

# Risks Versus Benefits of Different Types of Long-Acting Injectable Antipsychotics

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Since their introduction into clinical practice in the early 1960s, long-acting depot antipsychotics have been widely used as maintenance therapy for patients with schizophrenia. The improved pharmacokinetics of injectable long-acting antipsychotic therapies have provided more reliable drug delivery and reduced differences in peak and trough plasma levels of the drug. Studies that have compared short-acting oral antipsychotics with long-acting injectable antipsychotics, although imperfect, support injectable antipsychotics as having real benefit over oral antipsychotics on patient outcome owing largely to improved adherence. If patients forget or refuse to take their prescribed oral medications, weeks or months may go by before they experience an exacerbation; the effects of nonadherence become apparent too late to preempt the problem. On the other hand, if a patient fails to show up for an injection, the problem of nonadherence can be immediately addressed. When injectable medication is combined with an active psychosocial treatment program that will respond assertively to nonadherence, relapse rates may be reduced. By preventing or delaying relapse, consistent treatment can improve the patient's quality of life and lead to an overall reduction in the cost of care.

*(J Clin Psychiatry 2006;67[suppl 5]:15–18)*

The conventional antipsychotics revolutionized the treatment of psychotic disorders in the 1950s. Unfortunately, the conventional antipsychotics were relatively short-acting, and, because patients frequently discontinued their medication after being discharged from the hospital, high rates of relapse resulted. Preparations with pharmacokinetic profiles that exhibited prolonged, gradual time to peak plasma concentrations and extended elimination half-lives began to be developed. The introduction of long-acting depot antipsychotics in the early 1960s helped to address the problems of relapse. This article compares the risks and benefits of the 3 most commonly used long-acting injectable antipsychotics: fluphenazine decanote, haloperidol decanoate, and injectable risperidone microspheres.

## LONG-ACTING DEPOT VERSUS SHORT-ACTING ORAL DOSING

### Benefits

**Global outcome.** It is generally accepted that depot antipsychotics confer greater benefit than oral antipsy-

chotics on global outcome.<sup>1,2</sup> A systematic meta-analysis<sup>3</sup> of depot antipsychotic drugs summarized in the Cochrane database found that improvement in global functioning was significantly greater ( $p = .001$ ) in patients assigned to depot drugs than in patients taking oral agents, although relapse rates were not significantly different. Patients who volunteer to participate in such studies are generally not those for whom depot antipsychotics are indicated. It is possible that depot delivery of antipsychotic medication confers greater benefit than oral medication when administered to patients who have been recognized as often failing—either willfully or inadvertently—to take their oral medications regularly.<sup>4</sup>

**More reliable delivery.** The decision to use depot antipsychotics instead of oral preparations is commonly based on considerations of treatment adherence. Many patients who are not opposed to treatment and who at times can recognize the value of treatment still intermittently or continually fail to take their medications because they have cognitive impairment or because they lack daily routine. Taking a medication at the same time, in the same situation, at the same location every day is one of the basic tenets of successful adherence behavior for the management of a chronic disease such as schizophrenia or bipolar disorder.<sup>5,6</sup>

Because adherence issues are paramount in the treatment of schizophrenia, a missed appointment for an injection affords the clinician an opportunity to redouble efforts to ensure the patient receives the medication. Real-time, valid data facilitate clinical intervention, whereas with oral medication, clinicians do not know when the patient

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*This article is derived from a series of planning teleconferences held in July and August 2005 and supported by an educational grant from Janssen Medical Affairs, L.L.C.*

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stops taking his or her drugs.<sup>4</sup> Facilitating adherence is more than merely offering a patient the option of accepting or refusing depot medication. Physicians and patients need to have a plan in place that must be enacted if the patient fails to take his or her injection. If the patient is generally cooperative and may simply have forgotten to come to the clinic on the day of the injection, a simple outreach call may be all that is needed. However, if the patient has a history of dangerous behavior when ill or if the patient has some intrinsic antipathy to taking medication, a more assertive outreach program, perhaps supported by outpatient commitment, may be necessary to reengage the patient into treatment.<sup>7</sup> The long-acting depot preparations of antipsychotics have been primarily used in the maintenance treatment of patients with psychotic disorders, usually after stabilization of acute psychotic exacerbations is completed through administration of oral or short-acting intramuscular antipsychotic drugs.<sup>8</sup>

**Improved bioavailability.** One therapeutic advantage of depot injections over oral medication is bioavailability. The absorption of oral antipsychotics is variable because oral antipsychotics are converted to inactive metabolites by nonspecific enzymes in the gut wall.<sup>4</sup> They are then rapidly metabolized during the first pass of blood gathered into the portal venous system as it goes through the liver. Thus, only a small portion of each day's ingested dose reaches the central nervous system (CNS). In contrast, long-acting depot preparations bypass the deactivating processes of the liver, and a relatively higher concentration of the unaltered drug is selectively available to the CNS. This results in a more predictable and stable plasma level of active drug; however, the rate-limiting step in the kinetics of these drugs is the slow rate of absorption from the injection site.

Other factors also contribute to the bioavailability of medication. Depot medication tends to have a higher correlation between dose and plasma concentration than is found with oral preparations.<sup>9</sup> However, interindividual variability in plasma concentrations may be produced by the same dose in different patients, so no single dose of any of these drugs can be claimed as optimal for all patients. Some patients actively metabolize drugs either because of intrinsic genetic propensities or because degradative enzyme activity is enhanced by other medications that patients are taking or by smoking. Since the pharmacokinetics of depot antipsychotics are more predictable in comparison with oral compounds, side effects related to the daily peak concentration of oral medications may be eliminated. Improved bioavailability may allow for a lower total drug dose that provides similar clinical outcomes and greater dosing precision since within-subject variability is reduced. Dosing must be tailored across a substantial range to give adequate therapeutic benefit without triggering distressing extrapyramidal side effects.

## Risks

**Relapse.** Antipsychotic drugs are used to control the positive symptoms of schizophrenia as well as reduce the risk of acute relapse or at least delay episodes. The greatest risk of relapse tends to occur in the first few months of recovery from a psychotic exacerbation. Patients hospitalized for treatment of a psychotic exacerbation are often discharged still partially ill, which puts them at increased risk for neglecting to take their medication regularly and the consequent reappearance of their psychotic features.

Studies that compare relapse rates associated with oral versus injectable antipsychotics have been inconclusive. The major finding of a 1-year prospective longitudinal study<sup>7</sup> of 93 antipsychotic-responsive inpatients at 3 different New York City hospitals was that the adherence behavior of the group of patients who were converted from an oral to a depot antipsychotic before discharge was better, particularly during the first month postdischarge. However, other interventions are needed to maintain adherence over time. A retrospective survey<sup>10</sup> that compared the readmission rate after discharge between patients taking oral antipsychotics and those receiving long-acting depot medication found that the patients receiving the latter had a significantly lower ( $p < .05$ ) rehospitalization rate. However, a meta-analysis<sup>11</sup> of 70 randomized studies in the Cochrane Schizophrenia Group's Register (May 2002) concluded that fluphenazine decanoate does not reduce relapse more than oral antipsychotics.

Results from a naturalistic, multicenter study<sup>8</sup> to determine whether plasma concentrations of haloperidol could influence relapse rates in 48 patients treated for schizophrenia showed that higher plasma haloperidol levels ( $\geq 4$  ng/mL) were more effective in preventing relapse. Clinical stability was achieved when plasma levels were kept over this threshold value. The prolonged availability of the drug in patients' plasma and brain provided continuity of effect. Increased plasma concentrations of agents may be associated with reduced relapse rates.

**Adverse events.** Optimal treatment strategies achieve the highest rate of response with the lowest incidence of adverse events. The risks of developing extrapyramidal adverse events and tardive dyskinesia have been extensively investigated in relation to antipsychotic use and have been found to be dose dependent.<sup>2</sup> A 6-month, randomized clinical trial<sup>12</sup> that compared fluphenazine decanoate with haloperidol decanoate in patients with chronic schizophrenia found no differences in therapeutic effect or in the incidence and severity of extrapyramidal side effects. In general, equivalent dosages of depot drugs pose no greater risk for adverse effects than oral drugs.<sup>6</sup> Depot dosing may actually lower the rate of motor side effects when compared with oral therapy by constraining the peak levels below the moderate-to-severe threshold of reversible motor side effects.<sup>13</sup>

**Irritation upon injection.** Another untoward effect of depot drugs is that some patients experience discomfort or pain at the injection site. Because injections are administered over a patient's lifetime, it is important that care is taken to minimize discomfort and to reduce the incidence of problems at the injection site. Leakage of even small amounts of the medication will result in absorption of an inaccurate dose, and in addition, owing to the irritant nature of many of these drugs, leakage into subcutaneous tissue and onto the skin can cause pain, irritation, and lesions. Rotating injection sites and limiting the volume of the injection can reduce such local reactions, and assuring deep intramuscular injection (the Z-track technique of injecting the medication) may reduce leakage.<sup>14</sup>

## PHARMACOKINETICS

### Fluphenazine and Haloperidol Decanoate

Two long-acting conventional depot antipsychotics—fluphenazine and haloperidol decanoate—are available in the United States. The pharmacokinetic profiles of these depot antipsychotics are similar in that the agents are synthesized by esterification of the active drug to a long-chain fatty acid. The ester that is formed between the antipsychotic and the long-chain fatty acid is then dissolved in a liposoluble solution, such as vegetable oil, which renders the solution ready for injection.<sup>6</sup> Because these depot preparations are oil-based solutions, Z-track injection techniques are required to limit leakage after injections. A review<sup>6</sup> of early research with high doses of these conventional depot antipsychotics found that large-volume injections resulted in substantial redness, swelling, and, ultimately, palpable masses that reflected scarring and, in some cases, even abscesses.<sup>14</sup> After the material was injected, it stayed relatively localized in the injection site for several weeks. The gradual cleavage of the ester bond resulted in release of the active metabolite and then independent degradation of the fatty acid.

An early peak concentration of fluphenazine results within 8 to 10 hours after the injection, followed by a sustained plateau. For this reason, an effective level of the drug is achieved more quickly than with either haloperidol decanoate or long-acting injectable risperidone, without substantial risk of later climbing to excessively high levels. Supplementation with oral medication is needed for less time following the initiation of treatment with fluphenazine decanoate than with either of the other preparations. The elimination half-life for fluphenazine decanoate is about 14 days, and steady-state concentrations are generally reached in approximately 4 to 6 weeks.<sup>15</sup>

The plasma concentrations of haloperidol decanoate do not peak early, but rather take about 3 weeks after an initial injection to reach their peak. If multiple doses are given in quick succession early, it may become apparent later that levels higher than are needed for maintenance were inad-

vertently achieved. The elimination half-life for haloperidol decanoate is somewhat longer than that for fluphenazine decanoate (about 21 days),<sup>4</sup> and, therefore, can take 2 to 3 months to reach steady-state concentrations depending on prior dosage, clinical state, and other considerations.<sup>4,16</sup>

### Long-Acting Injectable Risperidone

The pharmacokinetic profile of the long-acting injectable atypical antipsychotic risperidone is substantially different from that of the conventional depot antipsychotic preparations. Unaltered risperidone is embedded in a copolymer consisting of glycolic acid and lactate that is similar to that used in temporary, dissolvable sutures. Microspheres of the lactide-coglycolide polymer in which risperidone is embedded are provided as a powder, which is then suspended in an aqueous diluent for injection into the patient. A very small amount of the drug, approximately 1% of the total dose, is released following a single intramuscular injection of long-acting risperidone, followed by a lag time of 3 weeks.<sup>17</sup> After about 3 weeks, the polymer microspheres are hydrolyzed, breaking down the polymer and releasing unaltered risperidone gradually into the system. Patients receive injections every 2 weeks; steady-state plasma concentrations are achieved after 4 injections and are maintained for 4 to 6 weeks after the last injection. This main release of risperidone extends across weeks 4 through 6 after the initial injection and subsides by week 7. Because of this delay, full oral antipsychotic supplementation should be given during the first 3 weeks of treatment to maintain therapeutic levels until the release of the drug from the injection site has begun. Several additional weeks of oral supplementation at lower doses may be needed until steady state levels are achieved.

Because long-acting risperidone is a water-based solution, Z-track injection technique is not required. Both patient and clinician ratings suggest that there is little, if any, pain or inflammation associated with the injections<sup>18,19</sup> and limited or no redness, swelling, or irritation.<sup>20</sup>

## SWITCHING CONSIDERATIONS

Switching patients from oral medication to injectable preparations must be done with care. In every case, it is important to give patients several test doses of the same oral medication prior to the use of that depot injection to identify those few people who will be sensitive to or intolerant of the specific drug. Test dosing will also determine sensitivity to extrapyramidal effects.

Switching from short-term oral treatment to depot maintenance therapy requires that the 2 treatments overlap while the depot dose is adjusted and reaches peak level. Given the rapid rise to a peak level with fluphenazine decanoate followed by a prolonged plateau at that dose, oral doses should be rapidly decreased by half after the first intramuscular injection, and can often be discontinued after

the second. A slow approach to loading of haloperidol decanoate, keeping patients slightly longer on oral haloperidol treatment along with the injection, and then gradually trying to identify an optimal, well-tolerated maintenance dose may be the best strategy. Frequent examinations for extrapyramidal side effects will permit sensible maintenance dose selection.<sup>8,21</sup> Oral antipsychotic treatment can usually be tapered and discontinued after the first 2 to 3 injections of haloperidol.

Unlike with fluphenazine and haloperidol decanoate, dose loading with long-acting risperidone is not possible because there is essentially no release from the depot site for 3 weeks following the first injection, which is followed by a gradually increasing release as steady-state kinetics are achieved. Gefvert et al.<sup>22</sup> assessed the pharmacokinetics of long-acting risperidone at doses of 25 mg, 50 mg, or 75 mg given every 2 weeks in an open-label, nonrandomized, multisite trial that comprised 13 stable patients with schizophrenia. Each patient received 5 injections every 2 weeks at the dose level prescribed by the treating physician. Stable plasma concentrations were reached after the third injection, and steady-state concentrations of the active moiety were reached after the fourth injection. Steady-state plasma concentrations were maintained for 4 to 5 weeks after the last injection and then declined rapidly. These findings support full supplementation with oral antipsychotics for 3 weeks after an initial injection, followed by 3 to 4 additional weeks of gradual tapering of the oral medication as the patient approaches steady-state kinetics.

### SUMMARY

Long-acting conventional antipsychotics—fluphenazine decanoate and haloperidol decanoate—and the long-acting injectable formulation of the atypical antipsychotic risperidone are effective in the maintenance treatment of patients with schizophrenia. The improved pharmacokinetics of injectable long-acting antipsychotic therapies compared with oral agents encourages rational dosing strategies and provides more reliable drug delivery, reduced differences in peak and trough plasma levels of the drug, and greater dosing precision. Taken together, these benefits reduce the risks of relapse and adverse events because the clinician can more accurately assess the status of antipsychotic treatment adherence and response. When long-acting injectable medication is combined with an active psychosocial treatment program, global functioning, especially among patients with any history of willful or inadvertent nonadherence, may be improved. Consistent treatment will improve the patient's quality of life and lead to an overall reduction in the cost of care by preempting any need for hospitalization. Patients must get on and stay on a trajectory of recovery to ultimately resume meaningful activities for themselves and to have full, rewarding relationships.

*Drug names:* fluphenazine (Prolixin, Permitil, and others), haloperidol (Haldol and others), risperidone (Risperdal Consta).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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