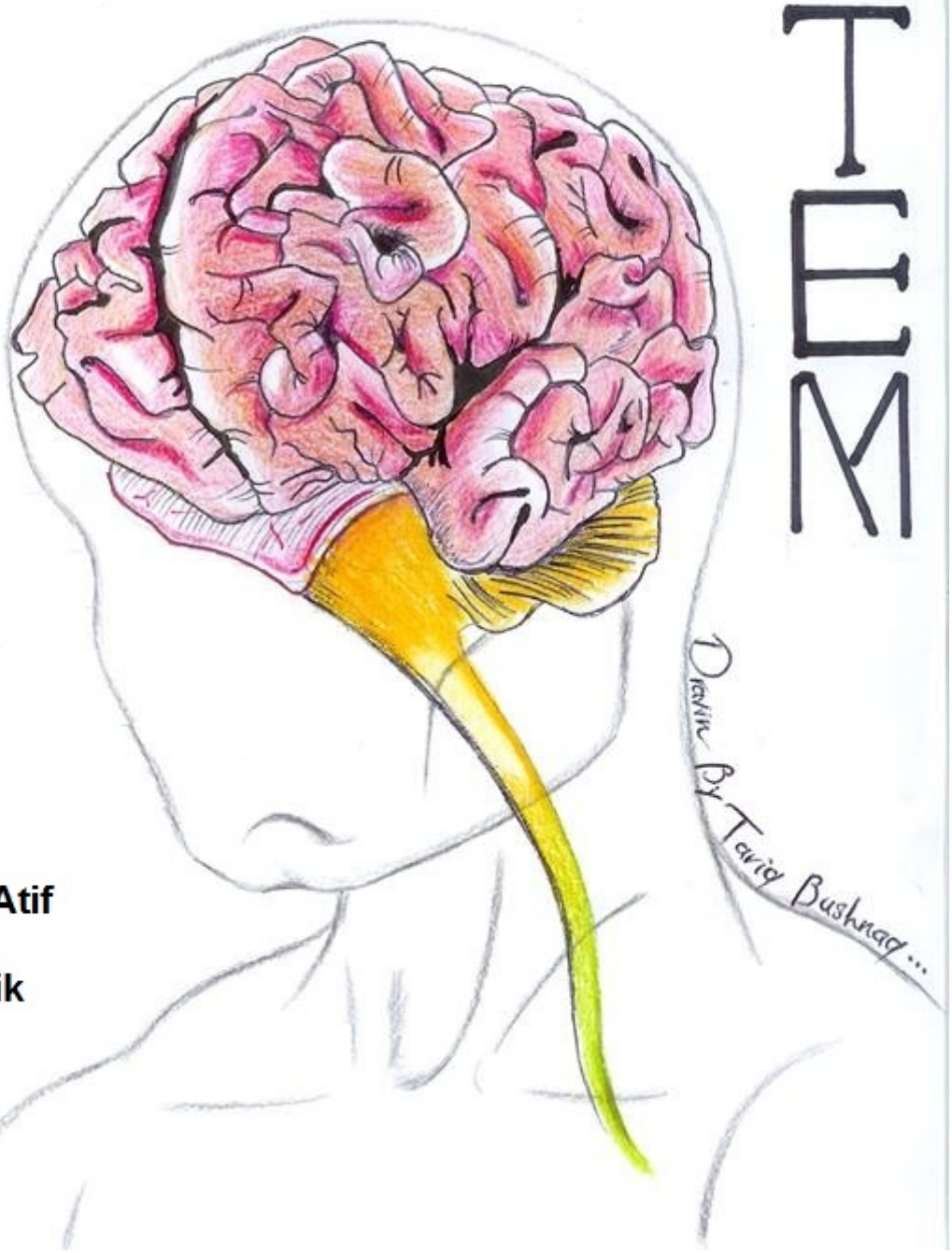
CENTRAL NERVOUS SYSTEM

- ○ Handout
- ● Sheet
- ○ Slide

- ○ Anatomy
- ○ Physiology
- ○ Pathology
- ○ Biochemistry
- ○ Microbiology
- ● Pharmacology
- ○ PBL



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ANTIPSYCHOTIC DRUGS

- We will talk about schizophrenia is more complex than the previous topic (depression), schizophrenia is the worst case of psychosis it means continuous symptoms of psychosis, negative symptoms and cognitive impairment for long time (different studies say from week to year)
- Normally people can have mild psychosis but it is not continuous, also some drugs like amphetamine can cause psychosis but NOT schizophrenia
- Schizophrenia is becoming very common, we are seeing this in our streets, 1% of the population is affected, for example in USA 10,000 people suffer from it.
- we diagnose the patient with schizophrenia when we see the patient is confused, talking non sense and depressed with **positive symptoms** which are the characteristic of . Let's compare it with depression, where the patient doesn't have positive symptoms (hallucinations) , depression is losing hope in life and in many cases ends up with suicide
- it is NOT a genetic issue, only 10% of the patients are linked towards schizophrenic genes , so we call it **schizophrenic risk genes**. (risk genes can be found in any disease e.g: diabetes mellitus, depression, mania … etc, but the presence of this genes doesn't mean the presence of the disease). If you take two identical twins you'll find one of them will be schizophrenic and the other is not, or both can be schizophrenic if they are linked to the same environment, so we conclude that schizophrenia is not a genetic disease.

- **<u>Symptoms of schizophrenia:</u>**
- **Positive symptoms :** psychosis, dilution, hallucinations, disorganized thoughts, disturbances, the patient talk one sentence in one topic then jump to another topic (he can't make 2 sentences together)
  in hallucinations we notice <u>the idea of reference,</u> they have mania, talking about their deep childhood thoughts. Hallucinations and psychosis are very complex.
- **Cognition impairment :** he can't learn and has memory problems.
- **Mood symptoms**
- **Negative symptoms :** the patient is depressed and he can't feel happy

- Positive symptom usually comes from overactivation of CNS, so those patients **have too much dopamine.** An old theory -which is right - says that every patient with hallucination when he is given an antidopaminergic drug (anti D2), the hallucination will stop within one week, however this drug will not make any difference for the other symptoms.
- **NOTE** : positive symptoms can be treated, but negative symptoms can't be treated
- **Mechanism of hallucinations :** dopamine has many pathways, so many of those pathways can be activated increasing dopamine specially in mesolembic part of brain causing hallucinations, BUT things have been changed with time, in 80s and 90s they found a role of serotonin in the story. So they treated hallucination they used D2 antagonist and 5HT2A antagonist (by drug is called : clozapine , we will talk about in a this sheet) this drug treats the positive symptoms and has some effect to reduce the negative symptoms but not in all patients.
- **The bottom line of treatment (the gold standard) :**
  using **D2 antagonist** and **5HT2A antagonist** (remember from the last lecture: 5HT2A antagonist producing antianxiety, antidepression and antipsychotic effects)
- Schizophrenic treatment is for life, however the drug won't cure the patient, we only dump these symptoms, and if we stop the drug the patient will relapse. Relapse takes time, it needs 6 months to happen after stopping the drug.

  We treat the patients with drug indefinitely; a dropout from clinical trials is 70%! They get in by their choice and then dropout because the side effects are very bad. Schizophrenia is complex even more than depression, because the patient has problems in cognition and in his thoughts

  So anti- Schizophrenic drugs are lifelong drugs, whereas anti-depressents have a chance for clinical trial, then they may become a lifelong treatment.
- **We have 3 types of antipsychotic drugs :**

  1-Typical type : typical old drugs that deals with psychosis by blocking D2 receptors. They has activity only on positive symptoms but not negative symptoms , so they are not used widely anymore

  2-Atypical type : Antagonize D2 receptors and 5HT2A receptors

  3-Partial antagonist (third generation) : Partial agonist for D2 receptors

- The response of the drug reaches only 30% in maximum cases, while in antidepressants it reaches 50%. So you will try many drugs and eventually you may return to the old drugs
- These drugs have NO tolerance, NO addiction and NO euphoric activity but have physical dependence (NOTE : tolerance only develops to sedative effect, but generally there is NO tolerance towards the anti-psychotic effect)
- Withdrawal symptoms include nausea, vomiting, insomnia, and headache. These symptoms may persist up to 2 weeks and they can be maintained with a tapered reduction of drug dosage
- 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
- What do we mean by **"etrapyramidal side effects"** ?
  movement in our life depends on dopamenergic and cholinergic activity, so when you block dopamine receptors (as in antipsychotic) , acetylcholine will be activated causing **parkinsonism**, but with long run (years of dosage) of deactivating dopamine receptor, sensitization of these receptors occurs and this will cause **tardive dyskinesia (flying tongue / flying kiss)**
  So new type of drugs (atypical) also inhibit D2, however the incidence of these extrapyramidal effects is low (getting down from 10-20% in typical drugs (old) to 2-5% in new drugs.

  <u>exrapyramidal side effects are:</u>
  1- acute dystonia : it is spasm in muscles of the muscles of tongue, face, back and may limit seizure, it is not common and treated by antiparkinsonism

  2-**akathisia** : it is motor restlessness but NOT an anxiety or agitation, happens in 1-2% of the patients, can be treated by decreasing the dose or giving antiparkinsonism, binzodiazipine (antianxiety) and propranolol to decrease anxiety.

  3-**parkinsonism :** bradykinesea, rigidity, variable tremor, mask face and shuffling gate. It is treated by antiparkinsonism

4- **tardive dyskinesia** :it is involuntary movement due to increase dopamine (can be called **flying tongue**) happens after months or years of treatment, it is worst with withdrawal.

- ## Typical group of drugs :
- **Haloperidol :**

it has very strong affinity towards D2, so it produces very nice anti positive psychotic symptoms activity, but it produces very strong exrapyramidal side effects because the blockage of the receptors is nearly complete, and with long time sensitization of receptors takes place. It has also other side effects such as : sedation and hypotension this drug is still used in Jordan as a depot (injection stays for one month in the body) its half life is 3-4 weeks.

- ## Atypical group of drugs :
- **Clozapine :**

the best drug ever for treatment of negative symptoms, however the side effects of it are too bad, so we leave it as a **last resort drug** and use it when the patient have tried many other drugs and he didn't respond.
it doesn't bind to D2 receptor with high affinity while it binds to 5HT2A receptor with more affinity. It doesn't produce extrapyramidal side effects.

why we don't start treatment with clozapine?
clozapine and **olanzapine** have very low extrapyramidal side effects, and they may show greater efficacy toward negative symptoms than other antipsychotic drugs. But they cause **weight gain, hyperglycemia, increase LDL and HDL,** and **diabetes mellitus**. clozapine only produces **agranulocytosis** (WBC count will decrease, so the patient will be more susceptible toward infections).

Clozapine : cause **weight gain, diabetes mellitus** and **agranulocytosis**
Olanzapine : cause **weight gain, diabetes mellitus** but **NO agranulocytosis**

- **Respiridol :**

  it is the most prescribed drugs in Jordan, as same as clozapine but have higher hypotension activity, and low incidence of extrapyramidal side effects (extrapyramidal side effects can occur if you increase the dose more than 6mg/day), the good news that there is **NO gain weight** and **NO insulin resistance**

  it is a good drug to start with, but it cause hypotension, sedation and has a high effect on prolactine causing **hyperprolactenemia**
  [NOTE : dopamine normally has an inhibitory effect on prolactine, so inhibiting dopamine will cause hyperprolactenemia]

  it has endocrine effects, In women, these disturbances include: galactorrhea, loss of libido, delayed ovulation and menstruation or amenorrhea. In men, these disturbances include: gynecomastia and impotence. (1-5% of population)

- **Ziprasidone :**

  As respiridol, however the **weight gain and hyperprolactonemia are less**. It has lower efficacy than respiridol that is why we still prefer using respiridol over ziprasidone. ziprasidone is the best prescribed drug for those who take care too much about their weight

- **Third generation (partial D2 agonist) :**

- **Aripirazole :**

  It is a partial; agonist for D2 and 5HT2A receptors, it is very good drug, but it is very expensive (200 JD/month), it became very popular in the last 6 years and it is the most prescribed drug in USA.

  it has different mechanism of action, partial agonists when occupying the receptor the produce less activation of dopamine, and this will decrease the positive activity.
  it has comparable activity- like respiridol- on negative symptoms

this drug cause **dizziness**, so now we have a black box [this drug should NOT be used in patients over than 65 years old]
in geriatrics we care too much about dizziness, so we don't use drugs that affects it

- In 2014, Amiprizole is found as **IM depot** to deal with the story of compliance. By using this depot we give the patient 1 injection for one month (IM depot is 400 mg)
  but these depot cause variation in its activity because it is metabolized by cytochrome P450, CYP3A4, and CYP2D6.
  ** poor metabolizers of CYP2D6 or patients who take drugs that inhibit CYP2D6 or CYP3A4 >>>> we give them 300 mg
  ** poor metabolizers of CYP2D6 and CYP3A4 or patients who take drugs that inhibit CYP2D6 and CYP3A4 >>>> we give them 200 mg

  this drug (in IM depot) has **pharmacogenetics dose adjustment** , so we test the patient for CYP2D6 whether he is poor or strong metabolizer, and then we prescribe the dose according to his state.

THE END

- **SUMMARY :**
- Schizophrenia is continuous psychosis symptoms including : **positive symptoms** (hallucinations and dilutions) , **cognition impairment**, **negative symptoms** (depression), **mood symptoms**
- positive symptoms can be treated but negative ones can't be treated
- schizophrenia is NOT genetic disease
- we have 3 groups of antipsychotics: **typical group, atypical group, third generation (partial agonist)**
- extreapyramidal side effects : blockage of dopamine receptor will cause parkinsonism, then after years this blockage will cause receptor sensitization and this will produce tardive dyskineia, akathisia and acute dystonia
- **1-typical group :**
  - Blocking D2 receptors
  - Strong extrapyramidal side effects + sedation + hypotension
  - e.g: **Haloperidol**
- **2-atypical group :**
  - Blocking D2 and 5HT2A receptor

- Lower extrapyramidal side effects than typical group
- **Clozapine :** last drug resort, low extrapyramidal side effects ,side effects are (sedation + hypotension + weight gain + diabetes mellitus + agranulocytosis)
- **Olanzapine :** same as clozapine but NO agranulocytosis
- **Respiridol :** most prescribed drug in Jordan, MORE hypotension, LESS weight gain, hyperprolactenemia and endocrine effects
- **Ziprasidone :** VERY LOW gain weight, LESS hyperprolactonemia

- **3-third generation (partial agonist) :**
  - Partial agonist for D2 and 5HT2A receptors
  - **Aripirazole :** very expensive , side effects include (dizziness)
  - it have pharmacogenetics issue

"وتحسبُ أنك جُرمٌ صغيرٌ .. وفيك انطوى العالمُ الأكبر"

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