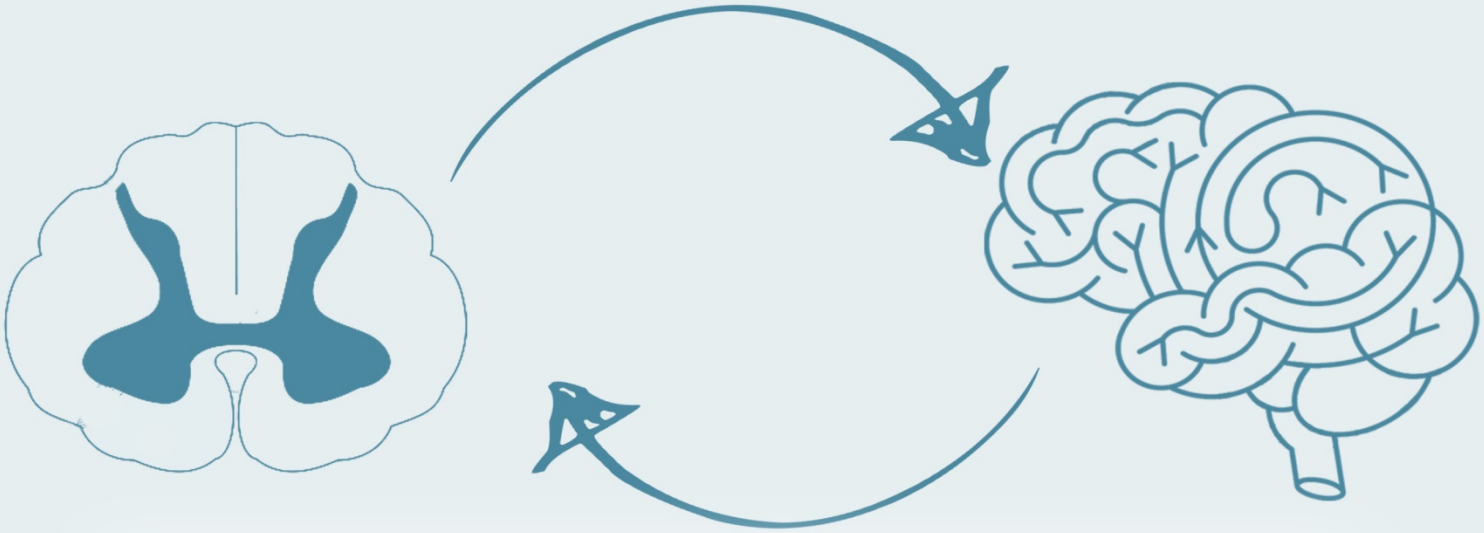

CNS

pharmacology

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number	5
Done by	Maram Alsamee
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Drugs used in Alzheimer's disease

This disease is common in the elderly. It is a degenerative disease.

(سمي ***بأرذل العمر*** في القرآن الكريم)

Acetylcholinestrase inhibitors, originally used as potent and very effective insecticides, proved to be the only useful drugs in the treatment of Alzheimer disease.

1-Tacrine:

is a centrally acting cholinesterase inhibitor and has indirect cholinergic agonistic activity. It was the first centrally acting cholinesterase inhibitor approved for the treatment of Alzheimer's disease. Tacrine's efficacy is modest, and hepatic toxicity is significant. Because of its hepatic toxicity, tacrine has been almost completely replaced by newer cholinesterase inhibitors like *donepezil, rivastigmine, and galantamine.*

Donepezil may be given once daily because of its long half-life, and it lacks the hepatotoxic effect of tacrine.

2-Memantine:

Excitotoxic activation of glutamate transmission via NMDA

receptors has been postulated to contribute to the pathophysiology of Alzheimer's disease.

Memantine is an MDA receptor antagonist which may slow the progression of the disease. This drug appears to be better tolerated and less toxic than the cholinesterase inhibitors.

Sedative-Hypnotic Drugs:

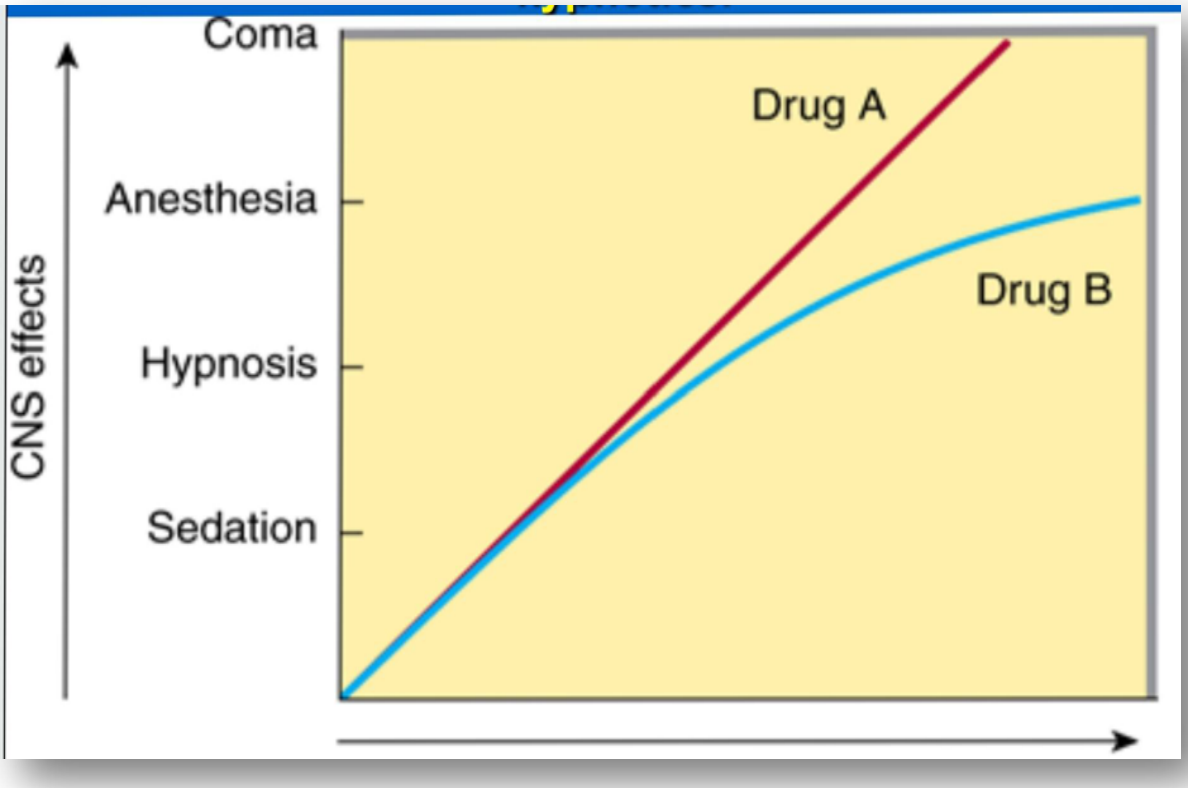
Sedative (anxiolytic) agent reduce anxiety and exert a calming effect. The degree of central nervous system depression caused by a sedative should be minimum.

A hypnotic drug produces drowsiness and encourages the onset and maintenance of a state of sleep.

These drugs have originally a wide spectrum of activity ranging from decreased *anxiety >> sedation>> hypnosis>> anaesthesia>> death*

Old drugs showed this spectrum, but the newer drugs are targeted toward sedation, hypnosis or decreased anxiety.

- *Dose-response curves for two hypothetical sedative-hypnotics*.



The linear slope for **drug A** is typical of many of the ***older sedative-hypnotics***, including the ***barbiturates and alcohol***. 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 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. These drugs will produce sedation, and with increasing the dose, they will produce hypnosis and maybe anesthesia, but no coma or death.

Other drugs can produce only sedation, but others which produce hypnosis, will produce both sedation and hypnosis.

The clinical uses of these drugs:

1. Relief of anxiety (which is a normal response to stress)
2. For insomnia, they induce sleep
3. For sedation and amnesia before and during medical and surgical procedures.
4. Epilepsy and seizure states.
5. Control of ethanol orother sedative-hypnotic withdrawal states.
6. Muscle relaxation in specific spastic muscular disorders
7. Diagnostic aids in psychiatry.

Common Basic Features of CNS Depressant drugs:

- All these drugs should cross the BBB.
- Have overlapping actions.
- General CNS depressants.
- Have abuse potential.
- Have additive effects.

Ideal Anxiolytic:

Calm the patient without too much day time sedation and drowsiness and without producing dependence. They should be used for a short term.

Ideal Hypnotic:

- Patient should go asleep quickly, the lag time of sleep should be shortened.
- Maintains sleep of sufficient quality and duration.
- Patient awakes refreshed without "hangover" (مخلفات)

Older drugs like the barbiturates and alcohol were used to induce hypnosis and relieve anxiety but they were not good hypnotics or anxiolytics because they cause hangover which is unpleasant feeling on the next day.

Sleep Cycles:

-In normal people, sleep is divided into two cycles.

-Each sleep cycle lasts for about 90 to 120 minutes.

-A night has four to six different sleep cycles.

-Disturbance of these cycles by physical, mental factors, or drugs, results in sleep problems

There are 2 types of sleep cycles:

-The rapid eye movement sleep (REM)

-Non rapid eye movement sleep (NREM)

Non rapid eye movement sleep:

Has 3 stages 1,2,3.

- Stage 3 is also known as Slow Wave Sleep or Deep Sleep.

- Predominates in the first half of the night.
- Deep sleep has been associated with body and brain restitution (e.g. daytime function or feeling rested or energetic upon awaking).

REM Sleep:

- Rapid eye movement (REM) sleep.
- More frequent in the second half of the night.
- Associated with promotion of emotional and/or mental functions, including memory.

The eyes move due to cholinergic burst during the night which is characterized by tachycardia and some movements of skeletal muscles also sometimes it is accompanied with coronary vasospasm.

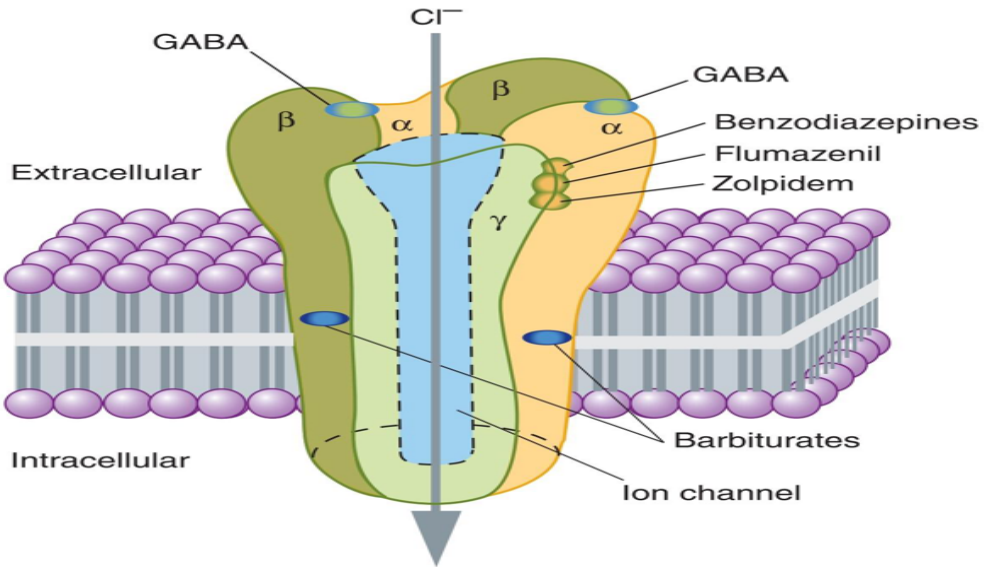
- Associated with promotion of emotional and/or mental functions, including memory.

Numerous drugs can affect sleep cycles but the ideal hypnotic and sedative drugs do not.

1-Benzodiazepines:

- The most important group in sedative-hypnotic drugs.
- 200 synthesized.
- Work on GABA receptors and increase the affinity of GABA to GABA I receptor by increasing the frequency of Cl- channel opening events leading to hyperpolarization and postsynaptic inhibition and decreased transmission.

GABAA Receptor:



GABA receptor is a Pentameric molecule(2 alpha, 2 beta, 1gamma)and in between runs the chloride channel.Binding sites of GABA are located between adjacent **α1**and **β2** subunits. *Binding site for benzodiazepines lies between α1and α2 subunits*.(doctor said Benzodiazepine binds on the alpha subunit, same as the barbiturate but they differ in the receptor) .GABA receptors in different areas of the CNS consist of various combinations of the essential subunits, Benzodiazepines bind to many of these.

Zolpidem binds only to isoforms containing α1 subunits

Benzodiazepines(1960s):

Weak bases, absorbed in the intestine and then rapidly reach the brain, then redistributed in the body. In liver they will be metabolized into active or inactive metabolites depending on the compound itself. *They are weak inducers of liver enzymes in comparison to the barbiturate which are potent liver enzymes inducers.*

Examples of benzodiazepines:

Diazepam, Chlordiazepoxide, Flurazepam and Lorazepam

As we said those drugs are used as sedative, hypnotic or sometimes anesthetic drugs. However, ***LORAZEPAM*** is mainly used as an anesthetic agent.

(Most benzodiazepines undergo microsomal oxidation (phase I reactions), including N- dealkylation and aliphatic hydroxylation catalyzed by cytochrome P450 isozymes, especially CYP3A4. The metabolites are subsequently conjugated (phase II reactions) to form glucuronides that are excreted in the urine. However, many phase I metabolites of benzodiazepines are pharmacologically active, some with long half-lives.)

Metabolism of these compounds produces metabolites that could be active or inactive, and the active is further metabolized into inactive and then eliminated or metabolized to another active metabolites.

Table in slide 17not required.

Benzodiazepines are good drugs because:

- They have a wide margin of safety, you can use small dosesto induce sedative action or largers one to induce hypnosis.
- they have few side effects.

Tremor, N.V., Weight loss, Convulsions.

2- Barbiturates:

Were used since(1935) and they are still used .They were replaced by benzodiazepines because barbiturates caused many problems. They produce the full spectrum of activity (antianxiety> sedation> hypnosis>anesthesia> coma> DEATH)

- "Good" drugs for suicide, used to be a leading cause of death in 1960s; either accidental or suicidal.

- Barbiturate also facilitate the actions of GABAA at multiple sites but appear to increase the duration of GABAA gated Cl- channel opening.
- Might also depress excitatory neurotransmitters like glutamic acid.
- Hangover Effects.(unlike benzodiazepines)
- They are potent liver enzymes inducers.

Interactions: With other drugs due to induction of liver enzymes.

Classifications :

- Thiopental (ultra short acting).
- Amobarbital (short acting)
- Pentobarbital (intermediate acting).in large animal surgeries
- Phenobarbitl (long acting). Used in epilepsy

3-Buspirone:

Buspirone has selective anxiolytic effects, and its pharmacologic characteristics differ from those of other drugs described in this chapter.

Buspirone relieves anxiety without causing marked sedative, hypnotic, or euphoric effects. 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, and needs a few weeks to work.

Safe: Tachycardia, GIT distress, paraesthesia and papillary constriction.

- No dependence or tolerance.
- No rebound or withdrawal.
- No additive effects with other CNS depressants.

• Minimal abuse liability

****So it could be the drug of choice for the treatment of simple anxiety***

4-Zolpidem :

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

5-Ramelteon:

- Not a prescription drug, it is mainly a natural supplement.
- Melatonin receptor agonist (MT1 and MT2).
- Not a controlled substance.
- Melatonin is a hormone secreted by the pineal gland involved in circadian rhythm.
- Have effects on sleep and endocrine system.
- Might be useful for jet lag.

6-Antihistamines :

Hydroxyzine, Diphenhydramine and Promethazine.

• These are antihistamines which have sedative side effects.

• Non prescription drugs.

• Have anticholinergic side effects (dryness, urinary retention ….).

• No problems of tolerance and dependence

Used in children

7- B-adrenergic Blockers :

- Have sedation as a side effect especially those that can cross the BBB ex***: propranolol***.
- Reduce the sympathetic manifestations of anxiety (tremor, nervousness, tachycardia, sweatin...).
- The most useful drugs in performance anxiety (Stage Fright Anxiety or Phobia), because they do not depress the CNS.

8-Antidepressants

- Used in a few anxiety situations *like Phobic and Panic Disorders. Obsessive-compulsive states*

9-Chloral Hydrate 1800s:

- Old fashioned, still effective.
- Metabolized into **TCE**.
- Causes bad smell and taste, gastric irritation , allergy , and arrhythmia.

10- Others

Paraldehyde

Meprobamate

Muscle Relaxant , 1951, good for geriatric patients.