

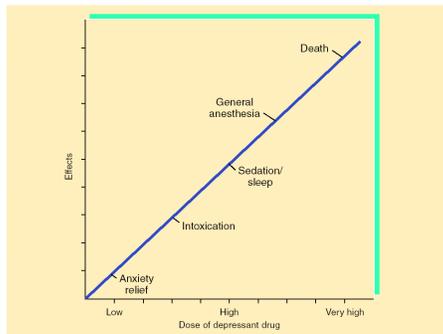
CNS Depressants

- 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

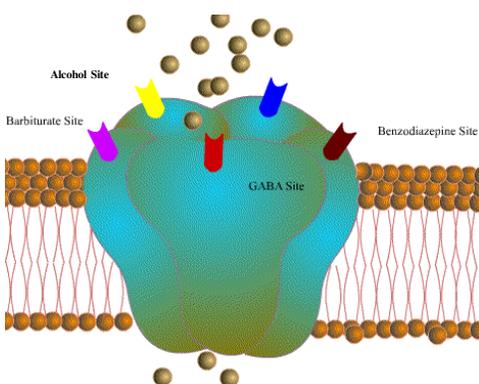
Effects per dose of a depressant drug



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		Generic Name	Street Name
		Amobarbital	Downers, blue heavens, blue velvet, blue devils
		Pentobarbital	Nembies, yellow jackets, abbots, Mexican yellows
		Phenobarbital	Purple hearts, goof balls
		Secobarbital	Reds, red birds, red devils, lilly, F-40s, pinks, pink ladies, seggy
		Tuinal	Rainbows, reds and blues, toolies, double trouble, gorilla pills, F-66s

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- Superseded by more selective drugs for most uses, but ~ 12 different barbs currently available, most for oral use, 4 for injection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
 - ultrashort (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 transmitters 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

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)

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.

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, Fioracet)
 - 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”

Always be wary of “new drug” claims

“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



Diazepam
Valium
Xanax

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 13.5 Kinetic Classification of Benzodiazepines

Type	Half-life (hours)
Long half-life	
Flurazepam (Dalmane)	75
* Diazepam (Valium)	50
Intermediate half-life	
* Alprazolam (Xanax)	15
Lorazepam (Ativan)	15
Short half-life	
Triazolam (Halcion)	4
Midazolam (Versed)	1

- 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) Ativan – lorazepam
- Halcion - triazolam (4) • Serax - oxazepam
- Restoril - temazepam • 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”

- <http://www.consumerreports.org/cro/2012/05/off-label-drug-prescribing-what-does-it-mean-for-you/index.htm>
- 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)

- After their introduction in the 1960’s, benzodiazepines became THE most widely prescribed psychotherapeutic drugs until nearly the 1990’s.
- Because they were an improvement over earlier drugs, they ended up being over-prescribed without appropriate caution.

<http://www.youtube.com/watch?v=FEIq1as2ppc>

Problems With Benzodiazepines

- Great for short term use, but dependency & abuse still possible with extended use (Schedule IV drugs)
- Significant cognitive/memory storage impairment
- <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC209268/>
- [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

Table 2. Misused or Abused Drugs Most Commonly Involved in Emergency Department (ED) Visits: 2009

Drugs	Number of ED Visits	Number of ED Visits per 100,000 Population
Alcohol in Combination with Other Drugs*	519,650	169.3
Underage Drinking**	199,429	227.2
Illicit Drugs	973,591	317.1
Cocaine	422,896	137.7
Marijuana	376,467	122.6
Heroin	213,118	69.4
Pharmaceuticals	1,244,679	405.4
Pain Relievers	595,551	194.0
Narcotic Pain Relievers	397,160	129.4
Oxycodone Products	175,949	57.3
Hydrocodone Products	104,490	34.0
Drugs to Treat Insomnia and Anxiety	433,600	141.2
* Benzodiazepines	373,328	121.6
Antidepressants	104,940	34.2

* Use of alcohol in combination with other drugs is recorded by DAWN for patients of all ages.
 ** Underage drinking includes both use of alcohol in combination with other drugs and use of alcohol only for persons aged 20 or younger.
 Source: 2009 SAMHSA Drug Abuse Warning Network (DAWN).

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 benzo 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-T4Czlo> 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
[Spooof Lunesta commercial](http://www.fda.gov/forconsumers/consumerupdates/ucm107757.htm)
 - Take these at bedtime only; DO NOT DRIVE, may increase bizarre sleep-walking, sleep eating in some with no memory of event
 - <http://www.fda.gov/forconsumers/consumerupdates/ucm107757.htm>
 - http://www.nytimes.com/2007/03/15/business/14sleep.web.html?ref=science&_r=0
- Research on Ambien just raised a more general drug issue: lack of attention to sex differences in drug response <http://www.cbsnews.com/news/sex-matters-drugs-can-affect-sexes-differently/>

Other Alternatives to CNS Depressants

- Antihistamines (for sedative/hypnotic effects)
 - diphenhydramine (Benedryl) (OTC)
 - hydroxyzine (Atarax, Visteril)
 - promethazine (Phenergan)
- Melatonin (OTC supp) or a melatonin agonist (prescrip) Rozerem to help one fall asleep
- Beta-blockers (decrease body signs of anxiety)
 - propranolol (Inderal), atenolol (Tenormin), metoprolol (Lopressor),
- Antidepressants
 - trazodone (Desyrel), amitriptyline (Elavil) & doxepin (Sinequan) used for sleep
 - SSRIS 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.

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- 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.
- (We won’t cover individual anesthetics except nitrous oxide and GHB as substances of abuse.)