Note : doctor said that any information written in the slides & he didn't talk about it isn't required and he wont ask about it, only what he said in the lectures is included in the exam.

Today we will continue talking about **Anxiolytic & Hypnotic** drugs:

- The main players in this group are the ***Benzodiazepines*** which have 5 clinical usage:
  1- Sedative or hypnotic
  2- Anxiolytic
  3- Anterograde amnesia
  4- Muscle relaxant
  5- Anticonvulsant

  -The problem of them is the dependence & very bad withdrawal symptoms.

- Two groups of drugs have been introduced to the markets:

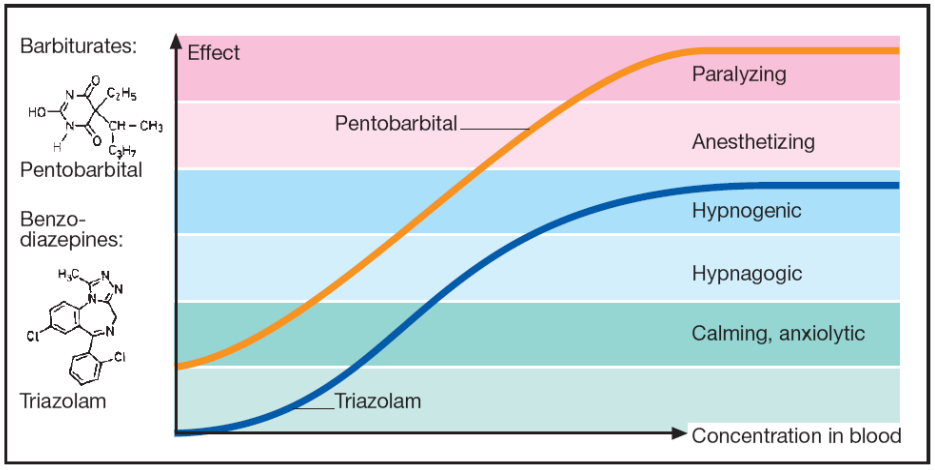
  1- The first one is the ***Z-drugs or (****zolpidem)* –which is present in Jordan-:
  - is a Hypnotic drug
  - Doesn't have the problem of dependence and withdrawal symptoms
  - BUT remember that we have to give half-dose for ladies than men, so the prescription is based on the **gender**.

  2- The second drug is ***Buspirone*** :
  - Is**n't** hypnotic drug
  - It's an **Anxiolytic drug only**, means without (hypnosis, anticonvulsants, muscle relaxant, and anterograde amnesia)
  - It's a nice drug & doesn't produce withdrawal symptoms, tolerance or dependence.
  - But the main problem that its need time to work, we need 3 weeks for *buspirone* to work because it works on Serotonin; {any drug works on (serotonin, dopamine or NE) needs time to work because of the remodeling that happen through the usage to it}, so it isn't suitable for panic disorder or whenever you need to treat anxiety fast.
  - Side effects include: headaches, dizziness, and nervousness.
  - This drug is considered as a Modulator; in some parts works as partial agonist, while in other works as partial antagonist for serotonin receptors, so it has a complicated mechanism of action.

*so the substituent for benzodiazepines to produce a hypnotic activity is *zolpidem* which becomes the most hypnotic drug to be prescribed, and by the time we graduate (إن شاء الله☺) *zelpidem + other z-drugs* will be very common drugs in the community not only in hospitals.
*But we still use the *benzodiazepines* as hypnotic drugs esp. in hospitals because we need to produce calming activity in addition to hypnotic activity.

*the idea is that we have 2 different problems: first, Anxiety or panic disorder, here you don't need hypnosis, but you need anxiolytic activity of drug.
Second problem, in hospitals when they want the patient to sleep, you give him a drug that reduce anxiety & also give hypnotic activity which is an advantage to him. But do we really need it?? The answer is No, but in some conditions you may use it(the drug which has dual activity)

- ***Barbiturates*** are very old drugs, since 1950:
  - They used as BOTH hypnotic & anxiolytic drugs.
  - But they produce bad activity, and not used anymore because the ceiling activity of the drug stops not in hypnosis like new drugs, but they stop in complete paralysis & more important respiratory depression & complete CNS depression, and this really high ceiling effect like Morphine is enough to produce this bad effect when increasing the dose of Barbiturates.



C. Concentration dependence of barbiturate and benzodiazepine effects

we may see them now only in two clinical applications:

1- Anticonvulsant or antiepileptic & we will discuss this later in antiepileptic drugs

2- Induction of anaesthesia, sometimes you need fast drug which produce CNS depression to the level of unconsciousness (Benzodiazepine ceiling activity will reach us only to hypnosis >> conscious level), so we use a drug called ***Thiopental* , ultra short-acting barbiturate**, which start within **30 seconds** & will produce complete CNS depression, of course at high dose{ if the anaesthetic asked the patient to count to ten and give him Thiopental, the patient will reach only to five then he will be completely unconscious}. And will work for **20 minutes.**

- Since 2009, we don't use thiopental, we use other drug called Propolol for induction of anaesthesia .we will talk about it in details with anaesthesia.

- The important thing about Barbiturates is the adverse effects of them, you will see that people use them to suicide because they are available. In Jordan its not a real problem because the suicide attempts are low in number, but in other countries like Australia , about 2300 suicide/year in 2006. Iran reached the 4th common suicidal attempts in the world.

***Dr read these notes from slides** :
- "Adverse effect of Barbiturates: 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".

-about the withdrawal symptoms of Benzodiazepines: "Features of withdrawal and dependence vary. Commonly there is a kind of **psychological dependence** based on the fact that the treatment works to reduce patients' anxiety or sleep disturbance and therefore they are unwilling to stop. If they do stop, there can be relapse, where original symptoms return" the idea of this that patient will not be motivated to stop using the drug because the symptoms that we first use the drug to treat will relapse when the patient stops it.

-"Withdrawal of BDZs should be gradual after as little as 3 weeks' use, but for long-term users it should be very slow, e.g. about 6–12 weeks. Withdrawal should be slowed if marked symptoms occur and it may be useful to substitute a long t1/2 drug (e.g. diazepam) to minimize rapid fluctuations in plasma concentrations. In difficult cases withdrawal may be assisted by concomitant use of an antidepressant."

- The last slide or table shows that drugs we used for sedation or anxiolytic : Buspirone(only anxiolytic), for hypnosis we use : Zolpidem(only hypnotic), but other drugs may used for both effects depend on the dose.

- What we need to understand from this is ***Lorazepam*** used:

1-2 mg once or twice daily as sedative or anxiolytic.
2-4 mg at bedtime as Hypnotic.

Antidepressants

- Depression is very common, affecting many people. So, it is very important to know how to deal with it.
- 20% or 40 million American going to be depressed during their life, and its more common in females than males (3:1).
- In Jordan the percentage will be around 10% of population may become depressed during their life.
- As a doctor, whatever your speciality you need to understand very well how to deal with depression.
- We mainly facing two problems: depression & psychosis or schizophrenia, but depression is more common
- From pharmacological view: "**The optimal use of antidepressant require a clear understanding of their mechanism of action, pharmacokinetics, potential drug interaction and the deferential diagnosis of psychiatric illnesses."**
- If you're a psychiatric you need to try multiple drugs with same patient, and you have to choose from 30 types of antidepressants, and from 50 antipsychotic. How? Depending on the pharmacology, so you have to understand it very well.

"**A World Health Organization (WHO) Prediction:**
•Depression is currently the FOURTH most significant cause of suffering and disability worldwide
And sadly, it will be the SECOND most debilitating human condition by the year 2020." Also by 2020, 50% of Jordanian newborn will have Asthma (it's not related to our subject but we have to understand this)

- Some **myths** you need to understand about depression:
    1. Old view, if the patient is depressed don't treat him because the treatment will cause more problems>> this is wrong, although these drugs aren't safe & will produce many effects because they affect CNS & sometimes produce side effects more than therapeutic effect, but most views become more clear that you really need to treat those patients, and if you don't they will end up having bipolar disorder or mania or schizophrenia

    2. 54% believe that depression is a weakness not an illness>> this is wrong, it's a disease
    3. 62% believe that depression isn't a health problem
    4. 50% or more believe that depression is "normal" & will not seek treatment
    5. This is in Jordan "depression is عيب">> this is absolutely wrong, its not shame if you go to psychiatric whatever your problem is, you have to deal with it as a disease like diabetes, hypertension or asthma, and please make the patient trust you and trust himself.

- Ladies are more affected by depression, because normally they're more affected by environmental changes, it's about 2-3 times more than men.

- To understand this think that first birth for lady is a twins or even one; this lady used to enjoy her own life, then she found herself with a baby who is totally dependent on her, very big switch in her life>> this may cause what is so called **(post partum depression),** if her husband didn't really support her. And its more common in ladies who deliver twins.
- Based on this, if someone rich became poor, lost his job, failed at medical school… all these conditions may lead to depression.

- **Depression** is **heterogeneous** disease, in a way like cancer; means that every single patient with depression has different mediators or different causes, but it is all about those three {Dopamine, Serotonin or NE}

- To understand the complexity of depression you have to know that:

  -**Dopamine** is responsible for (Attention / Pleasure / Emotions / Reward / Motivation / Movement)
  -**Serotonin** is responsible for (Regulates mood / Appetite / Sleep / Sexuality / Emesis / impulsiveness & aggression)
  -**NE** is responsible for (Alertness / Observance / Daydreaming / HR & BP / Stress)

  - The idea that they work together: for example: mood regulation comes with pleasure, appetite with aggression, and so on .., and this what really represent your personality.
  - So, combination of the changes of activity at the level of any of these 3 mediators produces the heterogeneousity of depression.

- You will find that in some patients serotonin is high, while its low in others, and both of them are depressed, from those who have low serotonin some of them will laugh if you tell him a joke while other wont!

- Depends on that there is (Typical depression & Atypical depression), and within each type patients are heterogeneous, some will sleep more & weight gain others not.

- So, we have different response to drugs between different patients even with same type of depression, and if the patient doesn't respond we have to change the drug strategy and try another type of treatment.

- **Depression symptoms** :

  1. Cognitive: hopelessness, poor confidence & negative thoughts (patient thinks that he is not important, nobody needs him, everybody is making fun of him..).
  2. Emotional : sad, unable to feel pleasure(not all patients), irritability.
  3. Physical /psychomotor : decrease libido & energy, sleep changes (70% sleep less,30% sleep more), Appetite changes (70% eat less, 30% more).

- Treatment based on three things :
    1. Antidepressant medications>> **not enough**
    2. There is a huge role of psychotherapy >> individualized psychotherapy and Cognitive behavioural therapy has most evidence for efficacy of treatment.
    3. Sometimes exercise & body awareness has been found to be helpful.

*70% of patients will respond if we combine antidepressants with psychotherapy.
*only 35% will respond to antidepressants alone.
*psychotherapy doesn't always have to be by psychiatric, maybe by sociologist or other.

- We have 2 theories for treatment:
    - We measure the amount of mediators and for example we find serotonin low, so we give a drug the increases serotonin level and so the patient will respond
    - MAO (mono amino oxidase) theory, said that if we give MAO inhibitor, inhibiting the metabolism of (serotonin,, dopamine,NE) the mood of patient will improve & that help in treatment of depression.
    - But in some patients the mediators level isn't low or high, & they will say those patients will not respond to the drugs, this depression is not caused by mediators, in fact there is something happening in their mind producing this type of depression.

  *this means that we don't know the cause of depression, although we know there is a role of NTs, & from this coming the idea of importance of psychotherapy, but still we need to treat them with drugs to prevent ending up with mania or psychosis.
  *psychotherapy alone will have response in only 20% of patients.
  *we have some of **Placebo effect** in treatment.

- If we look at the table of antidepressants prescriptions in USA per year in the slides, we will see that:
  -First one called ***Sertraline (Zoloft)*** is the most prescribed drug as antidepressant>> have 29.652**millions** prescription per year

  -second one is called ***Escitalopram***

  -3rd is ***Fluoxetine (Prozac)*** very common in Jordan
  - other drugs

  ** if you count all prescriptions for them >> it is around **200million** prescription of antidepressants in 2007 in USA only!!!!!! And now is more.
  ** the most prescribed drugs in the world is antidepressants & antipsychotic followed by Hypnotic drugs.
  **The patient usually needs 12 prescription per year, so divide 200/12= about 20million people are affected by depression in America

- Antidepressants classes :
    1. SSRI (selective serotonin reuptake inhibitors)
    2. NDRI (NE dopamine reuptake inhibitors)
    3. SNRI (serotonin NE reuptake inhibitors)
    4. TCA (tri-cyclic antidepressants)

    *we can target specific or multiple mediators (DA, NE, Serotonin) with different classes of drugs.

- We have 5 groups of antidepressants, will start with the first and old group called ***TCA (Try-Cyclic Antidepressants)*** :
    - Absolutely non-selective; they inhibit the reuptake of (serotonin. Dopamine,NE), increasing their activity in the synapse –leading to better mood-.

    - They also bind to& block other receptors, producing side effects:
      Muscarinic Ach receptors >> dry mouth, constipation, blurred vision & urinary retention.
      Alpha-adrenoceptors>>cardiac effects , orthostatic hypotension
      Histamine (H1) receptors>>drug-induced sedation

*they are bad, non-selective, **more potent** drugs but some patients need this activity because of the same story of heterogenousity that's why they are still in use.

The end
Good luck ☺

Done by : Ala'a Aladdasi

"نولد عدة مراتٍ..
مرّة عندما نلج هذه الدنيا من بطون أمَّهاتنا..
ومّرة عندما نجد أنفسنا في هذه الدنيا ، نجد موقعنا الحقيقيَّ من الإعراب..
ومّرةً عندما نستطيع ان نترك أثراً فيها..
بعض الناس يكتفون بالولادة الأولى .. الولادة البيولوجيَّة .. يعيشون ولكن لا يحيون حقاً .. يتنفسّون .. يأكلون .. ينامون. يتكاثرون ..ولكن لا يحيون.
والبعض لا يكتفي أبداً ، بل يولد عدة مرات في حياته..
ويكون لولاداته تلك اثراٌ في ولادة عالمٍ جديد ..
ولادة حضارةٍ جديدة .. لعالم جديد أفضل "..
د. أحمد خيري العمري