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An update on recently approved long-acting injectable second-generation antipsychotics: Knowns and unknowns regarding their use

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Abstract

There are now 9 available FDA-approved second-generation long-acting injectable antipsychotics including aripiprazole (3), olanzapine (1), paliperidone (3), and risperidone (2). These high-cost medications are commonly used with the goal of improving adherence and patient outcomes. With almost 2 decades of use, key aspects have been well studied, including population pharmacokinetics, CYP interactions and various clinical and economic outcomes. However, there are still unknowns with these medications. Issues including adherence, transition from oral antipsychotics, renal dosing, pharmacogenomics, and managing missed doses will be addressed in the context of 4 patient cases.

Keywords: schizophrenia, bipolar disorder, long-acting injectable antipsychotic, risperidone, paliperidone, aripiprazole

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Introduction

Since the risperidone microsphere injection, known as Risperdal Consta, was approved by the FDA in 2003, 8 additional long-acting injectable (LAI) second-generation antipsychotics (SGAs) have come to market in the United States. Available LAI antipsychotic (LAIA) products vary in cost, dosing interval, oral overlap requirements upon initiation, drug interactions, dose adjustment requirements for renal/hepatic impairment, and logistics of administration.[1-9] Aripiprazole products include aripiprazole monohydrate (AM), aripiprazole lauroxil (AL) and aripiprazole lauroxil loading dose (Initio).[1-2] Paliperidone products include paliperidone palmitate with formulations administered every 1, 3, or 6 months (PP1M, PP3M and PP6M, respectively).[3-5] Risperidone products include microsphere suspension (RMS)[6] and subcutaneous injection (RSQ).[7] Olanzapine is available as an LAIA administered every 2 to 4 weeks.[9]

Proposed benefits of LAIs, dating back to studies of haloperidol and fluphenazine decanoate, often focus on improved patient adherence.[10-13] Practically, missed doses of LAIAs are more evident than missed doses of oral medications, thereby making adherence easier to track. Aside from LAIAs, numerous other factors have demonstrated a significant impact on adherence (eg, insight, duration of illness, therapeutic alliance with providers, reminder systems, behavioral interventions, and substance use disorders).[14-16]

Take Home Points:

1. Adherence may be improved with long-acting injectable antipsychotics, but other factors including insight, engagement in treatment, tolerability, court-ordered treatment, cost, and logistics also must be considered.
2. Pharmacokinetic differences between long-acting injectable antipsychotics including drug interactions, onset, and duration of action should be considered when selecting both medication and formulation.
3. History of response to and tolerability of oral medications, as well as acuity of illness, can be used, in addition to labeled recommendations, to guide dose and duration of oral antipsychotic overlap.
4. Research study design and applicability to real-world practice must be included in evaluation of literature on long-acting injectable antipsychotics.
5. Paliperidone and risperidone products may require renal dose adjustment.
6. Polymorphisms in CYP2D6 activity may result in unexpected nonresponse or intolerance to aripiprazole products.

The LAIAs are unique among psychotropics in that prolonged duration of action allows for administration intervals ranging from every 2 weeks to every 6 months (Tables 1 and 2).[1-9] Clinically, this prolonged action is expected to minimize fluctuations in serum concentrations to maximize tolerability and minimize risk of symptom recurrence in the event of delayed doses. Because of the prolonged release profile, absorption rather than elimination is the rate-limiting step to achieve steady state concentrations.[8]

When LAIAs are used, agent-specific pharmacokinetic parameters are paramount in decisions regarding medication selection, dose, injection site, and dosing interval. Special caution must be used when patients have chronic renal impairment or acute kidney injury which can alter elimination of paliperidone and risperidone (Table 3) and possibly olanzapine.[17-19] All available LAIAs are substrates of p-glycoprotein (Pgp; variable data for olanzapine)[20-23], and concurrent use with Pgp inducers or inhibitors may significantly alter activity. Additionally, aripiprazole, paliperidone, and risperidone metabolism is variably impacted by polymorphisms and interactions with CYP2D6 and CYP3A4 (Table 4).[1-7,21,23]

TABLE 1: Product guidelines for paliperidone and risperidone[3-8]

	Paliperidone				Risperidone		
Formulation	**Oral**	**PP1M**	**PP3M[b]**	**PP6M[c]**	**Oral**	**RMS**	**RSQ**
Dosing interval	Daily	4 wk	12 wk	6 mo	1-2 times daily	2 wk	4 wk
Dose conversions	12 mg	234 mg	819 mg	1560 mg	5-6 mg	50 mg	...
	9 mg	156 mg	546 mg	1092 mg	4 mg	37.5 mg	120 mg
	6 mg	117 mg	410 mg	...	3 mg	37.5 mg	90 mg
	3 mg	78 mg	273 mg	...	2 mg	25 mg	...
		39 mg	...	...	1 mg	12.5 mg	...
Oral overlap	...	None[a]	...	...	...	3 wk	None
Storage/Preparation	...	20° to 25°C In suspension; need to shake vigorously			...	2° to 8°C 25° C up to 7 d Requires reconstitution	
Administration	...	Deltoid for loading doses; deltoid or gluteal for maintenance	Deltoid or gluteal	Gluteal only	...	Deltoid or gluteal	SQ
Needle	...	1.5" 22-G (gluteal or deltoid ≥90 kg)	1.5" 22-G (gluteal or deltoid ≥90 kg)	1.5" 20-G	...	2" 20-G (gluteal)	5/8"
		1" 23-G (deltoid <90 kg)	1" 23-G (deltoid <90 kg)			1" 21-G (deltoid)	18-G

G = gauge; PP1M = paliperidone palmitate 1-month; PP3M = paliperidone palmitate 3-month; PP6M = paliperidone palmitate 6-month; RMS = risperidone microsphere injection; RSQ = risperidone subcutaneous; SQ = subcutaneous.

[a]For initiation, load with 234 mg on Day 1 and 156 mg on Day 8, then 117 mg/mo (starting Day 36).This loading protocol is expected to achieve steady state concentrations consistent with 6 to 12 mg of PO paliperidone. Patients on more than 6 mg oral paliperidone or 2 mg risperidone may require supplemental oral doses or earlier first maintenance dose administration of PP1M.

[b]Only after patient has maintained stability on 4 monthly maintenance doses of PP1M.

[c]Only after stability on PP1M (4 months) or PP3M (1 dose).

TABLE 2: Product guidelines for aripiprazole[1-2,8]

Formulation	Oral	AM	AL
Dose	10 mg/d	400 mg every 4 wk	441 mg every 4 wk
	15 mg/d		662 mg every 4 wk OR 882 mg every 6 wk OR 1064 mg every 8 wk
	≥ 20 mg/d		882 mg every 4 wk
Oral overlap	. . .	14 d OR 400 mg ×2	21 d OR 30 mg ×1 + ALI 675 mg ×1 + AL dose above
Storage/Preparation	. . .	Store below 30°C	20° to 25°C
		Vials and syringe kits	Shake vigorously ×30 sec
		Require reconstitution	Does not require reconstitution
Administration	. . .	Deltoid or gluteal	441 mg: Deltoid or gluteal
			662 mg, 882 mg, or 1064 mg gluteal only
Needle	. . .	Deltoid non-obese 1" 23-G	441 mg Deltoid 1" 21-G or 1.5" 20-G
		Gluteal non-obese or deltoid obese: 1.5" 22-G	441 mg Gluteal 1.5" 20-G or 2" 20-G
		Gluteal obese: 2" 21-G	662 mg, 882 mg, or 1064 mg Gluteal: 1" 20-G or 2" 20-G

AM = aripiprazole monohydrate; AL = aripipirazole lauroxil; ALI = aripiprazole lauroxil initiation dose; G = gauge.

Olanzapine LAI use is limited by logistic requirements for the Risk Evaluation and Mitigation Strategies (REMS) program. Because of the risk of postinjection delirium/sedation syndrome with symptoms consistent with olanzapine toxicity, the REMS program stipulates that each dose be administered in a REMS registered facility with rapid access to emergency services. Patients must be observed for at least 3 hours after each injection at the facility and have someone to accompany them after the appointment. With this REMS program, enrollment is required for the patient, facility, provider, and the pharmacy.[9] Since use of this product is limited, the focus of this review will be on LAIAs other than olanzapine. Key information regarding products, dosing, and interactions is included in Tables 3-6 for reference.

The maintenance LAI aripiprazole products (AM and AL) vary in dose and dosing interval (ranging from 4 to 8 weeks). Additionally, AL has a loading dose formulation with more rapid absorption and shorter half-life ($t_{1/2}$).[10] Risperidone and paliperidone products comprise most of the available LAI SGAs with dose frequency ranging from every 2 weeks to every 6 months.[3-7] Aripiprazole may be more prone to CYP-related pharmacogenomic differences and drug interactions compared to risperidone and paliperidone.[21,23] The following cases will focus on aripiprazole, paliperidone, and risperidone products.

TABLE 3: Product guidelines for olanzapine[9]

Formulation	Oral	First 8 Weeks LAI Dose	Maintenance LAI Dose
Dose	10 mg/d	210 mg every 2 wk OR 405 mg every 4 wk	150 mg every 2 wk OR 300 mg every 4 wk
	15 mg/d	300 mg every 2 wk	210 mg every 2 wk OR 405 mg every 4 wk
	20 mg/d	300 mg every 2 wk	300 mg every 2 wk
Oral overlap	. . .	Not required	Not required
Storage/Preparation	. . .	Store at or below 30°C	
		Kits with vials and diluent	
		Require reconstitution to 150 mg/mL (volume varies depending on vial size)	
		Wear gloves to reconstitute and avoid product contact with skin	
Administration	. . .	Deep intramuscular gluteal sites only	
		Aspirate for several seconds after needle insertion before administering dose	
Needle	. . .	Standard (included in kit): 1.5" 19-G	
		For obese patients, 2" 19-G or larger (not included in kit)	

G = gauge; LAI = long-acting injectable.

TABLE 4: Renal dosing for SGA LAI[1-7,9,17,18]

Product	Renal Elimination	Dosing Recommendations
Aripiprazole	25% as metabolites <1% as unchanged drug	No dose adjustment needed for any products
Olanzapine	57% as metabolites 7% as unchanged drug	No dose adjustment recommended by manufacturer Potential for 1.6-fold increase in levels; avoid use in moderate to severe renal dysfunction
Paliperidone	80% 59% as unchanged drug	CrCL ≥90 mL/min no dose adjustment needed CrCL 80 to 89 mL/min -PP1M or PP3M: no dose adjustment -PP6M: use not recommended CrCL 50 to 79 mL/min[a] -PP1M: loading dose 156 mg followed by 117 mg and 78 mg as maintenance -PP3M: Transition from PP1M dose (78 mg PP1M to 273 mg PP3M) -PP6M not recommended CrCL <50 mL/min: use not recommended for any products
Risperidone	70%, primarily as active metabolite clearance <60% with CrCL <60 mL/min	CrCL >60 mL/min: no dosage adjustment needed CrCL 10 to 60 mL/min: -Initiate RMS with 12.5 mg to 25 mg every 2 wk[a] -RSQ: may only be used if patients tolerate 3 mg oral risperidone daily at steady state CrCL <10 mL/min: Avoid use of all products

CrCl = creatinine clearance; PP1M = paliperidone palmitate 1-month; PP3M = paliperidone palmitate 3-month; PP6M = paliperidone palmitate 6-month; RMS = risperidone microsphere injection; RSQ = risperidone subcutaneous.

[a]May consider higher initial dose if patients require higher oral doses for symptom control, tolerate those doses, and have stable renal function in the upper quartile of this range.

Patient Case 1

J.T. is a 24-year-old with a 4-year history of schizophrenia admitted involuntarily to an inpatient psychiatry unit with symptoms of paranoid delusions (movements being tracked) and auditory hallucinations resulting in agitation and insomnia (afraid to sleep). Past medical history is unremarkable except for baseline obesity (weight 100 kg, BMI 30 kg/m^2). This is the second hospitalization in 12 months attributed to partial nonadherence with daily oral olanzapine 20 mg at bedtime. The patient states "I don't like how it makes me feel", when asked why they do not take their medication consistently. Family is inquiring about LAIAs so J.T. "won't miss doses" and requests that this be part of the patient's court-ordered treatment after discharge.

LAIAs and Tolerability

The first step in this case is to explore potential reasons for nonadherence. As cited in the literature, top reasons for nonadherence to psychotropic agents include negative subjective response to medication, poor therapeutic alliance, complexity of regimen, and history of substance use.[14-16] Antipsychotics are associated with numerous adverse effects, from movement disorders and metabolic disorders to sedation and sexual dysfunction. In patients who are nonadherent due to tolerability issues, it is important to determine if it is a result of peak-related effects (eg, sedation), dose-related effects (eg, parkinsonism), or a reaction that occurs across the dose spectrum (eg, metabolic syndrome, sexual dysfunction). Since LAIAs have lower maximum serum concentration (C_{max}) but area under the curve similar to oral medications,[8] switching to an LAIA may be expected to help with peak-related adverse reactions. However, in cases of dose-related reactions that persist throughout the day, switching to an LAIA may not achieve average serum concentrations low enough to alleviate this reaction. In cases where poor adherence to oral medications is the rationale for LAIA use, it is unreasonable to expect the same patient to remember to take additional medications to manage antipsychotic-related adverse effects (eg, anticholinergics for parkinsonian symptoms or propranolol for akathisia). In cases of metabolic syndrome or sexual dysfunction, additional laboratory monitoring (eg, glucose, lipids, and prolactin as they temporally relate to initiating the antipsychotic) can help to assess how much medications are contributing to these symptoms.

Impact of LAIAs on Adherence

There is a wealth of literature addressing the impact of LAIAs on medication adherence. Outcomes of interest include adherence rates, time to discontinuation, readmissions, hospital days, and health care costs. A meta-analysis[10] and systematic review[11] of first-generation antipsychotic

TABLE 5: Dose adjustments for pharmacogenomic and interaction considerations[1-7,19-22]

Medication Metabolism P-gp	Dose Adjustment[a]
Aripiprazole 3A4 (major) 2D6 (major) P-gp substrate (both parent and active metabolite)	2D6 Poor Metabolizers -AM: 300 mg -AM + inhibitor: 200 mg -AL: No labeled recommendations *-Consider reducing to next lower strength or 50% decrease* Strong 3A4 OR 2D6 Inhibitors: -AM: Reduce dose (400 mg → 300 mg or 300 mg → 200 mg) -AL: Reduce to next lower strength *-Consider empiric 50% decrease* Strong 3A4 AND 2D6 Inhibitors/2D6 Poor Metabolizer: -AM: 200 mg (or 160 mg if added to stable regimen of 300 mg) -AL: Avoid use other than 441 mg monthly if tolerated *-Consider dose consistent with 75% decrease* 3A4 Inducers -AM: Avoid use -AL: Increase 441 mg to 662 mg; no labeled adjustment for other doses *-Consider TDM if there is a compelling case to use* *-Avoid use if patient requires >15 mg for oral maintenance dose* P-gp: -No labeled recommendations for patients on concurrent P-gp inducers or inhibitors. Monitor closely for adverse effects with concurrent use of known inhibitors and reduced efficacy with inducers. -Limited evidence suggests P-gp polymorphisms do not impact aripiprazole area under the curve, C_{max}, or $t_{1/2}$ but low P-gp activity may decrease clearance.
Olanzapine UGT1A4 CYP1A2 (major) CYP3A4 (minor) Intermediate P-gp substrate	No specific labeled recommendations for dose adjustment with concomitant interacting medications 1A2 or UGT Inducers: *-Consider higher dose if on 300 mg total monthly dose* *-Avoid use if patient requires >20 mg oral maintenance dose* 1A2 or P-gp Inhibitors: *-Consider lower dose* *-Do not recommend concomitant use in patients who are intolerant to >10 mg/d or 300 mg/mo*
Paliperidone 3A4 (minor) P-gp substrate **Risperidone** 2D6 (major) 3A4 (minor) P-gp substrate	2D6 Poor Metabolizers OR concurrent use of 2D6 Inhibitors: -Paliperidone: No adjustment -Risperidone: Variable data •Possible increased risk of dose related toxicity •Assess response and tolerability of PO medication at steady state prior to initiating and titrating LAI For both Risperidone and Paliperidone: 3A4 Inhibitors: -Variable data; likely due, in part, to P-gp inhibition -Possible increased risk of dose-related toxicity -Assess response and tolerability of oral medication at steady state prior to initiating and titrating LAI 3A4 Inducers: -Variable data; likely due, in part, to P-gp induction -Possible risk of subtherapeutic doses -Assess response to oral medication prior to initiating LAI P-gp Inhibitors: may increase serum and/or CNS concentrations P-gp Inducers: may decrease serum and/or CNS concentrations

AM = aripiprazole monohydrate; AL = aripipiraxole lauroxil; C_{max} = maximum serum concentration; LAI = long-acting injectable; P-gp = P-glycoprotein $t_{1/2}$ = half-life; TDM = therapeutic drug monitoring.

[a]Italics indicate dose adjustment based on pharmacokinetic data, not manufacturer recommendation.

TABLE 6: Managing missed doses[1-7]

	Time Since Last Dose	Treatment Plan[a]	
AL	441 mg 6-7 wk	7 d previous oral dose	ALI 675 mg ×1
	441 mg >7 wk	21 d previous oral dose	ALI 675 mg ×1 + 30 mg oral ×1
	8-12 wk	7 d previous oral dose	ALI 675 mg ×1
	662 mg monthly or 882 mg every 4-6 wk		
	10-12 wk	7 d previous oral dose	ALI 675 mg ×1
	1064 mg every 8 wk		
	12 wk	21 d previous oral dose	ALI 675 mg ×1 + 30 mg oral ×1
	662 mg, 882 mg, or 1064 mg		
AM	Injection no. 2 or no. 3 >5 wk	14 d oral overlap with injection	
	Injection no. 4 and later; >6 wk	14 d oral overlap with injection	
OP		No specific manufacturer recommendations	
		During first 8 wk, resume previous dosing	
		During maintenance dosing, consider the following with close monitoring for efficacy and adverse effects	
2-Wk Dosing	>2 and <4 wk	Resume same dose	
	≥4 and <8 wk	For 150 mg or 210 mg consider single dose of 300 mg or 405 mg respectively ×1 then resume previous dose 4 wk later	
		For 300 mg dose, resume 300 mg every 2 wk	
	≥8 wk	Repeat dosing scheme from first 8 wk	
4-Wk Dosing	≥4 and <8 wk	Resume previous dosing	
	≥ 8 and <12 wk	Consider single dose of corresponding 2-wk dose from first 8 wk, then resume 4-wk dosing on Day 14	
	≥12 wk	Repeat dosing scheme from first 8 wk	
PP1M	4 to 6 wk	Resume previous dose (consider deltoid site for more rapid absorption)	
	>6 wk to 6 mo	Maintenance dose 39-156 mg: Give 2 maintenance doses 1 wk apart	
		Maintenance dose 234 mg: Give 2 doses of 156 mg 1 wk apart	
	> 6 mo	Reinitiate with loading regimen of 234 mg Day 1 and 156 mg Day 8	
PP3M	<4 mo	Resume previous dose	
	4-9 mo	273 mg → PP1M 78 mg IM Days 1 and 8 then PP3M 273 mg Day 39	
		410 mg → PP1M 117 mg IM Days 1 and 8 then PP3M 410 mg Day 39	
		546 mg → PP1M 156 mg IM Days 1 and 8 then PP3M 546 mg Day 39	
		819 mg → PP1M 156 mg IM Days 1 and 8 then PP3M 819 mg on Day 39	
PP6M	<27 wk (6.75 mo)	Resume previous dose	
	6.75-8 mo	1092 mg → PP1M 156 mg Day 1 then 1092 mg PP6M Day 30 1560 mg → PP1M 234 mg Day 1 then 1560 mg PP6M Day 30	
	8-11 mo	1092 mg → PP1M 156 mg Days 1 and 8 then 1092 mg PP6M Day 30	
		1560 mg → PP1M 156 mg Days 1 and 8 then 1560 mg PP6M Day 30	
RMS	2-5 wk	*Resume previous dose*	
	>5 wk	*Resume previous dose with 3-wk oral overlap*	
RSQ	>4 wk	Resume previous dose as soon as possible	

AL = aripiprazole lauroxil maintenance; ALI = aripiprazole lauroxil initiation dose; AM = aripiprazole monohydrate; OP = olanzapine pamoate; PP1M = paliperidone palmitate 1-month; PP3M = paliperidone palmitate 3-month; PP6M = paliperidone palmitate 6-month; RMS = risperidone microsphere injection; RSQ = risperidone subcutaneous.

[a]Italics indicate recommendation based on pharmacokinetic data, not manufacturer recommendation.

(FGA) LAIs revealed variable outcomes on these measures. When compared to placebo, FGA LAIs demonstrated improvement in rates of relapse and study retention, but increased rate of movement disorders.[11] When FGA LAIs were compared to oral FGA, the meta-analysis did not reveal significant differences in relapse, study retention, movement disorders, or mortality, while global functioning was slightly improved. A systematic review[10] reported

discrepant results regarding readmissions in mirror-image studies, but a trend of decreased hospital days and time to readmission across prospective studies. The authors cited methodological issues as a potential contributor to variable results. Published literature for SGA LAIs predominantly includes industry-sponsored clinical trials and retrospective evaluations of Medicaid claims databases. Studies vary in results regarding the aforementioned outcomes; however, they tend to favor the LAIAs over oral antipsychotics.[12,13]

Although clinical trials demonstrate improved adherence and outcomes, certain aspects of trial design must be considered to guide real-world expectations. First, clinical trials typically involve 1 to 2 weeks of oral antipsychotic stabilization and, often, only patients who respond to the oral medication are included to be randomized to LAIA or placebo injection. This type of enriched trial design may result in higher reported rates of response than we see in practice and the switch to placebo injection results in expected decompensation after response to oral antipsychotics. Second, clinical trials may involve arrangements for travel, reimbursement, or vouchers for participation, blister packs for oral medications, frequent phone call follow-up and reminders for appointments – all of which have been associated with improved adherence.[16] For example, a patient in a clinical trial may have transportation arranged before and after the study visit at a time convenient to them. This would greatly improve adherence compared to a patient who may need to navigate public transportation and timing of travel to and from an outpatient clinic for injection appointments.

An understudied aspect of LAIA treatment to consider when evaluating efficacy and adherence literature is whether treatment is voluntary or court-ordered. It is unknown how many patients receiving LAIAs are receiving them as part of a court order. Practices and statutes regarding court-ordered medication treatment vary between states[24] and even between community mental health centers. Evidence[25] suggests patients receiving medications under a court order perceive a higher degree of coercion which may negatively affect the ability to develop a therapeutic alliance. The full impact of these factors is beyond the scope of this review but should be considered when reviewing studies assessing adherence.

Case 1 Continued

Upon further discussion, it is determined that olanzapine caused J.T. to experience constipation, sedation, and feelings of fogginess. On the inpatient unit, J.T. is transitioned to risperidone and titrated to 4 mg at bedtime to maximize sleep benefit and minimize daytime sedation. Agitation resolves and paranoia/auditory hallucinations improve. J.T. does not endorse constipation or fogginess but questions whether the medication is still necessary. You discuss with J.T. that sleep, voices, and fearfulness have improved and that if medication is stopped abruptly, symptoms are likely to return. You assure J.T. that feelings of fogginess and constipation are not likely to develop if they do not occur during initiation of medications, and the team will continue to monitor for long-term effects which will include laboratory monitoring.

The psychiatrist plans to transition J.T. to a LAIA per stipulations of the court-ordered treatment. The team and patient's family ask about the differences between risperidone/paliperidone products.

Paliperidone and Risperidone LAIAs: Practical Considerations and Dosing Strategies

There are a few practical issues to discuss with patients regarding injection options. When initiating risperidone or paliperidone LAIAs, the initial dosing interval ranges from 8 days (PP1M loading doses) to 2 weeks (RMS) to 4 weeks (RSQ), and duration of oral overlap per labeling ranges from no overlap (RSQ, PP1M) to 3 weeks of oral overlap (RMS; Table 1). Injection sites include deltoid (PP1M, RMS), gluteal (PP1M after 2 loading doses; RMS all doses) or abdominal subcutaneous (RSQ only; Table 1). All products need to be administered by a health care provider. Once stabilized on the initial regimen, paliperidone may be administered at intervals ranging from 4 weeks to 6 months and risperidone every 2 to 4 weeks.

Prior to initiating an LAIA, insurance coverage for the product must be confirmed. There is variability between state Medicaid systems in coverage of these agents and whether there are preferred products. For those with commercial health insurance, products are variably covered as a prescription benefit or as a medical benefit (which requires clinics to *buy and bill* for the medication; not all are set up for this practice). Prior to initiation, especially in the acute inpatient setting, it is crucial to ensure that the intended product is covered and can be continued after discharge.

Whether a patient is transitioning from oral paliperidone or risperidone, the same PP1M loading regimen is used (ie, 234 mg IM on Day 1 followed by 156 mg IM on Day 8).[3] Maintenance doses should be individually determined based on continued response and tolerability. Absorption of PP1M starts on Day 1, however, the time to maximum serum concentration is not achieved until Day 13.[4] Due to this delay, it is common in practice to continue oral medication for the first 4 to 7 days in cases where patients require higher doses for initial stabilization or in cases where patients have demonstrated higher dose requirements for

maintenance LAIA treatment. This practice is based on the pharmacokinetic properties and clinical experience as there are no clinical trials that include this method of dosing. For patients requiring these high oral doses (eg, 12 mg paliperidone or ≥4 mg risperidone), it may be reasonable to decrease the oral dose by 50% 4 to 7 days after the first loading dose and monitor closely for symptom recurrence and dose-related adverse effects. The remaining oral dose can be discontinued within 4 days after the second loading dose. If symptoms worsen with discontinuation, the oral medication should be resumed at the previous dose and continued until receipt of the maintenance injection.

Using oral medication during this transition requires frequent and careful monitoring for both response and tolerability. Although population kinetics provide guidance, great interpatient variability in absorption may exist. For patients who are naïve to LAIAs, a conservative approach is warranted. When determining expected LAIA maintenance dose, one must consider whether the oral dose was the true maintenance requirement rather than a higher dose needed for acute stability and management of agitation. The flexibility of dosing intervals may also be used to avoid decompensation by administering the first maintenance dose as early as possible. For example, with PP1M, maintenance doses may be administered within 7 days of scheduled date, or as early as Day 29 after the first loading dose.

Case 1 Conclusion

The family confirms that LAIAs are covered under their insurance plan with a reasonable co-pay and request that J.T. be started on PP1M since it has a loading regimen, and they will not need to monitor oral overlap after discharge. The patient preferred the smaller needle size compared to RSQ. The team asks how to convert from the 4 mg risperidone dose to PP1M.

Since this patient weighs >90 kg, the gluteal needle should be used for all injections including the first 2 deltoid loading doses (Table 1). After 2 weeks of oral risperidone 4 mg, the patient received 234 mg PP1M on Day 14 (left deltoid) and 156 mg PP1M on Day 20 (right deltoid). Oral risperidone was decreased to 2 mg on Day 18 and discontinued on Day 21 for discharge with instructions to family to monitor closely for symptom recurrence. The first maintenance injection of 156 mg was scheduled 22 days after discharge (Day 29 from initial loading dose) to be administered in either gluteal or left deltoid site.

Patient Case 2

L.S. is a 64-year-old with a history of schizophrenia who was admitted to the hospital for an acute ischemic stroke. Past medical history includes insulin-dependent diabetes, peripheral neuropathy, hypertension, and chronic kidney disease. Because of complications of stroke, L.S. is not able to swallow, and the team would like alternative options for paliperidone 6 mg daily (home medication, last dose 3 days prior to consult). It is anticipated that L.S. will be intermittently unable to take oral medications for 4 to 8 weeks, and an enteral tube is not an option. For the last 2 years, L.S. has maintained stability on paliperidone 6 mg daily without symptom recurrence or psychiatric hospitalization. Current creatinine clearance (CrCL) is 35 mL/min (consistent with prior 12 months). You are consulted to determine if an LAIA is an option to maintain stability.

Paliperidone and Risperidone: Renal Dosing and Therapeutic Drug Monitoring

This case presents an opportunity to use known pharmacokinetic properties and potentially use therapeutic drug monitoring (TDM) to make an informed decision regarding treatment. Paliperidone has variable recommendations for renal dosing between oral and LAIA products (Table 3).[4,17,18] For a patient with a CrCL of 35 mL/min, the recommended maximum oral dose is 3 mg/d. The paliperidone LAIAs are not recommended, per labeling, for CrCL<50 mL/min.[4-6] These recommendations are based on limited data from single dose studies and extensive renal elimination of paliperidone (80% with 59% eliminated as unchanged drug). Risperidone, on the other hand, has renal dosing recommendations for CrCL as low as 10 mL/min for both oral and RMS.[6] The labeling for RSQ recommends demonstrating tolerability with at least 3 mg of risperidone prior to initiating.[7] Risperidone is estimated to have 70% renal elimination, predominantly as the metabolite 9-OH-risperidone (paliperidone).

In a case of a patient who previously tolerated a maintenance oral dose of risperidone or paliperidone in the setting of chronic but stable renal impairment, an LAIA may be considered. With an elimination $t_{1/2}$ of 24 to 51 hours in renal dysfunction, the medication levels can be considered at steady state after 1 to 2 weeks and tolerability indicates that the patient is effectively clearing medication. If enteral administration is possible, oral paliperidone can be converted to risperidone and administered as a liquid. For patients who are unable to take any medication by mouth or enterally, LAIA is the only option for risperidone or paliperidone. Although RMS has dosing recommendations for CrCL as low as 10 mL/min, it requires 3 weeks of oral overlap. The RSQ has a more rapid onset and does not require oral overlap, however, it requires that the patient tolerate at least 3 mg of risperidone, so toxicity is a concern. Per labeling, PP1M is not recommended for CrCL<50 mL/min, however, it may be considered in a patient who tolerates oral paliperidone. Since the rate limiting step in the

pharmacokinetics of LAIA is absorption, there are 2 potential approaches. If the patient is psychiatrically stable, a modified loading dose of 156 mg followed by 117 mg on Day 8 could be used to target a more conservative serum concentration. Of note, this is the same loading dose recommended in the package insert for those with mild renal impairment (CrCL 50-79 mL/min). If the patient were more than 5 days from the last PO dose and experiencing recurrence of psychotic symptoms, it would be reasonable to administer 156 mg on both Day 1 and Day 13 (anticipated time to maximum serum concentration) if tolerating.[4] For patients without a history of PP1M, it would be risky to administer the standard loading dose as absorption may differ from population kinetics and the standard loading dose achieves levels consistent with 6 to 12 mg of oral paliperidone. For maintenance dosing, TDM can be used to assess serum concentrations at expected C_{max} and prior to the first maintenance dose. Timing of TDM can be challenging, since samples often must be sent out to a specific lab, which can delay results.

Case 2 Continued

After discussion, L.S. is initiated on PP1M with 156 mg on Day 1 (7 days after last PO dose and emergence of occasional auditory hallucinations without symptoms of delirium). On Day 8, hallucinations are improved, and L.S. has normal blood pressure and heart rate, and no signs of extrapyramidal symptoms. A level is sent out, and you opt for a conservative second loading dose of 117 mg (given symptom improvement) while awaiting results with plan for another level on Day 30 and dose of 117 mg on Day 38. The lab obtained on Day 8 results on Day 14 with a level of 15 ng/mL. The team asks what next steps they should take.

The reference range for paliperidone and risperidone is 20 to 60 ng/mL.[26] There is great interpatient variability in response and tolerability within this range. Since the second modified loading dose has already been administered, further adjustment can include dose or timing of the first maintenance injection. In this case, if the patient continued to respond without adverse effects and renal function remained stable, it would be reasonable to continue with 117 mg as maintenance dose without obtaining further levels. This would be consistent with the oral 6 mg paliperidone dose conversion. Ideally, the Day 30 level results would also be used to guide further dosing.

Other Considerations in Renal Impairment

While this case presents a unique circumstance with several factors to consider, patients with schizophrenia have high rates of diabetes and cardiovascular disease putting them at risk for CKD. Prior to initiating any paliperidone or risperidone LAIA, baseline renal function should be assessed, especially if risk factors for CKD are present. For patients with wide fluctuations in renal function, or severe kidney disease who would benefit from LAIA initiation, aripiprazole may serve as a safer alternative since aripiprazole elimination is not dependent on renal function.[1-2] Olanzapine does not have labeled dose adjustments for any level of renal impairment (oral or injectable) and there is a paucity of literature to guide dosing in CKD. A pharmacokinetic modeling study found that area under the curve of olanzapine is up to 1.5-fold higher in patients with CrCL $<$60 mL/min.[19] Patients receiving chronic maintenance treatment with paliperidone or risperidone LAI should have renal function checked annually and TDM with trough levels prior to injections should be considered in cases of declining renal function, changes in symptoms or adverse effects. Furthermore, patients with acute kidney injury may develop increased paliperidone or risperidone levels if serum creatinine remains elevated for an extended period and these patients should be monitored for extrapyramidal symptoms or other signs of toxicity.

Patient Case 3

M.P. is a 40-year-old with a history of Bipolar I Disorder admitted for acute mania approximately 3 months after tapering off quetiapine because of metabolic syndrome (gained 10 kg over a 3-month period and experienced an increase in A1c from 5.2% to 7% after a 6-month period). Past medications include lurasidone (stopped due to intolerable akathisia) and risperidone (stopped due to gynecomastia). When not taking prescribed medications, M.P. has a history of recurrent hospitalizations. When taking medications, M.P. is actively involved with family and works 30 to 40 hours per week in a research lab. Aripiprazole is initiated and titrated to 20 mg daily by hospital Day 7. Symptoms of mania improve, and the patient does not endorse akathisia or other adverse effects.

Tolerability Considerations for Aripiprazole

When patients have a history of dose-related (akathisia) or non-dose-related (metabolic syndrome and gynecomastia) adverse effects, it is important to assess the likelihood of these adverse effects with aripiprazole prior to initiating the LAIA. Aripiprazole has a lower rate of metabolic syndrome and gynecomastia compared to quetiapine and risperidone respectively.[27,28] However, akathisia does occur with aripiprazole and may have a higher incidence in patients with affective disorders.[29] For this reason, it is crucial to establish tolerability at steady state with oral aripiprazole before initiating LAIA. Due to prolonged $t_{1/2}$ of 75 hours (96 hours for metabolite and up to 146 hours in poor metabolizers), it can take up to 3 weeks to achieve steady state concentrations with oral aripiprazole.[1,2,30,31]

Case 3 Continued

After 1 week of 20 mg aripiprazole and discussion with the treatment team, the patient agrees to a trial of aripiprazole LAIA "so I don't get tempted to stop it or skip doses" and is discharged from the hospital with plans to receive LAIA as an outpatient. M.P. is discharged with instructions to continue 2 more weeks of oral medication allowing team to assess tolerability at steady state concentrations. Prior authorization is obtained from the commercial insurance plan to cover either AM or AL. M.P. asks about differences between the 2 products and whether genetic testing can help decide which medication is best. You discuss the option of initiating AM 400 mg with a 14-day oral overlap, AM with a 2-dose loading regimen (not FDA-approved), AL 882 mg monthly with a 21-day overlap, or AL with 2 loading injections and no oral overlap and plan for 882 mg monthly maintenance dose. M.P. prefers the options with no overlap but asks why the dose is so much higher for AL than AM (Table 2).[1,2,30]

AM vs AL

The AL product is a prodrug, with a molecular weight of 660.7 g/mol that requires 2 steps of hydrolysis to be converted to active medication.[2,8] This compares to AM, which is active medication with a molecular weight of 466.4 g/mol.[1] The difference in molecular weight drives much of the difference in dose between products as the C_{max}, time to steady state, $t_{1/2}$, and duration of effect are similar.[1,2] In pharmacokinetic studies, higher serum concentrations were achieved with AM vs all labeled AL dosing strategies.[30] If approved by insurance, patients who require higher oral maintenance doses, may require AL 1064 mg more frequently than the labeled every 8 weeks. On the other hand, for patients who respond to or only tolerate lower doses of PO aripiprazole, the AL product provides more flexibility in dosing, with the lowest dose (441 mg monthly) providing levels approximately 50% lower than AM 400 mg monthly.

Both AL and AM have dosing recommendations in labeling based on pharmacogenetics and CYP interactions (Table 4).[1,2,21] If pharmacogenetic testing is available, 2D6 metabolizer status may be used to guide initial dosing of PO or LAI products, however it is not currently standard practice to obtain pharmacogenetic testing prior to initiation. Instead, dosing can be guided by the oral dose that is effective and tolerated, keeping in mind the prolonged time to steady state for aripiprazole.

Patient Case 4

B.B. is a 30-year-old with history of schizophrenia who presents to the hospital with acute psychosis. B.B. was previously stabilized on PP3M 546 mg for 3 years, with the last dose being 5 months ago. When receiving PP3M, B.B.'s symptoms would sometimes worsen during the last 2 weeks of the dosing interval, but otherwise B.B. was stable and was not hospitalized for 2 years. The missed dose was because of moving from a different state to live with family and a delay in establishing psychiatric care. Family would like to get B.B. back on LAIA as soon as possible. Upon admission, paliperidone 6 mg daily is initiated.

The first step in this case would be to establish rapport with the patient to determine their treatment goals and interest in resuming LAIA. The next step is assessing the logistic feasibility of LAIA including establishing an outpatient provider and plan for obtaining LAIA (active insurance coverage or plans for samples/patient assistance program). If the patient prefers another trial of oral medication and is not court-ordered to treatment, it is a reasonable choice with close follow-up. Although the last dose of PP3M was 5 months ago, the duration of release of PP3M means that medication was still being absorbed until recently.[4,8] We want to determine if nonadherence is because of lack of insight or refusal of medications rather than logistical complications of the move.

Managing Missed Doses

Once patient buy-in, outpatient follow-up, and access to medication is established, the paliperidone and risperidone LAIA products have labeled guidance for dealing with missed doses (Table 5).[3-7] In this case, the recommended dose to resume treatment is 156 mg PP1M on Day 1 and Day 8 then resume PP3M 546 mg on Day 39. The other issue to address in this case is the *wearing off* that previously occurred during last 2 weeks of dosing interval. There are a few options to address this issue. First, establish if there were other potential causes of decompensation (stressors, substance use). If the 546 mg dose was well-tolerated, one option would be increasing to 819 mg for future doses. To provide clarity, TDM can be used to assess whether there is a significant decrease in levels at the end of the dosing interval. Once treatment has been reestablished for this patient, oral paliperidone 3 to 6 mg could be trialed at the end of the interval to see if it helps with recurrence of symptoms without adverse effects. An alternative option would be administering the dose every 10 weeks instead of every 12 weeks; however this may not address the period of decompensation (PP3M will not achieve peak absorption until after the 2-week period of decompensation) and may put the patient at risk of accumulation over time. It may be prudent to use TDM to determine whether decompensation is associated with significant changes in serum concentrations. Finally, the site of administration and needle should be considered before deciding to increase the dose of PP3M. For patients $\geq$90 kg, the 1.5-inch gluteal needle should be

used for deltoid injections to ensure the dose is administered intramuscularly. In the case of *wearing off*, however, the gluteal site should be considered regardless of weight as the $t_{1/2}$ of elimination is prolonged compared to deltoid injections. In the case of the PP3M the range increases from ~90 days (deltoid) to ~120 days (gluteal).[4]

Conclusion

Transitioning patients to LAIA formulations may provide benefits in tolerability (lower peak concentrations), efficacy (less fluctuation in concentrations), and adherence. The LAIAs are not a single-step solution to adherence and require consideration of numerous patient-specific factors to guide safe and effective use. Patient preference for a particular medication or dosing interval is a first step. Potential for variable pharmacokinetics (renal function, use of CYP or P-gp inducers/inhibitors, pharmacogenetic testing) can be used to guide initial dosing and help determine whether TDM would be clinically useful. To optimize dose selection, an ideal duration of oral antipsychotic should be long enough to reach steady state concentrations and achieve symptom improvement without adverse effects. Simply administering medication may confirm adherence to medication but is not sufficient to optimize patient outcomes. Comprehensive engagement in systems of care, minimizing use of substances, and reassessing dosing throughout treatment for efficacy and tolerability are essential to maximize the beneficial outcomes of LAIAs.

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