

Strategies for Improving Compliance in Treatment of Schizophrenia by Using a Long-Acting Formulation of an Antipsychotic: Clinical Studies

John M. Kane, M.D.

Despite evidence showing the importance of continuous medication in preventing relapse in patients with schizophrenia and the harmful consequences that relapse can have, clinical efforts often focus on hospital-based treatment or treatment of acute exacerbations of schizophrenia rather than on ensuring appropriate and effective relapse prevention. Inadequate compliance with antipsychotic treatment further deters from the goal of long-term management of schizophrenia; however, appropriate use of injectable, long-acting antipsychotic medications—especially atypical antipsychotics—has the potential to increase compliance and thus improve the long-term prognosis of patients with schizophrenia. A long-acting formulation of the atypical antipsychotic risperidone has undergone large-scale clinical testing, during which it showed significant improvement on measures of disease severity while maintaining an acceptable side effect profile. (*J Clin Psychiatry* 2003;64[suppl 16]:34–40)

Long-term pharmacologic treatment is the cornerstone in the management of schizophrenia. Numerous controlled trials have demonstrated the value of continuous antipsychotic treatment in preventing relapse at all phases of the illness.¹ Even after a single episode, it is clear that the absence of pharmacotherapy is associated with significantly higher relapse rates in comparison to continued treatment.²

Despite the overwhelming amount of data demonstrating the importance of continued medication in relapse prevention and the serious and varied consequences of relapse (hospitalization, family burden, increased risk for aggressive or self-injurious behavior, etc.), clinical efforts to ensure appropriate and effective relapse prevention strategies are often far from optimal.

SYSTEMS OF CARE AND DISEASE MANAGEMENT

Unfortunately, in many systems of care, far more attention and resources are devoted to the management of acute

exacerbations and hospital-based treatment than to strategies focusing on long-term, community-based disease management.

There are several critical ingredients in effective disease management. First, systems of care must be in place to facilitate access, continuity of care, and an appropriate mix of medical and psychosocial interventions. Second, the clinical team must have a clear and firm grounding in evidence-based medicine and the data and guidelines available to inform clinical practice. Third, the clinical team must be able to provide necessary psychoeducation, translating the information referred to previously into understandable and personally meaningful recommendations to patients and significant others.

The optimum use of long-acting injectable antipsychotics is an example of a potentially valuable strategy that is often not utilized because one or more of the ingredients described above is not adequately available or implemented.

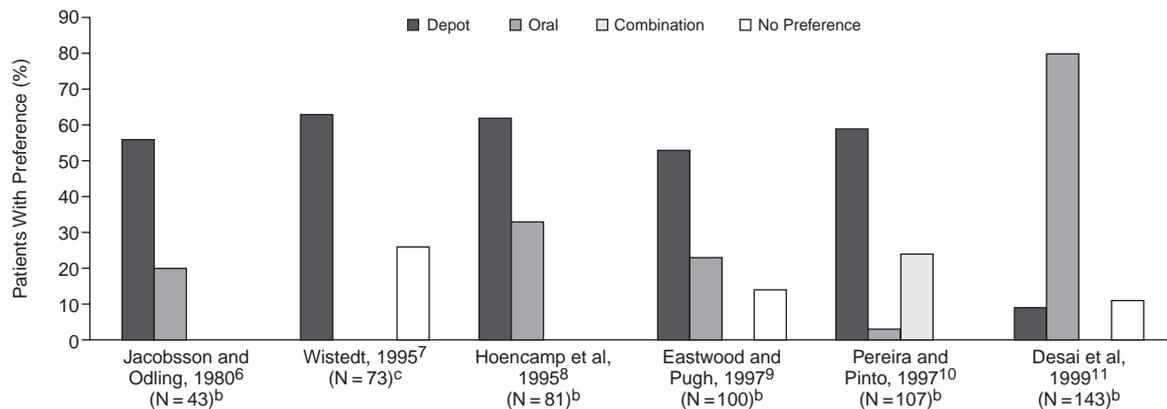
THE ROLE OF LONG-ACTING ANTIPSYCHOTICS

A considerable amount has been written about rates of poor or partial compliance, the risk of psychotic relapse (and other problems) associated with inadequate compliance, and the difficulty clinicians have in identifying in whom and when compliance problems are occurring or will occur in the future.^{3,4} A critical advantage of long-acting injectable medication is that if a patient does become noncompliant, the clinical team should know immediately (because an injection has been missed) and be able

From Albert Einstein College of Medicine, Bronx, and the Department of Psychiatry, The Zucker Hillside Hospital, North Shore–Long Island Jewish Health System, Glen Oaks, N.Y.

This article is derived from the teleconference "Partial Compliance: The Need for Long-Acting Atypical Antipsychotics," which was held March 27, 2002, and supported by an unrestricted educational grant from Janssen Pharmaceutica, L.P.

Corresponding author and reprints: John M. Kane, M.D., Department of Psychiatry, The Zucker Hillside Hospital, North Shore–Long Island Jewish Health System, 75-59 263rd St., Glen Oaks, NY 11004.

Figure 1. Patient Preference: Depot Versus Oral Antipsychotic Medications^a

^aData from Walburn et al.⁵ The total number of patients in each study is given; missing data are not taken into account.

^bOptions not represented were not available to patients as answer choices.

^cAlthough included as an answer choice, oral antipsychotics were preferred by 0 patients, and the combination of depot and oral antipsychotics was not available to patients as an answer choice.

to initiate efforts to deal effectively with the problem (e.g., calling the patient and/or significant other, making a home visit). At the same time, since the medication is not out of the system as rapidly as when oral medication is discontinued, there is some time advantage in allowing for the necessary interventions. In addition, if a patient does relapse, an accurate evaluation can be made as to whether the patient was taking medication prior to the relapse. Among patients taking oral medication, it can be difficult to determine the timing and extent of poor or partial compliance associated with a relapse.

In addition, although there are few high-quality data regarding patient attitudes toward depot medication, the data that are available show generally positive attitudes among patients who have had experience with long-acting injectable medication (Figure 1).⁵ Interestingly, the 1 report in which patients favored oral medication involved patients switched from a conventional depot to an oral atypical drug (i.e., risperidone).¹¹

A major obstacle to the use of long-acting injectable drugs at present is the lack of availability of an atypical compound in a long-acting formulation. Although patients express a preference in many cases for atypical drugs, the ability of these medications to enhance long-term compliance in oral medication-taking is modest at best.^{12,13}

LONG-ACTING RISPERIDONE

The availability of a long-acting, atypical antipsychotic medication provides an extremely valuable management strategy for the treatment of schizophrenia. An injectable, long-acting formulation of risperidone (Risperdal Consta) was recently approved by the U.S. Food and Drug Administration. Given the chemical structure of risperidone (and

other atypical or newer-generation antipsychotics), it is not possible to esterify the drug molecule in order to create a decanoate, as is done with the conventional drugs haloperidol and fluphenazine. The “microsphere” technology has made it possible to develop a long-acting formulation of risperidone that allows the maintenance of stable blood levels for at least 2 weeks. This novel approach involves encapsulating risperidone in a lactide, glycolide polymer (a common biodegradable polymer that has been used in sutures, bone plates, and extended-release pharmaceuticals). Each microsphere is about one tenth of a millimeter in size, approximately equivalent to the width of a human hair.

The microspheres are combined at the time of injection with a saline-based solution and injected into the muscle. Since the solution is saline-based (rather than the oil-based solutions typically used in the decanoate formulations), it is less likely to cause discomfort or irritation at the injection site. The polymer gradually breaks down over time, and the active risperidone is released along with lactic acid, glycolic acid, and H₂O.

Pharmacokinetic studies have been conducted to help establish an appropriate dosage range for clinical trials.¹⁴ The pharmacokinetic properties of long-acting risperidone are such that peak blood levels of risperidone are reduced approximately 30% in comparison to daily oral medication, which could result in even fewer adverse effects with a compound that has demonstrated very good tolerability with oral administration.

CLINICAL TRIALS WITH LONG-ACTING RISPERIDONE

Three major clinical trials have been conducted with long-acting risperidone. A 12-week, multicenter, random-

Table 1. Background Characteristics of the Patients in 4 Treatment Groups^a

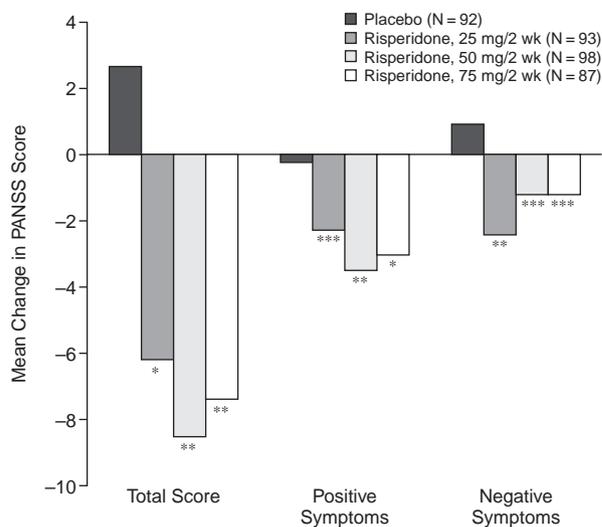
Characteristic	Placebo (N = 98)	Long-Acting Risperidone		
		25 mg (N = 99)	50 mg (N = 103)	75 mg (N = 100)
Sex				
Men	82	69	82	68
Women	18	31	18	32
Age, y				
Mean ± SE	37.7 ± 1.0	38.9 ± 1.0	36.2 ± 0.9	38.1 ± 1.1
Range	18–54	18–55	19–55	18–55
Race/ethnicity				
African American	38	41	39	49
White	46	37	44	39
Hispanic	12	13	11	9
Other	4	8	7	3
Schizophrenia type				
Paranoid	80	77	72	74
Undifferentiated	18	21	21	23
Disorganized	2	2	6	3
Catatonic	0	0	1	0
Hospitalization status at baseline				
Inpatient	48	49	48	50
Outpatient	52	51	52	50
Previous hospitalizations	(N = 89)	(N = 96)	(N = 101)	(N = 94)
Median (range)	4.0 (0–28)	3.5 (0–99)	4.0 (0–50)	4.0 (0–63)

^aAdapted with permission from Kane et al.¹⁵ and data from Kane et al.¹⁶ All values shown as percentages unless otherwise noted.

ized, double-blind, parallel-group study^{15,16} was conducted comparing placebo and long-acting risperidone in doses of 25, 50, or 75 mg injected intramuscularly every 2 weeks. The 41 participating centers, which were located in the United States, enrolled inpatients or outpatients aged 18 to 55 years who met DSM-IV criteria¹⁷ for schizophrenia and had baseline total scores between 60 and 120 on the Positive and Negative Syndrome Scale (PANSS).¹⁸ Exclusion criteria included receiving conventional depot antipsychotics during the 120 days before the trial began, substance dependence, presence of tardive dyskinesia or history of neuroleptic malignant syndrome, presence of clinically significant electrocardiographic abnormality, presence or risk of pregnancy, current suicidal ideation, or risk of violent behavior.

Patients' symptoms were assessed every 2 weeks with the PANSS and every week with the Clinical Global Impressions scale (CGI).¹⁹ The change in the PANSS total score between baseline and endpoint was the primary efficacy measure, and a reduction of $\geq 20\%$ in the PANSS total score was the preestablished criterion for clinical improvement.

Patients underwent screening for 1 week and then entered the 1-week run-in phase. As they gradually discontinued taking oral antipsychotic medications other than risperidone, patients began taking oral risperidone, which was titrated from 2 mg/day to 4 mg/day for a minimum of 3 days. Patients who entered the 12-week double-blind phase were administered intramuscular injections of pla-

Figure 2. Mean Positive and Negative Syndrome Scale (PANSS) Scores at Endpoint in Patients With Schizophrenia Who Were Treated With Placebo or 25, 50, or 75 mg of Long-Acting Injectable Risperidone for 12 Weeks^a

^aReprinted with permission from Kane et al.¹⁵

* $p < .05$, ** $p < .01$, *** $p < .001$ vs. placebo for change from baseline to endpoint (Dunnett's multiple comparison method).

cebo or 25, 50, or 75 mg of long-acting risperidone every 2 weeks, according to random assignment. Because peak plasma levels are not achieved until 2 to 3 weeks after the first injection, patients receiving 25, 50, or 75 mg of long-acting risperidone also took 2, 4, or 6 mg, respectively, of oral risperidone for 3 weeks. Patients receiving placebo injections took oral placebo during those 3 weeks.

Of the 554 patients with a diagnosis of schizophrenia who were screened, 461 began the run-in phase. The double-blind phase included 400 participants who received a minimum of 1 injection. These 400 subjects' background characteristics are summarized in Table 1. Three hundred seventy patients were assessed with the PANSS at least once after baseline, i.e., completion of the run-in phase.

The mean PANSS total score at baseline was 81. Significantly greater improvement in mean PANSS total scores, positive symptoms, negative symptoms (Figure 2), and mean CGI scores was observed at endpoint in all 3 risperidone groups in comparison with placebo. Seventeen percent of patients in the placebo group as well as 47% in the 25-mg, 48% in the 50-mg, and 39% in the 75-mg long-acting risperidone groups met the a priori criterion for clinical improvement, i.e., $\geq 20\%$ decrease in PANSS total score.

Discontinuation rates were 68% in the placebo group and 51% to 52% in the long-acting risperidone groups. Similar percentages of patients in each of the 4 treatment groups ended treatment during the first 15 days; however, more patients in the placebo group than in the active treat-

Table 2. Reasons for Discontinuation During the Double-Blind Phase of a Study Comparing 3 Doses of Long-Acting Risperidone and Placebo^a

Reason	Placebo (N = 98)	Long-Acting Risperidone		
		25 mg (N = 99)	50 mg (N = 103)	75 mg (N = 100)
Any reason	68	52	51	52
Insufficient response	30	22	15	12
Adverse event	12	11	12	14
Withdrew consent	10	7	13	11
Lost to follow-up	6	2	3	6
Noncompliance	4	0	3	3
Ineligibility	0	3	3	2
Death	1	0	0	0
Other	5	6	4	4

^aAdapted with permission from Kane et al.¹⁵ All values shown as percentages.

ment groups discontinued subsequently. The most common reasons for dropping out of the study are provided in Table 2.

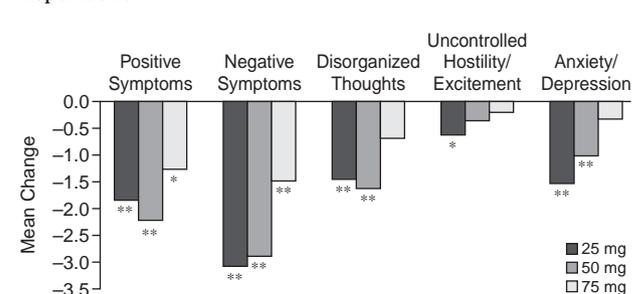
There were no significant differences between the percentage of patients (80% to 83%) in the placebo and active treatment groups who reported adverse effects. According to rating scale scores, reversible drug-induced motor side effects such as extrapyramidal side effects (EPS) were mild when assessed at the end of the run-in phase and did not increase in severity over the 12 weeks of the double-blind phase. Ten percent of patients receiving 25 mg, 24% receiving 50 mg, and 29% receiving 75 mg of long-acting risperidone as well as 13% of patients receiving placebo spontaneously reported adverse events related to motor side effects. Patients in all treatment groups experienced only a small amount of pain at the injection site after the first injection and even less pain after subsequent injections, as measured by a patient-rated visual analog scale.

In this 12-week trial, which involved both inpatients and outpatients with, on average, moderate symptoms at baseline, long-acting risperidone demonstrated significantly greater efficacy than placebo across all clinical measures. Long-acting risperidone was well tolerated with little weight gain, no significant cardiovascular effects, and no significant difference from placebo on ratings of reversible motor side effects. Though spontaneously reported reversible motor side effects occurred somewhat more frequently in the 50-mg group (24%) and the 75-mg group (29%) in comparison to placebo (13%) or 25 mg (10%), these differences were not statistically significant.

A second trial²⁰ involved a double-blind, international, multicenter, 12-week study comparing the safety and efficacy of long-acting risperidone (25, 50, and 75 mg given every other week) and oral risperidone. Patients were inpatients or outpatients with a diagnosis of schizophrenia or schizoaffective disorder.

Subjects received oral risperidone during the first 8 weeks of this 20-week study. Antipsychotics other than risperidone were discontinued and risperidone was intro-

Figure 3. Mean Changes From Baseline to Endpoint in Positive and Negative Syndrome Scale (PANSS) Factor Scores in the 3 Dosage Groups of Patients Receiving Long-Acting Risperidone^a



^aData from Fleischhacker et al.²¹

**p* < .01.

***p* < .001 vs. baseline.

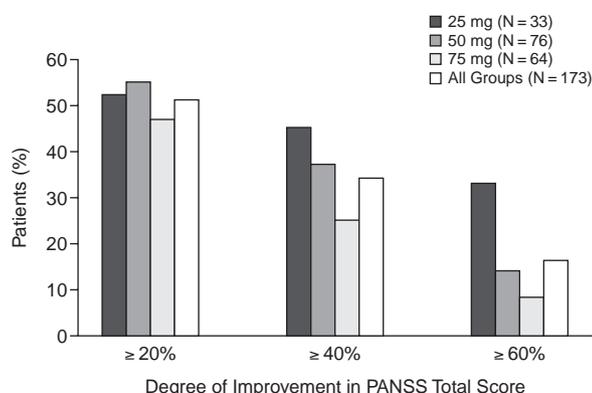
duced during the first 2 weeks of the 8-week run-in period. Physicians attempted to optimize the oral dose of risperidone during the next 2 weeks (at either 2, 4, or 6 mg/day). Patients then continued on their optimal oral dose for 4 weeks before randomization to continue on oral treatment or be switched to an equivalent dose of long-acting risperidone (i.e., 25, 50, or 75 mg every 2 weeks). During the first 2 weeks of the 12-week double-blind phase, patients continued to receive oral risperidone if they were randomly assigned to receive long-acting injections.

The overall objective of this study was to establish that symptom stability is maintained during the transition from an oral to a long-acting formulation and to determine whether patients might gain short-term benefits from the transition.

Eight hundred one patients were screened, and 640 received double-blind treatment. There were no differences between the groups receiving oral (N = 321) or long-acting medication (N = 319) in terms of age, sex, illness severity, or diagnostic subtype. No significant differences were observed on rates of discontinuation due to adverse effects (5%–6%) or discontinuation due to lack of efficacy (4%–5%). Similar improvements in PANSS total scores (-6.3 ± 0.7 with oral risperidone and -5.4 ± 0.7 with long-acting risperidone; 95% CI = -0.90 to 2.78) as well as factor scores from baseline to endpoint were seen in the 2 groups. No significant differences in measures of EPS were observed. Prolactin levels decreased by 10% to 19% among the patients receiving long-acting risperidone. Mean body weight increases at endpoint were similar and minimal in the 2 groups (0.3 kg with oral risperidone and 0.5 kg with long-acting risperidone).

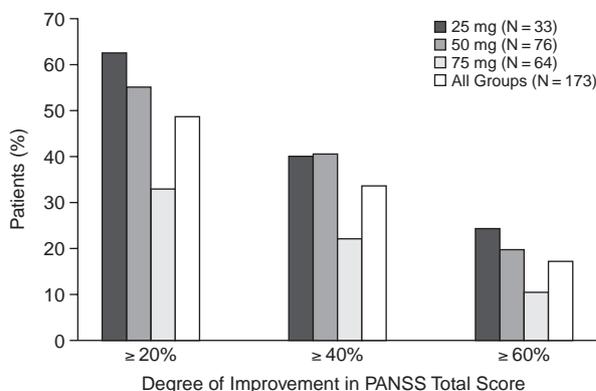
The third major study²¹ was an open-label, multicenter, international trial examining the long-term safety and efficacy of long-acting risperidone. Inpatients or outpatients with a diagnosis of schizophrenia or schizoaffective disorder who were symptomatically stable and had been re-

Figure 4. Percentage Improvement from Baseline to Endpoint in Positive and Negative Syndrome Scale (PANSS) Total Scores for 173 Stable Patients With Schizophrenia or Schizoaffective Disorder Who Switched From Conventional Depot Antipsychotics to Long-Acting Risperidone^a



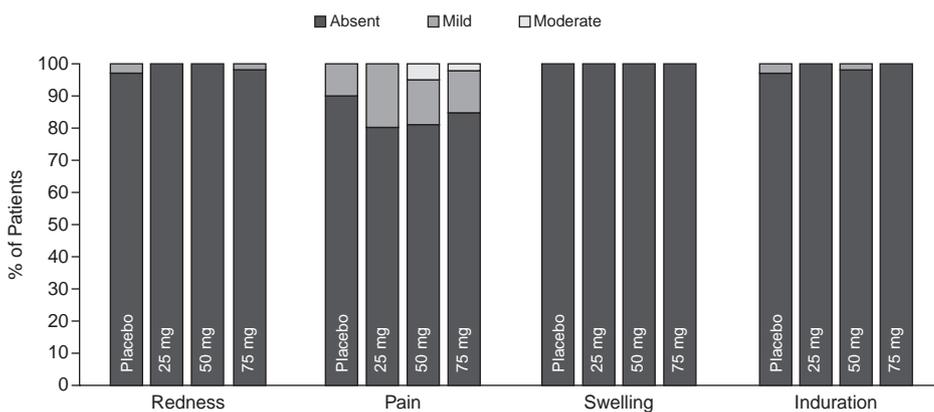
^aAdapted with permission from Lasser et al.²² Percentage improvement = (change score/baseline score - 30) × 100.

Figure 5. Percentage Improvement from Baseline to Endpoint in Positive and Negative Syndrome Scale (PANSS) Total Scores for 318 Stable Patients With Schizophrenia or Schizoaffective Disorder Who Switched From Oral Risperidone to Long-Acting Risperidone^a



^aAdapted with permission from Gharabawi et al.²³ Percentage improvement = (change score/baseline score - 30) × 100.

Figure 6. Investigator Ratings of Redness, Pain, Swelling, and Induration in 182 Patients Within 5 Minutes After Receiving the Fifth Biweekly Injection of Placebo or Long-Acting Risperidone^a



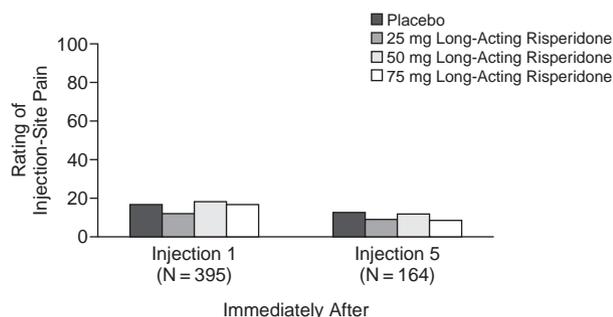
^aAdapted with permission from Lasser et al.²⁴

ceiving a stable dose of oral risperidone for at least 4 weeks prior to study entry were eligible to participate.

Seven hundred eighty-six patients were screened, and 725 received at least one injection of long-acting risperidone. Patients received biweekly injections of 25, 50, or 75 mg depending on their baseline oral dose. Oral dosing was continued for 2 to 3 weeks after the initial injection. Doses of long-acting risperidone could be increased or reduced during the trial according to clinical judgment. The length of the trial was 1 year. Sixty-four percent of patients completed the 1-year trial. All groups experienced statistically significant improvement from baseline on the PANSS total score as well as on positive and negative symptoms (Figure 3).

Subanalyses^{22,23} of the 12-month study revealed that stable patients, who had mean baseline total PANSS scores of about 64, experienced substantial improvement in PANSS scores when they switched to injections of long-acting risperidone, regardless of whether they switched from conventional depot antipsychotics or oral risperidone. Percentage improvement in PANSS total scores was ≥ 20% for 51.5% of patients previously treated with conventional depot antipsychotics (Figure 4) and 49.7% of patients previously treated with oral risperidone (Figure 5). Improvement ≥ 60% was seen in 15.6% of those on prior conventional depot antipsychotic therapy and 17.9% of those on prior oral risperidone therapy. Patients who switched from conventional depot antipsychotics experi-

Figure 7. Patient Ratings of Injection-Site Pain (0 = no pain; 100 = unbearable pain) Within 5 Minutes After Receiving an Injection of Placebo or Long-Acting Risperidone^a



^aData from Lasser et al.²⁴

enced significant ($p < .01$) improvement on all PANSS factor scores except hostility/excitement, and those who switched from oral risperidone had significant ($p < .05$) improvement on all 5 factor scores.

Among all 725 patients, rates of discontinuation for lack of efficacy were somewhat higher and improvement in total PANSS score was somewhat lower in the 75-mg group;²¹ however, it must be emphasized that the assignment to long-acting risperidone dose was not random, but determined by oral dose at baseline. It might be anticipated that those patients requiring higher doses at baseline were less treatment responsive than patients requiring lower doses.

Low rates of discontinuation for adverse effects were observed across all 3 treatment arms (4%–6%). Measures of reversible motor side effects improved in all 3 groups over the course of treatment. Only 2% of patients spontaneously reported pain at the injection site, and subjective ratings using a visual analogue scale were low following the first injection and decreased over time.

Injection-site pain and irritation were also examined in a 10-week, double-blind, placebo-controlled study²⁴ of 3 doses (25, 50, and 75 mg) of long-acting risperidone injections given every 2 weeks to 182 patients. Investigators reported that redness, swelling, and induration were absent in at least 95% of patients and pain in at least 70% within 5 minutes after the injection (Figure 6). Patients in all 3 dosage groups reported only minimal pain after the first injection and even less pain after the fifth injection (Figure 7).

CONCLUSION

Taken together, these results suggest that the long-acting injectable form of risperidone is safe, well-tolerated, and at least as efficacious as oral risperidone. Although dosage requirements will most likely vary between individuals, it appears that for most patients doses of 25 to 50 mg every 2 weeks are likely to be optimal.

The availability of a long-acting atypical antipsychotic provides a major opportunity to enhance disease management in schizophrenia.

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

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

REFERENCES

- Kane JM. Schizophrenia. *N Engl J Med* 1996;334:34–41
- Robinson D, Woerner M, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry* 1999;56:241–247
- Kramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. *Psychiatr Serv* 1998;49:196–201
- Fenton WS, Blyler CR, Heinssen RK. Determinants of medication compliance in schizophrenia: empirical and clinical findings. *Schizophr Bull* 1997;23:637–651
- Walburn J, Gray R, Gournay K, et al. Systematic review of patient and nurse attitudes to depot antipsychotic medication. *Br J Psychiatry* 2001;179:300–307
- Jacobsson L, Odling H. Psykologiska aspekter på depåbehandling vid schizofrena syndrom. *Lakartidningen* 1980;77:3522–3526
- Wistedt B. How does the psychiatric patient feel about depot treatment, compulsion or help? *Nord J Psychiatry* 1995;49(suppl 35):41–46
- Hoencamp E, Knegeting H, Kooy JJS, et al. Patient requests and attitude towards neuroleptics. *Nord J Psychiatry* 1995;49(suppl 35):47–55
- Eastwood N, Pugh R. Long-term medication in depot clinics and patients' rights: an issue for assertive outreach. *Psychiatr Bull* 1997;21:273–275
- Pereira S, Pinto R. A survey of the attitudes of chronic psychiatric patients living in the community toward their medication. *Acta Psychiatr Scand* 1997;95:464–468
- Desai NM, Huq Z, Martin SD, et al. Switching from depot antipsychotics to risperidone: results of a study of chronic schizophrenia. *Adv Ther* 1999;16:78–88
- Dolder CR, Lacro JP, Dunn LB, et al. Antipsychotic medication adherence: is there a difference between typical and atypical agents? *Am J Psychiatry* 2002;159:103–108
- Mahmoud RA, Engelhart LM, Oster G, et al. Risperidone versus conventional antipsychotics: a prospective randomized, naturalistic effectiveness trial of outcomes in chronic schizophrenia. Presented at the 36th annual meeting of the American College of Neuropsychopharmacology; Dec 8–12, 1997; Waikoloa, Hawaii
- Eerdekens M, Rasmussen M, Vermeulen A, et al. Kinetics and safety of a novel risperidone depot. In: *New Research Abstracts of the 153rd Annual Meeting of the American Psychiatric Association*; May 18, 2000; Chicago, Ill. Abstract NR669:238–239
- Kane JM, Eerdekens M, Lindenmeyer J-P, et al. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry* 2003;160:1125–1132
- Kane JM, Eerdekens M, Keith S, et al. Efficacy and safety of Risperdal Consta, a long acting injection risperidone formulation. Presented at the 40th annual meeting of the American College of Neuropsychopharmacology; Dec 9–13, 2001; Waikoloa, Hawaii
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994
- Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261–276
- Guy W. *ECDEU Assessment Manual for Psychopharmacology*. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
- Chue P, Eerdekens M, Augustyns I, et al. Efficacy and safety of long-acting risperidone microspheres and risperidone oral tablets. Presented at the 11th Biennial Winter Workshop on Schizophrenia; Feb 24–March 1, 2002; Davos, Switzerland

21. Fleischhacker WW, Eerdeken M, Xie Y, et al. Long-term safety and efficacy of long-acting injectable risperidone. Presented at the 35th annual meeting of the American College of Neuropsychopharmacology; Dec 9–13, 2001; Waikoloa, Hawaii
22. Lasser R, Bossie CA, Zhu Y, et al. Does constant therapy infer optimal efficacy in schizophrenia? moving to an advanced pharmacotherapeutic option [poster]. Presented at the 41st annual meeting of the American College of Neuropsychopharmacology; Dec 10, 2002; San Juan, Puerto Rico
23. Gharabawi G, Lasser R, Bossie CA, et al. Enhanced one-year outcomes with three doses of long-acting injectable risperidone in 336 chronically psychotic, stable patients switched from oral risperidone [poster]. Presented at the 41st annual meeting of the American College of Neuropsychopharmacology; Dec 9, 2002; San Juan, Puerto Rico
24. Lasser RA, Ramstack JM, Grandolfi GP, et al. Long-acting injectable risperidone (Risperdal Consta): manufacture using medisorb microsphere technology, pharmacokinetics, and injection-site assessments [poster]. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa