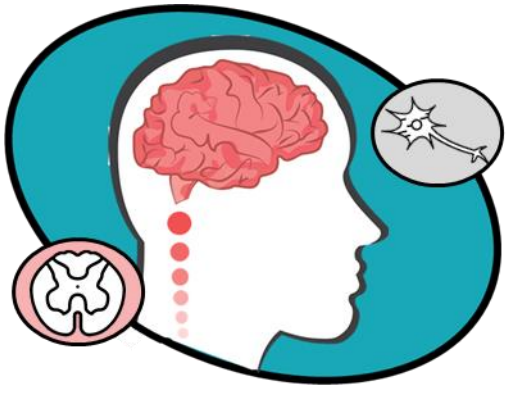

CNS

Pharmacology

Sheet Slide

Number

lecture lecture

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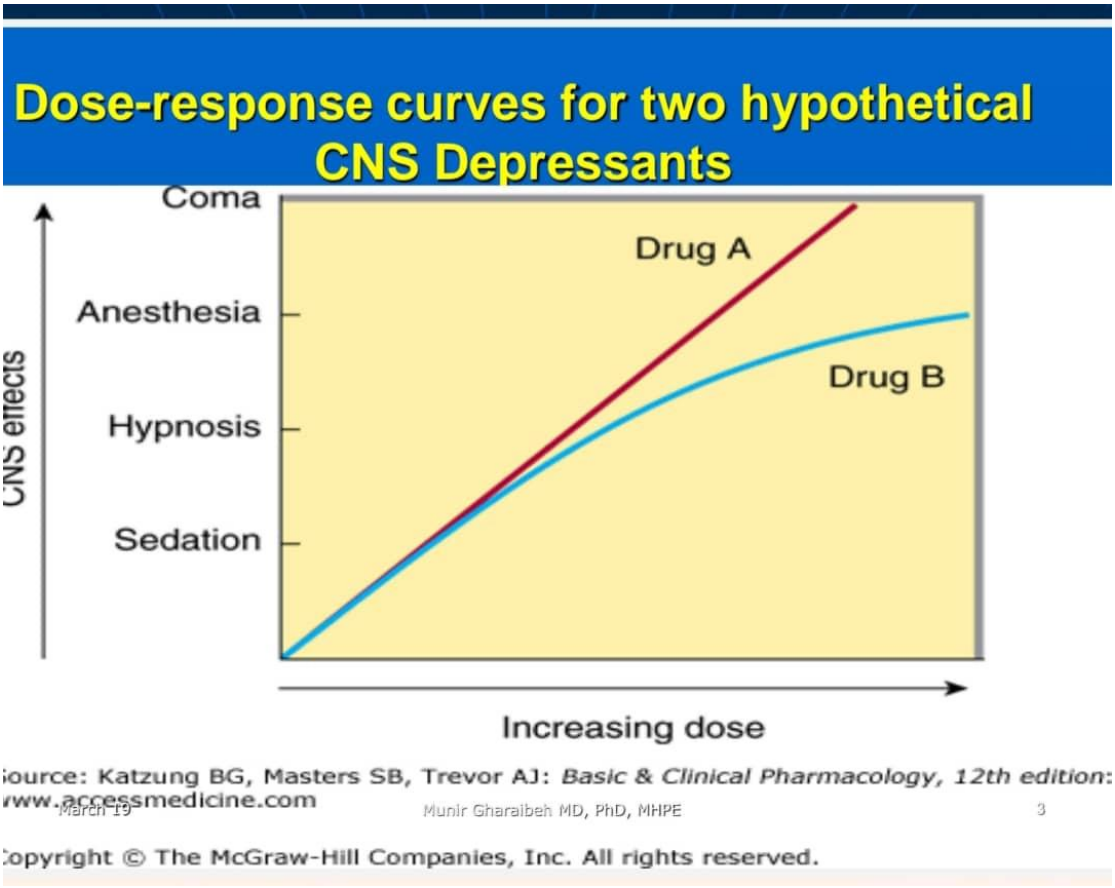
Sedative-Hypnotic Drugs

Note: you don't have to refer to slides. I add some extra notes which I have read to simplify the memorization.

Introduction

An effective sedative (anxiolytic) agent should reduce anxiety and exert a calming effect. A hypnotic drug should produce drowsiness and encourage the onset and maintenance of a state of sleep.
Hypnotic effects involve more pronounced depression of the central nervous system than sedation, and this can be achieved with many drugs in this class simply by increasing the dose. Graded dose-dependent depression of central nervous system function is a characteristic of most sedative-hypnotics. For example, if there is a patient suffer from anxiety, by giving him the proper dose, we treat the condition. But if we increase the dose, he might suffer from drowsiness and hypnosis. If we increase the dose more and more, he could go to a stage of anesthesia and then coma and death. Also, high dose of these drugs could exert anti convulsant effect.
Because there is always a risk to take high doses of these drugs by mistake and thus causing coma and death, newer drug don't go through all of these stages, instead, they exert certain function. To understand what I mean more, read the following paragraph.

Two examples of such dose-response relationships are shown in the Figure below. Slope for drug A is typical of many of the older sedative-hypnotics, including the barbiturates and alcohols. With such drugs, an increase in dose higher than that needed for hypnosis may lead to a state of general anesthesia. At still higher doses, these sedative hypnotics may depress respiratory and vasomotor centers in the medulla, leading to coma and death. Deviations from a linear dose-response relationship, as shown for drug B, require proportionately greater dosage increments to achieve central nervous system depression more profound than hypnosis. This appears to be the case for benzodiazepines and for certain newer hypnotics that have a similar mechanism of action.



Clinical uses of sedative –hypnotics

-For relief anxiety

-For insomnia

-For sedation and amnesia before and during medical and surgical procedures. Extra: these drugs cause a form of conscious sedation allowing the patient to be receptive to instruction during procedures like endoscopy.

-For treatment of epilepsy and seizure state. For example we use them in status epilepticus.

- As intravenous anesthesia

-For muscle relaxation in specific neuromuscular disorders. Extra: an example of this point is using these drugs to treat spasticity in neurodegenerative diseases.

-for diagnosis aid in the treatment in psychiatry

-For control of ethanol or other sedative –hypnotic withdrawal state. *Ethanol is a toxic drug that depress CNS, stopping this toxic material suddenly is associated with many withdrawal symptoms, so we use sedative drugs to manage the withdrawal symptoms.*

Common Basic Features of hypnotic-sedative drugs:

- General CNS depressants.
- Have overlapping actions.
- Have abuse (addictive) potential.
- Have additive effects.

Explanation of last point: when giving two drugs and the two drugs are sedative, the effect will increase. So the effect can be additive.

Extra: an example of additive effect is, in extreme anxious patients we usually give SSRI and benzodiazepines to increase the effect of sedation.

Ideal Anxiolytic

- Calm the patient without too much day time sedation and drowsiness and without producing dependence. Please here keep in mind, we need to reduce the overthinking that the patient is suffering from but without exerting too much sedation that could lead to disturbance in sleep cycles or loss of consciousness.

Ideal Hypnotic

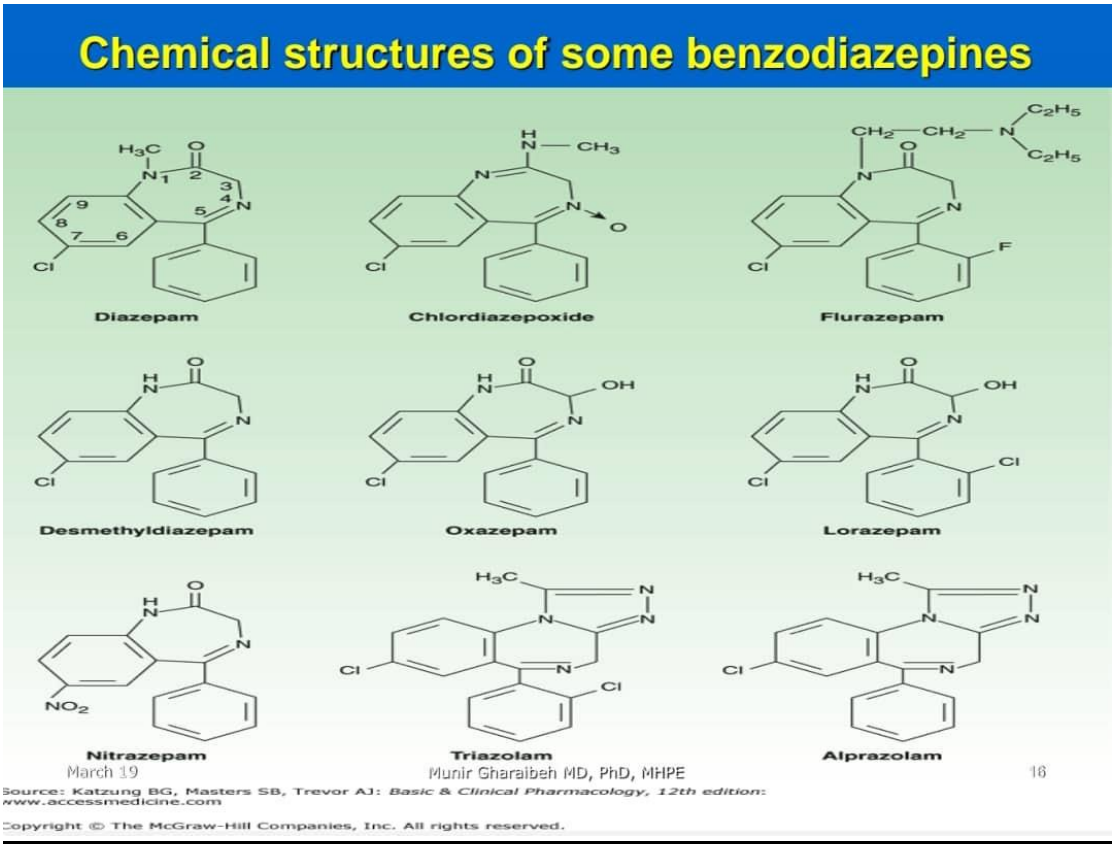
- Patient should go asleep quickly.
- Maintains sleep of sufficient quality and duration.
- Patient awakes refreshed without “hangover”

Explanation of the last point: *what we should avoid in the treatment is hangover, which means unpleasant feeling when waking up. Normally, when we wake up after sleep, we feel that we are refreshed and comfortable. Unlike us, alcoholic people when they wake up after long sleep because of drinking, their mood will be bad and that's what we mean by hangover.*

Benzodiazepines

Benzodiazepines are widely used anxiolytic drugs. Also, they are a synthetic compound (not coming from plants).

Look at the figure below.



-Keep in mind that Midazolam and diazepam is used for general anesthesia as an IV injections.

A. 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 central nervous system (CNS).] The GABA receptors are composed of a combination of five α, β, and γ subunits, each with 4 transmembrane-spanning subunits [Note: GABA receptors in different areas of the CNS consist of various combinations of these subunits]. Binding of GABA to its receptor between α and β subunits triggers an opening of the central ion channel, allowing entrance of chloride through the pore. The influx of chloride ions causes hyperpolarization of the neuron and decreases neurotransmission by inhibiting the formation of action potentials. Benzodiazepines modulate GABA effects by binding to a specific, high-affinity site (distinct from the GABA-binding site) located at the interface of the α1 subunit and the α2 subunit on the GABA receptor (in Katzung which is our reference, the binding is between α and γ). Benzodiazepines increase the frequency of channel openings produced by GABA. Note: [Binding of a benzodiazepine to its

receptor site increases the affinity of GABA for the GABA-binding site].

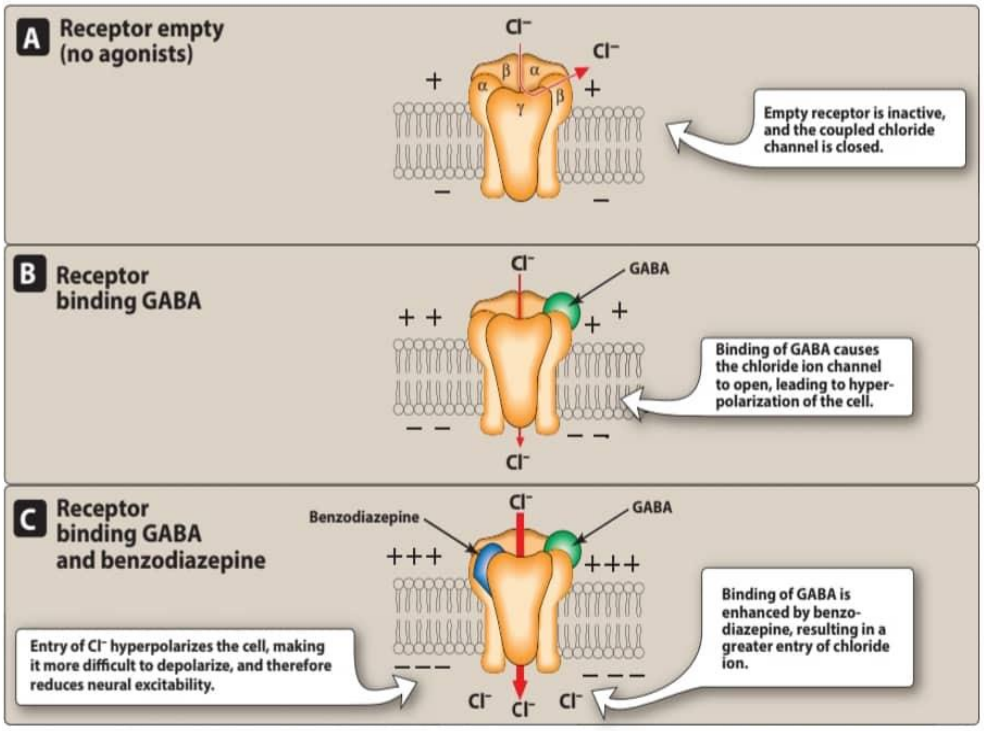


Figure 9.3
Schematic diagram of benzodiazepine–GABA–chloride ion channel complex. GABA = γ-aminobutyric acid.

Note: Zolpidem binds only to isoforms containing α1 subunits

B. Doses

Benzodiazepines cause dose dependant CNS effect. For example, 2 ml gram is good as anti-anxiety. 5mlg causes hypnosis. 10 ml gram is used to treat status epilepticus. So it has wide spectrum of use.

C. Metabolism

the drug could be in active form and transformed by liver enzymes to inactive metabolite, or could be in inactive form and transformed by liver enzymes to active metabolite. Also, it could be transformed from active form to another metabolite which is active too.

D. General features

-Have wide margin of safety (Therapeutic index is 100). Imagine that other drugs like digitalis has just 2.5 therapeutic index.

-Have few side effects.

-These drugs are additive, so if we combine it with other sedative drug it could cause instead of sedation, hypnosis. And instead of hypnosis, coma and death.

-Fortunately these drugs have anti dote which is flumazenil. Flumazenil acts by antagonize GABA receptor.

E. Pharmacokinetics

Benzodiazepnies are Weak bases, that are absorbed in the intestine. Their effect is terminated by redistribution. Also they are Weak inducers of liver enzymes.

F. adverse effects:

- CNS depression but Tolerance develops against it (Extra: tolerance develop by downregulation of GABA receptors)
- Blurring of vision.
- Hallucinations.
- Paradoxical Reactions: Instead of depression, these drugs could cause excitement by inhibition of inhibition.
- GI, Blood effects which are Rare.

Extra: If you want to memorize just one of these side effects and keep it in your mind for long period, memorize just the first adverse effect (CNS depression like drowsiness) because in reality these drugs are very safe, and all adverse effect written in textbooks are mainly related to this effect.

Finally, Withdrawal of Benzodizepines is associated with Rebound Insomnia and Anxiety. Also, Tremor, Nausea, Vomiting, Weight loss and Convulsions could occur. Please note that any withdrawal effect will cause the opposite pharmacological effect. For example, the pharmacological effect of benzodiazepines could be anti-convulsant , So when we stop the drug suddenly, Not surprisingly that convulsions could reoccur.

Barbiturates

not surprisingly that benzodiazepines are safer than barbiturates

A. mechanism of action:

The binding site of barbiturates on the GABA receptor is distinct from that of the benzodiazepines. Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride channel openings. In addition, barbiturates can block excitatory glutamate receptors.

B. General features:

- Barbiturates cause Hangover Effects: Remember it from introduction of the sheet :P

- Barbiturates are considered Liver enzyme inducers.

The most famous example of liver enzymes inducers is barbiturates, and because of that, it could cause many drug-drug interactions. For example, if you take another drug that is metabolized by liver enzymes with barbiturate, the action of the drug will be reduced because of induction of it's metabolism by barbiturates. Also, Barbiturates could be used In premature infants who suffer from jaundice to induce liver enzymes that degrade bilirubin.

- *Because their therapeutic index is narrow (10), and people were taking it in high doses and without prescription*, it was The leading cause Death in (1950s-1960s).

- Barbiturates cause Drug Automatism.

Drug automatism means forgetting the last dose you take and keep taking the drug many times. This could happen because barbiturates cause loss of recent memory.

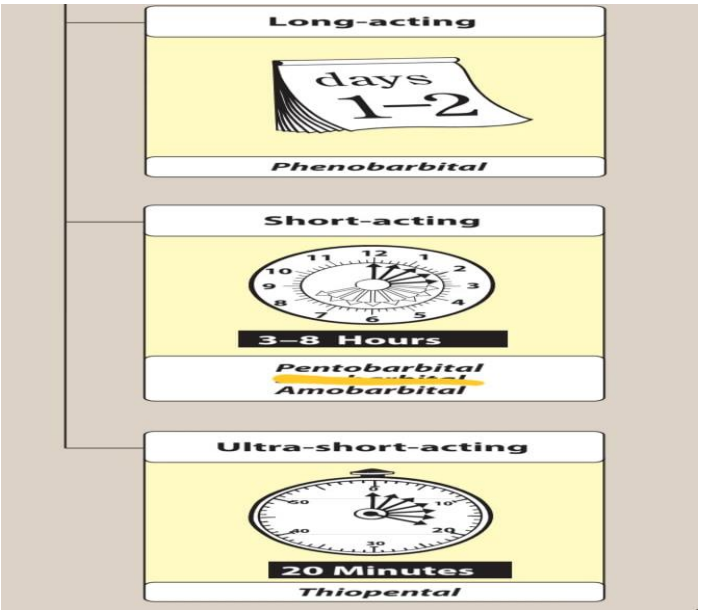
-they are associated with Abuse, Tolerance, Dependence and Withdrawal.

Keep in mind that's barbiturates are the drug of abuse, unlike benzodiazepines.

Barbiturates classification

- Thiopental (ultra short acting, and could be used as Intravenous anesthesia before surgeries)
- Amobarbital (short acting)
- Pentobarbital(intermediate acting).

■ Phenobarbital (long acting).



Note :Although phenytoin doesn't cause drowsiness and drug abuse, phenobarbital is still used as anti-epileptic drug.

Buspirone

Buspirone has selective anxiolytic effects, and need 1 week to work (Extra :because it needs time to work, in reality we use this drug to treat chronic anxiety not acute one) . its pharmacologic characteristics differ from benzodiazepines. Buspirone relieves anxiety without causing marked sedative or hypnotic. Unlike benzodiazepines, the drug has no anticonvulsant or muscle relaxant properties. Buspirone does not interact directly with GABAergic systems. It may exert its anxiolytic effects by acting as a partial agonist at brain 5-HT 1A receptors, but it also has affinity for brain dopamine D 2 receptors. Because of it's unique mechanism of action it has no additive effect. Buspirone treated patients show no rebound anxiety or withdrawal signs or drug abuse. These drugs are safe but could cause Tachycardia, GIT distress, paresthesia and pupillary constriction.

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the rest of the lecture are read quickly by the doctor, I but whaat in the slides

Zolpidem

■ Good sedative.
■ Wide spectrum but weak.
■ Binds to benzodiazepine receptor.
■ Short acting.
■ Preserves normal sleep.
■ GI side effects (diarrhea).
■ CNS : additive.

Note : Zolpidem best activity is in anxiolytic.

Ramelteon

■ Melatonin receptor agonist (MT1 and MT2), so it's a natural drug.
■ Not a controlled substance.(doesn't need prescription)
■ Melatonin is secreted from pineal body and involved in circadian rhythm and sleep cycles.
■ Have effects on sleep and endocrine system.
■ Might be useful for jet lag

Explanation of last point : people who travel from one country to another will suffer from changed circadian rhythm and sleep cycles , so we give them ramelton.

Note: Ramelton is good as hypnotic drug (ideal hypnotic drug).

Antihistamines :

■ Hydroxyzine ■ Diphenhydramine. ■ Promethazine.

- Antihistamines have sedative side effects.
- Non prescription drugs.
- Have anticholinergic side effects (dryness, urinary retention ….).
- No problems of tolerance and dependence.

Note: the sedative effect of antihistamines which could be found in drugs which treat cough, is one of the side effect that was observed. We could give these drugs in children to help them to sleep well.

β - adrenergic Blockers

■ Reduce the sympathetic manifestations of anxiety (tremor, nervousness, tachycardia, sweating…..).

■ The most useful in performance anxiety (Stage Fright Anxiety or Phobia), because they do not depress the CNS.

Note : In general, these drugs treat the manifestation that is associated with anxiety, like tremor and sweating. For example, when student enter an exam , he could have tremor and sweating, so here appear the the benefit of B-adrenergic Blockers.

Antidepressants

■ General anxiety.

■ Phobic and Panic Disorders.

■ Obsessive-compulsive states.

Extra : in real life general anxiety firstly is treated with SSRI

Chloral Hydrate

■ 1800s.

■ Effective.

■ Metabolized into TCE. Extra: TCA is an abbreviation for Trichloroethylene.

■ Causes bad smell and taste , gastric irritation , allergy , and arrhythmia.

Others

■ Paraldehyde.

■ Meprobamate:
Muscle Relaxant , 1951 good for geriatric patients.

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