What Team Members Other Than Prescribers Need To Know About Antipsychotics

The Care Transitions Network

National Council for Behavioral Health
Montefiore Medical Center
Northwell Health
New York State Office of Mental Health
Netsmart Technologies
Learning Objectives

• Psychiatrists and nurse practitioners are the team members who prescribe antipsychotics

• Other members of a mental health team need a basic understanding of these medications
  • Other team members can provide support for patients and their families about medication decision making
  • Provide guidance to patients and their families about when and how to ask prescribers questions

• This presentation will focus on essential psychopharmacology that team members who are not prescribers need to know
  • We will omit technical aspects that only prescribers need to know
Outline

• Overview of Available Antipsychotics
• Indications for Use
• Outcomes of Interest
  • Symptom Improvement
  • Side Effects
• Choosing Which Antipsychotic to Use
  • Differences between antipsychotics
    • Symptom improvement
    • Side effects
    • Available delivery mechanisms
Advent of Antipsychotics

• Before the era of antipsychotics (before the 1950s), two of three psychotic patients spent most of their lives in state asylums
• After the introduction of antipsychotics, there was a marked reduction in hospitalization for psychosis
• Currently, more than 95% of patients with psychotic disorders live outside the hospital, even though many continue to relapse or have residual symptoms
Timeline of Biologic Treatments for Psychotic Disorders

ECT
Chlorpromazine
Reserpine
Haloperidol
Fluphenazine
Thioridazine
Loxapine
Perphenazine
others

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Chlorpromazine (Thorazine)

• Chlorpromazine was discovered by chance after initially being synthesized as an antihistamine

• It was initially used due to its sedative properties to reduce autonomic response to surgical stress

• When used for psychosis, it had a dramatic effect, unlike any other treatment before
Antipsychotics

• There are now a large number of antipsychotics
• All currently available antipsychotics work in part through the central dopamine D$_2$ receptor
• Most block the D$_2$ receptor, but some both partially block and also are agonists at the D$_2$ receptor
• Besides having an effect on psychosis, the dopamine system is involved in motor movement and regulation of prolactin levels
  • Some antipsychotics have side effects related to these systems
• Besides their dopamine system effects, antipsychotics vary in how much they affect other neurotransmitter systems
  • This produces variability in side effects depending upon the system affected
First Generation Antipsychotics

• The first antipsychotics developed are now grouped together as First Generation Antipsychotics (FGAs)
• A large number of antipsychotics were developed
• Their mechanism of action was similar
• Their side effects did differ but all were prone to induce motor system side effects (among others)
Selected First Generation Antipsychotics

- Thorazine (chlorpromazine)
- Mellaril (thioridazine)
- Stelazine (trifluoperazine)
- Prolixin (fluphenazine)
- Trilafon (perphenazine)
- Navane (thiothixene)
- Loxitane (loxapine)
- Haldol (haloperidol)
Second Generation Antipsychotics

• The development of clozapine showed that one could develop antipsychotics that 1) were more effective than earlier antipsychotics and 2) did not have the motor side effects common with earlier antipsychotics. Unfortunately, clozapine had other substantial side effects. However, the finding that it was possible to improve on the FGAs led to a new round of medication development.

• Clozapine and the antipsychotics developed afterward are grouped as Second Generation Antipsychotics (SGAs).

• The SGAs vary in their mechanism of action and side effects.
Second Generation Antipsychotics

- Clozaril (clozapine)
- Risperdal (risperidone)
- Invega (paliperidone)
- Zyprexa (olanzapine)
- Seroquel (quetiapine)
- Geodon (ziprasidone)
- Abilify (aripiprazole)
- Latuda (lurasidone)
- Fanapt (iloperidone)
- Saphris (asenapine)
FDA Approved Indications

• All antipsychotics are FDA indicated for the treatment of schizophrenia and related disorders
  • Vary between medications if for schizophrenia only or also for schizoaffective disorder
  • Some but not all are approved for persons under 18
• Some antipsychotics also have indications for other treatment
  • Agitation
  • Bipolar Disorder
  • Some types of depression
  • Tourette’s Disorder
• Clozapine has the unique indications of 1) treatment resistant schizophrenia and 2) suicidal behavior among people with schizophrenia
In the remainder of this presentation, we will be reviewing the efficacy and side effects when antipsychotics are given to patients with schizophrenia and related disorders.
Outcomes of Interest
Symptoms of Psychosis

Disorganized Symptoms
- Grossly Disorganized or Catatonic Behavior
- Disorganized Speech

Positive Symptoms
- Delusions
- Hallucinations

Negative Symptoms
Antipsychotic Symptom Effects

• Antipsychotics have substantial beneficial effects on positive and disorganization symptoms

• Effects on negative symptoms are more limited

• Early in their development, antipsychotics were found to be effective at both 1) treating an acute episode of psychosis and 2) if given as maintenance treatment decreasing the risk of relapse
Side Effects

- Antipsychotics differ in the side effects they produce
- We will review the range of side effects first before discussing medication differences
Acute Motor Side Effects

• Parkinsonian syndrome
• Acute dystonias
• Akathisia
Parkinsonian syndrome is characterized by...

- Masklike faces
- Resting tremor
- Cogwheel rigidity
- Shuffling gait
- Psychomotor retardation

Can be confused with negative symptoms or depression
Parkinsonian syndrome

Sir William Richard Gowers Parkinson Disease sketch 1886
Dystonias: Involuntary contractions of major muscle groups

Image from Dr. J. Heilman; used under GNU Free Documentation License
Akathisia

• A motor restlessness manifested by the urge to move about and/or an inability to sit still

• Can be confused with psychotic agitation
Metabolic Side Effects

• Weight gain
• Increased blood glucose
• Dyslipidemia
• Hyperprolactinemia
Other Common Side Effects

- Sedation
- Dizziness
- Cognitive Dysfunction
- Blurred Vision
- Dry Mouth
- Constipation
- Urinary Retention
- Sexual Dysfunction
- Menstrual Irregularities
Rare Side Effects

- Neuroleptic malignant syndrome is a very rare but potentially life-threatening disorder characterized by fever, confusion, rigid muscles, and other symptoms
- Decreases in white blood cells
- Development of diabetes
A Side Effect That Usually Happens After Prolonged Treatment

• As the name implies, tardive dyskinesia (TD) usually starts later in treatment

• TD consists of abnormal movements of the mouth, face, tongue, arms, legs or other muscle groups

• For some people, the movements continue even after antipsychotics are stopped

• The elderly develop TD earlier in treatment and at higher overall rates than the non-elderly
With so many available antipsychotics, how do you choose which one to use?
Clozapine (Clozapine) Remains Unique

• It is the only antipsychotic that is FDA-approved for treatment resistant psychotic symptoms

• It is the only antipsychotic that is FDA-approved for treatment of patients with schizophrenia who are persistently suicidal

• BUT globally, clozapine has the most severe side effects
Major Clozapine Side Effects

- Drooling
- Rapid heart beat
- Low blood pressure/dizziness
- Sedation
- Constipation
- Fever
- Myoclonus -- sudden, involuntary jerking of a muscle or group of muscles
- Seizures
- Nausea & vomiting
- Inflammation of the heart muscle
- Decrease in white blood cells
  - Blood tests are required weekly for 6 months, every 2 weeks months 6-12 and monthly thereafter
- Obesity and metabolic syndrome
Conclusions About Clozapine

• Clozapine should be considered for all patients who don’t improve on other antipsychotics but because of its side effects it should not be given to patients who improve with other antipsychotics
What to choose if your patient does not need clozapine
Factors Influencing Medication Choice

- Efficacy for symptom improvement
- Differences in side effects
- Formulations available (oral only vs. oral and long-acting versions)
Meta-Analysis

• A statistical technique allowing the combining of a group of studies to come to conclusions based not just on one study but a variety of studies

• We will review 3 meta-analyses

• The first (Leucht 2013) used data from 43,049 patients to compare 13 antipsychotics available in the US on symptom improvement and side effects
Efficacy for Symptom Improvement

• All the studied antipsychotics produced more improvement than placebo
• Clozapine was significantly more effective than the other antipsychotics
Efficacy for Symptom Improvement

- After clozapine, olanzapine (Zyprexa), risperidone (Risperdal) and paliperidone (Invega) were more effective than the other antipsychotics but the difference was small.
All-Cause Discontinuation

• Stopping treatment for any reason
  • Symptoms not improving
  • Side effects that are not tolerable
  • Other factors such as lack of insight
All-Cause Discontinuation

• All antipsychotics were better than placebo
• Olanzapine (Zyprexa), clozapine (Clozaril), paliperidone (Invega) and risperidone (Risperdal) had significantly lower all-cause discontinuation rates than other antipsychotics
Factors Influencing Medication Choice

• Efficacy for symptom improvement
• Differences in side effects
• Formulations available (oral only vs. oral and long-acting versions)
Weight Gain

• All antipsychotics except haloperidol (Haldol), ziprasidone (Geodon) and lurasidone (Latuda) caused more weight gain than placebo
Weight Gain

- Olanzapine (Zyprexa) produced significantly more weight gain than the other antipsychotics
Need to Give Antiparkinson Medications

- Clozapine (Clozaril) produced less EPS than all other antipsychotics or placebo
Need to Give Antiparkinson Medications

- The rates for olanzapine (Zyprexa), quetiapine (Seroquel), aripiprazole (Abilify), iloperidone (Fanapt) and asenapine (Saphris) did not differ from placebo.
Need to Give Antiparkinson Medications

- Haloperidol (Haldol) produced **more** EPS than all other antipsychotics except chlorpromazine for which the difference was not significant.
Increase in Prolactin

- Paliperidone (Invega) and risperidone (Risperdol) were associated with more prolactin elevation than all other antipsychotics.
Increase in Prolactin

• After paliperidone and risperidone, haloperidol (Haldol) and chlorpromazine (Thorazine) were associated with the most prolactin elevation.
Sedation

- Paliperidone (Invega) and iloperidone (Fanapt) were not more sedating than placebo
Sedation

- Among the other antipsychotics, clozapine (Clozaril) and chlorpromazine (Thorazine) were the most sedating
Tardive Dyskinesia Meta-Analysis

• Carbon and colleagues (2017) used data from 9,157 patients to examine TD risk

• TD risk is greater with First Generation Antipsychotics than with Second Generation Antipsychotics
Factors Influencing Medication Choice

• Efficacy for symptom improvement
• Differences in side effects
• **Formulations available (oral only vs. oral and long-acting versions)**
Non-Adherence In The Treatment Of Chronic Disorders

• In developed countries, about 50% of patients with chronic diseases adhere to long-term therapy\(^1\)

• 33–69% of all medication-related hospital admissions in the US are due to poor medication adherence\(^2\)

• One-third of all prescriptions are never filled\(^3\)

• >50% of filled prescriptions are associated with incorrect administration (not taken as prescribed)\(^3\)

Given the frequency of non-adherence, adherence enhancement supports should be available to all patients.

Long-acting injectable medications are one support to consider.
# LAI Antipsychotics Available in the United States

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Usual time between injections</th>
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<tbody>
<tr>
<td><strong>First Generation Antipsychotic</strong></td>
<td>Fluphenazine decanoate</td>
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<td>Haloperidol decanoate</td>
<td>1 month</td>
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<tr>
<td><strong>Second Generation Antipsychotic</strong></td>
<td>Risperidone LAI</td>
<td>2 weeks</td>
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<tr>
<td></td>
<td>Olanzapine pamoate</td>
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<td>Paliperidone palmitate</td>
<td>1-3 months</td>
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<td>Aripiprazole monohydrate</td>
<td>1 month</td>
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<tr>
<td></td>
<td>Aripiprazole lauroxil</td>
<td>1 month-6 weeks</td>
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</tbody>
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If One Antipsychotic is Good, Can Two be Better?
Meta-Analysis of 2 Antipsychotics

- Galling and colleagues (2017) studied adding a second antipsychotic to ongoing use of the first antipsychotic for patients who did not improve sufficiently with the first antipsychotic
- 31 studies were included in the analysis
- Overall, there was **no benefit** to adding a second antipsychotic in overall symptom reduction or in rates of all-cause discontinuation
How long should an antipsychotic be given before deciding that it does not work sufficiently?
Treatment Duration

• An adequate trial of an antipsychotic is generally 6 weeks (except in special circumstances)
• A patient should have 2 suboptimal antipsychotic trials before their illness is considered treatment refractory
• One of these trials ideally should be with an LAI to rule out non-response due to poor adherence
• After 2 failed trials, the next recommendation is clozapine
Summary

• All antipsychotics improve symptoms—they had to have demonstrated efficacy in order to get FDA approval

• Clozapine has positive effects that other antipsychotics do not have for the treatment of resistant psychotic symptoms and of recurrent suicidal ideation among people with schizophrenia

• Among the remaining antipsychotics, olanzapine and risperidone/paliperidone may cause more improvement in symptoms but the degree of differential improvement is small

• Antipsychotics vary in the side effects they produce
Summary

• A variety of antipsychotics are available in long-acting formulations and they differ in the time between injections

• The large number of antipsychotics available allows flexibility for choosing an antipsychotic for a particular individual
Next Steps

Consider asking your patients the following questions....

1. Since last time, are there any days you forgot or skipped medications? If so, why?
2. Have you ever talked to your doctor about long acting injectable medication?
3. When was the last time you had bloodwork?

Encourage your patients to talk to the doctor about missed medications, about the LAI option, and about bloodwork to monitor metabolic side effects.

Alert the psychiatrist about significant medication nonadherence or any distressing side effects the patient brings up.
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