

Hospitalization Rates in Patients During Long-Term Treatment With Long-Acting Risperidone Injection

Pierre Chue, MBBCh*

Pierre-Michel Llorca, MD†

Inge Duchesne, MA‡

Adriane Leal, MD§

Dominique Rosillon, PhD||

Angelika Mehnert, PhD¶

*Clinical Associate Professor, University of Alberta, Edmonton, Canada

†Hôpital Gabriel Montpied, Clermont Ferrand, France

‡Director, CNS Health Economics, Janssen Pharmaceutica NV, Beerse, Belgium

§Biostatistician, SGS Biopharma SA, Wavre, Belgium.

||Head Biometrics, SGS Biopharma SA, Wavre, Belgium

¶Director, CNS Health Economics, Janssen Pharmaceutica NV, Beerse, Belgium

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ABSTRACT

Background: Patients with schizophrenia or schizoaffective disorder are at high risk of relapse, which may lead to hospitalization.

Objective: To assess hospitalization rates during 1 year of treatment with long-acting risperidone injection.

Subjects, Materials, and Methods: The study was a 1-year, international, open-label trial of long-acting risperidone injection in inpatients and outpatients classified as stable. Patients had to have been receiving a stable dose of their current antipsychotic medication for at least 4 weeks before entering the study. After a 2-week run-in (oral risperidone, 1-6 mg/day), patients entered a 12-month, open-label phase in which they received long-acting risperidone injection

25 mg, 50 mg, or 75 mg, every 2 weeks, depending on their previous dose of oral risperidone. Oral risperidone supplementation was supplied for the first 2 to 3 weeks. The dose of long-acting risperidone injection could be increased or decreased by the investigator if necessary.

Results: Of 397 patients who received a modal dose of long-acting risperidone injection, 25 mg or 50 mg (the commercially available dose range), 24% were inpatients and 76% were outpatients at baseline. The number of patients requiring hospitalization decreased continuously and significantly, from 38% in the 3 months before treatment to 12% during the last 3 months of treatment ($P < 0.001$). Of baseline inpatients, 71% were discharged during treatment. Overall, the 1-year re-hospitalization rate was 17.6%, with a rate of 15.9% for baseline outpatients. The rates of psychiatric hospitalizations were 15.4% and 14.3% for all patients and outpatients, respectively.

Conclusions: The need for hospitalization was significantly reduced in outpatients and inpatients with stable schizophrenia or schizoaffective disorder who received long-acting risperidone injection.

INTRODUCTION

Schizophrenia and schizoaffective disorder are chronic conditions in which relapses are likely to occur throughout the patient's life.^{1,2} During a relapse, the patient may need to be admitted to hospital for acute treatment to bring psychotic symptoms under control.

Relapses impact upon the course of the illness leading to poorer outcome, treatment refraction, and a delayed or reduced likelihood of recovery.^{3,4} In addition, relapse and hospitalization account for a significant proportion of healthcare costs in schizophrenia and schizoaffective disorder. Only about 10% of patients with schizophrenia require long-term hospital or intensive community care, but this care accounts for 74% of the direct costs of the illness.⁵ The cost of a single relapse has been estimated to be about GBP10,000 (approximately US\$16 000) in the UK.⁶ In the United States, the total cost of re-hospitalizations that occur within 2 years after discharge for patients with schizophrenia is about \$2 billion.⁷ In a Canadian study, the total cost (direct and indirect) of schizophrenia was \$2.35 billion and psychiatric hospitalizations accounted for 10% of this total.⁸

In patients not receiving antipsychotic medication, relapse rates are very high. Even in patients receiving continuous medication, estimates suggest that 3.5% of patients will relapse per month, with the rate rising to 11% per month in noncompliant patients.⁷ This can lead to 1-year relapse rates approaching 70%. The introduction of antipsychotic treatment in the 1950s led to a reduction in relapse rates, although rates reported in

clinical trials with conventional antipsychotic agents could still be as high as 40% to 50% per year.^{9,10} Conventional depot formulations (introduced in the 1960s) can reduce relapse and hospitalization rates compared with their oral equivalents.^{11,12} Whereas part of this effect is a result of the increased adherence to treatment regimens that is seen in patients receiving depot medication,¹³ depot medications have a number of other advantages, including an improved pharmacokinetic profile (lower peak drug levels may reduce the frequency of dose-related side effects), continuous delivery of medication, and bypass of the extensive first-pass metabolism undergone by oral agents.¹⁴

Conventional depot agents are, however, associated with the same clinical challenges as conventional oral agents, with patients on long-term depot treatment often experiencing residual psychotic symptoms.^{15,16} Conventional depot agents are also associated with the same range of potentially serious side effects—such as higher risk of motor side effects and tardive dyskinesia—as their oral equivalents.¹⁷ The “atypical” antipsychotics, introduced in the 1990s, have a safety and tolerability profile that is superior to that of conventional agents, particularly with regard to motor side effects.^{18,19} The atypical agents are also more effective than conventional antipsychotics in reducing relapse rates and preventing hospitalization,²⁰⁻²² although they possess many of the limitations of oral medication, such as low treatment adherence and fluctuating serum drug levels. Indeed, the lack of a long-acting, injectable formulation of an atypical agent has meant that the options available to psychiatrists for safe and effective long-term treatment of their patients are limited.

Long-acting risperidone injection is the first long-acting, injectable formulation of an atypical antipsychotic. The

efficacy of long-acting risperidone injection in treating the symptoms of schizophrenia and schizoaffective disorder has been demonstrated in both short- and long-term trials.^{23,24} In the present study, we assessed hospitalization rates during 1 year of treatment with long-acting risperidone injection in patients with schizophrenia or schizoaffective disorder.

SUBJECTS, MATERIALS, AND METHODS

Hospitalization rates were assessed as part of a 1-year, international, open-label trial of long-acting risperidone injection (25 mg, 50 mg, or 75 mg, every 2 weeks).²³ Safety and efficacy data from the trial have been presented previously in detail.²³ In this paper, hospitalization results for the commercially available dose range of long-acting risperidone injection (25 mg and 50 mg) are presented.

Patients

Patients were at least 18 years of age with a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV criteria.²⁵ Patients could be inpatients or outpatients, but their condition was required to be “stable” as judged by the investigator, and they had to have been receiving a stable dose of their current antipsychotic medication for at least 4 weeks before entering the study. Participants were required to be in good general health, with blood biochemistry, hematology and urinalysis tests within the laboratory’s reference range. Patients with values outside the reference range could be included if the test results were considered by the investigator to be not clinically relevant.

Patients were excluded if they had a diagnosis of substance abuse or dependence within 3 months of starting the trial, or had a history of tardive dyskinesia, neuroleptic malignant syndrome, drug allergy or hypersensitivity. Patients

with documented disease of the central nervous system, acute, unstable or untreated somatic disease, or a clinically significant electrocardiogram were also excluded, as were women who were pregnant, breast-feeding or without adequate contraception. Patients who were expected to require antipsychotics other than risperidone to control their symptoms, those who had participated in an investigational drug trial within the 30 days before selection, those known to be unresponsive to risperidone and those treated with a depot antipsychotic within one treatment cycle of screening, or with clozapine within 2 months of screening, were also ineligible to participate in the trial.

Written informed consent was obtained from each patient, or the patient’s guardian or legal representative. The final protocol and relevant amendments were reviewed and approved by independent ethics committees. The trial was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki and its subsequent revisions.

Trial Design

Before treatment with long-acting risperidone injection was started, patients entered a 2-week run-in, during which antipsychotics other than risperidone were discontinued. During this run-in period, all patients received oral risperidone, 1 to 6 mg/day, at a dose determined by the investigator. Baseline assessments were performed at the end of the 2-week run-in.

During the 12-month open-label phase, patients received long-acting risperidone injection, 25 mg, 50 mg, or 75 mg, every 2 weeks, with the initial dose depending on the dose of oral risperidone at the end of the run-in period (1-2 mg/day oral risperidone □ 25 mg; 3-4 mg/day oral risperidone □ 50 mg; 5-6 mg/day oral risperidone □ 75 mg). Oral

Table 1. Patient Baseline Characteristics

	Long-acting risperidone injection 25 mg or 50 mg
Sex, n (%)	
Male	249 (63)
Female	148 (37)
Age, years	
Mean \pm SD	43.6 \pm 15.2
Range	18-84
Hospitalization status, n (%)	
Inpatient	96 (24)
Outpatient	301 (76)
Diagnosis, n (%)	
Schizophrenia	329 (83)
Schizoaffective disorder	68 (17)

risperidone supplementation at the same dose as at the end of the run-in period was mandatory for the first 2 to 3 weeks of treatment with long-acting risperidone injection. During the trial, the dose of long-acting risperidone injection could be increased by 25 mg (from 25 to 50 mg or from 50 to 75 mg) if the patient experienced psychotic symptoms and had no or only minimal extrapyramidal symptoms. This increase in dose could take place only at scheduled visits. The dose of risperidone depot could also be reduced by 25 mg (from 75 to 50 mg or from 50 to 25 mg) during the trial at the investigator's discretion.

Safety and efficacy data from the trial have been presented previously.²³ In this paper, hospitalization results for the commercially available dose range of long-acting risperidone injection (25 mg and 50 mg) are presented.

Hospitalization

Information on hospitalizations in the previous 3 months was collected at baseline, and every 3 months thereafter. As

with several previous studies,^{7,26-28} the re-hospitalization rate was used as a proxy measure of relapse. For patients who were outpatients at baseline, "re-hospitalization" was defined as the first hospitalization, whereas for those who were inpatients at baseline it was defined as the first new hospitalization after discharge. Separate analyses were carried out for psychiatric hospitalizations and

Table 2. Frequency Distribution of the Number of Hospitalizations for Any Reason (including baseline hospitalization) Required During 1 Year of Treatment With Long-Acting Risperidone Injection

Number of hospitalizations	Number of patients n (%)
0	253 (64)
1	116 (29)
2	24 (6)
3 or more	4 (1)

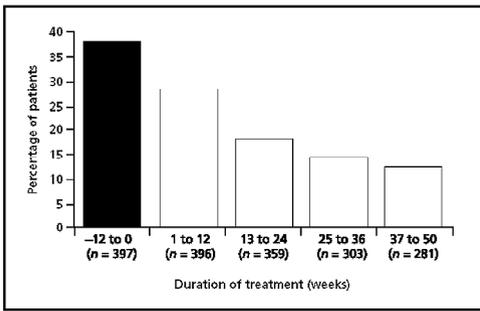


Figure 1. Percentage of patients hospitalized prior to and during 1 year of treatment with long-acting risperidone injection (n = number of patients in each period; $P < 0.0001$ for change over time).

hospitalizations for any reason (including those for psychiatric reasons, other medical conditions and social reasons).

Statistical Analysis

Hospitalization rates were computed for the 3 months before treatment with long-acting risperidone injection and for each 3-month period during treatment. Over-time comparisons were carried out using Generalized Estimating Equations (GEE).²⁹ GEE were computed using the SAS GENMOD procedure, version 8.2.³⁰ The average rate per 3-month period during treatment was compared with the rate during the 3 months before treatment using an appropriate contrast.

The crude rate of hospitalization is the proportion of patients who were re-hospitalized, compared with the total number of patients at baseline. The Kaplan-Meier (K-M) rate of re-hospitalization is the rate estimated from the K-M survival curves after 365 days of treatment. K-M estimates were calculated using the SAS LIFETEST procedure, version 8.2.³⁰

RESULTS

In total, 397 patients who received a modal dose of long-acting risperidone injection, 25 mg or 50 mg, every 2 weeks, were included in the analysis. Baseline characteristics are shown in Table 1. At baseline, 96 patients (24%) were hospitalized and 301 (76%) were outpatients. A total of 281 (71%) patients completed all five scheduled assessments, 63% of those who were inpatients at baseline, and 73% of outpatients.

Concomitant medications were used by 86% of patients in the trial. The most commonly used medications were sedatives (54% of patients), anticholinergics (30%), analgesics (27%), antidepressants (16%), systemic antibacterial agents (16%), muscle relaxants (13%), ophthalmologicals (12%), and anti-epileptics (10%).

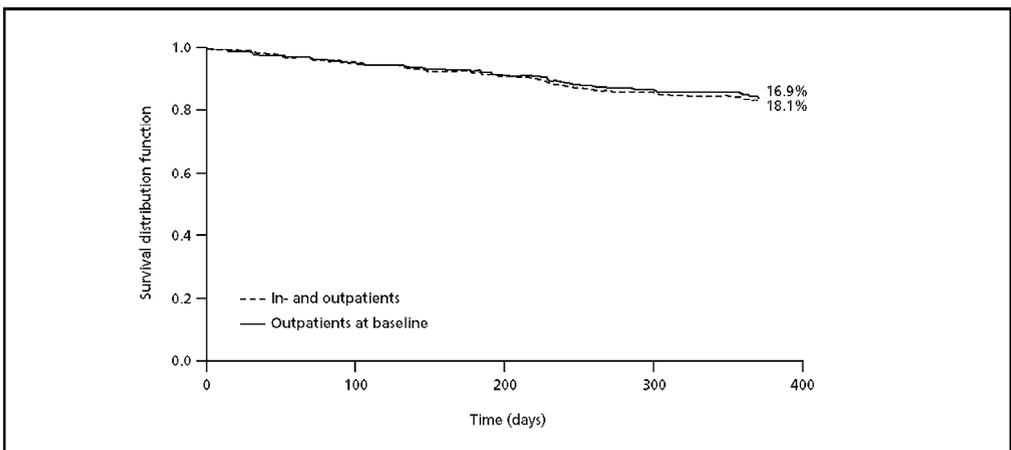


Figure 2. One-year Kaplan-Meier survival curves for psychiatric hospitalization in patients receiving long-acting risperidone injection.

Table 3. Percentage of Patients Requiring Re-Hospitalization During 1 Year of Treatment With Long-Acting Risperidone Injection

Patient group	n	Re-hospitalization rate (%)	
		Crude	Kaplan-Meier
<i>All patients</i>			
All hospitalizations			
Outpatients	301	15.9	18.8
Overall	369	17.6	20.5
Psychiatric hospitalizations			
Outpatients	301	14.3	16.9
Overall	369	15.4	18.1
<i>Non-elderly patients*</i>			
All hospitalizations			
Outpatients	275	16.4	19.1
Overall	335	18.2	20.9
Psychiatric hospitalizations			
Outpatients	275	14.9	17.4
Overall	335	16.4	19.0

*Aged < 65 years (n = 335).

Hospitalization

Including those patients who were hospitalized at baseline, 144 patients (36%) required at least one hospitalization during 1 year of treatment with long-acting risperidone injection (Table 2). Of the 301 patients who were outpatients at baseline, only 15.9% required hospitalization for any reason during the study. Overall, 80% of hospitalizations were for psychotic illness.

Hospitalization rates during treatment were significantly lower than before the treatment period ($P < 0.0001$) and, moreover, the rate of hospitalization decreased continuously during treatment with long-acting risperidone injection, from 38% during the 3 months immediately before study entry to 12% during the last 3 months of treatment ($P < 0.0001$; Figure 1). Of the 96 patients hospitalized at baseline, 68 (71%) were

discharged from hospital at some point during the trial.

Re-Hospitalization

Of the 96 patients who were hospitalized at baseline, 28 were not discharged and did not, therefore, contribute to the re-hospitalization analysis. The 1-year re-hospitalization rates (crude and K-M estimates) are shown in Table 3. Overall, the 1-year crude rate of re-hospitalization for any reason was 17.6%, with the rate for those who were outpatients at baseline being 15.9%. When only psychiatric hospitalizations were considered, the overall crude 1-year re-hospitalization rate was 15.4% (K-M risk, 18.1%; Figure 2).

Given the age range of the study population, a subgroup analysis was performed and re-hospitalization rates were assessed specifically for the patients

below 65 years of age; ($n = 335$). The re-hospitalization rate in this group was 18.2%, while the rate of psychiatric re-hospitalization was 16.4% (Table 3).

DISCUSSION

During 1 year of treatment with long-acting risperidone injection, the need for hospitalization decreased continuously and significantly, with a hospitalization rate of only 12% in the last 3 months. Although 3 months may be considered a short period for the assessment of pre-trial hospitalization, the fact that patients were classified as stable suggests that substantial changes in disease severity or artificially inflated hospitalization rates in the pre-trial period are unlikely. Moreover, the results of the study show a continual decrease in hospitalization over time throughout the study.

The decrease in hospitalization rate did not seem to be related to patients dropping out of the study. The reasons for early discontinuation included withdrawal of consent (14.3%), insufficient response (7.8%), and adverse events (4.9%).²³ The dropout rate was low at 35% with respect to the length of treatment, and was similar in out patients and inpatients.²³ Importantly, a high proportion of patients who were hospitalized at baseline improved sufficiently to be discharged from the hospital after starting treatment with long-acting risperidone injection, despite being classed as “stable” at baseline.

Numerous trials have shown that conventional antipsychotic agents are capable of reducing relapse rates in patients with schizophrenia. In patients receiving conventional agents, reported 1-year relapse rates are generally in the range of 30% to 40%,^{10,20,22,27,31} although some authors report rates of around 50% in certain patient populations, such as those who were noncompliant,⁷ those living in stressful environments¹⁰ and

those with a history of five or more episodes.¹⁰ With oral atypical antipsychotics, relapse rates can be reduced to around 20% to 30%.^{20,22,26,27,31,32} The patients included in these studies of conventional or atypical agents were generally outpatients, and all the studies looked at psychiatric hospitalizations only. Furthermore, some studies included only patients who responded to initial, acute-phase treatment,^{22,26,27,31} or restricted participants to those below 65 years of age.^{20,26,27}

The 1-year re-hospitalization rates seen with long-acting risperidone injection (K-M rate estimates in the various subpopulations of 18.8% to 20.9% when considering hospitalizations for all reasons, and 16.9% to 19.0% when considering psychiatric hospitalizations only) were lower than those reported for both conventional antipsychotics and oral atypical agents, regardless of the subgroup analyzed. Thus, the relapse rates in a subgroup of patients below 65 years of age receiving long-acting risperidone injection were only slightly higher than those for the overall group. This may be an artefact of patient selection in this trial, although the results are consistent with those obtained from an analysis of the Medicaid database in California, which suggests that younger age is an independent risk factor for hospitalization.³³ As the present study was open-label and uncontrolled, comparative, controlled trials are now needed to define fully the benefits of long-acting risperidone injection on hospitalization rates, compared with other antipsychotic agents.

In conclusion, the need for hospitalization was significantly reduced in outpatients and inpatients with schizophrenia or schizoaffective disorder who received long-acting risperidone injection. Hospitalization rates in patients receiving long-acting risperidone injection were lower than those

generally reported in the literature for conventional and oral atypical antipsychotics.

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