Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication

AUTHORS: John Lauriello, MD, Austin R Campbell, PharmD, BCPP
SECTION EDITOR: Stephen Marder, MD
DEPUTY EDITOR: Michael Friedman, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Oct 2023.**
This topic last updated: **Jul 07, 2023.**

INTRODUCTION

The unpleasant adverse effects of antipsychotic drugs combined with patients' disbelief of having an illness, which is common among individuals with schizophrenia, result in high rates of nonadherence to antipsychotics in the treatment of schizophrenia.

Long-acting injectable (LAI) antipsychotics are a pharmacologic strategy for treating patients with schizophrenia who relapse due to nonadherence to antipsychotic medication. Rather than the daily pill-taking required with oral antipsychotics, LAI antipsychotics are administered by injection at two- to four-week intervals.

This topic addresses the use of LAI antipsychotics in the treatment of schizophrenia. The pharmacology, administration, comparative side effects, and treatment of schizophrenia with standard (non-LAI) antipsychotics are discussed separately, as is the management of antipsychotic side effects. The epidemiology, clinical manifestations, and diagnosis of schizophrenia are reviewed separately.

- (See "Schizophrenia in adults: Maintenance therapy and side effect management".)
- (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)
- (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

- (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Schizophrenia in adults: Epidemiology and pathogenesis".)

LONG-ACTING INJECTABLE ANTIPSYCHOTICS

Six antipsychotic medications are currently available in the United States as long-acting injections. Naming conventions vary among agents. This topic uses the format: medication name followed by "LAI."

- Aripiprazole extended release (aripiprazole LAI)
- Aripiprazole lauroxil (aripiprazole lauroxil LAI)
- Fluphenazine decanoate (fluphenazine LAI)
- Haloperidol decanoate (haloperidol LAI)
- Olanzapine pamoate (olanzapine LAI)
- Paliperidone palmitate, four-week (paliperidone LAI)
- Paliperidone palmitate, 12-week (paliperidone 12-week LAI)
- Paliperidone palmitate, six-month (paliperidone six-month LAI)
- Risperidone microspheres (risperidone LAI, risperidone extended release)
- Risperidone extended-release subcutaneous injection (risperidone SQ LAI)

LAI antipsychotics commonly used outside the United States include:

- Flupentixol decanoate
- Pipotiazine palmitate
- Zuclopenthixol decanoate

ANTIPSYCHOTIC NONADHERENCE

Maintenance treatment with antipsychotic medication is effective in reducing the rate of relapse in schizophrenia [1]. However, patients taking oral antipsychotics for schizophrenia have an estimated adherence rate of less than 60 percent [2,3]. For a significant subset, nonadherence leads to relapse and hospitalization, which in some cases can be repeated and frequent.

Factors contributing to medication nonadherence among individuals with schizophrenia include:

- Many patients with the disorder do not believe they have an illness and therefore reject treatment. This is particularly likely in patients early in their course of illness.

- Antipsychotic drugs can cause immediate unpleasant side effects, neurologic consequences, metabolic changes, and the potential for long-term movement disorders.
- Some patients treated with antipsychotic drugs experience residual hallucinations or delusions that "convince" them to stop the medication.

INDICATIONS

We suggest use of long-acting injectable (LAI) antipsychotics for patients with schizophrenia who have a history of good response to an oral antipsychotic but relapse due to medication nonadherence. We have found that LAI antipsychotics may help some patients break a cycle of multiple hospitalizations resulting from unstable illness, often compounded by chaotic social structure and substance use.

LAI antipsychotics may be indicated for schizophrenia under other circumstances, including:

- Patients who, after stopping antipsychotics, become symptomatic with behaviors leading to highly adverse consequences (eg, arrests, assaults, self-harm, loss of employment or housing). In addition to a possible effect on relapse, use of an LAI antipsychotic in these cases can provide early identification of nonadherence (ie, a missed visit for LAI antipsychotic administration).
- Patients with schizophrenia whose illness may be considered treatment resistant. If the patient then responds to an LAI antipsychotic trial, then the prior lack of response to an oral antipsychotic may have been due to nonadherence. However, an alternative explanation may be that the oral ingestion process did not build a high enough blood and subsequent brain drug level.
- Patients who respond well to a specific oral antipsychotic medication but have a side effect that is dose dependent (eg, extrapyramidal symptoms or sexual dysfunction). These patients may benefit from the consistent blood level without higher daily peaks provided by the corresponding LAI antipsychotic.
- Individuals requiring treatment with antipsychotics but who may have poor or unpredictable absorption with oral medications due to intestinal bypass or other malabsorption issue. In these individuals, LAIs can provide a reliable and consistent delivery of medication.
- Patients who prefer administration of an LAI product. Some patients, given the choice, may favor receiving an injectable product every 2, 4, 6, 8, or 12 weeks over taking oral

medication one or more times per day.

Although not rigorously studied, based on our clinical experience, LAI antipsychotics should be used in conjunction with cognitive and behavioral techniques that help patients understand their illness and need for treatment. Such concurrent treatment is unfortunately not routinely available, leading to an overreliance on long-acting medication as the sole treatment. (See "Schizophrenia in adults: Psychosocial management".)

Contraindications — Contraindications to LAI antipsychotics include hypersensitivity to the medications or formulations. Haloperidol LAI and fluphenazine LAI are contraindicated in severe central nervous system depression and coma. Unique contraindications include Parkinson disease for haloperidol LAI and subcortical brain damage, blood dyscrasias, and hepatic disease for fluphenazine LAI [4,5].

PHARMACOLOGY

Each of the available long-acting injectable (LAI) antipsychotics has an individual chemical makeup that is essentially that of the parent oral compound. The first-generation antipsychotics, fluphenazine LAI and haloperidol LAI, are potent dopamine blockers with less receptor activity for other neurotransmitters. The second-generation antipsychotics, aripiprazole LAI, aripiprazole lauroxil LAI, paliperidone LAI, paliperidone 12-week LAI, risperidone LAI, risperidone subcutaneous (SQ) LAI, and olanzapine LAI, rely on a blockade of both dopamine and serotonin receptors.

The form of pharmacologic delivery of the LAI antipsychotics determines the immediacy of release, the sites of injection, and the potential interval between doses. The delivery system varies among the drugs. A method effective for one compound has not necessarily been applicable to the next. The first-generation LAI antipsychotics, fluphenazine LAI and haloperidol LAI, both utilize an ester form of the oral compound attached to a fatty acid (decanoic acid) chain. Once esterified, they are dissolved in an oil. Upon injection, the ester slowly disassociates from the oil allowing a gradual release of the medication over time.

The second-generation LAI antipsychotics have required other means of delivery. Risperidone LAI utilizes a microsphere technology. The active compound, risperidone, is embedded into microspheres made of a polymer that degrades similarly to dissolvable suture. Risperidone SQ LAI utilizes a biodegradable polymer for its delivery. Rather than having risperidone imbedded, it is suspended in a polymer solution. Once injected, the solution solidifies into a biodegradable

risperidone-containing depot, which results in an initial release followed by a sustained release of medication [6,7].

Paliperidone LAI and paliperidone 12-week LAI are long-acting formulations of paliperidone, a metabolite of risperidone. Both products utilize a crystal salt of paliperidone and palmitic acid; however, paliperidone 12-week LAI uses larger particle size, resulting in slower dissolution and a longer dosing interval [8]. Similarly, olanzapine LAI is a crystal salt of olanzapine and pamoic acid. Aripiprazole LAI, paliperidone LAI, and olanzapine LAI are suspended in water and injected. Once injected, the carrier salts slowly dissolve, releasing active medication. An advantage of paliperidone LAI and olanzapine LAI is the more immediate release of medication. Aripiprazole lauroxil LAI is a prodrug of aripiprazole. After intramuscular injection aripiprazole lauroxil undergoes enzyme-mediated hydrolysis to form the N-hydroxymethyl aripiprazole intermediate, which is rapidly converted to aripiprazole via water-mediated hydrolysis [9,10].

SELECTION

Selection of a long-acting injectable (LAI) antipsychotic for the treatment of schizophrenia is based primarily on prior treatment response. Typically, patients are transitioned to the LAI formulation of the same oral antipsychotic they responded to. If patients had previously responded to an LAI medication, we often choose that one again. However, other factors in the selection include patient comorbidities, potential side effects, clinician familiarity, availability, and cost.

As with oral medications, we favor second-generation LAI antipsychotics because of their more favorable side effect profile. Head-to-head comparisons either between or within groups of first- and second-generation LAI antipsychotics are limited. However, similar to comparisons among oral agents, no difference in efficacy for schizophrenia has consistently been found between first- and second-generation LAI agents [11,12].

Among LAI agents, there is no evidence indicating that any single agent is more effective than other agents, however, some agents have higher quality data supporting their use. In a network meta-analysis, including 78 trials and greater than 11,000 individuals with nonaffective psychoses, most LAI agents were superior to placebo in preventing relapse. Additionally, treatment resulted in fewer dropouts compared with placebo [13]. However, only paliperidone (three-month formulation and one-month formulation), aripiprazole, and olanzapine were supported by moderate to high certainly of evidence for each outcome. Relative reduction in relapse rates versus placebo for these antipsychotics are as follows:

- Paliperidone 12-week LAI: 0.27, 95% CI 0.17-0.42
- Paliperidone one-month LAI: 0.39, 95% CI 0.3-0.5
- Aripiprazole LAI: 0.29, 95% CI 0.21-0.39
- Olanzapine LAI: 0.37, 95% CI 0.26-0.35

While others, including risperidone LAI and haloperidol LAI, also resulted in a lower relative risk of relapse and treatment dropout than placebo, the evidence was of lower quality overall.

ADMINISTRATION

As with oral antipsychotics, dosing of the long-acting injectable (LAI) antipsychotics is optimized when clinical effectiveness is achieved while minimizing side effects. The table summarizes the delivery system, injection interval, and dosing of each LAI antipsychotic drug (table 1).

The first-generation antipsychotics, fluphenazine LAI and haloperidol LAI, are administered via intramuscular injection in the deltoid or gluteal muscles. Due to their oil based nature and high viscosity, a Z-track injection technique is used to minimize leakage of the compound from the injection site (figure 1) [14]. Dosing of the first-generation LAI antipsychotics is based on the patient's dose of oral medication. Dose conversion formulations are given for each of the products discussed below. These formulations should be interpreted with caution in certain populations (ie, poor metabolizers, and older adults) since LAI antipsychotics do not undergo first pass metabolism, which could possibly lead to variant concentrations.

Fluphenazine LAI — The dosing conversion from the oral fluphenazine tablets to the LAI is approximately 1 mg oral administered daily to 1.25 mg LAI administered every three weeks [15]. Patients should continue to supplement the LAI with oral medication for at least the first week after receiving the LAI due to its delay in achieving therapeutic plasma concentrations.

Haloperidol LAI — The initial dose of haloperidol LAI is 10 to 20 times the previous daily dose of oral haloperidol, given in four-week intervals [5]. However, the initial haloperidol LAI injection should not exceed 100 mg regardless of previous antipsychotic requirements in patients who are haloperidol LAI naive. In cases where conversion requires administration of greater than 100 mg, the dose should be given in two separate injections, with 100 mg administered on day 1 and the remainder given in three to seven days.

The usual maintenance dose is 10 to 15 times the previous daily dose of oral haloperidol given as a single injection. When haloperidol LAI has been initiated using a loading strategy, maintenance dosing is typically started in the third month of therapy.

Several loading-dose strategies have been evaluated for haloperidol LAI [16,17]. Use of these techniques reduces the time required to achieve therapeutic plasma concentrations and eliminates the need for overlap with oral medication.

- A common strategy involves giving an initial injection of 20 times the oral daily dose. If the dose of haloperidol LAI exceeds 100 mg then the dose should be administered as two separate injections. For large initial doses of haloperidol LAI (ie, ≥400 mg) the total dose is sometimes given in a series of three injections (table 1). Four weeks after initiation, the total dose is reduced by 25 percent and given as a single injection. The dose is again reduced by 25 percent of the original at the eight-week mark and the patient is continued on this dose as maintenance.

- Another method is to initiate haloperidol LAI at the anticipated maintenance dose and supplement the patient with oral haloperidol. If this approach is taken, oral medication should be gradually tapered over a one-month period. We typically reduce the dose by 25 percent at weekly intervals; however, some patients may require faster or slower tapering schedules depending on individual response. While this strategy increases the time necessary to achieve steady state concentrations, it offers the clinician more control over the total amount of haloperidol the patient receives each day.

Second-generation LAI antipsychotics differ from first-generation drugs in aspects of administration and dosing.

Aripiprazole LAI — Two formulations of aripiprazole LAI are currently available. One formulation is given intramuscularly (gluteal or deltoid) every four weeks while the other is given intramuscularly (gluteal only) every eight weeks. Upon initiation, each of these require two weeks of overlap with a stable oral dose of an antipsychotic. In some countries, alternative initiation doses are offered [18,19]. Lower doses are recommended for either formulation for patients who are known poor metabolizers of CYP2D6 and for patients also receiving treatment for 14 days or more with medications that are strong inhibitors of CYP3A4 or 2D6. Additional dose reductions are made for patients with more than one of these factors. Full details are provided in the individual drug monographs from Lexicomp. Further information regarding dosing and administration of aripiprazole LAI are found on the table (table 1). (See "Overview of pharmacogenomics", section on 'CYP2D6 variants'.)

Aripiprazole lauroxil LAI — Maintenance dosing of aripiprazole lauroxil LAI is based on the patient's current dose of oral aripiprazole (table 1). Once a dose has been determined, the medication may be initiated utilizing one of two strategies:

- Supplementation with oral aripiprazole for an additional 21 days after receiving the initial maintenance injection [9].

- A loading dose strategy utilizing a 675 mg injection of nano-crystalline milled dispersion particles – This method requires administration of the 675 mg aripiprazole lauroxil LAI in either the deltoid or gluteal muscle with an additional one-time 30 mg dose of oral aripiprazole. This one-time 30 mg oral dose is given regardless of the individual's previous oral daily aripiprazole dose. The first maintenance dose may be administered on the same day as this initiation regimen or up to 10 days thereafter. Avoid injecting both products into the same muscle [20,21].

The 675 mg loading dose and the 441 mg maintenance dose of aripiprazole lauroxil LAI can be administered in the deltoid or gluteal muscles. All other doses should be given in the gluteal muscle only. Injections are given every four weeks for the 441 mg and 662 mg strengths; the 882 mg strength can be administered every four or six weeks. The 1064 mg strength is administered every two months. Serum drug concentrations for both the 882 mg every six weeks and the 1064 mg every two months regimens resemble those for 662 mg every four weeks [22].

Dose reductions are recommended in individuals who are taking strong inhibitors of CYP3A4 or CYP2D6 for two or more weeks and in known poor metabolizers of CYP2D6. In cases where only one CYP pathway is impacted, patients should be reduced to the next lower strength of aripiprazole lauroxil LAI. For patients taking 882 mg every six weeks or 1064 mg every two months, the next lower dose is 441 mg every four weeks. In cases where both CYP3A4 and CYP2D6 are impaired, either by enzyme inhibitors or genetic deficiencies, only the 441 mg strength of aripiprazole lauroxil LAI is recommended.

Olanzapine LAI — Dosing of olanzapine LAI is based on the patient's dose of oral medication; however, the conversation ratio is dose dependent (table 1). Supplementation of the initial LAI dose with oral olanzapine is not necessary. Olanzapine LAI should only be administered via deep intramuscular gluteal injection [23]. Due to the potential for a severe adverse reaction to olanzapine LAI, patients must be observed for at least three hours after every injection. (See 'Postinjection delirium sedation syndrome' below.)

Paliperidone LAI — The initial loading dose of paliperidone LAI consists of a 234 mg injection in the deltoid muscle on day 1 followed by another deltoid injection of 156 mg one week later. This second injection may be administered four days before or after the weekly time point [24]. The recommended maintenance dose of 117 mg is begun four weeks after the second injection and may be administered in either the deltoid or gluteal muscles [25]. No overlap with oral

paliperidone is necessary after initiating paliperidone LAI. Some patients may benefit from lower or higher maintenance doses of paliperidone LAI; dosing recommendations range from 39 to 234 mg given monthly. For those patients switching from paliperidone ER, injection dose is based on oral dosing (table 1). Paliperidone is primarily excreted through the urine, so dose adjustments are necessary in patients with mild renal dysfunction. If creatinine clearance is 50 to 80 mL/min, then paliperidone LAI should be initiated at 156 mg on day 1 followed by 117 mg one week later. The monthly maintenance dose is 78 mg every four weeks. Adjust monthly maintenance dose based on tolerability and efficacy within the strengths of 39, 78, 117, or 156 mg. The maximum monthly dose in individuals with renal impairment is 156 mg. Paliperidone LAI is not recommended in individuals with Cl_{cr} <50 mL/min.

Paliperidone 12-week LAI — Initiation of paliperidone 12-week LAI may occur only after a patient has been established on monthly paliperidone LAI for a period of at least four months, with the last two months at the same dose [26]. Once these criteria are met, patients may be converted to paliperidone 12-week LAI, utilizing a dose equivalent that is 3.5 times higher than the last administered dose of monthly paliperidone LAI (table 1). Paliperidone 12-week LAI is then administered in place of the next scheduled monthly injection, then every three months thereafter. As an example, a patient who received appropriate loading doses of monthly paliperidone LAI and then maintained on 117 mg every four weeks for the next three months could receive 410 mg of paliperidone 12-week LAI in place of the fourth maintenance monthly injection.

Paliperidone six-month LAI — Initiation of paliperidone six-month LAI may occur after the individual has been established on paliperidone (monthly) LAI for a minimum of four months or paliperidone 12-week LAI for at least one cycle (three months). Once these criteria are met, the individual can be converted to paliperidone six-month LAI based on the previous paliperidone LAI (monthly) or paliperidone 12-week LAI dose (table 1). Paliperidone six-month LAI is administered by gluteal injection in place of the next scheduled injection and then every six months thereafter. As an example, an individual who is maintained on 546 mg of paliperidone 12-week LAI could receive 1092 mg of paliperidone six-month LAI injection every six months.

Risperidone LAI/microsphere — There are two risperidone microsphere formulations currently available. Both are administered via deep intramuscular injection; however, utilization of the deltoid or gluteal muscles as the injection site is dependent on the specific product [27,28]. For patients who are not on any form of risperidone, the medication is initiated at a dose of 25 mg every two weeks. For patients who do not respond to this dose, upward titration by 12.5 to 25 mg may be made at four-week intervals to a maximum of 50 mg per injection.

Due to the long-acting formulation's delay in release of medication, patients that are converting from oral risperidone to LAIs should be continued at the full oral dose for from one to three weeks, depending on the formulation chosen, after the first LAI injection [27,28]. Recommended dose conversions from oral to intramuscular are found in the table (table 1).

Risperidone SQ LAI — Risperidone SQ LAI is administered via subcutaneous injection into the abdominal area or back of the upper arm [7,29]. Supplemental oral risperidone is not recommended. Two products are available each with specific dose and frequency based on current oral risperidone dose. Recommended dose conversion from oral to subcutaneous is found in the table (table 1).

EFFICACY

Long-acting injectable (LAI) formulations of fluphenazine [30], haloperidol [31,32], aripiprazole [33,34], aripiprazole lauroxil [35], risperidone [36-38], risperidone subcutaneous [6,39], paliperidone [40,41], paliperidone 12-week [42], and olanzapine [43,44] have shown efficacy in schizophrenia compared with placebo in randomized trials.

Adherence and relapse — Meta-analyses of randomized trials [30,45,46] and subsequent trials of newer agents [36,47,48] comparing medication adherence and relapse rates with LAI versus oral antipsychotics have been mixed, although overall there may be a benefit with LAI. In a meta-analysis of 25 observational studies, individuals on LAI had higher odds of being adherent to their medication (odds ratio 1.89, 95% CI 1.52-2.35) than individuals treated with oral medications [49]. Trials have also demonstrated benefits in important patient outcomes such as longer time to relapse with LAIs versus oral antipsychotics [50].

Hospitalization rate — Several studies suggest that LAIs might decrease rehospitalization rates in some patients with schizophrenia [49,51-53]. As examples:

- In a randomized trial, 489 subjects with early-phase schizophrenia (eg, one year or less of antipsychotic use) were treated with either the LAI aripiprazole once monthly (AOM) or usual care/clinician's choice [53]. Time to first hospitalization was greater for subjects receiving AOM as compared with usual care (hazard ratio 0.56, 95% CI 0.34-0.92). The number needed to treat with AOM to prevent one hospitalization was seven.

- In a meta-analysis of 25 observational studies, individuals treated with LAI had lower odds of hospitalization (odds ratio 0.62, 95% CI 0.54-0.71) and fewer emergency department admissions (incidence rate ratio 0.86, 95% CI 0.77-0.97) compared with those treated with oral antipsychotics [49].

- In a population-based cohort study from a nationwide registry in Sweden that included 29,823 patients with schizophrenia, LAI antipsychotics were associated with a 22 percent lower risk of rehospitalization compared with equivalent oral formulations (hazard ratio 0.78, 95% CI 0.72-0.84) [51]. Additionally, all LAIs were associated with lower rehospitalization rates compared with oral olanzapine (hazard ratio ranges 0.65-0.80).

However, not all studies have found reduced hospitalization rates with LAI. As an example, in a randomized trial of 369 patients with unstable schizophrenia or schizoaffective disorder risperidone LAI did not reduce hospitalization rates after two years compared with an oral antipsychotic (39 versus 45 percent; hazard ratio 0.87, 95% CI 0.63-1.2) [54]. It is possible that the patients in this study had more severe illness than in others that suggest a benefit with LAI.

Illness severity and global functioning — Clinical trials in patients with unstable schizophrenia (ie, frequent recurrence, substance use disorder) have measured a broader range of clinical outcomes, including medication effect on social functioning and illness severity. Results of these trials have been mixed, possibly in part because of heterogeneity in patient populations and specific interventions [54-56]. As examples:

- In a trial that randomly assigned 369 patients with unstable schizophrenia or schizoaffective disorder to risperidone LAI or oral antipsychotics for two years, psychiatric symptoms, quality of life, global functioning scale, and neurologic side effects were not significantly different between treatment groups [54].

- In a 15-month randomized clinical trial of 450 patients with schizophrenia who had been taken into custody by the criminal justice system at least two times in the previous two years, subjects were assigned to open-label treatment with paliperidone LAI or one of seven daily oral antipsychotics [55]. Paliperidone LAI was associated with lower treatment failure rates (eg, arrest/incarceration, suicide, psychiatric hospitalization, or increased services needed) compared with patients receiving oral antipsychotics (39.8 versus 53.7 percent). Additionally, subjects receiving paliperidone were found to have a delay in time to first treatment failure versus oral antipsychotics (416 versus 226 days; hazard ratio 1.43, 95% CI 1.09-1.88). Patients taking paliperidone LAI were more likely to experience extrapyramidal symptoms, weight gain, and prolactin elevation compared with patients taking oral antipsychotic drugs. However, medication adherence rates, to the extent that they could be measured or estimated, were higher in the paliperidone LAI group compared with oral antipsychotics.

ADVERSE EVENTS

Local injection site complications, such as pain or redness, have been observed in up to 10 percent of individuals receiving long-acting injectable (LAI) antipsychotics. At a comparable dose, the LAI antipsychotics have lower maximum blood levels and lesser dose-related side effects (including sedation and hyperprolactinemia) compared with their oral counterparts, due to differences in pharmacokinetics. There is no advantage to LAIs compared with oral antipsychotics with side effects unrelated to dose and blood level (including tardive dyskinesia and metabolic syndrome). Each LAI has the same US Food and Drug Administration (FDA) warnings, precautions, and contraindications as its parent compound. (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects" and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

Postinjection delirium sedation syndrome — Patients receiving olanzapine LAI in clinical trials experienced a rare (less than 1 percent) but serious adverse event termed “postinjection delirium sedation syndrome” (PDSS) [57,58]. PDSS is believed to be due to inadvertent intravascular injection of olanzapine LAI, leading to an increased blood level of the agent. Symptoms resemble an overdose of oral olanzapine and include confusion, disorientation, anxiety, dizziness, excessive sedation, and extrapyramidal symptoms.

The majority of patients experiencing these effects developed symptoms within the first hour after an injection. Due to the potential for PDSS, patients, providers, institutions, and pharmacies need to be registered and receive training before olanzapine LAI can be dispensed [23,59,60]. Patients must be directly observed by a health care professional at the registered facility for at least three hours after every injection.

The FDA reported in June 2013 that it was investigating two deaths occurring three to four days after the patient was injected with olanzapine LAI [61,62]. Both patients were found to have very high blood levels of olanzapine postmortem. The causes of these deaths have not been determined; they raise concerns that PDSS might have been missed during the three-hour prescribed observation period or occurred after that period.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Psychotic disorders".)

SUMMARY AND RECOMMENDATIONS

- **Indications** – We suggest the use of long-acting injectable (LAI) antipsychotics, rather than oral antipsychotics, for patients with schizophrenia who relapse due to medication nonadherence (**Grade 2C**). (See 'Indications' above.)

- **Selection** – As with oral medications, we favor second-generation LAI antipsychotics over first-generation antipsychotics because of their favorable side effect profile. However, head-to-head comparisons either between or within groups of first- and second-generation LAI antipsychotics are limited and do not consistently show differences in efficacy; however, some agents have higher quality data supporting their use. (See 'Selection' above.)

  Selection of an LAI antipsychotic for the treatment of schizophrenia is based primarily on prior treatment response. Typically, patients are transitioned to the LAI formulation of the same oral antipsychotic they responded to. However, other factors in the selection include patient comorbidities, potential side effects, clinician familiarity, availability, and cost.

- **Administration** – As with oral antipsychotics, dosing of the LAI antipsychotics is optimized when clinical effectiveness is achieved while minimizing side effects. Dosing of the first-generation LAI antipsychotics is based on the patient's dose of oral medication. (See 'Administration' above.)

- **Efficacy** – LAI antipsychotics have shown efficacy in reducing symptoms of schizophrenia compared with placebo in randomized trials. Studies suggest benefits over oral medications for time to relapse, adherence, and hospitalization rates in individuals with schizophrenia. (See 'Efficacy' above.)

- **Adverse events** – Local injection site reactions, such as pain or redness, are the most common complication of LAI antipsychotic treatment. While many of these reactions are tolerable, more severe site reactions may warrant termination of the LAI. (See 'Adverse events' above.)

  Postinjection delirium sedation syndrome is a rare but serious adverse syndrome seen after injection of olanzapine LAI. Symptoms include confusion, sedation, and extrapyramidal symptoms. Provider training is required. (See 'Postinjection delirium sedation syndrome' above.)

Topic 15250 Version 37.0