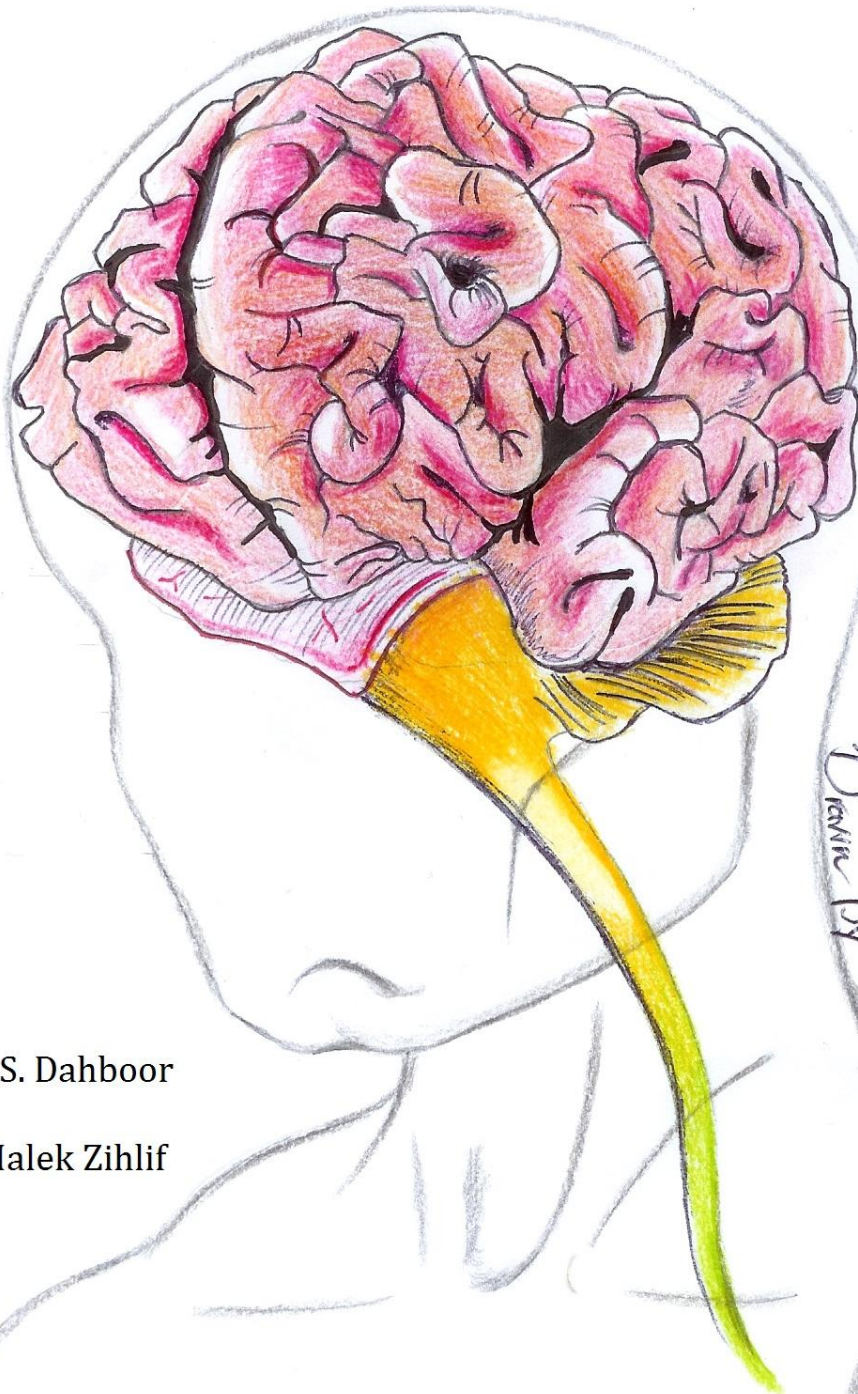


CENTRAL NERVOUS SYSTEM

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Lec #: 4



Anxiolytics and Hypnotics

** Revision :

In the previous lecture , we started talking about Benzodiazepines . The prescription of these drugs is very critical i.e. depending on the case , you have to prescribe the best drug with the best kinetics and the least side effects . Remember that we have three categories of Benzodiazepines : Long-acting , intermediate-acting and short-acting . Each category is preferred in a specific situation as follows :

Category	Use
Long-acting Benzodiazepines	<p>Anxiety (The patient is anxious and stressed so s/he must be covered by the drug for the whole day and that's why we use long-acting Benzodiazepines) .</p> <p>Diazepam is used as an anxiolytic (Diazepam isn't a good hypnotic) .</p> <p>However , Flurazepam is better if the patient suffers from anxiety linked to insomnia (Flurazepam is a good hypnotic) .</p>
Intermediate-acting Benzodiazepines	<p>Used when the patient can't sleep for more than 3-5 hours (can't continue sleeping for 7-8 hours) . Examples include Lorazepam and Temazepam which have a duration of action of ~10 hours .</p>
Short-acting Benzodiazepines	<p>Used when the patient can't get into sleep . An example is Triazolam .</p>

Remember the issue of (**hangover**) on awakening after the use of hypnotics (especially the long and intermediate acting agents) .

****Mechanism of action :**

These drugs enhance GABA receptors' affinity to their ligand . This induces Chloride ions influx which leads to a state of hyperpolarization i.e. depressing the CNS activity .Accordingly , Benzodiazepines are the drugs of choice in cases of **panic attacks/panic disorder** in which the patient is extremely anxious and stressed . One application of the use of these drugs is their administration before dental procedures for those who have dental phobia . The use of Benzodiazepines in this case places the patient in a state of (**sedative anesthesia**) which can be described as a state between awakening and sleep and by that the stress and fear are reduced. Here in Jordan we as doctors are not allowed to use them because we are not trained enough .

Doctor Malik reminds you to choose the best drug for each situation . For example it's preferred to give intermediate-acting Benzodiazepines in cases of panic attacks (they start working within one hour) . Long-acting agents are not the best choice in this case because they need longer time to start working .

**** Note :** The doctor mentioned that Lorazepam(commonly called: صليبا) and Alprazolam(commonly called: Ronaldo or Brazil) are related to drug abuse . This is not related to the topic of this lecture but keep it in your mind since we'll be discussing it in the upcoming lectures at the end of the course .

Now let's talk about another use of Benzodiazepines which is **muscle relaxation** :

At high doses , Benzodiazepines relax the spasticity of skeletal muscles probably by increasing presynaptic inhibition in the spinal cord .



Generally speaking , we have five groups of muscle relaxants.

All of them are centrally acting i.e. CNS depressants (the only exception is a drug called **Dantrolene** which works by inhibiting Na^+ release from the sarcoplasmic reticulum in myocytes)
(correction thinks it should be Ca^+ NOT Na^+)

The main side effects of muscle relaxants are fatigue and sedation (due to inhibition) .

Benzodiazepines don't deviate from the general rule i.e. they relax the muscles depressing the CNS .

Muscle relaxants are used in anesthetic procedures before operations
(ex. : **Tubocurarine**) .

Diazepam is useful in the treating a muscle spasm such as occur in muscle strain (الشد العظلي), and in treating spasticity from degenerative disorder such as multiple sclerosis as well as cerebral palsy (but not used as a drug of choice)

Another use for Benzodiazepines in addition to their use in the aforementioned degenerative diseases is their involvement in anesthetic procedures . Diazepam is commonly given before operations (pre-op = pre-operation) to :

- 1- relax the muscles .
- 2- reduce anxiety . يعني عصفورين بجز واحد .

Note : It's true that Benzodiazepines can be used as muscle relaxants . However , they're not considered the drugs of choice for muscle relaxation . The main use of Benzodiazepines is as anxiolytics and hypnotics .



** The third use of Benzodiazepines is :**Anterograde amnesia** – فقدان

لخطي للذاكرة

-Benzodiazepines do produce temporary impairment of memory.

-The short-acting agents (ex. : Triazolam) are employed in premedication for endoscopic and bronchoscopic procedures such as angioplasty. While doing these procedures , the patient is actually awake . S/he might not tolerate the stressful conditions surrounding him/her during the procedure (more common in females) so the only solution is to produce temporary amnesia i.e. temporary impairment of memory . The best agents for this purpose are the short-acting Benzodiazepines since we need to impair the memory for 1-2 hours only (the duration of the procedure) . Of course , long-acting Benzodiazepines are not suitable in this case since we don't want to impair the memory for a long time .

**Note: this use of benzodiazepines is one of the biggest issues in drug abuse and we will talk about it later .

** The last use of Benzodiazepines is :**Anti-convulsion (Anti-epilepsy)** .

-several Benzodiazepines have anticonvulsant activity and are used to treat epilepsy and other seizure disorders.

-Clonazepam is useful in chronic treatment of epilepsy, whereas diazepam is the drug of choice in terminating grand-mal epileptic seizures / status epilepticus .Let's clarify !

Benzodiazepines are not used frequently as anti-convulsants . They're used commonly in one case known as **status epilepticus**



.Usually , the epileptic attack lasts for ~ 2-3 minutes . Status epilepticus indicates an epileptic attack that lasts for ~ 10-15 minutes !(status means continuous and hence the name) .It's a life-threatening condition . You have to do something as fast as possible ! The patient is shaking / jerking forcibly so the first thing to do is to stabilize him . After that an anti-convulsant must be administered .Certainly ,oral anticonvulsants cannot be used in this case , IV injections are difficult to be given as well . In this case you either inject the patient with an anticonvulsant intramuscularly or you can use a special rectal suppository (this suppository is not like usual suppositories, it is a suppository with lubricant that's designed specifically for this purpose . It resembles injections somehow . It can be found in first aid kits) . The drugs of choice in this case are Benzodiazepines especially **Diazepam** .

Done with the uses of Benzodiazepines . Let's discuss their side effects ☺

**** Side effects of Benzodiazepines :**

(1) **Drowsiness and confusion**: the two most common side effects.

Explanation : All CNS depressants (examples include Benzodiazepines , alcohol and Barbiturate) cause drowsiness and confusion .

(2)**Ataxia occurs at high doses** and **precludes activities that require fine motor coordination**

(3) **Cognitive impairment can occur** .

Explanation of (2) and (3) : At high doses , all CNS depressants (including alcohol , barbiturate , ... , etc.) depress the function of the cerebellum that's responsible for the balance of walking . This leads to **ataxia** (the patient can't walk on a straight line , he keeps swaying . This sign indicates that the patient has taken a high dose of one of the CNS depressants . He could be drunk for example) .In addition , the depression of the CNS caused by Benzodiazepines leads to decreased coordination between different



parts of the brain . This coordination is needed in specific actions that require high degree of neural communication . The best example is driving which requires coordination between different fine movement skills .You are NOT allowed to drive if you are under the effect of any CNS depressant(anxiolytics , hypnotics , ...) due to impairment of fine movement and cognition. Not surprisingly , High percentages of car accidents have been recorded in drivers under the effect of CNS depressants . You have to warn your patient about the risk of driving if s/he takes any CNS depressant.(Cognitive impairment in this case doesn't mean loss of understanding and conceptualization abilities , it only refers to decreased coordination between brain compartments that affects the ability to do certain skills) .

(4) Triazolam often shows rapid development of tolerance, early morning insomnia, daytime anxiety.

Done with the side effects , let's talk now about an important topic :

**** Interactions and precautions :**

Generally ,Benzodiazepines by their own are considered safe drugs . However , they become fatal in some cases by depressing the respiratory centers. We are going to discuss two of these cases :

1 -Benzodiazepines are metabolized by the liver , accordingly ; there might be a problem in their metabolism in those who have liver diseases that leads to accumulation of high doses of the drug which suppress the respiratory centers ,that's why they're used cautiously in treating patients with liver diseases.

2 -Benzodiazepines commonly cause respiratory depression when taken with other CNS depressants especially alcohol . Around 11000 cases of death by respiratory depression due to this reason are recorded in America yearly !



**** In a nutshell :**Death by respiratory depression rarely occurs due to the use of Benzodiazepines alone i.e. they're considered safe drugs . It usually occurs in those who have liver disease or when other CNS depressants are used along with Benzodiazepines .

Referring to the slides : Alcohol and other CNS depressant enhance the sedative-hypnotic effect of Benzodiazepines .

Another point is that Benzodiazepines don't have euphoric activity unless taken with alcohol or other CNS depressant that enhances dopamine release and activates reward centers . This will be clarified in the upcoming lectures when talking about drug abuse☺

**** Dependence and withdrawal symptoms :Important**

stage1- A patient who suffers from insomnia , anxiety , panic attack , ... takes Benzodiazepine for more than 2 weeks



stage2-This patient develops tolerance and physical dependence . His body becomes dependent on the drug and he can't sleep without it !



stage3-Stopping the drug abruptly leads to the appearance of withdrawal symptoms such as anxiety and insomnia which are the same as the indications that we used the drug to treat ! - Refer to sheet 1 to revise the concept of withdrawal symptoms -



If the patient in the previous scenario comes to you ,you may not be able to know the real identity of the anxiety and insomnia he suffers from . Are they a part of the original problem (stage 1) ? Are they withdrawal symptoms (stage 3) ? The issue is complex , so you have to avoid withdrawal symptoms by tapering the dose when you want to stop the drug and not stopping it abruptly. Also remember our golden rule : Benzodiazepines must not be prescribed for more than 2 weeks to avoid physical dependence . What you have to understand is that the prescription of Benzodiazepines must be controlled by medical supervision and continuous follow ups, so don't go to the pharmacy asking for hypnotic drugs without a prescription . Another point that must be kept in mind is that in dealing with chronic cases of insomnia and anxiety , you must treat the real causes of the problem by changing the habits and the life style of the patient which ended up in anxiety and insomnia . Drugs are not the solution here since tolerance and dependence toward them will eventually build up .Instead , you have to change the life style as mentioned by encouraging the patient to do sports and reduce caffeine intake for example .

Important :

** What to give in the case of Benzodiazepines overdose ? In another words , what's the antidote of these drugs ? Flumazenil .

Referring to the slides : Flumazenil is the only benzodiazepine receptor antagonist available for clinical use. The drug is available by IV administration only. Onset is rapid but duration is short, with a half-life of about one hour. Because of this , many cases require frequent dosing of this antidote .

** What to give in the case of opioids overdose ? In another words , what's the antidote of opioids such as morphine , heroin , ... ? Naloxone .

For your information (not for the exam) :

** the antidote of digoxin is digoxin immune FAB

** the antidote of warfarin is vitamin K



We have finished discussing Benzodiazepines , now we'll talk about **non-Benzodiazepines hypnotics and anxiolytics :**

1-Z-drugs

2-Melatonin agonists.

Keep in mind that non-Benzodiazepines have been approved by FDA to be used in **inducing sleep** , however ; frequent awakening during sleeping might still occur that's why intermediate-acting Benzodiazepines are still needed in order to maintain sleep ! Keep in mind that generally , the side effects of non-Benzodiazepines are less than the side effects of Benzodiazepines .

**** Z-drugs (Zolpidem and Zaleplon) :**

-They are one of the most commonly prescribed hypnotics worldwide (more than 40 million prescriptions per year !) . Zolpidem is commonly used in Jordan , whereas Zaleplon is common in US , Britain and Japan .

-The reason behind their common use is that the level of tolerance and physical dependence toward them is very low .

-Their activity is similar to that of Benzodiazepines , however ; their effect on the CNS regarding muscle relaxation and anxiety is low i.e. they are mostly used as hypnotics . They are not used as anticonvulsants nor anxiolytics .

-Although they are commonly used , they are not over-the-counter i.e. they need a medical prescription . This is due to their adverse effects (important) :

- 1- These drugs are linked to eating , cooking , walking and driving during sleep ! This side effect is noticed in 1/100000 of the users of this drug . This side effect could be very dangerous , the patient may harm himself without consciousness !



2- These drugs produce very little hangover effect(drowsiness and confusion during the day due to the use of this drug are not common) . However , loss of coordination in fine movement is highly linked to the use of these drugs and for unknown reasons , it's more common in females .
Accordingly , a patient that's under the effect of Z drugs is not allowed to drive . To confirm this a study was done : They found that the percentage of car accidents caused by female drivers after 10 mg administration of Zolpidem is 15% compared to 3% in male drivers after administration of the same dose . We conclude that the administration /dosage of this drug is affected by gender . 10 mg is usually prescribed for males whereas 5 mg is prescribed for females i.e. half the dose of males .

Revise Z-drugs by the following slide ☺

- **An hypnotic agent that act on the same receptors as benzodiazepines. Nonetheless, it has no anticonvulsant effect nor muscle relaxation.**
- **It shows minimal withdrawal effects and little or no tolerance effect occur with prolonged use.**
- **Currently it is the most frequently prescribed hypnotic drug in the United States.**
- **Although zolpidem potentially has advantages over the benzodiazepines, clinical experience with the drug is still limited.**
- **Adverse effects includes nightmares, agitation, headache, daytime drowsiness.**

**** Melatonin agonists (Ramelteon) :**

Melatonin levels in the suprachiasmatic nucleus rise and fall in a circadian fashion . Concentrations increasing in the evening as an individual prepares for sleep, and then reaching a plateau and ultimately decreasing as the night progresses.(For clarification :Circadian rhythms are physical, mental and behavioral changes that follow a roughly 24-hour cycle, responding primarily to light and darkness in an organism's environment.)

المقصود تغيرات دورية (مثلًا في تركيز هرمون معين) تتبع الساعة البيولوجية للجسم

Scientists came with the following idea : Since melatonin level increases at night (maximally before sleep) , then we can induce sleep by producing a melatonin-like drug . Certain drugs were used at the beginning but they had a problem which is their short half-lives i.e. they were unsuccessful . Later on , scientists thought of activating the receptor by a new melatonin agonist that has an improved half-life which is (Ramelteon) .

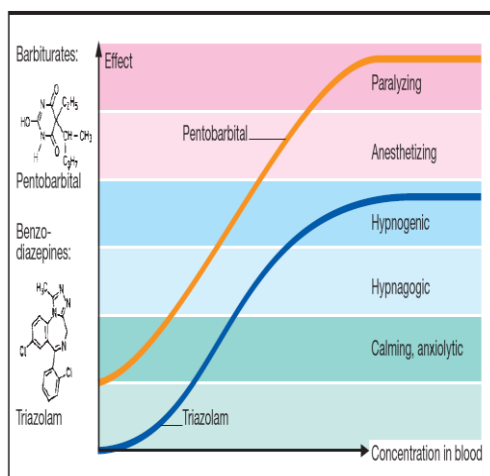
Ramelteon is a new drug relatively . It's still under the (post-market surveillance) i.e. they are still studying its side effects and kinetics .

The doctor read the following :

- **RAMELTEON** binds to both **MT₁** and **MT₂** receptors with high affinity.
- Binding of **Melatonin** to **MT₁** receptors **promotes the onset of sleep.**
- Binding of **Melatonin** to **MT₂** receptors shifts the timing of the circadian system.
- **RAMELTEON** is efficacious in combating both transient and chronic insomnia

**Barbiturates:

- The most widely used drugs to commit suicide . They're really problematic thus they are not approved anymore (they have been subsidized) . Let us clarify this by comparing them with Benzodiazepines . Notice the following curve :



C. Concentration dependence of barbiturate and benzodiazepine effects

The orange curve (the above one) represents one of the barbiturates . Notice that at its highest efficacy (E max) , it can cause paralysis , anesthesia , CNS and respiratory depression , coma and eventually death . So these drugs are killers by their own !

The blue curve (the lower one) represents Triazolam (short-acting benzodiazepine). Notice that at its highest efficacy it has only a hypnogenic effect . Previously in this sheet we said that Benzodiazepines are safe by their own . They cause death when used with another CNS depressants like alcohol .



-Doctor Malik asks you to read about these drugs from his slides . The most important Barbiturates you need to know are these two :

✎ **Thiopental** : was previously used in anesthetic procedures (Remember it as follows : We used to use Thiopental to induce anesthesia) .

✎ **Phenobarbital** :was used as an anticonvulsant in cases of febrile epilepsy in children (It has been banned , however ; some doctors still use it !) .

-Keep in mind that Barbiturates are old drugs that are – generally – not used anymore . They are still being abused to commit suicide .

-Hangover is highly noticed after the use of Barbiturates .

-The doctor read the following about the side effects of Barbiturates :

- a. **Respiratory depression: they suppress the hypoxic receptors that response to CO₂, and overdosage is followed by respiratory depression and death.**
for many decades, barbiturates poisoning has been a leading cause of death among drug overdose.
- b. **Enzyme induction: they induce the CYP450 microsomal enzymes in the liver, and thus interact with many drugs.**
- c. **CNS effects: cause drowsiness, impaired concentration.**
- d. **Drug hangover: hypnotic doses produce a feeling of tiredness after patient awake (many hours).**
- e. **Physical dependence: sudden withdrawal may cause tremors and anxiety and weakness**

This is all what you need to know about Barbiturates 😊

** Note : There is one drug left which is **Buspirone** . This is an anxiolytic that's not commonly used . The doctor will not ask us about it .

** Remember the golden rule :All of the anxiolytics/sedatives/hypnotics should be used only for symptomatic relief i.e. NEVER EVER make their use a habit !
Minimize their use and prescription as much as possible .



End of the sheet .

Dedicated to Baraa Alsyouf , Tamara Ayasrah , Majdoiln Alshurafa , Duaa Younis , Ghadeer Alsabatin , Bushra AlNababteh , Ala'a AlQhaiwi , Noor Hammad , Salsabeela BaniHamad , Ola Atif , Deema AlNammora , Lajneh and correction team.

Written by : Doa'a S. Dahboor

Remember me in your Dua'a

AND

Best of luck 😊😊😊😊😊