YU - MEDICINE
PASSION ACADEMIC TEAM

Central Nervous System

Sheet# 1 (Part 1) - Pharmacology

Lec. Title : Anxiolytic & Hypnotic Drugs (Sedative Hypnotics)

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If you come by any mistake , please kindly report it to shaghafbatch@gmail.com

Only for anxiety/panic disorders/agoraphobia (social anxiety) as a disease with no apparent cause.

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

Sheet# 1

Benzodiazepines :

Neural cells internal charge is negative while the outside is positive due to chloride. When chloride enters the cells, negativity increases leading to hyperpolarization. The cells during this time are depressed and inactive. There is no action potential. Benzodiazepines increase chloride entrance by increasing the frequency of chloride channels opening. Benzodiazepines do not work alone but they need the help of GABA. Benzodiazepines attach to receptors and GABA gets activated in the cells and bind to GABA A receptors to allow entrance of chloride channels.

*THEY ONLY WORK ON THE FREQUENCY OF CHLORIDE CHANNEL OPENING!

*BENZODIAZEPINES WORK INDIRECTLY! GABA WORKS DIRECTLY!

BARBITURATE WORKS DIRECTLY AND INDIRECTLY!

GABA A receptors are ionotropic and have binding sites for benzodiazepines and barbiturate.

Benzodiazepines work on GABA and increase the frequency of opening of channels while barbiturates increase the duration of channel opening.

So, barbiturates have a longer lasting CNS depression effect.

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.**

Sheet# 2

Benzodiazepines is not a sedative unless the dosage is increased. Anymore increasing leads to hypnosis then anesthesia. Finally, depression of vital centers in the brain stem takes place. In low therapeutic doses, it calms but does not affect mental abilities. Sedatives lead to confusion, drowsiness and sleepiness.

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

Barbiturate is different. Any tiny change in dosage leads to hypnosis, then anesthesia etc.

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

Sheet# 3

Anterograde amnesia: the brain stops forming new memories. Benzodiazepines cause anterograde amnesia. This makes it very helpful for labor and endoscopy patients. It can also be used as an anticonvulsant for status epilepticus.

Clorazepate: for partial epilepsy.

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.

Sheet# 4

Clonazepam: for petite mal epilepsy/absence seizures.

Benzodiazepines also have muscle relaxant activity and can be used in cerebral palsy. It is a congenital spastic disorder.

Benzodiazepines have no painkiller effect and no antipsychotic activity. They only work indirectly. GABA accepts benzodiazepines.

Barbiturate can cause tolerance. Benzodiazepines cause dependency but on a lesser scale than barbiturates. Monitor its intake.

Generalized anxiety disorder: use long-acting benzodiazepines due to prolonged anxiety and fear.

Multiple sclerosis: accompanied by spasms so benzodiazepines help.

Lorazepam: generalized mal epilepsy

Benzodiazepines can be used for insomnia.

Easy to fall asleep but disturbed sleep (frequent awakening during sleep): long-acting benzodiazepines.

Hard to fall asleep but long sleep: short acting benzodiazepines.

Classification of benzodiazepines is very important.

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.

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

Sheet# 5

PHARMACOLOKINETICS:

Benzodiazepines go to CNS then to fatty tissues. They are hard to get rid of. They are lipophilic.

Elimination from CNS is only due to redistribution!!!

What dictates duration of action? Redistribution.

If you increase the benzodiazepines dosage, they work on CNS then fatty tissues and completely fill those tissues up. The excess benzodiazepines go back to the CNS to continue the action until fatty tissues are empty again.

Benzodiazepines are lipid soluble which is why they are redistributed to fatty tissues.

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

Sheet# 6

DEPENDENCE:

They cause psychological and physical dependence. When the patient stops the drugs, they go through withdraws.

Its dependence is a lot less than barbiturates due to indirect action and only increasing the frequency of channel opening.

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.

Sheet# 7

ADVERSE EFFECTS:

. Confusion and drowsiness due to sedation effect due to increased dosage.

. Unsteady gait, lack of coordination and skillful tasks.

Short acting: stronger hangover/early morning insomnia and day long anxiety

Long-acting weaker hangover

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

Sheet# 8

Flumazenil also has a place on GABA instead of the benzodiazepine's receptor. This makes is a benzodiazepines antagonist. However, it is short acting and is rapidly metabolized in the liver. It also causes convulsions due to antagonism.

Benzodiazepines can cause convulsions due to withdrawal and paradoxical effects.

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.

Sheet# 9

ANTIDEPRESSANTS:

Stops depressing mood. NOT CNS depression. Sedative: calmness with lack of concentration confusion drowsiness etc.

Antidepressants can cause sedation.

We can give benzodiazepines followed by antidepressants since they take a while to start working.

Drug abuse: addiction

Drug misuse: improper medical use

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.

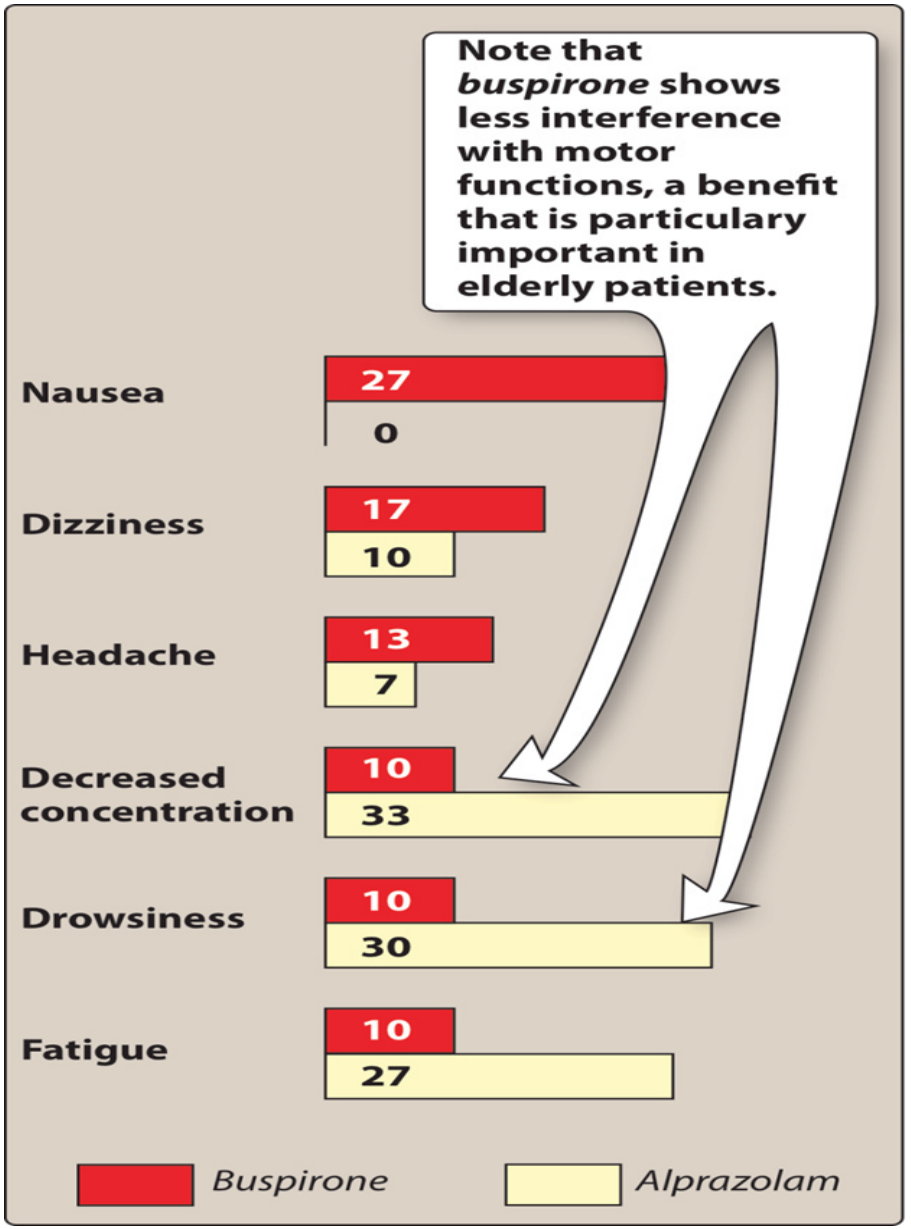
Sheet# 10

BUSPIRONE:

For long term anxiety. Does not hinder skillful tasks. Does not cause sedation. Causes a bit of dizziness but not drowsiness. Unlikely dependence.

Alcohol is a CNS depressant and works with benzodiazepines (they increase CNS depression) but not buspirone.

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.