Good evening doctors. .

Dr Malek started a quick revision about last lecture's topics, I noticed that much was mentioned in the previous sheet but these are the main points that were emphasized on.

- GABA (Gama amino benzoic acid) is the main target for our drugs (benzodiazepines)
- Benzodiazepines are the main hypnotic drugs

  Barbiturates were used in the past, they are not really preferred because of their narrow therapeutic index, also overdose may cause death and respiratory depression, it was one of the main drugs used for suicide back in the 60's, so you can conclude that barbiturates are not great drugs.
- Benzodiazepines replaced barbiturates for being more easy to deal with.

  They are considered as an easy target.

An overview about the mechanism of GABA(Gama amino benzoic acid:)

GABA(Gama amino benzoic receptor) A (not B) has an inhibitory activity, the goal of binding is an alloseteric site, were the connection between GABA and its receptor is activated, with the result of increasing the frequency of chloride channels to open to produce more inhibitory activity. While barbiturates increase the period of opening these channels.

The end result is: chloride ions entering the cell and a state of hyper polarization overshadowing, so we can decrease anxiety in patients who can't sleep using hypnotics.

All benzodiazepines produce similar activity

Applications:

Anti-anxiety: be careful as these drugs are prohibited for everyday stress, yet used with pathological stress and chronic anxiety that cannot be solved by psychotherapy or changing the lifestyle of the patient

Spinal cord: decreasing the connection between the muscles and the brain with a result of muscle relaxation (inhibiting the spinal cord activity), as we increase the dose more inhibition is expected. Also used in treating muscle spasms produced due to excessive muscle strain.

Preoperation: Diazepam given with morphine (Diazepam is used to increase the effect of muscle relaxation and to decrease anxiety). Ipratropium and diprapropium are other muscle relaxants.

Hypnosis: patients suffering from hypertension and diabetes lose the proper ability to sleep; they are anxious and less immune so we must induce sleep. Hypnosis is important mainly before

operations in hospitals. However the doctor preferred to describe them as community drugs as many people are suffering from insomnia.

Note: remember that there is a difference in doses when drugs are used to treat insomnia and anxiety, for example a drug called lorazepam when used as an antianxietic 1-2 mg daily, however when used as hypnotic 4mg are prescribed daily (double the dose). This leads us to the conclusion that low doses induce a calming effect, while higher doses produce a hypnogenic effect.

Insomnia has multiple presentations. Some patients sleep for a duration of 3-4 hours only, others lack the ability to induce sleep, or suffer from discontinuous periods of sleep. Here, my friends, lies the importance of understanding the kinetics of pharmacology, duration and onset of action. Bezodiazepines have different durations of action. Depending on the case, we give the appropriate drug.

Enough with revision, now let the journey begin with new information (minute 8:00)

Benzodiazepines are divided into three categories depending on the duration of action:

Many people face withdrawal effects of benzodiazepines.

- **Short acting (Triazolam):** this drug is fast usually given 1 hour before sleep, helps the patient to "gear off". Duration of action is 1-3 hours only

- **Long acting (Flurazepam):** duration of action is 8-12 hours and more. Used if patients do not sleep at all. Long acting drugs tend to take a longer time to start acting.
- **Intermediate acting (Temazepam):** duration of action is 4-8 hours, used in patients who are not sleeping continuously, this drug should bless him with 6 hours of continuous sleep. (most common drug)patients on temazepam will not suffer from a noticeable hangover, but if they did you must change the dose or find another suitable drug.

You as a doctor must prepare the patient for suffering from a hangover especially if he was using the long acting drugs. It's also important to know the expected side effects.

One of the most common obstacles in using hypnotics is the inter individual variation (a common issue in CNS) this means that people do not have a fixed duration of sleep, some might sleep for six hours and show no inconvenience and others may sleep for 8 hours and still feel tired.
Hypnotics should be used only for a limited time, less than 2-4 weeks to be spared from tolerance and withdrawal symptoms.

Anticonvulsant: benzodiazepines are considered CNS depressants, these drugs decrease the transmission, leading to activation of GABA which is the main inhibitor, so they are considered good anti-epileptics, and it's used in low doses so there is no need to use high doses as in

hypnosis. Other more efficient drugs are used in anti-epilepsy (their use as anti-epileptics have subsided).
An important feature of Diazepam is that it is used as a drug of choice in seizure-epilepticus (a type of seizure that lasts for 15 minutes, unlike the normal seizure which lasts for 2-3 minutes). Profound tonic and clonic features are seen within this case. In cases of normal epileptic seizures, the patient should be left alone; we only interfere in this case.
If a patient undergoes this condition we have to hold him and give him diazepam intramuscularly (high doses).

Anterograde amnesia: (loss of memory for a short period of time) this is used during performing a procedure on a conscious patient, angioplasty or catheterization, endoscopy or bronchoscopy, if the patient was a female we wouldn't want her to remember what has happened during the surgery. Short acting drugs are usually used such as Triazolam. The patient is to be given a calming dose not a hypnotic dose. By the time of operation, the patient would be relaxed and ready to operate on.

All of the benzodiazepines have similar effects; however, every application has a certain drug of choice. For example, in cases of anxiety, we have to use long acting drugs (such as clorazipam); while the drug of choice in case of muscle relaxant is Diazepam.

Side effects of Benzodiazepines:

1. **Drowsiness and Confusion**: in CNS depression those are the two most common side effects, we have to concentrate on getting a good management as we are inhibiting the CNS.

2. **Ataxia**: this occurs with high doses and precludes activities that require fine motor coordination. Remember that this patient can't drive and can't play pool, also these drugs are bad for medical students. Fine motor coordination can happen at normal doses. As a medical student, you should not take them because normal doses can produce anterograde amnesia, confusion, and drowsiness. This means that you won't remember what you study.

   In order not to forget, benzodiazepines are like alcohol so a person who had an overdose won't be able to walk in a straight line (Ataxia).

3. **Cognitive impairment**: (إدراك) the ability of mental development is reduced especially in children; so benzodiazepines are relatively contraindicated with children. If there is no rational use, try to avoid them. They are only used in epilepsy (here benefit outweighs risk).

Interactions and precautions:

The doctor discussed a problem that is affecting our society:

- Ignorant people have started to mix alcohol with lorazepam, so they are present in the ER with vomiting, so they are drunk with profound ataxia, alcohol enhances the sedative effect of these drugs (عند الغرب ولكن في الاردن الله ينتقم من إلي فتح الخمارات) as Dr Malik said.

Saliba (clonazepam) is a known drug in Jordan used irresponsibly producing a state of unawareness and bad people synergize its effect by drinking alcohol or taking other medication to become euphoric. Excessive CNS depression causes euphoria.
Benzodiazepine alone has no euphoric activity ☺ only in very high doses.

- Benzodiazepines should be avoided with patients having acute narrow angle glaucoma because it increases the intracranial pressure in the eye
- Used cautiously in treating patients with liver diseases as its metabolized there.

IMPORTANT!! Benzodiazepine dependence Syndrome:

One of the most complicated issues when leaving the drug after a usage of 6 months or more.

Physiological and physical dependence can develop if the patient is exposed to high doses over a prolonged period, so tolerance occurs and the GABA will be down regulated.

After one month of the prescription the patient will start taking pills on his own but we as doctors should raise awareness and explain what could happen to the patients.

Benzodiazepine withdrawal syndrome is caused by stopping the drug or during dosage reduction, sometimes these symptoms might occur couple of days after the discontinuation of the drug this is because of the long half lives. This can be calculated by this simple equation ($4*t^{1/2}$). So if a drug with a half life of 1 day we need 4 days to get rid of it.

Withdrawal symptoms include: confusion, anxiety, agitation, insomnia, and tension.

Attention! anxiety and insomnia? how can I differentiate if those are symptoms of withdrawal or the symptoms I already treated and they recurred? So the patient will keep buying the drug alone without consulting the doctor.

Another example on how people misuse the drugs; once, a woman lost her child in an accident so she was given IV diazepam for 7 days to relieve her, at last she will become addicted as she will resort to the drug every time she remembers her son.

Conclusion: we do not use these drugs in everyday stress.

<u>In case of overdose:</u> Antidote is Flumazanil which is available in IV administration only

Zolpidem:

It is considered as the most prescribed drug in Jordan and the United States for Hypnosis.

This drug acts on the same receptors as benzodiazepines; however, it has neither an anticonvulsant effect nor muscle relaxation.

Zolpidem has no anti-anxiety effect (its binds to α-alpha 1 subunit) so it only produces a hypnotic effect

It shows minimal withdrawal effects and little or no tolerance effect even with prolonged use .

It's relatively a new drug with a limited clinical experience.

Adverse effects include: nightmares, agitation, headache, daytime drowsiness

It's a hypnotic drug so patients might experience a state of deep sleep and sleepwalking which might lead to a dangerous situation sometimes (such as jumping out from the window). Sleepwalking is becoming an issue.

***New studies revealed the fact that there is a variation between individuals in response especially between males and females, they found that females are more affected (drowsiness and hangover) than males. This is the first drug to be prescribed for females in different doses than males (Gender dependant).

We start with males in 10 mg of Zolpidem and with females 5 mg. This is the first gender oriented drug.

Remember that side effects with this drug are rare. SO, it's the best hypnotic drug until now.

This drug has no anti-anxiety effect; because it has a different mechanism of action than benzodiazepines. It only binds to the alpha subunits of the receptor, which only induces hypnosis without an anxiolytic effect.

Buspirone:

This drug solved the problem of anxiety dependence on benzodiazepines, because it works in different mechanism of action; has efficacy comparable to benzodiazepines.

This drug has no hypnotic activity ☺

Its action is mediated by serotonin receptors, if I decrease the serotonin level the patient will become calm and depressed, so to treat depression we elevate serotonin levels to increase happiness and alertness furthermore, mood equalization. So serotonin is the main biogenic amine.

One way to suppress anxiety is to decrease serotonin levels by deactivation of its receptors, becaue high levels of serotonin produce anxiety.

The most important receptor is the 5HT-A1 it is responsible for alertness and anxiety so if it was inhibited, an end result of calming and anxiolytic effect would occur.

Buspirone is a partial agonist on this receptor or might act as an antagonist, which will lead to inhibition of the endogenous serotonin from binding to its receptor. Reducing full activity of serotonin will produce an anxiolytic effect. To describe the effect of this drug, we use the word modulator.

The end result is inhibition of serotonin levels in brain (calming activity).

The anxiolytic effect of buspirone may take more than one week to become established, making the drug unsuitable for management of acute anxiety states, since we are not affecting the direct neurons (glutamate and GABA), we need time to start the activity 3 weeks at least.

Any effect on serotonin or dopamine will take a longer time to act, because they do not act directly.

The frequency of adverse side effects is rare, but the most common side effects are: headaches, dizziness, nervousness occurring in no more than 10% of the patients.

Yanal Shawareb

THANK YOU ☺