

## Central Nervous System Depressants: Sedatives, Hypnotics, and Anxiolytics, and CNS Stimulants

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**Important note: The corresponding material presented in lecture will cover just the “highlights” of what is in this file. Be sure to study this file in its entirety, and be sure to read the corresponding text chapter(s).**

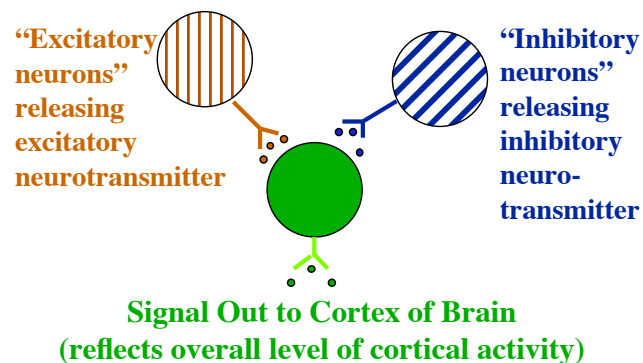
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## General Concepts of CNS Organization

- Specific brain regions have specific functions.
- There is considerable integration between CNS and peripheral nervous systems (ANS, somatic) via efferent and afferent pathways.
- Excitatory and inhibitory neurotransmitters work in opposition to one another to maintain – or alter – various CNS functions and the level of activity of those functions.
- The cerebral cortex is main regulator of how “awake/alert” you are (or aren’t), and it has significant influences on other parts of the brain.
- Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the CNS and the spinal cord.

The Overall Level of Cerebral Cortical Activity,  
Many Other Aspects of CNS Function, are  
Controlled by a Balance Between “Excitatory”  
and “Inhibitory” Neurons/Neurotransmitters



## CNS Depressants

- Many groups of drugs → generalized CNS depression (mainly via actions on the cerebral cortex), but one main group is widely used therapeutically for this purpose: *benzodiazepines*
- All CNS depressants, regardless of class, potentiate the CNS depressant actions of all others

## All CNS Depressants, Regardless of Class, Potentiate the CNS Depressant Actions of All Others

**Example:** Let's rate the intensity of CNS depression caused by a drug on a scale of 0-10, with 0 = no effect, 10 = profound (perhaps even fatal) CNS depression.

CNS depressant effect of Drug A\*, given by itself = 2

CNS depressant effect of Drug B\*, given by itself = 2

Give both A and B and the outcome is >>> 4\*

\*If drugs A and B are in different classes, e.g., one is a benzodiazepine, the other is alcohol.

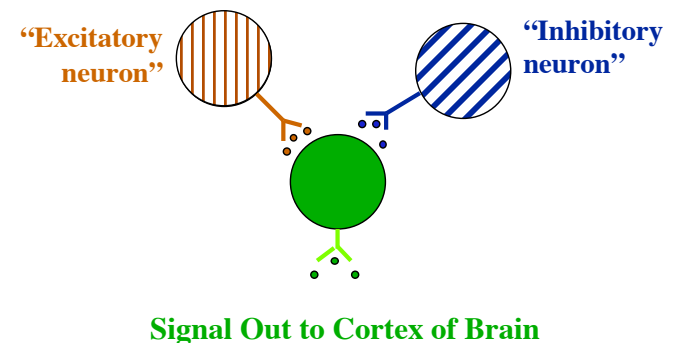
## When Might CNS Depressants Be Needed or Used?

- Relieve anxiety
- Manage sleep disorders
- Prevent, treat seizures
- Before or during anesthesia
- Recreational

## Dose-Dependency of Effects of CNS Depressants

- As doses (brain drug levels) rise the degree of CNS depression intensifies:
  - “Excitement” – what appears to be CNS stimulation, but is actually *selective inhibition of inhibitory neural pathways in the cerebral cortex*, then...
  - Anxiolytic effects, then...
  - Sedation, then...
  - Hypnosis (induction of sleep), then,,
  - Coma, ventilatory and CV depression, death

What would happen to the level of the “signal out” neuron’s activity if we gave a drug and dose that selectively depressed the activity of only the “inhibitory neuron” shown below?



## **Gamma-Amino Butyric Acid (GABA)**

- Is brain and spinal cord's *main inhibitory neurotransmitter*
- Acts on specific GABA receptors to ↓ neuron function
- Actions ↑ by nearly all CNS depressants, but in different ways depending on drug class
- GABA itself has no therapeutic use: it can't cross blood-brain barrier to act in CNS

## **Gamma Hydroxybutyrate (GHB)**

- When administered, crosses B-B-B, is metabolized to GABA, which → CNS depression
- Used as sedative, hypnotic, anesthetic adjunct drug in Europe (but NOT in US)
- Most common use is probably as one of several “date rape” drugs
- CNS depressant actions ↑↑↑ by other CNS depressants, including alcohol, with sometimes fatal outcomes
- State and Federal laws ban manufacture, possession, use (it's a felony!)

## **Benzodiazepines: The Main Class of CNS Depressants**

**Prototype: Diazepam (VALIUM)**

## **Benzodiazepine Pharmacokinetics**

- Eliminated by metabolism, excretion, or both, depending on the drug
- Some benzos → many metabolites
  - Some metabolites are active, others inactive
  - Some metabolites may have half-lives very different from original drug, e.g., the “hangover” (residual CNS depression) from a single dose of some benzodiazepines is not due to the original drug (it has completely disappeared due to metabolism), but to long-lasting active metabolites

## **Physical Properties, Pharmacokinetics, & Clinical Use**

- No predictable relationship between onset and duration... e.g., some act quickly and have long-lasting effects, others act quickly and only briefly, etc.
- Those with high lipid solubility...
  - have fastest onset (rapid access to brain), and so are used when quick effects needed (e.g., help going to sleep, stopping acute seizures, inducing anesthesia)
- Those with low lipid solubility...
  - slower onsets, mainly given orally, long-term, for longer-lasting effects (e.g., ↓ of anxiety s/sx)

## **Benzodiazepine Receptors**

- **Benzos act as agonists on specific benzo receptors in the brain and spinal cord to potentiate actions of GABA**

## **Benzodiazepines: Some Advantages Over Other Classes of CNS Depressants**

- **Do not induce P-450 system (i.e., few DDIs due to altered drug metabolism)**
- **High therapeutic index when given orally and with no other CNS depressants**
- **Low(er) risk of tolerance, dependence than older anxiolytics or hypnotics/sedatives**

## **Benzodiazepines as Anxiolytics/Sedatives**

- **Almost always preferred to other drugs for anxiety, sedation, but..**
- **Still widely misused, abused, overused**
- **Rebound ↑ CNS stimulation (↑↑ anxiety) when abruptly stopped...**
- **↑ risk of seizures in patients with history of epilepsy upon suddenly stopping**

## Some Benzodiazepine Anxiolytics\*

- alprazolam (XANAX)
- clorazepate (TRANXENE)
- chlordiazepoxide (LIBRIUM)
- *diazepam* (VALIUM)
- *lorazepam* (ATIVAN)
- oxazepam (SERAX)

\*Diazepam and lorazepam are the only ones you need to know specifically. You also need to know lorazepam as the “drug of choice” [(along with phenytoin) for treatment of emergency seizures -- status epilepticus]

## Benzodiazepines as Hypnotics

- Hypnotic drug: one that induces sleep
- Hypnotic dose > sedative/anxiolytic dose
- All benzos can → sleep, but only some have “ideal” pharmacokinetics that → sleep quickly enough to be useful as hypnotics
- Nightmares, daytime drowsiness for some pts.
- Misused, abused, overused (best to limit to 7-10 days at a time)
- Suddenly stopping: worse insomnia, altered sleep patterns, and ↑ risk of seizures in patients with epilepsy
- Use for sleep ↓ as use of benzo-like agents (see zolpidem, etc., later) rises

## Some Benzodiazepine Hypnotics

- flurazepam (DALMANE)
- temazepam (RESTORIL)
- triazolam (HALCION)

For “name recognition” only.

## Other Benzo Uses

- Preanesthetic adjunct, “conscious sedation”
- Cause **antegrade amnesia**
  - midazolam (VERSED) is by far the most popular agent
    - fast, short acting
    - less irritating to veins than most alternatives
- **Relief of muscle sprains, strains** (diazepam)
- **Anticonvulsant** [lorazepam mainly for status epilepticus — given IV]

## Conscious Sedation

- More properly known as *sedation plus analgesia*
- Goal is to quickly but briefly render the patient sedated (but conscious), with intact ventilation and gag reflexes, plus little/no recall of events for a short time after drug given
- Commonly done with a combination of IV midazolam (VERSED) + fentanyl, (fast-acting, short-acting, and very potent opioid *analgesic*)

## Benzodiazepines Have NO Analgesic Activity

## Side Effects

- Expected responses due to progressive CNS depression + ataxia
- **Elderly pts.** far more susceptible to cognitive impairment, confusion, falls, etc.
- For all drugs, doses, uses: caution Pt. re: dangers

## Benzodiazepine Toxicity

- **Oral agents, taken with no other CNS depressant(s)**
  - deep sleep is most likely outcome of “massive” overdoses, with mild-moderate CV and respiratory depression
  - rarely fatal
- **Benzo (any route) + any other CNS depressant**
  - ↑↑ risk of respiratory arrest. CV depression, death
- **IV agents:** generalized CNS depression + risk of respiratory arrest (or at least inadequate ventilation) + CV depression (↓ HR, contractility, BP) are main concerns, even when benzo used alone
- **For ALL severe ODs:** treatment = flumazenil + symptomatic supportive care

## Flumazenil (ROMAZICON)

- A specific antagonist (blocker) at benzodiazepine receptors
- Used to diagnose or treat known or suspected overdoses of a benzodiazepine
- Has NO effects on receptors for other drugs, including nonbenzo CNS depressants, alcohol, opioids, etc.

## Other Benzo Issues

- Tolerance with continued use slight when used for hypnotic and anxiety-relieving effects, but more important when used for seizure control (anticonvulsant/anti-epileptic effects)
- Physical dependence – occurs, since a withdrawal syndrome can occur upon abrupt discontinuation: anxiety, insomnia, tremors, sweating
- Benzo withdrawal syndrome rarely fatal unless seizures occur (pts. with epilepsy have greatest seizure risk)
- Prevent problems by proper prescribing, educating patient about risks of excessive/prolonged use

## Flunitrazepam (ROHYPNOL) “Roofies”

- Originally developed as benzodiazepine hypnotic and anesthetic adjunct, now a popular “date-rape” drug
- Not approved (or legal) in US
- High lipid solubility
- About 10-x potency of diazepam
- Causes “typical” benzo effects, including amnesia, and effects are dramatically intensified/potentiated by alcohol

## Some New Benzodiazepine-Like Hypnotics

Zalpelon (SONATA)

Zolpidem (AMBIEN, AMBIEN CR)

Eszopiclone (LUNESTA)

Chemically are not benzodiazepines, but do exert their hypnotic effects by binding to benzo receptor sites.

Are not approved for use as anxiolytic drugs

Lower abuse/dependency, replacing benzos as preferred (but more expensive) hypnotics.

See your text for main differences between these and benzodiazepines.

## **Barbiturates: Another (and Old) Class of General CNS Depressants**

- Once widely used, now seldom used, for inducing sleep, managing anxiety disorders
- Many general pharmacologic properties of barbiturates are very similar to those of alcohol (ethanol)

## **Barbs and Benzos: Similarities**

- Enhance GABA effects on neurons
- Dose-dependent CNS depression
- Interact with all other CNS depressants to → ↑ CNS depression
- No analgesic activity

## **The Problems With Barbiturates (and Alcohol)**

- Induce the P450 system → *many* DDIs
- Very low therapeutic index
- Risks of abuse, dependency, tolerance rather high
- Overdoses and withdrawal more likely fatal (mainly because acute and life-threatening seizures occur)
- No antidote for OD, as there is with benzos

## **Barb Tolerance and Dependence**

- Tolerance to desired effect(s) develops more, and more quickly, than tolerance to lethal dose (→ ↓ therapeutic index)
- Acute withdrawal more likely to be fatal (seizures → apnea)

## **Barbiturates: The Status**

- **Phenobarbital** safe, effective, OK to use long-term for epilepsy
- **Some rapid-acting/very short-acting barbiturates** commonly used during anesthesia
- **Otherwise:** use for anxiety, insomnia, not rational or justified

## **Miscellaneous Agents**

- **Antihistamines** (1<sup>st</sup> generation only, eg, diphenhydramine, which is the most widely used OTC sleep aid)
- **Ethanol**

## **Ethanol (EtOH)**

- **Pattern of CNS depression, dose-dependency, similar to barbiturates**
- **Dose-dependent stimulation (low blood levels) or inhibition (high doses or chronic use) of P450 system** → many drug-drug interactions
- **Tolerance, dependence are common with long-term use**
- **Therapeutic index ↓ as tolerance develops**
- **Withdrawal from severe dependence often fatal (because of seizures) unless managed properly**

## **CNS Stimulants**

### **Examples:**

**Dextroamphetamine (DEXEDRINE)**

**Amphetamine mixture (ADDERALL)**

**Methylphenidate (RITALIN)**

See Exam 1 notes... autonomic / indirect-acting sympathomimetics.

## Main Actions of CNS Stimulants

- Are, basically, indirect-acting sympathomimetics that enter the CNS quite well, release excitatory neurotransmitters in brain
- **CNS stimulatory actions** are dose-dependent
  - At relatively low doses, seem to selectively activate (stimulate) INHIBITORY pathways in the brain, → suppression of inattention, hyperactivity, etc.
  - At higher doses, cerebral cortical stimulation → ↑ arousal and awakeness, ↓ appetite (anorexigenic effect)
- **Peripheral sympathomimetic actions** (review your autonomics notes)

## Main Legitimate Uses

- Management of narcolepsy
- Adjunct to management of severe or morbid (life-threatening) obesity
- Management of ADD-ADHD

...And there are many more illegitimate/illegal uses for these “uppers”

## Side Effects, CIs, Toxicity

**CNS:** seizures, potentially fatal

**Peripheral autonomic:** See “indirect-acting sympathomimetics” from Exam 1/autonomics notes

## Abuse Potential

- **Very high:** these are Schedule II drugs: great risk of physical, psychologic dependence, strict legal controls over use, possession, etc.
- **Tolerance** develops quickly (which → need for ↑ doses to maintain desired effects)