Current PSYCHIATRY

Out of the pipeline: IM risperidone

Long-acting atypical antipsychotic

One year of biweekly injections reduced symptoms and restored function beyond the usual response to oral antipsychotics

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Patients with chronic schizophrenia are notoriously inconsistent in adhering to medications.[1] Partial compliance is a serious problem because the resulting psychotic relapses often lead to progressive neurologic and clinical deterioration as well as social and vocational impairment.

Long-acting, "depot" formulations of first-generation antipsychotics (haloperidol decanoate and fluphenazine decanoate) have been used over the past 25 years to ensure adherence in the least-compliant patients. These formulations, however, are not widely used because of the risks of tardive dyskinesia (TD) and other movement disorders.

Atypical antipsychotics—with their reduced risk of TD—have become the standard of care in managing schizophrenia and related psychosis over the long term.[2] All are administered orally, however, and—until now—none has been available in a long-acting formulation.

The FDA recently approved a long-acting, injectable form of risperidone *(Table 1)*, based on

Table 1

Injectable, long-acting risperidone: Fast facts

Drug brand name: Risperdal Consta

Class: Long-acting injectable atypical antipsychotic

FDA-approved indications: Schizophrenia

Approval date: Oct. 29, 2003

Manufacturer: Janssen Pharmaceutica

Dosing forms: 25 mg, 37.5 mg, 50 mg

Recommended dosage: Most adult patients will be started at 25 mg every 2 weeks, with dosages titrated upward as needed

Estimated date of availability: By January 2004

Dosing equivalencies (approximate):
25 mg IM biweekly = 3 mg/d oral
37.5 mg IM biweekly = 4.5 mg/d oral
50 mg IM biweekly = 5 to 6 mg/d oral

results of a 12-week, placebo-controlled trial and a 1-year open-label trial. The clinical and functional improvements seen in chronic schizophrenia patients who received long-acting risperidone for 1 to 3 years may change prevailing notions of the potential to stabilize and restore function in this severe brain disorder.

Table 2

Receptor-binding profile of risperidone long-acting formulation

Receptor type	Effects
Dopamine D2	Antagonism (< haloperidol)
Serotonin 5HT2A	Antagonism (170 times > haloperidol)
Alpha 1	Low affinity
Alpha 2	Low affinity
Histaminic	Low affinity
Muscarinic	No affinity

HOW LONG-ACTING RISPERIDONE WORKS

Long-acting injectable risperidone has the same mechanism of action as oral risperidone. The injectable form is delivered into muscle tissue by microspheres that encapsulate the drug into a biodegradable polymer. The microspheres undergo gradual hydrolysis, resulting in a gradual release of risperidone into the blood stream. The drug then crosses the blood-brain barrier to block dopamine D2 and serotonin 5HT2A receptors in brain tissue, which is accepted as the pharmacodynamic basis for the efficacy of atypical antipsychotics. Risperidone's receptor-binding profile is shown in *Table 2*.

CLINICAL PHARMACOKINETICS

Full release of long-acting risperidone from the gradually hydrolyzing microspheres starts about 3 weeks after an intramuscular (IM) injection. Thus, supplemental oral risperidone is recommended during the first 3 weeks of IM injections. Release is then maintained for 4 to 6 weeks. Steady-state plasma levels are reached after four biweekly injections. Risperidone is absorbed completely from the microspheres, which are biodegradable to carbon dioxide and water.

In plasma, risperidone is oxidized by the cytochrome P-450 isoenzyme CYP 2D6 to 9-hydroxy risperidone, an active metabolite similar to risperidone in its pharmacologic characteristics and efficacy. Risperidone is also metabolized via N-dealkylation. The plasma protein binding of risperidone is 90% and that of 9-hydroxy risperidone is 77%. After several biweekly IM injections of 25 or 50 mg during clinical trials, median trough and peak plasma concentrations of active moiety fluctuated between 9.9 and 19.2 ng/ml and 17.9 and 45.5 ng/ml, respectively.

Risperidone plasma concentrations may be affected by interactions with other psychotropics that inhibit or induce the oxidative enzyme CYP 2D6 *(Table 3)*.

Clearance of risperidone and 9-hydroxy risperidone is decreased by 60% in patients with severe kidney disease, as compared with healthy subjects. Plasma levels and maximum drug concentrations are 25 to 32% lower with long-acting risperidone than with oral risperidone. This difference may account for the injectable formulation's more favorable side-effect profile because lower peaks means a lower likelihood of side effects.

Long-acting IM risperidone's lower plasma peaks may account for its lower risk of side effects

Table 3

Potential drug-drug interactions with risperidone long-acting microspheres

Drug	CYP enzyme affected	Effect on plasma concentration of risperidone
Fluphenazine	2D6	Increase
Paroxetine	2D6	Increase
Carbamazepine	2D6	Decrease

RESULTS FROM CLINICAL TRIALS

Long-acting risperidone was tested at doses of 25, 50, and 75 mg in a 12-week, double-blind trial of 400 patients with acute relapse of schizophrenia.[4] During the 3-week initial titration, patients also received the usual dosage of oral risperidone (3 to 5 mg/d) for schizophrenia. Oral risperidone can be discontinued 3 weeks after the first injection (ie, 1 week after the second injection). Measurement of serum concentrations is not needed because the microspheres encapsulating risperidone have been shown in bioavailability studies to begin disintegrating and releasing risperidone 3 weeks after being deposited into muscle tissue.

All three doses were more effective than placebo in reducing total, positive, and negative symptom scores, as measured by the Positive and Negative Syndrome Scale (PANSS). The 75-mg dose showed no greater efficacy than the 50-mg dose.

In a second, open-label study, 775 stable outpatients with schizophrenia or schizoaffective disorder received biweekly injections of 25, 50, or 75 mg of long-acting risperidone for 1 year. All three doses improved the baseline PANSS scores significantly, above and beyond the patients' stable clinical status. These results indicate that injectable long-acting risperidone can further stabilize schizophrenia beyond the usual response to oral antipsychotics.[5]

Notably, patients' quality-of-life scores—as measured by the 36-item Short-Form Health Survey (SF-36)—were significantly lower than U.S. norms at baseline. At the end of the study, patients' scores had increased to within the norm range.[6] The completion rate in this 1-year study was 65%; patients dropped out because of insufficient response (7%) or adverse events (5%), or they withdrew consent (15%) or were lost to follow-up (3%).

SAFETY AND TOLERABILITY

Few side effects were seen in the 12-week and 1-year trials. Extrapyramidal symptoms as measured by the Extrapyramidal Symptom Rating Scale declined from baseline by 67% with the 25-mg dose, by 50% with the 50-mg dose, and by 33% with the 75-mg dose in the 12-week study. Patients who had TD at baseline also improved by the end of the 1-year study, suggesting that long-acting risperidone has a low risk of TD.[7] Also:

- Although prolactin levels were elevated compared with baseline, they were 18% lower with long-acting risperidone than with oral risperidone, possibly because of lower plasma peaks of the drug in the long-acting formulation.
- Injection site pain or redness was minimal, as measured by patient ratings.
- Mean weight gain after 12 weeks was 0.5 kg with the 25-mg dose, 1.2 kg with the 50-mg dose, and 1.9 kg with the 75-mg dose. After 52 weeks, weight gain was 1.8 kg, 2.1 kg, and 2.7 kg, respectively.
- QTc prolongation—as measured with random ECGs—was negligible with all doses.

REPARATIVE EFFECTS?

Based on clinical trial results, long-acting risperidone appears to be highly effective in treating and preventing relapse of acute psychotic episodes in schizophrenia. Its injectable formula-

tion ensures that compliance is far more consistent than with oral atypical antipsychotics.

Patients who had been disabled with chronic schizophrenia improved dramatically after about 1 year of biweekly injections of long-acting risperidone. Many were able to return to school to finish a degree, go back to holding full-time jobs, or develop close personal relationships such as dating. Total PANSS scores after 1 year of treatment approached the low 40s in some patients, which is similar to what a healthy person might score on the PANSS on certain days. This pattern, which justifies the term "recovery," suggests that uninterrupted, long-term atypical antipsychotic treatment may have reparative and/or neuroprotective effects on the brain in schizophrenia.[8]

Candidates for long-acting injectable risperidone include:

- first-episode patients
- patients with a history of partial or complete noncompliance
- patients who become violent or assaultive when they relapse
- and those receiving depot injections of haloperidol decanoate or fluphenazine decanoate.

Long-acting injectable atypical antipsychotics may become the standard of care for treating new-onset schizophrenia.[9] The goal would be to return patients to baseline functioning as soon as possible, rather than resorting to a long-acting antipsychotic only after repetitive relapses, adverse neuroplastic changes, and psychosocial decline.

References

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Related resources

- Lasser R, Bossie C, Zhu Y, Gharahawi G. Does constant therapy infer optimal efficacy in schizophrenia? Moving to an advanced pharmacotherapeutic option. *Schizophr Res* 2003;60:291.
- Risperdal Consta Web site. www.risperdalconsta.com

DRUG BRAND NAMES

Carbamazepine • Tegretol
Fluphenazine • Prolixin
Haloperidol • Haldol
Paroxetine • Paxil

DISCLOSURE

The author participated in the 12-week controlled clinical trial of long-acting, injectable risperidone and in an open-label extension for more than 3 additional years.

Dr. Nasrallah reports that he also receives research/grant support from and is a consultant to and speaker for AstraZeneca Pharmaceuticals, Janssen Pharmaceutica, and Pfizer Inc., and is a consultant to and speaker for Bristol-Myers Squibb Co. and Abbott Laboratories.

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Bottom Line

Long-acting risperidone offers the option of biweekly injections of an atypical antipsychotic for treating chronic schizophrenia. In a 1-year trial, many patients' quality-of-life and symptom scores improved with uninterrupted therapy, and relatively few side effects were seen.