to CNS Depressants
- Antihistamines (for sedative/hypnotic effects)
  - diphenhydramine (Benadryl) (OTC)
  - hydroxyzine (Atarax, Vistaril)
  - promethazine (Phenergan)
- Melatonin (OTC supp) or a melatonin agonist (prescrip) Rozerem to help one fall asleep
- Beta-blockers (decrease body signs of anxiety)
  - propanolol (Inderal), atenolol (Tenormin), metoprolol (Lopressor),
- Antidepressants
  - trazodone (Desyrel), amitriptyline (Elavil) & doxepin (Sinequan) used for sleep
  - SSRI's now used for most anxiety disorders – we’ll cover these later in the semester

Anti-anxiety Drug Not Working on GABA
- Selective 5HT-1A agonist buspirone (Buspar) (antianxiety but not CNS depressant)
  - Delayed (2-4 weeks) antianxiety action without sedation, incoordination, memory problems, depressant interactions, dependency (good for those with abuse risk or drinking problem). May not be as effective for panic disorder.
  - Side effects: headache, dizziness, nausea

Before we leave prescription CNS Depressants let’s mention 2 groups of medical drugs that are in this category that we are not covering in detail.
- Anticonvulsants: the majority of the many drugs used to control seizures enhance the calming action of GABA like other depressants.
  - (We’ll come back to a few of the anticonvulsants being used as psychotherapeutic drugs later in the semester.)
- General Anesthetics: Exert dose-dependent CNS depressant effects
  - Additional complication of inhaled anesthetics – decrease/displace the inhalation of oxygen. Except in the hands of a trained anesthesiologist there is a very real risk of hypoxia and brain damage.

Before we leave prescription CNS Depressants let’s mention 2 groups of medical drugs that are in this category that we are not covering in detail.
- (We won’t cover individual anesthetics except nitrous oxide and GHB as substances of abuse.)