Anxiolytic and Hypnotic Drugs

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Objectives

1. Identify the major chemical classes of sedative-hypnotics.
2. Describe the pharmacodynamics of benzodiazepines, including interactions with neuronal membrane receptors.
3. Compare the pharmacokinetics of commonly used benzodiazepines and barbiturates and discuss how differences among them affect clinical use.
4. Describe the clinical uses of sedative-hypotics.
5. Describe the common adverse effects and drug interaction of sedative-hynotics
6. Understand tolerance and dependence induced by sedative-hypnotics.
7. Understand the therapeutic indications and adverse effects of benzodiazepines antagonists

BENZODIAZEPINES

- The most widely used anxiolytic drugs.

- They have largely replaced barbiturates in the treatment of anxiety, because benzodiazepines are;

1. safer and
2. more effective

Mechanism of Action

- The targets for benzodiazepine actions are the γ-aminobutyric acid (GABA A) receptors.

- Note: GABA is the major inhibitory neurotransmitter in the CNS.

- **Bzs binding to BZ receptors (BZ1 or BZ2) to facilitate GABA-induced chloride channels hyperpolarization = GABA-mediated inhibitory neurotransmission.**

Note that;

- **BDZ increase frequency of opening of Cl^- channels.**

- **(while barbiturates increase the duration of opening of Cl^- channels** after binding to barbiturate site on GABA-A receptors

Actions

- **Have neither antipsychotic activity nor analgesic action.**
- **Reduction of anxiety**: At low doses are anxiolytic.
- **Sedative and hypnotic actions** (artificially produced sleep); at higher doses.
- **Anterograde amnesia**: The temporary impairment of memory. This also impairs a person's ability to learn and form new memories.
- **Anticonvulsant**: used to treat epilepsy (status epilepticus)
- **Muscle relaxant**: At high doses

Therapeutic uses

- **Anxiety disorders:**

1. Panic disorder, GAD, social anxiety disorder,etc……
2. Used for short periods of time because of their addiction potential.
3. The longer-acting agents as clonazepam, lorazepam and diazepam, are often preferred in treatment for prolonged periods of time.

- **Muscular disorders**: muscle strain, multiple sclerosis and cerebral palsy.
- **Amnesia**: The shorter-acting agents premedication for endoscopic, bronchoscopic and certain dental procedures.
- **Seizures**: diazepam and lorazepam are the drugs of choice in grand mal epileptic seizures and status epilepticus.
- **Sleep disorders**: long-acting flurazepam, intermediate-acting temazepam and short-acting triazolam.

PHARMACOKINETICS

Absorption: most of them are well absorbed orally.

Fate: are metabolized by the liver to active compounds. The drugs' effects are terminated not only by excretion but also by redistribution.

Toxicity of Benzodiazepines

Classification of benzodiazepines

Long-acting benzodiazepines 1-3 days	Intermediate - acting benzodiazepines 16 hours hours	Short-acting benzodiazepine 3-8 hours
Clorazepate Chlordiazepoxide Diazepam Flurazepam Quzepam	Alprazolam Estazolam Lorazepam Temazepam	Oxazepam Triazolam

Dependence

- **Psychological and physical dependence;** if high doses of the drugs are given over a prolonged period.

- **Withdrawal symptoms;** confusion, anxiety, agitation, restlessness, insomnia, tension, and (rarely) seizures.

- Because of the long half-lives of some benzodiazepines, withdrawal symptoms may occur slowly and last a number of days after discontinuation of therapy.

- Benzodiazepines with a short half-life, such as triazolam, induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated such as flurazepam

Adverse effects

- **Drowsiness and confusion**: the most common.
- **Ataxia**: occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile.
- **Cognitive impairment**: (decreased long term recall and retention of new knowledge).
- **Tolerance, early morning insomnia (Hangover), and daytime anxiety, amnesia and confusion**: rapid development with Triazolam.

BENZODIAZEPINE ANTAGONIST

- **Flumazenil** is a GABA-receptor antagonist that can rapidly reverse the effects of benzodiazepines.
- IV administration only.
- Onset is rapid, but duration is short.
- Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine.

- May **precipitate withdrawal** in dependent patients or **cause seizures** if a benzodiazepine is used to control seizure activity.

- Seizures may also result if the patient ingests tricyclic antidepressants (TCAs).

- **Side effects**; Dizziness, nausea, vomiting and agitation are the most common

OTHER ANXIOLYTIC AGENTS

Antidepressants

- first-line agents, especially in patients with concerns for addiction or dependence.
- SSRIs, such a escitalopram, or
- selective serotonin and norepinephrine reuptake inhibitors (SNRIs, such as venlafaxine)
- used alone, or in combination with a low dose of a benzodiazepine during the first weeks of Treatment until the antidepressant begins to produce an anxiolytic effect.

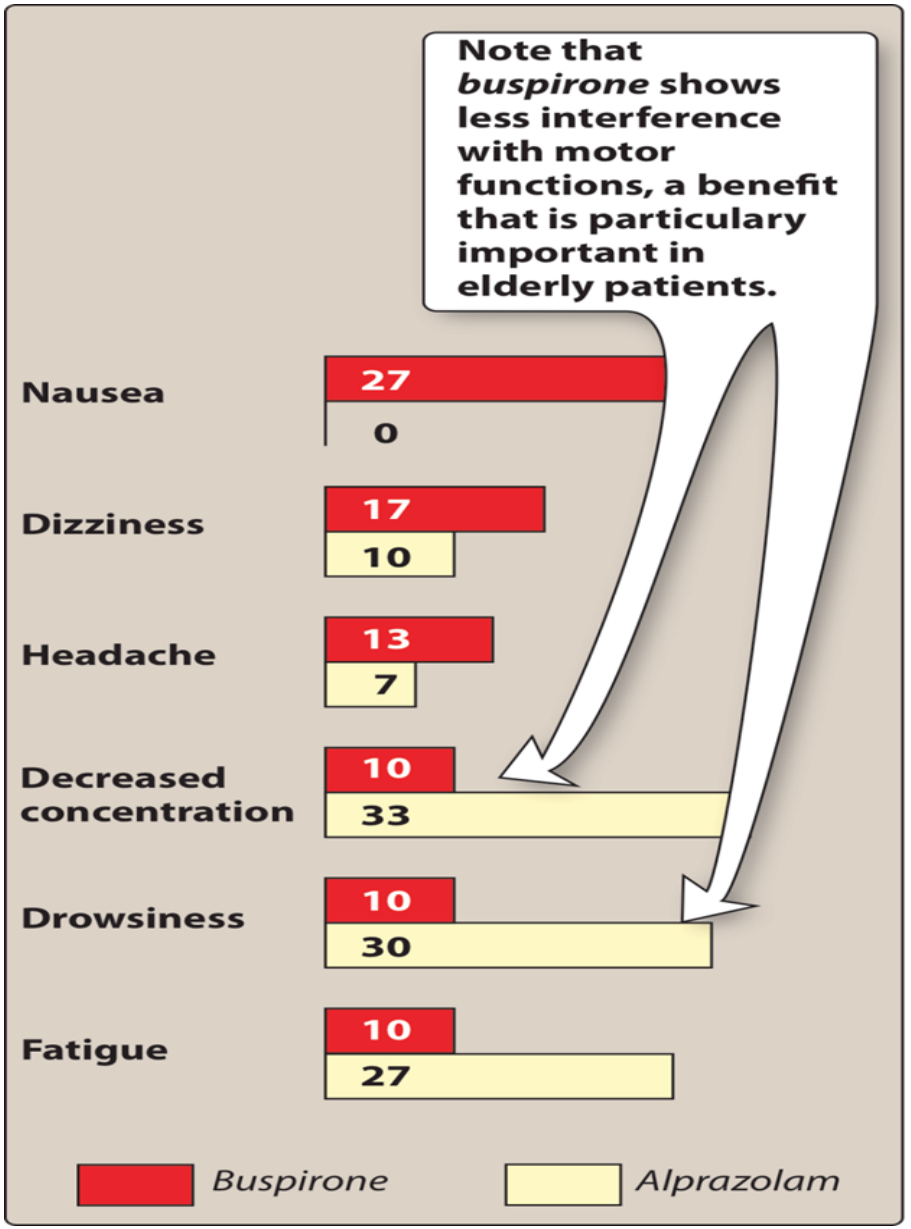
- SSRIs and SNRIs have a lower potential for physical dependence than the benzodiazepines, and have become first-line treatment for GAD.

- Long-term use of antidepressants and benzodiazepines for anxiety disorders is often required to maintain ongoing benefit and prevent relapse.

Buspirone

- Is not effective for short-term or “as-needed” treatment of acute anxiety states.
- **Mechanism of action**; mediated by serotonin (5-HT 1A) receptors, although other receptors could be involved, because buspirone displays some affinity for DA 2 dopamine receptors and 5-HT 2A serotonin receptors.
- Lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation.

Buspirone Versus Alprazolam

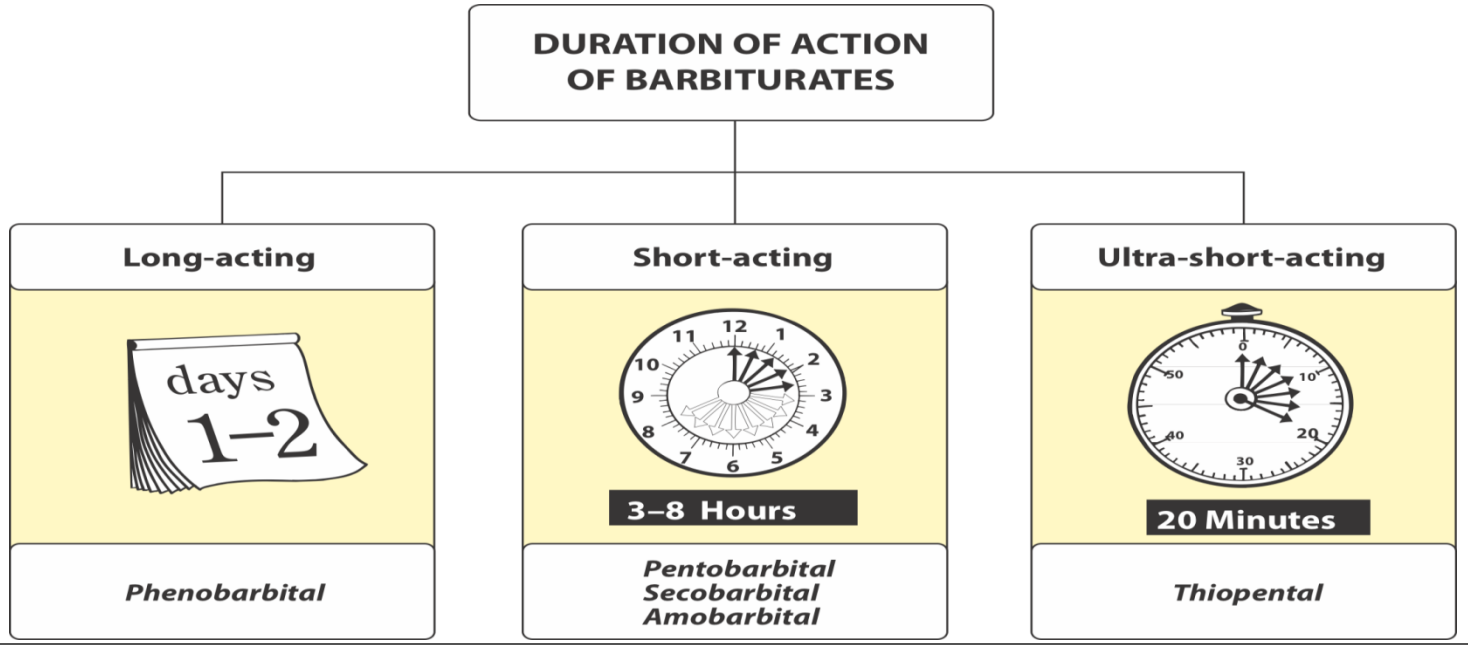


Adverse effects

- Hypothermia
- Increase prolactin and growth hormone.
- Headaches
- Dizziness,
- Nervousness, and light-headedness.
- Dependence is unlikely.
- It does not potentiate the CNS depression of alcohol.
- Buspirone has the disadvantage of a slow onset of action.

Barbiturates

- Largely replaced by benzodiazepines because they:
- Induce tolerance
- Induce drug-metabolising enzymes
- Cause physical dependence
- Associated with withdrawal symptoms
- Narrower therapeutic window compared to benzodiazepines



Barbiturates

- MOA: decreased neural activity
- Main sedative and hypnotic effect: by binding to $GABA_A$ receptors (at a different site than benzodiazepine interaction site) – potentiate GABA action by prolonging the duration of the chloride channel opening

- Furthermore, by blocking the excitatory glutamate receptors

- Anaesthetic effect: by blocking the high-frequency Na-channels

Barbiturates

Action and Mechanism	Therapeutic Use	Drugs
Depression of CNS: -Low dose: sedation -Higher dose: hypnosis -Highest dose: anaesthesia -Toxic dose: coma and death	Anaesthesia	Ultra-short-acting: Thiopental (I.V)- replaced by other agents
	Anticonvulsant	Long-acting: Phenobarbital
	Sedative and hypnotic	Short-acting: Secobarbital and Amobarbital – no longer recommended

Barbiturates

- PK properties:

- Redistribute widely throughout the body:

  Brain → splanchnic areas → skeletal muscles → adipose tissues

- Readily cross the placenta → fetus depression

- Barbiturates induce liver CYP450 enzymes

- Metabolized in liver and excreted in urine

Barbiturates

- Adverse effects:

- *CNS*: drowsiness, impaired concentration, mental and physical sluggishness. Synergism with *ethanol*
- *Drug hangover*: feeling of tiredness after waking-up from a hypnotic dose of barbiturates
- *Respiratory depression* (toxicity): due to suppression of the hypoxic and chemoreceptor response to CO_2

Barbiturates

- Physical dependence:

  Abrupt withdrawal: tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium and cardiac arrest. It can result in death

- Poisoning:

- Respiratory depression
- Central cardiovascular depression
- Treatment: **no specific antidote.**
- **Artificial respiration** and stomach purging would help

OTHER HYPNOTIC AGENTS

Zolpidem

- acts on benzodiazepine receptors (BZ 1) & facilitate GABA mediated neuronal inhibition.

- Its action is antagonized by flumazenil.

- No anticonvulsant or muscle-relaxing properties.

- Few withdrawal effects
- Minimal rebound insomnia
- Little or no tolerance occurs with prolonged use
- Short duration of action.

Note:

- The nonbenzodiazepine drugs, zolpidem, zaleplon, and eszopiclone, do not significantly alter the various sleep stages and, hence, are often the preferred hypnotics.

Antihistamines

- as diphenhydramine, hydroxyzine and doxylamine,
- are effective in treating mild types of insomnia.
- Have numerous undesirable side effects (such as anticholinergic effects) that make them less useful than the benzodiazepines.