

# Clinical Guidelines

## Dosing and Switching Strategies for Long-Acting Risperidone

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The availability of a long-acting injectable atypical antipsychotic may increase compliance with medication regimens in patients with schizophrenia. Currently, long-acting risperidone is the only such agent. It is now available or approved in 33 countries, including Austria, Germany, Mexico, the Netherlands, New Zealand, and the United Kingdom. Long-acting risperidone was most recently approved for use in the United States. Guidelines for dosing and initiating treatment in both patients who are currently taking another antipsychotic and those who are taking no antipsychotic are discussed below (Table 1). Drs. Marder, Ereshefsky, and Kane, who are authors of articles in this Supplement, and Drs. Conley and Turner, who have substantial clinical experience using long-acting risperidone, contributed to this article.

### STARTING LONG-ACTING RISPERIDONE

#### Starting Dose for an Adult With Schizophrenia

In general, the initial dose of long-acting risperidone should be 25 mg every 2 weeks (Table 2).

Good clinical practice is to treat patients with the lowest effective dose of a medication. In a 12-week, double-

blind, placebo-controlled trial of long-acting risperidone,<sup>1</sup> 25 mg/2 weeks, the lowest tested dose, effectively treated both positive and negative symptoms of schizophrenia. This dose may provide the optimal balance between safety and efficacy because the rates of adverse events were similar for 25 mg/2 weeks of long-acting risperidone and placebo. Regardless of the starting dose, patients who switch from an oral antipsychotic and those who have been taking no antipsychotic should receive oral antipsychotic coverage for the first 3 weeks of long-acting risperidone treatment. This 3-week oral antipsychotic coverage is needed because the first dose of long-acting risperidone takes 3 weeks to be released into the blood and reach therapeutic levels.

The appropriate starting dose of long-acting risperidone might be influenced by the patient's prior antipsychotic dosage history. Patients who are experiencing their first episode of schizophrenia should begin with 25 mg/2 weeks, and they should be monitored closely for side effects. Given what is currently known about the pharmacokinetic and pharmacodynamic profiles of long-acting risperidone, a dose lower than 25 mg/2 weeks might also benefit patients who are experiencing their first episode. However, until a lower dose becomes available, the lowest dose administered should be 25 mg/2 weeks, since the entire contents of the dosage vial should be administered to ensure accurate delivery of the drug.

Rarely, patients have a clear history of needing high doses of antipsychotics for refractory schizophrenia, e.g., some patients have been stabilized for a long time on a high dose of a conventional depot antipsychotic. For these patients, starting with 37.5 or 50 mg/2 weeks might be appropriate. Generally, clinicians should begin the patient with 37.5 mg/2 weeks. If symptoms persist after the 37.5-mg/2 week dose has achieved steady state plasma concentration (i.e., after at least 4 injections of 37.5 mg/2 weeks), the dose could be increased to 50 mg/2 weeks. Some clinicians in countries in which long-acting risperidone is already marketed have started a few severely ill patients at 50 mg/2 weeks.

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**Table 1. Summary of Recommended Dosing and Switching Strategies for Long-Acting Risperidone**

Issue	Guideline
Prescribing a starting dose for adult with schizophrenia	25 mg/2 wk
Administering a test dose	If the patient has never taken oral risperidone, give a hypersensitivity challenge with 1–2 mg/d of oral risperidone for 2 consecutive d
Switching to long-acting risperidone	
From oral antipsychotics	Start with 25 mg/2 wk of long-acting risperidone Continue coverage with current oral antipsychotic for 3 wk
From depot conventional antipsychotics	Administer long-acting risperidone instead of the conventional depot antipsychotic at the next scheduled injection date No coverage with an oral antipsychotic is necessary
Achieving steady-state	Occurs after 4 consecutive injections given every 2 wk, ie, about 8 wk after the first injection
Managing missed doses	
Before steady-state plasma concentration is achieved	If > 2 wk have passed since the last injection, administer long-acting risperidone as soon as possible and provide coverage with an oral antipsychotic for 3 wk
After steady-state plasma concentration is achieved	If 3–6 wk have passed since the last injection, administer a dose of long-acting risperidone as soon as possible and monitor the patient for symptoms If ≥ 6 wk have passed since the last injection, administer long-acting risperidone as soon as possible and provide coverage with an oral antipsychotic for 3 wk
Discontinuing concomitant anticholinergic medication (only if patients have no extrapyramidal symptoms [EPS])	
For patients previously taking an oral antipsychotic	Continue the anticholinergic medication as long as the oral antipsychotic associated with EPS is being taken and then taper and discontinue the anticholinergic medication over the first 3 wk after the oral antipsychotic is discontinued
For patients previously taking a depot conventional antipsychotic	Taper and discontinue the anticholinergic medication over at least 1 mo after the depot conventional antipsychotic is discontinued (some patients may require months of continued anticholinergic treatment)
Managing breakthrough symptoms	Determine the type of symptoms For anxiety, prescribe a benzodiazepine For depression, prescribe an antidepressant For immediate control of psychosis, prescribe an oral antipsychotic

**Table 2. Starting Doses of Long-Acting Risperidone for 3 Example Patients<sup>a</sup>**

Patient	First Episode	Clear History of Needing a High Dose of an Antipsychotic	Dose
A	Yes	...	25 mg/2 wk <sup>b</sup>
B	No	No	25 mg/2 wk
C	No	Yes	37.5–50 mg/2 wk

<sup>a</sup>All patients who are not switching from treatment with a depot conventional antipsychotic should receive oral antipsychotic coverage for the first 3 weeks after starting long-acting risperidone.

<sup>b</sup>Once available, lower doses might provide the optimal risk-benefit ratio.

Symbol: ... = not applicable.

### Need For a Test Dose of Oral Risperidone

For patients who have never taken oral risperidone, a hypersensitivity challenge with a test dose of 1 to 2 mg/day of oral risperidone for 2 consecutive days is recommended before the first injection of the long-acting formulation is administered. Those who have taken oral risperidone in the past will not require a test dose.

Because a test dose is given at a low dose for a short time, it is unlikely to reveal more than an immediate hypersensitivity to risperidone. Clinicians should remember that most reactions, including allergic skin reactions,

rarely occur within only a couple of days of treatment initiation. Also, a test dose of oral risperidone will not predict the optimal dose of long-acting risperidone. Patients who take a test dose should continue taking their current antipsychotic treatment.

### SWITCHING TO LONG-ACTING RISPERIDONE

#### From an Oral Atypical or Conventional Antipsychotic

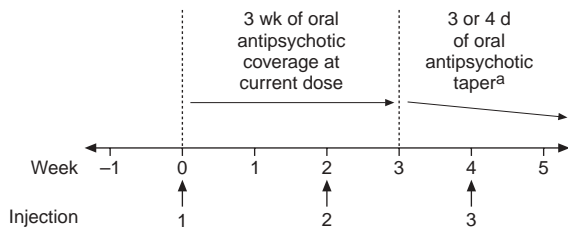
Patients who are taking any oral antipsychotic may immediately begin taking long-acting risperidone (Figure 1). They should continue to take the current dose of the oral antipsychotic for the 3 weeks following the first injection.

Coverage with an oral antipsychotic is needed for the first 3 weeks, until the first dose of long-acting risperidone reaches therapeutic levels. After this 3-week period, clinicians may begin to decrease the dose of oral antipsychotic. For many patients, the length of the taper will be 3 or 4 days. Exceptionally ill patients may benefit from a more gradual taper, i.e., lasting up to 3 or 4 weeks.

#### From a Conventional Depot Antipsychotic

Generally, physicians should introduce long-acting risperidone treatment by administering long-acting risperidone

**Figure 1. Timeline for Switching Patients From an Oral Conventional or Atypical Antipsychotic to Long-Acting Risperidone**



<sup>a</sup>For exceptionally ill patients, the taper might need to last up to 3 or 4 weeks.

Symbol: arrows pointing to weeks indicate the time of injections.

instead of the conventional depot antipsychotic at the next scheduled injection date (Figure 2).

Patients who have been regularly receiving effective doses of a conventional depot antipsychotic, e.g., 25 to 50 mg/2 weeks of fluphenazine decanoate and 100 to 200 mg/4 weeks of haloperidol decanoate, for about 6 months or more will generally maintain an adequate plasma drug level for at least 1 or 2 months after their last injection. Therefore, patients should not require a dose of the depot conventional antipsychotic when they receive their first injection of long-acting risperidone. Patients whose injection interval has been 2 to 4 weeks should be able to receive long-acting risperidone instead of their next scheduled depot antipsychotic injection.

### From Sedating Antipsychotics

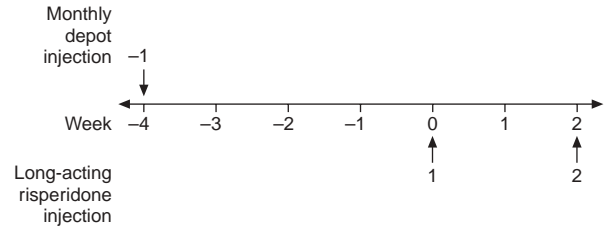
Clinicians should inform patients that they might experience a reduction in daytime and nighttime sedation and, therefore, feel more awake and energetic while taking long-acting risperidone.

During the transition from current antipsychotic treatment to long-acting risperidone therapy, clinicians and patients should monitor and discuss how well the patient is coping with decreased sedation. Difficulty adjusting to the decrease in sedation might be managed with benzodiazepine or antihistamine (e.g., diphenhydramine) treatment regardless of whether the patient had previously been taking a conventional oral antipsychotic, an atypical oral antipsychotic, or a conventional depot antipsychotic. Extending the length of the taper of the previous oral antipsychotic may be considered for those patients having difficulty adjusting to a decrease in sedation.

### From Multiple Antipsychotics

Before switching patients who are taking more than one antipsychotic to long-acting risperidone, physicians should ascertain whether a regimen of multiple antipsychotics is necessary. Often, patients' partial compliance with their

**Figure 2. Timeline for Switching Patients Who Have Been Regularly Receiving a Depot Conventional Antipsychotic Dosed Monthly to Long-Acting Risperidone**



Symbol: arrows pointing to weeks indicate the time of injections.

medication regimen may be the reason that they seem to need multiple antipsychotics.

Combinations of antipsychotics often provide patients with an excessively high dose of antipsychotic medication that is no more efficacious than monotherapy. Many patients who are prescribed multiple antipsychotics do not take them as directed. Some clinicians supplement an oral atypical antipsychotic with a low dose of a conventional depot antipsychotic simply to ensure that an adequate plasma level of medication is present when patients are only partially compliant with oral therapy.

Benefits of switching from combinations that include one or more oral antipsychotics to a long-acting injectable antipsychotic like risperidone include a more accurate assessment of compliance and less fluctuation in plasma drug levels, which may relate to improved efficacy and reduced side effects.

The transition from polypharmacy to long-acting risperidone monotherapy should be made slowly. When possible, each of the current antipsychotics should be gradually discontinued until the patient is taking only long-acting risperidone. When determining the starting dose of long-acting risperidone, physicians should consider the combined dose of other antipsychotics that patients are currently receiving. Some clinicians might discontinue one or more antipsychotics before beginning long-acting risperidone therapy, and others might taper other antipsychotics after the first injection of long-acting risperidone.

### CONCOMITANT ANTICHOLINERGIC MEDICATION

Physicians should assess whether an anticholinergic medication is needed. If patients have no extrapyramidal symptoms (EPS), anticholinergic medication should be slowly discontinued.

Anticholinergic drugs can limit the benefit of some antipsychotics, e.g., by decreasing the improvement in cognition, and have other side effects such as dry mouth

**Table 3. Example for Treating Patients Who Have Missed Doses of Long-Acting Risperidone**

Example Patient	Achieved Steady-State Plasma Drug Level <sup>a</sup>	Time Since Last Injection, wk	Strategy
A	Yes	3–4	Administer next dose as soon as possible
B	Yes	4–6	Administer next dose as soon as possible; monitor closely for symptoms
C	Yes	≥ 6 <sup>b</sup>	Administer next dose as soon as possible; coverage with oral antipsychotic for 3 wk
D	No	> 2	Administer next dose as soon as possible; coverage with oral antipsychotic for 3 wk

<sup>a</sup>Steady-state plasma level is achieved after 4 consecutive doses of long-acting risperidone are administered every 2 weeks.

<sup>b</sup>Steady-state plasma level might not be maintained if 6 or more weeks have passed since the last injection.

**Table 4. Example for Treating Patients Who Have Breakthrough Symptoms That Occur During Long-Acting Risperidone Treatment**

Example Patient	Type of Symptoms	Treatment
A	Anxiety	Benzodiazepine
B	Depressive	Antidepressant
C	Psychotic	Oral antipsychotic followed by an increased dose of long-acting risperidone, if needed <sup>a</sup>

<sup>a</sup>Detailed guidelines for managing psychotic symptoms are given in Figure 3.

and constipation. These medications are also associated with withdrawal symptoms such as nausea, vomiting, and sweating and psychological dependency in some patients.

Patients should continue to take the current dose of anticholinergic medication until the previous antipsychotic is discontinued. The physician should then assess the patient for motor side effects. If the symptoms are no longer present, the anticholinergic medication should be slowly discontinued while the antipsychotic associated with EPS is cleared from the body.

Oral conventional and atypical antipsychotics generally clear the body about 2 to 3 weeks after they are discontinued. Therefore, the anticholinergic should be tapered and discontinued over the first 3 weeks after the oral antipsychotic associated with EPS is discontinued.

Because depot conventional antipsychotics can take months to clear from the body, parkinsonian symptoms can continue for months in patients switched from these agents. Therefore, the anticholinergic drug dosage should be slowly tapered based on the patient's dose, length of treatment, and eagerness to end anticholinergic treatment.

Patients who have switched from a depot conventional antipsychotic should taper and discontinue the anticholinergic medication over at least 1 month after discontinuing the previous antipsychotic. Some patients may require months of continued anticholinergic treatment after discontinuing the depot conventional antipsychotic.

## MANAGING MISSED DOSES

The appropriate strategy for patients who miss doses depends on whether a steady-state plasma concentration of long-acting risperidone has been reached, which generally occurs after 4 injections, i.e., about 8 weeks after the first injection (Table 3).

Patients who have received at least 4 consecutive injections every 2 weeks will have achieved a steady-state plasma concentration of long-acting risperidone. Therefore, they are generally unlikely to require a change in their treatment if only 3 to 6 weeks have passed since their last injection. They should receive their next dose as soon as possible, and clinicians should monitor them for symptom recurrence.

If more than 6 weeks have elapsed since the last injection, treatment with long-acting risperidone should be restarted as soon as possible, and coverage with an oral antipsychotic provided for 3 weeks.

If patients have received less than 3 or 4 consecutive doses, they are unlikely to have maintained a steady-state plasma level of long-acting risperidone. These patients should also receive the next injection as soon as possible, and coverage with an oral antipsychotic should be provided for the first 3 weeks.

## MANAGING BREAKTHROUGH SYMPTOMS

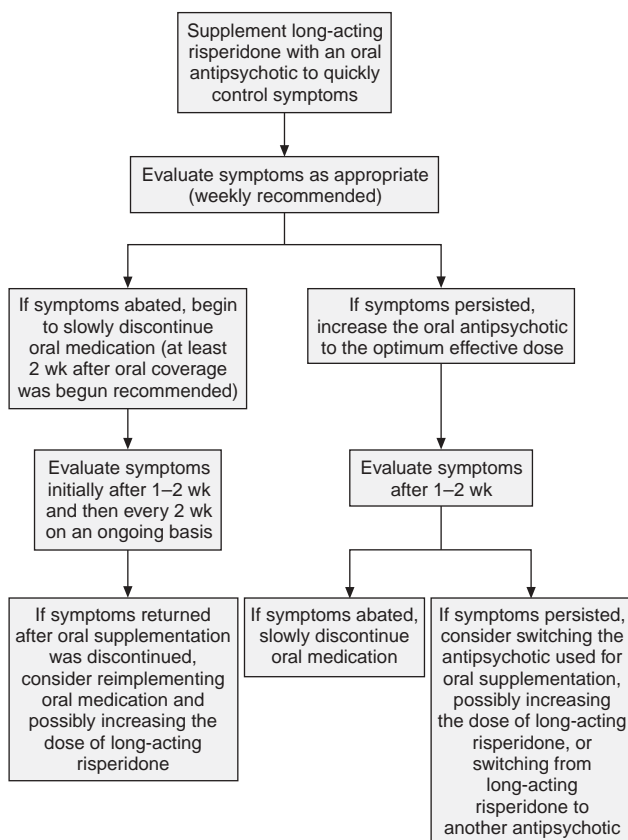
When a patient who has been doing well on long-acting risperidone treatment experiences breakthrough symptoms, clinicians should determine what type of symptoms the patient is experiencing, e.g., psychotic, depressive, or anxiety symptoms, and then devise a strategy effective for those symptoms (Table 4).

The cause of anxiety symptoms should be evaluated before a treatment is chosen. If anxiety symptoms are manifestations of akathisia, they may be treated with propranolol or a dose reduction of the antipsychotic. Otherwise, anxiety symptoms may be managed with a short course of a benzodiazepine.

Clinically important depressive symptoms in patients on long-acting risperidone therapy should be treated as they would be in patients who are taking an oral antipsychotic. Generally, an antidepressant should be added to the patient's treatment regimen.



**Figure 3. Steps for Treating Breakthrough Psychotic Symptoms That Occur During Long-Acting Risperidone Treatment**



**Table 5. Guidelines for Storing and Administering Long-Acting Risperidone<sup>a</sup>**

Store long-acting risperidone and its diluent...
Always away from light
Generally in a refrigerator at temperatures of 2 to 8°C (36 to 46°F)
For up to 7 days, outside a refrigerator at temperatures no greater than 25°C (77°F), if necessary
Administer long-acting risperidone by...
Bringing the diluent to room temperature, ie, about 25°C or 77°F (by warming the container with the palms of the hands), to reduce the risk of discomfort during injection
Using within 6 hours of reconstituting the preparation
Shaking the preparation within 2 minutes before administering

<sup>a</sup>Data on file, Janssen Pharmaceutica, L.P., Titusville, N.J.

For breakthrough psychotic symptoms, clinicians should first supplement long-acting risperidone with an oral antipsychotic to quickly control symptoms (Figure 3). The optimal oral agent will depend on the patient's symptoms and preference. If the symptoms were part of a breakthrough episode that has been successfully treated, the oral medication can be discontinued. If the symptoms are severe and persist with an adequate dose of oral antipsychotic supplementation or return when the oral formu-

lation is discontinued, increasing the dose of long-acting risperidone by increments of 12.5 mg/2 weeks might be advised. The increased dose of long-acting risperidone will take 3 weeks to begin to elevate the patient's plasma drug level, with a new steady state not being reached for 3 to 4 injections; therefore, a higher dose of long-acting risperidone is unlikely to have any immediate effect on a recurrence of psychotic symptoms.

### CHANGING THE DOSE OF LONG-ACTING RISPERIDONE

Physicians should wait until the drug has achieved steady-state plasma concentration at the present dose, i.e., after about 4 injections or about 8 weeks after the first injection of that dose, before deciding whether the dose should be lowered or increased.

Clinicians might lower the dose for patients who experience intolerable adverse events or those whose symptoms are mild enough that they might be controlled at a lower dose.

Sometimes, physicians may need to consider raising the dose of long-acting risperidone after a steady-state plasma level has been achieved. The dose can be increased by an increment of 12.5 mg/2 weeks if recurrent psychotic symptoms cannot be fully controlled by a period of supplementation with an oral antipsychotic. For example, a higher dose of long-acting risperidone might be indicated if symptoms improve while a patient is on oral supplementation but then return when the oral antipsychotic dose is reduced or discontinued. Because oral and long-acting formulations have different pharmacokinetic profiles,<sup>2</sup> an increased dose of long-acting risperidone might be appropriate for patients who are experiencing psychotic symptoms and are more sensitive to the side effects of oral than long-acting antipsychotics. Clinicians should remember that if the dose of long-acting risperidone is raised a few times to treat brief psychotic episodes, patients might end up being maintained at higher doses of the long-acting formulation than are necessary.

### TIPS FOR ADMINISTERING LONG-ACTING RISPERIDONE INJECTIONS

Physicians and nursing staff should take steps to make themselves and their patients become comfortable with the administration of long-acting risperidone.

Staff who prepare and administer the injections will require some training.

- Staff must learn the guidelines for the storage and preparation of long-acting risperidone (Table 5).

- Practice and education should help nursing staff feel more comfortable reconstituting long-acting risperidone, which is an aqueous-based suspension and thinner than the oil-based solutions of depot conventional antipsychotics.

Staff can also take steps to minimize patients' nervousness about receiving injections.

- Try to keep patients from seeing the needle, even when the preparation is being reconstituted.
- Inform patients how the injection will be administered.
- Let patients know that injections of long-acting risperidone are water-based and, therefore, should be less painful than injections of conventional antipsychotics, which are oil-based.<sup>3</sup>

After the first injection, many patients will find that they are less sore than they expected and will be less reluctant to receive the next injection. Injection-site reactions such as redness, swelling, and induration are rare and usually only mild when they do occur.<sup>4</sup>

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*Drug names:* diphenhydramine (Benadryl and others), fluphenazine decanoate (Prolixin Decanoate and others), haloperidol decanoate (Haldol and others), propranolol (Inderal and others), risperidone (Risperdal).

*Disclosure of off-label usage:* The authors of this article have determined that, to the best of their knowledge, propranolol is not approved by the U.S. Food and Drug Administration for the treatment of anxiety.