PREVENTING RELAPSE TODAY: MAKING A DIFFERENCE FOR A LIFETIME
Learning Objectives

• Recognize the impact of relapse on patient outcomes

• Implement strategies to optimize adherence to treatment for schizophrenia

• Differentiate the pharmacologic and clinical profiles of long-acting injectable antipsychotics
Important Aspects About Schizophrenia
Preventing Relapse Today: Makes a Difference for a Lifetime

• *Irreversible functional decline occurs with each relapse*

• Thus, preventing relapse is a key goal in many international clinical guidelines for schizophrenia

• “Minimizing risk of relapse in a remitted patient is a high priority, given the potential clinical, social, and vocational costs of relapse”

With Every Relapse, Patients are at Risk of Irreversible Lifetime Functional Impairment

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Deteriorating course, brain tissue loss, and treatment resistance with repetitive relapses after the first episode in schizophrenia

Unfortunately, Majority of Patients with Schizophrenia Will Relapse


About 80% of first-episode patients suffered a relapse within 5 years.

Relapse Rates among Patients Experiencing a First Psychotic Episode

- Risk of First Relapse over 24 months: 54%
- Risk of First Relapse over 5 years: 82%
- Risk of Second Relapse over 5 years: 78%
Stopping Medication is the Most Powerful Predictor of First-Episode Relapse

- Relapse risk is $5 \times$ higher after a first-episode patient stops antipsychotic medication
- Predictors of nonadherence in first year:
  - Early adolescent premorbid adjustment ($P<.01$)
  - Worse premorbid cognitive function ($P=.01$)
  - Parkinsonian side effects ($P=.01$)
  - Worse executive function ($P=.02$)

Sample of 104 patients with first-episode schizophrenia who responded to treatment of their index episode, but were at risk for relapse.

Consistent Medication Treatment is Key in Preventing Relapse

• ~ 50% of patients who discontinue/do not take antipsychotics will relapse within 3 to 10 months

• With drug discontinuation, there is no reliable indicator to differentiate the minority who will not relapse, from the majority who will relapse

• What I tell patients and families: within 2 years about 75% relapse when off medications vs 25% when on medications – medications are not perfect, but much better than not taking them

• Risk of relapse is 3 × as high (75/25 = 3) when not taking medication

• Number needed to treat (NNT) is 2 (1/(.75-.25) = 2)

• For every 2 persons taking medication vs not taking medication you avoid 1 relapse event over a 2-year period

Urgent!
Suicide Attempts Increase When Therapy is Interrupted

Data obtained from drug-dispensing and hospital discharge records (Netherlands) for patients with schizophrenia (sample size, 603) in database (N=865,000) with drug interruption and ≥ 30-day gap in treatment. Risk estimates were controlled for differences in age and gender.

When Treatments Fail

- Wrong diagnosis and thus incorrect treatment
- Wrong dose of the right medication
- Inadequate duration of treatment
- “Treatment resistance”
- Think about nonadherence
When Treatments Fail

- Wrong diagnosis and thus incorrect treatment
- Wrong dose of the right medication
- Inadequate duration of treatment
- “Treatment resistance”
- Think about *nonadherence*

Medication adherence is poor across most chronic physical and psychiatric disorders

~ 75% of patients with schizophrenia become nonadherent within 2 years of hospital discharge

Nosé M et al. Psychol Med. 2003;33(7):1149-1160;
Partial Adherence in Schizophrenia Begins Early and Prevalence Increases over Time

Unfortunately, We Overestimate Adherence

- Nonadherence viewed as failure → consistent bias to overestimate adherence/underestimate nonadherence
- We assume lack of adequate response as “treatment-resistance” and lack of efficacy for the antipsychotic for that patient
  - This is a possible explanation for high dosing of antipsychotics, polypharmacy with other antipsychotics, and combination treatment with anticonvulsants
- This is a no-win cycle: adherence is even more of a challenge with complex regimens

- Poor adherence to antipsychotic medication is common and likely exists in your practice
- Poor adherence will drive poor outcomes

## Risk Factors for Nonadherence

(but differs for each patient and can change over time)

<table>
<thead>
<tr>
<th>Patient-related</th>
<th>Environment/Relationship-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Poor insight</td>
<td>• Lack of family/social support</td>
</tr>
<tr>
<td>• Negative attitude</td>
<td>• Problems with therapeutic alliance</td>
</tr>
<tr>
<td>toward medication</td>
<td>• Practical problems (financial, transportation, etc.)</td>
</tr>
<tr>
<td>• Prior nonadherence</td>
<td></td>
</tr>
<tr>
<td>• Substance abuse</td>
<td></td>
</tr>
<tr>
<td>• Cognitive impairment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-related</th>
<th>Societal-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Side effects</td>
<td>• Stigma attached to illness</td>
</tr>
<tr>
<td>• Lack of efficacy/</td>
<td>• Stigma caused by medication side effects</td>
</tr>
<tr>
<td>continued symptoms</td>
<td></td>
</tr>
</tbody>
</table>

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Medication-Related Side Effects and Nonadherence

- Potential drivers
  - Level of distress rather than severity (as perceived by the patient and not by the clinician; eg, what is “mild” or “severe” is in the eye of the beholder)
  - Attribution to the medication (eg, “my teeth itch” can drive poor adherence)
  - Varies from patient to patient

- Most commonly associated with nonadherence
  - Weight gain (patient attitudes vary and may be offset by efficacy after many failures)
  - Sedation
  - Akathisia
  - Sexual dysfunction
  - Parkinsonian symptoms
  - Cognitive problems

- Influencing clinician response to a side effect is objective severity and ultimately safety and risk

Interventions: *First Address Communication Style*

- Basic premise of **MOTIVATIONAL INTERVIEWING**: a patient’s ambivalence to change is normal and that all patients vary in their readiness to change
- Use open-ended questions and reflective listening
- Remember **RULE**
  - **Resist** making too many suggestions
  - **Understand** the patient’s motivation
  - **Listen** with a patient-centered empathic approach
  - **Empower** the patient

Don’t Forget About

• Addressing substance use
• Intensive Case Management
• Assertive Community Treatment
• Vocational rehabilitation
• Cognitive remediation
What’s the next step?

• If the adherence problem is that the patient *will not*, focus intervention on strengthening perceived benefits of medication and minimizing perceived costs/harms – use **Motivational Interviewing**

• If the adherence problem is that the patient *cannot*, then address barriers to adherence
  • Pill boxes in obvious locations
  • Self-monitoring tools
  • Establishment of routines
  • Consider **Long-Acting Injectable Medication**

Clinical Update:
Available and Emerging Long-Acting Injectable Antipsychotics
Potential Advantages of LAI Antipsychotics

- Reduces dosage deviations
- Eliminates guessing about adherence status
- Helps disentangle reasons for poor response to medication: can focus on psychosocial issues/stressors, or possibility of substance use, etc., as a cause for exacerbation of illness or relapse
- Eliminates need for the patient to remember to take a daily pill
- Enables prescribers to avoid first-pass metabolism; therefore, a better relationship between dose and blood level exists
- Results in predictable and stable plasma levels
- Eliminates abrupt loss of efficacy if dose missed
- Many patients prefer them, especially if already receiving them

LAI antipsychotics can address the guess-work about adherence status and patients often prefer them, provided that they are offered this as a choice

LAI = long-acting injectable
Potential Obstacles of LAI Antipsychotics

- **Anti-shot sentiment/stigma**
  - Most clinicians report using LAI atypical antipsychotics in < 10% of patients
  - Psychiatrists have not offered an LAI antipsychotic to nearly two-thirds of their patients
- Lack of infrastructure in outpatient settings
- Need to refrigerate, store, reconstitute, etc.
- Overburdened public agencies
- Frequency of injections and consequent inconvenience for staff and patients
- Need to take concomitant medications orally
- Acquisition cost

Real-World Studies Favor Use of LAI Antipsychotics

As study design shifts toward real-world populations, LAI formulations display significant advantages.

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As study design shifts toward real-world populations, LAI formulations display significant advantages.

In RCTs, patients may be more motivated and more likely to adhere to the oral medication comparator than in the “real-world”.

Is There a Case For *Earlier* Use of LAI Antipsychotics?

- Potentially decrease the percentage of time spent experiencing psychotic symptoms
  - In the first 2 years, experiencing psychotic symptoms is the strongest predictor of long-term symptoms and disability

- Potentially decrease number of psychotic episodes
  - Patients experience a decrease in treatment response with subsequent exacerbations
  - Neuropathological brain changes often progress with subsequent clinical episodes

- LAI antipsychotics allow for swift identification of overt nonadherence and eliminate covert nonadherence

- Should we Rx LAI antipsychotics at the time of the first admission?

LAI Antipsychotics Lower the Risk of Rehospitalization After First Hospitalization for Schizophrenia

Any depot injection compared with equivalent oral formulation

<table>
<thead>
<tr>
<th>Rehospitalization</th>
<th>Adjusted Hazard Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.36</td>
<td>0.17-0.75</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Patients Are Willing to Accept LAI Antipsychotic Therapy When Properly Informed

• In a survey of patients with > 3 months of LAI antipsychotic experience:
  
  • Injectable antipsychotics were the preferred formulation
  
  • 70% of patients felt better supported in their illness by virtue of regular contact with the doctor or nurse who administered their injection
LAI Options in the United States

- First-generation antipsychotics (all are in sesame seed oil)
  - Haloperidol decanoate
  - Fluphenazine decanoate

- Second-generation antipsychotics (all IM formulations are water-based)
  - Risperidone- or paliperidone-containing formulations
    - Risperidone microspheres
    - Risperidone subcutaneous LAI
    - Paliperidone palmitate monthly
    - Paliperidone palmitate every 3 months
  - Aripiprazole-containing formulations
    - Aripiprazole monohydrate
    - Aripiprazole lauroxil
  - Olanzapine pamoate
FGA LAIs in More Detail

• **Haloperidol decanoate**
  - Approved for use in the USA in 1986; among inpatients in New York state, the average dose is 135 mg administered monthly (maximum approved dose is 450 mg/4 weeks)
  - Available as 50 and 100 mg/ml in 1- and 5-ml ampules/vials, 21G needles used; do not exceed 3 ml injection volume
  - No oral supplementation; no refrigeration needed

• **Fluphenazine decanoate** (IM or sc)
  - Fluphenazine enanthate was approved for marketing in 1967 and in 1972, fluphenazine decanoate replaced it as it has a longer half-life; among inpatients in New York state, the average dose is ~38 mg administered every 2 weeks (maximum approved dose is 100 mg/2 weeks)
  - Available as 25 mg/ml 5-ml vials, 21G needles used
  - No oral supplementation; no refrigeration needed
What’s Different Among the Risperidone- or Paliperidone-Containing LAIs?

<table>
<thead>
<tr>
<th></th>
<th>Risperidone Subcutaneous</th>
<th>Risperidone Microspheres</th>
<th>Paliperidone Palmitate Monthly</th>
<th>Paliperidone Palmitate Every 3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year Approved</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Active Moiety</strong></td>
<td>Risperidone and paliperidone</td>
<td>Risperidone and paliperidone</td>
<td>Paliperidone</td>
<td>Paliperidone</td>
</tr>
<tr>
<td><strong>Approved Indications (all adult)</strong></td>
<td>Schizophrenia</td>
<td>Schizophrenia; bipolar I disorder maintenance treatment (monotherapy or adjunctive to lithium or valproate)</td>
<td>Schizophrenia; schizoaffective disorder (monotherapy or adjunctive to mood stabilizers or antidepressants)</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td><strong>Dosage Forms/Strengths</strong></td>
<td>Syringe kits: 90 mg, 120 mg</td>
<td>Vial kits: 12.5 mg, 25 mg, 37.5 mg, 50 mg</td>
<td>Injectable suspension: 39 mg, 78 mg, 117 mg, 156 mg, 234 mg</td>
<td>Injectable suspension: 273 mg, 410 mg, 546 mg, 819 mg</td>
</tr>
<tr>
<td><strong>Requires Adding Diluent/Liquid</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Injection Type</strong></td>
<td>Subcutaneous</td>
<td>Intramuscular</td>
<td>Intramuscular</td>
<td>Intramuscular</td>
</tr>
<tr>
<td><strong>Injection Sites</strong></td>
<td>Abdomen</td>
<td>Deltoid or gluteal muscle</td>
<td>Deltoid or gluteal muscle</td>
<td>Deltoid or gluteal muscle</td>
</tr>
<tr>
<td><strong>Needle Gauge and Length</strong></td>
<td>18 G and 5/8-inch</td>
<td>20 G and 2-inch, 21 G and 1-inch</td>
<td>22 G and 1.5-inch, 23 G and 1-inch</td>
<td>22 G and 1 or 1.5-inch</td>
</tr>
<tr>
<td><strong>Injection Volume</strong></td>
<td>0.6 mL (90 mg), 0.8 mL (120 mg)</td>
<td>Approximately 2 mL</td>
<td>156 mg/mL; range 0.25 mL (39 mg) to 1.5 mL (234 mg)</td>
<td>312 mg/mL; range 0.9 mL (273 mg) to 2.6 mL (819 mg)</td>
</tr>
<tr>
<td><strong>Injection Interval</strong></td>
<td>4 weeks</td>
<td>2 weeks</td>
<td>4 weeks</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

What’s Different Among the Risperidone- or Paliperidone-Containing LAIs? (cont’d)

<table>
<thead>
<tr>
<th></th>
<th>Risperidone Subcutaneous</th>
<th>Risperidone Microspheres</th>
<th>Paliperidone Palmitate Monthly</th>
<th>Paliperidone Palmitate Every 3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand Name (US)</strong></td>
<td>Perseris™</td>
<td>Risperdal Consta®</td>
<td>Invega® Sustenna®</td>
<td>Invega Trinza®</td>
</tr>
<tr>
<td><strong>Starting Dose</strong></td>
<td>90 or 120 mg</td>
<td>25 mg</td>
<td>234 mg day 1 and 156 mg day 8 (deltoid)</td>
<td>After treatment with 1-month paliperidone palmitate for at least 4 months: 273 mg, 410 mg, 546 mg, 819 mg (3.5 × the last dose of the once monthly formulation)</td>
</tr>
<tr>
<td><strong>Maintenance Dose</strong></td>
<td>90 or 120 mg</td>
<td>25 mg, maximum 50 mg/2 weeks</td>
<td>117 mg, range 39–234 mg/4 weeks</td>
<td>Same as above</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>9–11 days</td>
<td>3–6 days</td>
<td>25–49 days</td>
<td>84–95 days (deltoid), 118–139 days (gluteal)</td>
</tr>
<tr>
<td><strong>Oral Supplementation?</strong></td>
<td>No</td>
<td>21 days after the initial injection and after any change in dose</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Stored Refrigerated?</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

## What’s Different Among the Long-Acting IM Aripiprazole-Containing Formulations?

<table>
<thead>
<tr>
<th></th>
<th>Aripiprazole Monohydrate</th>
<th>Aripiprazole Lauroxil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand name (US)</strong></td>
<td>Abilify Maintena®</td>
<td>Aristada® (and Aristada Initio®)</td>
</tr>
<tr>
<td><strong>Year Approved</strong></td>
<td>2013</td>
<td>2015 (2018)</td>
</tr>
<tr>
<td><strong>Other Indications</strong></td>
<td>Bipolar disorder</td>
<td>No</td>
</tr>
<tr>
<td><strong>Injection Sites</strong></td>
<td>Deltoid or gluteal</td>
<td>Deltoid (441 mg dose and NCD 675 mg dose*) or gluteal (all doses)</td>
</tr>
<tr>
<td><strong>Needle Gauge</strong></td>
<td>21 G, 22 G, or 23 G</td>
<td>20 G or 21 G</td>
</tr>
<tr>
<td><strong>Injection Volume</strong></td>
<td>2 mL (400 mg)</td>
<td>1.6 to 3.9 mL</td>
</tr>
<tr>
<td><strong>Injection Interval</strong></td>
<td>Every 4 weeks</td>
<td>Every 4 weeks (all doses), every 6 weeks (882 mg), or every 2 months (1064 mg)</td>
</tr>
<tr>
<td><strong>Starting Dose</strong></td>
<td>400 mg</td>
<td>441, 662, 882, or 1064 mg</td>
</tr>
<tr>
<td><strong>Maintenance Dose</strong></td>
<td>300 or 400 mg (adjust for CYP2D6 or CYP3A4 inhibitors; can’t give with CYP3A4 inducers)</td>
<td>441, 662, 882, or 1064 mg (adjust for CYP2D6 or CYP3A4 modulators)</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>29.9 days (300 mg), 46.5 days (400 mg)</td>
<td>53.9–57.2 days; 15–18 days (NCD formulation)</td>
</tr>
<tr>
<td><strong>Oral Supplementation</strong></td>
<td>Yes (14 days)</td>
<td>1 day with NCD 675 mg*, otherwise 21 days</td>
</tr>
<tr>
<td><strong>Reconstitution</strong></td>
<td>Yes, but dual-chamber syringe available</td>
<td>No</td>
</tr>
<tr>
<td><strong>Refrigeration</strong></td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*NCD = a single dose of 30 mg of oral aripiprazole and initial injection of nano-crystal formulation (Aristada Initio®) can substitute for 21-day oral aripiprazole supplementation.

What About Olanzapine pamoate?

- OLAI is a crystalline salt of olanzapine and pamoic acid in water, approved in 2009 for schizophrenia; no other approved indications

- Efficacy was established in 2 double-blind, randomized clinical trials of OLAI for the treatment of acute schizophrenia and for the maintenance of response

- Therapeutic OLAI dosages are 150 mg every 2 weeks, 210 mg every 2 weeks, 300 mg every 2 weeks or every 4 weeks, and 405 mg every 4 weeks

- Gluteal injection only, 19G needle, 1–2.7 mL volume, reconstitution required, stored at room temperature, no oral supplementation but higher dose at start

- OLAI has essentially the same general tolerability as that of oral olanzapine; however, with the depot there is the additional risk of a post-injection delirium sedation syndrome occurring at a rate of 0.07% of injections, requiring a risk-management plan that includes observing the patient for 3 hours after each injection

OLAI = olanzapine pamoate.

How Do They All Compare?

Prevention of relapse or recurrence as quantified using number needed to treat versus placebo (versus 45 mg/4 weeks for olanzapine pamoate), data from US registration trials.
A Closer Look at Efficacy in Schizoaffective Disorder

Table 2. Paliperidone palmitate once-monthly for schizoaffective disorder: effect sizes – hazard ratio and number needed to treat.

<table>
<thead>
<tr>
<th>Participant group</th>
<th>Placebo</th>
<th>Paliperidone palmitate</th>
<th>NR (95% CI)</th>
<th>NNT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>N</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>All participants</td>
<td>57</td>
<td>170</td>
<td>33.5</td>
<td>25</td>
</tr>
<tr>
<td>Monotherapy participants</td>
<td>24</td>
<td>73</td>
<td>32.9</td>
<td>9</td>
</tr>
<tr>
<td>Adjunctive therapy participants</td>
<td>33</td>
<td>97</td>
<td>34.0</td>
<td>16</td>
</tr>
<tr>
<td>Adjunctive therapy participants, antidepressants</td>
<td>15</td>
<td>40</td>
<td>37.5</td>
<td>7</td>
</tr>
<tr>
<td>Adjunctive therapy participants, mood stabilizers</td>
<td>18</td>
<td>57</td>
<td>31.6</td>
<td>9</td>
</tr>
</tbody>
</table>

b. Relapse by type of symptom

<table>
<thead>
<tr>
<th>Type of relapse</th>
<th>Placebo (N = 170)</th>
<th>Paliperidone palmitate (N = 164)</th>
<th>HR (95% CI)</th>
<th>NNT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Psychotic symptoms</td>
<td>53</td>
<td>31.2</td>
<td>21</td>
<td>12.8</td>
</tr>
<tr>
<td>Mood symptoms</td>
<td>48</td>
<td>28.2</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Mood symptoms, depression</td>
<td>23</td>
<td>13.5</td>
<td>8</td>
<td>4.9</td>
</tr>
<tr>
<td>Mood symptoms, mania</td>
<td>16</td>
<td>9.4</td>
<td>5</td>
<td>3.0</td>
</tr>
<tr>
<td>Mood symptoms, mixed</td>
<td>9</td>
<td>5.3</td>
<td>5</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Data from Table 2 in [43], with NNT values calculated by the author.

HR: hazard ratio; NNT: number needed to treat; ns: not significant (95% CI for the NNT includes infinity).
A Closer Look at Efficacy in Bipolar Disorder

<table>
<thead>
<tr>
<th>Type of recurrence</th>
<th>Placebo (N = 133)</th>
<th>Aripiprazole monohydrate (N = 132)</th>
<th>NNT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Any mood episode</td>
<td>68</td>
<td>51.1</td>
<td>35</td>
</tr>
<tr>
<td>Mania</td>
<td>40</td>
<td>30.1</td>
<td>12</td>
</tr>
<tr>
<td>Depression</td>
<td>19</td>
<td>14.3</td>
<td>20</td>
</tr>
<tr>
<td>Mixed</td>
<td>9</td>
<td>6.8</td>
<td>2</td>
</tr>
</tbody>
</table>

Data from Figure 3 in [45], with NNT values calculated by the author.

A negative value for NNT results when the favorable outcome was observed more frequently with placebo.

NNT: number needed to treat; ns: not significant (95% CI for the NNT includes infinity).
Late Stage of Clinical Development

• BB-0817 – Phase 3
  – 6-month risperidone polyurethane implant

• Paliperidone palmitate 6-month – Phase 3

• Risperidone in situ microparticles – Phase 3
  – Risperidone once-monthly intramuscular formulation; does not require oral supplementation
  – Biodegradation of this risperidone formulation occurs slowly, providing a sustained and controlled release of medication for up to 1 month

• TV-46000 – Phase 3
  – Risperidone extended-release injectable suspension for subcutaneous use as maintenance treatment in adult patients with schizophrenia
How to Choose?
Amenities of Care

• How often are the injections administered?
• What is the needle gauge?
• What is the injection volume?
• Is there a choice of injection site?
• Does this product require reconstitution?
• Is oral supplementation required?
• Does this product need refrigeration?
• Are there any special requirements for observation?
• Are there any important drug-drug interactions, and can they be remedied?
• Missed doses: What is the “grace period?”
• Is reimbursement an issue if used “off-label”?
How to Choose a Long-Acting Injection

1. Is the patient demonstrating adequate efficacy and tolerability on oral fluphenazine, haloperidol, risperidone, paliperidone, olanzapine, or aripiprazole?

   - Offer and switch to the corresponding LAI formulation
   - “How would you like to take your medication once a month”?
   - For patients receiving oral risperidone, consider paliperidone palmitate for convenience
     - No requirement for oral upon initiation
     - Less frequent injections
     - Supplied in prefilled syringes
     - Smaller needle bore, lower injection volume
     - No requirement for refrigeration

How to Choose a Long-Acting Injection (cont’d)

1. Is the patient demonstrating adequate efficacy and tolerability on oral fluphenazine, haloperidol, risperidone, paliperidone, olanzapine, or aripiprazole? (continued)

• For patients receiving oral fluphenazine or haloperidol, concomitant oral anticholinergics for the management of motoric adverse effects are problematic – especially because anticholinergic agents can interfere with memory and other cognitive functions.
  • Exposure to benztropine or other anticholinergics can also increase the risk to develop tardive dyskinesia, and can make existing tardive dyskinesia worse.

How to Choose a Long-Acting Injection (cont’d)

1. Is the patient demonstrating adequate efficacy and tolerability on oral fluphenazine, haloperidol, risperidone, paliperidone, olanzapine, or aripiprazole? (continued)

• For patients receiving oral olanzapine, olanzapine pamoate will require close monitoring

• For patients receiving oral aripiprazole there are two competing formulations of LAI aripiprazole in the US – aripiprazole monohydrate and aripiprazole lauroxil – they have differing doses and injection intervals, as well as initiation strategies

2. Is the patient being treated acutely?

- Consider LAI antipsychotics that do not require oral supplementation and where the clinical trials have demonstrated acute efficacy – paliperidone palmitate or olanzapine pamoate, and possibly aripiprazole lauroxil/NCD

- A new subcutaneous long-acting injectable formulation of risperidone is also now available – administered monthly with no oral supplementation required – and efficacy established with acute use
  - Dosage equivalents are 3 mg/d oral = 90 mg sc, 4 mg/d oral = 120 mg sc

3. Are weight gain and metabolic adverse effects a concern for this individual patient?

- Consider an aripiprazole LAI, paliperidone palmitate, risperidone subcutaneous long-acting injectable, and risperidone microspheres among the second-generation LAI antipsychotics; avoid olanzapine pamoate
- Can possibly consider the first-generation LAI antipsychotics as well

How to Choose a Long-Acting Injection (cont’d)

4. Are prolactin-related adverse effects a clinical concern for this individual patient?

• Consider an aripiprazole LAI
• Avoid paliperidone palmitate, risperidone microspheres, risperidone subcutaneous long-acting injectable, or the first-generation LAI antipsychotics

5. Is acquisition cost the primary concern?

- The first-generation LAI antipsychotics may be the only option available but using concomitant oral anticholinergics for the management of motoric adverse effects add complexity and can interfere with memory; overall health care costs are not always lower!
- There are sometimes shortages of first-generation LAI antipsychotics
- *Patient-assistance programs* should be considered for out-patients who are not covered to receive second-generation LAI options.

6. What about bipolar disorder?

- Approval by the FDA is currently limited to risperidone microspheres (monotherapy or as adjunctive therapy to lithium or valproate) and aripiprazole monohydrate (monotherapy).
- Observation: oral olanzapine is also approved for bipolar maintenance.

- What about the use of olanzapine pamoate, risperidone subcutaneous, paliperidone palmitate (paliperidone is the active metabolite of risperidone), or aripiprazole lauroxil for the maintenance treatment of bipolar disorder?
  - Logic tells us that these would likely be effective, but these are off-label uses, and may not be reimbursable by some health plans.

Practical Take-Aways
Practical Take-Aways

- Poor adherence to antipsychotic medication is common and likely exists in your practice.
- Poor adherence will drive poor outcomes.
- LAI antipsychotics can address the guess-work about adherence status and patients often prefer them, provided that they are offered this as a choice.
Posttest Question

How common is nonadherence to oral antipsychotic medication in persons with schizophrenia at 1 year post-discharge from an inpatient stay?

1. 25%
2. 50%
3. 75%
4. About 90%
Posttest Question

How common is nonadherence to oral antipsychotic medication in persons with schizophrenia at 2 years post-discharge from an inpatient stay?

1. 25%
2. 50%
3. 75%
4. About 90%
Motivational Interviewing to promote medication adherence involves:

1. Using a “no-nonsense” approach to advocate for medication treatment adherence by listing all the established facts supporting the need to take medication daily
2. Taking a psychodynamic point of view to explore the underlying emotional conflicts surrounding medication adherence
3. Giving cognitive-behavioral therapy type homework for patients to help them reframe their attitude towards medication adherence
4. Using open-ended questions and reflective listening to understand the patient’s motivation regarding treatment and ultimately empower the patient
Long-acting injectable antipsychotics are:

1. All based in sesame seed oil and thus painful to administer
2. All injected in either the deltoid or gluteal muscle
3. All require additional oral antipsychotic medication upon initiation
4. All relatively underutilized