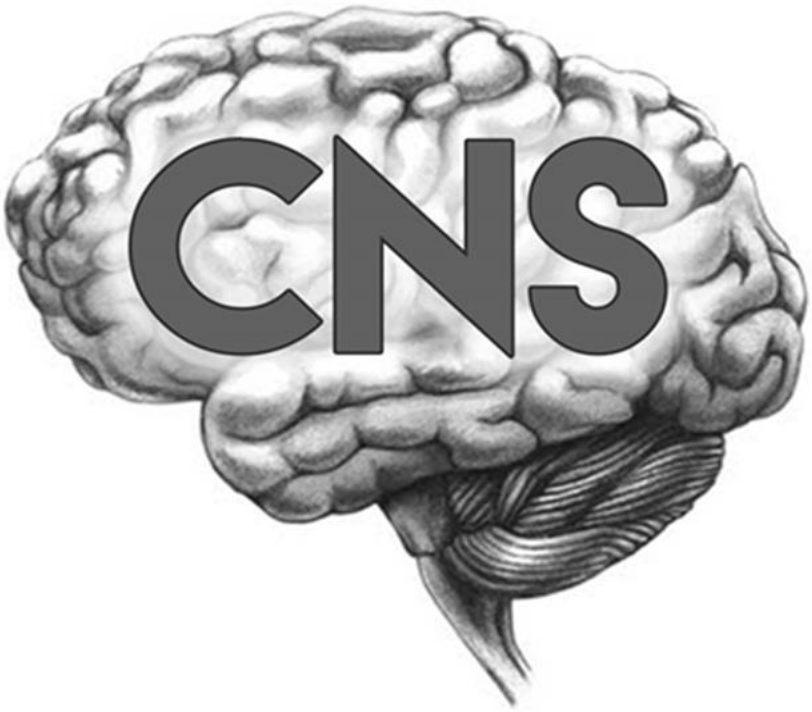

PHARMACOLOGY

☑ Sheet ○ Slide ○ Handout

Number

5

Subject

Degenerative disorders, bipolar disease&CNS stimulants

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Date: 00/00/2016

Price:

-This sheet has been written according to sec.3 record
- Topics of this sheet:

1. Therapy of **degenerative disorders:**
   -**Parkinson** disease
   -**Alzheimer** disease
2. **Bipolar** disease.
3. **CNS stimulation**.

Lets start :")

1-Parkinson disease

Last lecture we started talking about Parkinson's disease →a quick review:

- It's a degenerative disease in which there is a decrease in dopamine and increase in Ach.
  (actually the Ach does not increase too much but compared with the low level of dopamine its considered high).
- The target of the therapy is :
  to restore the dopamine/ACH balance >>in other words we try to increase dopamine AND decrease Ach→ This can be achieved by restoring the dopamine **AND** antagonize the excitatory effect of cholinergic neurons.

- **Pharmacological Approaches of Parkinson's disease treatment :**

A-restoring dopamine by replacement therapy**:**

1- We start with **Levadopa /Carpidopa** replacement therapy which effectiveness decreas with time " *wearing off* ".so we try to increase the level of dopamine by :
2- Giving **Selegiline**. however ,with time we need more and more dopamine so
3- We give **COMT inhibitors**.

#**Note**: the most important side effects are the: (Dyskinesia :affects 15% of patient) and the (Hallucination: affects 5-7 % of patient)

B-restoring dopamine by activation of its receptors (D2-agonist):

-They are great drugs , they act Longley (for 5 years at least ,while L-dopa2-3 years-before you start to note sth like wearing off phenomena)
so "wearing off" phenomena starts early at the first approach and late at the late one.

they produce less dyskinesia but a very high incidence of hallucination occurs, generally they cause a collection of S+S called>> ***dirty old man*** :hallucination ,sexual activity, gambling,,etc .

C-antagonize the excitatory effect of cholinergic neurons by Antimuscrunic drugs **:**

- ✓ As we said before in Parkinson, there is high amount of ACH → so we want to suppress the Ach.
- ✓ Blocking of the cholinergic transmission produces effects like augmentation (rise) of dopaminergic transmission>> so :
- ✓ Reducing the Ach levels in the brain by blocking the muscarinic receptors>> lead to blockage of the cholinergic transmission >>this produce effects similar to rise of dopaminergic transmission, so there is a balance between the dopamine & acetylcholine levels.

there are couple of important Qs regarding Antimuscrunic drugs used in parkinson's:

- ✓ Can we start treatment with these drugs??
- ✓ Do these drugs treat the rigidity,tremor, stiffness of the patient ??

ANS:

- No for both, because these drugs have <u>much lower efficacies than Levodopa</u> and <u>play only an adjuvant role</u> in anti-parkinsonism therapy (we only <u>add them</u> with other strategies of treatment). DO NOT USE THEM ALONE.

>>What are these drugs??

1) Benztropine.
2) Biperidine.
3) Atropin.

→They are the same,But we give **Biperidine** because it **has better activity and penetration**.

Side effects:

- They may cause **mood change.**
- **Atropine like side effects** احفظهم زي اسمك:

1) Visual problems (blurred vision)→so they are contraindicated in glaucoma.
2) Constipation; by interfering with the gastrointestinal peristalsis.
3) Urinary retention.
4) Dryness of the mouth.

Important note

If **the patient has schizophrenia** -and take a haloperidol drug, and you want to treat him from Parkinson like effect→the drug of choice in this case is **antimuscuranic drugs only**.

(explanation : as we know haloperidol side effects appear on the patient as Parkinson like effects and extrapyramidal side effects like Akathisia " which result from overproduction of dopamine" So if we treat those patients with dopaminergic drugs" like Levodopa" their condition will becomes worse than before).

To sum up:

- Treatment of Parkinson: Start with Levodopa &Carbidopa, when the "wearing-off" response begins, give COMT inhibitors or MAO inhibitors then try giving the dopamine agonists drugs.
- Anti-cholinergic drugs don't have an important role in treating Parkinson. We may give them if the patient can't tolerate the dopaminergic drugs.

2-ALzheimer disease {وَمَنْ نُعَمِّرْهُ نُنَكِّسْهُ فِي الْخَلْقِ أَفَلَا يَعْقِلُونَ}

→It's really a big issue that you need to deal with it as a Doctor.
→It mainly affect people who are greater than 65 years old.
→Unfortunately,There is no definitive treatment for Alzheimer because nobody knows the reason behind it, you will see your patient degenerating without being able to really help him.

→The patient will have dementia (doesn't know their children or where they lived☹, some of them even can't recognize themselves).
→The problem is not only about losing memory; he will also lose his abilities and cognition, he will lose everything ☹ .

→The good news that the prevalence of Alzheimer disease in Jordan is less than other countries, however its becoming more popular nowadays, because people live longer.

❖ Treatment:

Always remember that there is no treatment for Alzheimer disease, we only treat the symptoms, which will lead to just little improvement

As we said there is no specific cause so no real treatment,However pharmacologist suspect two causes and based on those 2 causes>> **the aims** of Alzheimer Tx :

A)) Improving cholinergic transmission within the CNS (First choice of treatment):

>>Many studies have linked the progressive loss of cholinergic neurons , and presumably cholinergic transmission within the cortex, to the memory loss which is the hallmark (trademark) symptom of Alzheimer disease.

**in other world: Alzheimer is linked with memory and memory is linked to ACH
if there is decreased Ach>>> decreased memory.

>>so the aim is to increase Ach by replacing it. but in reality we don't give ACH itself directly instead we give **cholinergic drugs .** these are:

➢ Acetylcholine esterase inhibitors:

1- Donepezil 2-Galantamine

- ✓ They inhibit the metabolism of acetylcholine by inhibiting choline esterase thus increasing the level of acetylcholine>> Inhibition of Acetyl cholinesterase within CNS will improve cholinergic transmission.

- ✓ The inhibition of cholinesterase is specifically toward the brain rather than the periphery, SO we need drugs that are effective in crossing the BBB.
- ✓ Are they really effective in treatment of Alzheimer disease??

No, these agents provide a **modest reduction** in the rate of loss of cognitive functioning in Alzheimer disease**.**

- ➢ For **how long** should the patient take them?

Nobody knows but they may improve the cognition for (6months to1 year),after that either the patient take the drug or not it's the same,so they have a small improvement which will disappear after a while.
>That's why we said you will stand watch your patient's brain degenerate without being able to help him.

- ➢ **Side effects :**

Opposite to the anticholinergics; opposite to the atropine like effect
(Anything with secretion)

1- Diarrhea.
2- Salivation.
3- Lacrimation.
4- Muscles gramps.

Notes

- **Cholinergic drugs act** :

1-**Directly**: by stimulating the cholinergic receptors
. Ex: Bethanechol.(isn't used because its penetration is low).

2-**Indirectly**: by inhibiting choline esterase.
Ex: Neostigmine & Physostigmine **OR** Galantamin & Donepezil. (it's the drug that is used in Alzheimer)

- If your patient has a **myasthenia graves** and you want to increase the ACH in the periphery , you give him " Neostigmine "which doesn't cross BBB.
- If your patient have **atropines toxicity** athis brain , give him a drug as feostigmine.

B)) preventing the excitotoxicity actions of NMDA glutamate receptors in selected brain areas (Second choice of treatment):

- One of the suggested neurodegenerative processes : is that stimulation of **glutamine receptors**, particularly of the **NMDA type,** has been shown to result in excito-toxic & "killing effects" on neurons. So>>
- Antagonists of NDMA glutamine receptors are often neuro-protective, preventing the loss of neurons following ischemic and other injuries.
- Our aim of treatment here is to decrease activity of NDMA receptors by giving anti-NDAM to inhibit the excitotoxic& killing effects of these receptors.

NDMA receptors antagonists: (Memantine)

- This drug has a better activity and it's better than antimuscrunic drugs , it will improve the symptoms of the patient for 1 years **and** reduce the progression of neurons degenerating**.**
- It has shown to prevent or slow the rate of memory loss in Alzheimer dementia, even in patients with moderate to severe cognitive loss.
- However, they may produce: **confusion** and **restlessness** .

To sum up:

- ✓ Treatment of Alzheimer doesn't include " cureness" or alter the underlying neurodegenerative process , it's only palliative (calming) and provides modest short-term benefit .
- ✓ Main drugs to be used:
  1- Donepezil + Galantamine
  2- Memantine

3-Bipolar disorder

- A big issue, common although we don't see it.
- It is too important to know that there is depression and bipolar depression.
- Many of those patients that being diagnosed as depressed have also mania.
- Bipolar mania is so-close to depression.

Bipolar disorders two types:

[1] – ***Manic***, here the patient is always happy, but sometimes may have depression.

→In other worlds: - with all our respect for all human beings -, but the patient is مجنون.

→Easy to control somehow, although the patient has to take the drug all of his life

[2]- ***Depression with hypomania***, very difficult and so complex.

→May be misdiagnosed as depression OR schizophrenia.

→If it is misdiagnosed and treated as depression, this will increase the manic attack. antidepressant drugs like Sertraline +Flouxetine should not be given for manic patients as they increase the manic attacks.

rem: we don't prescribe Sertraline +Flouxetine to manic patients or patients with hyperactivity or restlessness or convalescences , in case we want to give such a patient an antidepressant we give him paroxetine. (we may give him anti-obsessive activity drugs)

→If it misdiagnosed and treated as schizophrenia, anti-schizophrenic drugs may have some anti-manic activity.

Treatment choices:

How to treat bipolar disorders whether type1 or 2 ?

** According to patient symptoms , we have these drugs to choose from :

Lithium \ Anti-convulsion \ Carbamazepine \ Lamotrigine.

** Classic Antipsychotics: not favorable, but to control the **acute** manic attack. Haloperidol, Olanzapine but not Clozapine because agranulocytosis is a fatal side effect. (rem :the last two drugs cause gain in the body weight >> risk of DM)

(1)-Lithium

→I am **antidepressant** in origin and I have a nice activity in **mania**, producing **mood stabilization.** We can consider this drug as a magical one (anti-depressant+ anti-mania at the same time)

→The strong question is How to get depression and mania at the same time in the same patient?

كيف يمكن للمرء أن يكون مكتئب ومجنون في آنٍ واحد؟!

As you know, too much dopamine is responsible for manic attack only but not for depression, so how come?

Bipolar is a swinging disorder, today the patient is so happy and pleasant, next day turning into depressed mood and so forth so on.

There is no real theory beyond this, one theory which Dr.Malik is interested in is that: → with very high level of dopamine >> manic attacks occur>> during the attacks desensitization of dopamine receptors in the brain occur as a feedback inhibition due to the massive amount of dopamine (the desensitization is proposed to occur via decreasing the number of receptors)→with low no. of dopamine receptors the patient get depression>> then another rise in dopamine level with manic attack, in response, desensitization of dopamine receptors with depression and so on.

So for bipolar treatment, I need a drug that can treat both problems, the drug of choice is **Lithium**. Lithium characteristics:

- No psychotropic effect on non-Bipolars.
- Affects nerve membranes, multiple receptor systems and intracellular 2nd messenger impulse transduction systems. (Decrease the 2nd messenger).
- Interacts with serotonin (decrease it).
- Potential to up-regulate CNS gene expression, stabilizing neurons with associated multiple gene expression change.

- Real narrow therapeutic index, we don't give it except we have an access to drug monitor.
- Higher concentrations (1.0mEq/L and up produce bothersome effects, higher than 2 mEq/L can be serious or fatal.
- Every type of side effect you can see:
  Neurological, gastrointestinal, enlarged thyroid, rash, weight gain, memory difficulty, kidney dysfunction, cardiovascular.

USMLE questions:

→ Which of the following drugs produce inhibition of ADH?
→ Which of the following drugs increase urination?
→ Which of the following drugs induce kidney toxicity and kidney failure?
The answer for all of them is **Lithium**

- The first sign of Lithium toxicity is always toward the renal side effects, but all other side effects may happen in the beginning with different severity, if your patient complaining from frequent urination →kidney toxicity.
- Lithium and Na level:
  When administrating Lithium you should tell your patient not to change salt content of his food in order to have stable level of Na, why?
  Na and Lithium they compete in reabsorption, if Na level get decreased then Lithium reabsorption will increase causing toxicity.
  Unlike Thiazide (antihypertensive), in which you tell your patient to reduce the salt content, in order not to build high level of Na, because Thiazide mechanism of action is to deplete Na from the vessels.

CVS -flash back

When administrating Digoxin, tell your patient to tell you if he\she will take antibiotics in addition, because part of Digoxin metabolism is mediated by microflora which may be the target of this antibiotic, so if its metabolism decreases because of deceased microflora

now moving into the 2nd drug used in bipolar disorder:

(2)- Valproic Acid (anti-epileptic)

• An anti-epileptic, it is the most widely used anti-manic drug.
• Augments the post-synaptic action of GABA at its receptors (increasing synthesis and release).
• Best for rapid-cycling and **acute-mania**.
• Therapeutic blood levels: 50-100 Mg/L

What is the idea behind using anti-convulsants?
If there is too much electricity in the brain it can reduce it by inhibition of Na entrance OR inhibition of Ca entrance OR increase the activity of GABA (like the benzodiazepines and barbiturates..etc.) .
Here we are concerned with the drugs that have activity on **tonic colonic seizures** (generalized type of seizures accompany manic attacks).
rem : we had studied different types of anticonvulsants like phenytoin , carbamazepine, valproic acid and ethosuximide (rem. This drug is for absence seizures)

- The drug of choice for generalized seizure is Valproic acid, Lamotrigine OR Carbamazepine.
- Valproic acid, Lamotrigine are the best drugs because they have multiple mechanisms of action; they block Ca, increase GABA and they have re–stabilization effect of the membrane across the nerves.
- If your patient has mania start with Valproic Acid, and if there is no depression don't give Lithium.
- **Side effects** include GI upset**, sedation**, lethargy, tremor, metabolic liver changes and possible loss of hair.
- Sedation because it is a CNS depressant (rem. It induces GABA), producing sedation in 20% of patients, if the patient cannot tolerate this bad sedation then move to Lamotrigine first OR Carbamazepine.

- **Root of administration**: oral administration with a loading dose of 20 mg\kg\day.

We can notice that when we prescribe Lithium we prescribe it in initial low dose then we start increasing the dose with continuous monitoring, while in Valproate we start with a high dose and even we initially we load the patient with the drug.

(3) - Lamotrigine

* The first alternative of Valproic acid in case of sedation intolerance. (specially in elderly)
* There is no sedation with Lamotrigine, but produces bad rash (Steven- John syndrome) in 10 – 15%, which may be fatal. (google this syndrome >> it's REALLY BAD!!)
* Is the best drug for mania and epilepsy.

(4) - Anti-psychotics

→prescribed as sometimes mania is accompanied with psychosis. (patients will have "circle-way of thinking")
→Clozapine, Risperidone, and Olanzapine, Aripiprazole.
→Start with Olanzapine and keep Clozapine the final alternative because of agranulocytosis, in Japan they start with Aripiprazole.
→Ari**p**iprazole (**p**artial agonist) is more expensive than Olanzapine with less side effects, is a pharmacogenetic guided drug>> administrated according to CYP3A4 and CYP3A5 polymorphism, if these genes were fully functioning then give the complete dose, if one allele is lost then reduce the dose, if both alleles are lost then reduce the dose even more.
To sum up,

ONLY mania	→Valproic acid OR Lamotrigine.
With psychosis	→ Olanzapine, Risperidone, Aripiprazole, Clozapine.
Depression with hypomania	→Start with Lithium. OR →Start with Valproic acid in addition to an antipsychotics.

4-CNS stimulants

Note: this part was the last part in the lecture, so Dr.Malik explained it very fast about 4 min ,however there is many important information in slides, we wrote them down to make things more clear ".

→CNS-Stimulant is a substance>>which tends to increase behavioral activity when administered.

→**Why** do we need to stimulate the brain?

1) To increase the **concentration** of the patient, such in (**ADHD**) Attention Deficit Hyperactivity Disorder ; lack the ability to be involved in any one activity for longer than a few minutes.
2) To stimulate the **loss of appetite** (it works as anorectic agents),such in obesity cases .
3) To **wake & alert** a person who has sleep-less disorders, such as in Narcolepsy; it is a relatively rare sleep disorder, which is characterized by uncontrollable bouts of sleepiness during the day.
4) To Enhance the **motor activity** and Decrease feeling of fatigue.
5) To get **Excitement, Euphoria**.

→Signs and symptoms for patient who is taken these drugs :
كيف تكشفه

1- Elevate Mood
2- Increase Motor Activity
3- Increase Alertness
4- Decrease need for Sleep

*In case of overdose lead to convulsion and death.

→Contraindications

•in patients with anorexia, insomnia, asthenia, psychopathic personality, a history of homicidal or suicidal tendencies.

→*CNS* stimulants:

1. Nicotine (smoking).
2. Methylphenidate.

Nicotine:

- It is the active ingredient in tobacco. Used in smoking cessation therapy.
- It's used as a drug to help in increasing the concentration, decreasing stress ,give a little euphoria ,HOWEVER remember that { يَسْأَلُونَكَ عَنِ الْخَمْرِ وَالْمَيْسِرِ ۖ قُلْ فِيهِمَا إِثْمٌ كَبِيرٌ وَمَنَافِعُ لِلنَّاسِ وَإِثْمُهُمَا أَكْبَرُ مِنْ نَفْعِهِمَا }
- There is a difference between smoking and nicotine !!
  smoking has many others toxic and bad components and not only the nicotine ,that's why smoking is really a big problem .
- side effect of nicotine :
  - sympathetic and parasympathetic effect when they reach the synaptic ganglia, however it depends on the dose :
    - Low doses (1-2 mg): euphoria, arousal, relaxation, improves attention, learning, problem solving and reaction time.
    - High doses (around 20 cigarettes/hour): CNS paralysis, severe hypotension (medullary paralysis).
  - Irritability and tremors.
  - Intestinal cramps, diarrhea.
  - Increase HR & BP.

Methylphenidate "know this drug ,only" **:**

- We use this drug in Jordan and the whole world.
- **Is the Best choice for (ADDH) اضطراب نقص الانتباه مع فرط النشاط ;** It is taken daily by 4-6 million children in the USA for ADHD, better than amphet**amine**; **because** it enters the brain much slowly and does not increase dopamine levels rapidly ,So it needs time to produce euphoria, fatigue**.**
- **Adverse effects:**
  - GIT effects are the most common; abdominal pain and nausea.

- In seizure patients, methylphenidate seems to increase the seizure frequency, especially if the patient is taking antidepressants.

Withdrawal syndrome:

- Nicotine is an addictive substance; so physical dependence develops rapidly and can be severe.
- **When "quitting" use** "زي لما الواحد بده يبطل تدخين" **many signs appear in this patient :**

→Irritability, anxiety, depression, impatience, trouble sleeping, restlessness, hunger or weight gain, and difficulty concentrating.

- So For people who are willing to stop smoking, we deal with their physical dependence by:

1- **Bupropion**(it's an anti-depressant , actually we don't use it "

IN Jordan we use these ways:

2- offering nicotine patches and chewing gum that release nicotine in gradually lowered doses

3- **Varenicline** الاسم العلمي ;" Champix"

→It's a very nice drug because it works as partial agonist for nicotine receptors so the withdrawal signs will be very low. However, it's an expensive drug.

Final note:

Before giving any drug to your patients,it's important to deal with their psychotic problem; يعني الارادة هي الاساس قبل استخدام اي دوا

The end
sorry for any mistake