Lecture #8

In the previous lecture we started talking about schizophrenia or psychosis; which is a big issue that we have to deal with. The pathophysiology is unknown, risk factors aren't really clear. It may have a genetic component yet it isn't absolutely genetic nor is it totally environmental, we even reject the genetics idea about it because it isn't genetic, so don't link things together. Remember there are predisposing genes that can predispose us to any type of diseases such as allergic rhinitis, asthma, diabetes, or even hypertension. That does not mean we will get the disease.

Now regarding schizophrenia, generally, there are two types of symptoms;

Concerning the positive symptoms: we are talking about hallucination, delusion, talking in an illogical manner. Such symptoms are simple in responding to the drugs targeting them. But we are having a problem with the negative symptoms. Where are these negative symptoms coming from?

If you link the idea of more Dopamine in the case of more dopaminergic activation in the mesolimbic pathway, then we can simply say that positive thoughts come from extra dopaminergic activity that give the patient these negative symptoms.

So bottom line there is a greater occupancy of D2 receptors by Dopamine hence the greater dopamine stimulation. The problem however, is in the negative thoughts that we are facing with schizophrenic patients, which resemble in one way or another depression. they don't really have anything to do with D2 receptors because whenever we give dopaminergic receptors a strong and fast D2 specific antagonist we are reducing the positive symptoms yet the negative ones aren't reduced by an absolute and complete dopaminergic antagonist so we are treating the positive but not the negative symptoms.

This forced us to think of something else, so we may have an involvement of serotonin, we may have an involvement of cholinergic stimulation. The end result that you will notice whenever reading about any case regarding schizophrenia there is a complex communication in the brain that gets disturbed. These disturbances are mainly built upon the

dopaminergic overstimulation however there are other pathways that play a major role in the causation of the negative symptoms that we see in schizophrenia.

So basically these negative thoughts don't have a clear explanation that's we try drugs to deal with them.

The old drugs; Typical anti-schizophrenia drugs/antipsychotic drugs which only bind to D2. This will produce extra side effects which is because of non selective binding.

Between effects on serotonin, norepinephrine , dopamine, they are binding mostly toward D2. They are very effective on positive symptoms, but not effective on negative symptoms. These are the old Typical drugs. Do we still use them? This is the same scenario as depression ***where there will be patients who won't respond to the new atypical drugs (30% of schizophrenics) so these 30% we will use the old drugs with them.*** *But remember the old drugs only treat the positive symptoms.*

Typical antipsychotics :

Chlorpromazine:

- dopaminergic antagonist, mostly works on D2 anatognism; will reduce activation of extra dopamnergic ideas we see in schizophrenics.

Does chlorpromazine have any activity on the negative thoughts? Very weak activity

New generation drugs which are the mainstream (which are of huge importance to us) have different mechanisms of actions and these mechanisms link two things, the dopaminergic antagonism and serotonin antagonism. Which serotonin receptors : 5HT2A, 5HT2C. if we anatognise these two receptors, add to that the dopaminergic antagonism which was

the area of target by the old type, we may then have small activity on the negative thoughts.

Negative thoughts of schizophrenic patients will NEVER go away, always keep that in mind, even with treatment they will never get out of the negative hopelessness thoughts that they have, simple try to get him out of these ideas, by discarding the old type of drugs.Never ever start the treatment with the old type, as it lacks this activity against the negative thoughts, we only think about the new generation which is a different story.

Distinction between typical and atypical groups is not clearly defined but rests on:

-Incidence of extrapyramidal side effects (less in atypical group)

-Efficacy in treatment resistant group of patients

-Efficacy against negative symptoms only the new type

-20-30% of patients won't respond to new drugs, even positive thoughts in those patients won't respond to the new drugs so we need to go back to old drugs.

-Extrapyramidal side effects: mostly in the old type

Now there are different theories but mainly

If you occupy D2 receptors a lot (which is main characteristic of old type) occupation percentage of D2 is more than 80% in the old type → tardive dyskinesia [involuntary movement slow] , slight parkinsonism.

These side effects if you occupy D2 → antidopaminergic

Decrease in dopamine →Parkinson's like syndrome

We then have to agonize the dopamine

(in a schizophrenic; he has too much dopamine once we antagonize it the patient will have deficiency in dopamine so Parkinson like effect) so patients will have it, but mostly will have extra pyramidal side effects)

The old drugs occupy D2 longly, most of D2 receptors in the mesolimbic pathway.

This produces two things*: (this shows a link between dopaminergic and cholinergic activity in the brain*) occupy dopaminergic, so this over activity of cholinergic which in one of the theories says that this increase in cholinergic produces these extra pyramidal side effects.The other idea, occupation of these D2 receptors, results in UPREGULATING dopaminergic receptors in many other parts of the brain including pyramidal parts. But let's focus on the involuntary motor movement part which produces extrapyramidal effects.

So the extra pyramidal side effects either come from:

1) disturbed balance between the cholinergic and dopaminergic within the CNS

2) occupying these D2 receptors to get upregulation to these D2 receptors again (*but this upregulation doesn't have anything to do with the positive symptoms that we see*) so we see more motor involuntary movement (extrapyramidal) so you should consider either of the two as an explanation .

These are present more in the typical type/old type, why because we occupy D2 a lot which produces the disruption or over regulation of receptors themselves which produce involuntary movement which are extrapyramidal side effects such as a "flying tongue" or "flying kiss" but these occur after a long time.

The nice thing about the atypical drugs, their affinity towards D2 receptors decreases so occupancy between 50-80% of the receptors which is enough to suppress the positive symptoms of schizophrenia and is not enough to produce extrapyramidal effects.

Please note that extrapyramidal side effects differ from Parkinson like disease; In young patients it's Parkinson like disease, in older patients it's more toward tardive dyskinesia.

This Parkinson like disease occurs on the first week while extrapyramidal side effects occur within years because the link

between dopaminergic and cholinergic is disturbed or over expression of D2 receptors is going to need time

Parkinson like symptoms linked with antipsychotics, we are giving antidopaminergic,so are seen after 1-2 weeks. So doctors prescribe these antipsychotics and especially if the patient was young (age 19-25) we give him anti-parkinson (anticholinergic drugs)

New type "atypical"

-No longer full occupation of D2 receptors

-treats the negative symptoms [How? Reduce D2 occuaption and affinity and increase affinity towards serotonin receptors { **antagonize 5HT2A and 5HT2C}]**

- bottom line:

Negative thoughts comes from the relationship between serotonin and dopamine, thus when we antagonize receptors 5HT-2A,2C, we are inhibiting some dopaminergic activity in somewhere else in the brain where the negative thoughts are coming from. This is what's written in books and what Dr.Malek believes in.

Why do these drugs have better ability to occupy these negative thoughts? Because they occupy serotonin receptors.

Well if these negative thoughts resemble depression which is treated with increasing serotonin in the synapse (SSRI) and here we are treating the same symptoms by antagonizing the serotonin receptors 2A and 2C, but here we are inhibiting the relationship in schizophrenia patients between serotonin and dopaminergic activation so if we inhibit 5HT-2A,2C there is a link between those and dopaminergic activation so it's like we are attacking the dopaminergic activation seen in a schizophrenic from a different point of view.

{in depression we are either using MOA inhibitor which increases Dopamine and Serotonin and Norepinephrine or we give SNRI to increase NE and serotonin or SSRI or Norepinephrine dopamine reuptake inhibitor (which isn't that effective) but we are agonizing the neurotransmitters) so negative

thoughts of schizophrenia treated by antagonizing serotonin receptors VS while agonizing receptors in depression treatment }

<u>There is a link between 5HT-2A,2C with dopaminergic activation, So deactivating 5HT-2A,2C we are reducing dopaminergic activation.</u>

-So the negative thoughts didn't come from decrease in serotonin as in depression-

Here we think negative thoughts come from upregulation of the dopaminergic, so if we effect the serotonin receptors reducing the dopaminergic activation we can deal with these negative ideas.

How effective is this approach? We don't cancel out the negative thoughts but we reduce it because there is another story concerning the negative thoughts

Old Drugs:

In the table below, always notice these 3 things whenever we describe the antipsychotics:

1) **Sedation**
2) **Hypotension**
3) **Extrayramidal effects**

The best drug is the one with activity on schizophrenia without these 3 effects, does such a drug exist? No

First Generation Antipsychotic Drugs					
Compound			Seda-tion	Hypo-tension	Motor (EP) Effects
Phenothiazines					
Chlorpromazine			+++	++	++
Fluphenazine			+	+	++++
Haloperidol			+	+	++++

Chlorpromazine: is non selective so it is going to be very sedative, very hypotensive and cause EP effects because its occupying more than 80% of receptors.

Sedation comes from H1 and Hypotension from α1 since its non selective activity.

More selective drug is **Fluphenazine** however the EP effects are much more increased because it is selective mostly to D2 and occupies it longly. **Haloperidol** same case

We don't focus on that table because as we said they are old drugs and only used with the (30% of patients who don't respond to the new drugs).

Schizophrenia patients within the population are 0.7-1% , which is alot. These 1% will become schizophrenic at any point in their life not a specific age.

New dugs/ atypical antipsychotics:

-***Risperidone*** (Risperdal®) :

-it is very popular in Jordan. Has sedative activity because binds to H1, hypotensive activity because binds to α1,has motor effects if given a high dose, so this drug is not prescribed more than 6mg per day for any patient, so if exceeded the 6mg boundary then EP effects become clear since more receptors are being occupied (more than 80% occupation). It has good selectivity on D2 and 5HT-2A,2C so a nice drug for positive and negative symptoms.

So Risperidone is a nice drug on positive and negative symptoms as long as you don't increase the dose, it has a problem with EP effects in the long run or with high dose. Also sedative and hypotensive. (there are patients who complain that these two drugs tires them and affects their cognitive function as well, so they are weak as if having a hangover all day long)

-There is a relationship between Dopamine and Prolactin. Dopamine inhibits the release of prolactin, so a patient taking antidopaminergic has an increased level in prolactin if the occupation to D2 is high. So this will be noticed in Old drugs as

well as Risperidone producing hyper-prolactinemia (Risperidone has a problem similar to Spirolactone causing Gynecomastia)

Risperidone is the drug of choice in most cases. No weight gain problem nor diabetes, its drawback is with the previously mentioned endocrine problem.

-One of the most prescribed drugs in Jordan.

In **women**, these disturbances include:

- **galactorrhea**
- **loss of libido**
- delayed ovulation and menstruation or amenorrhea.

In **men**, these disturbances include:

- **gynecomastia**
- **impotence**

This is all due to the complex relationship between neurotransmitters and endocrine system.

-***Olanzapine/Clozapine***:

these two drugs are like brothers very similar to one another. They have low affinity towards D2 meaning, they occupy 60% of the receptors, no EP effects, and have nice activity on 5HT-2A,2C. they are great drugs however, they produce a bad weight gain problem, they increase the appetite hence the weight gain and also disturbs triglycerides to cause a Diabetes –like syndrome. To sum up, great drugs with the drawback of weight gain and metabolic problems . [Last drug resort]

Clinical trials are showing that schizophrenic patients are more susceptible to cardiovascular problems and incidents (MI, Stroke,Atherosclerosis), and these incidents are due to metabolic problems. ***So applying antipsychotics that have a thing to do with metabolism then you are increasing the chances of cardiovascular incidents. That s why such drugs are referred as LAST DRUG RESORT.***

When is it a last resort? When the patient turns out to be within the refractory/resistant (30% category) we use Clozapine, why so? ***Because clozapine has an extra activity on D4 receptors***. So this extra antagonism on dopaminergic receptor D4 gives the drug a good characteristic to deal with refractory patients. So we seek Clozapine as a last drug resort and never start treatment with it because of the already mentioned metabolic problems.

Second Generation Antipsychotic Drugs

Compound	Sedation	Hypo-tension	Motor effects
Risperidone Risperdal	++	+++	+/++ Dose dependent
Clozapine Clozaril	++	++	-
Aripiprazole Abilify	0/+	0/+	0/+ 27

Clozapine and olanzapine:

- VERY low EP side effects because doesn't occupy D2 longly

-Blocks D1, D2, D4, α-adrenergic, 5HT2, muscarinic, and histamine H1 receptors, Hence, Sedation, Hypotension, Anti-Positive and Anti-Negative effects.

"May show greater efficacy against negative symptoms than other antipsychotic drugs" however, " Both drugs have high efficacy, but cause significant weight gain and diabetes".

-Agranulocytosis is a potentially fatal side effect for Clozapine (1.3% get this side effect) this adds to making Clozapine a drug of last resort.

So we use Olanzapine as long as we monitor the weight gain, many doctors don't use it because of risk of cardiovascular events.

-Aripiprazole:

- it's a great new drug, not present in Jordan, (will be the mainstream by the time we graduate), and will replace all of these, it is the best for schizophrenia.
- **This drug is a <u>partial agonist on D2</u> and even <u>a partial agonist on serotonin receptor</u> so it does not produce side effects; no sedation no hypotension, no motor effects**.
- - Has Affinity for muscarinic, α_1-adrenergic, serotonin and histamine receptors but that's weak
- -Few extrapyramidal side effects
- -The only problem remaining is with weight gain, so we have to monitor that. Weight gain comes from the metabolic disturbances resulting from serotonin receptors affected in the brain. The weight gain here isn't so bad, there are no triglyceride disturbances nor diabetes like syndrome as in olanzapine and Clozapine and doesn't have endocrine effect as in Risperidone, and no sedation and no hypotension.

To sum up:

-Old Drugs: Extrapyramidal Side effects because of more than 80% occupation on D2 receptors

-New Drugs: Low EP side effects because occupation is low on D2 and increase occupation on 2A, 2C serotonin receptors which produce bad metabolic problems.

-Then partial agonist idea was introduced, nice drugs yet have metabolic problems.

***Despite** all these side effects, Schizophrenia must be treated. Psychotherapy is good but doesn't resolve it really.*

Bottom line:

The optimal use of antidepressant/ antipsychotics require a clear understanding of their mechanism of action, pharmacokinetics, potential drug interaction and the deferential diagnosis of psychiatric illnesses.

There is no perfect drug, you have to risk and benefit your patient, if the risk is less than the benefit , we give the drug, if the risk is greater than the benefit we don't. It is that simple. Don't leave your patient with depression or psychosis without treatment.

Done by: Mona Makhamreh

Introduction to anti-epileptic drugs

- 1 person in 20 will have an epileptic seizure at some time in their life
- Epilepsy is diagnosed on the basis of two or more epileptic seizures in a year.
- Around 450,000 people in the UK have epilepsy (40 million people worldwide)
- A seizure is triggered by a sudden interruption in the brain's highly complex electro-chemical activity

Pathological Basis:

- Abnormal electrical discharge in the brain
- Coordinated activity among neurons depends on a controlled balance between excitation and inhibition
- Any local imbalance will lead to a seizure
- Imbalances occur between glutamate-mediated excitatory neurotransmission and gamma-aminobutyric acid (GABA) mediated inhibitory neurotransmission
- Congenital defects, head injury, trauma, hypoxia, infection, meningitis, brain abscess, viral encephalitis or even fungal encephalitis.
- Brain tumor, vascular occlusion, drug withdrawal, CNS depressants like alcohol, fever in children, febrile convulsion, hypoglycemia all these can cause a seizure but not necessarily an epilepsy

Types of seizures:

1)Partial: within a contained part in the brain with or without loss of consciousness

a)Simple Partial : Simple seizure activity while the person is alert

b)Complex partial : complex seizure activity with changes in awareness of surroundings (unconscious)

2) Generalized: within the entire brain sites

a) Absence: the person is sitting with you then suddenly for 30 seconds- 1 minute becomes drawn out of this world
b) Myoclonic: jerking and movement of the body, the patient is awake
c) Tonic and clonic: much more complex, stiffness falling jerking of the body

Done by: Mona Makhamreh