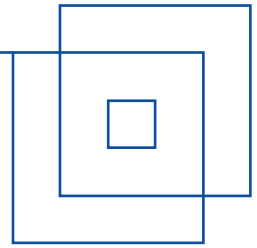


CHOOSING AN LAI ANTIPSYCHOTIC AGENT



Patient History

These questions will help in making decisions on the appropriate agent to use:

- 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

CLASS	DELIVERY	AGENT
First Generation Antipsychotic	Oil	Fluphenazine decanoate Haloperidol decanoate
Second Generation Antipsychotic	Microspheres	Risperidone LAI
	Crystal	Olanzapine pamoate Paliperidone palmitate Aripiprazole monohydrate Aripiprazole lauroxil

Depot Delivery Technology: Oil-based

- Long period before they achieve clinically effective results
- Takes many months to achieve steady state and/or 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 from at least 3 weeks and up to 6 weeks until 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, taking months to achieve a steady state

FGAs: Decanoates¹

- 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.
- Once injected intramuscularly, the medication slowly leaves the oil reservoir.
- Once in the bloodstream, the antipsychotic is separated from the fatty acid.
- 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.
- 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

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 slowly broken down to release risperidone.
- Risperidone LAI is administered every 2 weeks.

Olanzapine²

- 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.
- 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.
- 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 Syndrome³

- 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.
- 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.
- 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

Paliperidone⁴

- 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.
- 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 in muscle, it's slowly absorbed into systemic circulation and converted to 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 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

¹Ereshefsky et al. 1984; Barnes & Curson 1994; Denkey & Axelsson 1996

²Taylor 2009

³Taylor 2009

⁴Citrome et al. 2010