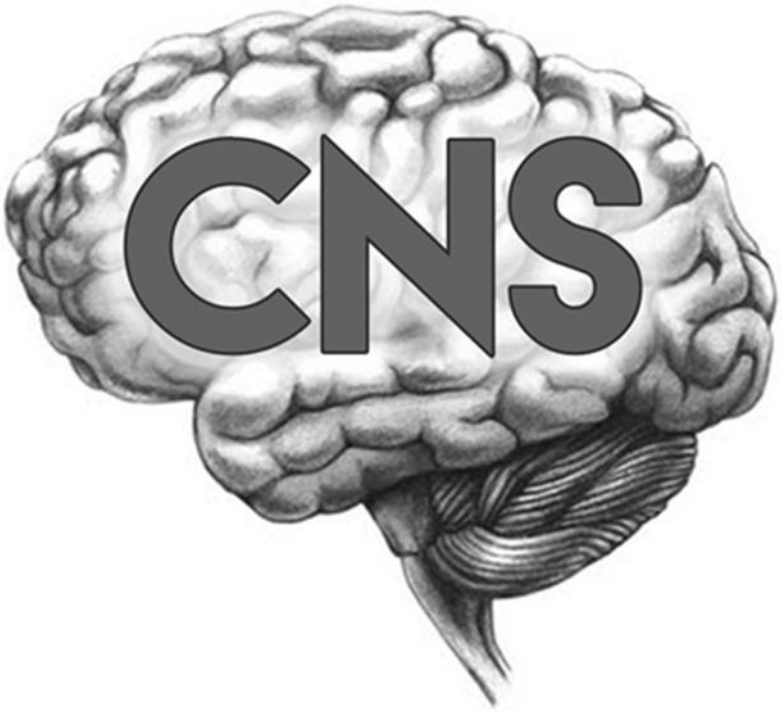

PHARMACOLOGY

✓Sheet ○Slide ○Handout

Number

4

Subject

Antipsychotics & Antiparkinsons

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Antipsychotics & Antiparkinsons

Antipsychotic drugs (Schizophrenia treatment)

Quick Overview ..

Typical antipsychotics - old	**Atypical antipsychotics - new**
Chlorpromazine & Haloperidol	Risperidone, Clozapine, Olanzapine, Quetiapine, Aripiprazole, Ziprasidone
Dopamine antagonists {with high selectivity}	less Dopamine antagonist * {less selectivity} + Serotonin antagonist
against *Positive* thoughts/ symptoms	against *Positive* symptoms + effective against *negative* symptoms
* Atypical antipsychotics have less risk to produce **motor (extra pyramidal) side effects** -the previous lec.- compared to typical drugs.	

1>> Risperidone

The most famous one in Jordan, it is;

* Dopamine antagonist >> see down

* Serotonin antagonist >> atypical antipsycotic

* Histamine antagonist >>>>>> produces strong Sedation

* Alpha adrenergic antagonist >>>>> produces Postural Hypotension

Produces Extrapyramidal side effects **EPS** **at high doses**; increasing the dose = increasing the binding to Dopamine receptors = the pt will have EPS.

Don't memorize this line the maximum dose for Risperidone = 4mg, giving 6mg will produce EPS

However minority may develop EPS at the normal dose. To make sure the pt won't get these side effect, **anti cholinergic drugs** (antacetylcholine like Atropine) **are prescribed with Risperidone.**

Remember from Endocrine, **Dopamine inhibits Prolactin secretion**, so using dopamine antagonist {especially Risperidone} will increase Prolactin level, and **Dopamine has an effect on Gonadotropin** (decrease FSH and LH). So women will experience (galactorrhea + loss of libido + delayed ovulation and menstruation or amenorrhea), while men will get (gynecomastia + impotence), all these are SIDE effects and are more linked to Risperidone.

2>> Clozapine and Olanzapine

Olanzapine is the 2nd famous one. They are;

* Dopamine antagonist >> less selectivity {weaker binding} >> **No EPS** even at high dose

* Serotonin antagonist >> atypical antipsycotic

* Histamine antagonist >>>>>> produces strong Sedation

* Alpha adrenergic antagonist >>>>> produces Postural Hypotension

The less selectivity towards Dopamine receptors and more towards Serotonin causes increasing in appetite, leading to **significant weight gain** (5kg in 10 weeks) **and diabetes**, combined with universal metabolic disturbances {the pt will have hypercholesterolemia, hyperlipidemia..} . This will limit their usage.

▪ Most pt will prefer Risperidone and its side effects {endocrine & sexual} rather than weight gain. The doctor preferred Clozapine & Olanzapine.

Agranulocytosis is a potentially fatal side effect (happens in 2% of pt which is a lot) **for Clozapine, so its usage should be the last resort/ choice, although it shows greater efficacy against negative symptoms than others. Don't start with Clozapine.**

3>> Quetiapine

Has fewer EPS/ has no increased risks for EPS

It is an atypical antipsychotic, shares sedation, orthostatic hypotension, weight gain (2-3kg in 10 weeks). As you see till now this is the least problematic drug.

Cause **anticholinergic side effects– dry mouth, constipation**

Does not elevate prolactin

This is a nice but expensive drug, remember that Schizophrenia is a chronic disorder and need lifelong treatment.

***** **What is the efficacy of 1+2+3? It does not exceed 60%. {Not high}**

This means from 100 schizophrenic pt that were given any one of these drugs only 60 one will response. To solve this, you have to interchange between these drugs.

Do not change the drug except you are sure that it doesn't work AND after 3 months of usage. If the pt doesn't respond after this, you should change the strategy move to **4**.

4>> Aripiprazole =200 JD per month (very expensive)

This is a **Dopamine {D2 receptor} Partial agonist ? See down**

Has affinity for muscarinic, α1-adrenergic, serotonin and histamine receptors. With Few EPS & Few weight gain. >> nice one

The major side effect is feeling dizzy. Not prescribed to elderly since they're already dizzy.

As mentioned Aripiprazole is a partial agonist on D2 and serotonin receptors, this means the intensity حدة of side effect will be less since it is NOT a full antagonist {there will not be a potent sedation or potent orthostatic hypotension}.

* Being a partial agonist means the binding to the receptor won't give the full agonist-mediated response {will give a weak response} and this means that this drug is acting like an antagonist in presence of the agonist.

بالعربي.. الدواء يرتبط بالمستقبل ويحدث استجابة لكن ليست كاملة، وبارتباطه هذا يمنع الدوبامين من الارتباط لاحداث الاستجابة؛ فالدواء يعمل كذلك كمضاد/ معارض وهذا التاثير غير كامل ايضا لاحداثه الاستجابة غير الكاملة.

النتيجة أن الأعراض المصاحبة للدواء تكون أقل حدة.

5>> Ziprasidone, not discussed.

Summery?

* Schizophrenia is a complex disease that we do not know its cause -unknown etiology-.

* It is characterized by increased dopaminergic neuronal activity, that is why pt has hallucinations and the other +ve symptoms. The -ve symptoms are related to serotonin so that these -ve symptoms are treated by the new drugs that block both dopamine & serotonin receptors producing many side effects.

* Typical type drugs = EPS

* Atypical type drugs = no EPS

  - Endocrine effect; Risperidone
  - Weight gain & diabetes; Clozapine & Olanzapine
  - Agranulocytosis; Clozapine
  - Dizziness; Aripiprazole but stays a nice drug
  - Anticholinergic effects; Quetiapine

* For how long should the pt take the drug? For their whole life.

* Taking a drug does not necessarily mean developing its side effects.

Antiparkinson drugs

* Most of the drugs that affect the central nervous system act by altering some steps in the neurotransmission process. They may act presynaptically by influencing the production, storage, release, or termination of action of neurotransmitters. Other agents may activate or block postsynaptic receptors. Several major differences exist between the neurons in ANS and those in the CNS, for example CNS communicates using 10 different neurotransmitters (ANS has norepinephrine and ACT). - *was read from slides.*

*** Parkinson** is a neurodegenerative disease. It is devastating (destructive) illness, characterized by tremors, muscular rigidity, bradykinasia (slow in the voluntary movements). most patient are over 65 years old. The cause is unknown for most patients, rare to be secondary to viral encephalitis. - *was read from slides.*

• Two main events are happened;

1) Loss of normal Dopaminergic neuronal function.

Dopaminergic system appears to serve as a tonic , sustaining influence on the motor activity, rather than participating in specific movements (these nerves fire tonically rather than in response to specific muscle movements or sensory input). - *was read from slides*.

2) Degenerating (with time/ aging) **of the neurons responsible to release dopamine.**

Loss of inhibition on cholinergic neurons leads to overproduction of Acetylcholine.

 # How to treat? ..

From slides: { Therapy aimed to **restoring dopamine and antagonizing the excitatory effect of cholinergic neurons**, this restoring the balance between dopamine/ACT balance in the CNS. }

1>> Levodopa & Carbidopa

* **Levodopa** is a metabolic precursor of dopamine and used to restore the dopamine level in brain, since dopamine can not cross the BBB while Levodopa can.

* **Levodopa must be administered whith Carbidopa**, if not, much of the drug will be decarboxylated to dopamine in the periphery and only small percentage (1%) will reach the brain.

Carbidopa, a dopamine decarboxylase inhibitor that does not cross BBB, potentiates Levodopa action by inhibiting its metabolism and increasing its bioavailability to the CNS.

*** **With time**, pt will experience a decline in the response; because of less nerouns that can change levodopa to dopamine will be avalaible (the previous mentioned points). So **you need to increase the dose**.

"In the new patient, the therapeutic response is consistent, while in advanced cases, the number of neurons decrease and fewer cells are capable of taking up Levodopa and converted to dopamine for subsequent storage and release" >> the pt is highly depending on the Exogenous dopamine (drug).

" Subsequently, **motor control fluctuation developed**. The phenomena that called **"wearing off""**.

So, when you are administering a high dose, there is a high amount of dopamine entering the brain in a time **{High Peak}** -yes it is responsible for antiparkinson activity- but there is too much activity resulting in sth like EPS is named **Dyskinesia**.

-- Note, This does not happen at the beginning, when the pt is given a little amount of dopamine to replace his little deficiency, however with time because of the declining response the dose will be increased, increasing the incidence of Dyskinesia.

Adverse effect of High Dopamine

1) Nausea, vomiting.

Dopamine can stimulate the emetic centre, but there is a tolerance to this happens after 2-3 weeks of taking the drug.

2) Dopamine has an action on the heart (may cause tachycardia & ventricular extrasystolic)

3) Over activity of dopamine in the receptors in the brain may produce **hallucination** (5-7%), **confusion** and abnormal involuntary movements may occur, **dyskinesia** (10%)>> these are schizophrenia symptoms, so Levodopa can cause **schizophrenic attacks** when the level of dopamine is highly increased {at peaks}.

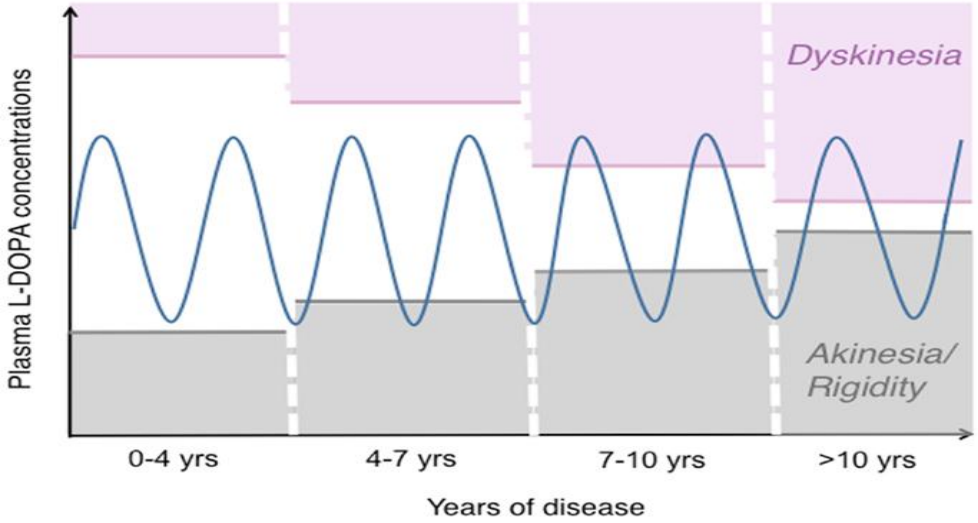
Peak-trough fluctuation.

Peaks (the highest concentration of the drug -when it is administered-)

Troughs (the lowest concentration of the drug)

By knowing that the pt is dependent on the drug/ has no endogenous source for dopamine,, in Troughs there is low dopamine = parkinson symptoms return, and this is the **wearing off** phenomenon {wearing off the dopamine activity}. How to solve it? By other drugs 2 + 3 that increase the dopamine level in brain. See down.

-- As we can see due to wearing off eventually the same dose will lead to side effects (parkinsons at troughts and schizophrenic at peaks).



*** Relief provides by Levodopa is only sytemic {symptomatic} (you can not stop the process of the degeneration), and it lasts only while the drug is present in the body.**

2>> Selegiline

This drug decreases the metabolism of dopamine by inhibiting MAO type B (dietary restriction is not required), so selegiline increases dopamine levels in the brain.

"Selegiline exhibits little therapeutic benefit when used independently, but Enhances the action of Levodopa, and when administered together, Selegiline substantially reduce the required dose of Levodopa"

At high doses it cause hypertension, however; the therapeutic dose that is given is low and does not affect tyramine metabolism .

3>> Catechol-O-methyltransferase (COMPT) Inhibitors

Entacapone & Tolcapone

* **Entacapone** is the one found in markets, **it does not cause hepatic failure while Tolcapone does.**

****** So parkinson treatment is;**

Firstly, start with Levodopa & Carbidopa then (after 2-3 years) add Selegiline, then if needed add COMPT inhibitors (Entacapone & Tolcapone)

Is this effective? Well, not that much. You are dealing with a degenerative disease at some point you will reach a time that giving these drugs will not be effective at all. What to do? Start with 4

4>> Dopamine receptors agonist

Here we do not want to replace dopamine as before, instead we want to activate its receptor.

* This group includes (1) two older agents, Bromocriptine and Pergolide. (2) two newer agents, Ropinirole and Pramipexole. **>> just know Ropinirole**

* "These agents has longer duration of action than that of Levodopa, thus have been effective in patients exhibiting fluctuation in their response to Levodopa. Initial therapy with the newer agents is associated particularly with less risk of developing dyskinesias and motor fluctuations in compare to Levodopa" *-was read from slides*

**** Why not to start with them? Because of there side effects**

Nausea, hallucination, and hypotension happens in 20% of pt taking the new agents, while in the previous story (Levodopa + Carbidopa....) the side effects was only to 7%.

**** Are they (Dopamine agonists) more effective? Yes**, however there side effects {psychosis by activating D2 receptors and} limit there utility.

5>> Amantidine?

This is an antiviral drug Amantidine (effective in the treatment of influenza) has an antiparkinsonism action. It cause an increase in the release of dopamine, blocking cholinergic receptors, block some of the NDMA glutamate receptors.

Amantadine has less efficacy than Levodopa and tolerance develops more readily, However, it has lower side effects (restlessness, agitation, hallucination, very bad dizziness)

Has a mild action , and it is a bad drug, not really used !

At the end starting with Dopamine agonist or Levodopa strategy is depending on you as a doctor and your pt, it is not written in any guide lines. And all these drugs **will not stop** the degenerating process.

6>> Antimuscarinic agents - Next lec.