Improving Outcomes in Schizophrenia: Long-acting Depots and Long-term Treatment
page 247 in syllabus

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Learning Objectives

• Evaluate potential advantages and disadvantages of depot and oral formulations of antipsychotics

• Utilize strategies to integrate depot antipsychotics into clinical practice

• Implement strategies to improve long-term adherence and outcomes in schizophrenia
A 23-year-old patient with first-episode schizophrenia started antipsychotic treatment 2 weeks ago. He is tolerating the medication well, but his parents are anxious to see an improvement in his symptoms. Approximately which percentage of first-episode patients require at least 8 weeks of antipsychotic treatment before showing a therapeutic response?

1. 5%
2. 7%
3. 9%
4. 11%
Pretest Question 2

Jack is a 37-year-old patient with schizoaffective disorder. He is overweight (BMI = 34) and has a family history of cardiovascular disease. Which of the following antipsychotics may be the best choice for avoiding treatment-induced cardiometabolic side effects?

1. Lurasidone
2. Olanzapine
3. Iloperidone
Pretest Question 3

Paula is a 53-year-old patient with schizophrenia and a long history of treatment nonadherence. She has recently been hospitalized secondary to "forgetting to take" her oral ziprasidone for the past 3 months. Which of the following antipsychotics is available in a long-acting depot formulation?

1. Asenapine
2. Iloperidone
3. Aripiprazole
4. Ziprasidone
What Happens When Patients With Schizophrenia **DO NOT** Take Their Antipsychotic Medication?
Gray Matter Loss in Adult Patients With Schizophrenia at Baseline and 5-Year Follow-Up

Baseline

5-Year Follow-Up

Talairach coordinate (axial): z=3

Talairach coordinate (axial): z=3

Excessive gray matter loss was related to an increased number of hospitalizations (increased psychotic episodes)

Loss of Gray Matter in Unmedicated Patients With Schizotypal Personality Disorder or Schizophrenia

Gray Matter Loss Is Worse in Patients With a Longer Duration of Untreated Psychosis

Colored voxels depict brain areas of significantly greater gray matter loss in patients with a long duration of untreated psychosis (>18 wks) compared to those with a short duration (<18 wks)

Do Antipsychotics Rot the Brain?

Total cerebral gray matter

Consequences of Nonadherence on Functional Outcomes

- Nonadherence is associated with:
  - Alcohol-related problems
  - Reduced mental functioning
  - Reduced satisfaction with life
  - Psychiatric hospitalizations
  - Use of emergency psychiatric services
  - Arrests
  - Violence
  - Victimization
  - Substance use

Even Partial Nonadherence Is Detrimental

- Nonadherent patients are defined here as those who miss <50% of their medication for 2 or more weeks.
- Missing even <25% of medication for >2 weeks increases the risk of psychotic relapse.

What Happens When Patients With Schizophrenia **DO** Take Their Antipsychotic Medication?
Effectiveness of Antipsychotics

FIN-11 Study

- Long-term antipsychotic use is associated with lower mortality compared to no antipsychotic use in patients with schizophrenia

Risk of death from any cause vs. cumulative use of any antipsychotic drug

* Mortality = unadjusted absolute risk per 1000 person-years
† No antipsychotic drug = patients (18,914) who had not used any antipsychotic drugs during follow-up

Antipsychotic Treatment Improves Cerebral Functioning

Baseline untreated patients with first-episode schizophrenia have decreased neuronal activity.

Patients treated with antipsychotics for 6 wks have increased neuronal activity compared to baseline.

Patients treated with antipsychotics for 6 wks have increased neuronal activity compared to controls.

Time as a Drug

- Long-term continuation of treatment often leads to steady further improvement in schizophrenia symptoms.
- Although some patients with schizophrenia show an early robust response to treatment, time to response may take time, especially in treatment-resistant patients.
- Therapeutic effects on non-positive symptoms may require time.
- Superior efficacy of one antipsychotic over another may require time.

Treatment Response May Take Time

522 patients with first-episode schizophrenia taking haloperidol or risperidone

- 22% of patients required 4 wks to show a response
- 11% of patients required 8 wks to show a response

Some Patients May Require a Year Before Responding to Treatment

13% of patients did not show 20% improvement on the Heinrichs-Carpenter Quality of Life Scale until 1 year of clozapine treatment

Efficacy of Antipsychotics on Positive and Negative Symptoms of Schizophrenia

Ziprasidone 80–160 mg/d (ZSTD)  
Ziprasidone 80–120 mg/d (ZLOW)  
Haloperidol 5–20 mg/d (HAL)

3-Year continuation study

Estimated PANSS total mean score (loess smoothed curve)

Weeks

PANSS Severity level

Low

$p=0.015$ (ziprasidone 80–160 mg vs. haloperidol, slope)

$^*p<0.05$ (ziprasidone 80–160 mg vs. haloperidol)
Efficacy of Antipsychotics on Negative Symptoms of Schizophrenia

Continued Improvement on Brief Psychiatric Rating Scale (BPRS) With Quetiapine

Continued Improvement on the Scale for Assessment of Negative Symptoms (SANS) With Quetiapine

Continued Improvement / Delayed Response to Aripiprazole

Awakeners Analysis:
Total PANSS ITT Population

- **p<0.05**
- **p<0.01**

Long-term Differences Between an Atypical and a Conventional

Switching Antipsychotics May Not Be the Best Choice

• In CATIE, patients who were switched from one antipsychotic to another had:
  – Higher discontinuation rates than patients who did not switch (70% vs. 50%)
  – Limited success in symptom improvement

• Optimize treatment with one antipsychotic (including a longer trial duration) before attempting a switch

The Bottom Line

For some patients…

- Antipsychotic treatment may continue to ameliorate symptoms of schizophrenia if maintained for an extended period of time
- Continuous maintenance antipsychotic medication results in ~70% reduction in risk of relapse
- Find a treatment that is tolerable for the patient and shows at least some therapeutic benefit and stick with it

Treatment Adherence

Antipsychotics Don't Work At All If They Aren't Taken
Assessing Nonadherence

- **Patient self-report**
  - Unreliable

- **Physician report**
  - Overly optimistic

- **Pill counts**
  - Easily manipulated

- **Rx renewals**
  - Medication must be obtained from a single source

- **Microelectric monitoring of pill caps**
  - Expensive

- **Physiological monitoring**
  - Invasive

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She seems like an adherent patient

Ouch!
Strategies to Improve Adherence

• Basic communication
  – Take the patient's preferences into account
  – Explain the benefits and hazards of treatment options

• Strategy-specific interventions
  – Adjust medication timing and dosage for least intrusion
  – Minimize adverse effects and maximize effectiveness
  – Utilize long-acting depot formulations

• Psychosocial interventions

• Maximize cognitive functioning

• Evaluate adherence regularly

Choosing the "Right" Antipsychotic for the "Right" Patient

Maximizing Efficacy While Minimizing Adverse Effects
Functional Groups Responsible for Therapeutic Effects

Cardiometabolic side effects, including weight gain, insulin resistance, and increased fasting triglycerides
Maximize Treatment Efficacy While Minimizing Side Effects for the Individual Patient

<table>
<thead>
<tr>
<th>Drug</th>
<th>D2 Antag</th>
<th>D2 PA</th>
<th>D3</th>
<th>5HT1A</th>
<th>5HT2A</th>
<th>5HT2C</th>
<th>5HT7</th>
<th>α1</th>
<th>M1</th>
<th>M3</th>
<th>H1</th>
</tr>
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<tbody>
<tr>
<td>Aripiprazole</td>
<td>+++</td>
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<td>Asenapine</td>
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<tr>
<td>Clozapine</td>
<td>+</td>
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<td>Iloperidone</td>
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<td>Lurasidone</td>
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<td>Olanzapine</td>
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<td>Paliperidone</td>
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<tr>
<td>Quetiapine</td>
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<td>Ziprasidone</td>
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</tbody>
</table>

**Therapeutic Effects**
- Reduced positive symptoms
- Reduced negative symptoms
- Procognitive
- Antidepressant
- Reduced EPS
- Reduced hyper-prolactinemia
- Antidepressant
- Reduced EPS
- Reduced negative symptoms
- Procognitive
- Hypnotic

**Side Effects**
- EPS: Hyper-prolactinemia; Increased negative symptoms; Increased cognitive deficits; Sedation
- Relatively lower risk of EPS
- Unknown
- Cardiometabolic
- Unknown
- Dizziness; Hypotension
- Constipation; Sedation; Dry mouth; Blurred vision
- Cardiometabolic; Constipation; Sedation; Dry mouth; Blurred vision

+ weak binding affinity (100>Ki<1000)
++ moderate binding affinity (10>Ki<100)
+++ strong binding affinity (1>Ki<10)
++++ very strong binding affinity (Ki<1)
? No data yet available

*Binding property due primarily to the metabolite norquetiapine
# Minimizing the Risk of Side Effects

## SEDATION
- Aripiprazole
- Iloperidone
- Lurasidone
- Paliperidone
- Risperidone
- Ziprasidone
- Asenapine
- Olanzapine
- Clozapine
- Quetiapine

## WEIGHT GAIN
- Aripiprazole
- Lurasidone
- Ziprasidone
- Asenapine
- Iloperidone
- Paliperidone
- Risperidone
- Quetiapine
- Olanzapine

## EPS
- Clozapine
- Iloperidone
- Quetiapine
- Aripiprazole
- Asenapine
- Olanzapine
- Ziprasidone
- Paliperidone
- Risperidone

**Best choice**

**Worst choice**

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Long-acting Depot Formulations
Impact on Clinical Decisions

• Oral antipsychotics
  – Unknown compliance may prevent evaluation of medication effectiveness
    • Change medication?
    • Increase dose?
    • Augment?

• Long-acting injectables
  – Known adherence allows for evaluation of medication effectiveness
  – Missed dose can trigger intervention
  – Patient–clinician interaction

Why Use Long-acting Injectable Antipsychotics?

**Advantages**

- Assured medication delivery and continuous antipsychotic coverage
- No need to remember to take medication every day
- Clinician can be immediately notified of nonadherence
- Drug remains in system for weeks after a missed dose
- Reduce relapse frequency and rehospitalization rates
- Avoidance of first-pass metabolism, so there is a better relationship between dose and blood level of drug
- Lower peak plasma level may be associated with reduced side effects
- Peak plasma level occurs less often, so may lead to reduced side effects

**Disadvantages**

- Cost/insurance coverage
- Oral to LAI conversion
- Perceived stigma
- Negative perception/stigma
- Lack of personnel to administer depot

Depot Injections Are Associated With a 50-65% Lower Risk of Rehospitalization Than Their Oral Counterparts

Depots Offer a 30% Relative Reduction in Relapse Risk Compared to Oral Antipsychotics


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FLUPHENAZINE DECANOATE

Commercialized in 1973
# Fluphenazine Decanoate Dosing

<table>
<thead>
<tr>
<th><strong>Initial Dose</strong></th>
<th>12.5–25 mg (0.5–1 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maintenance Dose</strong></td>
<td>Increase in 12.5-mg increments up to 100 mg max</td>
</tr>
<tr>
<td><strong>Dosage Forms</strong></td>
<td>25 mg/mL; 5-mL, multiple-dose vials</td>
</tr>
<tr>
<td><strong>Injection Site</strong></td>
<td>Intramuscular or subcutaneous</td>
</tr>
<tr>
<td><strong>Needle Gauge</strong></td>
<td>21</td>
</tr>
<tr>
<td><strong>Injection Volume</strong></td>
<td>25 mg/mL</td>
</tr>
<tr>
<td><strong>Dosing Schedule</strong></td>
<td>2 weeks</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$68 for 5-mL vial</td>
</tr>
<tr>
<td><strong>Tips and Pearls</strong></td>
<td>✓ Treatment should be suspended if absolute neutrophil count falls below 1000/mm³</td>
</tr>
</tbody>
</table>

Fluphenazine Decanoate Efficacy and Tolerability

• Standard dose (12.5–50 mg/2 weeks) found superior to low dose (1.25–5 mg/2 weeks) in terms of 1-year relapse rate (56% vs. 7%)
  – However, tardive dyskinesia was decreased in the low-dose group

• A Cochrane Review determined that relapse rates were not superior for fluphenazine decanoate vs. placebo in short-term studies

• However, relapse rates were significantly improved over placebo in one longer-term (>1 year) study

HALOPERIDOL DECANOATE

Commercialized in 1986
## Haloperidol Decanoate Dosing

<table>
<thead>
<tr>
<th>Section</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Dose</strong></td>
<td>10–20X the oral dose; 100 mg on day 1 and balance 3–7 days later</td>
</tr>
<tr>
<td><strong>Maintenance Dose</strong></td>
<td>10–15X the oral dose up to 400 mg/4 weeks max</td>
</tr>
<tr>
<td><strong>Dosage Forms</strong></td>
<td>50 and 100 mg/mL, 1- and 5-mL ampules/vials</td>
</tr>
<tr>
<td><strong>Injection Site</strong></td>
<td>Intramuscular</td>
</tr>
<tr>
<td><strong>Needle Gauge</strong></td>
<td>21</td>
</tr>
<tr>
<td><strong>Injection Volume</strong></td>
<td>50 or 100 mg/mL; not to exceed 3 mL</td>
</tr>
<tr>
<td><strong>Dosing Schedule</strong></td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$18 for 50 mg/mL; $34 for 100 mg/mL</td>
</tr>
<tr>
<td><strong>Tips and Pearls</strong></td>
<td>✓ Treatment should be suspended if absolute neutrophil count falls below 1000/mm³</td>
</tr>
</tbody>
</table>

• A Cochrane Review found no differences in global impression, mental state, or side effects between haloperidol depot and oral formulations

• Haloperidol decanoate was found to be equivalent in efficacy and tolerability compared to other first-generation long-acting injectable agents

Risperidone Depot (Risperdal® Consta®)

Commercialized in 2003
## Risperidone Depot Dosing

<table>
<thead>
<tr>
<th><strong>Initial Dose</strong></th>
<th>25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maintenance Dose</strong></td>
<td>25 mg up to 50 mg/2 weeks max</td>
</tr>
<tr>
<td><strong>Dosage Forms</strong></td>
<td>Vial kits: 12.5 mg, 25 mg, 37.5 mg, 50 mg</td>
</tr>
<tr>
<td><strong>Injection Site</strong></td>
<td>Intramuscular</td>
</tr>
<tr>
<td><strong>Needle Gauge</strong></td>
<td>20 or 21</td>
</tr>
<tr>
<td><strong>Injection Volume</strong></td>
<td>2 mL</td>
</tr>
<tr>
<td><strong>Dosing Schedule</strong></td>
<td>2 weeks</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$128 for 12.5 mg; $257 for 25 mg; $385 for 37.5 mg; $514 for 50 mg</td>
</tr>
</tbody>
</table>
| **Tips and Pearls** | ✓ Supplement with oral formulation for 21 days  
 ✓ Must be kept refrigerated  
 ✓ Also indicated for bipolar I maintenance (adjunct) |
Mean PANSS total score at each visit and at study endpoint (all $p<0.001$ vs. baseline)
Relapse Prevention With Risperidone Long-acting Injectable (RLAI) vs. Oral Quetiapine

PALIPERIDONE PALMITATE
(INVEGA® SUSTENNA®)
Commercialized in 2009
# Paliperidone Palmitate Dosing

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Dose</strong></td>
<td>234 mg on day 1; 156 mg on day 8</td>
</tr>
<tr>
<td><strong>Maintenance Dose</strong></td>
<td>117 mg; range: 39–234 mg/month</td>
</tr>
<tr>
<td><strong>Dosage Forms</strong></td>
<td>Injectable suspension: 39 mg, 78 mg, 117 mg, 156 mg, 234 mg</td>
</tr>
<tr>
<td><strong>Injection Site</strong></td>
<td>Initial injections: intramuscular in deltoid</td>
</tr>
<tr>
<td></td>
<td>Subsequent injections may be deltoid or gluteal</td>
</tr>
<tr>
<td><strong>Needle Gauge</strong></td>
<td>22 or 23</td>
</tr>
<tr>
<td><strong>Injection Volume</strong></td>
<td>156 mg/mL; range: 0.25–1.5 mL</td>
</tr>
<tr>
<td><strong>Dosing Schedule</strong></td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$256 for 39 mg; $513 for 78 mg; $771 for 117 mg; $1028 for 156 mg; $1542 for 234 mg</td>
</tr>
<tr>
<td><strong>Tips and Pearls</strong></td>
<td>✓ No refrigeration necessary</td>
</tr>
<tr>
<td></td>
<td>✓ No oral supplement required</td>
</tr>
</tbody>
</table>
Efficacy of Paliperidone Palmitate

Risperidone Compared to Paliperidone

• Similar pharmacology for risperidone and 9-OH risperidone, but very different kinetics between Consta and Sustenna

• Similar efficacy and tolerability

• Both recommend that patient have a test dose of risperidone (for either Consta or Sustenna) or paliperidone (OK for Sustenna) if never received before

OLANZAPINE PAMOATE
(ZYPREXA® RELPREVV®)
Commercialized in 2009
### Olanzapine Pamoate Dosing

<table>
<thead>
<tr>
<th><strong>Initial Dose</strong></th>
<th>210–300 mg/2 weeks (depends on stabilizing oral dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maintenance Dose</strong></td>
<td>210–300 mg/2 weeks (depends on stabilizing oral dose)</td>
</tr>
<tr>
<td><strong>Dosage Forms</strong></td>
<td>Vial kits: 210, 300, 405 mg</td>
</tr>
<tr>
<td><strong>Injection Site</strong></td>
<td>Intramuscular gluteal</td>
</tr>
<tr>
<td><strong>Needle Gauge</strong></td>
<td>19</td>
</tr>
<tr>
<td><strong>Injection Volume</strong></td>
<td>150 mg/mL; range: 1.0–2.7 mL</td>
</tr>
<tr>
<td><strong>Dosing Schedule</strong></td>
<td>2 weeks, 4 weeks</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$540 for 210 mg; $772 for 300 mg; $1042 for 405 mg</td>
</tr>
</tbody>
</table>
| **Tips and Pearls** | ✓ No oral supplementation required  
✓ 3-hr post-injection monitoring required due to risk of post-injection delirium from vascular breach |
Efficacy and Tolerability of Long-acting Injectable Olanzapine

ARIPIPRAZOLE DEPOT (ABILIFY® MAINTENA®)
Commercialized in 2013
## Aripiprazole Depot Dosing

<table>
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<tr>
<th>Category</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Dose</strong></td>
<td>400 mg</td>
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<tr>
<td><strong>Maintenance Dose</strong></td>
<td>300–400 mg/4 weeks</td>
</tr>
<tr>
<td><strong>Dosage Forms</strong></td>
<td>Vial kits: 300 mg, 400 mg</td>
</tr>
<tr>
<td><strong>Injection Site</strong></td>
<td>Intramuscular gluteal</td>
</tr>
<tr>
<td><strong>Needle Gauge</strong></td>
<td>21</td>
</tr>
<tr>
<td><strong>Injection Volume</strong></td>
<td>200 mg/mL; range: 0.8 mL (160 mg)–2 mL (400 mg)</td>
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<tr>
<td><strong>Dosing Schedule</strong></td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$1050 for 300 mg; $1408 for 400 mg</td>
</tr>
<tr>
<td><strong>Tips and Pearls</strong></td>
<td>✓ Supplement with oral formulation for 14 days</td>
</tr>
<tr>
<td></td>
<td>✓ Slower cross-titration from other antipsychotics required</td>
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<tr>
<td></td>
<td>✓ Refrigeration not required</td>
</tr>
</tbody>
</table>

Aripiprazole Depot

• Microsphere formulation with 2-week oral overlap

• Phase 1: Single-blind oral stabilization phase with aripiprazole monotherapy based on meeting all stability criteria for 4 consecutive weeks
  – Mean daily dose prior to randomization: 19.2 mg

Stability criteria used to advance between phases:

a. Outpatient status; PANSS total ≤80, with no score >4 on core psychosis items

b. CGI-Severity ≤4 (moderately ill) and comparably low scores on suicidality scales

Aripiprazole Depot: Relapse Prevention Study

• Phase 2: Aripiprazole IM stabilization phase
  – Transition to depot starting at 400 mg
  – 88.6% remained at the 400-mg dose
  – Among the 710 who entered this phase, 576 (81%) were successfully converted to depot

• Phase 3: Randomization phase: depot vs. placebo
  – Among the 403 randomized patients, 96.3% stayed on the 400-mg dose

• Conclusion: Aripiprazole depot superior to placebo on measures of relapse risk (HR 5.03, 95% CI 3.15-8.02, p<.0001)

• Double-blind side effects that occurred ≥5% and >2X placebo: tremor (5.9%)

Aripiprazole Depot: Relapse Prevention Study

Patient is showing adequate response to oral fluphenazine.
Patient is showing adequate response to oral haloperidol.
Patient is showing adequate response to oral **risperidone**.
Fluphenazine LAI

Patient is showing adequate response to oral paliperidone

Haloperidal LAI

Risperidone LAI

Paliperidone LAI

Aripiprazole LAI

Olanzapine LAI

Patient is showing adequate response to oral **olanzapine**

Patient is showing adequate response to oral **aripiprazole**
Patient requires a faster-acting agent

Olanzapine LAI

Risperidone LAI

Paliperidone LAI

Aripiprazole LAI

Haloperidol LAI

Fluphenazine LAI

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Fluphenazine LAI

Haloperidal LAI

Risperidone LAI

Paliperidone LAI

Aripiprazole LAI

Olanzapine LAI

Fewer injections/month necessary

Cardiometabolic concerns

- Fluphenazine LAI
- Risperidone LAI
- Paliperidone LAI
- Paliperidone LAI
- Aripiprazole LAI
- Olanzapine LAI

Aripiprazole LAI

Haloperidal LAI

Fluphenazine LAI

Risperidone LAI

Paliperidone LAI

Olanzapine LAI

Aripiprazole LAI

Prolactin concerns

Fluphenazine LAI

Haloperidal LAI

Risperidone LAI

Paliperidone LAI

Olanzapine LAI

Aripiprazole LAI

Cost concerns

Summary

• Antipsychotic treatments ameliorate symptoms of schizophrenia for many patients and should be initiated early in the disease course

• Treatment nonadherence greatly increases the risk of poor functional outcomes in schizophrenia; even partial nonadherence increases the risk of relapse

• Minimization of treatment side effects may help maximize treatment adherence; establishing a strong treatment alliance and optimizing treatment for the individual patient can increase adherence

• A growing body of evidence suggests that the full benefits of antipsychotic treatment may require long treatment duration

• Long-acting depot formulations of antipsychotics offer the benefit of better ensuring treatment adherence
Posttest Question 1

A 23-year-old patient with first-episode schizophrenia started antipsychotic treatment 2 weeks ago. He is tolerating the medication well, but his parents are anxious to see an improvement in his symptoms. Approximately which percentage of first-episode patients require at least 8 weeks of antipsychotic treatment before showing a therapeutic response?

1. 5%
2. 7%
3. 9%
4. 11%
Posttest Question 2

Jack is a 37-year-old patient with schizoaffective disorder. He is overweight (BMI = 34) and has a family history of cardiovascular disease. Which of the following antipsychotics may be the best choice for avoiding treatment-induced cardiometabolic side effects?

1. Lurasidone
2. Olanzapine
3. Iloperidone
Posttest Question 3

Paula is a 53-year-old patient with schizophrenia and a long history of treatment nonadherence. She has recently been hospitalized secondary to "forgetting to take" her oral ziprasidone for the past 3 months. Which of the following antipsychotics is available in a long-acting depot formulation?

1. Asenapine
2. Iloperidone
3. Aripiprazole
4. Ziprasidone