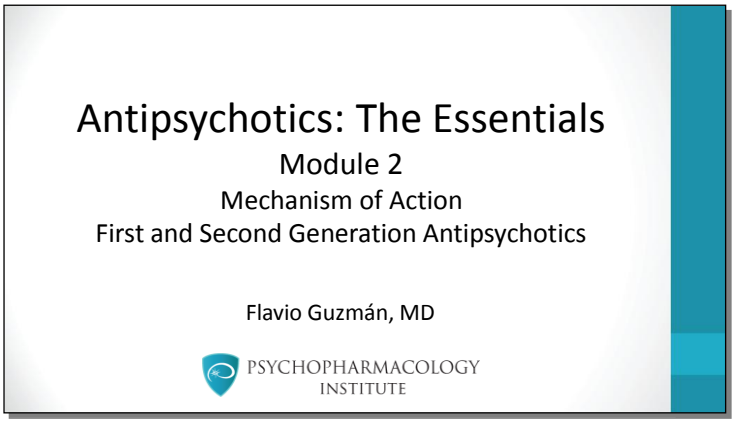
Antipsychotics: The Essentials

Module 2: Mechanism of Action of First and Second Generation Antipsychotics

PSYCHOPHARMACOLOGY INSTITUTE

Slide 1



In this module I talk about the mechanism of action of first and second generation antipsychotics. I will discuss the mechanism of action of aripiprazole in a different video.

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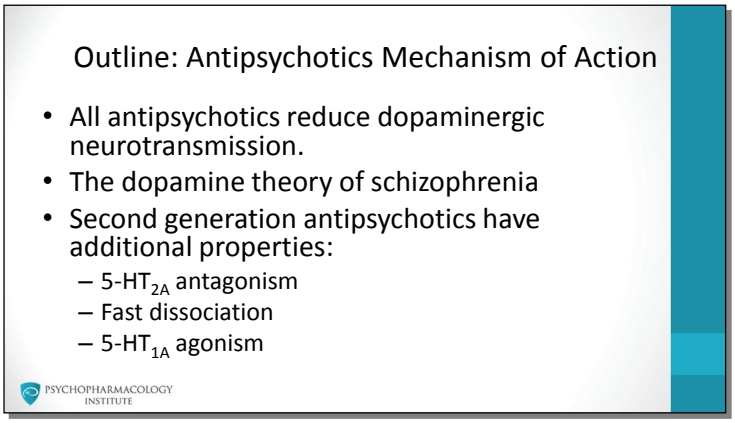

This slide is an outline of the key topics we are going to discuss in the following minutes.

We'll see how all antipsychotics reduce dopaminergic neurotransmission.

Also, we'll review the dopamine hypothesis of schizophrenia.

Finally, I'll present some relevant pharmacological properties of second generation agents, such as: 5HT2A antagonism, fast dissociation from D2 receptors and 5-HT1A agonism.

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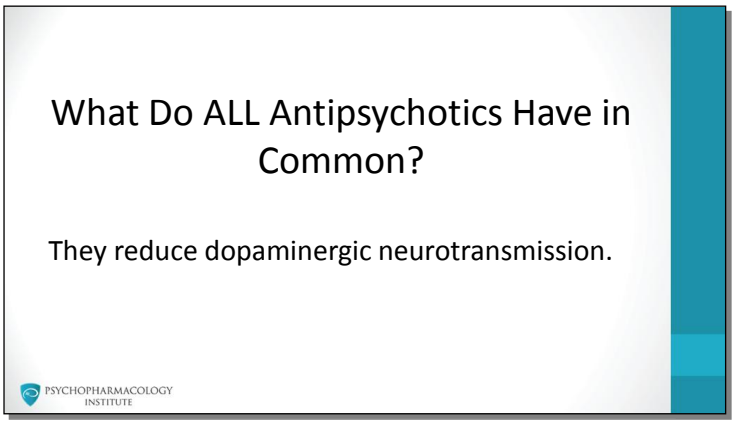

Let's start by answering this very important question: What do ALL antipsychotics have in common?

The answer is relatively simple: They all reduce dopaminergic neurotransmission. In the upcoming slides we'll see how and where this takes place and why dopaminergic blockade is important in psychosis pathophysiology.

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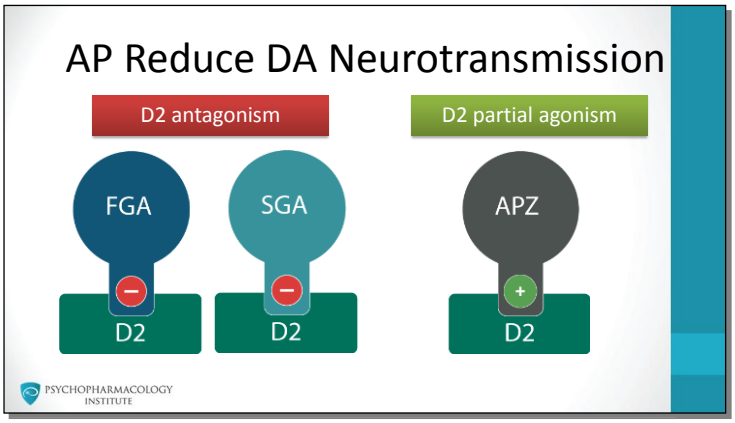

Now we'll study how antipsychotics reduce neurotransmission in dopamine pathways.

There are two options: the first is through **D2 antagonism,** both first and second generation antipsychotics can block D2 receptors.

The second option is through partial agonism: at this time the only approved second generation antipsychotic is aripiprazole, we'll discuss its mechanism of action in other video.

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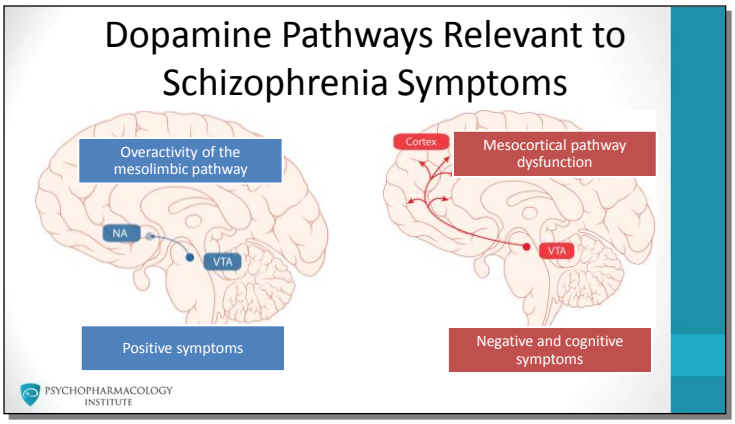

As we discussed in the dopamine pathways video, there are 4 pathways key to antipsychotics pharmacology. Blockade of two of these pathways can lead to adverse effects. The other two pathways are relevant to schizophrenia symptoms.

In this figure the mesolimbic pathway is shown in blue, the dopamine theory postulates that positive symptoms such as delusions, hallucinations and thought disorder might be caused by an over activity of this pathway.

In the other figure, the mesocortical pathway is depicted in red. Recent findings suggest that a dysfunction of the mesocortical pathway may be part of the neurobiology of negative and cognitive symptoms.

So, in review, an excessive activation of the dopamine mesolimbic pathway is related to positive symptoms, while negative and cognitive symptoms might be caused by mesocortical dysfunction.

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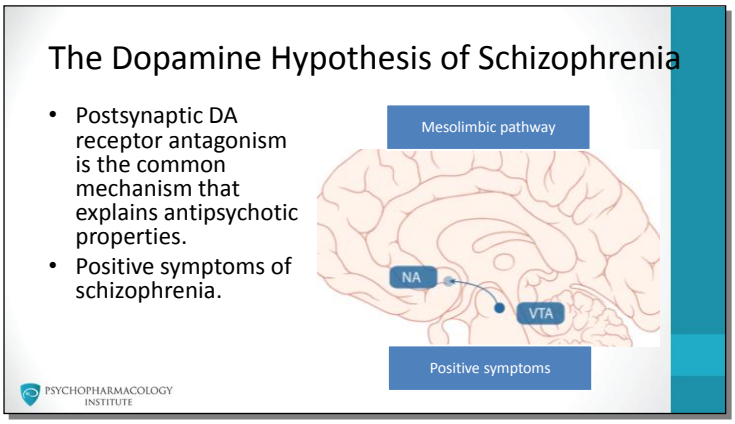

The dopamine hypothesis of schizophrenia postulates that postsynaptic dopamine antagonism is the common mechanism that explains antipsychotic properties.

The pharmacologist and clinician Stephen Stahl argues that it would be more appropriate to refer to this theory as “the dopamine hypothesis of positive symptoms of schizophrenia”. The reason is that there are more pathways and psychopathological dimensions that are not included in this theory.

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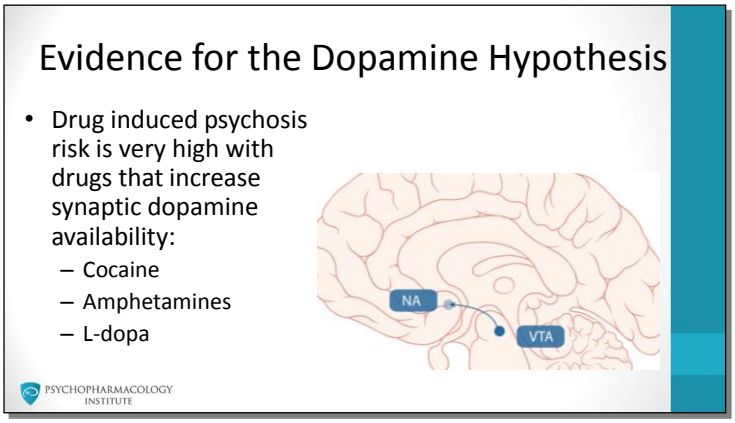

So, what is the evidence that backs up the dopamine hypothesis of schizophrenia?

Drug induced psychosis risk is very high with drugs that increase synaptic dopamine availability. This includes drugs such as cocaine, amphetamines and L-dopa.

In fact, this can be a potential complication for patients suffering Parkinson's disease treated with L-dopa.

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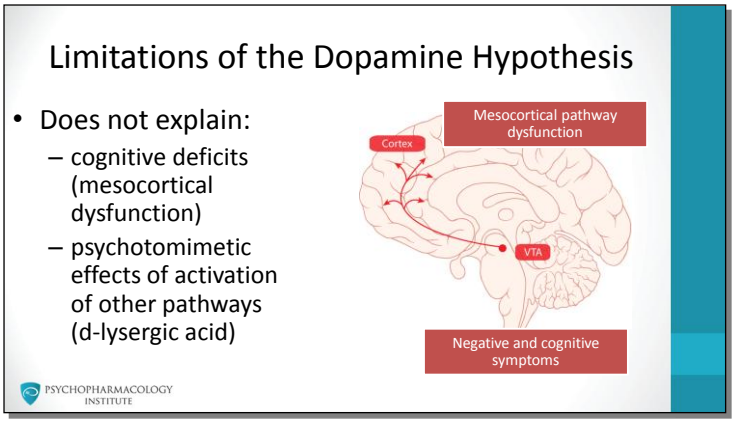

As I mentioned before, schizophrenia neurobiology is very complex and the dopamine theory has limitations.

The first limitation is that it doesn't explain cognitive deficits in schizophrenia patients.

The second limitation is that psychotomimetic effects of activation of other pathways are not included in this theory. For example, d-lysergic acid is a 5-HT2A agonist that can produce psychotic symptoms.

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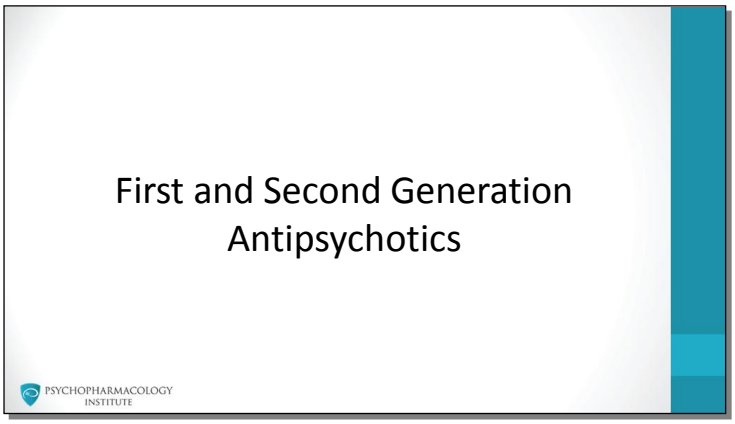

Let's discuss now the mechanism of action of first and second generation antipsychotics.

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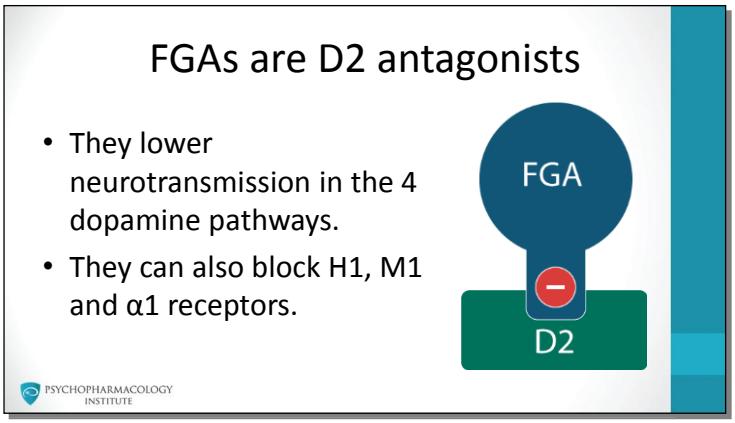

First generation or conventional antipsychotics are D2 antagonists, they lower dopaminergic neurotransmission in the four dopamine pathways.

In addition, they can also block other receptors such as histamine-1, muscarinic-1 and alpha-1.

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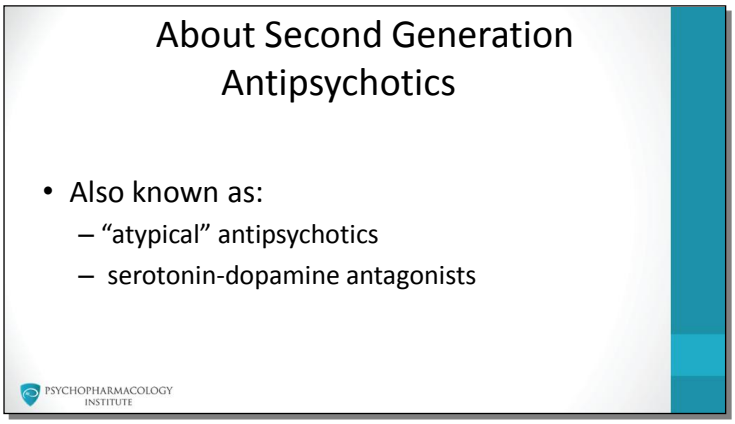

Second generation antipsychotics are also known as "atypical" antipsychotics. This term was originally used to refer to a lower risk of extrapyramidal effects for the antipsychotic clozapine.

The other less used term is serotonin-dopamine antagonists, this describes one of their key features, which is the ability to block serotonin receptors.

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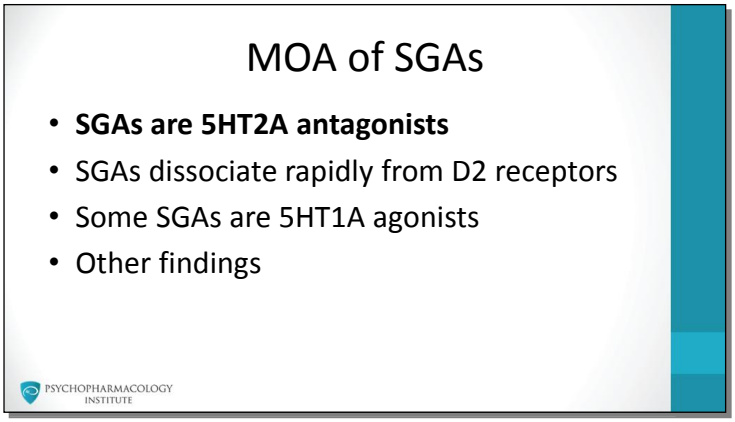
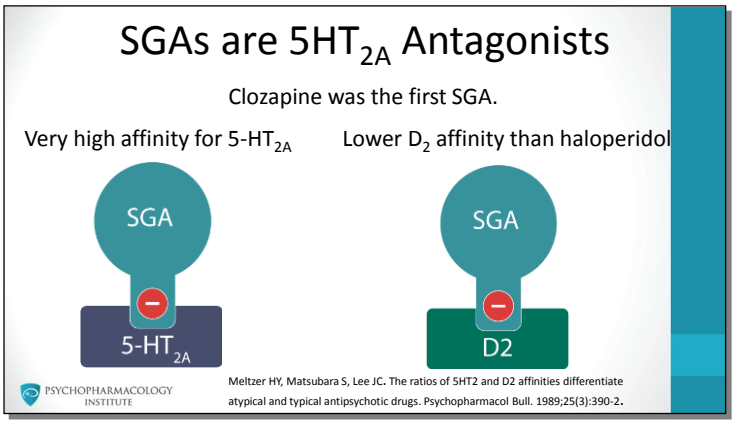


We are reviewing the mechanisms of second generation antipsychotics in four parts. These are the most accepted theories on how antipsychotic drugs might work.

In the next slides we'll see why 5HT2A antagonism is important.

Slide 13



One of the most important features of second generation antipsychotics is their 5-HT2A antagonism. In this slide we'll use clozapine as an example, this is because this was the first drug in its group.

Clozapine has very high affinity for 5–HT2A receptors, and a lower D2 affinity than haloperidol. This led researchers such as Herbert Meltzer to propose that the differential antipsychotic effect of clozapine is related to its high 5-HT2/D2 ratio.

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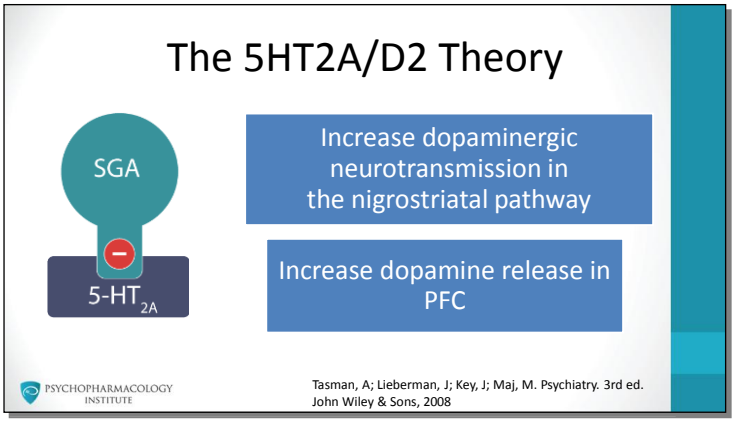

How does the 5HT2A/D2 theory of atypicality explain the low risk of extrapyramidal symptoms?

5HT2A antagonism can increase dopaminergic neurotransmission in the nigrostriatal pathway, reducing the risk of extrapyramidal symptoms. It could also theoretically improve negative and cognitive symptoms in schizophrenia by increasing dopamine release in the prefrontal cortex.

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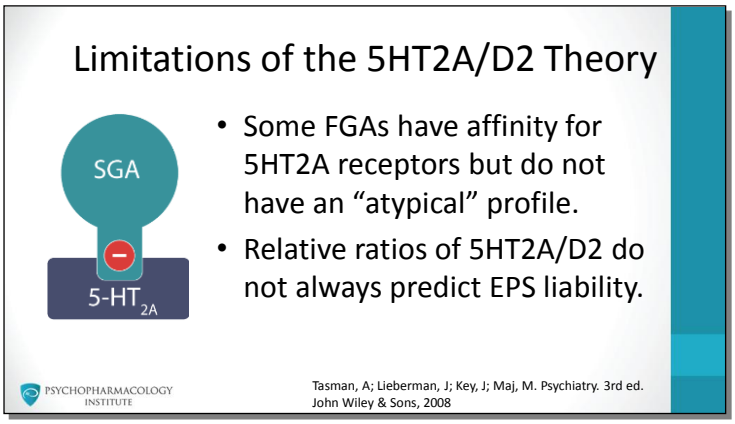

The 5HT2A/D2 theory has its limitations too.

Some FGAs have affinity for 5HT2A receptors but do not have an "atypical" profile.

Relative ratios of 5HT2A/D2 do not always predict EPS liability.

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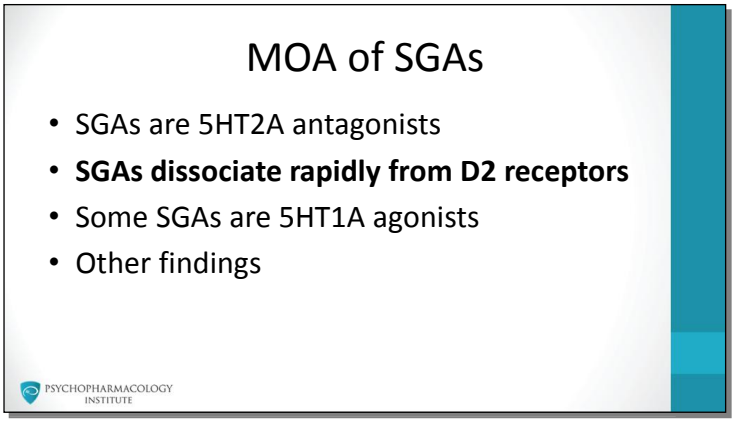

Moving now to the second part, let's review rapid dissociation from D2 receptors as a possible mechanism of atypicality.

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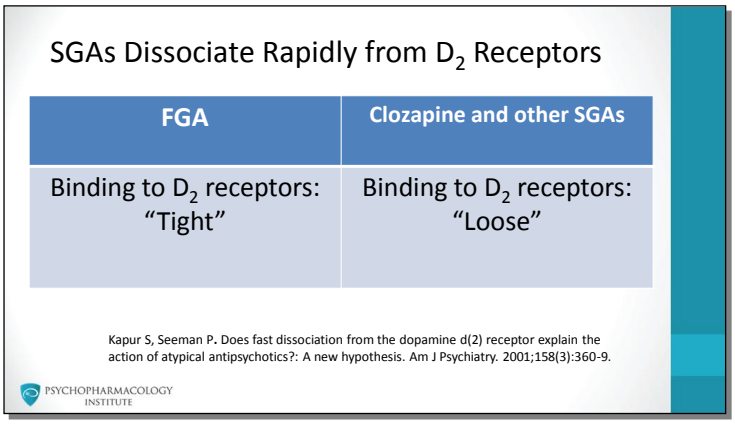

Another theory of "atypicality" proposes that second generation antipsychotics dissociate rapidly from D2 receptors, this would be a possible explanation for the lower risk of EPS of drugs such as clozapine and quetiapine.

This table compares first and second generation antipsychotics in terms of their binding to D2 receptors.

Conventional antipsychotics tend to bind more "tightly" to dopamine receptors than dopamine itself.

Clozapine and the other second generation agents bind to D2 receptors more "loosely", so in the presence of dopamine they tend to come off the receptor more easily.

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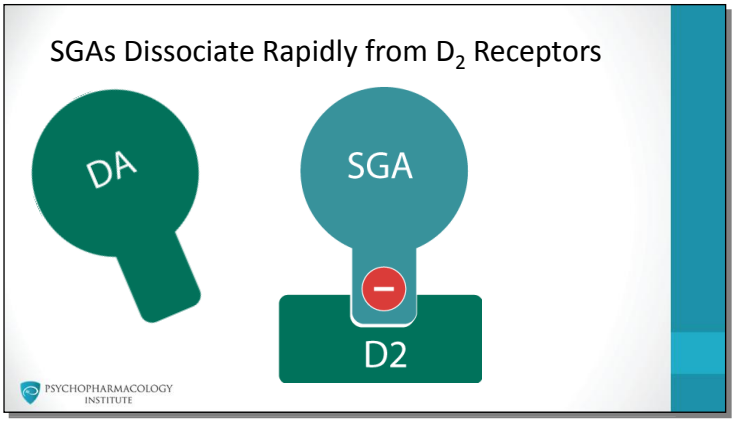
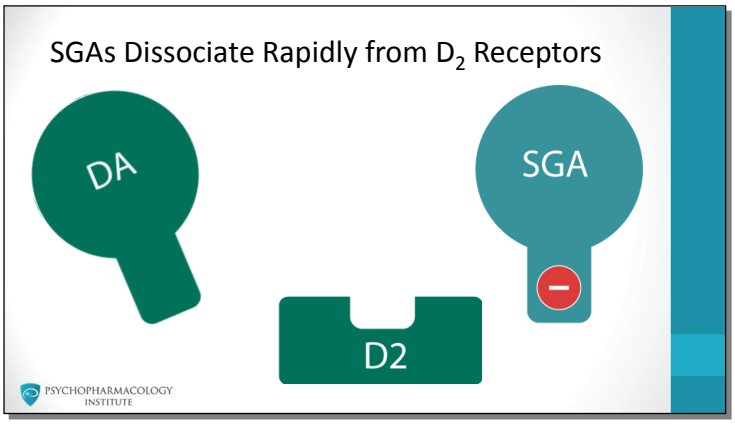


This short sequence depicts fast dissociation from D2 receptors. In this image we can see the "loose" binding of a second generation agent to the receptor.

Slide 19



In this slide we see that in the presence of dopamine, the drug easily dissociates from the receptor.

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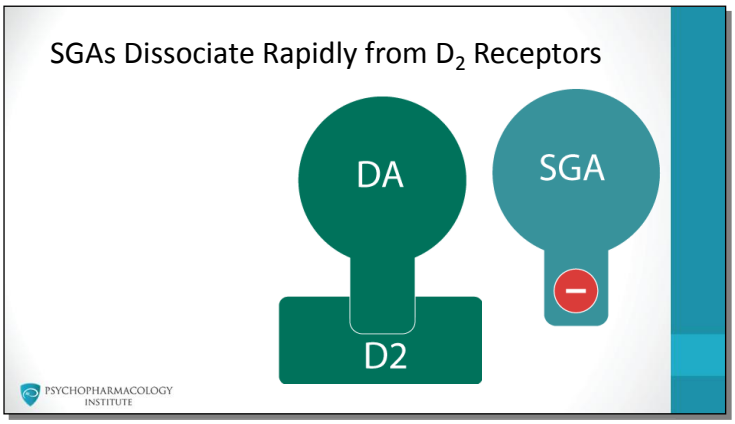
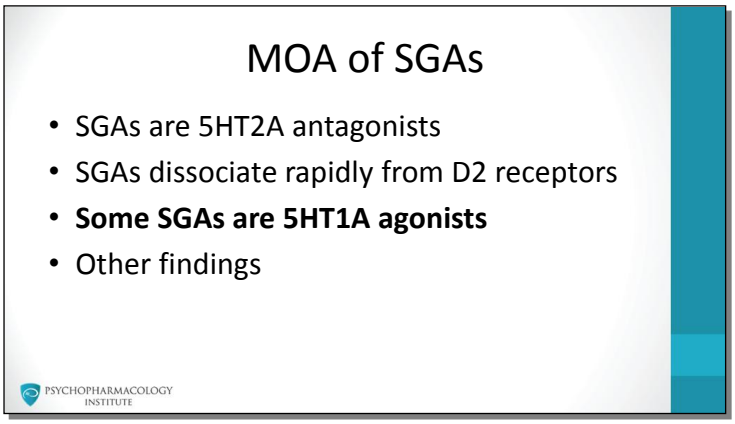


Now here we can see how dopamine finally binds the D2 receptor.

Slide 21



Some second generation antipsychotics can also bind to 5HT1A receptors.

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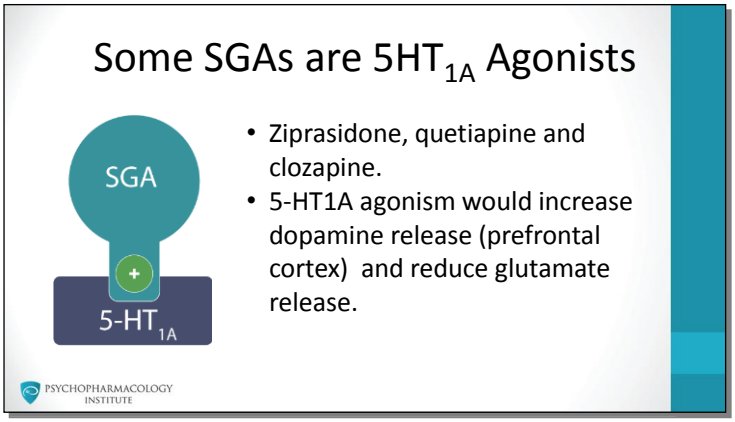

Another property of second generation antipsychotics is that some of them are 5HT1A agonists. This includes drugs such as ziprasidone, quetiapine and clozapine.

What is the importance of this?

5HT1A agonism would increase dopamine release in the prefrontal cortex and also reduce glutamate release.

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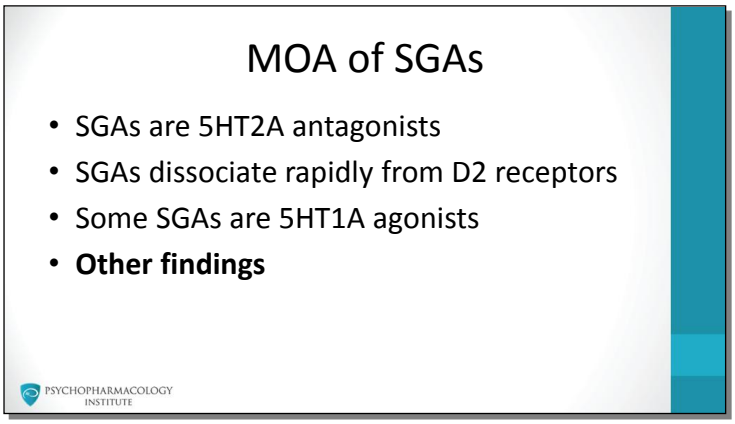
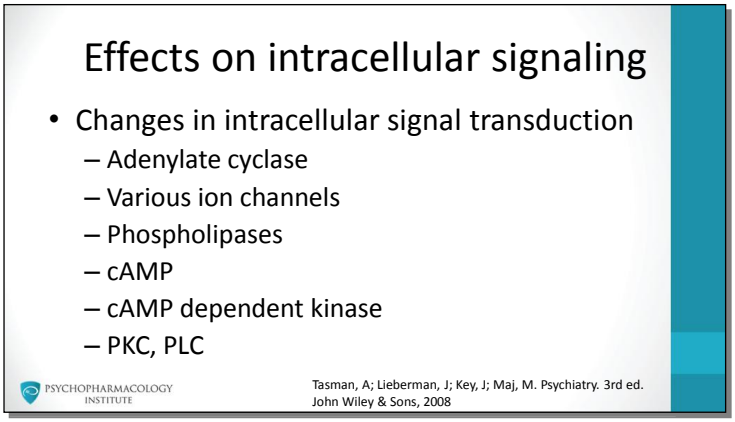


In the next slide we'll see the effects of antipsychotics on intracellular signaling.

Slide 24



There a number a studies suggesting that antipsychotic action is associated with adaptive modifications that involve changes in intracellular signal transduction and gene expression in target neurons.

These changes appear to be initiated by binding to dopaminergic, serotonergic, muscarinic, adrenergic and other receptors. Most of these receptors belong to the G-protein-coupled receptors family.

Downstream effectors include:

- Adenylate cyclase
- Various ion channels
- Phospholipases
- cAMP
- cAMP dependent kinase
- Protein kinase C, Protein lipase C

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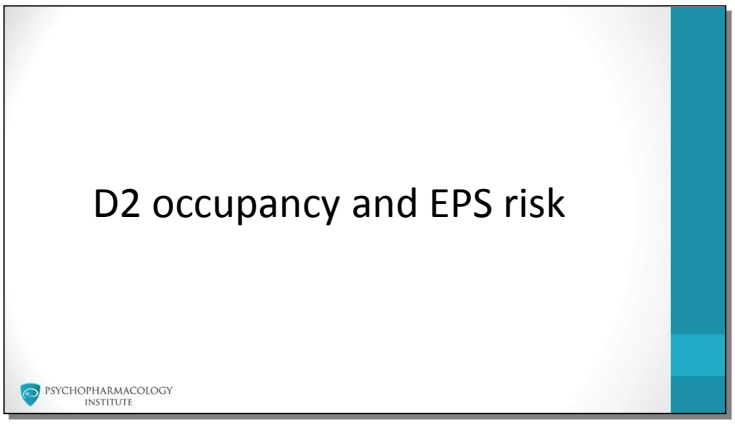

In the next slide we see the relationship between D2 occupancy and risk of extrapyramidal side effects.

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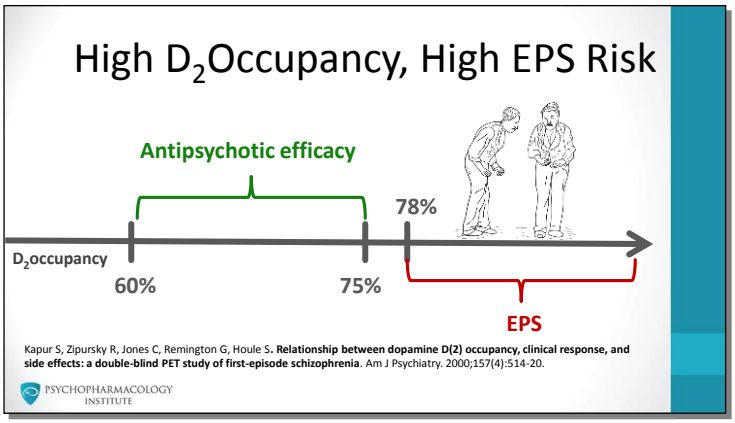

PET studies show that D2 receptor occupancy predicts both clinical efficacy and EPS.

In this graphic we see that occupancies in the range between 60 and 75% are associated with clinical antipsychotic efficacy. If we increase the antipsychotic dose above a 78% occupancy, there is an increased risk of extrapyramidal symptoms.

In clinical terms, this means that the optimal dosing of any antipsychotic agent is one that occupies between 60 to 75% of D2 receptors.

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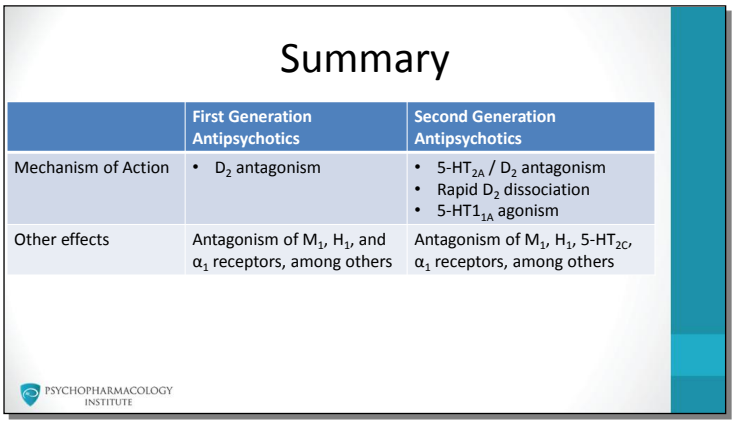

This table summarizes some core concepts on the mechanism of action of first and second generation antipsychotics. Conventional agents are D2 antagonists, while second generation antipsychotics have a high 5-HT_{2A}/D2 ratio. This means that they block more potently 5-HT_{2A} receptors than D2 receptors. They also show rapid dissociation from D2 receptors, and some of them such as quetiapine, ziprasidone and clozapine have 5-$HT1_{1A}$ agonism.

Depending on each individual agent, both first and second generation antipsychotics can block muscarinic-1, histamine-1 and alpha-1 receptors, among others.

References and further reading for "Dopamine Pathways and Antipsychotics" and "Mechanism of Action of First and Second Generation Antipsychotics"

- Brunton LB, Lazo JS, Parker KL, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill; 2010.
- Stahl, S M. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 3rd ed. New York: Cambrigde University Press; 2008
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- Meltzer HY, Matsubara S, Lee JC**.** The ratios of 5HT2 and D2 affinities differentiate atypical and typical antipsychotic drugs. Psychopharmacol Bull. 1989;25(3):390-2.
- Kapur S, Seeman P**.** Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: A new hypothesis. Am J Psychiatry. 2001;158(3):360-9.