The Use of Long Acting Injectable Antipsychotics: More Practical Considerations

The Care Transitions Network
Objectives

• In Part 4 of our series, we will address common questions that have come up from previous webinars.

• We will review important concepts such as cost and insurance coverage.

• We will expand to include benefits of and rationale for LAI use in first episode psychosis and practical considerations including choice of an agent.
Outline

- Benefits in First Episode Psychosis
- Choosing an LAI Agent
- Cost and Insurance Coverage Review
- Additional questions from the audience
Benefits in first episode psychosis

Based on question:

“Is there any information about the benefit of LAIs for younger patients?”
Non-adherence in the Treatment of Chronic Disorders

• In developed countries, about 50% of patients with chronic diseases adhere to long-term therapy

• 33–69% of all medication-related hospital admissions in the US 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)

1. WHO Report 2003; Adherence to long-term therapies: evidence for action;
Prognosis

• The option of LAI should be discussed early to optimize the benefits of improved adherence.

• One third of patients with schizophrenia have mild symptoms and mild functional impairment.

• With standard care, full recovery or symptomatic and functional capacity is only achieved in ≤ 15%.

Jääskeläinen et al. 2013
Prognosis

• The remaining two-thirds of patients have moderate to severe symptoms and functional impairment.

• Approximately 10-30% have persistent, unremitting psychotic symptoms throughout the illness course.

Mason et al. 1995; Wiersma et al. 1998
Harrison et al. 2001; Svedberg et al. 2001
Kua et al. 2003; Thara et al. 1994
Meltzer 1997; Wiersma et al. 1998
Prognosis

- Following the first psychotic episode, most experience an improvement or even full remission.
- Typically this is followed by further relapses and partial or full remissions.
- Functional deterioration is often time-limited, most apparent during the first 3 years of illness.

McGlashan & Fenton 1993
Evans et al 2005
Prognosis

• There is evidence that relapses are associated with development of treatment resistance.

• After each relapse, approximately 1 in 6 patients fail to remit.

• Treatment resistance increases cumulatively with each successive relapse.

• Time between start of medication and remission may also increase with successive psychotic episodes.

Wiersma et al. 1998
Emsley et al. 2012
Lieberman et al 1996
Improving Prognosis

• Most experience an improvement or full remission following the first psychotic episode.

• The option of LAI should be discussed early to optimize the benefits of improved adherence.

• Goals:
  • Decrease non-adherence
  • Decrease successive relapses
  • Maintain the functional gains
  • Decrease cumulative treatment resistance

Jääskeläinen et al. 2013
First episode patients will accept LAIs

• In a prospective, randomized trial examining acceptance and adherence to LAI vs oral risperidone in first episode schizophrenia (with nonadherence defined as >14 days):
  
  • Of 26 patients randomly assigned to risperidone LAI, **73% accepted the LAI recommendation.**
  
  • Patients accepting risperidone LAI were significantly more likely to be adherent than patients staying on oral risperidone (89% RLAI vs 59% ORAL, P = 0.035).
  
  • In this study, **most first episode patients taking oral antipsychotics accepted a recommendation of LAI.**

Weiden et al. 2009
LAIls are often preferred by those who try them

- Studies of multi-episode patients suggest their attitudes towards LAIs are frequently positive.

- Patients who remain on LAIs often cite they prefer them over oral medications (Walburn et al. 2001).

- Patients who remain on LAIs feel they prevent relapse (Iyer et al. 2013).
Confidentiality

• Young people in their first episode of psychosis who tend to respond well to monotherapy.

• This population may have limited privacy due to living in dorms.

• Using long acting formulations means that no one sees them taking pills.
Improved Clinical Outcomes

• Some studies suggest clinical outcomes are better for first episode patients on LAIs.

• In a 12 month trial (Subotnik et al. 2015) comparing 86 patients with recent onset of schizophrenia randomized to either LAI vs oral risperidone:
  • For the LAI group vs. Oral group:
    • Psychotic exacerbation and/or relapse rate was lower. (5% vs. 33%, P< 0.001)
    • Mean levels of hallucinations and delusions were better controlled throughout follow up.
    • Discontinuations due to inadequate clinical response were less common.
    • Adherence to oral risperidone was better

• Other studies of outcomes with LAIs in FEP (Malla et al. 2016) show no clinical benefit, so more research is needed to clarify their benefits.
Frontal Lobe Myelination as possible mechanism of antipsychotic action

• In healthy individuals, the development of brain myelination continues into middle age.

• In schizophrenia, imaging and post-mortem studies show:
  • Deficits in frontal lobe myelination.
  • Antipsychotic medications initially increase frontal lobe white matter volume.
  • In chronic stages, volume subsequently declines prematurely.

Bartzokis et al 2011
Improving adherence with LAIs may prevent White Matter Volume Loss

• In a prospective pre-randomized open-label MRI study of frontal lobe white matter volumes changes over 6 months comparing:
  • 11 patients with first episode schizophrenia on risperidone LAI
  • 13 patients with first episode schizophrenia on oral risperidone
  • 14 healthy controls

• LAI group:
  • White matter volume had a non-significant increase.

• Oral risperidone group:
  • White matter volume significantly decreased.

• Healthy Control group:
  • White matter volume change was intermediate between the oral risperidone and LAI groups and nonsignificant.

Bartzokis et al 2011
Improving adherence with LAIs may promote Intracortical Myelin Development

• In a similar study by the same group examining frontal lobe intracortical myelin volume changes over 6 months comparing:
  • 9 patients with first episode schizophrenia on risperidone LAI
  • 13 patients with first episode schizophrenia on oral risperidone
  • 12 healthy controls

• LAI group:
  • Intracortical myelin volume significantly increased \( (p=0.005) \).

• Oral risperidone group:
  • Intracortical myelin volume increased but not significantly \( (p=0.39) \).

Bartzokis et al 2012
LAs optimize adherence, frontal myelination, and cognition in first episode schizophrenia

- These 2 studies patients receiving risperidone LAI had:
  - better medication adherence
- Better adherence through LAI medications may improve
  - development of myelination in first-episode patients
- Increased frontal white matter volume was associated with:
  - Improved cognitive performance in executive function tasks:
  - Faster reaction times in tasks measuring working memory
  - Faster reaction times in tasks measuring mental flexibility
- These 2 studies were preliminary and had small numbers of patients, but the data is promising and replication is needed.

Bartzokis et al 2011 & 2012
Choosing an LAI

Based on the questions:

“With several LAIs currently available, what are considerations for choosing an LAI?”
Patient History

• Are they currently prescribed an oral antipsychotic available as a LAI?

• Is there a history of good response to an agent available as a LAI?

• Is there history of medical co-morbidities (obesity, diabetes, metabolic syndrome) that suggest use of one antipsychotic class over another?

• Is there history of poor tolerance to certain oral agents or preferences based on side effect profile?

• Is the patient in their first episode and antipsychotic naïve?
# Antipsychotic class/Depot Delivery Technology

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<thead>
<tr>
<th>CLASS</th>
<th>DELIVERY</th>
<th>AGENT</th>
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<tr>
<td>First Generation Antipsychotic</td>
<td>Oil</td>
<td>Fluphenazine decanoate</td>
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<td></td>
<td>Haloperidol decanoate</td>
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<td>Second Generation Antipsychotic</td>
<td>Microspheres</td>
<td>Risperidone LAI</td>
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Depot Delivery Technology: Oil-based

- Long period before they achieve clinically effective results

- Takes many months to achieve steady state

- Can increase time to steady state with more frequent loading initially

- Takes many months to eliminate

- Pharmacokinetics vary widely within and between patients
Depot Delivery Technology: Microspheres

• Pharmacokinetics more predictable than with oil-based technology

• Three week period of no release of medication following initial injection

• Requires oral medication for at least the first 3 weeks and for as long as 6 weeks until the LAI reaches steady state.
Depot Delivery Technology: Crystals

• Sustained delivery of clinically effective doses from first day of injection (initial oral supplementation required for aripiprazole).

• Well-defined, predictable pharmacokinetic profiles.

• Take months to achieve steady state.

• Can increase time to steady state with more frequent loading initially.
FGAs: Decanoates

• The First Generation Antipsychotic LAIs are combinations of the specific antipsychotic agent and a long chain fatty acid.

• The process of combining the antipsychotic agent with a long chain fatty acid is called esterification.

• Esterification makes the antipsychotic fat soluble so that it can be dissolved in oil.

• For agents available in the United States, the long chain fatty acid decanoic acid.

Ereshefsky et al. 1984; Barnes & Curson 1994; Den key & Axelsson 1996
FGAs: Decanoates

• Once injected intramuscularly, the medication slowly leaves the oil reservoir.

• Once in the bloodstream, the antipsychotic is separated from the fatty acid.

Ereshefsky et al. 1984
Barnes & Curson 1994
Den key & Axelsson 1996
FGAs: Decanoates

• Advantages of decanoates include they are the most inexpensive LAIs.

• For Medicaid coverage in New York State, they do not require prior authorization.

• They come in reusable bottles that do not require refrigeration.

• A disadvantage is that their pharmacokinetics can vary widely within and between patients.

Ereshefsky et al. 1984; Barnes & Curson 1994; Den key & Axelsson 1996
FGAs: Decanoates

- Advantages over SGA LAIs include lower metabolic side effect profile.

- Disadvantages compared to SGA LAIs include higher risk of EPS.

- Formulations available in the United States include:
  - Fluphenazine decanoate
  - Haloperidol decanoate

Ereshefsky et al. 1984; Barnes & Curson 1994; Den key & Axelsson 1996
SGAs: Risperidone Microspheres

• Risperidone LAI was the first non-oil based LAI.

• Risperidone is encapsulated in microspheres that require cold storage.

• Microspheres are composed of biodegradable polymers that are slowly broken down to release risperidone.

• Risperidone LAI is administered every 2 weeks.
Olanzapine

• Olanzapine pamoate is the first of the crystal-based LAIs.

• It is a salt of pamoic acid and olanzapine suspended in water.

• After the micron-sized crystals are injected into muscle tissue, the pamoate salt slowly dissolves, releasing free olanzapine and pamoic acid.

• The long acting properties result from the slow rate at which the crystalline salt dissolves.

Taylor 2009
Olanzapine

• Olanzapine pamoate can be administered at 2 – 4 week intervals

• Patients can switch abruptly from oral to LAI

• It does not need to be refrigerated

• It comes in a powder requiring reconstitution
Olanzapine

• A post-injection syndrome which is rarely seen but unique to this agent.

• Olanzapine pamoate crystals are relatively insoluble in muscle, but rapidly dissolve in blood.

• Theorized mechanism is damaged blood vessels during injection with leakage of blood into the injection site.
**Post-injection Delirium/Sedation Syndrome**

- Symptoms are similar to an oral olanzapine overdose.
- **Delirium-like symptoms** (occurring in 97% of cases) include disorientation, confusion, ataxia, dysarthria, irritability, anxiety, and aggression.
- **Sedation-related symptoms** (occurring in 87% of cases) include changes in level of consciousness such as somnolence.
- **General malaise** including nonspecific symptoms of weakness, dizziness, or not feeling well were reported in 67% of cases.

Taylor 2009
Post-injection Delirium/Sedation Syndrome

• The majority of cases occur in the first hour following the injection.

• Patients should remain in clinic for observation for 2 hours after each injection.

• Patients should be advised to not drive or operate heavy machinery the same day after injection.
Post-injection Delirium/Sedation Syndrome

• Reduce risk by using proper injection technique to prevent contact with the bloodstream.

• To assure deep intramuscular application:
  • 1.5 inch (35mm) 19 gauge needle is recommended.
  • For obese patients, a 2 inch (50mm) needle is recommended.

• Aspiration prior to injection (check for visible blood).

• If blood is visible in the aspirate:
  • Withdrawal of the syringe
  • Inject into the alternate buttock
**Paliperidone**

- Paliperidone palmitate is the second crystal-based LAI developed.
- It is a salt supplied in an aqueous suspension in pre-filled syringes.
- Originally it was only available in once monthly formulation.
- It is now also available in dosing frequency of every 3 months.

Citrome et al 2010
Paliperidone

• It is a metabolite of risperidone with several advantages over microspheres:
  • Immediate loading
  • Oral supplementation not required (after initial loading doses)
  • Four week dosing interval (after initial loading doses)
  • Greater dosing range
  • Refrigeration and reconstitution are not required
Aripiprazole monohydrate

• Crystalline aripiprazole monohydrate is a dry powder requiring resuspension with sterile water at room temperature immediately before administration.

• It is available in prefilled dual chamber syringes and single dose vials.

• Once injected into muscle, it is slowly absorbed into systemic circulation due to its low solubility, there is no release vehicle or release controlling membrane.

• Oral supplementation is required for 14 days after first dose.
Aripiprazole lauroxil

- Aripiprazole lauroxil, a prodrug ester of aripiprazole, is available supplied as an aqueous suspension in prefilled syringes.

- Once injected into muscle, it is slowly absorbed into systemic circulation and converted to its active form.

- It offers a 6 week dosing option.

- Oral supplementation is required for 21 days after first dose.
Aripiprazole

• Aripiprazole differs from other SGAs as it is a partial dopamine agonist.

• Differences from other agents includes decreased metabolic side effect profile and lower risk of hyperprolactinemia.
Considerations in First Episode Psychosis

• FGAs are not considered first line in first episode psychosis
  • more potential EPS and TD vs. SGAs; higher relapse rates

• Olanzapine’s is not considered first line in first episode psychosis
  • More burdensome regarding metabolic side effects

• By default remaining options available as LAIs:
  • Aripiprazole
  • Risperidone
  • Paliperidone
Insurance Coverage of LAIs
Benefit Verification:
Factors affecting coverage

• **Check coverage**
  • Is the benefit category medical or pharmacy?
  • Is the LAI not on formulary and if so is there a formulary exception process?

• **Determine Access**
  • Does the LAI require prior authorization?
  • Does the patients meet the payer’s necessary requirements for use of the LAI?
  • Are there quantity limits to what is covered?

• **Product acquisition**
  • What are the payer’s requirements for obtaining the LAI? Buy and bill? Specialty pharmacy? Retail pharmacy?

• **Patient cost-sharing**
  • Co-pay or Co-insurance? Ask about patient’s cost-sharing obligations and whether they vary by benefit category or site of care.

• **Site of care classification**
  • What is the site of care? Identify the site of care and determine how the payer classifies the site.
Factors Affecting Coverage

• **Type of Payer**
  • Medicaid
  • Medicare
  • Private payer (including State Health Insurance Marketplace)

• **Benefit Category**
  • Medical benefit
  • Pharmacy benefit

• **Site of Service**
  • Physician office
  • Community Mental Health Clinic
  • Partial hospitalization
  • Outpatient
  • Inpatient

*The Benefit Category and Site of Service influence how the LAI is obtained.*
Obtaining the LAI

• Several options exist for obtaining LAIs depending on preferences and payer requirements.
  • Order LAI and submit claim *(buy and bill)*
  • Specialty Pharmacy
  • Retail Pharmacy (in certain circumstances)

• It is important to always check with each of the patients’ payers prior to ordering or administering the LAI to verify the policies for a given patient’s insurance.
Benefit Category

- There are 2 benefit structures commonly used to cover costs of LAIs:
  - Medical Benefit
  - Pharmacy Benefit

- The benefit category determines whether the LAI is obtained via the “buy-and-bill” process or via a specialty pharmacy.
When an LAI is covered as a pharmacy benefit

• The prescription is submitted to the pharmacy (specialty, retail, or mail order).

• The pharmacy ships the medication to the site of service.

• In some cases, the payer may specify that the prescription be filled by a specialty pharmacy.

• In these cases, the pharmacy is responsible for submitting the claim for the LAI.

• The healthcare professional bills for administering the injection and any other professional services.
When the LAI is covered as a medical benefit

• Providers and CMHCs may be able to purchase and administer the LAI in the office-setting.

• This process, known as “buy-and-bill” allows the healthcare professional to use their NPI number to bill for different components of treatment.

• These include cost of purchasing the medication, the injection/administration, and any other services (such as E&M service).
Site of Service

• The site of service can influence which benefit category covers the LAI.

• If site of service is an outpatient location such as the physicians office or CMHC
  • Benefit category can be medical or pharmacy
  • Roughly 80% of the time, LAIs will be covered as a pharmacy benefit.

• If site of service is a partial hospitalization program
  • Usually coverage category is medical benefit

• Contacting the payer directly as part of an insurance benefit verification is the best way to determine benefit structure and coverage.
Stay Tuned for Future Topics

• This concludes our four part series on Long Acting Injectable antipsychotics.

• We will continue monthly webinars focused on evidence based education on a series of topics.

• Please let us know which topics would be most helpful for us to include in future webinar series.
References


• WHO Report 2003; Adherence to long-term therapies: evidence for action.


References


References


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