REVIEW ARTICLE

Overview of Long-Acting Injectable Schizophrenia Medications

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Schizophrenia is a serious mental disorder characterized by psychotic symptoms including hallucinations, delusions, and disordered behavior or thinking.[1-3] Negative symptoms of schizophrenia, including avolition, apathy, and anhedonia, are also common and often precede positive symptoms. According to the National Institute of Mental Health, schizophrenia has a prevalence of 0.25% to 0.64% in the United States.[1] The World Health Organization estimates that 24 million people are affected by schizophrenia globally.[4]

Schizophrenia is a lifelong illness that typically presents in the late teenage years and early 20s, with most individuals diagnosed between 16 and 30 years of age.[5] As a lifelong disease, schizophrenia is associated with significant health, social, and economic burdens.[1,4] In fact, it is estimated that schizophrenia is among the top 15 causes of disability worldwide. Affected individuals are at risk for premature mortality related to concomitant medical conditions as well as an elevated risk for suicide. This disorder is often disruptive to daily life, creating difficulties with socialization, self-care, and attendance at work or school.[6]

Schizophrenia is a complex and incompletely understood neurodevelopmental disorder.[7] Genetic and environmental factors are known to play a role, and excess dopamine in the mesolimbic tract is commonly implicated.[7,8] There are no imaging studies or laboratory tests for diagnosing schizophrenia, and diagnosis is primarily based on a thorough health history and review of symptoms.[9] According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision*, patients must experience at least 2 of the following symptoms for a significant portion of a month to be diagnosed with schizophrenia[10]:

- delusions
- hallucinations
- disorganized speech
- grossly disorganized or catatonic behavior
- negative symptoms (a lessening or absence of normal behaviors and functions related to motivation and interest, or verbal/emotional expression)

Notably, at least 1 of the symptoms must be delusions, hallucinations, or disorganized speech. These symptoms must impair function at work or school, relationships, or self-care and persist for at least 6 months. Other conditions such as schizoaffective disorder, bipolar disorder, and substance abuse should be considered in the differential diagnosis.

Pharmacotherapy is a key component of schizophrenia treatment, and the 2020 American Psychiatric Association (APA) guidelines for schizophrenia recommend that patients with schizophrenia be treated with antipsychotic medication.[9,11] Initial treatment is individualized and will depend on patient presentation and personal treatment goals. The general goals of treatment include:

- promoting and maintaining recovery;
- maximizing quality of life and function; and
- reducing or eliminating symptoms of schizophrenia.

In patients with acute schizophrenia, the goal of antipsychotic treatment is short-term improvement of behavioral symptoms such as hostility or agitation that are distressing to the patient and result in situations that are dangerous for the patient or others.[7]

Antipsychotic Treatments

Numerous antipsychotic treatments are available for schizophrenia and are historically categorized as either first-generation antipsychotic (FGA) or second-generation antipsychotic (SGA) agents.[11-13] The FGAs (also known as typical antipsychotics) were developed in the 1950s and are inhibitors of dopaminergic transmission. Many of these agents also have noradrenergic, cholinergic, and histaminergic blocking activity. The SGAs (also known as atypical antipsychotics) transiently block dopamine receptors and affect serotonin transmission.

The current APA practice guidelines make no recommendations for a specific treatment option and indicate no general preference for FGA versus SGA agents with the exception of specific situations.[11] The guidelines suggest that a treatment algorithm with evidence-based rankings of the various antipsychotics is not feasible given the limited number of direct comparative trials as well as the heterogeneity among the trials; however, APA recommends that clinicians select an agent based on patient-specific factors. Knowledge of basic differences among the agents is key for appropriate treatment selection.

Formulations

Antipsychotic agents come in a variety of formulations. All 23 antipsychotic agents marketed in the United States have an oral formulation.[14] It may consist of an immediate-release tablet, extended-release tablet, capsule, sublingual tablet, and/or oral liquid. Immediate-release injectable formulations (intravenous or intramuscular) are also available. Although important in acute settings, they are less often used for long-term schizophrenia maintenance treatment.

Long-Acting Injectable Antipsychotic Formulations

Long-acting injectable (LAI) formulations are important options for the long-term maintenance treatment of patients with schizophrenia, and the APA notes that these agents are "particularly useful for patients with a history of poor or uncertain adherence" and "may be preferred by some patients."[11] There are currently 6 LAI antipsychotics available in 15 formulations in the United States (Table 1).[15-30] Characteristics common to all agents include the need for administration by a healthcare professional and a boxed warning regarding increased mortality when used in elderly patients with dementia-related psychosis. However, selection of an LAI for an individual patient requires advanced knowledge of drug and formulation characteristics. Tables 1 and 2 discuss basic administration and dosing information for each formulation, and a summary for each drug available as an LAI is provided below.

First-Generation LAIs

Fluphenazine and haloperidol are FGAs available as LAIs. Both agents comprise an esterified form of the oral compound attached to decanoic acid (a fatty acid chain) and dissolved in an oil from which the drug is slowly released.[29] The FGAs are generally associated with more extrapyramidal symptoms than SGAs and thus typically are not used as first-line agents.[13]

Second-Generation LAIs

Aripiprazole, olanzapine, paliperidone, and risperidone are SGAs formulated as LAIs.[17-30] Although SGAs are less likely to cause extrapyramidal effects and are generally better tolerated than first-generation medications, adverse effects such as weight gain and metabolic syndrome are more common and can be concerning for many patients.[11,13,29]

Aripiprazole

Aripiprazole monohydrate is available as the once-monthly injection Abilify Maintena (Otsuka) and has more recently been formulated as Abilify Asimtufii (Otsuka), which

is administered bimonthly.[17,18] Both agents require a 2-week overlap period with an oral antipsychotic.

Aripiprazole lauroxil (Aristada, Alkermes) is the extended-release prodrug of aripiprazole.[19,20,29] This formulation has numerous dosing and dosing interval options, and may be advantageous for some patients as it can be initiated without significant oral overlap when started with its Aristada Initio companion.

Olanzapine

Olanzapine pamoate (Zyprexa Relprevv, Cheplapharm) is the single LAI formulation of olanzapine.[21] Olanzapine is unique among the SGAs because it has a boxed warning for post-injection delirium or sedation and a restricted distribution program. It requires administration in a registered healthcare facility with access to emergency response services, and patients must be observed by a healthcare professional for at least 3 hours after injection.

Paliperidone

Paliperidone palmitate has 3 branded LAI formulations: Invega Sustenna, Invega Trinza, and Invega Hafyera, all of which are marketed by Janssen.[21-23] These agents differ in their dosing frequencies and, subsequently, their strengths. Initiation of Invega Trinza and Invega Hafyera requires established therapy with Invega Sustenna prior to use.

Risperidone

Risperidone offers the most diverse LAI formulations of the SGAs. Clinicians must carefully review these formulations because they differ in route of administration, dosing frequency, and conversion from oral therapy.[25-28,30] Risperidone is the only SGA LAI with potential for subcutaneous administration (Perseris, Indivior and Uzedy, Teva formulations).

Comparative Efficacy and Safety

Several meta-analyses have compared the efficacy and safety of LAI products. Although some efficacy and safety differences have been noted, the results are inconsistent, and no clear conclusions can be drawn regarding a preferred agent. A large network meta-analysis specific to LAIs found no differences in relapse rates among the second-generation LAIs; paliperidone (every-3-month formulation), aripiprazole LAI, and fluphenazine LAI were found to be superior to haloperidol LAI for this outcome.[31] All-cause discontinuation rates were lower with aripiprazole LAI compared with risperidone LAI and monthly paliperidone, indicating potential advantages in tolerability/acceptability for aripiprazole LAI. This meta-analysis did not differentiate between the formulations of aripiprazole LAI that are currently available (aripiprazole and aripiprazole lauroxil); however, a separate network meta-analysis found no significant differences in efficacy or safety between these aripiprazole LAI formulations.[32]

Conclusion

Long-acting injectable antipsychotics are an important treatment option for patients with schizophrenia. These agents may help improve adherence and lower the treatment burden compared with daily oral medications. There are numerous LAI formulations available, including both first-generation (fluphenazine and haloperidol) and second-generation (aripiprazole, olanzapine, paliperidone, and risperidone) agents. Differences in dosage frequency, route of administration, or adverse effects may be important when selecting an LAI for a particular patient. All LAIs require demonstration of tolerability with an oral formulation, and the complexity of the transition from oral to LAI may also impact both prescriber and patient preferences.

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Table 1. LAI Antipsychotic Formulations

Generic	Brand	Administration route	Administration frequency	Alternative dosage forms
First-generation LAIs				
Fluphenazine decanoate	N/A	• IM • SC	Every 4-6 wk	• Injection solution • Oral concentrate • Oral elixir • Oral tablet
Haloperidol decanoate	Haldol Decanoate (Janssen)	IM	Monthly	• Injection solution • Oral concentrate • Oral tablet
Second-generation LAIs				
Aripiprazole monohydrate	Abilify Maintena (Otsuka)	IM	Monthly	• ODT • Oral solution • Oral tablet
	Abilify Asimtufii (Otsuka)	Gluteal IM	Every 2 mo	
Aripiprazole lauroxil	Aristada (Alkermes)	• Deltoid IM (441-mg dose) • Gluteal IM	Every 1-2 mo	N/A
	Aristada Initio (Alkermes)	• Deltoid IM • Gluteal IM	Single dose for Aristada treatment initiation	
Olanzapine pamoate	Zyprexa Relprevv (Eli Lilly)	Gluteal IM	Every 2-4 wk	• Injection solution • ODT • Oral tablet
Paliperidone palmitate	Invega Hafyera (Janssen)	Deltoid IM	Every 6 mo	Extended-release oral tablet
	Invega Sustenna (Janssen)	• Deltoid IM • Gluteal IM	Monthly	
	Invega Trinza (Janssen)	• Deltoid IM • Gluteal IM	Every 3 mo	
Risperidone	Perseris (Indivior)	SC	Monthly	• ODT • Oral solution • Oral tablet
	Risperdal Consta (Janssen)	• Deltoid IM • Gluteal IM	Every 2 wk	
	Risvan (Rovi)	• Deltoid IM • Gluteal IM	Monthly	
	Rykindo (Shandong Luye)	Gluteal IM	Every 2 wk	
	Uzedy (Teva)	SC	Monthly or every 2 mo	

IM, intramuscular; LAI, long-acting injectable; N/A, not applicable; ODT, orally disintegrating tablet; SC, subcutaneous.

Based on references 14-30.

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Table 2. LAI Antipsychotic Dosing

Generic	Brand	Dosing strategy	Comments
First-generation LAIs			
Fluphenazine decanoate	N/A	• For every 10-mg/d dose of oral fluphenazine hydrochloride, inject 12.5 mg of fluphenazine decanoate every 3 wk • Usual initial and maintenance doses: 12.5-25 mg IM or SC approximately every 4-6 wk • Maximum dose: 100 mg	After initial conversion, adjust dose as clinically necessary at time of each injection
Haloperidol decanoate	Haldol Decanoate (Janssen)	• Initial dose of haloperidol decanoate: 10-20 times the previous daily dose of oral haloperidol • Usual maintenance dose: 10-15 times the previous daily dose of oral haloperidol given monthly • Maximum dose: 100 mg	Doses >100 mg should be administered as 100 mg followed by the balance in 3-7 d
Second-generation LAIs			
Aripiprazole monohydrate	Abilify Maintena (Otsuka)	Initial and maintenance dose: 400 mg IM monthly after tolerability is established with oral aripiprazole	Continue oral aripiprazole (or other antipsychotic) for 14 d after first injection
	Abilify Asimtufii (Otsuka)	Initial and maintenance dose: 960 mg IM every 2 mo after tolerability is established with oral aripiprazole	
Aripiprazole lauroxil	Aristada (Alkermes)	Establish tolerability with oral aripiprazole prior to LAI initiation • 10 mg daily oral dose → 441 mg IM every month • 15 mg daily oral dose → 662 mg IM every month or 882 mg IM every 6 wk or 1,064 mg IM every 2 mo • ≥20 mg/d → 882 mg IM every month Maintenance doses: • 441 mg IM monthly • 662 mg gluteal IM monthly • 882 mg gluteal IM monthly or every 6 wk • 1,064 mg gluteal IM every 2 mo	Initial dose may be given in conjunction with Aristada Initio and a single dose of oral aripiprazole or with oral aripiprazole for 21 d
	Aristada Initio (Alkermes)	A single 675-mg IM injection + the first Aristada injection + 30 mg oral aripiprazole	Single dose for Aristada treatment initiation
Olanzapine pamoate	Zyprexa Relprevv (Eli Lilly)	Establish tolerability with oral olanzapine prior to LAI initiation • 10 mg daily oral dose → 210 mg IM every 2 wk or 405 mg IM every 4 wk; after 8 wk, maintenance dose of 150 mg IM every 2 wk or 300 mg IM for 4 wk • 15 mg daily oral dose → 300 mg IM every 2 wk; after 8 wk, maintenance dose of 210 mg IM every 2 wk or 405 mg IM every 4 wk • 20 mg daily oral dose → 300 mg IM every 2 wk; after 8 wk, maintenance dose of 300 mg IM every 2 wk	Discontinue oral olanzapine without taper
Paliperidone palmitate	Invega Sustenna (Janssen)	Establish tolerability with oral paliperidone or risperidone prior to LAI initiation • Initial dose: 234 mg IM on day 1, then 156 mg IM on day 8 • Maintenance dose: 39-234 mg IM monthly	Discontinue oral paliperidone immediately after initial LAI dose
	Invega Trinza (Janssen)	For use only after 4 mo of adequate treatment with Invega Sustenna • Initial dose: 3.5 times the last Sustenna dose – 78 mg Sustenna → 273 mg IM – 117 mg Sustenna → 410 mg IM – 156 mg Sustenna → 546 mg IM – 234 mg Sustenna → 819 mg IM • Maintenance dose: 273-819 mg IM every 3 mo	Initiate Invega Trinza treatment on the day of next scheduled Invega Sustenna injection
	Invega Hafyera (Janssen)	For use only after previous treatment with Invega Sustenna for at least 4 mo or Invega Trinza for at least one 3-mo injection cycle • Initial and maintenance dose: dependent on last dose of Sustenna or Trinza and administered every 6 mo – 156 mg Sustenna → 1,092 mg IM – 234 mg Sustenna → 1,560 mg IM – 546 mg Trinza → 1,092 mg IM – 819 mg Trinza → 1,560 mg IM	Initiate Invega Hafyera treatment on the day of the next scheduled Sustenna or Trinza injection
Risperidone	Perseris (Indivior)	Establish tolerability with oral risperidone prior to LAI initiation • 3 mg daily oral dose → 90 mg SC • 4 mg daily oral dose → 120 mg SC • Maintenance dose: 90 or 120 mg SC monthly	Initiate Perseris the day after the last dose of oral therapy
	Risperdal Consta (Janssen)	Establish tolerability with oral risperidone prior to LAI initiation • Initial and maintenance dose: 25 mg IM every 2 wk • Can increase to 37.5-50 mg IM every 2 wk	Continue oral risperidone (or other antipsychotic) for 3 wk, then discontinue oral therapy
	Risvan (Rovi)	Establish tolerability with oral risperidone prior to LAI initiation • 3 mg daily oral dose → 75 mg IM monthly • 4 mg daily oral dose → 100 mg IM monthly	Initiate Risvan 1 day after the last dose of oral therapy
	Rykindo (Shandong Luye)	Establish tolerability with oral risperidone prior to LAI initiation • Initial and maintenance dose: 25 mg IM every 2 wk • Can increase to 37.5-50 mg IM every 2 wk	Continue oral risperidone for 1 wk after first LAI injection, then discontinue oral therapy
	Uzedy (Teva)	Establish tolerability with oral risperidone prior to LAI initiation • 2 mg daily oral dose → 50 mg SC monthly or 100 mg SC every 2 mo • 3 mg daily oral dose → 75 mg SC monthly or 150 mg SC every 2 mo • 4 mg daily oral dose → 100 mg SC monthly or 200 mg SC every 2 mo • 5 mg daily oral dose → 125 mg SC monthly or 250 mg SC every 2 mo	Initiate Uzedy the day after the last dose of oral therapy

IM, intramuscular; LAI, long-acting injectable; N/A, not applicable; SC, subcutaneous.

Based on references 14-30.