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# Long-acting injectable antipsychotics: What to do about missed doses

## Use a stepwise approach based on the unique properties of the specific medication

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Antipsychotic agents are the mainstay of treatment for patients with schizophrenia,<sup>1-3</sup> and when taken regularly, they can greatly improve patient outcomes. Unfortunately, many studies have documented poor adherence to antipsychotic regimens in patients with schizophrenia, which often leads to an exacerbation of symptoms and preventable hospitalizations.<sup>4-8</sup> In order to improve adherence, many clinicians prescribe long-acting injectable antipsychotics (LAIs).

LAIs help improve adherence, but these benefits are seen only in patients who receive their injections within a specific time frame.<sup>9-11</sup> LAIs administered outside of this time frame (missed doses) can lead to reoccurrence or exacerbation of symptoms. This article explains how to adequately manage missed LAI doses.

### First-generation long-acting injectable antipsychotics

Two first-generation antipsychotics are available as a long-acting injectable formulation: haloperidol decanoate and fluphenazine decanoate. Due to the increased risk of extrapyramidal symptoms, use of these agents have decreased, and they are often less preferred than second-generation LAIs. Furthermore, unlike many of the newer second-generation LAIs, first-generation LAIs lack literature on how to manage missed doses. Therefore, clinicians should analyze the pharmacokinetic properties of these agents (*Table 1*,<sup>12-28</sup> *page 12*), as well as the patient's medical history and clinical presentation, in order to determine how best to address missed doses.

continued



## Long-acting antipsychotics

### Clinical Point

When addressing missed doses of risperidone long-acting injection, check to see if the medication has reached steady state

Table 1

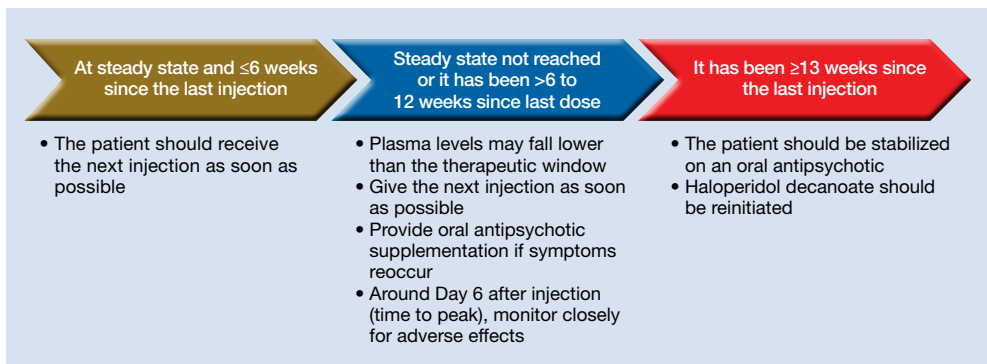
## Pharmacokinetic properties of haloperidol and fluphenazine decanoate

	Haloperidol decanoate	Fluphenazine decanoate
Dosing interval	Every 4 weeks	Every 2 to 4 weeks
Plasma peak after administration	6 days	24 hours
Time to reach steady state	3 to 4 months	4 to 6 weeks
Half-life	3 weeks	8 to 14 days
Therapeutic window	3 to 15 ng/mL	0.2 to 2 ng/mL

Source: References 12-28

Figure 1

## Recommendations for addressing missed doses of haloperidol decanoate long-acting injection



**Haloperidol decanoate** plasma concentrations peak approximately 6 days after the injection.<sup>12</sup> The medication has a half-life of 3 weeks. One study found that haloperidol plasma concentrations were detectable 13 weeks after the discontinuation of haloperidol decanoate.<sup>17</sup> This same study also found that the change in plasma levels from 3 to 6 weeks after the last dose was minimal.<sup>17</sup> Based on these findings, *Figure 1* summarizes our recommendations for addressing missed haloperidol decanoate doses.

**Fluphenazine decanoate** levels peak 24 hours after the injection.<sup>18</sup> An estimated therapeutic range for fluphenazine is 0.2 to 2 ng/mL.<sup>21-25</sup> One study that evaluated fluphenazine decanoate levels following discontinuation after reaching steady state found there was no significant difference in plasma levels 6 weeks after the last dose of fluphenazine, but a significant decrease in levels 8 to 12 weeks after the last dose.<sup>26</sup> Other studies found that fluphenazine levels were detectable 21 to 24 weeks

following fluphenazine decanoate discontinuation.<sup>27,28</sup> Based on these findings, *Figure 2 (page 14)* summarizes our recommendations for addressing missed fluphenazine decanoate doses.

### Second-generation LAIAs

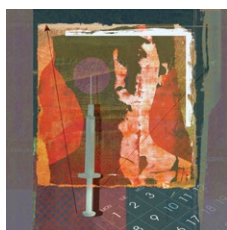
Six second-generation LAIAs are available in the United States. Compared with the first-generation LAIAs, second-generation LAIAs have more extensive guidance on how to address missed doses.

**Risperidone long-acting injection.** When addressing missed doses of risperidone long-acting injection, first determine whether the medication has reached steady state. Steady state occurs approximately after the fourth consecutive injection (approximately 2 months).<sup>29</sup>

If a patient missed a dose but has not reached steady state, he or she should receive the next dose as well as oral antipsychotic supplementation for 3 weeks.<sup>30</sup> If



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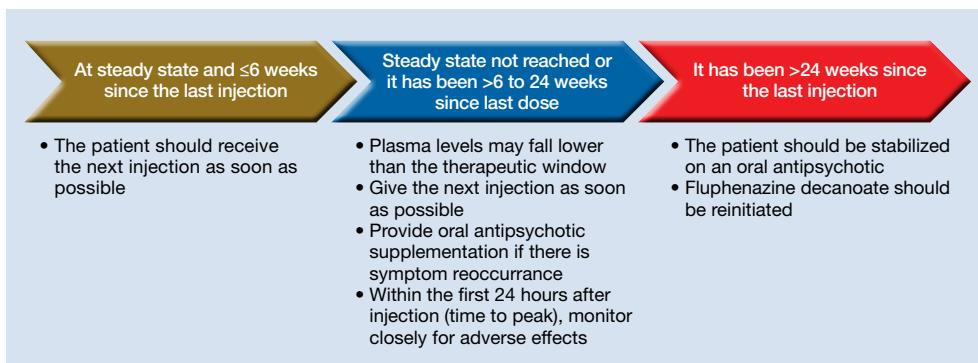
## Long-acting antipsychotics

### Clinical Point

To address a missed paliperidone monthly injection, determine if the patient is receiving initiation or maintenance dosing

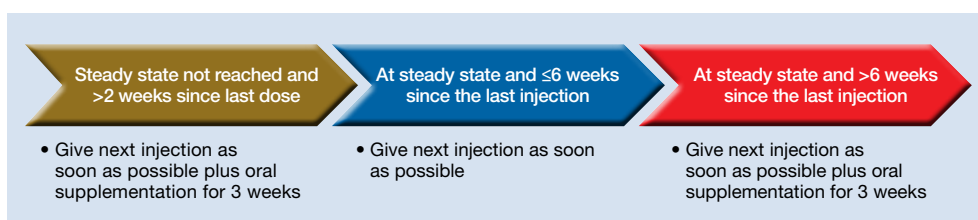
**Figure 2**

## Recommendations for addressing missed doses of fluphenazine decanoate long-acting injection



**Figure 3**

## Recommendations for addressing missed doses of risperidone long-acting injection



the patient has reached steady state and if it has been  $\leq 6$  weeks since the last injection, give the next injection as soon as possible. However, if steady state has been reached and it has been  $>6$  weeks since the last injection, give the next injection, along with 3 weeks of oral antipsychotic supplementation (Figure 3).

**Paliperidone palmitate monthly long-acting injection.** Once the initiation dosing phase of paliperidone palmitate monthly long-acting injection (PP1M) is completed, the maintenance dose is administered every 4 weeks. When addressing missed doses of PP1M, first determine whether the patient is in the initiation or maintenance dosing phase.<sup>31</sup>

*Initiation phase.* Patients are in the initiation dosing phase during the first 2 injections of PP1M. During the initiation phase, the patient first receives 234 mg and then 156 mg 1 week later, both in the deltoid muscle. One month later, the patient receives a

maintenance dose of PP1M (in the deltoid or gluteal muscle). The second initiation injection may be given 4 days before or after the scheduled administration date. The initiation doses should be adjusted in patients with mild renal function (creatinine clearance 50 to 80 mL/min).<sup>31</sup> Figure 4 (page 15) summarizes the guidance for addressing a missed or delayed second injection during the initiation phase.

*Maintenance phase.* During the maintenance phase, PP1M can be administered 7 days before or after the monthly due date. If the patient has missed a maintenance injection and it has been  $<6$  weeks since the last dose, the maintenance injection can be given as soon as possible (Figure 5, page 15).<sup>31</sup> If it has been 6 weeks to 6 months since the last injection, the patient should receive their prescribed maintenance dose as soon as possible and the same dose 1 week later, with both injections in the deltoid muscle. Following the second dose, the patient can resume their regular monthly

Figure 4

## Recommendations for addressing missed doses of paliperidone palmitate monthly long-acting injection during the initiation phase

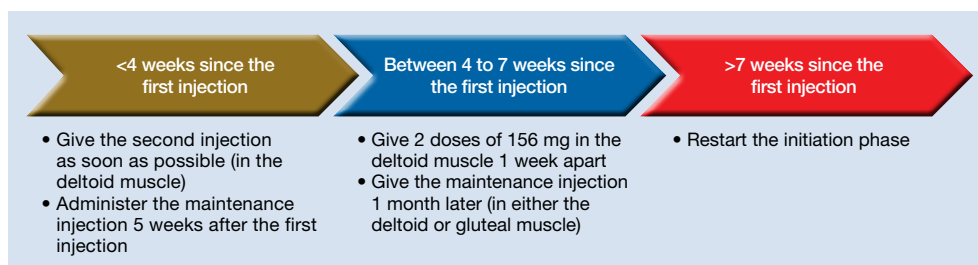
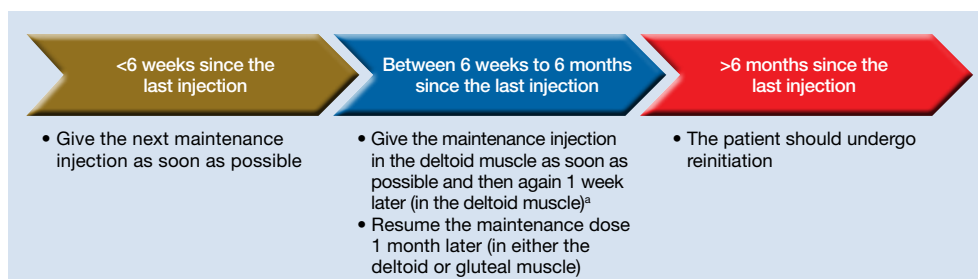


Figure 5

## Recommendations for addressing missed doses of paliperidone palmitate monthly long-action injection during the maintenance phase



<sup>a</sup>Except for a maintenance dose of 234 mg. In this case, the patient should receive 2 doses of 156 mg in the deltoid muscle and then 234 mg 1 month later

### Clinical Point

**Paliperidone 3-month long-acting injection can be given 2 weeks before or after the date of the scheduled dose**

maintenance schedule, in either the deltoid or gluteal muscle. For example, if the patient was maintained on 117 mg of PP1M and it had been 8 weeks since the last injection, the patient should receive 117 mg immediately, then 117 mg 1 week later, then 117 mg 1 month later. An exception to this is if a patient's maintenance dose is 234 mg monthly. In this case, the patient should receive 156 mg of PP1M immediately, then 156 mg 1 week later, and then 234 mg 1 month later.<sup>31</sup> If it has been >6 months since the last dose, the patient should start the initiation schedule as if he or she were receiving a new medication.<sup>31</sup>

**Paliperidone palmitate 3-month long-acting injection (PP3M)** should be administered every 3 months. This injection can be given 2 weeks before or after the date of the scheduled dose.<sup>32</sup>

If the patient missed an injection and it has been <4 months since the last dose, the next scheduled dose should be given

as soon as possible.<sup>32</sup> If it has been 4 to 9 months since the last dose, the patient must return to PP1M for 2 booster injections 1 week apart. The dose of these PP1M booster injections depends on the dose of PP3M that the patient had been stabilized on:

- 78 mg if stabilized on 273 mg
- 117 mg if stabilized on 410 mg
- 156 mg if stabilized on 546 mg or 819 mg.<sup>32</sup>

After the second booster dose, PP3M can be restarted 1 month later.<sup>32</sup> If it has been >9 months since the last PP3M dose, the patient should be restarted on PP1M. PP3M can be reconsidered once the patient has been stabilized on PP1M for ≥4 months (Figure 6, page 16).<sup>32</sup>

**Aripiprazole long-acting injection** is administered every 4 weeks. If a patient misses an injection, first determine how many consecutive doses he or she has received.<sup>33</sup> If the patient has missed the second or third injection, and it has been



## Long-acting antipsychotics

### Clinical Point

If a patient misses a dose of aripiprazole long-acting injection, determine how many consecutive doses he or she has received

Figure 6

## Recommendations for addressing missed doses of paliperidone palmitate 3-month long-acting injection

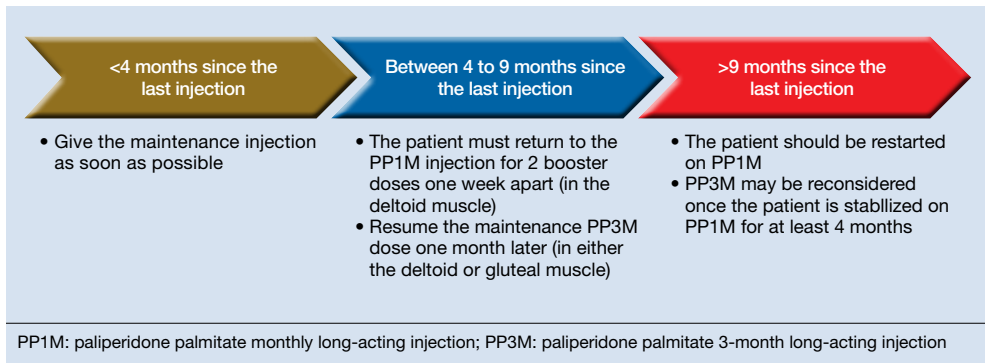
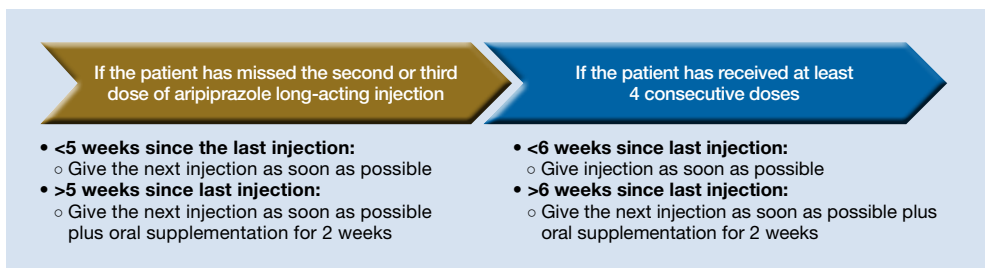


Figure 7

## Recommendations for addressing missed doses of aripiprazole long-acting injection



<5 weeks since the last dose, give the next injection as soon as possible. If it has been >5 weeks, give the next injection as soon as possible, plus oral aripiprazole supplementation for 2 weeks (Figure 7).

If the patient has received  $\geq 4$  consecutive doses and misses a dose and it has been <6 weeks since the last dose, administer an injection as soon as possible. If it has been >6 weeks since the last dose, give the next injection as soon as possible, plus with oral aripiprazole supplementation for 2 weeks.

**Aripiprazole lauroxil long-acting injection.** Depending on the dose, aripiprazole lauroxil can be administered monthly, every 6 weeks, or every 2 months. Aripiprazole lauroxil can be administered 14 days before or after the scheduled dose.<sup>34</sup>

The guidance for addressing missed or delayed doses of aripiprazole lauroxil

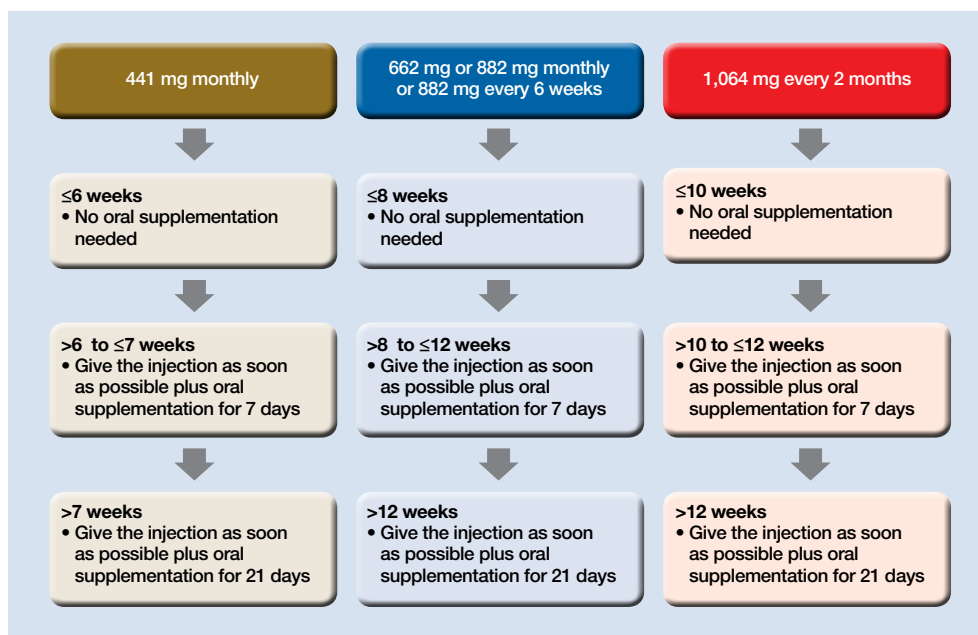
differs depending on the dose the patient is stabilized on, and how long it has been since the last injection. Figure 8 (page 17) summarizes how missed injections should be managed. When oral aripiprazole supplementation is needed, the following doses should be used:

- 10 mg/d if stabilized on 441 mg every month
- 15 mg/d if stabilized on 662 mg every month, 882 mg every 6 weeks, or 1,064 mg every 2 months
- 20 mg/d if stabilized on 882 mg every month.<sup>34</sup>

**Olanzapine pamoate long-acting injection** is a unique LAIA because it requires prescribers and patients to participate in a risk evaluation and mitigation strategies (REMS) program due the risk of post-injection delirium/sedation syndrome. It is administered every 2 to 4 weeks, with

Figure 8

## Recommendations for addressing missed doses of aripiprazole lauroxil long-acting injection



### Clinical Point

For aripiprazole lauroxil, consider the dose the patient is stabilized on and how long it's been since the last injection

Table 2

## Olanzapine pamoate long-acting injection dosing recommendations

Oral olanzapine daily dose	Olanzapine LAI dosing during the first 8 weeks	Olanzapine LAI dosing after the first 8 weeks
10 mg	210 mg every 2 weeks or 405 mg every 4 weeks	150 mg every 2 weeks or 300 mg every 4 weeks
15 mg	300 mg every 2 weeks	210 mg every 2 weeks or 405 mg every 4 weeks
20 mg	300 mg every 2 weeks	300 mg every 2 weeks

LAI: long-acting injectable  
Source: Reference 35

loading doses given for the first 2 months of treatment (Table 2<sup>35</sup>). After 2 months, the patient can proceed to the maintenance dosing regimen.

Currently, there is no concrete guidance on how to address missed doses of olanzapine long-acting injection; however, the pharmacokinetics of this formulation allow flexibility in dosing intervals. Therapeutic levels are present after the first injection, and the medication reaches steady-state levels in 3 months.<sup>35-37</sup> As a result of its specific formulation, olanzapine pamoate long-acting injection provides sustained olanzapine

pamoate plasma concentrations between injections, and has a half-life of 30 days.<sup>35</sup> Consequently, therapeutic levels of the medication are still present 2 to 4 weeks after an injection.<sup>37</sup> Additionally, clinically relevant plasma concentrations may be present 2 to 3 months after the last injection.<sup>36</sup>

In light of this information, if a patient has not reached steady state and has missed an injection, he or she should receive the recommended loading dose schedule. If the patient has reached steady state and it has been ≤2 months since the last dose, he or she should receive the next dose as



## Long-acting antipsychotics

### Clinical Point

Olanzapine long-acting injection requires participation in a risk evaluation and mitigation strategies program

Figure 9

## Recommendations for addressing missed doses of olanzapine pamoate long-acting injection

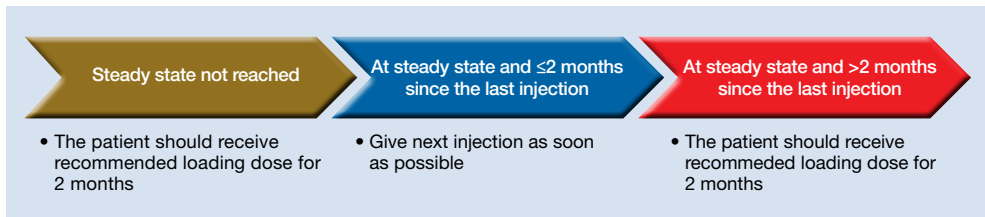
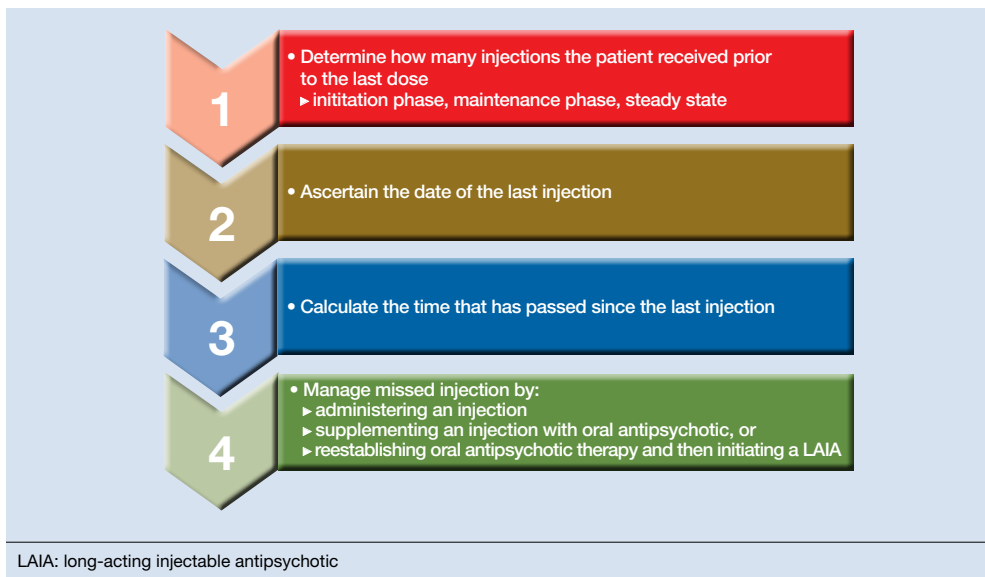


Figure 10

## Stepwise approach to the management of missed doses of long-acting injectable antipsychotics



soon as possible. If steady state has been reached and it has been >2 months since the last injection, the patient should receive the recommended loading dosing for 2 months (Figure 9). Because of the risk of post-injection delirium/sedation syndrome, and because therapeutic levels are achieved after the first injection, oral olanzapine supplementation is not recommended.

### Use a stepwise approach

In general, clinicians can use a stepwise approach to managing missed doses of LAIAs (Figure 10). First, establish the number of LAIA doses the patient had received prior to the last dose, and whether these injections were administered on schedule.

This will help you determine if the patient is in the initiation or maintenance phase and/or has reached steady state. The second step is to establish the date of the last injection. Use objective tools, such as pharmacy records or the medical chart, to determine the date of the last injection, rather than relying on patient reporting. For the third step, calculate the time that has passed since the last LAIA dose. Once you have completed these steps, use the specific medication recommendations described in this article to address the missed dose.

### Address barriers to adherence

When addressing missed LAIA doses, be sure to identify any barriers that may



have led to a missed injection. These might include:

- bothersome adverse effects
- transportation difficulties
- issues with insurance/medication coverage
- comorbidities (ie, alcohol/substance use disorders)
- cognitive and functional impairment caused by the patient's illness
- difficulty with keeping track of appointments.

Clinicians can work closely with patients and/or caregivers to address any barriers to ensure that patients receive their injections in a timely fashion.

### The goal: Reducing relapse

LAIAs improve medication adherence. Although nonadherence is less frequent with LAIAs than with oral antipsychotics, when a LAIA dose is missed, it is important to properly follow a stepwise approach based on the unique properties of the specific LAIA prescribed. Proper management of LAIA missed doses can prevent relapse and recurrence of schizophrenia symptoms, thus possibly avoiding future hospitalizations.

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### Related Resources

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#### Drug Brand Names

Aripiprazole long-acting injection • Abilify Maintena	Paliperidone palmitate monthly long-acting injection • Invega Sustenna
Aripiprazole lauroxil long-acting injection • Aristada	Paliperidone palmitate 3-month long-acting injection • Invega Trinza
Fluphenazine decanoate • Prolixin decanoate	Risperidone long-acting injection • Risperdal Consta
Haloperidol decanoate • Haldol decanoate	
Olanzapine pamoate long-acting injection • Zyprexa Relprevv	

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continued on page 56

### Clinical Point

**Use pharmacy records or medical charts, and not patient reporting, to determine the date of the last injection**

## Bottom Line

Although long-acting injectable antipsychotics (LAIAs) greatly assist with adherence, these agents are effective only when missed doses are avoided. When addressing missed LAIA doses, use a stepwise approach that takes into consideration the unique properties of the specific LAIA prescribed.



## Long-acting antipsychotics

### Clinical Point

Identify and address barriers that may have led to missed injections, such as adverse effects or comorbidities

### Long-acting injectable antipsychotics continued from page 19

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