Strategies to Improve Treatment Adherence in Schizophrenia: A Focus on Long-Acting Injectable Antipsychotics

Presented by: Richard Jackson, MD
Associated Clinical Professor of Psychiatry
Wayne State University, School of Medicine
Detroit, Michigan

Faculty Disclosure

- **Dr. Jackson:** Consultant—Alkermes, Sunovion; Clinical Research—Lundbeck, Neos, Neurocrine, Otsuka Pharmaceuticals, Takeda, Teva; Speakers’ Bureau—Alkermes, Sunovion

- **Dr. Kane:** Consultant or Received Honoraria—Alkermes, Allergan, Eli Lilly, Forum, Genentech, Lundbeck, Intracelluar Therapies, Janssen, Johnson & Johnson, Neurocrine, Otsuka, Pierre Fabre, Reviva, Roche, Sunovion, Takeda, Teva; Grant Support—Otsuka, Janssen; Stock/Shareholder—MedAvante, Inc., Vanguard Research Group, LB Pharmaceuticals, Inc.
Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

• This activity has been independently reviewed for balance.

Learning Objectives

• Apply routine assessment strategies to identify and monitor adherence to antipsychotic therapy

• Explain the latest clinical data on long-acting injectable (LAI) antipsychotics, including safety, efficacy, tolerance, and implications on adherence

• Translate to practice the latest evidence with respect to treatment selection and identification of patient populations that would most benefit from LAIs

• Implement a shared-decision making approach to management that addresses patient preferences, concerns, and unique needs

Overview

• Assessment and Monitoring of Adherence

• LAIs: Efficacy and Safety

• LAIs: Patient Selection

• Shared Decision Making

• Summary and Recommendations
A Basic Fact

- Difficulty with adhering to chronic medical treatments is a human characteristic
- It isn’t just people with psychosis, it is most people
- Despite your excellent relationships with your patients, your patients are human so they have adherence problems like everyone else
- Help should be the norm, not just given to select people


Non-adherence in the Treatment of Chronic Disorders

- In developed countries, about 50% of patients with chronic diseases adhere to long-term therapy
- 33% to 69% of all medication-related hospital admissions in the United States are due to poor medication adherence
- One-third of all prescriptions are never filled
- > 50% of filled prescriptions are associated with incorrect administration (not taken as prescribed)

Antipsychotic Non-adherence in Adult Outpatients with Schizophrenia – Point Prevalence

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-adherence</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balouch-Kleinman V, et al. Schizophr Res. 2011;133(3):176-181</td>
<td>29.8%</td>
<td>Patients/relatives</td>
</tr>
</tbody>
</table>
Poor Antipsychotic Adherence over Time in Schizophrenia

Analysis of 34,128 VA patients with schizophrenia receiving regular outpatient mental healthcare. Poor antipsychotic adherence defined as annual MPR < .80. 18% had poor antipsychotic adherence in all 4 years.

Detection of Antipsychotic Non-adherence

Criterion standard (n = 19) is MEMS MPR ≤ .80 over 12 weeks, compared with patient self-report, physician impressions, and unannounced in home pill counts. Patient and physician reports correlated with BPRS.

Potential Clinical Consequences of Undetected Medication Non-adherence

- Unidentified non-adherence may lead to unnecessary
  - Antipsychotic medication changes
  - Dosage increases
  - Concomitant antipsychotic medications
  - Labeling of patients as “treatment resistant”

- Identify patient adherence patterns then find the best treatment option
Characteristics of Selected First- and Second-Generation LAIs: United States

| Antipsychotic | Route | Starting Dose | Maintenance Dose | Time to Peak | Steady State | Parenteral Administration
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluphenazine decanoate Oil</td>
<td>Varies</td>
<td>25 and 100 mg/mL ampoules/vials/syringes</td>
<td>Varies, 12.5 mg</td>
<td>2–4 days</td>
<td>2–3 months</td>
<td>No</td>
</tr>
<tr>
<td>Haloperidol decanoate Oil</td>
<td>4</td>
<td>50 and 100 mg/mL ampoules</td>
<td>Varies, 300 mg</td>
<td>6–7 days</td>
<td>2–3 months</td>
<td>No</td>
</tr>
<tr>
<td>Risperidone LAI Water</td>
<td>25, 37.5, 50 mg vial kits</td>
<td>25 mg</td>
<td>25 mg</td>
<td>3 weeks</td>
<td>4–6 weeks</td>
<td>1.5–2 months</td>
</tr>
<tr>
<td>Olanzapine pamoate Water</td>
<td>2 or 4</td>
<td>210, 300, 405 mg vial kits</td>
<td>Varies, up to 300 mg/2 weeks</td>
<td>4 days</td>
<td>3 months</td>
<td>At least 3 hours</td>
</tr>
<tr>
<td>Paliperidone palmitate Water</td>
<td>Monthly</td>
<td>78 mg</td>
<td>117 mg</td>
<td>156 mg</td>
<td>234 mg</td>
<td>pre-filled syringes</td>
</tr>
<tr>
<td>Paliperidone palmitate-3 month formulation Water</td>
<td>Monthly</td>
<td>Depending on 1-month dose</td>
<td>75 mg</td>
<td>(25–150 mg)</td>
<td>13 days</td>
<td>7–11 months</td>
</tr>
<tr>
<td>Aripiprazole LAI Water</td>
<td>Monthly</td>
<td>300, 400 mg vial kits and dual chamber syringe</td>
<td>400 mg</td>
<td>2 weeks</td>
<td>5–7 days</td>
<td>4–8 months</td>
</tr>
<tr>
<td>Aripiprazole lauroxil Water</td>
<td>Monthly</td>
<td>441 mg</td>
<td>662 mg</td>
<td>882 mg</td>
<td>819 mg</td>
<td>pre-filled syringes</td>
</tr>
</tbody>
</table>

Most Common Adverse Effects with SGA-LAIs

- **RLAI**: The most common adverse reactions in clinical trials in patients with schizophrenia (≥5%) were headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increase, pain in extremities and dry mouth. The most common adverse reactions in clinical trials in patients with bipolar disorder were weight increase (≥3% in monotherapy trial), and tremor and parkinsonism (≥10% in adjunctive therapy trial).

- **PLAI**: The most common adverse reactions (incidence ≥5% and occurring at least twice as often as placebo) were injection-site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder.

- **OLAI**: The most common adverse reactions (≥5% in at least 1 of the treatment groups and greater than placebo) associated with OLAI treatment included: headache, sedation, weight gain, cough, dyspepsia, nausea, somnolence, dry mouth, nasopharyngitis, increased appetite, and vomiting.

- **ALAI**: The most common treatment-emergent adverse reactions (occurring in ≥5% of ALAI patients and greater than placebo) were insomnia (10.0 vs 9.0%), tremor (5.9 vs 1.5%), and headache (5.9 vs 5.2%). Akathisia occurred in 6.3% of patients receiving ALAI in the stabilization phase and 5.6% of ALAI patients in the double-blind treatment phase (vs 6.0% for placebo-treated patients).


LAI Antipsychotics vs Placebo
**13-Week Acute RCT Paliperidone Palmitate:**

**PANSS Total Scores – Efficacy with the First Dose**

- Placebo (n = 160)
- PP 25 mg (n = 155)
- PP 100 mg (n = 161)
- PP 150 mg (n = 160)

*PP vs Placebo: All unadjusted P-values < .05 as early as Day 8 for 25 and 150 mg groups, and as early as Day 22 for 100 mg eq.*

*PANSS = Positive and Negative Syndrome Scale; PP = paliperidone palmitate; RCT = randomized controlled trial.


**Aripiprazole Once-Monthly vs Placebo in Acute Schizophrenia:**

**Primary Endpoint – PANSS Total**

- Placebo (n = 196)
- Aripiprazole lauroxil 441 mg (n = 196)
- Aripiprazole lauroxil 882 mg (n = 204)

*P-values are for aripiprazole lauroxil 441-mg and aripiprazole lauroxil 882-mg dose group vs placebo.

**Aripiprazole Lauroxil vs Placebo in Acute Schizophrenia:**

**PANSS Total Change**

- Placebo (n = 196)
- Aripiprazole lauroxil 441 mg (n = 196)
- Aripiprazole lauroxil 882 mg (n = 204)

*P-values are for aripiprazole lauroxil 441-mg and aripiprazole lauroxil 882-mg dose group vs placebo.

Prevention of Relapse with Selected LAI Antipsychotics vs Placebo
(vs 45 mg/4 weeks olanzapine pamoate)


Number Needed to Treat
Paliperidone palmitate LAI flexibly dosed 39–156 mg/4 weeks
Olanzapine pamoate LAI 150 mg/2 weeks
Olanzapine pamoate LAI 300 mg/2 weeks
Olanzapine pamoate LAI 405 mg/4 weeks
Aripiprazole-OM 400 mg/4 weeks

10
10
5
7
4
4
5
4

Treatment and Dosage

Paliperidone Palmitate 3-Monthly vs Placebo


Estimated Proportion of Patients without Relapse

P < .001

Time Since Randomization (days)

3-Month formulation of paliperidone palmitate (n = 160)
Placebo (n = 145)

LAI Antipsychotics vs Oral Antipsychotics
No Differences in Study-Defined Relapse/All-Cause Discontinuation between LAIs and Oral Antipsychotics

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Studies</th>
<th>Total</th>
<th>RR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>Fluphenazine</td>
<td>8</td>
<td>0.79</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>1</td>
<td>0.99</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Chlorpromazine</td>
<td>2</td>
<td>1.50</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Zuclopenthixol</td>
<td>1</td>
<td>0.79</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>21</td>
<td>0.93</td>
<td>0.35</td>
</tr>
</tbody>
</table>

| All-Cause Discontinuation | Fluphenazine | 7     | 1.00 | 0.98    |
|                          | Haloperidol  | 1     | 0.79 | 0.52    |
|                          | Olanzapine LAI | 2   | 1.24 | 0.25    |
|                          | Risperidone LAI | 9   | 1.00 | 0.98    |
|                          | Zuclopenthixol | 1    | 0.51 | 0.44    |
|                          | Total       | 20    | 1.03 | 0.65    |

No difference in adherence between pooled LAIs and oral APs (measured in 10 studies)

LAI Antipsychotics Not Different Regarding Adverse Event Dropout Rate in Long-Term Studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>M-H, Risk Ratio, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arango 2005</td>
<td>0</td>
<td>26</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Barnes 1983</td>
<td>1</td>
<td>19</td>
<td>0.89 (0.06, 13.23)</td>
</tr>
<tr>
<td>Del Guidice 1975</td>
<td>0</td>
<td>27</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Falloon 1978</td>
<td>0</td>
<td>20</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Gaebel 2010</td>
<td>8</td>
<td>355</td>
<td>0.80 (0.32, 2.00)</td>
</tr>
<tr>
<td>Hogarty 1979</td>
<td>5</td>
<td>55</td>
<td>10.02 (0.57, 176.70)</td>
</tr>
<tr>
<td>Potapov 2008</td>
<td>3</td>
<td>20</td>
<td>1.00 (0.23, 4.37)</td>
</tr>
<tr>
<td>Rifkin 1977</td>
<td>8</td>
<td>23</td>
<td>4.87 (1.14, 20.72)</td>
</tr>
<tr>
<td>Schooler 1979</td>
<td>10</td>
<td>143</td>
<td>1.03 (0.44, 2.39)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>688</td>
<td>692</td>
<td>1.34 (0.70, 2.58)</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.17; Chi² = 6.84, df = 5 (P = .23); i² = 27%
Test for overall effect: Z = 0.88 (P = .38)

M-H = Mantel-Haenszel


PROSIPAL: Time to Relapse

- **Time to relapse** was significantly longer in the PP group compared to the oral AP group (HR = 1.5, 95% CI [1.1; 2.2])
- The 85th percentile for time to relapse was 469 days in the PP group vs 249 days in the oral AP group
- This represents a 29.4% RR reduction in favor of PP

Paliperidone Palmitate vs Oral Antipsychotics in Schizophrenia Patients with History of Incarceration and Substance Abuse

Kaplan-Meier Curves of (A) Estimated Time to First Treatment Failure and (B) Estimated Time to First Psychiatric Hospitalization or Arrest/Incarceration for PP vs Oral Antipsychotics

<table>
<thead>
<tr>
<th>Oral Antipsychotic (n = 218)</th>
<th>PP (n = 226)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Participants at Risk</td>
<td>92</td>
</tr>
<tr>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>0.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Log-Rank P Value: .011
HR (Oral Antipsychotic vs PP): 1.43
95% CI of HR: (1.09, 1.88)

33% vs 5% Relapse in 86 First-Episode Schizophrenia Patients Randomized to Oral Risperidone vs Risperidone LAI

Excellent levels of adherence: RLAI = 95% vs Oral Risperidone = 33%.

In Mirror Image Studies, LAIs Reduce Risk of Hospitalization Compared with Oral Antipsychotics

LAs showed strong superiority over oral antipsychotics.
Fewer Hospitalizations and Bed Days When Switching from RLAI to PLAI Than from RLAI to Oral Antipsychotics

Propensity Score Matched Survival Analysis

LAIs vs Oral Antipsychotics: Cohort Studies
Hospitalization Risk (N = 29, n = 32,274)

Total N = 29, n = 32,796; follow-up = 18.9 ± 10.2 months.
OAP = oral antipsychotic.

LAIs vs Oral Antipsychotics: Cohort Studies
All-Cause Discontinuation (N = 11, n = 22,715)

Total N = 29, n = 32,796; follow-up = 18.9 ± 10.2 months.
LAI Antipsychotics vs LAI Antipsychotics

Acute 13-Week Efficacy of Paliperidone Palmitate Comparable to Risperidone LAI

Mean Doses:
- PP approx. 109 mg monthly
- RLAI approx. 31 mg q 2 weeks

PANSS Change from Baseline (LS Mean)

<table>
<thead>
<tr>
<th>Day</th>
<th>PP (n = 389)</th>
<th>RLAI (n = 376)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>-22.6 ± 15.9</td>
<td>-26.9 ± 15.6</td>
</tr>
<tr>
<td>15</td>
<td>-23.6 ± 15.6</td>
<td>-26.9 ± 15.6</td>
</tr>
<tr>
<td>22</td>
<td>-23.6 ± 15.6</td>
<td>-26.9 ± 15.6</td>
</tr>
<tr>
<td>36</td>
<td>-23.6 ± 15.6</td>
<td>-26.9 ± 15.6</td>
</tr>
<tr>
<td>64</td>
<td>-23.6 ± 15.6</td>
<td>-26.9 ± 15.6</td>
</tr>
</tbody>
</table>

Non-inferiority Trial vs Risperidone LAI
Change in PANSS Total Scores (13 Weeks)

In a Chinese schizophrenia patient population:
- Non-inferiority of PP to oral risperidone (RLAI arm) was observed as early as day 8 (the first assessment time point)
- Non-inferiority of PP to RLAI was demonstrated at every subsequent time point assessed

Least-squares mean difference in PANSS total score: -2.3 points (95% CI: -5.30 to 0.63) between paliperidone palmitate and risperidone LAI
Paliperidone Palmitate vs Haloperidol LAI: Time to Efficacy Failure

Efficacy failure (independent committee): psychiatric hospitalization; need for crisis stabilization; meaningful increase in outpatient visits; inability to discontinue OAPs within 8 weeks due to insufficient benefit; discontinuation of LAI due to insufficient benefit; ongoing or repeated need for OAPs beyond 8 weeks.


Risperidone LAI vs FGA-LAIs (n = 4532, 2700 patient years)

Zuclopenthixol decanoate = 52.2%, perphenazine decanoate = 37.2%, haloperidol decanoate = 5.0%, flupenthixol decanoate = 4.4%, fluphenazine decanoate = 1.3%.

FGA = first-generation antipsychotic.

QUALIFY: Study Design

Patients underwent screening for eligibility (1–14 days); patients stratified according to age > 35 or ≤ 35 years with expected ratio of 1:2.

IM = intramuscular; R = randomization.
QUALIFY: Patient Disposition

QUALIFY: Aripiprazole Once-Monthly vs Paliperidone Palmitate – QLS Domains

QUALIFY: Aripiprazole Once-Monthly vs Paliperidone Palmitate – QLS by Age Group
How to Choose an LAI

1. Is the patient demonstrating adequate efficacy and tolerability on oral fluphenazine, haloperidol, risperidone, paliperidone, olanzapine, or aripiprazole?
   - Switch to the corresponding LAI formulation
   - For patients receiving oral risperidone, can consider using paliperidone palmitate for convenience
     - No requirement for oral supplementation upon initiation, less frequent injections, supplied in pre-filled syringes, smaller needle bore, lower injection volume, no refrigeration required, 3-month formulation now available for persons already receiving paliperidone palmitate
   - For patients receiving oral fluphenazine or haloperidol, need to weigh the potential disadvantages of using concomitant oral anticholinergics for the management of motoric adverse effects
     - These agents add complexity to the regimen (an oral tablet/capsule)
     - Anticholinergic agents can interfere with memory and other cognitive functions

2. Is the patient being treated acutely and does not want oral medication?
   - Consider LAI antipsychotics that do not require oral supplementation and where the clinical trials have demonstrated acute efficacy, either paliperidone palmitate or olanzapine pamoate

3. Are weight gain and metabolic adverse effects a concern for this individual patient?
   - Consider aripiprazole monohydrate, paliperidone palmitate, or risperidone microspheres among the second-generation LAI antipsychotics, in that order
   - Can consider the first-generation LAI antipsychotics as well

4. Is prolactin elevation a clinical concern for this individual patient?
   - Consider aripiprazole monohydrate
   - Avoid paliperidone palmitate, risperidone microspheres, or the first-generation LAI antipsychotics

5. Is cost the primary concern?
   - The first-generation LAI antipsychotics may be the only option available

6. Are any of the following people or entities NOT enrolled in the Olanzapine Pamoate Patient Care Program: patient, prescriber, healthcare facility, pharmacy?
   - Olanzapine pamoate cannot be used

Patient Choice

- The need for patient involvement, empowerment, and choice is widely recognized
- Many clinicians may be unaware that their counseling style may stifle a patient’s ability to ask questions
- Patients fear challenging the authority of their doctors or being labeled as “difficult”
Shared Decision Making

- Shared decision making means that you and your patients make medication choices within the evidence base.
- Patients are supported to consider options. The goal is to achieve informed preferences.
- The clinician and patient are equal partners. The decisions are made together.
- Evidence-based medicine is used, but is tailored to the individual.


Patients Do Choose LAI Antipsychotic Therapy When Properly Informed

- In a survey of psychiatrists:
  - Patient refusal was cited as a primary reason for not prescribing LAI formulations.
- In a survey of patients without experience with these agents:
  - 79% cited having never been informed about the option by their psychiatrist.
  - 75% of psychiatrists felt that they informed the patient, but only 33% of patients felt informed.


Patients Do Choose LAI Antipsychotic Therapy When Properly Informed (cont’d)

- In a survey of patients with > 3 months of experience with an LAI formulation:
  - LAI 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.

Psychiatrists Cite Multiple Reasons for Not Prescribing LAI Formulations

EPS = extrapyramidal symptom.


Sufficient Adherence to Dose
Patient Refusal
Antipsychotic Not Available as LAI
Costs
Not Sufficient Adherence to Dose
Poorer Control of Effect Compared to Oral Drug
High EPS Risk with LAI

LAI Formulations: Balancing Pros and Cons for Patients

- Continuous antipsychotic coverage
- No need to remember
- Less conflict over suspected non-adherence
- Confidentiality
- Possibly decreased relapse & hospitalization rates
- More appointments with some agents
- Perceived stigma
- Conversion from oral to LAI
- Fear of pain
- Inflexible dosing / stopping
- Lack of experience
- Negative clinician appraisal

Addressing Common Negative Perceptions

- Injections are a hassle
  → Depending on the medication you choose, it could be as infrequent as 4 × a year. You won’t have to remember to take meds every day
- Someone always nags me about taking my pills
  → Won’t happen again
- Control over me → control over your illness
Addressing Common Negative Perceptions (cont’d)

• What if I want to stop?
  → You can stop anytime, and if you do, there is less chance of a withdrawal reaction

• Means I’m sicker
  → It actually means you are more likely to stay well

• Start with 1 injection and let’s see how it goes

• Why not give it a try!? You might just like it!

Summary

• LAI antipsychotics are superior to placebo in the acute and maintenance treatment of schizophrenia

• Superiority of LAI antipsychotics to oral antipsychotics depends on design and patient characteristics

• LAI antipsychotics do not seem to differ much regarding efficacy, but effectiveness and tolerability differences may be larger