When and how to use long-acting injectable antipsychotics

William Klugh Kennedy, PharmD, BCPP, FASHP

Vicki L. Ellingrod, PharmD, BCPP, FCCP
Series Editor

Long-acting injectable antipsychotics (LAIs) are a pharmacotherapeutic option to help clinicians individualize schizophrenia treatment. LAIs have been available since the 1960s, starting with fluphenazine and later haloperidol; however, second-generation antipsychotics were not available in the United States until 2007[1,2] and more are in development (***Box***).[3,4]

Up to one-half of patients with schizophrenia do not adhere to their medications.[5] LAI use may mitigate relapse in acute schizophrenia that is caused by poor adherence to oral medications. LAIs may have a lower risk of dose-related adverse effects because of lower peak antipsychotic plasma levels and less variation between peak and trough plasma levels. LAIs may decrease the financial burden of schizophrenia and increase individual quality of life because patients spend fewer days hospitalized due to acute exacerbations.[6]

Some widely used schizophrenia treatment algorithms, such as the Harvard Schizophrenia Algorithm, neglect LAIs. Also, LAIs have not been well studied for maintenance treatment of bipolar disorder (BD) even though nonadherence is a substantial problem in these patients. Patients, families, and legal guardians may choose LAI antipsychotics over oral formulations to decrease the frequency and severity of psychotic relapse or for convenience because patients who receive LAIs do not need to take a medication every day.

Dr. Kennedy is Clinical Associate Professor of Pharmacy Practice and Psychiatry, Mercer University, Memorial University Medical Center, Savannah, GA.

Understanding the similarities and differences among LAIs[7] and potential interpatient variability of each LAI allows prescribers to tailor the dosing regimen to the patient more safely and efficiently (***Table, page 42***).[1,8-11] All LAI antipsychotic formulations rely on absorption pharmacokinetics (PK) rather than elimination PK, which generally is true for sustained-release oral formulations as well. Absorption half-life duration and absorption half-life variability are key concepts in LAI dosing.

Clinical pearls

Before prescribing an LAI, check that your patient has no known contraindications to the active drug or delivery method. Peak-related adverse effects typically are not contraindications, although they may prompt you to start at a lower dose.

Ensure that your patient will have long-term outpatient access to the LAI and the entire treatment team—inpatient and outpatient—is committed to LAI treatment.

Practice Points

- Long-acting injectable antipsychotics (LAIs) are an important therapeutic option for patients with schizophrenia that **allows clinicians to tailor pharmacotherapy** to each patient's needs.
- When selecting a specific LAI, **consider class similarities and individual antipsychotic differences**.
- Although some LAIs are expensive, they potentially **reduce the financial burden of schizophrenia and improve quality of life**.

Do not rule out first-generation LAIs such as haloperidol and fluphenazine. The Clinical Antipsychotic Trials of Intervention Effectiveness study, Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study, and other published data suggest older antipsychotics are not inferior to newer medications.[12,13]

Verify that your patient has had an oral trial of the active drug—ideally in the last 12 months—that resulted in at least partial positive response and no serious adverse drug effects (ADEs). Oral medications' shorter duration of action may help identify ADEs before administering an LAI.[1]

Discontinue the oral medication as quickly as evidence, guidance, and good clinical judgment allow. Develop a plan to transition from oral to LAI that you will follow unless the patient develops intolerable ADEs or other problems. There is no evidence to suggest that patients who receive partial LAI therapy decompensate less frequently or less severely than those who take oral medication.

If antipsychotic polypharmacy is necessary, document your rationale.

In patients who are naïve to a specific LAI dosage form, ensure that the first dose does not exceed FDA and evidence-based guidelines for the initial dose (eg, 100 mg intramuscular [IM] for haloperidol decanoate).[1]

Consider a loading dose strategy to minimize the time a patient has to take an oral and LAI antipsychotic combination.[14]

Ensure that the total volume injected intramuscularly is not >3 ml per injection site per dose.

Use the recommended injection technique for the particular LAI (eg, Z-tract).[1,15]

Individualize the dose and dosing interval based on patient response, peak-related adverse effects (time to peak is approximately 5 half-lives for most drugs), and possible reduced symptom control at the end of the dosing interval.[8]

If your patient does not respond as expected, taking an antipsychotic plasma level to assess drug metabolism and other PK factors and characteristics may be useful.

Box

Long-acting injectable antipsychotics in development

Aripiprazole microsphere long-acting injectable (LAI) is a phase III investigational drug that at press time was being reviewed by the FDA. This formulation appears to be similar to risperidone LAI. The active antipsychotic differs in side effect profile and pharmacokinetics. Because the pharmaceutical science of microsphere construction allows many variations, it is not possible to determine the strengths and weaknesses of aripiprazole LAI compared with risperidone LAI microspheres at this time. The dosing intervals currently under investigation are 14 and 28 days.[3]

Iloperidone crystalline LAI is a phase II-III investigational drug. FDA registration documents and early publication and presentation data report that iloperidone LAI will be a crystalline salt structure pharmaceutically similar to paliperidone and olanzapine LAI formulations.[4] The dosing interval under investigation is 28 days.

LAI options

Fluphenazine decanoate is an older, inexpensive LAI with considerable interpatient variability in absorption rate and peak effects, and a relatively short duration of action. Dosing every 7 days may be necessary to avoid peak plasma level adverse effects or symptom recurrence. Variable PK make it difficult to accurately calculate an empiric conversion dose from oral to LAI; therefore, start at the low end (eg, 1.2 to 1.6 times the total daily oral dose) or 12.5 or 25 mg for the initial IM fluphenazine decanoate dose. A short overlap period—usually 1 to 2 weeks—may be necessary. Successful subcutaneous administration is possible.[2]

Haloperidol decanoate. A 28-day dosing interval is effective for most patients. It is possible to administer a loading dose so that no overlapping taper is required. My

Clinical Point

Do not rule out first-generation LAIs; data suggest older antipsychotics, such as haloperidol and fluphenazine, are not inferior to newer drugs

Discuss this article at www.facebook.com/CurrentPsychiatry

Table

Characteristics of long-acting injectable antipsychotics

Antipsychotic	Oral elimination half-life	Formulation	Absorption half-life	Time between injections	Clinically relevant PK/PD variability[a]	Oral overlapping taper necessary?	Loading dose possible?
Fluphenazine	1 day	Decanoate in organic oil	14 days	7 to 21 days	+++	Yes	No
Haloperidol	1 day	Decanoate in organic oil	21 days	28 days	+/-	No	Yes
Olanzapine	1.5 days	Pamoate crystalline	30 days	14 to 28 days	++	Maybe	No
Risperidone	1 day	Microspheres	5 days	14 days	++	Yes	No
Paliperidone	1 day	Palmitate crystalline	45 days	28 days	+	No	Yes

[a]More + indicates greater variability among patients

PD: pharmacodynamics; PK: pharmacokinetics

Source: References 1,8-11

Clinical Point

Administering olanzapine pamoate requires enrollment in a national registry that documents the incidence of rare but serious ADEs

team has had good results using an initial loading dose 15 to 20 times the effective oral dose and a second dose 28 days later of 10 times the oral daily maintenance dose, with the same dose every month thereafter. If a patient is receiving his or her first haloperidol decanoate injection, the initial dose should not exceed 100 mg. The remainder of the loading dose may be administered 3 to 7 days later if no adverse effects occur. Similar to fluphenazine decanoate, haloperidol decanoate is relatively inexpensive. When considering giving a haloperidol decanoate loading dose >400 mg or a maintenance dose >200 mg every 28 days, carefully document the rationale (eg, rapid metabolism).[16]

Olanzapine pamoate. Clinicians who administer olanzapine pamoate must enroll in a national registry that documents the incidence of rare but serious ADEs, particularly hypotension, orthostatis, and post-injection delirium/sedation syndrome (0.1% incidence) at every injection, not just for drug-naïve patients. Patients should be observed for 3 hours after every dose and oral medication overlap may be necessary in some cases.[10] Similar to clozapine, these monitoring difficulties and the expense may have inhibited olanzapine LAI use, even in patients who are likely to benefit.

Risperidone microspheres. This agent has been evolutionary, if not revolutionary, in schizophrenia treatment and data on its efficacy for BD will be available soon. Its 2-week dosing interval, necessity of oral overlap, and anecdotal reports of "dose dumping" possibly because of fragility of the microsphere formulation suggest the need for an improved version, which was addressed by the introduction of paliperidone palmitate.[10,17,18]

Paliperidone palmitate has a 28-day dosing interval. No overlapping oral taper is necessary. Details of a week-long, 2-dose loading dose strategy is provided in the package insert.[11] It may be safe to use a more aggressive loading dose strategy.[15,19]

References

1. Haloperidol decanoate [package insert]. Irvine, CA: Teva Parenteral Medicines, Inc; 2009.
2. Fluphenazine decanoate [package insert]. Schaumburg, IL: APP Pharmaceuticals, LLC; 2010.
3. A study of ALKS 9072 in subjects with chronic stable schizophrenia. http://clinicaltrials.gov/ct2/show/NCT01493726. Published December 12, 2011. Accessed December 16, 2011.

4. Hill CL, Phadke D, Boyce KM. Four-week iloperidone depot injectable: safety and pharmacokinetic profile in patients with schizophrenia and schizoaffective disorder. Poster presented at: 161st annual meeting of the American Psychiatric Association; May 3-8, 2008; Washington, DC.
5. Lacro JP, Dunn LB, Dolder CR, et al. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. J Clin Psychiatry. 2002;63(10):892-909.
6. Keith SJ, Kane JM, Turner M, et al. Academic highlights: guidelines for the use of long-acting injectable atypical antipsychotics. J Clin Psychiatry. 2004;65(1):120-131.
7. McEvoy JP. Risks versus benefits of different types of long-acting injectable antipsychotics. J Clin Psychiatry. 2006;67 (suppl 5):15-18.
8. Gitlin M, Midha KK, Fogelson D, et al. Persistence of fluphenazine in plasma after decanoate withdrawal. J Clin Psychopharmacol. 1988;8(1):53-56.
9. Wilson WH. A visual guide to expected blood levels of long-acting injectable risperidone in clinical practice. J Psychiatr Pract. 2004;10(6):393-401.
10. Zyprexa Relprevv [package insert]. Indianapolis, IN: Eli Lilly and Company; 2011.
11. Invega Sustenna [package insert]. Titusville, NJ: Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc; 2011.
12. Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353(12): 1209-1223.
13. Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia. Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry. 2006;63(10):1079-1087.
14. Wei FC, Jann MW, Lin HN, et al. A practical loading dose method for converting schizophrenic patients from oral to depot haloperidol therapy. J Clin Psychiatry. 1996;57(7):298-302.
15. Samtani MN, Vermeulen A, Stuyckens K. Population pharmacokinetics of intramuscular paliperidone palmitate in patients with schizophrenia. Clin Pharmacokinetics. 2009; 48(9):585-600.
16. Kapur SJ, Zipursky R, Jones C, et al. Relationship between dopamine D2 occupancy, clinical response and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry. 2000;157(4):514-520.
17. Deeks ED. Risperidone long-acting injection: in bipolar I disorder. Drugs. 2010;70(8):1001-1012.
18. Risperdal Consta [package insert]. Titusville, NJ: Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc; 2011.
19. Samtani MN, Haskins JT, Alphs L, et al. Initiation dosing of deltoid intramuscular paliperidone palmitate in schizophrenia – pharmacokinetic rationale based on modeling and simulation. Poster presented at: 49th annual NCDEU meeting; June 29-July 2, 2009; Hollywood, FL.

Related Resources

- Rothschild AJ. The evidence-based guide to antipsychotic medications. Arlington, VA: American Psychiatric Publishing, Inc.; 2010.
- Cañas F, Möller HJ. Long-acting atypical injectable antipsychotics in the treatment of schizophrenia: safety and tolerability review. Expert Opin Drug Saf. 2010;9(5):683-697.

Drug Brand Names

Aripiprazole • Abilify
Fluphenazine deconoate • Prolixin Deconoate
Haloperidol deconoate • Haldol Deconoate
Iloperidone • Fanapt
Olanzapine pamoate • Zyprexa Relprevv
Paliperidone palmitate • Invega Sustenna
Risperidone • Risperdal Consta

Disclosure

Dr. Kennedy receives grant or research support from Janssen and Johnson and Johnson.

Clinical Point

Paliperidone palmitate has a 28-day dosing interval, and no overlapping oral taper is necessary