Solutions to Common Issues in the Use of Long-Acting Injectable Antipsychotics

Stephen R. Saklad, PharmD, BCPP

Clinical Professor Emeritus

Email: saklad@uthscsa.edu

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Learning Objectives:

- 1. Identify common clinical challenges encountered when prescribing long-acting injectable antipsychotics.
- 2. Discuss strategies for addressing adherence, dosing, and missed injections with LAIs.
- 3. Evaluate approaches for managing adverse effects, drug interactions, and optimizing patientcentered outcomes.

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Common situations encountered with the use of long-acting injectable (LAI) antipsychotics can be discouraging to clinicians. Some are more common and easily remembered, while others may be encountered less often. This article serves as a practical guide to addressing these issues.

Storage and Reconstitution Requirements

LAIs have a range of storage requirements (Table 1). Some formulations, such as certain risperidone products, require refrigeration to maintain stability.¹,² In contrast, others, including paliperidone palmitate,³⁻⁶ aripiprazole,⁷,⁸ aripiprazole lauroxil,⁹,¹⁰ olanzapine,¹¹ and different risperidone formulations,¹²,¹³ require storage at controlled room temperature (15°C to 30°C). Specific products may have allowances for short-term storage outside their primary recommended range.¹,² Compliance with each product's storage instructions is essential to maintain the drug's stability and intended slow-release properties. These requirements are important not only for pharmacy and clinic storage but also for patients with planned travel that includes a pre-arranged injection site, as international travel may present additional concerns.¹⁴

Some LAIs are formulated as lyophilized powders or liquids that require reconstitution prior to injection.¹,⁷,^{11–13} The reconstitution process often involves product-specific techniques, such as vigorous shaking or the use of vial adapters, to ensure proper suspension. For example, olanzapine LAI necessitates a specific diluent and technique, including wearing gloves to prevent skin contact and eye protection from potential aerosolization.¹¹,¹⁹ Conversely, many newer LAI formulations are available in prefilled syringes and do not require reconstitution.^{2–10} The type and volume of the diluent and the mixing protocol are critical and differ between products. Using multiple LAIs that need reconstitution in a single clinic can lead to errors; therefore, the clinician should review the specific product's instructions before each use. Incorrectly reconstituted medications must be discarded.

Injection Site Selection and Technique

The appropriate injection site is an important aspect of LAI administration, as it can influence the rate of drug absorption.¹⁵,¹⁶ Injection volume and patient preference are key considerations. Most LAIs are given intramuscularly (IM) in either the deltoid or gluteal muscle. Some formulations with smaller volumes are specified for subcutaneous (SC) injection.

Since the deltoid has significantly greater blood flow per volume of muscle than the gluteus, initiating paliperidone palmitate in the deltoid provides therapeutic drug concentrations sooner. Some LAIs, like olanzapine (Relprevv), are given by gluteal injection only. Higher doses of aripiprazole lauroxil and the paliperidone palmitate 6-month formulation require the gluteal muscle due to their large injection volume. Recording and rotating the injection site is advised (Table 2).

Tolerability testing with the same oral medication for at least a few days is recommended to determine efficacy before using the LAI formulation. While aspiration to check for blood return before an IM injection is routinely recommended, it should be avoided with aripiprazole lauroxil products as this can clog the needle.⁹,¹⁰ If an aripiprazole lauroxil needle clogs, it should be replaced, and the injection administered rapidly at a different site. Recommendations for needle gauge and length depend on the specific LAI, the injection site, and patient factors like body weight.

Oral Overlap and Initiation Regimens

For several LAIs, an initial period of oral antipsychotic supplementation, or "oral overlap," is required to ensure adequate therapeutic concentrations are maintained as the injectable medication is slowly released.¹⁷ Examples include risperidone, aripiprazole monohydrate, and aripiprazole lauroxil. Some risperidone LAIs do not need an oral overlap due to an early-release "double peak" property.²,³ For most LAIs, the initiation of treatment involves loading doses to achieve therapeutic concentrations more rapidly. The aripiprazole-based formulations offer optional initiation methods that avoid the need for an oral overlap.^{7–10} Proper adherence to these regimens is essential to bridge the interval until the LAI reaches therapeutic concentrations (Table 2).

Post-Injection Monitoring

The administration of olanzapine (Relprevv) carries a <0.1% risk of Post-Injection Delirium/Sedation Syndrome (PDSS), necessitating a 3-hour observation period in a registered healthcare facility with ready access to emergency response services. This monitoring allows for the detection of symptoms like excessive sedation or delirium due to rapid absorption. While PDSS is a unique risk to olanzapine (Relprevv), routine post-injection monitoring for acute adverse effects and injection site reactions is important for all LAIs.

Management of Missed Doses

Maintaining a consistent schedule for LAI injections is critical, and missed appointments are a common issue. A good clinician-patient relationship is foundational to avoiding missed doses. Proactive strategies can lessen patient barriers and improve adherence. These include implementing reminder systems (phone calls, text messages), involving family or caregivers, and helping with transportation. For LAIs with long intervals between doses, reminders become even more important. Scheduling the next appointment immediately after the current one and providing a reminder card can improve follow-through. Proactive scheduling around holidays and vacations reinforces the importance of timely injections. Having a clear policy for managing missed appointments and promptly following up with patients is essential.¹⁸

Rescheduling and Managing Delayed Injections

When patients miss scheduled injections, a plan should be available to explain to the patient. Recommendations for managing missed doses vary depending on the LAI and the interval since the last injection (Table 3). Many products have a dosing window, allowing the injection to be given before or after the scheduled date. To manage a missed dose, clinicians need to know the time since the last dose, the specific product, and the dose. The appropriate action may involve administering the next injection as soon as possible, sometimes with supplemental oral antipsychotics. For certain LAIs, like paliperidone palmitate, specific re-initiation guidelines exist based on the interval since the last dose. Similarly, aripiprazole LAIs have distinct recommendations. Using pharmacy or medical records to determine the product, dose, and date of the last injection will ensure the correct catch-up protocol is used.

Addressing Insufficient Duration of Effect

Some patients may experience symptoms returning before their next scheduled injection.^{17,20} This can be due to several factors, including absorption rate, metabolism, dosing, and timing. The absorption rate is a function of the product formulation, dose, injection site, and needle size. Drug interactions and genetic

polymorphisms can alter the elimination rate. In most cases, the reason for early loss of effect is too low a dose, too long an injection interval, or both.

Strategies for Optimizing Duration

When a patient's duration of effect is insufficient, several strategies are available. One approach is to increase the LAI dose if it is well-tolerated. A higher dose can provide a longer period of therapeutic drug concentrations. Another strategy is to shorten the injection interval.^{17,20} These strategies may be "off-label" and require payer approval. For patients experiencing symptoms only toward the end of the dosing interval, supplementing with a low dose of the corresponding oral antipsychotic can serve as a bridge until a dose or interval adjustment can be made.¹⁸ Finally, switching to a LAI with a longer duration of action may be appropriate.

Management of Clinically Significant Drug Interactions

Drug interactions with LAIs can lead to symptom breakthrough, increased adverse effects, or altered duration of action. These can occur through pharmacokinetic mechanisms (affecting absorption, distribution, metabolism, or excretion) or pharmacodynamic mechanisms (additive or antagonistic effects).¹⁷

Many antipsychotics are metabolized by cytochrome P450 (CYP) enzymes. CYP inhibitors can increase plasma concentrations, while CYP inducers can accelerate metabolism, leading to decreased concentrations and reduced efficacy. ¹⁰ Some LAIs are also substrates of P-glycoprotein (P-gp) transporters. ²¹ Clinically significant interactions include the reduction of aripiprazole and risperidone concentrations by carbamazepine and the increase of olanzapine concentrations by fluvoxamine. ¹⁷ Pharmacodynamic interactions can also occur, such as the additive QTc prolonging effects with paliperidone. ⁴ A thorough review of the patient's complete medication history, including prescription, over-the-counter, and supplemental products, is crucial. Drug interaction databases and pharmacist consultations can aid in management (Table 4). ²¹

Addressing Recreational Drug Use

The co-occurrence of substance use disorders is common in patients receiving LAIs and can worsen the course of illness, impact adherence, and increase relapse risk. Recreational drugs can interact with LAIs, reducing their effectiveness or exacerbating symptoms.²² For example, cannabis can worsen psychotic symptoms, while alcohol can amplify sedative effects. Regular, non-judgmental assessment of substance use allows clinicians to monitor for interactions, manage symptom exacerbation, and tailor treatment strategies.²²

Management of Common Adverse Effects

Drug-Induced Parkinsonism (DIP)

DIP is characterized by motor symptoms like tremor, rigidity, and bradykinesia.²³ While less common with second-generation agents, it can still occur, particularly at higher doses. Management strategies include reducing the LAI dose, switching to an agent with a lower risk (e.g., aripiprazole-based products), adding amantadine, or short-term use of an anticholinergic medication. Long-term anticholinergic use should be avoided due to adverse effects on cognition and an increased risk of tardive dyskinesia.²⁴

Sedation

Sedation is a common side effect, particularly with agents like olanzapine. If persistent, management strategies include dose reduction or switching to a less sedating LAI, such as aripiprazole, risperidone, or paliperidone. It is important to distinguish medication-induced sedation from the negative symptoms of schizophrenia.

Akathisia, Anxiety, or Restlessness

Anxiety can be a primary symptom of schizophrenia or a side effect of antipsychotics (akathisia). If an antipsychotic was recently started or the dose increased, akathisia is likely. The best option is to reduce the LAI dose. If a rapid, short-term adjunctive medication is needed, mirtazapine, an anticholinergic, or vitamin B6 have shown efficacy, with vitamin B6 having the most favorable adverse effect profile.²⁵

Insomnia

Insomnia is a frequent issue. Management can include changing the administration time of oral sedating medications, sleep hygiene education, and cognitive behavioral therapy for insomnia (CBT-I).²⁶ Short-term use of a hypnotic may be considered if other strategies are insufficient.

Prolactin Elevation

Certain LAIs, particularly risperidone and paliperidone, can elevate prolactin levels, leading to endocrine side effects.²⁷ Management involves reducing the dose, switching to a prolactin-sparing agent (aripiprazole, olanzapine), or adding aripiprazole as an adjunctive medication. Regular monitoring for clinical symptoms is more beneficial than obtaining serum prolactin concentrations.

Injection Site Reactions

Local reactions like pain, redness, and swelling can occur. Proper injection technique, including using the appropriate needle size and rotating sites, can minimize these reactions. Symptomatic management typically involves local measures like ice packs or warm compresses. These reactions usually resolve in a few days.

Addressing Patient Requests to Return to Oral Antipsychotics

Patients may request to return to oral antipsychotics for various reasons, including a mistaken belief they are "cured," discomfort with injections, a desire for more autonomy, or concerns about adverse effects. Understanding the patient's reasoning through a collaborative discussion is the first step. The risks and benefits of switching should be reviewed, including the increased likelihood of symptom return. The decision on when to initiate the oral medication should consider the pharmacokinetic properties of the LAI. For many second-generation LAIs, the corresponding oral medication can be started around the time of the next scheduled injection. Close monitoring for symptom recurrence is essential during the transition.

Managing Symptoms Not Effectively Covered by an LAI

Patients on a LAI may still experience breakthrough symptoms. A systematic approach involves assessing for contributing factors like medical illness, substance use, or stressors. Optimizing nonpharmacological treatments and addressing co-occurring conditions is important. If the LAI is being

administered correctly, adjusting the dose or frequency may be considered. For rapid relief, supplementation with a low dose of the corresponding immediate-release oral antipsychotic can be used.

Integrating an Oral Antipsychotic for Added Activity

While combining antipsychotics can be viewed as inappropriate polypharmacy, judiciously adding a second medication to target specific, inadequately controlled symptoms can be a best practice. For example, patients with bipolar depression may benefit from an added oral medication, as this is not effectively covered by any current LAI (Table 6).²⁸ In a patient with refractory schizophrenia on clozapine with adherence issues, a LAI can provide a safety net. A comprehensive treatment plan should also integrate nonpharmacological therapies.

Conclusion: Optimizing LAI Treatment

Successful maintenance of LAI treatment requires a comprehensive, proactive approach. This begins with a collaborative treatment plan, careful attention to preparation and administration, and effective strategies to enhance adherence. Clinicians must be prepared to manage insufficient duration of effect, potential drug interactions, and common adverse effects. Addressing patient preferences, including requests to return to oral medication, requires a non-judgmental, collaborative process. By managing these common issues, healthcare professionals can optimize LAI treatment, leading to improved clinical outcomes, enhanced quality of life, and a reduced risk of relapse for individuals living with serious mental illness.

Table 1: Storage and Reconstitution Requirements

Medication Name (Product)	Storage Requirements	Reconstitution Required	
Aripiprazole Lauroxil (Aristada (10), Aristada Initio (9))	Controlled Room Temperature	No	
Aripiprazole Monohydrate (Abilify Maintena (7), Abilify Asimtufii (8))	Controlled Room Temperature	No (Abilify Maintena <i>also</i> available as a vial that needs reconstitution)	
Olanzapine Pamoate (Zyprexa Relprevv (11)	Controlled Room Temperature	Yes	
Paliperidone Palmitate (Invega Sustenna (4), Invega Trinza (5), and Invega Hafyera (6), Erzofi (3))	Controlled Room Temperature	No	
Risperidone (Perseris (12), Risvan (13))	Controlled Room Temperature	Yes	
Risperidone (Uzedy (2))	 Refrigerator, 2°C to 8°C (36°F to 46°F) ≤90 days, 68°F to 77°F; 20°C to 25°C Protect from light 	No	
Risperidone (Risperdal Consta (1))	 Refrigerator, (36°F to 46°F; 2°C to 8°C ≤7 days, ≤77°F; 25°C Protect from light 	Yes	

Key: Controlled Room Temperature is defined by the US Pharmacopeia (USP) to be thermostatically maintained between 20°C and 25°C (68°F and 77°F), with brief excursions from 15°C to 30°C (59°F to 86°F) as found in pharmacies, clinics, hospitals, warehouses, and during shipping,

Table 2: Injection Sites, Technique, and Initiation Regimen

Medication Name	Recommended Injection Site(s)	Injection Technique	Oral Overlap / Initiation Regimen
Risperidone LAI (Risperdal Consta)	Deltoid or Gluteal	IM	Yes (3 weeks)
Paliperidone Palmitate (Invega Sustenna)	Deltoid (initiation)Deltoid or Gluteal (maintenance)	IM	No / Initiation Doses
Paliperidone Palmitate (Invega Trinza)	Deltoid or Gluteal	IM	No (after ≥4 months of Invega Sustenna)
Aripiprazole Monohydrate (Abilify Maintena)	Deltoid or Gluteal	IM	Yes (14 days) or Two dose initiation
Aripiprazole Monohydrate (Abilify Asimtufii)	Gluteal	IM	No (if on Abilify Maintena currently) or Yes (14 days) or Two dose initiation
Aripiprazole Lauroxil (Aristada)	 Deltoid or Gluteal (441mg) Gluteal only (≥662mg) 	IM injection given rapidly, do not aspirate first	Yes (21 days) or Aristada Initio
Aripiprazole Lauroxil (Aristada Initio)	Gluteal only	IM	Used as single dose for initiation only
Olanzapine Pamoate (Zyprexa Relprevv)	Gluteal only	IM (deep)	No
Paliperidone Palmitate (Invega Hafyera)	Gluteal only	IM	No (after adequate treatment with Invega Sustenna or Invega Trinza)
Risperidone LAI (Perseris)	Subcutaneous	SC	No ("double peak")
Risperidone (Uzedy)	Subcutaneous	SC	No ("double peak")
Paliperidone Palmitate (Erzofri)	Deltoid (first dose)Deltoid or Gluteal (maintenance)	IM	No (uses larger initiation dose)

Table 3: Management of Missed Doses for Common LAI Antipsychotics

Medication Name	Dosing Window (from	Time Since Last Injection	Action to Take
	Scheduled)		
Aripiprazole	+7 days	<5 weeks (2nd or 3rd dose)	Administer missed dose ASAP
		>5 weeks (2nd or 3rd dose)	Administer missed dose ASAP + oral aripiprazole for 14 days
Monohydrate (Abilify Maintena)		<6 weeks (≥4 consecutive doses)	Administer injection ASAP
		>6 weeks (≥4 consecutive doses)	Administer next injection ASAP + oral aripiprazole for 14 days
Aripiprazole Monohydrate (Abilify	+14 days	8 to 14 weeks	Administer next dose ASAP
Asimtufii)		>14 weeks	Restart initiation regimen
Olanzapine Pamoate (Zyprexa Relprevv)	+28 days	≤2 months (at steady state)	Administer next injection ASAP
			Restart loading dose regimen for 2 months
		4 to 6 weeks	Resume regular monthly injections
Paliperidone Palmitate (Erzofri)	±7 days	6 weeks to 6 months	 Resume the dose if stabilized on <234 mg If stabilized dose is 234 mg, then: 1. 156 mg deltoid ASAP 2. 156 mg second deltoid 1 week later 3. Resume previous 234 mg regimen 1 month after second 156 mg deltoid in deltoid or gluteal
		>6 months	Restart initiation regimen
Paliperidone Palmitate (Invega Sustenna)	+14 days	<6 weeks (maintenance)	Administer next injection ASAP

		(maintenance)	 Administer next dose in deltoid ASAP Repeat same dose 1 week later in deltoid Resume monthly
		>6 months (maintenance)	Restart initiation regimen
Paliperidone Palmitate (Invega Trinza)	±14 days	3.5 to 4 months	Administer next dose ASAP
		4 to 9 months	Use special reinitiation regimen. See Table 3a
		≤6 weeks (at steady state)	Administer next injection ASAP
Risperidone LAI (Risperdal Consta)		>6 weeks (at steady state)	Administer next injection ASAP + oral supplementation for 3 weeks
Risperidone LAI (Risvan)			Administer missed dose ASAP
Risperidone LAI (Perseris)			Administer missed dose ASAP

Table 3a — Invega Trinza 4 to 9 month Missed Dose Reinitiation Regimen

Last Dose of Invega	Administer Invega Sustenna 2 Doses 1 Week Apart into Deltoid (mg)		Administer Invega Trinza on Day 36
Trinza (mg)	Day 1	Day 8	and Monthly into Deltoid or Gluteal (mg)
273	78	78	273
410	117	117	410
546	156	156	546
819	156	156	819

Table 4: Clinically Significant Drug Interactions with Common LAI Antipsychotics

LAI Antipsychotic	Interacting Drug or Class	Potential Effect	Management Recommendation
All LAIs	QT interval-prolonging drugs	Increased risk of QTc prolongation	Use with caution, monitor ECG
	CNS depressants (e.g., alcohol)	Increased risk of sedation and respiratory depression	Avoid concomitant use
Aripiprazole (Abilify Asimtufii)	Strong Inhibitors of CYP2D6 & CYP3A4	Increased aripiprazole exposure	Avoid use
Aripiprazole (Abilify Maintena)	Carbamazepine	Decreased aripiprazole concentrations	Consider higher dose of aripiprazole
	Strong CYP3A4 Inhibitors (e.g., ketoconazole)		Reduce aripiprazole dose
	Strong CYP3A4 Inducers (e.g., rifampin)	Decreased aripiprazole concentrations	Avoid use
Olanzapine (Zyprexa Relprevv)	Fluvoxamine	Increased olanzapine concentrations	Consider lower dose of olanzapine
	Diazepam		Use with caution, monitor blood pressure
Paliperidone Palmitate (Invega Sustenna)	Carbamazepine	Decreased paliperidone concentrations	Consider managing with oral paliperidone
	Strong CYP3A4/P-gp Inducers (e.g., rifampin)	Decreased paliperidone exposure	Consider managing with oral paliperidone
Risperidone (Risperdal Consta)	Fluoxetine / Paroxetine	_	Consider lower dose of risperidone
	Carbamazepine		May require higher dose of risperidone

Table 5: Management Strategies for Common Adverse Effects of LAI Antipsychotics

Adverse Effect	Management Strategies	
Drug-Induced Parkinsonism (DIP)	 Reduce LAI dose Switch to lower-risk antipsychotic (clozapine, quetiapine) Add amantadine Consider anticholinergic (short-term) 	
Sedation	 Reduce dose if possible Switch to less sedating antipsychotic (aripiprazole, paliperidone) 	
Insomnia	 Optimize timing of concomitant medications Sleep hygiene training CBT-I Consider short-term hypnotic 	
Clinical Evidence of Prolactin Elevation	 Reduce LAI dose Switch to prolactin-sparing antipsychotic (aripiprazole, olanzapine) Add adjunctive aripiprazole 	
Akathisia	 Reduce LAI dose Switch to lower-risk antipsychotic Use adjunctive medication (Vitamin B6, mirtazapine, or an anticholinergic) until dose reduction or switching LAI is completed 	
Injection Site Reactions	 Local symptomatic treatment (ice, heat, or topical steroid) Proper injection technique (site rotation, needle size) Avoid massaging injection site 	

Table 6 — Medications Approved for Bipolar Disorder

Medication	Available as LAI?	For Mania or Mixed Features	For Depression
Aripiprazole	Yes	Yes	No
Asenapine	No	Yes	No
Cariprazine	No	Yes	Yes
Chlorpromazine	No	Yes	No
Iloperidone	No	Yes	No
Lithium	No	Yes	No
Lumateperone	No	No	Yes
Lurasidone	No	No	Yes
Olanzapine	Yes	Yes	No
Olanzapine-Fluoxetine	No	No	Yes
Paliperidone	Yes	No	No
Quetiapine	No	Yes	Yes
Risperidone	Yes	Yes	No
Valproate	No	Yes	No
Ziprasidone	No	Yes	No

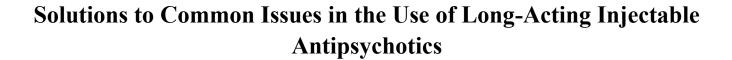
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CNS SPECTRUMS

CME Review Article



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Target Audience: This activity has been developed for the healthcare team or individual prescriber specializing in mental health. All other healthcare team members interested in psychopharmacology are welcome for advanced study.

Learning Objectives: After completing this educational activity, you should be better able to:

• Manage common factors that can occur during long-acting injectable (LAI) antipsychotic treatment in order to optimize maintenance of treatment, including for schizophrenia and bipolar I disorder



Accreditation: In support of improving patient care, this activity has been planned and implemented by HMP Education and Neuroscience Education Institute (NEI). HMP Education is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Instructions for Optional Posttest and CME Credit

- 1. Read the article
- 2. Successfully complete the posttest at https://nei.global/CNS/LAI-06
- 3. Print your certificate

Questions? Email customerservice@neiglobal.com.

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• Psychology: APA CE credits

AMERICAN
PSYCHOLOGICAL
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Faculty Author / Presenter
Stephen R. Saklad, Pharm.D., BCPP

Clinical Professor Emeritus

Consultant/Advisor: Alkermes, BMS, Genomind, Janssen, Lundbeck, Otsuka

Speakers Bureau: BMS, Otsuka PsychU, Neurocrine, Teva

Board Member: Alkermes, BMS, Genomind

The remaining Planning Committee members, Content Editors, Peer Reviewer, and NEI planners/staff have no financial relationships to disclose. NEI and HMP Education planners and staff include Caroline O'Brien, MS, Ali Holladay, Moriah Carswell, Andrea Zimmerman, EdD, CHCP, Brielle Calleo, and Bahgwan Bahroo, MD, LFAPA.

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