Changing the Treatment Landscape

Embracing Long-Acting Injectable Antipsychotics

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Learning Objectives

1. Review the evidence base of long-acting injectable antipsychotics (LAI) compared to oral antipsychotics with regard to adherence, hospitalization, relapse, and mortality.
2. Identify the role of LAIs in the treatment continuum and discuss their use earlier in the schizophrenia disease course.
3. Compare LAIs with regard to pharmacokinetic profiles, loading dose strategies, and chronic dosing.
4. Incorporate LAIs into treatment regimens using case-based examples.

Background

Schizophrenia is a lifelong illness estimated to affect 1% of the world's population and is estimated to contribute to $156 billion annually in direct and indirect costs, one of the most costly diseases worldwide.[1,2] It is marked by significant psychotic symptoms, negative symptoms, and cognitive deficits. Suicidal thoughts and acts of violence are of particular concern when the person is acutely ill. Additionally, schizophrenia can be severely disabling and cause significant distress and disruption to the patient and their family.

Multiple treatment modalities are utilized for the treatment of schizophrenia, with antipsychotic medications being the current mainstay of treatment. While schizophrenia treatments continue to evolve over time, recent advancements have included: a developing nosology with changing diagnostic criteria, increases in genetic and biomarker identification, better recognition and management of medical comorbidities, introduction of neuromodulation technologies, psychosocial rehabilitation and treatment, and consideration of subgroups in diagnosis.[3-6] Even with these advances, there continue to be challenges in the treatment of schizophrenia, including inadequate symptom response that continues even with many recent medication developments, high rates of relapse and rehospitalization, high rates of morbidity and early mortality with the disease, and inadequate medication adherence.

Preventing relapse is a key goal, as relapse and rehospitalization are costly, stigmatizing, and often traumatizing. Avoiding relapse and rehospitalization are essential objectives for remission and recovery and are now included in many international clinical guidelines.[6-8]

Irreversible functional decline can occur over the course of a lifetime in patients with schizophrenia.[7-9] With each relapse, decrements in functioning may occur, and with a longer duration of acute illness, even more functional declination can occur. Van Haren and colleagues completed MRIs in 96 patients with schizophrenia versus 113 matched healthy controls to determine how the progression of illness effected the frontal gray matter in relation to the number of psychotic relapses.[10] With an increasing number of hospitalizations, there was a decrease in superior frontal gray matter; this excessive gray matter density decrease was found to be related to an increased number of psychotic episodes, although atypical antipsychotic medications were found to attenuate these changes.[10]

As early as ten to fourteen days post discharge, 25% of patients are partially adherent.[18] At one year, the prevalence increases to 50%, and at two years, as many as 75% of patients are nonadherent.[19]

The risk of relapse in schizophrenia is high, with about 80% of first episode patients suffering a relapse within five years.[11] In a five-year study, the risk of relapse in the first 24 months for patients with schizophrenia is 54%. Additionally, for first-episode patients, medication discontinuation is the most powerful predictor of relapse.[11-12]

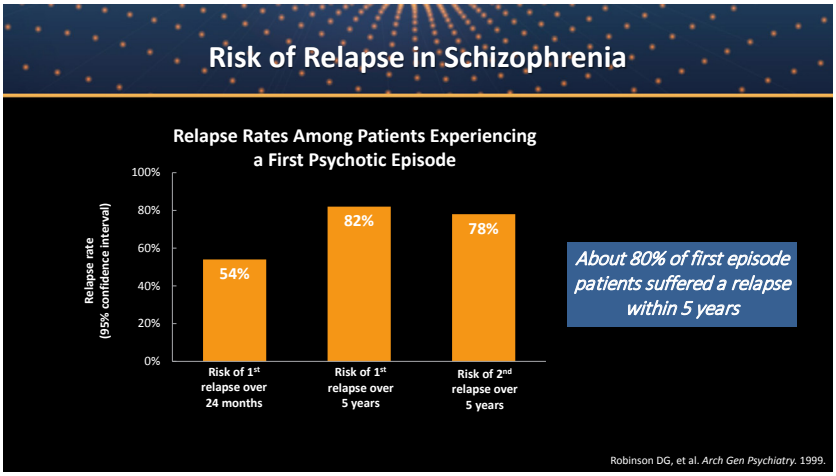
Nonetheless, it is estimated that between 15% - 25% of recently hospitalized patients don't take all of their medication within seven days of being discharged.[13] Patients with schizophrenia who are initiated on oral second-generation antipsychotics (SGAs) have shown poor medication adherence and continuation after discharge, with one recent study estimating that almost half are off medications by six months post-discharge.[14] Further, recent studies suggest people with schizophrenia are nearly twice as likely to be hospitalized if they miss just one to ten days of medication and that 52% of those with poor attitudes towards adherence will relapse by one-year post-discharge.[15-16] Lack of continuity of care with resultant nonadherence to therapy leads to significant decrements in patients' quality of life, increases the economic burden of managing their illness, and can potentially lead to an overall poorer prognosis.[17]

As seen, partial adherence in schizophrenia begins early and increases over time. As early as ten to fourteen days post discharge, 25% of patients are partially adherent.[18] At one year, the prevalence increases to 50%, and at two years, as many as 75% of patients are nonadherent.[19] This partial adherence has a negative impact on global patient outcomes. If a patient experiences no therapy gap within one year, the risk of relapse is 6%.[15] This rate goes up over time, with gaps in therapy >30 days leading to 22% of patients being rehospitalized. Unfortunately, many times nonadherence is viewed as a treatment failure, which is consistent with bias to overestimate adherence and underestimate nonadherence.

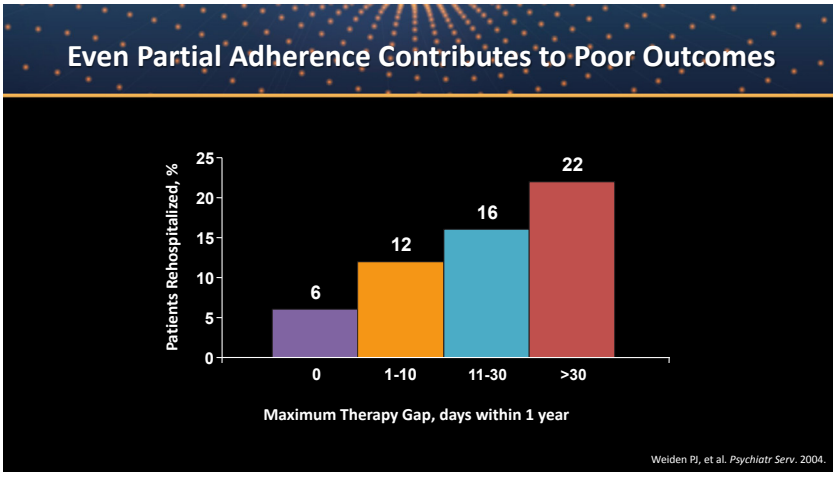
There are numerous factors which contribute to nonadherence, such as the presence of persistent positive, negative, or cognitive symptoms, distress from side effects, change in relationships with people who support or supervise medication-taking, length of time the patient is stable, and the presence or absence of comorbid substance abuse.[20] Recognizing that over 90% of patients miss at least one dose of medication, and on average, one third of all doses, it is critical to strategize methodologies that can minimize nonadherence and optimize the chances of remission and recovery.[21]

There are many intervention mechanisms to employ for the modification of adherence. If the adherence problem is that the patient refuses to take their medications, consider focusing the intervention on strengthening the perceived benefits of medication and minimizing the perceived costs and concerns. If the adherence problem is that the patient frequently forgets to take their medication, then the clinician should suggest pill boxes in obvious locations, self-monitoring tools, establishment of routines, and consideration of long-acting injectable antipsychotics (LAIs).[20]

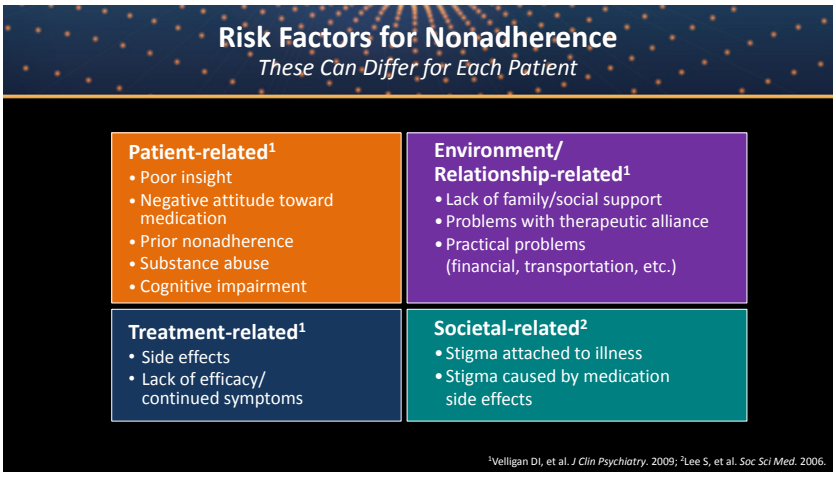
Slide 1. Risk of Relapse in Schizophrenia



Slide 2. Partial Adherence Contributes to Poor Outcomes



Slide3. Risk Factors for Nonadherence



Long-Acting Injectable Antipsychotics

Historically, the use of depot or LAIs was reserved for the last stages of treatment.[22] Many early randomized controlled clinical trials did not demonstrate superiority of LAIs over oral treatments for schizophrenia and their place in treatment was reserved for only those considered very ill or highly nonadherent.[23]

There are numerous advantages to the use of LAIs for the treatment of schizophrenia, including reduction of dosage deviations, elimination of determining adherence status, stable and predictable plasma levels, elimination of abrupt loss of efficacy if a dose is missed, and the fact that many patients actually prefer them.[24-27]

In the past five years, however, the landscape has evolved and the introduction of many SGA LAIs has occurred in the US. These options expand the treatment armamentarium, and LAIs are becoming established as superior evidence-based treatments for schizophrenia. There are numerous advantages to the use of LAIs for the treatment of schizophrenia, including reduction of dosage deviations, elimination of determining adherence status, stable and predictable plasma levels, elimination of abrupt loss of efficacy if a dose is missed, and the fact that many patients actually prefer them.[24-27]

Current schizophrenia guidelines have different recommendations for the use of LAIs. The National Institute for Health and Clinical Excellence (NICE) guidelines consider LAIs for people with schizophrenia who would prefer such a treatment after an acute episode, or when combatting covert nonadherence (either intentional or unintentional) to antipsychotic medication is a clinical priority.[6] Other older guidelines, such as those from the American Psychiatric Association (APA) and Royal Australian and New Zealand College of Psychiatrists (RANZCP), recommend LAIs for those with recurrent relapses related to nonadherence.[7,8]

Although guidelines may suggest later use of LAIs, a systematic review and meta-analysis published in 2013 including 25 mirror-image studies from 28 countries and almost 6,000 patients over at least 12 months, demonstrated strong superiority of LAIs over oral antipsychotics in preventing hospitalization and in decreasing the number of hospitalizations. This finding was intriguing as mirror image studies are arguably more reflective of real-world populations than those enrolling in industry-sponsored randomized controlled trials.[28] This finding continues to be replicated with overwhelming evidence. A study in 2014 with over 23,000 patients from 58 studies confirmed the superiority of LAIs over oral treatment with hospital reduction rates 20 percentage points higher for LAIs compared to oral antipsychotics.[29] Medicaid claims data reported that in patients with previous nonadherence, who were started on LAIs were more adherent than those prescribed oral treatment. The data also showed lower odds of rehospitalization, particularly with SGA LAIs, as compared to oral antipsychotics.[30] More recently, the landmark study from Tiihonen and colleagues showed that in over 29,000 schizophrenia patients in Sweden, LAIs were associated with lower relapse rates and lower risk of treatment failure.[31] In this same cohort, they found that all-cause mortality was lowest in those treated with LAIs.[32]

A recent a 12-month randomized clinical trial of recent onset schizophrenia patients on risperidone LAI versus oral risperidone, found that psychotic exacerbation and/or relapse rates were lower for the LAI compared to the oral antipsychotic. The risperidone LAI better controlled hallucinations and delusions and was associated with better adherence and fewer discontinuations compared to oral treatment. The authors suggested based on these findings from a well-controlled trial that LAI antipsychotics should be offered earlier in the course of illness.[33] Also, in a recent publication following patients with schizophrenia for up to 20 years in over 50,000 people in a Finnish cohort, first episode patients on LAIs had a lower risk of hospitalization compared to those taking oral antipsychotics.[34]

Unfortunately, evidence does not always translate into practice. Most clinicians report using LAIs in <10% of patients, with psychiatrists only offering LAIs to half of their patients.[35-36] Only 12.4% of patients who were nonadherent to oral treatment were switched to an LAI formulation during a 3-year prospective study.[37] Potential obstacles to LAI use include an "anti-shot" sentiment or related stigma against obtaining antipsychotics through injections, required resources and staffing to maintain and provide injectable agents in an outpatient setting, and the pharmacokinetic complexity of dosing oral antipsychotics during the initiation and titration of LAIs.

Previous concerns about stigma of injectables appears to be decreasing, but oftentimes clinicians do not stay abreast of advances in the class, safety improvements, pharmacokinetic advantages, and changing views in patient preference.[38-40] Clinicians should consider the pros and cons of starting LAIs for first-episode psychosis for patients who may most benefit and maintain current knowledge of emerging data regarding available formulations, dosing strategies, and administration issues.[41]

Currently there are two long-acting injectable, first generation antipsychotics (FGAs) available on the US market, fluphenazine and haloperidol. Fluphenazine enanthate was approved for marketing in 1967 and was later replaced by fluphenazine decanoate due to its longer half-life. Haloperidol decanoate was approved in 1986. Both are based in sesame seed oil and recommended to be administered via a z-track method.[42,43] See table in *LAI Practical Tips Resource* for additional details regarding the pharmacokinetics of all LAIs. Advantages to use of the first generation LAIs are the lack of need for oral supplementation and lack of need for refrigeration. Obstacles to the use of FGA LAIs include the increased risk of movement disorders and oil-based delivery systems.

Risperidone Microspheres Long-Acting Injection

The initial SGA LAI product approved on the market was risperidone microspheres, polymeric microspheres of risperidone that gradually break down over several weeks.[44] The initial approval was for the treatment of schizophrenia based on oral data and a 12-week efficacy trial of the microspheres. It is now approved for bipolar disorder, as well.[45] The medication has a small initial release of the medication (<1%), but has a lag time of 3 weeks for release, thus requiring oral supplementation for 21 days at initiation and when increasing dose. The medication is given every two weeks, requires refrigeration and reconstitution, but does not require a post dose observation period.[45] Complete details on risperidone microspheres and all SGA LAIs are found in the *LAI Practical Tips Resource*.

Paliperidone Palmitate Long-Acting Injection

Risperidone's active metabolite, paliperidone (9-hydroxyrisperidone) is also available as a LAI, paliperidone palmitate. It is an aqueous suspension using a proprietary technique called "Nanocrystal" technology. Its acute efficacy was established in four short-term (one 9-week and three-13 week) double-blind, randomized, placebo-controlled, fixed-dose studies of acute relapses in adult inpatients

Slide 4. Decreased All Cause Mortality with LAIs

Decreased All Cause Mortality with LAIs

- All cause mortality study in Sweden of all patients 16-64 with schizophrenia diagnosis (N=29,823)
- Follow-up of up to 7.5 years
- Lowest mortality rate for SGA LAIs
- In pairwise comparisons, LAIs were associated with 33% lower mortality than equivalent orals (0.67, 0.56-0.80)

Taipale H, et al. *Schiz Res* 2018.

Slide 5. Potential Obstacles to LAIs

Potential Obstacles to LAIs

- ***Anti-shot sentiment/stigma***
- 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
- Less flexibility of dosing
- Pain at injection site, fear of needles
- Delayed disappearance of adverse effects

McEvoy JP. *J Clin Psychiatry*. 2006; Kane JM, et al. *J Clin Psychiatry*. 2003; Citrome L. *Expert Rev Neurother*. 2013; Weiden PJ, *J Clin Psychiatry*. 2015.

Slide 6. Currently Available Second Generation LAIs

Currently Available Second Generation LAIs

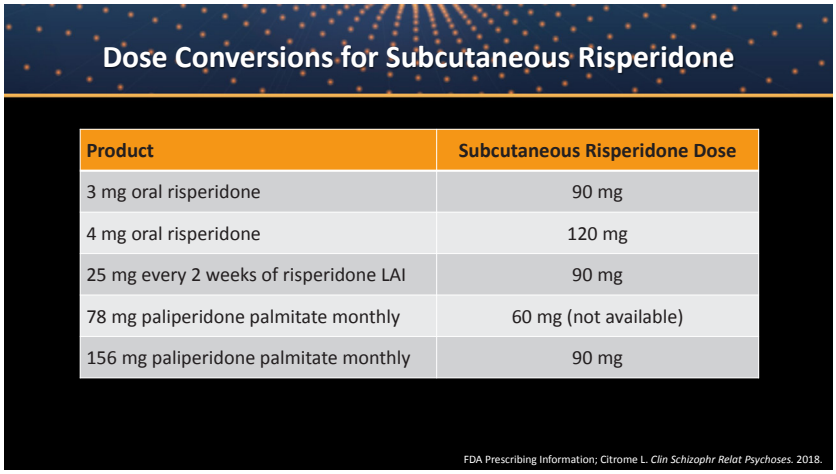
Key Component	Generic Name	Brand Name
Risperidone	Risperidone Long-acting Injection (IM)	Risperdal Consta®
	Risperidone Extended-Release (SQ)	Perseris®
Paliperidone	Paliperidone Palmitate (IM)	Invega Sustenna®
	Paliperidone Palmitate Extended Release (IM)	Invega Trinza®
Olanzapine	Olanzapine Pamoate (IM)	Zyprexa Relprevv®
Aripiprazole	Aripiprazole Extended-Release (IM)	Abilify Maintena®
	Aripiprazole Lauroxil Extended-Release (IM)	Aristada®
	Aripiprazole Lauroxil Nanocrystals Extended-Release (IM)	Aristada Initio®*

*Not an LAI; utilized during initiation
See *LAI Practical Tips for Practice* Resource provided

FDA Prescribing Information.

with schizophrenia. In three longer-term studies, treatment with paliperidone palmitate at doses between 39 mg and 156 mg significantly delayed the time to recurrence of symptoms of schizophrenia after 24 weeks of maintained symptom stability. Additionally, in a 15-month randomized, double-blind, placebo-controlled study, paliperidone palmitate monotherapy or combined with mood stabilizers/antidepressants delayed time to recurrence of psychotic or mood symptoms in persons with schizoaffective disorder.[46-48]

Slide 7. Dose Conversions for Subcutaneous Risperidone



Unlike risperidone microspheres, which is dosed every two weeks, paliperidone palmitate is dosed every four weeks, with a loading dose to avoid oral supplementation. No refrigeration, reconstitution, or post-dose observation period is required.

In addition to the monthly paliperidone palmitate, there is a three-month formulation which was approved in May of 2015 for use in people with schizophrenia who have been treated with the once-monthly formulation of paliperidone palmitate for at least 4 months. Efficacy in delaying time to relapse and adverse rates were similar between the two formulations in a non-inferiority study.[46-48]

The three-month formulation is denser with a different particle size than the once-monthly formulation, providing a slower rate of dissolution. The doses are available in a pre-filled syringe in an aqueous solution in a sufficiently small volume so that they can be administered in the deltoid muscle, although gluteal injection remains an option. The administration does require vigorous shaking for at least 15 seconds prior to administration, compared to 10 seconds with the monthly formulation.[46-50]

Subcutaneous Risperidone

The most recent SGA LAI introduced on the market is a sustained release formulation of risperidone, which is administered by subcutaneous injection every 4 weeks. The efficacy was demonstrated for the treatment of schizophrenia in adults in an 8-week study compared to placebo.[51,52]

This injection is reconstituted via a two-syringe mixing system. One syringe contains a prefilled liquid delivery system (Atrigel) and another syringe with risperidone powder. The two syringes require 60 cycles to mix the two together, with one cycle constituting pushing both syringes. The medication is then administered subcutaneously in the abdomen while the patient is supine. The patient should be educated on the potential development of a lump several weeks after the injection at the injection site. The patient should avoid rubbing and any placement of belts or clothing in the injection site area.[53] The injection kit should be refrigerated and needs to come to room temperature for 15 minutes prior to mixing. The injection kit can up stored unopened for up to 7 days prior to administration, but after removal from the fridge must be used within 7 days or discarded. No oral overlap is required with the risperidone subcutaneous injection, but established tolerability with the oral is recommended prior to utilization of the injection.[53]

Olanzapine Pamoate Long-Acting Injection

Olanzapine pamoate is the crystalline salt of olanzapine and pamoic acid in water. Its efficacy was established in two double-blind, randomized clinical trials for the treatment of acute schizophrenia and for the maintenance of response. The product offers several dosing strategies including: 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.[54,55]

While the LAI has the same general tolerability as that of oral olanzapine, with the LAI there is the additional risk of a post-injection delirium sedation syndrome (PDSS), occurring at a rate of 0.07% of injections. PDSS requires a risk-management plan that

includes observing the patient for 3 hours after each injection.[55]

Aripiprazole Monohydrate Long-Acting Injection

Several aripiprazole LAI products have recently come to the market. The original product, aripiprazole monohydrate, is a water-based formulation available in vial kits of 400 mg and 300 mg, and in dual chamber prefilled syringe kits. Aripiprazole monohydrate has established efficacy in both acute and maintenance treatment of schizophrenia and is approved for bipolar I maintenance treatment as monotherapy. The medication is dosed every 4 weeks, and requires oral supplementation for 14 days.[43,56]

As with oral aripiprazole, dosage adjustments are recommended in patients who are CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors and/or CYP2D6 inhibitors for >14 days. It should not be prescribed with CYP3A4 inducers if these will be used >14 days.[56]

Aripiprazole Lauroxil Long-Acting Injection

Aripiprazole lauroxil is a prodrug of N-hydroxymethyl aripiprazole, which is, in turn, a prodrug of aripiprazole. It employs a unique release mechanism that results in extended systemic release after administration. It is a water-based prefilled syringe and the aripiprazole is subsequently released from the muscle through an enzymatic process. This product is composed of micron-sized particles specifically designed for slow dissolution, which supports the long dosing intervals. Compared to aripiprazole monohydrate, aripiprazole lauroxil can be dosed every 4, 6, or 8 weeks. Although, with this product, a 21-day oral supplementation is required, unless aripiprazole lauroxil nanocrystal technology is utilized (see section on aripiprazole lauroxil nanocrystal technology in *LAI Practical Tips Resource*).[57,58] The same dosage adjustments are required for this product as the oral aripiprazole and aripiprazole monohydrate.[59]

Slide 8. Starting an LAI

Starting an LAI

Product	Oral Overlap	Loading Dose	Peak Levels
Aripiprazole Monohydrate	14 days	N/A	5-7 days
Aripiprazole Lauroxil	21 days ***or*** aripiprazole lauroxil nanocrystal technology	Aripiprazole lauroxil nanocrystal technology	4 days
Olanzapine Pamoate	N/A	210 mg/2 wks or 405 mg/4 wks for 8 wks; or 300 mg/2wks for 8 wks	7 days
Paliperidone Palmitate Once Monthly	N/A	D1-234 mg; D7- 156 mg; D35- monthly dose	13 days
Paliperidone Palmitate Every Three Months	N/A	Paliperidone palmitate monthly for 4 months (last 2 same doses)	30-33 days
Risperidone Microspheres	21 days	N/A	21 days
Subcutaneous Risperidone	N/A	N/A	4-6 hours

See *LAI Practical Tips for Practice* Resource provided

FDA Prescribing Information.

Slide 9. Dosage Conversions

Dosage Conversions

Product	Oral	Maintenance IM/SQ
Aripiprazole Monohydrate	N/A	Start with 400 mg/4 wks
Aripiprazole Lauroxil	10 mg 15 mg ≥20 mg	441 mg/4 wks 662 mg/4 wks, 882 mg/6 wks or 1064 mg/8 wks 882 mg/4 wks
Olanzapine Pamoate	10 mg 15 mg 20 mg	150 mg/2 wks or 300 mg/4 wks 210 mg/2 wks or 405 mg/4 wks 300 mg/2 wks
Paliperidone Palmitate	3 mg 6 mg 9 mg 12 mg	39-78 mg/4 wks 90 day 273 mg/12 wks 117 mg/4 wks 90 day 410 mg/12 wks 156 mg/4 wks 90 day 546 mg/12 wks 234 mg/4 wks. 90 day 819 mg/12 wks
Risperidone Microspheres	N/A	Start with 25 mg/2 wks
Subcutaneous Risperidone	3 mg 4 mg	90 mg/4 wks 120 mg/4 wks

See *LAI Practical Tips for Practice* Resource provided

FDA Prescribing Information.

Slide 10. Continuing an LAI

Continuing an LAI

Product	Frequency	Missed Doses
Aripiprazole Monohydrate	4 weeks	>2 wks: oral supplementation w/missed dose
Aripiprazole Lauroxil	4 weeks: 441, 662, 882 mg 6 weeks: 882 mg 8 weeks: 1064 mg	>2 weeks: 7 or 21 day oral supplementation w/missed dose; Aripiprazole lauroxil nanocrystal technology
Olanzapine Pamoate	2 weeks: 150, 210, 300 mg 4 weeks: 300, 405 mg	No direction
Paliperidone Palmitate Once Monthly	1 month	± 7 day grace period; >6 weeks: loading dose
Paliperidone Palmitate Every Three months	3 months	± 14 day grace period; > 4 months: loading dose
Risperidone Microspheres	14 days	No direction; oral supplementation w/missed dose
Subcutaneous Risperidone	4 weeks	No direction; receive next dose as soon as possible

See *LAI Practical Tips for Practice* Resource provided

FDA Prescribing Information.

Slide 11. Risperidone and Paliperidone Choices Differ

Risperidone & Paliperidone Choices Differ

	Risperidone Microspheres	Paliperidone Palmitate Monthly	Paliperidone Palmitate Every Three Months	Risperidone Subcutaneous
Year approved	2003	2009	2009	2018
Other indications	Bipolar disorder	Schizoaffective disorder	None	None
Injection sites	Deltoid or gluteal	Deltoid or gluteal	Deltoid or gluteal	Subcutaneous
Needle gauge	20G or 21G	22G or 23G (23G option for monthly only)	22G	18G
Injection volume	~2 mL	0.25 to 1.5 mL (monthly) 0.88 to 2.6 mL (3 month)	312 mg/mL; range 0.9 mL (273 mg) to 2.6 mL (819 mg)	0.6 mL (90 mg), 0.8 mL (120 mg)
Injection frequency	Every 2 weeks	Every 4 weeks (every 3 months for the 3-month formulation)	12 weeks	4 weeks
Starting dose	25 mg	234 mg Day 1 + 156 mg Day 8 in deltoid	After treatment with 1-month paliperidone palmitate for at least 4 months: 273 mg, 410 mg, 546 mg, 819 mg (3.5 times the last dose of the once monthly formulation)	90 or 120 mg
Maintenance dose	25 mg (max 50 mg)	117 mg (range 39 to 234 mg); dose for 3 month formulation = 3.5 x once monthly dose)	Same as above	90 or 120 mg
Oral supplement	Yes	No	No	No
Reconstitution	Yes	No	No	Yes
Refrigeration	Yes	No	No	Yes
Observation	No	No	No	No

Citrome L. *Expert Rev Neurother.* 2013.

Slide 12. Aripiprazole Choices Differ as Well

Aripiprazole Choices Differ As Well

	Aripiprazole monohydrate	Aripiprazole lauroxil
Indications	Schizophrenia, bipolar I maintenance	Schizophrenia
Available in the US	2013	2015
Strengths available	300 mg, 400 mg	441 mg, 662 mg, 882, and 1064 mg
Recommended dose	400 mg (300 mg in patients with adverse reactions)	441 mg, 662 mg, 882, and 1064 mg
Requires adding diluent	Yes, but pre-filled dual-chambered syringe available in addition to vial kits	No, pre-filled syringe "tap and shake"
Injection frequency	Monthly	Monthly (all doses) or q6 weeks (882 mg) or q8 weeks (1064 mg)
Injection site	Deltoid or gluteal	Deltoid (441 mg only) or gluteal
Needle sizes	1 inch 23G, 1.5 inch 22G, 2 inch 21G	1 inch 21G, 1.5 inch 20G, 2 inch 20G
Injection volume	1.5 mL and 2.0 mL, for the 300 mg and 400 mg strengths, respectively	1.6 mL, 2.4 mL, 3.2 ml, and 3.9 ml for the 441 mg, 662 mg, 882 mg, and 1064 mg strengths, respectively
Oral supplementation	14 days	21 days (1 day if NCD formulation is used to initiate)
Early injection	26 days after last injection	14 days after last injection
Oral supplementation missed doses "grace period"	As long as 2 weeks	As long as 4 weeks
OK with CYP2D6 and/or CYP3A4 inhibitors > 14 days	Yes, with dose adjustments	Yes, with possible dose adjustments
OK with CYP3A4 inducers > 14 days	No	Yes, with possible dose adjustments
Storage requirements	Room temperature	Room temperature

Adapted from Citrome L. *Expert Rev Clin Pharmacol.* 2016; Citrome L. *Expert Rev Neurother*. 2017; FDA Prescribing Information.

Slide 13. Olanzapine Choice Limited to One Option

Olanzapine Choice is Currently Limited to One Option

	Olanzapine Pamoate
Year approved	2009
Other indications	No
Injection sites	Gluteal
Needle gauge	19G
Injection volume	1.0 to 2.7 mL
Injection frequency	Every 2 or 4 weeks
Starting dose	Varies from 210 mg q2wk or 405 mg q4wk to 300 mg q2wk
Maintenance dose	Varies from 150 mg q2wk or 300 mg q4wk to 300 mg q2wk
Oral supplement	No
Reconstitution	Yes
Refrigeration	No
Observation	3 hours

Citrome L. *Expert Rev Neurother*. 2017.

Aripiprazole Lauroxil Nanocrystal Technology-Intermediate Injection

In order to reduce the time needed for oral supplementation for aripiprazole lauroxil, an intermediate acting injectable aripiprazole lauroxil is available. The injection is a nano-crystalline milled dispersion of aripiprazole lauroxil. The nanocrystal medications are formulated as nanometer-sized medication crystals ranging between 10 to 1,000 nm. When compared to the microcrystals of the aripiprazole lauroxil, the smaller medication particle size increases the rate of dissolution, thereby enhancing bioavailability. The therapeutic intent of this dosage form is to minimize the need for oral aripiprazole treatment overlap that follows the first injection of aripiprazole lauroxil.[57,59]

The recommended dosing for this use of this product in conjunction with an aripiprazole lauroxil injection is: 30 mg oral aripiprazole on day 1, aripiprazole lauroxil nanocrystal technology 675 mg on day 1, and aripiprazole lauroxil (441, 662, 882, 1064 mg) on same day as above or up to 10 days after.[59]

As previously stated, there are many different strategies for initiating LAI antipsychotics. Oral overlap and loading dose strategies are outlined in the following slide. Additionally, dosage conversions from an oral dose to an LAI dose are also provided. The frequency of injections and considerations for missed injections are provided here, as well as in the *LAI Practical Tips Resource.*

There are many different aspects of care to be considered when choosing an LAI antipsychotic for a patient, including: how often the injections are administered, needle gauge, injection volume, whether there is a choice of injection site, whether there is a requirement of reconstitution or refrigeration of the product, if there is an oral supplement requirement, whether there are any special requirements for observation post-injection, and if there is a "grace period" if a dose is missed.

When considering an LAI antipsychotic for a patient, clinicians should consider several therapeutic questions prior to treatment selection.[44]

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

If the patient is *not,* then offer a switch to the corresponding LAI formulation. For patients receiving oral risperidone, consider paliperidone palmitate for convenience, as it is dosed every 4 weeks rather than every 2 weeks. 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. Additionally, exposure to benztropine or other anticholinergics can also increase the risk to develop tardive dyskinesia and can make existing tardive dyskinesia worse.

For patients receiving oral olanzapine, olanzapine pamoate will require close monitoring. Consideration of the availability of the product should be well thought out prior to use. 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 to consider prior to treatment selection.

2 **Is the patient being treated acutely?**

If so, consider a LAI antipsychotic that does not require oral supplementation and where the clinical trials have demonstrated acute efficacy, such as in paliperidone palmitate or olanzapine pamoate.

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

If so, consider aripiprazole, paliperidone palmitate, or risperidone microsphere among SGA LAIs. Avoid olanzapine pamoate. The clinician could also consider an FGA LAI, as well.

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

If so, consider an aripiprazole LAI. Avoid paliperidone palmitate, risperidone microspheres, or the first-generation LAI antipsychotics.

5 **Is acquisition cost the primary concern?**

If so, the first-generation LAI antipsychotics may be the primary option available, but remain cognizant that using concomitant oral anticholinergics for the management of motoric adverse effects will add complexity to the treatment regimen and can interfere with memory.

Conclusions

In patients with schizophrenia, relapse prevention is of the utmost importance. Relapse is related to hospital readmission, suicide rate, and overall healthcare costs. Preventing relapse today can make a difference for a lifetime. Enhanced adherence to antipsychotics can decrease relapse rates. Unfortunately, nonadherence is common and there is an immense need to identify adherence barriers for patients. LAIs may reduce the risk of relapse and hospital readmission. Patients are often willing to accept LAI antipsychotic therapy when offered. New medication options are available for LAI therapy, including 2 and 3-month injection intervals. Of particular note, patients early in their illness have the most to gain, as well as the most to lose when it comes to appropriate selection of antipsychotic therapy.

Case 1: First Episode

A 24-year-old patient presents to the ER after displaying symptoms of paranoia, self-isolating, disorganized speech, irritability, and agitation. During the course of an inpatient hospitalization, the patient is diagnosed with schizophrenia.

The patient is stabilized on haloperidol 5 mg twice daily and discharged to the community for follow-up.

What treatment options would you discuss with the patient?

- ○ Continuation on the same oral medication
- ○ Alternative formulations of the current medication
- ○ Other available oral medications
- ○ Alternative formulations of other antipsychotic medications
- ○ All of the above

Discussion: For this patient, the provider should consider the patient's ability and desire to continue the medication post discharge. Given the data presented on the high level of nonadherence after discharge, the provider should inquire and discuss this with the patient and determine the best treatment option for when the patient returns to the community.

The patient may want to continue on the same medication which would be an option if the patient has the proper supports in the community. The provider should discuss alternative formulations of haloperidol with the patient, as the patient may prefer a long-acting injection versus daily oral medications. The provider at this time may discuss other available oral medication or LAIs, but switching medications immediately upon discharge is not a good idea. Since the patient was stabilized on haloperidol during the hospitalization, the patient should remain on this medication for a time prior to considering a switch to another antipsychotic. The provider could discuss other options for future considerations.

What risks are there to continuing the current treatment?

- ○ Nonadherence
- ○ Adverse effects
- ○ Residual symptoms
- ○ All of the above

There are risks to any medication regimen. When considering the risks to the current treatment regimen, nonadherence could occur. The current literature suggests it is very likely. Adverse effects could occur with any medication, but with haloperidol abnormal movements is one of the most likely. Residual symptoms, such as negative symptoms, can be a risk as well. Many times, there are residual symptoms which occur with any treatment regimen.

Would you make any recommended changes to the patient's current treatment regimen?

One could consider changing the medication to a LAI given the data on treatment prognosis and risk of nonadherence with oral antipsychotics. Offering a LAI, in particular in first episode patients, can help to reduce continued symptoms.

If the patient stated they were only going to take the medication long enough to get out of the hospital:

- ○ Would you consider different treatment options?
- ○ How would you present these choices to the patient?

Discussion: A different treatment option should be considered if the patient stated they were only going to take the medication long enough to get out of the hospital. The provider should attempt to have a discussion regarding the importance of medication adherence post-discharge and the option to take a medication once a month. The provider should also engage the caregivers and support of the patient as well for additional help in discussion with the patient.

Presenting the LAI as an option which can prevent future symptoms, hospitalizations, and reduce complications of schizophrenia would be beneficial to the patient. Providing the patient with the data surrounding nonadherence and the risks of not taking medications is vital. It is best to not present the injection as "a shot" you get each month. Providing the positives first is most important.

Case 2: Switching Agents

33-year-old patient with schizophrenia was diagnosed at age 23 and has been maintained on risperidone microspheres 37.5 mg Q2 weeks for the last 4 years.

Previous medication trials include:

- Olanzapine: weight gain
- Ziprasidone: too hard to remember to take twice daily
- Risperidone: after doing well on PO; switched to LAI formulation for convenience

Patient states coming in every two weeks is becoming problematic with work schedule. Would like to use something which requires less frequent appointments.

What agent would you recommend transitioning this patient to?

- ○ Paliperidone Palmitate every three months
- ○ Paliperidone Palmitate once monthly
- ○ Aripiprazole Lauroxil
- ○ Aripiprazole Monohydrate
- ○ Subcutaneous Risperidone

Given the patient is currently stabilized on risperidone, it would easy to switch the patient to the paliperidone palmitate monthly. The patient will likely continue to well, as this is the active metabolite of risperidone. If the patient continues on the monthly paliperidone palmitate, they could be switched to the paliperidone palmitate every three months. The patient needs to have four injections of the monthly paliperidone palmitate before receiving the paliperidone palmitate every three months.

The subcutaneous risperidone could also be considered as the patient would be switched to every four weeks. The only concern would be determining the dose of subcutaneous risperidone to administer to the patient.

The patient could be switched to any of the aripiprazole products, although oral tolerability would need to be determined prior to switching. Additionally, determining the dose of the medication may be challenging as the patient may not have ever tried aripiprazole.

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LONG-ACTING INJECTABLE ANTIPSYCHOTIC MEDICATIONS AND CONVERSION DOSING

Practical Tips for Practice

Long-Acting Injectable Antipsychotic Medications and Conversion Dosing: Practical Tips for Practice

	Usual Starting Dose	Target Dose	Max Dose	Dosing Interval	Loading Dose Option	Oral or Other Overlap*	Injection Site	Special Notes
Fluphenazine Decanoate[1]	12.5-25 mg IM/Subcut	12.5-50 mg (interval determined by patient response)	100 mg/dose	Q 2-4 weeks	Not established	Continue oral, decreasing dose by half after first injection, d/c oral therapy after second injection[1]	Gluteal Deltoid	Z-track recommended[2]
Haloperidol Decanoate[3]	10-20X daily PO dose IM	10-15X daily PO dose IM monthly	100 mg/1st injection; 450 mg/month	Q 4 weeks	Yes	Continue oral for the first 2 to 3 injections if not using loading dose[3]	Gluteal Deltoid	Z-track recommended[2] Do not administer > 3 ml per injection site
Risperidone Long-acting injection (Risperdal Consta®)[4]	25 mg IM Q 2 weeks + PO dose for 3 weeks	25-50 mg IM Q 2 weeks (range 12.5-50 mg)	50 mg Q 2 weeks	Q 2 weeks	No	Oral risperidone (or other oral antipsychotic) should be given with 1st injection and continued for 3 weeks	Gluteal Deltoid	None
Risperidone "extended release" (Perseris®)[5]	90 or 120 mg SQ Q 4 weeks	90 or 120 mg SQ Q 4 weeks	120 mg IM Q 4 weeks	Q 4 weeks	n/a	Establishment of tolerance by prior oral administration is recommended	Abdomen- SQ	Abdomen only Inject slow and steady
Paliperidone Palmitate monthly (Invega Sustenna®)[6]	234 mg IM day 1, then 156 mg IM day 8 (both in deltoid)#	117 mg IM Q 4 weeks (range 39-234 mg)	234 mg Q 4 weeks	Q 4 weeks	Yes	Establishment of tolerance by prior oral administration is recommended	Gluteal (after second injection) Deltoid	Deltoid Day 1 and 8 Injections Maintenance deltoid or gluteal
Paliperidone Palmitate three month (Invega Trinza®)[7]	Used only after establishment of four months of Paliperidone Palmitate once monthly injection (last 2 months with the same dose); dose based on Paliperidone Palmitate once monthly dose$	Based on Paliperidone Palmitate once monthly dose	819 mg Q 3 months	Q 3 months	No	Use of Paliperidone Palmitate monthly for the previous 4 months (last 2 months with the same dose)	Gluteal Deltoid	Inject slowly
Olanzapine Pamoate (Zyprexa Relprevv®)[8]	150, 210,300 mg IM Q 2 weeks 300 mg or 405 mg IM Q 4 weeks	150, 210, 300 mg Q 2 weeks or 300, 405 mg Q 4 weeks	300 mg Q 2 weeks; 405 mg Q 4 weeks	Q 2 weeks or Q 4 weeks	Yes	Establishment of tolerance by prior oral administration is recommended	Gluteal	Post dose monitoring: at least three hours; observe for delirium and sedation; inject steady continuous pressure
Aripiprazole Monohydrate (Abilify Maintena®)[9]	400 mg IM Q month	400 mg IM Q month	400 mg Q month	Q month	No	Oral aripiprazole 10-20 mg/day (or other oral antipsychotic already in use) should be given after the first injection for 14 consecutive days	Gluteal Deltoid	Inject Slowly
Aripiprazole Lauroxil nanocrystal technology (Aristada Initio®)[10]	675 mg IM	Single Dose Only	675 mg	At initiation of Aripiprazole Lauroxil or if indicated for reinitiating Aripiprazole Lauroxil	n/a	30 mg oral aripiprazole in combination when initiating Aripiprazole Lauroxil and if indicated for reinitiating Aripiprazole Lauroxil	Gluteal Deltoid	Rapid and Continuous Injection
Aripiprazole Lauroxil (Aristada®)[11]	441, 662, 882, or 1064 mg IM Q 4 weeks; 882 mg Q 6 weeks; 1064 mg Q 2 months	441, 662, 882, or 1064 mg IM Q 4 weeks; 882 mg Q 6 weeks; 1064 mg Q 2 months	1064 mg	Q 4 weeks (all doses) Q 6 weeks (882 mg only) Q 2 months (1,064 mg only)	Yes	Oral aripiprazole should be given after the first injection for 21 consecutive days if Aripiprazole Lauroxil nanocrystal technology not utilized	Gluteal (all doses) Deltoid (441 mg dose only)	Rapid and Continuous Injection

*Prior establishment of tolerability recommended
#Patients may be given the second initiation dose within a ±4-day flexible window
$Patients may be given the injection up to 2 weeks before or after the 3-month time point

1. Fluphenazine Decanoate Injection, USP [package insert]. Rockford, IL: Mylan Institutional LLC;2018.
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7. Invega Trinza ® [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.;2018.
8. Zyprexa Relprevv ® [package insert]. Indianapolis, IN: Eli Lilly and Company;2018.
9. Abilify Maintena ® [package insert]. Tokyo, Japan: Otsuka Pharmaceutical Co.,LTD.;2018.
10. Aristada Initio® [package insert]. Waltham, MA: Alkermes, Inc.;2018.
11. Aristada® [package insert]. Waltham, MA: Alkermes, Inc.;2018

	How Supplied	Need to Reconstitute	Refrigeration Needed*	Protect from Light	Pre-filled syringes	Needles Provided	Needle Size	Stability after Reconstitution (hrs)
Fluphenazine Decanoate[1]	25 mg/mL; 5 mL multi-dose vial	No	No	Yes	No	No	21 gauge or larger	NA
Haloperidol Decanoate[2]	50 mg/mL & 100 mg/mL; 1 mL single-dose vials and 5 mL multi-dose vials	No	No	Yes	No	No	21 gauge	NA
Risperidone Long-acting injection (Risperdal Consta®)[3]	12.5, 25, 37.5 & 50 mg dose packs	Yes	Yes (7 days maximum at room temp. not to exceed 77°F)	Yes	No	Yes	Gluteal: 20 gauge, 2" Deltoid: 21 gauge, 1"	May be used up to 6 hours after suspended (store at room temp.); resuspend if necessary before administering
Risperidone "extended release" (Perseris®)[4]	90, 120 mg syringe kits	Yes	Yes (7 days maximum at room temp. not to exceed 77°F)	No	No	Yes	18 gauge, 5/8"	May be stored for up to 7 days in its unopened original packaging at room temp. use within 7 days or discard
Paliperidone Palmitate once monthly (Invega Sustenna®)[5]	39, 78, 117, 156, & 234 mg kits	No	No	No	Yes	Yes	Gluteal all patients: 22 gauge, 1.5 " Deltoid: <90 kg: 23 gauge, 1" or ≥90 kg: 22 gauge, 1.5"	Resuspend if necessary before administering
Paliperidone Palmitate three months (Invega Trinza®)[6]	273, 410, 546, 819 mg kits	No	No	No	Yes	Yes	Gluteal all patients: 22 gauge, 1 ½" Deltoid: <90 kg: 22 gauge, 1" ≥90 kg: 22 gauge, 1 ½"	Resuspend if necessary before administering
Olanzapine Pamoate (Zyprexa Relprevv®)[7]	210, 300, & 405 mg single-use kits	Yes	No	No	No	Yes (2" needle not included)	Non-obese: 19 gauge, 1.5" Obese: 19 gauge, 2"	24 hours after suspended; resuspend if necessary before administering
Aripiprazole Monohydrate (Abilify Maintena®)[8]	300, 400 mg pre-filled syringes; 300, 400 mg single-dose vials	Vials and Syringes (via the dual chamber syringe kit)- Yes	No	Yes (pre-filled syringes)	Yes	Yes	Gluteal, non-obese pts or Deltoid, obese patients: 22 gauge, 1.5" Gluteal, obese patients: 21 gauge, 2" Deltoid, non-obese pts: 23 gauge, 1"	Not stated, give injection immediately upon reconstituting; resuspend if necessary before administering
Aripiprazole Lauroxil nanocrystal technology (Aristada Initio®)[9]	675 mg pre-filled syringe	No	No	No	Yes	Yes	Gluteal: 20 gauge, 1 ½", or 20 gauge, 2" Deltoid: 21 gauge, 1" or 20 gauge, 1 ½"	N/A
Aripiprazole Lauroxil (Aristada®)[10]	441, 662, 882, or 1064 mg pre-filled syringes	No	No	No	Yes	Yes	Gluteal all doses: 20 gauge, 1 ½" or 20 gauge, 2" Deltoid (441 mg only): 21 gauge, 1" or 20 gauge, 1 ½"	N/A

* Prior to reconstitution

1. Fluphenazine Decanoate Injection, USP [package insert]. Rockford, IL: Mylan Institutional LLC;2018.
2. Haloperidol Decanoate Injection [package insert]. Rockford, IL: Mylan Institutional LLC;2018.
3. Risperdal Consta® [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.;2019.
4. Perseris® [package insert]. North Chesterfield, VA: Indivior, Inc.;2018.
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6. Invega Trinza ® [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.;2018.
7. Zyprexa Relprevv ® [package insert]. Indianapolis, IN: Eli Lilly and Company;2018.
8. Abilify Maintena ® [package insert]. Tokyo, Japan: Otsuka Pharmaceutical Co.,LTD.;2018.
9. Aristada Initio® [package insert]. Waltham, MA: Alkermes, Inc.;2018.
10. Aristada® [package insert]. Waltham, MA: Alkermes, Inc.;2018.

Dosing Parameters

Recommended dosing of FLUPHENAZINE DECANOATE based on oral dose

Daily Oral Dose of Fluphenazine	Dose of Fluphenazine Decanoate every three weeks
10 mg/day	12.5 mg/3 weeks

Recommended dosing of HALOPERIDOL DECANOATE based on oral dose

Patients	Monthly 1st month	Maintenance after the 1st Month
Stabilized on low daily doses (up to 10 mg/day), elderly or debilitated	10-15X daily oral dose	10-15X previous daily oral dose
High dose, high risk or relapse, tolerant to oral haloperidol	20X daily oral dose	10-15X previous daily oral dose

Recommended dosing of RISPERIDONE LONG-ACTING INJECTION

All patients are recommended to start at 25 mg IM every two weeks 12.5 mg IM may be appropriate for some patients (e.g., renal or hepatic impairment) Do not combine different dosage strengths in a single administration

Recommended dosing of RISPERIDONE "Extended Release"

Oral risperidone dose	Risperidone Extended Release
3 mg	90 mg/4 weeks
4 mg	120 mg/4 weeks
May not be recommended if oral dose < 3 mg or > 4 mg daily	

Recommended dosing of PALIPERIDONE PALMITATE EXTENDED-RELEASE INJECTABLE SUSPENSION based on oral dose or renal function

Daily oral dose of paliperidone palmitate extended-release	Initiation (Deltoid only)	Dose of paliperidone palmitate every four weeks (deltoid or gluteal)
3 mg/day	Initiate with 234 mg IM on day 1 and 156 mg IM one week later	39-78 mg
6 mg/day	Initiate with 234 mg IM on day 1 and 156 mg IM one week later	117 mg
9 mg/day	Initiate with 234 mg IM on day 1 and 156 mg IM one week later	156 mg
12 mg/day	Initiate with 234 mg IM on day 1 and 156 mg IM one week later	234 mg
Mild renal impairment (CrCl ≥50 mL/min to < 80 mL/min)	Initiate with 156 mg IM on day 1 and 117 mg one week later	78 mg

Recommended dosing for a Missed Second Initiation Dose of PALIPERIDONE PALMITATE ONCE MONTHLY

Timing of Missed Second Initiation Dose	Dosing
Less than 4 weeks since first injection	Administer the 2nd injection dose of 156 mg in the deltoid muscle as soon as possible. Recommended to administer a third injection of 117 mg in either the deltoid or gluteal muscle 5 weeks after the 1st injection (regardless of the timing of the 2nd injection). Then resume regular monthly dosing in either the deltoid or gluteal muscle.
4 to 7 weeks since 1st injection	Resume dosing with two injections of 156 mg in the following manner: Administer a deltoid injection as soon as possible. Administer a second deltoid injection 1 week later. Then resume regular monthly dosing in either the deltoid or gluteal muscle.
More than 7 weeks since 1st injection	Restart dosing with recommended initiation: Administer a 234 mg deltoid injection on Day 1. Administer a 156 mg deltoid injection 1 week later. Then resume regular monthly dosing in either the deltoid or gluteal muscle.

Recommended Management of a Missed Maintenance Dose of PALIPERIDONE PALMITATE ONCE MONTHLY

Timing of Missed Maintenance Dose	Dosing
4 to 6 weeks since last injection	Resume regular monthly dosing as soon as possible at the patient's previously stabilized dose, followed by injections at monthly intervals
More than 6 weeks to 6 months since last injection	Resume the same dose the patient was previously stabilized on (unless the patient was stabilized on a dose of 234 mg, then the first 2 injections should each be 156 mg) in the following manner: Administer a deltoid injection as soon as possible. Administer a second deltoid injection 1 week later at the same dose. Then resume administering the previously stabilized dose in the deltoid or gluteal muscle 1 month after the second injection.
More than 6 months since last injection	Restart dosing with recommended initiation: Administer a 234 mg deltoid injection on Day 1. Administer a 156 mg deltoid injection 1 week later. Then resume administering the previously stabilized dose in the deltoid or gluteal muscle 1 month after the second injection.

Recommended dosing of PALIPERIDONE PALMITATE EXTENDED-RELEASE every three-month INJECTABLE SUSPENSION based on PALIPERIDONE PALMITATE EXTENDED-RELEASE every four-week INJECTABLE SUSPENSION

Paliperidone palmitate extended-release dose	Paliperidone palmitate extended-release every three-month injectable suspension dose
78 mg/4 weeks	273 mg/12 weeks
117 mg/4 weeks	410 mg/12 weeks
156 mg/4 weeks	546 mg/12 weeks
234 mg/4 weeks	819 mg/12 weeks

Recommended dosing for re-initiation of PALIPERIDONE PALMITATE every three-month INJECTION

- Missed dose more than 3 ½ months but less than 4 months since last injection: dose should be administered as soon as possible, then resume with 3-month injections

Recommended dosing of PALIPERIDONE PALMITATE EXTENDED-RELEASE every three-month INJECTABLE SUSPENSION if 4-9 months Since Last Injection

If the last dose of paliperidone palmitate every three months was:	Administer Paliperidone Palmitate once monthly, two doses one week apart (into deltoid muscle)		Then administer paliperidone palmitate every three months (into deltoid or gluteal muscle)
	Day 1	Day 8	1 month after Day 8
273 mg	78 mg	78 mg	273 mg
410 mg	117 mg	117 mg	410 mg
546 mg	156 mg	156 mg	546 mg
819 mg	156 mg	156 mg	819 mg

- If more than 9 months since last injection: re-initiate treatment with the 1-month paliperidone palmitate once monthly.

Recommended dosing of OLANZAPINE PAMOATE EXTENDED-RELEASE INJECTABLE SUSPENSION based on oral dose

Target Oral Dose	Dose during first eight weeks	Maintenance dose after eight weeks
10 mg/day	210 mg/2 weeks or 405 mg/4 weeks	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	300 mg/2 weeks	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300 mg/2 weeks	300 mg/2 weeks

Recommended dosing of ARIPIPRAZOLE LONG-ACTING INJECTION (DO NOT give sooner than 26 days)

All patients are recommended to start at 400 mg IM every month maintenance
300 mg IM monthly may be appropriate for some patients (e.g., strong CYP 2D6 or 3A4 inhibitors) or if patients experience adverse effects at a higher dose that were previously taking 400 mg
200 mg IM monthly may be appropriate for some patients (e.g. CYP 2D6 poor metabolizers taking CYP3A4 inhibitors, concomitant use of CYP 2D6 and/or 3A4 inhibitors) previously taking 300 mg or 400 mg
160 mg IM monthly may be appropriate for some patients (e.g. CYP 2D6 and CYP 3A4 inhibitors) previously taking 300 mg

Recommended dosing for missed doses of ARIPIPRAZOLE LONG-ACTING INJECTION

If second and third doses are missed:	> 4 weeks and < 5 weeks since last injection	> 5 weeks since last injection
	Administer injection as soon as possible	Restart oral aripiprazole for 14 days with next injection
If fourth or additional doses are missed:	If > 4 weeks and < 6 weeks since last injection	If > 6 weeks since last injection
	Administer injection as soon as possible	Restart oral aripiprazole for 14 days with next injection

Recommended dosing of ARIPIPRAZOLE LAUROXIL NANOCRYSTAL TECHNOLOGY (Bridge dosing for initiation of Aripiprazole Lauroxil)

One day, single-dose regimen of the following: Administer one time: 30 mg oral aripiprazole Administer one time: Aripiprazole lauroxil nanocrystal technology IM 675 mg injection (Before injection, tap vial 10 times and shake vigorously for 30 seconds, MUST inject RAPID and CONTINUOUS) Administer: Aripiprazole lauroxil IM (441, 662, 882, 1064 mg) injection (may administer within and up to 10 days after above injection)

Recommended dosing of ARIPIPRAZOLE LAUROXIL (AVOID injecting Aripiprazole Lauroxil Nanocrystal Technology and Aripiprazole Lauroxil in the same deltoid or gluteal muscle.)

Oral Aripiprazole Total Daily Dose	Intramuscular Aripiprazole Lauroxil Dose (Before injection, tap vial 10 times and shake vigorously for 30 seconds, MUST inject RAPID and CONTINUOUS)
10 mg per day	441 mg every month
15 mg per day	662 every month, 882 mg every 6 weeks, or 1064 mg every 2 months
20 mg or higher per day	882 mg every month

Recommended dosing for missed dose of Aripiprazole Lauroxil

Dose of pts. last aripiprazole lauroxil injection	Length of Time Since Last Injection		
441 mg	≤6 weeks	> 6 and ≤7 weeks	>7 weeks
662 mg	≤8 weeks	>8 and ≤12 weeks	>12 weeks
882 mg	≤8 weeks	>8 and ≤12 weeks	>12 weeks
1064 mg	≤10 weeks	>10 and ≤12 weeks	>12 weeks
Dosage and Administration for Re-initiation of Aripiprazole Lauroxil	No supplementation required	Supplement with a single dose of aripiprazole lauroxil nanocrystal technology OR 7 days of oral aripiprazole	Re-initiate with a single dose of aripiprazole lauroxil nanocrystal technology and a single dose of oral aripiprazole PO 30 mg OR supplement with 21 days of oral aripiprazole

Pharmacokinetic Parameters

	T1/2 (Single Dose)	T max
Fluphenazine Decanoate[1]	6-9 days	24 hours
Haloperidol Decanoate[2]	~16 days to 3 weeks	6 days
Risperidone long-acting injection (Risperdal Consta®)[3]	3-6 days (note: medication not appreciably released for approximately 3 weeks after the injection)	4-6 weeks
Risperidone "Extended Release" (Perseris®)[4]	9-11 days	4-6 hours
Paliperidone Palmitate monthly (Invega Sustenna®)[5]	25-49 days	~13 days
Paliperidone Palmitate three months (Invega Trinza®)[6]	84-95 days deltoid and 118-139 days gluteal	30-33 days
Olanzapine pamoate (Zyprexa Relprevv®)[7]	30 days	Within 1 week
Aripiprazole monohydrate (Abilify Maintena®)[8]	29.9-46.5 days gluteal	5-7 days gluteal; 4 days deltoid
Aripiprazole Lauroxil nanocrystal technology (Aristada Initio®)[9]	15-18 days	16-35 days
Aripiprazole Lauroxil (Aristada®)[10]	53.9-57.2 days	37-48 days

1. Fluphenazine Decanoate Injection, USP [package insert]. Rockford, IL: Mylan Institutional LLC;2018.
2. Haloperidol Decanoate Injection [package insert]. Rockford, IL: Mylan Institutional LLC;2018.
3. Risperdal Consta® [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.;2019.
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Long-Acting Antipsychotic Injections: Techniques and Considerations for Success

1. Select an environment for the injection process that maintains the dignity and privacy of the patient
2. Confirm the medication prescribed and time validity, dose, and method of administration
3. Check the patient's identity
4. Determine the desired injection site and confirm that the formulation is appropriate
5. Review the injection process with the patient and consent the patient to receiving the injection
6. Assess the body mass of the patient to aid in needle selection; ensuring the selected needle is appropriate for the formulation and desired injection site
7. Reconstitute (if necessary) and draw up the medication according to the product specific instructions
    a. Consider a separate needle for drawing up and administering haloperidol and fluphenazine decanoate formulations (NOTE: do not substitute for needles provided with all kits)
    b. Visually inspect the medication for clumps; additional taping and shaking may be necessary. If a suspended product is not used right away, it should be shaken vigorously to re-suspend. Suspension should be at room temperature prior to injecting.
8. For gluteal site injections:
    a. Place the patient in the prone position with toes pointing inward
    b. Select the injection site; preferably the ventrogluteal, which can be located by placing the heel of your opposing hand on the patient's greater trochanter (the bump of bone on the outside of the hip bone). The index finger of the hand is placed on the patient's anterior superior iliac spine and the middle finger is stretched dorsally towards but below the iliac crest (the thick curved upper border of the pelvic bone). The triangle formed by the index finger, the third finger and the crest of the ilium is the injection site.
    c. Cleanse the injection site with an alcohol wipe and allow the skin to dry for 30 seconds
    d. Z-track technique if indicated
    e. Position the needle close to the skin at the dorsogluteal site
    f. Insert the needle quickly and smoothly at an angle of approximately 90 degrees
    g. Aspirate for blood- if blood present then discard the needle and restart again
    h. Inject the medication
    i. Withdraw the needle rapidly and apply pressure to any bleeding point
    j. Do not massage the injection site
    k. Apply bandage
    l. Dispose of sharps and biohazard material appropriately and do not recap the needle

References:
1. Gray R, Spilling R, Burgess D, et al. Antipsychotic long-acting injections in clinical practice: medication management and patient choice. *Br J Psychiatry*. 2009;52:S51-56.
2. Cocoman A, Murray J. Intramuscular injections; a review of best practices for mental health nurses. *J Psychiatr Ment Health Nurs*. 2008;15(5):424-434.
3. Wynaden D, Landsborough I, McGowan S, et al. Best practice guidelines for the administration of intramuscular injections in the mental health setting. *Int J Ment Health Nurs*. 2006;15(3):195-200.

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