Atypical antidepressants and schizophrenia- Lecture 3

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We are almost done talking about antidepressants and how they are a very important group of drugs that we use to reduce the mortality and morbidity rates among the depressed, including SSRIs, SNRIs, MAOIs, TCAs (Typical antidepressants) which are very commonly described drugs, but we still have one group we didn't talk about previously and that is the"Atypical antidepressants".
They're a new family of drugs that was discovered after the year 2000 with the idea that activating serotonin receptors shouldn't be the only way to treat depression and that we should try blocking 5-HT2a and 5-HT2c instead. How did they discover this?

The idea behind this is that in the brain we have a lot of interconnected and complicated pathways, let's take **Schizophrenia** as an example, the patients do in fact have positive thoughts and symptoms (which is the result of having increased dopamine in some areas inside the brain) even thought they're depressed at the same time! which leads us to thinking that dopamine is increased in some areas of the brain and decreased in others **(which we should prevent)**. After trials they found that the activated serotonin receptors (5-HT2a and 5-HT2c) do suppress dopamine in those areas (that we found earlier to be low in dopamine). So they created those atypical antidepressants (atypical because they have some mechanisms that **oppose** the function of the other "typical" antidepressants!), these drugs work by **strongly blocking** (**5-HT2a and 5-HT2c**) (**major effect**) , they also **slightly** inhibit serotonin and NE **reuptake** (**minor effect**).

*Note: Blocking 5-HT2**A** is of **more importance** compared to that of 5-HT**C***

So what's the net effect on the brain after administering these atypical antidepressants?

We'll have:

1) **slight** increase in serotonin, **slight** increase in Norepinephrine.
2) **Larger** increase in dopamine especially in the areas we found to have its level to be decreased which should resolve depression or at least change its pathway.

First thing to know about atypical antidepressants; (Mirtazapine Torazodone) Is that these drugs **can be combined with SSRIs and SNRIs without causing serotonin syndrome** (As we said their effect on them is small).
This fact gives us an idea that we can try these drugs (Alone first, then combined) in patients that were resistant with SSRIs/SNRIs.
Another thing is that these drugs also bind histamine receptors to cause hypnosis! **Trazodone** is very effective in producing sedation to the level where we can use it as a hypnotic agent! **Mirtazapine** also has sedative effects but not as strong as trazodone.

Mirtazapine has a very strong appetite increasing capability mediated by its very strong antagonistic effect on 5-HT2a and 5-HT2c (It's more potent than trazodone in dopamine increasing ability) at the cost of more side effects such as being strongly related to the metabolic syndrome.

5-HT_2 antagonists - Atypical antidepressants

- Agents: Nefazodone, Trazodone, mirtazapine.

- Inhibition of 5-HT_{2A} receptors in both animal and human studies is associated with substantial antianxiety, antipsychotic, and antidepressant effects

- Nefazodone is a weak inhibitor of both SERT and NET, whereas trazodone is also a weak but selective inhibitor of SERT

5-HT2 antagonists- Clinical uses

- Depression: Mirtazapine can be advantagous in patients with depression having sleep difficulties

- Low doses of trazodone (50-100 mg) have been used widely both alone and concurrently with SSRIs or SNRIs to treat insomnia

5-HT_2 antagonists

1) Sedation : necessitates dosing at bedtime

2) Dose-related GIT SEs

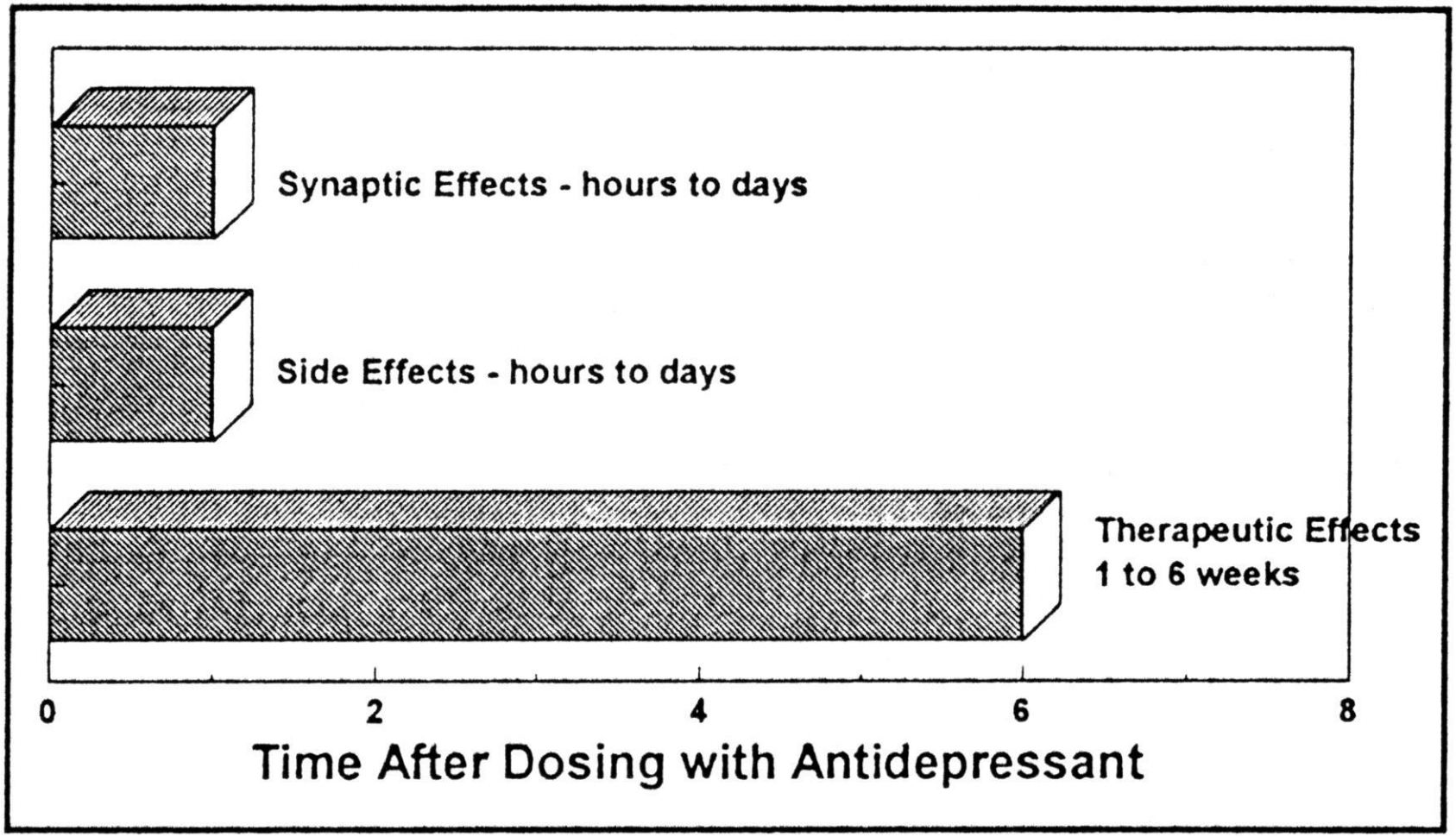
1) weight gain (mirtazapine)

Notes:
1) "Don't stop antidepressants before 6 months of use", some guidelines talk about 1 year but at least 6 months period must be waited.
This is very important because the **relapse rate** of major depression is **very high**, and if a patient used the drug for more than 6 months and his depression was treated we'll first stop the drug by tapering it and then we need to make sure no relapse occurs, and if that patient had a major depression episode again, they'll have to take antidepressants **for the rest of their lives**.

2) Mirtazapine+Trazodone have quicker onset of efficacy compared to typical antidepressants as they don't need BDNF gene modification etc.. (2 weeks to reach good efficacy!)

3) All antidepressants (typical atypical) are e ually effective in treating **typical** (major) **depression**

4) Major side effects of antidepressants are:
A) Decreased emotions
B) Those decreased emotions become blunt! (Blunting of emotions)
C) Change in the response to actions.



Onset of action of antidepressants. Synaptic effects and side effects of antidepressants begin before therapeutic effects are observed.

- Following the initiation of the antidepressant drug treatment there is generally a therapeutic lag lasting for 3-4 weeks. (It's less in atypical antidepressants)

- 8 weeks trial, then you allow to switch to another antidepressant.

- Partial response then add one another drug from different class.

- if the initial treatment was successful then 6-12 maintenance periods.

- If the patient has experience two episodes of major depression, then it is advisable to give an anti depressant life long.

We also use the name **psychosis** (Even tho schizophrenia is a type of psychosis, its the most important)

Schizophrenia - Disease of men

remember how depression was the disease of women?

- Pathogenesis is unknown.
- Onset of schizophrenia is in the late teens - early '20s. (Earlier in men, around 28years in women)
- Genetic predisposition -- Familial incidence.

Hereditary Influences may account for 10% of schizophrenia cases 20% now but just remember that we have predesposing genes (SNPs) for schizophrenia **(It's not a genetic disease, still needs environmental factors to occur)**

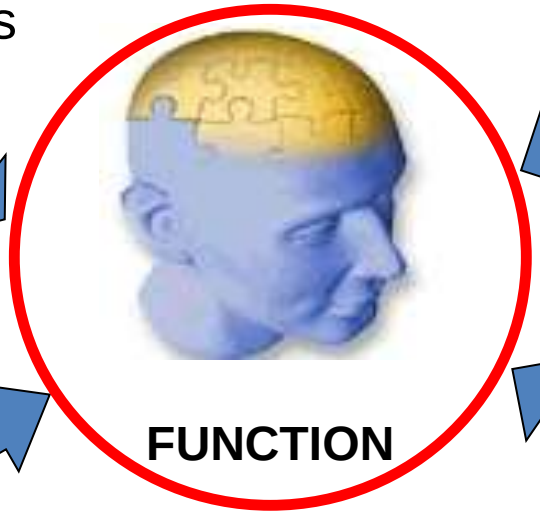
- Multiple genes are involved.
- Afflicts **1%** of the population worldwide.
- A thought disorder

As an example, in twins (similar in both their gene disposition and environmental factors, if one has schizophrenia the other has a 50% chance of developing it!

Schizophrenia - symptoms

Positive Symptoms
Hallucinations
Delusions (bizarre, persecutory)
Disorganized Thought
Perception disturbances
Inappropriate emotions

Negative Symptoms (the depression part)
Blunted emotions
Anhedonia
Lack of feeling



Cognition
New Learning
Memory

Mood Symptoms
Loss of motivation
Social withdrawal
Insight
Demoralization
Suicide

Schizophrenia

- Drugs currently used in the prevention of psychosis.

**** These drugs are not a cure ****

It's just controlled, similar to DM etc

- Schizophrenics must be treated with medications indefinitely, in as much as the disease in lifelong and it is preferable to prevent the psychotic episodes than to treat them.

SCHIZOPHRENIA IS FOR LIFE

There is no remission

Dopamine Theory of Schizophrenia

Many lines of evidence point to the aberrant increased activity of the dopaminergic system as being critical in the symptomatology of schizophrenia.

They found that blocking these receptors **stopped the positive** symptoms, but **made the negative worse.**

There is a greater occupancy of D2 receptors by dopamine => greater dopaminergic stimulation But,

inhibiting dopamine will cause 4 things (Typical anti-psychotics)

1) we treated the positive symptoms (MOST POTENT AGAINST POSITIVE SYMPTOMS)(good),

2) Worsening of negative symptoms (even more depression)(this is similar to what we talked about in the first part of this lecture; the different areas)**(limbic system the reward system is dopaminergic dependant)**

3) Dopamine inhibits prolactin levels, with these drugs we'll have **increased prolactin levels (multiple side effects are related to this)**

4) Extra-pyramidal side effects ~ Parkinsonism

Classification of Antipsychotic drugs

- Main categories are: (Only memorize those in red)
  - *Typical antipsychotics*

    Phenothiazines (**chlorpromazine** (less active, *used to treat hiccups-* **الحازوقة**), **perphenazine**, **fluphenazine, thioridazine et al**)

    Thioxanthenes (**flupenthixol**, **clopenthixol**)

    Butyrophenones (**haloperidol** (More active, especially used for acute attacks, post-partum/surgery hallucination), **droperidol**)

    we don't care about the side effects of blocking D2 in those attacks as they're dangerous for the patient

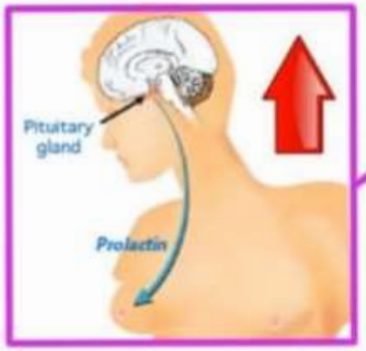
  - *Atypical antipsychotics* (e.g. **clozapine**, **risperidone**, **sulpiride**, **olanzapine**)

Extra-pyramidal side effects

nigrostriatal

more depression
mesocortical

less hallucinations
mesolimbic

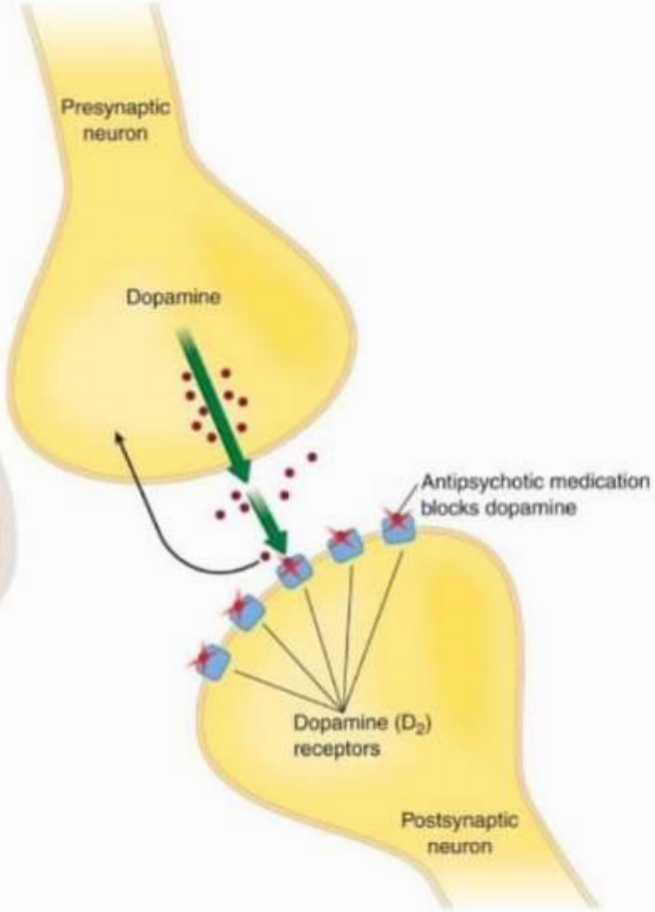


tuberoinfundibular

Increase in prolactin, causing different side effects such as sexual dysfunctions/gynecomastia etc..

1st generation (Typicals)

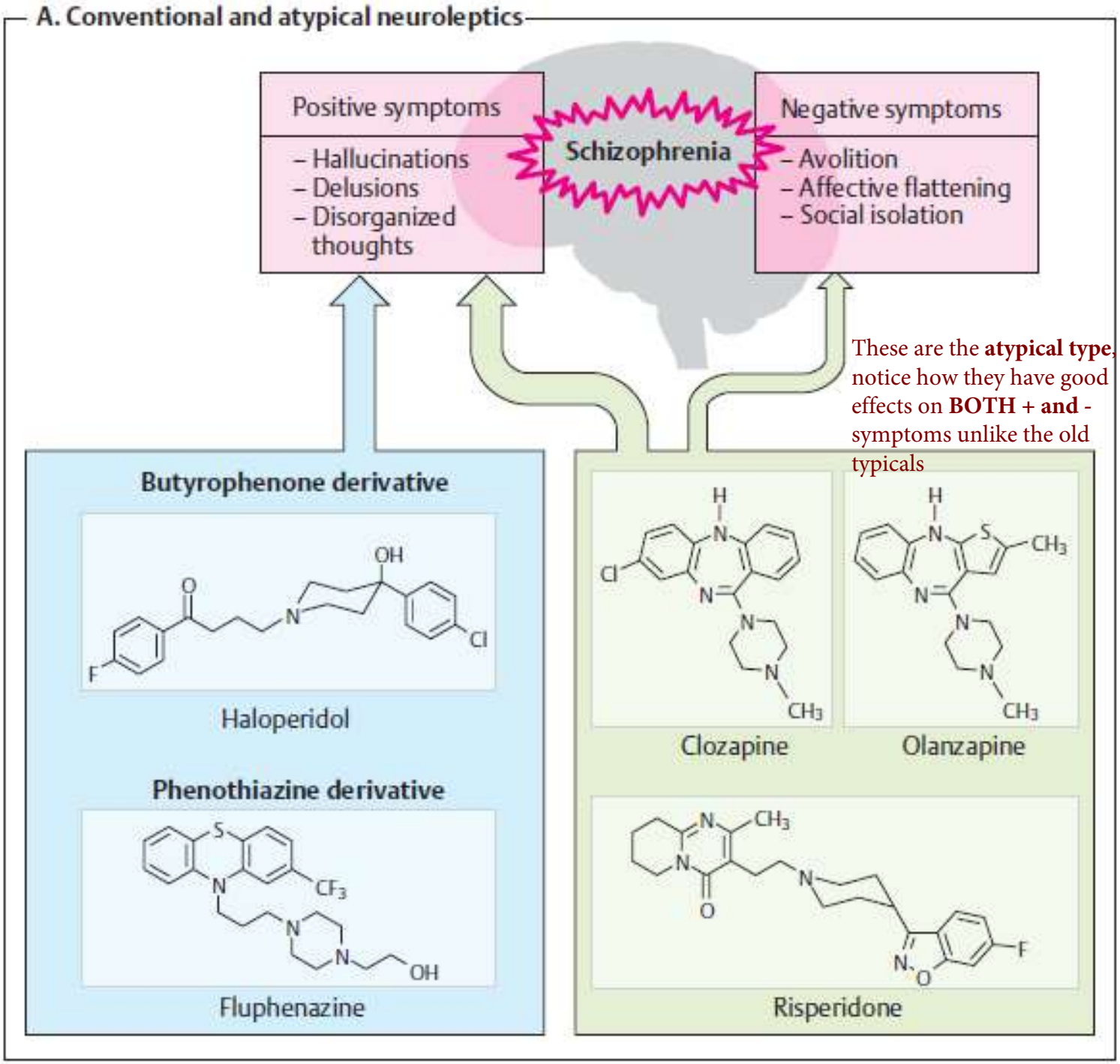
D2



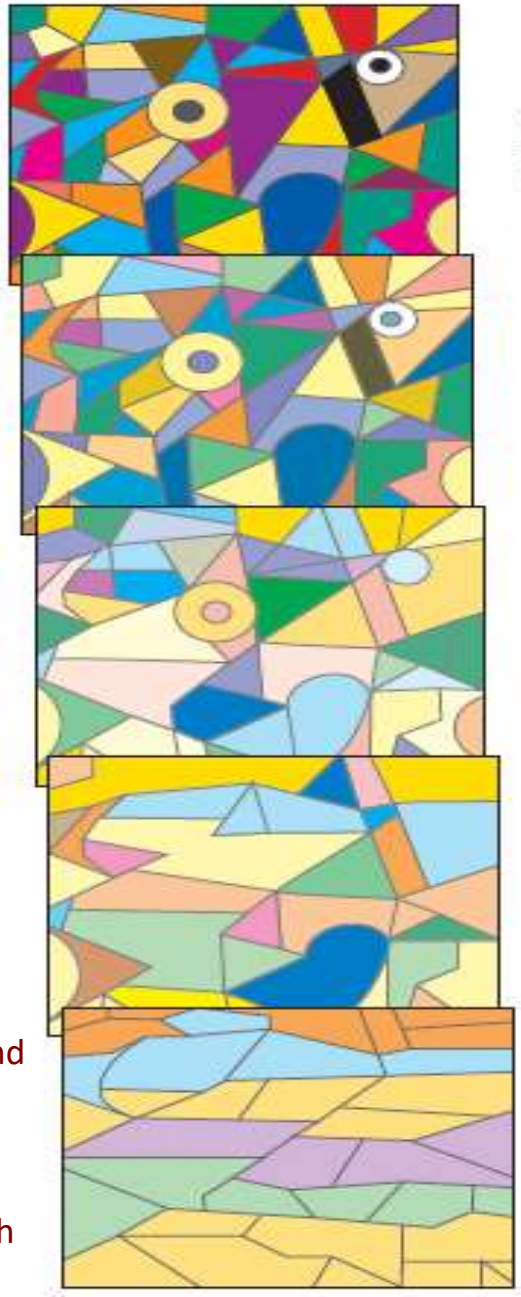
Schizophrenia Pathophysiology

Schizophrenia Pathophysiology	Pharmacologic Profile of APDs	
.Past		
Excess dopaminergic activity	Dopamine antagonists typical type	D_2-receptor
Present		
Renewed interest in the role of serotonin (5-HT)	Combined **antagonists**	$5\text{-}HT_2/D_2$

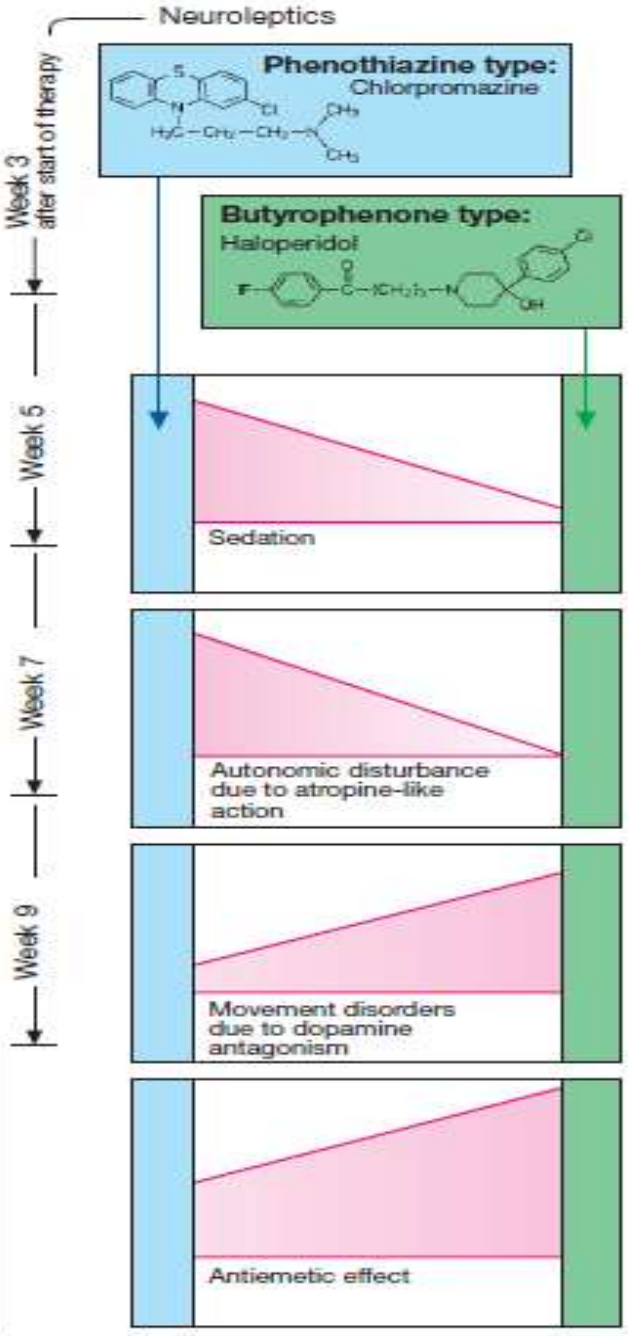
Similar to the idea of atypical antidepressants, but here we call them **atypical anti-psychotics**.


A. Conventional and atypical neuroleptics
Positive symptoms
– Hallucinations
– Delusions
– Disorganized thoughts
Schizophrenia
Negative symptoms
– Avolition
– Affective flattening
– Social isolation
These are the atypical type, notice how they have good effects on BOTH + and - symptoms unlike the old typicals
Butyrophenone derivative
Haloperidol
Phenothiazine derivative
Fluphenazine
Clozapine
Olanzapine
Risperidone

This drawing resembles how the mind of a schizophrenic patient looks like, look how the different shapes are all over the place



Normal, straight mind
(Its not perfect)
(Our goal)
Notice how it takes WEEKS to get to such effect.



Remember how we said that "schizophrenia for life"?
From this point arises another huge problem we face these days; adherence to anti-psychotics, patients are embarrassed from taking them, so they stop after their mind state is improved, which is dangerous.
We want to convince them that these drugs are their only way to stay "well", but that's not easy because of the side effects of them, even cognition is affected so these patients shouldn't work in jobs that demand focus and intelligence such as cashiers.

after 2-3 months of the patient stopping the drug (non-adherent patients) we'll have relapse of schizophrenia as it presented from the beginning if not even worse as if you did nothing.

Tolerance and dependence to antipsychotic drugs

- Not addicting
- Relapse in psychosis if discontinued abruptly

- Tolerance develops to sedative effects
- No tolerance to antipsychotic effect

Doctor stopped here. Good luck!