First vs Second Generation Antipsychotics

You can watch the video tutorial here

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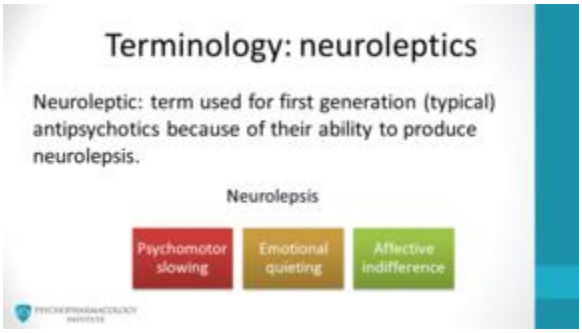
Terminology: neuroleptics



I'd like to clarify some terminology first. The terms neuroleptic, typical and atypical are commonly used in practice. It is interesting to understand their background and meaning.

What is a neuroleptic?
This is a term used to refer to first-generation antipsychotics (such as chlorpromazine or haloperidol) because of their ability to produce neurolepsis.

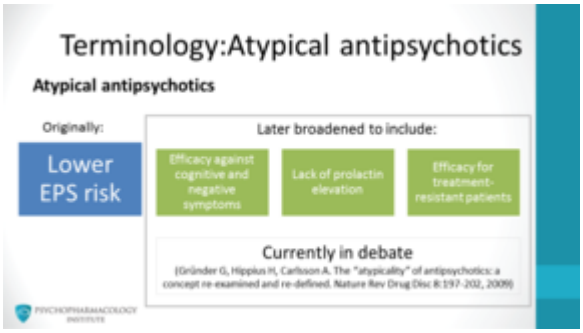
But, what is neurolepsis?

Clinicians in the fifties described this syndrome, which has three main features:

- Psychomotor slowing
- Emotional queting
- Affective indifference

Clinicians at the time thought this syndrome was a reliable sign of antipsychotic efficacy. Nowadays, it is clear that these effects are not required for drugs to have therapeutic action and also that the presence of these symptoms predicts low treatment adherence.

Terminology: Atypical antipsychotics



What is an atypical antipsychotic?

Originally, this term was used to describe a lower risk of EPS associated with clozapine use. Researchers found that at therapeutic doses, clozapine showed a much lower risk of extrapiramidal symptoms such as tardive diskinesia.

Later, the use of this term was broadened to include: efficacy against negative and cognitive symptoms, lack of prolactin elevation and efficacy in treatment resistant patients.

Currently, researchers argue that the addition of the features shown here in green have hampered antipsychotic drug research and that reframing the concept of atypicality could have a key role in the advance of this therapeutic field.

Classification table

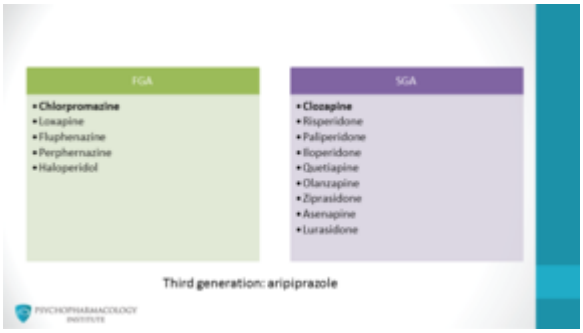
Classic and commonly used terms	Proposed new terms (WPA)
Neuroleptics (conventional antipsychotics, typical antipsychotics)	First generation antipsychotics
Atypical antipsychotics (serotonin-dopamine antagonists)	Second generation antipsychotics
Dopamine partial agonists (Aripiprazole)	Third generation antipsychotics

Let's see this table to review the concepts we just discussed. On the left I have listed the classic and commonly used terms, on the right the new terminology proposed by the World Psychiatric Association.

Neuroleptics, as we discussed are the drugs than fall under the category of conventional antipsychotics, or typical antipsychotics. The new terminology calls them first generation antipsychotics, these include drugs such as chlorpromazine, haloperidol, fluphenazine, among others.

The term atypical antipsychotics is the most commonly used for second generation antipsychotics. Based on their shared pharmacological properties, these drugs are also called dopamine-serotonin antagonists.
Drugs that act as dopamine partial agonists fall under the third generation antipsychotics category. However, this has been controversial.

List of first and second generation agents



Here are some examples of first and second generation antipsychotics.

As you can see, chlorpromazine is in bold letter, the reason for this is that it is the prototype for the phenothiazine class of drugs.

This was the first drug used as an antipsychotic, and is still in use. Other drugs in this group include loxapine, fluphenazine, perphenazine, haloperidol and loxapine.

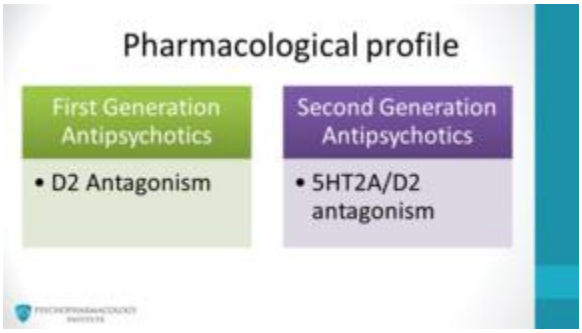
First generation antipsychotics are classified according to their chemical family, which predicts clinical profile.

Their pharmacological properties will be discussed in detail in other videos.

Clozapine was the first drug of the second generation antipsychotics. The pharmaceutical industry worked to develop drugs with pharmacological similarities to clozapine, with the intention to replicate clozapine effectiveness without its side effects.

The result is a list that includes: risperidone, paliperidone, iloperidone, quetiapine,olanzapine, ziprasidone, asenapine and lurasidone.

Pharmacological profile



Now let's see the differences regarding pharmacological profiles.

First generation antipsychotics are D2 antagonists, they act on different regions such as mesolimbic, mesocortical, nigrostriatal and tuberoinfundibular pathways.

Something worth noting is that both first and second generation antipsychotics have some degree of D2 antagonism. D2 antagonism has proven to be responsible for antipsychotic efficacy.

Besides D2 antagonism, first generation agents have effects on other receptors, such as muscarinic, adrenergic alpha 1 and histamine-1.

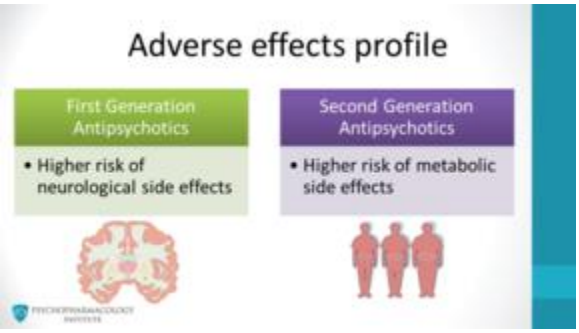
Blockade of these receptors is related with their side effects profile.

Second generation antipsychotics also block D2 receptors, but what makes them different from first generation agents is their ability to block 5HT2A receptors. As we saw in a previous slide, these drugs are also known as serotonin-dopamine antagonists.
In fact, they have higher affinity for 5HT2a receptors than D2 receptors.

Adverse effects profile

There are important differences regarding adverse effects profiles.

First generation antipsychotics are associated with higher risk of neurological side effects. Some of these include, tardive diskinesia, extrapyramidal symptoms dystonia, among others.



I've included this image depicting basal ganglia to highlight the effects that first generation antipsychotics have on the nigrostriatal dopamine pathway. We'll study this mechanism in other videos.

On the other hand, second generation antipsychotics gained popularity thanks to a lower risk of neurological side effects.

Later, it was discovered that these drugs are associated with an increased risk of developing metabolic side effects: these include hyperglycemia, weight gain and dyslipidemia.

This picture shows abdominal obesity, as a reminder of metabolic side effects.

Effectiveness: Are SGAs more effective than FGAs?

One question matter of clinical debate is whether second generation antipsychotics are more effective than first generation antipsychotics.

There are two important clinical trials that shed some light in this controversy.

The first are the Clinical Antipsychotic Trials of Intervention effectiveness, funded by the National Institutes of Mental Health.

The other is the Cost Utility of The Latest Antipsychotics in Severe Schizophrenia, conducted in the UK and funded by the National Health Service.

According to the results from these trials:

There is no evidence of benefit of second over first generation antipscyhotics in the treatment of negative symptoms of schizophrenia.

Clozapine has shown clear utility in treatment-resistant schizophrenia.

Take home points

So, what are the concepts you shouldn't miss from this video? Let's review:

- First generation antipsychotics are D2 antagonists and are associated with higher risk of EPS.
- Second generation antipsychotics: are 5HT2A/D2 antagonists, are associated with lower risk of EPS and with higher risk of metabolic side effects.
- Finally, there is no evidence that SGAs are significantly more effective than FGAs in the treatment of cognitive and negative symptoms of schizophrenia.