CLINICAL REVIEW

A Comprehensive Guide to Long-Acting Injectable Antipsychotics for Primary Care Clinicians

Abirami Krishna, MD, Shelby Goicochea, MD, Rishubh Shah, BS, Benton Stamper, PharmD, BCPS, Grant Harrell, MD, and Ana Turner, MD, FAPA

We propose a paper that provides education on commonly used long-acting injectable antipsychotics (LAIs) to improve primary care based mental health interventions in patients with severe mental illnesses (SMIs) such as schizophrenia, schizoaffective disorder, and bipolar disorders. With the expanding interface of primary care and psychiatry across all healthcare settings, it has become increasingly important for primary care clinicians to have a broader understanding of common psychiatric treatments, including LAIs. Long-acting injectable antipsychotics have been shown to be helpful in significantly improving treatment adherence, preventing disease progression, improving treatment response, decreasing readmission rates, and reducing social impairment. We discuss evidence-based indications and guidelines for use of long-acting injectable antipsychotics. We provide an overview of the treatment of SMI with LAIs, mainly focusing on the most commonly used long-acting injectable antipsychotics, advantages and disadvantages of each, along with outlining important clinical pearls for ease of practical application. Equipped with increased familiarity and understanding of these essential therapies, primary care clinicians can better facilitate early engagement with psychiatric care, promote more widespread use, and thus significantly improve the wellbeing and quality of life of patients with severe mental illness. (J Am Board Fam Med 2024;37:773–783.)

Keywords: **Antipsychotics, Bipolar Disorder, Long-Acting Injectable Antipsychotics, Mental Health, Primary Health Care, Psychiatry, Schizoaffective Disorder, Schizophrenia, Treatment Adherence and Compliance**

Introduction

With increasing shortages of psychiatric clinicians, primary care clinicians' roles have been expanding to meet these growing needs and require more sophisticated knowledge on treatment of psychiatric disorders. More than 50% of all psychiatric care is provided by a primary care provider and 70% of all primary care visits have a psychiatric chief concern.[9] Though primary care clinicians are becoming increasingly comfortable with the treatment of psychiatric conditions such as depression, many clinicians express discomfort with treating psychotic and bipolar disorders.[10] Nonadherence is the greatest risk factor for relapse of psychosis and mania, which can be mitigated through use of long-acting antipsychotic injectables (LAIs).[11–14] Recent studies comparing oral and LAIs have found that LAIs are associated with a 44% reduction in suicide attempts, 37% fewer all-cause hospitalizations, 48% fewer psychiatric hospitalizations, 12% reduction in hospitalizations for cardiovascular diseases, and 14% reduction in extrapyramidal symptoms.[3–4] LAIs have also been associated with lower risks of treatment failure compared with orals, and decreased risk of misuse.[15–19] Recent evidence-based guidelines recommend earlier and broader use of LAIs.[20] This article will explore general prescribing guidelines for LAIs and information regarding the most commonly prescribed LAIs.

The general mechanism of action for antipsychotics involves postsynaptic dopamine blockade in all areas of the brain, although its intended target is the receptors in the mesolimbic pathway thought to be responsible for the positive symptoms of schizophrenia (hallucinations, delusions) and inducing

Submitted 19 December 2022; revised 21 July 2024, 22 February 2023; accepted 26 February 2024.

From the University of Florida Health Jacksonville, Jacksonville, FL (AK, SG, BS, AT), University of Florida College of Medicine, Gainesville, FL (RS, GH).

Funding: No specific grant was received from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest: All authors declare that they have no conflicts of interests or competing interests.

Corresponding author: Ana Turner, MD, FAPA, University of Florida Health Jacksonville, 655 8th St W, Jacksonville, FL 32209 (E-mail: anat6112@gmail.com).

Table 1. Monitoring and Management of Side Effects.[23]

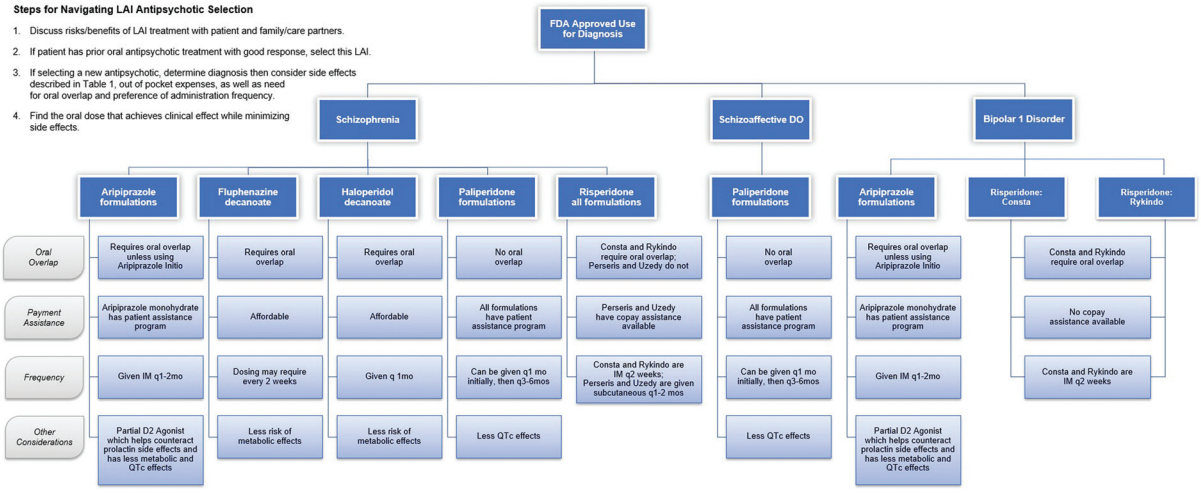
	Frequency	Monitoring	Management
Metabolic Syndrome	4 months after initiation, annually thereafter	Weight, circumference, lipid panel, fasting glucose or HbA1C	Lifestyle changes with diet and exercise are a first-line treatment, consider switching to antipsychotic with lower propensity for metabolic side effects if this will not destabilize the patient (d), medical treatment of metabolic syndrome may be necessary. Antipsychotics that have the lowest risk of metabolic syndrome are asenapine, aripiprazole (LAI available), lurasidone, ziprasidone, haloperidol (LAI available), cariprazine, brexpiprazole, and lumetaperone.[24]
Movement Disorders	Each visit clinically, formally q6 months-annually	Abnormal Involuntary Movement Scale, etc.	Lower dose or switch to lower potency antipsychotic if it will not destabilize the patient, such as clozapine or quetiapine. If unable to change/switch, first choice medication is a VMAT2 inhibitor for Tardive Dyskinesia and anticholinergic drugs for drug-induced parkinsonism.[25]
Agranulocytosis	First visit after initiation, then annually	ANC, discontinue if ANC <1000	Discontinue if ANC <1000.[23] and initiate broad spectrum antibiotics. Switch to another antipsychotic if it will not destabilize the patient, the antipsychotics with highest risk are clozapine, quetiapine, and olanzapine. If the patient must be re-trialed on the same medication, obtain a hematology consultation, wait until ANC normalizes above 1000.[23], and consider only the oral form.[26]
Prolonged QTc	After initiation in patients with sudden cardiac events in family or known risk for QT prolongation (ie, metabolic derangements, on other medications known to prolong QTc, etc.)	12-lead EKG	If QTc is greater than 500 ms, consider dose reduction or switch to alternate medication with low QTc prolongation and a referral to cardiology. If QTc greater than 470 ms in women or 440 in men but less than 500, decrease the dose of the medication or switch to drug with lower risk of prolongation if this will not destabilize the patient. Antipsychotics with the lowest risk of QTc prolongation are perphenazine, aripiprazole, paliperidone, asenapine (no LAI available), and lurasidone (no LAI available).[27]

Abbreviations: QTc, heart rate–corrected QT interval; ANC, absolute neutrophil count; LAI, long-acting injectable antipsychotics.

synaptic plasticity in the ventral striatum. Dopamine antagonism in the nigrostriatal pathway can lead to extrapyramidal side effects (dystonic reaction, akathisia, pseudoparkinsonism), whereas antagonism in the tuberoinfundibular tract leads to hyperprolactinemia causing weight gain, menstrual irregularity, and could cause difficulties achieving pregnancy.[21,22] Neuroleptic malignant syndrome is another movement disorder that is a potentially fatal reaction associated with antipsychotic use and requires emergent medical attention, prompt discontinuation of the drug and close monitoring. Like most antipsychotics, LAIs are not approved for dementia-related psychosis and carry a black box warning of increased mortality in these patients.[23] As part of medication management when prescribing antipsychotics, regular screenings should be completed to monitor metabolic side effects and antipsychotic-induced movement disorders, see Table 1.

Before initiating LAIs, clinicians must ensure that the patient tolerates the antipsychotic medication through a trial of the oral formulation. They must also discuss the risks and benefits of LAI treatment with the patient and family/care partners as

Figure 1. Typical treatment approaches of first identifying FDA approved uses, then key characteristics driving possible choice.



well as for obtaining the patient's agreement to LAI treatment. In general, medication selection is primarily based on prior oral treatment response, with consideration given to risk of side effects as described in Table 1, out of pocket expenses, as well as need for oral overlap and preference of administration frequency.[28] Some patients may benefit from monthly evaluation which can coincide with LAI administration versus those with significant difficulty coming to appointments may require LAIs with less frequent administration schedules. Dose selection relies on when clinical effectiveness is achieved while minimizing side effects, which is best assessed first with oral formulation.[23] At present there are fourteen LAI formulations available for use in the United States. Detailed prescribing information for 4 aripiprazole, 1 fluphenazine, 1 haloperidol, 3 paliperidone, and 4 risperidone LAI formulations are explored further below. Olanzapine decanoate was not included in the article because of its infrequent use possibly because of its risk of Post-Injection Delirium/Sedation Syndrome (0.07%) and with need for extensive monitoring post injection (approximately 3 hours).[29] According to expert guidelines there is no one LAI preferred over all others, but selection is based on past response of either oral or LAI formulations.[28] If no antipsychotic has been used before, Figure 1 summarizes typical treatment approaches of first identifying FDA approved uses, then key characteristics driving possible choice. In general, aripiprazole lauroxil, risperidone Uzedy and paliperidone formulations have the most ease of administration for patients given no need for oral overlap (if aripiprazole initio is available) and length between dosing (up to 2 months for aripiprazole lauroxil, 2 months for risperidone Uzedy, and 6 months for paliperidone palmitate).

Aripiprazole Long-Acting Injections

Abilify Maintena is the brand name for the once a month extended-release injection of aripiprazole monohydrate, and Abilify Asimtufii is the brand name for the once every 2 month injection. Both are FDA-approved for the treatment of schizophrenia and maintenance treatment of bipolar 1 disorder in adults. Aripiprazole is believed to have clinical benefit through a combination of partial dopamine D2 agonism, partial 5-HT-1A agonism, and 5-HT-2A antagonism. The extent of absorption is similar for both injection sites following administration of a single dose, but the rate of absorption was 31% higher for the deltoid muscle (Tmax 4 days) compared with the gluteal muscle (Tmax 5 to 7 days). After steady state is reached by the fourth injection, the extent of absorption and rate of absorption are similar for both injection sites. Before prescribing Abilify Maintena or Asimtufii, tolerability to oral aripiprazole should be established which may take up to 2 weeks because of the half-life of the oral medication. The recommended starting and maintenance dose of Abilify

Maintena is 400 mg monthly, but a starting and maintenance dose of 300 mg monthly should be used in patients who are known to be poor metabolizers of CYP2D6 or need a lower maintenance dose of 300 mg because of adverse reactions. Abilify Asimtufii is typically dosed 720 mg to 960 mg every 2 months. The most commonly observed adverse reactions occurring at an incidence of 5% or more and at least double that of placebo were increased weight gain, akathisia, injection site pain, and sedation. Oral aripiprazole at a dose of 10 to 20 mg should be taken for 14 consecutive days starting on the day of the first injection.[30]

Regarding pregnancy, neonates exposed to Abilify Maintena in the third trimester can experience extrapyramidal and/or withdrawal symptoms including changes in tone (ie, hypertonia or hypotonia), agitation, tremor, respiratory distress, somnolence, and feeding disorder. Aripiprazole has been shown to pass into breast milk in small amounts in a limited number of studies with most babies having no reported symptoms, however, breastfed babies should be monitored for increased sleepiness or trouble eating. Aripiprazole may lower breast milk production in a dose-dependent manner through suppression of prolactin.[31,32]

Abilify Maintena can cost between $2010 and $3009 per monthly injection.[33] Aripiprazole is available in other extended-release injection under the brand names Aristada and Aristada Initio (aripiprazole lauroxil) approved for use in schizophrenia, and Abilify Asimtufii approved for use in schizophrenia and bipolar 1 disorder. Aristada and Asimtufii allow for less frequent injections of every 2 months depending on the dose. Patients taking strong CYP3A4 or CYP2D6 inhibitors for greater than 2 weeks should have the dose of Aristada lowered to the next lower strength unless they are taking Aristada 441 mg in which case no dose adjustment is needed. Aristada should not be given earlier than 14 days following the previous injection.[34,35] Aristada can cost between $2887 to 3318 depending on the dose.[36]

Fluphenazine Decanoate

Fluphenazine LAI is typically initiated with 6.25 mg to 25 mg intramuscular (IM) or subcutaneously every 2 weeks.[37] If doses greater than 50 mg are required, gradually titrate by increments of 12.5 mg, however doses should not exceed 100 mg/injection.[56] Tmax is 0.3-1.5 days.[23] In patients who have not previously taken phenothiazines (such as fluphenazine) or who are at risk of hypersensitivity to phenothiazines, start with a short-acting formulation, such as oral or immediate-release fluphenazine to establish tolerability and effective dose before transitioning to the LAI.[38] The hypothesized dosing conversion from oral to decanoate of fluphenazine is approximately 1.25 times the oral dose (that is, 20 mg of oral fluphenazine is equivalent to approximately 25 mg of fluphenazine decanoate every 3 weeks, or 12.5 mg of decanoate for every 10 mg of oral fluphenazine daily. Sources differ on guidelines for oral supplementation, however the American Psychiatric Association (APA) recommends reducing the oral dose by half after the first injection, then discontinuing oral supplementation with the second injection.[23] (another source recommends doing so after at least 2 weeks.[39]). The patient may be able to have the dose reduced at the third dose to compensate for accumulation toward steady state to prevent adverse effects.[38] Other sources recommend that if oral supplementation is not completed on initiation of fluphenazine LAI, then weekly load injections of 1.6 times the total oral daily dose be given for 4 to 6 weeks.[40] Typical maintenance doses are 6.25-25 mg every 2 to 4 weeks. Peak plasma concentration of fluphenazine decanoate is reached in about 8 to 10 hours and time to achieve steady state is approximately 2 months.[23] Cost ranges from $47.18-$159.60.[41] Fluphenazine is extensively metabolized by the liver, though there are no clear guidelines on specific dosage adjustments in hepatic impairment, it is recommended that doses be reduced and titrated with caution in those with hepatic impairment.[40] Fluphenazine can produce mild and transient elevations of serum hepatic enzymes and rarely cholestatic liver injury. Caution is also advised in titration with renal and cardiac impairment and in the elderly.[42] Fluphenazine has a primary mechanism of action of dopamine D2 receptor blockade in the mesolimbic pathway, however similar to other first-generation antipsychotics, blockade also occurs in nigrostriatal, and tuberoinfundibular neural pathways. which can contribute to extrapyramidal side effects and hyperprolactinemia (which can be a barrier to achieving pregnancy). Fluphenazine also has adverse effects related to its anticholinergic (blurred vision, constipation, dry mouth, dry eyes, urinary retention), antihistaminic (sedation, weight gain) and α-adrenergic antagonistic properties (orthostasis, dizziness, hypotension, rebound tachycardia). It should be noted

that fluphenazine is a substrate of CYP2D6 enzymes, and should be used in caution with medications with CYP2D6 metabolism inducing activity.[43] The use of fluphenazine in pregnancy has not been well studied. Animal studies have found some changes in sperm exposed to fluphenazine, however this has not been well-studied in humans.[44]

Fluphenazine LAIs should only be used in pregnant patients when it is determined that the benefits to the patient outweigh the potential pregnancy and fetal risks as there is limited research regarding risks of fluphenazine use in pregnancy and breastfeeding. Phenothiazines can cross the placenta, however there is insufficient research to determine whether fluphenazine raises the risk of congenital malformations.[45–49] Third trimester exposure to antipsychotics in general has been associated with risk of extrapyramidal symptoms, agitation, hyper- or hypotonia, tremor, somnolence, respiratory distress, and feeding disorder.[45] The long-term effects of fluphenazine on neonate cognition and behavior have not been well studied. The manufacturer does not list clear recommendations for fluphenazine use in breastfeeding.[38], however other phenothiazines have not been recommended for use in breastfeeding.[50] There have been phenothiazine-related cases of drowsiness, lethargy, and developmental delays reported in nursing infants and hyperprolactinemia and galactorrhea in breastfeeding individuals which may interfere with normal lactation.[65,1]

Haloperidol Decanoate

For a patient with schizophrenia with moderate symptoms, initiate haloperidol oral formulation from 0.5 mg to 2 mg given 2 to 3 times daily. Starting oral dose in patients with severe, chronic or refractory symptoms of schizophrenia is higher at 3 mg to 5 mg given 2 to 3 times per day.[52] For acute therapy doses range between 6 to 20 mg daily and maintenance therapy doses range from 6 to 12 mg daily per consensus guidelines from the Patient Outcome Research Team (PORT).[37] The maximum oral dose is 100 mg/day.[52] Following stabilization with oral haloperidol, patients maintained on 10 mg daily or less can transition to haloperidol LAI at an IM depot dose 10 to 15 times the oral haloperidol equivalents. For patients maintained on oral haloperidol doses of greater than 10 mg daily who are at risk of decompensation at lower doses or have developed tolerance to haloperidol because of long-term use, the initial haloperidol LAI dose should be 20 times the oral dose with downward titration in subsequent monthly doses. Once the total needed is calculated, if the amount exceeds 100 mg, the first injection should be limited to 100 mg and the remaining balance injected 3 to 7 days later. Typically, the maintenance dose range of haloperidol LAI is 10 to 15 times the oral dose or 50 to 200 mg every 4 weeks, but should be titrated up or down depending on response and tolerability. There is limited clinical evidence with doses exceeding 450 mg per month. Peak plasma concentrations are reached after 6 days and the half-life is approximately 6 weeks.[53] Cost of haloperidol decanoate 100 mg/mL vial ranges from $19.62-$60.48.[54] Haloperidol is extensively and primarily metabolized by the liver and although there are no specific guidelines for dose adjustments in patients with hepatic impairment, it is suggested that doses be reduced or avoided when there is significant liver dysfunction in part because of increased risk of EPS from delayed clearance of the drug.[37] Significant reductions in haloperidol concentration have been found with coprescribed drugs or tobacco that induce the primary isoenzymes of CYP2D6 and CYP3A.[55,56] Haloperidol's mechanism of action is likely a result of antagonism of dopamine D2 receptors.[21,22] Haloperidol LAI should only be used in pregnant patients when the benefits to the patient outweigh the potential fetal risks as studies have not sufficiently determined safety and efficacy in pregnancy.[38] Neonates in 1 13-year prospective cohort study did not show difference in rates of congenital abnormalities compared with the control group even when conducting an analysis on first-trimester exposure, but there were 2 cases of limb defects in the antipsychotic group and none in the control group. It is not known whether haloperidol, other medications, or other factors caused limb defects.[39] There is limited information on the long-term neurobehavioral effects in children exposed during development, the manufacturer recommends against breastfeeding while receiving treatment.[53,57–59]

Paliperidone Long-Acting Injections

The monthly version of paliperidone palmitate extended-release formulation, Invega Sustenna, is FDA approved for schizophrenia and schizoaffective disorder in adults.[60] Invega Sustenna costs approximately $518.80-$11,416.[61] In patients without renal

impairment, Invega Sustenna is initiated with a 234 mg IM deltoid injection followed 8 days (±4 days) later with a 156 mg IM injection in the opposite deltoid. In patients with mild renal impairment (ie, creatinine clearance ≥50 mL/min to <80 mL/min), the initial injections should be lowered to 156 mg followed by 117 mg 8 days later. The medication is contraindicated in patients with a creatinine clearance <50 mL/min. The initial 2 injections should be initiated as deltoid injections as the rate of absorption is 28% higher on average compared with gluteal muscle injections following single dose IM injections.[23,60]

Although, on average, maximum plasma concentration (Tmax) is reached 13 days following injection, clinical improvement from Invega Sustenna can be seen by day 8.[62] Symptomatic improvement from paliperidone palmitate is likely a result of antagonism of dopamine D2 and serotonin 5-HT-2A receptors. Maintenance injections of Invega Sustenna can be administered in the deltoid or gluteal muscles at doses determined by clinical response and guided by conversion from oral paliperidone or oral risperidone. In patients with mild renal impairment defined as CrCl <80 mL/min >= 50 mL/min, monthly maintenance Invega Sustenna dose should be 78 mg and titrated to no higher than 156 mg monthly. No dose adjustment is needed for mild or moderate hepatic impairment; however, guidelines are unclear for severe hepatic impairment. The most common side effects (incidence ≥5% and occurring at least twice as much as placebo) are injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal symptoms. Paliperidone can prolong the QTc interval thus prescribe cautiously in patients with cardiac impairment or who have other risk factors that may prolong the QTc interval.[23,25] Extrapyramidal and withdrawal symptoms (agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) may occur in neonates who have been exposed in the third trimester of pregnancy. There is a slightly elevated risk for major birth defects (RR= 1.26, 95% CI 1.02-1.56) and cardiac malformations (RR = 1.26, 95% CI 0.88-1.81) in patients exposed to risperidone (the parent compound of paliperidone), however there are limited studies of whether this is replicated with paliperidone. Similarly, there are some reports of sedation, failure to thrive, jitteriness and EPS in breastfed infants exposed to risperidone.[63]

Paliperidone palmitate is available as a once every 3-month injection, Invega Trinza, FDA approved for schizophrenia in patients treated for ≥4 months with a stable dose of Invega Sustenna. The injection costs approximately $3,203-$1,1075 every 3 months. Tmax is achieved at approximately 30 to 33 days, but clinical improvement can be seen within the first few days to 2 weeks of administration of the injection. Invega Trinza has similar side effects to Invega Sustenna with the addition of headache and respiratory tract infection (upper respiratory tract infection, nasopharyngitis, pharyngitis, rhinitis).[64]

Paliperidone palmitate is also available as a once every 6 month injection, Invega Hafyera. It is FDA approved to treat schizophrenia in patients who have been on Invega Sustenna for at least 4 months, of which the last 2 months must have the same dose of Sustenna, or Invega Trinza for at least one 3 month cycle. Invega Hafyera will obtain a Tmax within 29 to 32 days, with the drug entering the plasma on day 1, but may continue to be present in the body for up to 18 months. Missed dose strategies are complex and require close monitoring and understanding of when the previous dose was administered. Adverse drug reactions do not differ significantly from other paliperidone products.[65]

Risperidone Long Acting Injections

Paliperidone is the active metabolite of risperidone. Risperidone LAIs will be briefly mentioned in this section. Of the Risperidone LAIs, Risperdal Consta (RC) is the oldest. This LAI is indicated for use in schizophrenia and Bipolar I disorder maintenance treatment. Typical dosing ranges from 25 mg to 50 mg every 2 weeks, not to exceed 50 mg per injection. RC requires oral overlap for the first 3 weeks after the initiation injection of RC.[66] A medication with a similar dosing frequency and FDA approved uses, Rykindo, only requires a 7 day overlap.[67] However, the every 2 week injection administration schedule continues to be a barrier given patient preference. Newer Risperidone LAIs have become available including the monthly subcutaneously injected Perseris, and Uzedy, an injection that is required to be given every 2 months, both only FDA approved for use in schizophrenia.[68,69] There is limited data regarding safety and efficacy of risperidone in pregnancy. Though it is known that risperidone can be transmitted in breast milk, the long-term cognitive effects on fetuses are unclear.[66]

Table 2. Summary

Medication	FDA Approval	Cost	Patient Assistance Program Available	Initial Oral Supplementation Required	Dosing	Special Characteristics
Aripiprazole lauroxil, Aristada	Schizophrenia	$2,945-$3,320	No, but copay assistance available	Oral overlap for 21 days, or no overlap if given 30 mg oral plus **Aristada Initio** 675 mg	441 mg-1064 mg monthly to every 2 months depending on dose	Also has partial D2 Agonism; CYP3A4 and CYP2D6 substrate
Aripiprazole monohydrate, Abilify Maintena and Abilify Asimtufii	Schizophrenia, Bipolar 1 Disorder Maintenance	$2,010-$3,009	Yes	Yes, 2 week oral overlap	**Maintena** 300-400 mg IM monthly **Asimtufii** 720-960 mg IM every 2 months	Also has partial D2 Agonism
Fluphenazine decanoate, Prolixin Dec	Psychosis	$47.18-$159.60	No	Yes	6.25 mg to 25 mg IM or subcutaneously every 2 to 4 weeks approximately 1.25 times the oral dose	CYP2D6 substrate
Haloperidol decanoate, Haldol Dec	Chronic Psychosis	$19.62-$60.48	No	Yes	10 to 15 times the oral haloperidol equivalents IM monthly; if the amount exceeds 100 mg, the first injection should be limited to 100 mg and the remaining balance injected 3 to 7 days later	CYP3A and CYP2D6 substrate
Paliperidone Palmitate (Invega Sustenna)	Schizophrenia, Schizoaffective Disorder	$518.80-$11,416 covered by most insurances	Yes	No	Pending CrCl, 78 mg-234 mg IM Monthly	Contraindicated in severe renal impairment; CYP3A4 substrate
Paliperidone Palmitate (Invega Trinza)	Schizophrenia	$3,203-$11,075 every 3 months, covered by most insurances	Yes	No, following 4 months of Invega Sustenna	273 mg-819 mg IM every 3 months	Contraindicated in severe renal impairment; CYP3A4 substrate
Paliperidone Palmitate (Invega Hafyera)	Schizophrenia	$13,991-$20,981 every 6 months, covered by most insurances	Yes	No, following 4 months of Invega Sustenna or one 3 month cycle of Invega Trinza	1092 mg-1560 mg IM every 6 months	Contraindicated in severe renal impairment; CYP3A4 substrate
Risperidone Consta	Schizophrenia, Bipolar 1 Disorder Maintenance	$1,157-1,303 covered by most insurances	No	Oral overlap for first 3 weeks	25-50 mg every 2 weeks	CYP3A4 and CYP2D6 substrate

Continued

Table 2. Continued

Medication	FDA Approval	Cost	Patient Assistance Program Available	Initial Oral Supplementation Required	Dosing	Special Characteristics
Risperidone Perseris	Schizophrenia	$2,189-$2916	No, but copay assistance available	No	Subcutaneous monthly	CYP3A4 and CYP2D6 substrate
Risperidone Rykindo	Schizophrenia, Bipolar 1 Disorder	Pricing unavailable at this time	No	Yes, oral overlap for 7 days	IM every 2 weeks	CYP3A4 and CYP2D6 substrate
Risperidone Uzedy	Schizophrenia	$1,306-$6495	No, but copay assistance available	No	Subcutaneous every 2 months	CYP3A4 and CYP2D6 substrate

*__Olanzapine decanoate__ was not included in the paper because of its infrequent use possibly because of its risk of Post-Injection Delirium/Sedation Syndrome (0.07%) and with need for extensive monitoring post injection (approximately 3 hours).[24]

Abbreviation: FDA, food and drug administration.

Risperidone doses should be increased when coprescribed with strong CYP3A4 inducers, and doses should be reduced when coprescribed with strong CYP2D6 inhibitors.[70]

Discussion

Each LAI discussed has its own unique qualities, some of the most notable clinical pearls have been included below and in Table 2. If cost is a deciding factor, the least expensive LAIs are haloperidol and fluphenazine. Of the LAIs included, only aripiprazole formulations, Risperidone Consta and Risperidone Rykindo are FDA-approved for bipolar 1 disorder and only Invega Sustenna is FDA-approved for schizoaffective disorder. For patients who have extensive cardiac history, a baseline prolonged QTc interval or on concomitant QTc prolonging agents, aripiprazole LAIs can be considered as they can lower the QT interval. Dose adjustments are required for mild renal impairment for paliperidone LAIs but there is contradiction in moderate to severe impairment. In patients with hepatic impairment, haloperidol LAI may require dosing adjustments and fluphenazine LAI is contraindicated. In terms of pharmacokinetics, the medication with the earliest onset of action is fluphenazine, however it is also dosed the most frequently (every 2 to 4 weeks) compared with the other LAIs. If oral medication adherence is a challenge, consider using a paliperidone LAI formulation, Perseris, Uzedy, or Aristada (only if Aristada Initio is used) as oral supplementation is not required. Meanwhile, oral supplementation is required for Abilify Maintena, Abilify Asimtufii, Haloperidol decanoate, Risperdal Consta, Rykindo and fluphenazine decanoate. Clinicians may also consider converting to Invega Trinza (3 month dosing), Invega Hafyera (6 month dosing), Abilify Asiumtufii (2 month dosing), Aristada (2 month dosing), or risperidone Uzedy (2 month dosing) as these injections have the longest duration between injections of the LAIs discussed.

Conclusion

LAIs have many advantages however remain underutilized. Equipped with a broader understanding and comfort with this effective intervention, clinicians can advocate better for administering such interventions and improving their patient's prognosis and overall wellbeing.

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