Slide 1

This is the last module, it’s a primer on selected antipsychotics.

Slide 2

About this module

• 13 antipsychotics will be studied
  – 3 first generation antipsychotics
  – 10 second generation antipsychotics
• Plan:
  – Binding profile (highlights, not exhaustive)
  – Basic prescribing information
  – Main clinical features of each AP

Before beginning with the discussion of each drug, let me give you a preview of how I’ve organized this module.

I have selected 13 antipsychotics, 3 are first generation agents and 10 are second generation agents. As you may see, there is an emphasis on second generation antipsychotics. This is because prescribers are often interested in knowing more about the new drugs they hear about.

Please keep in mind that first generation antipsychotics are still extremely valuable drugs, especially for situations in which costs of new drugs may be prohibitive.

If you are interested in learning up-to-date detailed information about first generation antipsychotics, I would recommend you to check a recent review published in Advances in Psychiatric Treatment by Dr. Owens. You can look for the title it in the references slide.

The structure for each antipsychotic is the following:

- First we’ll study the most relevant features regarding binding profiles. These are just highlights that often have clinical implications, we won’t go into exhaustive pharmacodynamic detail.
Second, I’ll describe basic prescribing information, mainly dosage range and dosage forms.

Third, I’ll present main clinical features of each drug.

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About this module

• All antipsychotics mentioned in this presentation are approved for the treatment of schizophrenia.

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Antipsychotics

• Chlorpromazine (Thorazine)
• Haloperidol (Haldol)
• Perphenazine (Trilafon)
• Clozapine (Clozaril)
• Olanzapine (Zyprexa)
• Risperidone (Risperdal)
• Paliperidone (INVEGA)
• Quetiapine (Seroquel)

• Ziprasidone (Geodon)
• Aripiprazole (Abilify)
• Iloperidone (Fanapt)
• Asenapine (Saphris)
• Lurasidone (Latuda)

The list of antipsychotics we’ll study is the following:

• Chlorpromazine (Thorazine)
• Haloperidol (Haldol)
• Perphenazine (Trilafon)
• Clozapine (Clozaril)
• Olanzapine (Zyprexa)
• Risperidone (Risperdal)
• Paliperidone (INVEGA)
Let’s begin with one of the oldest antipsychotics, chlorpromazine. This is a low potency first generation antipsychotic, as you remember, this means that high doses are required for achieving therapeutic effect.

One of the reasons why chlorpromazine is still relevant is that it is used as comparator for antipsychotic dose equivalence.

Let’s study its binding profile. Chlorpromazine has antagonist action at D2 receptors, this is linked to its efficacy as an antipsychotic. Regarding other receptors, chlorpromazine is an antagonist at histamine 1 receptors, alpha 1 and muscarinic receptors.

Histamine 1 antagonism is linked to one the effects most typically associated with chlorpromazine use: sedation.

Alpha 1 antagonism increases the risk of orthostatic hypotension, it’s important to keep in mind this side effect especially in an acute setting.

Chlorpromazine also blocks 5HT2A receptors, but not as potently as second generation drugs.
Chlorpromazine dosage ranges from 200 to 800 mg/day. Current suggested dosing is between 400 and 600 mg/day.

Regarding dosage forms, chlorpromazine is available as tablets of 10, 25, 50, 100 and 200 mg.

As capsules of 30, 75, 150 mg.

As ampul of 25 mg/ml, 1 ml and 2 ml.

As liquid drug 10 mg / 5ml.

And as suppository of 25 and 100 mg.

Chlorpromazine: Clinical Profile

Advantages
- Long established use
- High margin of safety
- Sedative

Disadvantages
- Tolerability less favorable than safety
- Generally too sedative for long term use

From a clinical perspective, chlorpromazine as advantages and disadvantages.

Among the advantages we can list:

- Long established use.
- High margin of safety.

Its sedative properties, this is an advantage for acute patients.

The disadvantages include:

- Tolerability is less favorable than safety.
- Generally it’s too sedative for long term use.
The next drug in our list is haloperidol. This is a high potency first generation antipsychotic that has high risk of causing EPS, it is available as long acting injection, which is an advantage in terms of treatment adherence for some patients.

Haloperidol has a relatively simple binding profile. It has very high affinity for D2 receptors, this strong D2 blocking property has a correlation in terms of extrapyramidal symptoms. It also has affinity for sigma receptors. Haloperidol doesn’t have significant affinity for histamine 1 or muscarinic receptors, this makes it a drug with low potential to cause sedation or anticholinergic effects.
Haloperidol- Prescribing Facts

• Dose range:
  – 1-40 mg/day orally
  – Efficacy can be obtained with low doses (less than 5 mg/day).

Haloperidol has a wide dosage range, from 1 to 40 mg/day orally.

Brain imaging studies show that low doses of haloperidol, less than 5 mg/day can occupy 80% of D2 receptors, this percentage of occupancy is associated with clinical efficacy.

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Haloperidol- Prescribing Facts

• Dosage forms:
  – Scored tablets: 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg, 20 mg.
  – Concentrate: 2 mg/ml
  – Solution: 1 mg/ml
  – Injection 5 mg/ml
  – LAI - Decanoate formulation:
    • 50 mg haloperidol as 70.5 mg/ml haloperidol decanoate.
    • 100 mg haloperidol as 141.04 mg/ml haloperidol decanoate.
  – 100 mg haloperidol 141.04 mg/ml haloperidol decanoate

Available dosage forms include:

• Scored tablets: 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg, 20 mg.
• Concentrate: 2 mg/ml
• Solution: 1 mg/ml
• Injection 5 mg/ml
• LAI - Decanoate formulation:
  • 50 mg haloperidol as 70.5 mg/ml haloperidol decanoate.
  • 100 mg haloperidol as 141.04 mg/ml haloperidol decanoate.

Owens D. Meet the relatives: a reintroduction to the clinical pharmacology of 'typical' antipsychotics (Part 1). Advances in Psychiatric Treatment 2012

In clinical terms, the advantages of haloperidol include:

- Long established use. Haloperidol was approved in 1967, since then it has been extensively used.
- It’s very useful in psychiatric emergencies. The lack of alpha 1 antagonism makes it a drug with low risk of causing orthostatic hypotension, which is an benefit for parenteral use.

The disadvantages:

- Because of its strong affinity for D2 receptors, it has very high liability to produce extrapyramidal symptoms.
- The perception of dosage is higher of what pharmacology suggests.

Perphenazine is an intermediate potency first generation drug that served as active comparator in the CATIE trial.
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Perphenazine has an intermediate affinity for D2 receptors, compared to haloperidol it’s a weaker D2 antagonist. It has significant alpha1 antagonist action and it’s also a histamine 1 antagonist.

This pharmacological profile should remind us of risk of orthostatic hypotension and sedation.

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The dosing range of Perphenazine goes from 12 to 24 mg/day. Here we can see two situations worth noting, the CATIE trial allowed up to 32 mg/day. Also in hospitalized patients, the daily dose can range from 16 to 64 mg.

The dosage forms are tablets and an injection.

There are available tablets of 2, 4, 8 and 16 mg.

The injection is a formulation of 5 mg/ml.
From a clinical perspective, the advantages of Perphenazine include:

- Long established use
- High margin of safety (remember its wide dosage range)
- The fact that we got to know it better through its use as active comparator in the CATIE trial.

We also need to consider its disadvantages:

- It has a short half-life: between 8 to 12 hours, ideally is best administered three times daily. This can be problematic in terms of treatment adherence.

Its potency and tolerability make easy for extrapyramidal symptoms to emerge undetected.

We’ll move now to the second generation drugs. Clozapine was the first of the second generation antipsychotics to be approved, it has unique therapeutic benefits and a unique side effects profile.
This drug has a very complex pharmacology. Because of the reasons I mentioned earlier the binding profile of clozapine has been intensively studied.

I’ll refer to some of the most relevant features, those that have implications because of hypothetical mechanisms of action or adverse effects.

Clozapine has a high 5HT2A/D2 ratio, this means despite being an antagonist for both receptors, it has higher affinity for 5HT2A receptors.

The drug is also an antagonist at histamine 1, muscarinic and alpha 1 receptors. This is relevant for potential side effects.

Antagonism at 5HT2C receptors has been associated to an increase in the risk of weight gain.

In addition, clozapine is an antagonist at D3 and D4 receptors. Also, the drug is a partial agonist at 5HT1A receptors.
Clozapine: Prescribing Facts

- **Dosage range:**
  - 300-450 mg/day
  - In some cases: higher than 500 mg/day (risk of seizures)
- **Dosage forms:**
  - Tablets: 12.5 mg, 25 mg (scored), 50 mg, 100 mg (scored)
  - Orally disintegrating tablets: 12.5 mg, 25 mg, 50 mg, 100 mg
- **Metabolized primarily by CYP1A2, with additional contributions by CYP2C19, CYP2D6 and CYP3A4**

The dosage range of clozapine goes from 300 to 450 mg/day. In some cases doses as high as 500 mg/day can be used, we must remember that seizure risk is dose dependent.

Dosage forms include tablets and orally disintegrating tablets. Tablets are available in presentations of 12.5 mg, 25 mg scored tablets, 50 mg, and 100 mg scored tablets.

Orally disintegrating tablets are available in formulations of 12.5, 25, 50 and 100 mg.

A pharmacokinetic fact worth noting is that clozapine is metabolized primarily by CYP1A2, with additional contributions by CYP2C19, CYP2D6 and CYP3A4.

Clozapine: Clinical Profile

- Effective for treatment-resistant schizophrenia.
- Reduces violence and persistent aggression in schizophrenia.
- Long-term treatment associated with reduction of risk of suicidal behaviors.

It’s important to take a moment to identify the three clinical features that make clozapine unique.

- The first is that clozapine is the only antipsychotic that has proven effective for treatment-resistant schizophrenia. For a definition of treatment-resistant schizophrenia I would recommend you to check the paper by Conley cited at the bottom of the slide.

The second concept is that clozapine reduces violence and persistent aggression in schizophrenia.

Last, but definitely not least, long-term treatment is associated with reduction of risk of suicidal behaviors.
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Clozapine – Adverse Effects Profile

- One of the antipsychotics with the lowest EPS risk
- One of the antipsychotics with the highest metabolic risk
- Risk of agranulocytosis
- Dose-dependent seizure risk
- Can be very sedating

Clozapine has a special adverse effects profile.

- It’s one of the antipsychotics with the lowest risk of causing EPS.

On the other hand, it’s one of the antipsychotics with the highest metabolic risk, the other is olanzapine.

As we saw in the module on adverse effects, the risk of agranulocytosis requires periodic blood monitoring.

It has a dose-dependent seizure risk.

Because of its antagonist effect at histamine 1 receptors it can be very sedating.

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Olanzapine

- SGA less “dirty” than clozapine.
- Available in combination with fluoxetine: OFC
- Dosage forms include parenteral formulations

Olanzapine is a second generation antipsychotic known to be less “dirty” in pharmacodynamic terms than clozapine.

It is available in combination with the antidepressant fluoxetine as olanzapine fluoxetine combination or OFC.

Dosage forms include parenteral formulations.
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Olanzapine has a binding profile similar to clozapine, but it interacts with less receptors.

It has a high 5HT2A/D2 ratio, like clozapine it is an antagonist at histamine 1, muscarinic, alpha 1 and 5HT2C receptors. Antagonist actions at 5HT2C and histamine 1 receptors are thought to be related to an increased risk of weight gain.

Because of its affinity for alpha 1 receptors, olanzapine can cause in some cases orthostatic hypotension. Since this drug is available as IM injection, we need to remember this side effect to avoid combining it with benzodiazepines.

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The dosage range of olanzapine goes from 10 to 20 mg / day. There are several dosage forms that include oral and parenteral formulations.

Tablets are available in doses of 2.5, 5, 7.5, 10, 15 and 20 mg.

Orally disintegrating tablets: 5, 10, 15 and 20 mg

Oral fluoxetine combination of 6 mg of fluoxetine and 25 mg of olanzapine, 6 and 50 mg, 12 and 25 and 12 and 50 mg.

An IM formulation for use in acute settings: 5 mg per ml, each vial contains 10 mg. This formulation is available in some countries.

A long acting injection of olanzapine pamoate: doses of 150, 300, 210, 405 mg
I’ve selected some interesting facts about the clinical profile of olanzapine:

- Olanzapine/fluoxetine combination was the first drug approved for bipolar depression.
- Associated with less EPS than FGAs.
- Weight gain is problematic with long term use.
- Can be very sedating.

Weight gain is problematic with long term use. Olanzapine and clozapine are associated with the highest risk of weight gain.

It can be a very sedating antipsychotic.