

# Using IM antipsychotics: Lessons from clinical practice

Long-acting risperidone reopens the discussion  
of injectable agents' role



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**K**nowing how to use IM risperidone—and other long-acting atypicals that are likely to be approved—will enable you to help your patients benefit from reliable antipsychotic dosing. Long-acting antipsychotics address the challenge that makes schizophrenia particularly difficult to treat: medication nonadherence because of psychotic illness' effect on insight, reality testing, and motivation.<sup>1,2</sup>

Too few schizophrenia patients in the United States—perhaps <5% of appropriate candidates—receive depot antipsychotics.<sup>1</sup> We believe these agents provide the best delivery system to our patients and welcome IM risperidone's approval.<sup>3</sup>

This article shares what we have learned from research and clinical practice about using injectable antipsychotics, with a focus on how to effectively use long-acting IM risperidone.

Table 1

## Administering long-acting injectable antipsychotics

Name	Preparation	Dose range	Interval	Injection site	Comment
<b>Fluphenazine</b>	25 mg/mL	5 to 75 mg each injection	Every 1 to 2 weeks	Deltoid or gluteal	Site reaction common
<b>Haloperidol</b>	50 or 100 mg/mL	25 to 200 mg each injection	Every 2 to 4 weeks	Deltoid or gluteal	Site reaction common
<b>Risperidone</b>	25, 37.5, or 50 mg in prefilled bottles	25 to 50 mg each injection	Every 2 weeks	Gluteal only	Requires reconstitution, proprietary kit

### CONVENTIONAL ANTIPSYCHOTICS

Once seen as an improvement over oral conventional antipsychotics, IM agents were relegated over time to a means of coercion (as in, “If you don’t take your medicine orally, we’ll force you to take a shot.”). Oral atypical antipsychotics, with improved side-effect profiles and possibly reduced relapse risk, also discouraged psychiatrists from using long-acting conventional antipsychotics as first-line medication.<sup>4</sup>

**Available agents.** Fluphenazine and haloperidol—the two long-acting conventional antipsychotics available in the United States (*Table 1*)—are esterified to a fatty acid (oil) to create an IM injectable prodrug. They can be given in gluteal or deltoid injection, although doses >2 cc should be given in the gluteus.

Hydrolysis releases the active drug, usually within 3 days. This interval allows loading doses to reach therapeutic blood levels rapidly when the goal is to stabilize patients in the hospital or during a short-term crisis stay. Disadvantages include:

- pain and lasting reactions at the injection site
- risk of extrapyramidal symptoms (EPS), neuroleptic malignant syndrome, and tardive dyskinesia.<sup>5</sup>

**Depot administration.** Fluphenazine depot is commonly given every 2 weeks, starting with 25 mg, but a weekly or monthly interval is not rare. The dose range is broad because the drug can be given in fine gradations from as low as 2.5 mg (0.1 cc) to 75 mg (3 cc). Thus, you can individually titrate it by varying the dose and/or interval.

Because haloperidol is usually given monthly and thus requires less-frequent dosing, it tends to be used more often than fluphenazine. Haloperidol can be given in shorter intervals but is rarely used at intervals >4 weeks. Usual dosing is 50 to 100 mg per shot but can range from small amounts to hundreds of milligrams.

**Transition from oral to IM.** Switching from an oral antipsychotic to a long-acting medication is straightforward. As long as test doses or history predetermine that patients have no untoward effects from fluphenazine or haloperidol, the first injection can be given and the oral agent maintained for 3 to 5 days.

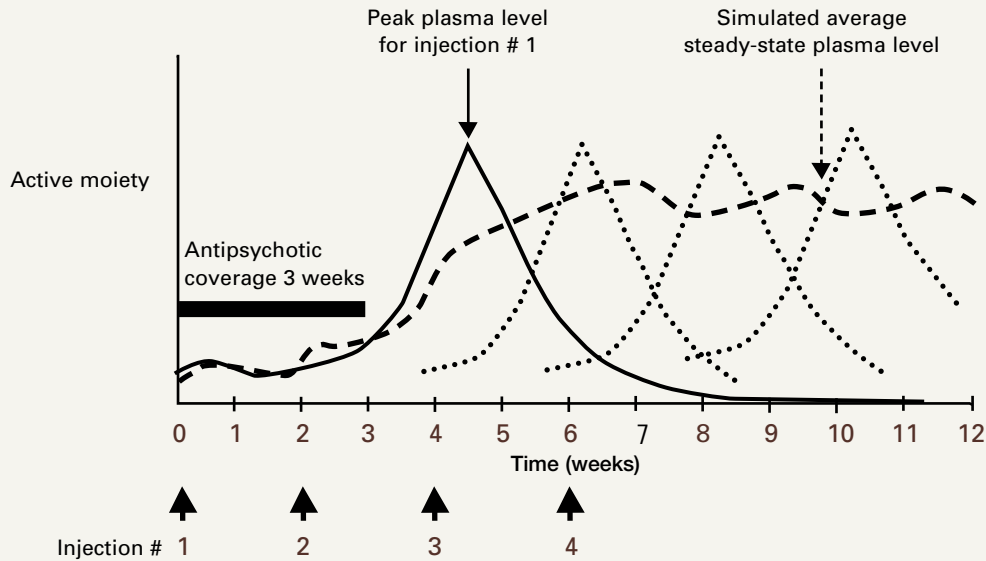
Monitor for dystonias and other emergent EPS. Some practitioners pretreat with anticholinergics to avoid these neurologic side effects. If you can monitor the patient over the first week, you can often avoid pretreatment and add side-effect medication as needed.

continued



Figure

### Long-acting IM risperidone: Steady-state blood levels by 4th dose



IM risperidone peak blood level from injection #1 does not occur until week 4. Subsequent peak blood levels for injections #2 through #4 (hashed peaks) follow at 2-week intervals.

Source: Adapted and reprinted with permission of Robert Lasser from a poster presented at the American Psychiatric Nurses Association annual meeting, Dallas, TX, 2002.

### LONG-ACTING IM RISPERIDONE

For technical and approval reasons, it took nearly a decade for a long-acting atypical to be developed and approved. Because risperidone could not easily be attached to an oil, the solution to making risperidone long-acting was to use microspheres.<sup>6</sup>

Microspheres are best conceptualized as a solid sphere of dissolvable suture-like material (glycolide-lactide polymers) embedded with risperidone bits. The microspheres are packaged dry and reconstituted at the clinic with aqueous diluent at the time of medication. Once reconstituted, it forms a suspension of microspheres in water.

**'Snow in a snow globe.'** Reconstituted long-acting risperidone appears like snow in a snow globe. With shaking, the microspheres become suspended but quickly settle in the bottle or syringe.

Shake to resuspend the microspheres if you are giving an injection more than 2 minutes after the initial reconstitution. Reconstituted microspheres can be given up to 6 hours after hydration.

Transfer the medication to the syringe via the proprietary exchange system, and use the specialized needle to inject the medication into the gluteal region. Once injected, the microspheres swell with water from local muscle, then break down.

**Delayed action.** The microspheres begin releasing risperidone in 3 to 4 weeks. Therapeutic levels last approximately 2 weeks until the microspheres gradually convert to carbon dioxide and water. This delayed action requires coverage with oral or other depot medication. Coverage is no longer needed after the medication reaches a steady state (*Figure*).

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**Tolerability.** As with any long-acting antipsychotic, establish risperidone's tolerability by history or test dosing. No set number of doses will ensure that a patient won't have an allergic reaction, but we usually recommend several days of oral dosing before the first injection.

**Dosing interval.** The approved dosing interval of every 2 weeks should work for most patients. Longer intervals are being studied but are not approved practice.

**From oral to IM.** Risperidone's manufacturer recommends at least 3 weeks of coverage by another agent when transitioning from oral to IM to ensure that long-acting risperidone reaches a therapeutic level before being used alone.<sup>7</sup> We use even longer coverage—4 to 6 weeks if feasible and acceptable to the patient. We worry more about under-medication than about possible overmedication caused by the overlap. We also consider other factors (*Table 2*).<sup>8</sup>

Knowing your patient's history is critical to ensuring a safe transition. Imagine two patients who are stable on the same antipsychotic dose. When under-medicated during a dose switch, the first recedes into his room and is isolative, whereas the second hits his mother. The first patient will more likely tolerate a quick switch without untoward consequences; the second will need a longer and slower overlap to prevent a recurrence of violent behavior.

## DOSING IM RISPERIDONE

Choosing a dose of long-acting risperidone can be difficult. Several points of reference are helpful, but no formula exists. The long-acting form of any antipsychotic behaves differently from its oral counterpart. The maximum daily blood level is lower and the daily trough higher, so that blood levels are governed in a more narrow range. This allows fewer dose- or blood level-related side effects and steadier blood levels.

Table 2

### Switching from another antipsychotic to long-acting IM risperidone

- If the patient is on a high dose of a low-potency antipsychotic (conventional or atypical), slowly taper the first drug after 3 to 4 weeks to reduce rebound effects.
- If the patient is on a long-acting conventional antipsychotic, some studies suggest starting IM risperidone when the next injection is due.<sup>8</sup> We usually give IM risperidone at the midpoint of the last interval, however, and are monitoring this approach for side effects.
- Continue antiparkinsonian medication, if being used, for 3 to 4 months after the transition from a conventional antipsychotic depot to prevent adverse side effects.

**Dosing equivalents.** Long-acting IM risperidone's preclinical pharmacokinetics data suggested that 25 mg every 2 weeks is equivalent to 2 mg oral per day, 50 mg to 4 mg/d, and 75 mg to 6 mg/d.<sup>3</sup> In clinical practice, we find equivalency is broader and represents a range of values. Thus, the 25-mg injection is equivalent to 2 to 4 mg of oral risperidone. Because oral risperidone's average dose is slightly greater than 4 mg/d, the 25-mg injection should work for most patients.

**Side effects.** With IM risperidone, the maximum blood level is approximately 30% lower than with the oral dose, so dose-related EPS and prolactin elevation may be less than would be expected for the oral dose range.<sup>9</sup> Individual sensitivities do exist, however. We have had some patients experience EPS at low doses and many others not experience EPS at high doses.

**Recommendations.** If evidence suggests that the patient might be stable on oral doses of 2 to 4 mg/d, start with the 25-mg, every 2-week injection. A recent study in which patients switched directly to long-acting risperidone, without intervening oral risperidone, supports this approach.<sup>10</sup>

continued



Table 3

### Tenets for using long-acting IM risperidone for inpatients

If the patient...	Then...
is receiving IM risperidone on admission and you decide to continue it	give the dose at the appropriate time if patient will not be discharged within 3 days of the injection appointment
is to be started on IM risperidone and to be discharged in <3 days	start treatment as an outpatient
is committed to the hospital for >3 weeks	start IM risperidone in the hospital
is admitted to be started on IM risperidone because starting as an outpatient has failed	start IM risperidone in the hospital

Monitor the patient's symptoms, being aware that the medication does not begin to take effect until 3 weeks after the first injection. That implies that the second injection is given before you know the efficacy of the first.

We try to maintain the patient on this regimen for several weeks, using oral supplementation if necessary and practical. If the patient requires supplementation throughout the four-injection, 2-month trial, we then:

- increase the dose to 37.5 mg
- repeat the 2-month trial with supplementation as necessary
- and, again, if the patient requires supplementation for the entire 2 months, increase to the 50-mg dose.

This plan requires patience by both clinician and patient but reduces overmedication.

#### SPECIAL CIRCUMSTANCES

**Missed doses.** Patients who are stable on a long-acting IM risperidone dose should be maintained indefinitely. As we have all experienced, however, indefinitely is rarely forever. Patients may need periodic dose adjustments or miss doses for a variety of reasons.

We find that patients who are up to a week overdue for an injection are still stable. When a patient arrives more than a week late, check for symptom worsening to determine if you need to supplement the injection with oral medication. If the patient has missed several months, you probably need to restart the initial process.

**Inpatient use.** Long-acting IM risperidone has been studied in hospitalized patients.<sup>11</sup> Getting approval for inpatient use may be difficult, however, if inpatient services and the outpatient pharmacy are on separate budgets.

Though IM risperidone may not take effect until several weeks after a patient's discharge, starting inpatient treatment may be appropriate. At our institution, we developed tenets for reviewing each case (*Table 3*).

Before we give any injection, we require that the system for outpatient injections—including place and payment source—be in place. Without these precautions, you may find you are unable to give the next injection at the proper interval.

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### DRUG BRAND NAMES

Fluphenazine • Prolixin  
Haloperidol • Haldol  
Risperidone (long-acting) • Risperdal Consta

### DISCLOSURE

Dr. Lauriello receives grant/research support from AstraZeneca Pharmaceuticals, Janssen Pharmaceutica, and Eli Lilly and Co. He is a consultant to or speaker for Eli Lilly and Co., Janssen Pharmaceutica, Pfizer Inc., and Bristol-Myers Squibb Co.

Dr. Keith is a consultant to or speaker for Bristol-Myers Squibb Co., Janssen Pharmaceutica, Novartis Pharmaceuticals Corp., and Pfizer Inc.

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Long-acting antipsychotics can provide reliable schizophrenia therapy. Careful dosing is important, as long-acting forms behave differently from their oral counterparts. When switching from an oral antipsychotic to IM risperidone, an overlap of 4 to 6 weeks helps prevent undermedication.

**BottomLine**

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