Long Acting Injectable (LAI) Atypical Antipsychotic Drugs: A Practical Guide for Nursing

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Disclosures

• I have no pertinent financial disclosures
• Information provided here is for on label application
• This presentation is for educational purposes only and is not a substitute for an individual’s judgment or a clinicians practice protocol
Objectives

1) Participants will understand the use of the long acting injectable (LAI) *atypical* psychotropic medications as a strategy to improve medication treatment adherence.

2) Participants will be able to discuss the advantages and disadvantages of LAIs.

3) Participants will be able to educate their patients about using LAIs as a treatment intervention to reducing relapse risk and disease progression.
Schizophrenia

• Schizophrenia is a chronic, neurodevelopmental disorder with neurodegenerative mechanisms.
  – Altering periods of remission & relapse
• Each relapse is detrimental and it takes the patient longer to return to previous level of functioning
• The first 5 years of the disease is marked by significant psychosocial deterioration

Potkin, Bera, Zubek, & Lau, (2013)
Patients in their first episode of psychosis have the best chance of remission and recovery when they receive “rapid and continuous” treatment.

Potkin et al. (2013)
Medication Regimen Adherence

Scope of the problem

• 50% of the general population do not take their medications as prescribed – Brown & Bussell (2011)

• 48.1% of veterans with bipolar disorder prescribed antipsychotics were partially adherent or non adherent with antipsychotic drugs – Sajotovic, Valenstein, Ganocyz, & Ignacio (2006)

• 34,000 veterans with schizophrenia
  – 33% non adherent in any one year
  – 60% non adherent in any four year period

Fig. 4: Factors associated with nonadherence.

- Haddock, Brain, & Scott (2014)
Fig. 2: Consequence of non-adherence to antipsychotic medications.
- Haddock, Brain, & Scott (2014)
History of LAI

• Long acting antipsychotic drugs came into the market 51 years ago
  – Frist Typical LAI: Fluphenazine Enantate in 1966
    • Coconut Oil base
  – First Atypical LAI: Risperidone
    • Water based
    • Innovative: Molecule coated in a polymer to form microspheres
Indications

• **Early phase or first episode psychosis**
  – This population is highly vulnerable for non adherence.
  – Study comparing relapse in patients taking oral antipsychotics vs. LAI in early phase
    • 33% for oral vs 5% for LAI
  – Hospitalization rates significant lower for LAI
  – Adverse effects / side effects is similar between oral and LAI
    • Subotnik, Casaus, & Ventura (2015)
Advantages

- Better tolerated
- Regimen is easier to manage / adherence
- More steady serum drug concentrations
  - Less frequent peak plasma levels results in lower s/e
- Reduced risk of accidental or deliberate overdose
- Avoidance of first pass metabolism
- Easier to determine cause of relapse or non-response
  - Non adherence (pt. declines injection) VS. lack of therapeutic response

Correll, Citrome, Haddad, Lauriello, Olfson, Calloway, & Kane (2016); DeBerris et al. (2016)
Disadvantages

- Injection site pain
- Slow dose titration
- Longer time to achieve steady state
- Clinical improvement may be delayed after dose increase
- Dosing options are more limited
- Adverse effects may endure after stopping medication
- Stigma
- Cost of drug

Correll et al., (2016); DeBerris et al. (2016)
LAIs VS. LAIs

• There is “little evidence” that one LAI is superior to another
  – Symptom improvement & relapse rates are similar for LAIs
  – There is some variability in quality of life indicators: side effect profile and frequency of injection
    Nabet et al. (2015)

• LAIs show superiority over oral antipsychotics in “mirror-image” studies
  Correll, et al., (2016)
ARISTADA

- Aripiprazole Lauroxil
- *Prefilled* syringes do not require reconstitution

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available Dose</th>
<th>Injection Interval</th>
<th>Oral Supplement</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aristada</td>
<td>441 mg 662 mg 882 mg</td>
<td>Q 4 weeks for all strengths Q 4 - 6 weeks for 882 mg</td>
<td>3 weeks</td>
<td>-Establish tolerability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Steady State 4-6 mo.</td>
<td></td>
<td>-Monitor for the emergence of compulsive or impulsive behavior</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-inject Observe</td>
<td></td>
<td>-Dose adjustment: Strong 3A4/2D6 inhibitors for more than 2 weeks = ↓ dose.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td></td>
<td>↑ dose with 3A4 inducers for more than 2 weeks</td>
</tr>
</tbody>
</table>

Aristada, (2016); Correll et al., (2016); Guzman, (2017)
ARISTADA

• Injection sites
  – 441mg in deltoid or gluteal
  – 662 mg in gluteal only
  – 882 mg in gluteal only

• Oral to IM dose conversion

Aristada, (2016)
**ARISTADA: Missed Dose**

- Recommendation for restarting oral aripiprazole after missed injection

<table>
<thead>
<tr>
<th>For Patients Receiving</th>
<th>Length of Time Since Last Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>441 mg monthly</td>
<td>≤6 weeks</td>
</tr>
<tr>
<td></td>
<td>&gt;6 and ≤7 weeks</td>
</tr>
<tr>
<td></td>
<td>&gt;7 weeks</td>
</tr>
<tr>
<td>662 mg monthly</td>
<td>≤8 weeks</td>
</tr>
<tr>
<td></td>
<td>&gt;8 and ≤12 weeks</td>
</tr>
<tr>
<td></td>
<td>&gt;12 weeks</td>
</tr>
<tr>
<td>882 mg monthly or every 6 weeks</td>
<td>≤8 weeks</td>
</tr>
<tr>
<td></td>
<td>&gt;8 and ≤12 weeks</td>
</tr>
<tr>
<td></td>
<td>&gt;12 weeks</td>
</tr>
</tbody>
</table>

- No Oral Supplementation Required
- Supplement With 7 Days Oral Aripiprazole
- Supplement With 21 Days Oral Aripiprazole

Aristada, (2016)
ARISTADA Administration

• When attaching the needle to the syringe DO NOT over tighten the needle as you could crack the hub and the medication could squirts out the crack.

Aristada, (2016)
# Abilify Maintena

- **Aripiprazole Monohydrate**
  - Vial kits & dual chamber syringe
  - Reconstitute & use within 30 minutes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available strengths</th>
<th>Injection &amp; interval</th>
<th>Oral Supplement</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abilify Maintena</td>
<td>300mg, 400mg</td>
<td>400mg Q 28 days</td>
<td>2 weeks</td>
<td>Establish tolerability for 2 weeks</td>
</tr>
<tr>
<td>Prefilled</td>
<td></td>
<td>400mg</td>
<td>Steady State</td>
<td>Generally no dose adjustment for: age, gender, race, smoking status, hepatic or renal functioning</td>
</tr>
<tr>
<td>Syringes &amp; vial kits</td>
<td></td>
<td>300mg= 3-4 mo.</td>
<td>Post inject observe</td>
<td>No</td>
</tr>
<tr>
<td>for dose adjustment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abilify Maintena, (2016); Correll et al., (2016); Guzman, (2017)
INITIATING ABILIFY MAINTENA

Once-monthly ABILIFY MAINTENA

Oral antipsychotic

Initiation

14 Days

Oral aripiprazole (10 mg to 20 mg) or current oral antipsychotic.

Abilify Maintena, (2016)
Abilify Maintena

- **Non-Obese**
  - Deltoïd: 1 inch (25 mm) x 23 gauge

- **Obese**
  - Deltoïd: 1.5 inch (38 mm) x 22 gauge
  - Gluteal: 2 inch (51 mm) x 21 gauge
Abilify Maintena: Missed Dose

<table>
<thead>
<tr>
<th>Which dose was missed?</th>
<th>How much time has passed since the last injection?</th>
<th>Next steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second or third dose</td>
<td>&gt;4 weeks and &lt;5 weeks</td>
<td>Administer injection as soon as possible</td>
</tr>
<tr>
<td></td>
<td>&gt;5 weeks</td>
<td>Restart concomitant oral aripiprazole for 14 days with the next administered injection</td>
</tr>
<tr>
<td>Fourth dose or any dose thereafter</td>
<td>&gt;4 weeks and &lt;6 weeks</td>
<td>Administer injection as soon as possible</td>
</tr>
<tr>
<td></td>
<td>&gt;6 weeks</td>
<td>Restart concomitant oral aripiprazole for 14 days with the next administered injection</td>
</tr>
</tbody>
</table>

Abilify Maintena, (2016)
## INVEGA SUSTENNA

### Paliperidone palmitate
- Prefilled syringes
- Starting doses MUST be in deltoid
- Maintenance dose in either deltoid or gluteal muscle

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available strengths</th>
<th>Injection &amp; interval</th>
<th>Oral Supplement</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invega Sustenna</td>
<td>78 mg 117 mg 156 mg 234 mg</td>
<td>2 starting doses 234 mg day 1 + 156 mg day 8 Maintenance 117mg @ day 36 Q 4 weeks</td>
<td>No</td>
<td>- Establish prior tolerability to risperidone or paliperidone&lt;br&gt;- ↑dose with strong CYP3A4 inducer&lt;br&gt;- Renal impairment = dose adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Steady State 7-11 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Post inject observe No</td>
<td></td>
</tr>
</tbody>
</table>

Guzman, (2017); Invega Sustenna, (2016)
**Dosing**  

**SUSTENNA**

- **Step 1 – Day 1**
  - Starting dose 1 of 2
    - 234mg in the deltoid *only*

- **Step 2 – Day 8**
  - Starting doses 2 of 2
    - 156mg in the deltoid *only*
      - Dosing window at day 8 is +/- 4 days

- **Step 3 – Day 36**
  - Starting of maintenance
    - 117mg in deltoid *or* gluteal
      - Dosing window is day 36 is +/- 7 days

- **First maintenance dose should be 5 weeks after the 1\textsuperscript{st} dose regardless of when 2\textsuperscript{nd} dose was given**

  *Invega Sustenna, (2016)*
## Invega Oral to SUSTENNA

### RECOMMENDED DOSING OF INVEGA SUSTENNA® FOR ADULTS WITH SCHIZOPHRENIA TRANSITIONING FROM INVEGA®

<table>
<thead>
<tr>
<th>Initiation dosing (deltoid)</th>
<th>Monthly maintenance dose in (deltoid or gluteal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 8</td>
</tr>
</tbody>
</table>
| 234 mg                      | 156 mg                                           | Patients stabilized on INVEGA® can attain similar steady-state exposure with INVEGA SUSTENNA®

### Dose conversion from INVEGA® to INVEGA SUSTENNA®

<table>
<thead>
<tr>
<th>INVEGA® extended-release tablet (daily)</th>
<th>INVEGA SUSTENNA® injection (once monthly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg</td>
<td>78 mg</td>
</tr>
<tr>
<td>6 mg</td>
<td>117 mg</td>
</tr>
<tr>
<td>12 mg</td>
<td>234 mg</td>
</tr>
</tbody>
</table>

Invega Trinza, 2016
## SUSTENNA Missed Monthly Dose

<table>
<thead>
<tr>
<th>Missed monthly maintenance dose</th>
<th>Dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4 to 6 weeks since last injection</strong></td>
<td>Resume regular monthly dosing as soon as possible at patient’s previously stabilized dose, followed by injections at monthly intervals.</td>
</tr>
<tr>
<td><strong>&gt;6 weeks to 6 months since last injection</strong>&lt;br&gt;“If the patient was stabilized on 234 mg, the first 2 doses should be 156 mg.”</td>
<td>Continue dosing at patient’s previously stabilized dose* by giving:&lt;br&gt;1. Deltoid injection as soon as possible&lt;br&gt;2. Deltoid injection 1 week later at same dose&lt;br&gt;3. Resume monthly deltoid or gluteal injections at patient’s previously stabilized dose 1 month after second dose</td>
</tr>
<tr>
<td><strong>&gt;6 months since last injection</strong></td>
<td>Restart dosing with normal starting plan:&lt;br&gt;1. 234-mg deltoid injection at Day 1&lt;br&gt;2. 156-mg deltoid injection 1 week later&lt;br&gt;3. Resume regular monthly dosing in either deltoid or gluteal muscle</td>
</tr>
</tbody>
</table>

*Inviva Sustenna, (2016)*
**INVEGA TRINZA**

- **Paliperidone palmitate**
  - Shake 15 sec vigorously – give in 5 minutes
  - Deltoid or gluteal muscle

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available Strengths</th>
<th>Injection &amp; interval</th>
<th>Oral supplement</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invega Trinza</td>
<td>273mg, 410mg, 546mg, 819mg</td>
<td>Starting dose-depends on mo. dose</td>
<td>No</td>
<td>Establish tolerability w/ SUSTENNA for 4 month</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance dose Varies</td>
<td>Steady State Continues at equivalent dose</td>
<td>Post inject observe No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q 3 mo.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Invega Trinza, (2016)
# TRINZA Missed Dose

<table>
<thead>
<tr>
<th>TIME SINCE LAST INJECTION</th>
<th>ACTION STEPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early or late by 2 weeks</td>
<td>Patients may be given the injection ±2 weeks from their scheduled 3-month dose.</td>
</tr>
<tr>
<td>Longer than 3½ months but less than 4 months</td>
<td>Previous dose should be administered as soon as possible, then continue with 3-month injections.</td>
</tr>
<tr>
<td>4 months up to and including 9 months</td>
<td>Do not administer the next dose, but use the reinitiation table below.</td>
</tr>
</tbody>
</table>

## REINITIATION REGIMEN AFTER MISSING 4 MONTHS TO 9 MONTHS OF INVEGA TRINZA®

If the last dose of INVEGA TRINZA® was:

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>First Dose</th>
<th>Second Dose</th>
<th>Third Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>273</td>
<td>Day 1</td>
<td>Day 8</td>
<td>1 month after day 8</td>
</tr>
<tr>
<td>78 mg</td>
<td>78 mg</td>
<td>78 mg</td>
<td>273 mg</td>
</tr>
<tr>
<td>410</td>
<td>117 mg</td>
<td>117 mg</td>
<td>410 mg</td>
</tr>
<tr>
<td>546</td>
<td>156 mg</td>
<td>156 mg</td>
<td>546 mg</td>
</tr>
<tr>
<td>819</td>
<td>156 mg</td>
<td>156 mg</td>
<td>819 mg</td>
</tr>
<tr>
<td>Longer than 9 months</td>
<td>Reinitiate treatment with INVEGA SUSTENNA® per its Prescribing Information. INVEGA TRINZA® can be resumed after ≥4 monthly INVEGA SUSTENNA® treatments.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Invega Trinza, (2016)
### Risperdal Consta

- **Risperidone microspheres**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available Strengths</th>
<th>Injection &amp; Interval</th>
<th>Oral Supplement</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperdal Consta</td>
<td>12.5mg, 25mg, 37.5mg, 50mg</td>
<td>Starting dose 25mg, Maintenance 25-50mg</td>
<td>3 weeks, Steady state 1.5 – 2 mo.</td>
<td>Establish tolerability, Microspheres must be refrigerated</td>
</tr>
<tr>
<td>Vial kits</td>
<td>Q 2 weeks</td>
<td>Post inject observe No</td>
<td></td>
<td>Monitor for hypotension in first 2 weeks, Rhinitis is common</td>
</tr>
</tbody>
</table>

Risperdal CONSTA

- Oral to IM conversion
  - Deltoid or gluteal muscle
  - Dose adjustments as needed

<table>
<thead>
<tr>
<th>ORAL</th>
<th>IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mg or less</td>
<td>25 mg Q 2 weeks</td>
</tr>
<tr>
<td>4mg or more</td>
<td>37.5 mg Q 2 weeks</td>
</tr>
<tr>
<td></td>
<td>50 mg Q 2 week max dose</td>
</tr>
</tbody>
</table>

Risperdal Consta, (2015)
**Managing missed doses**

The appropriate strategy for patients who have missed a dose or doses of RLAI will depend on whether a steady-state plasma concentration of RLAI has been reached. Generally, steady-state plasma concentrations are achieved after 4 injections.²

**Steady-state plasma concentration achieved**

The next dose of RLAI should be given as soon as possible if steady-state concentrations of RLAI have been achieved and only 3-6 weeks have passed since the last injection. Clinicians should monitor for symptom recurrence. If more than 6 weeks have elapsed since the last injection, risperidone long-acting should be initiated as soon as possible and 3 weeks of coverage with an oral antipsychotic should be given.²

Risperdal Consta, (2016)
ZYPREXA RELPREVV

- Olanzapine pamoate salt
  - Patients must be monitored for 3 hours post injection for Post Injection Delirium Syndrome (PDSS) – essentially overdose
  - Premarketing clinical trial: ~1 injection per 1400 injections or 0.07% of injection = 1.7% of patients
  - PDSS can occur in any patient at any injection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available strengths</th>
<th>Injection &amp; interval</th>
<th>Oral Supplement</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zyprexa</td>
<td>210 mg</td>
<td>Start dose</td>
<td>No</td>
<td>BLACK BOX PDSS *ONLY Gluteal IM</td>
</tr>
<tr>
<td>Relpevv</td>
<td>300 mg</td>
<td>varies</td>
<td>Steady state</td>
<td>Eli Lilly Patient Care Program to</td>
</tr>
<tr>
<td></td>
<td>405 mg</td>
<td>210mg-300mg</td>
<td>3 mo.</td>
<td>prescribe. Requires online training</td>
</tr>
<tr>
<td>Vial kits</td>
<td>2-4 weeks</td>
<td></td>
<td>Monitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>At least 3 hours</td>
<td></td>
</tr>
</tbody>
</table>
Zyprexa Oral to IM dosing

Recommended Dosing for ZYPREXA RELPREVV Based on Correspondence to Oral Olanzapine (ZYPREXA) Doses

Target Oral Olanzapine (ZYPREXA) Dose
- 10 mg/day
- 15 mg/day
- 20 mg/day

Starting ZYPREXA RELPREVV Dose
- 210 mg/2 weeks or 405 mg/4 weeks
- 300 mg/2 weeks

Maintenance ZYPREXA RELPREVV Dose After 8 Weeks of Treatment
- 150 mg/2 weeks or 300 mg/4 weeks
- 210 mg/2 weeks or 405 mg/4 weeks
- 300 mg/2 weeks
What is Post-Injection Delirium/Sedation Syndrome?

- Appears related to excessive olanzapine plasma concentrations
- Presentation consistent with many symptoms of oral olanzapine overdose
- Most patients developed symptoms of:
  - *Sedation*, ranging from mild in severity up to coma (lasting up to 12 hrs) and/or
  - *Delirium*, including confusion, disorientation, agitation, anxiety and other cognitive impairment
  - Other symptoms noted included extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension or convulsions
- Typically began with milder symptoms which progress in severity and/or number
- Presentation can appear similar to alcohol intoxication

<table>
<thead>
<tr>
<th>Time of Onset of Symptoms</th>
<th>% of Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 hour</td>
<td>~80%</td>
</tr>
<tr>
<td>&gt;1 to 3 hours</td>
<td>~ 14%</td>
</tr>
<tr>
<td>&gt;3 hours</td>
<td>~ 6%</td>
</tr>
</tbody>
</table>

* As of 18 June 2009.
Data on file, Lilly Research Laboratories, ZYP20090209A

Zyprexa Relprevv, (2016)
Monitoring LAIs

• Metabolic
  – Weight gain, changes in lipids, blood glucose
• Extrapyramidal
  – Akathisia, dyskinesia, dystonia
• Cardiovascular
  – Prolonged QT interval
• Hormonal
  – Plasma prolactin
• Side effects
  – Sedation, dry mouth, constipation

Correll et al. (2016)
Barriers to Using LAIs

• Prescribers perceptions & attitudes often prevent patients from knowing about LAIs
  – Belief that LAIs are not appropriate for 1\textsuperscript{st} episode patients
  – Provider over estimates patients regimen adherence
  – Presenting LAIs in a negative light or not discussing as treatment option

• Service barriers:
  – Clinic resources, nurses to administer injections

• Documentation of nonadherence for pre-auth

• Cost
  • Correll et al., (2016); Freudenreich, (2015); Kane (2016.)
Patient Profile

• Factors influencing LAI selection
  – Early phase or 1st episode schizophrenia
  – Patients with the *most to gain and most to lose*: education, employment
  – History of regimen nonadherence
  – Risk factors associated with nonadherence
    • Youth, drugs/alcohol, lack of insight
  – High risk for aggression, violence, self destructive behavior.
  – Patient preference for LAI
    • Correll et al., (2016)
Nurses Attitudes to LAIs

• LAIs require more patient/nurse contact, which is favorable

• LAIs with deltoid administration
  – Less socially embarrassing
  – More respectful
  – No sexual connotation
  – Faster/easier to administer
  – More convenient

  • Geerts, Martinez, & Schreiner (2013)
Recap

• LAIs:
  – Are well accepted by patients
  – Lead to better medication adherence
  – Are more convenient for some patients
  – Delay / prevent relapse
  – Are neuroprotective and early intervention may “modify the trajectory of schizophrenia and improved long term outcome.”

Subotnik et al. (2015); Kaplan, Casov, & Zummo (2013)
Moving Forward

- LAIs are no longer just maintenance treatment or last resort drugs. LAIs are moving to the top of pharmacologic interventions for treating first episode psychosis and for patient who struggle with regimen adherence.

- LAIs have the potential to

- Prevent a “malicious course” of disease
  - Sacchetti, Grunze, Leucht, & Vita (2015)
Questions
Reference


Reference


Reference


