Risperidone Long-Acting Injection in the Treatment of Schizophrenia Spectrum Illnesses: A Retrospective Chart Review of 19 Patients in the Vancouver Community Mental Health Organization (Vancouver, Canada)

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ABSTRACT

Background: Schizophrenia is a chronic debilitating disease that affects ~110,000 Canadians (0.55% lifetime prevalence). Risperidone long-acting injection (RLAI) is the first injectable, long-acting, atypical antipsychotic drug marketed in Canada.

Objective: The aim of this study was to assess the clinical effectiveness and hospitalization rates of patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder treated with RLAI in a community mental health care setting.

Methods: Data were collected between August 1, 2006 and September 30, 2006 via a retrospective chart review of outpatients diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder who received treatment from 1 of the 8 mental health teams within the Vancouver Community Mental Health Organization (VCMHO) in Vancouver, British Columbia, Canada. Collected data included: frequency and duration of institutional care, discharge and relapse rates, demographic variables, diagnosis history, RLAI medication history, and history of other medications. The overall severity of symptoms before and after RLAI treatment and the improvement in symptoms during
treatment were evaluated using the Clinical Global Impression Scales for severity (CGI-S) (1 = not ill to 7 = extremely ill) and improvement (CGI-I) (1 = very much improved to 7 = very much worse).

**Results:** Forty-four patients were identified as having received RLAI. The charts of 19 patients (10 men, 9 women; mean [SD] age at time of chart audit, 36.7 [11.7] years; mean [SD] age at primary diagnosis, 23.6 [7.4] years; race: white, 10 [52.6%]; Asian, 6 [31.6%]; American Indian, 1 [5.3%]; black, 1 [5.3%]; other, 1 [5.3%]) were included in the analysis. The majority of patients (78%) had been treated with another antipsychotic drug prior to treatment with RLAI: risperidone (77%), quetiapine (47%), zuclopenthixol (43%), olanzapine (43%), and loxapine (17%). Mean (SD) CGI-S Scale score declined significantly from 5.29 (1.3) before treatment initiation to 3.05 (1.0) posttreatment ($P = 0.001$). Mean (SD) CGI-I Scale score was 2.58 (0.71) ($P < 0.001$); 94% of patients had a CGI-I score ≤3. Mean (SD) duration of hospitalization decreased significantly from 15.7 (19.7) days before treatment to 2.4 (6.0) days after treatment ($P < 0.05$). Mean (SD) number of hospitalizations also decreased significantly from 2.0 (1.8) before treatment to 0.5 (1.3) after treatment ($P < 0.01$).

**Conclusions:** The results of this pilot study suggest that use of the atypical-antipsychotic medication RLAI significantly decreased duration and rates of hospitalization, compared with baseline, in these VCMHO patients with schizophrenia spectrum illnesses. *(Curr Ther Res Clin Exp. 2007;68:409–420)*

**Key words:** schizophrenia, atypical antipsychotics, hospitalization, risperidone long-acting injection, relapse.

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**INTRODUCTION**

Schizophrenia is a chronic debilitating disease that affects ~110,000 Canadians (0.55% lifetime prevalence). Schizophrenia often manifests in early adulthood, and the majority of patients (50%–70%) have chronic relapses, with high morbidity and above-average mortality. Patients with schizophrenia have been reported to have an increased risk for suicide, violence, substance abuse, homelessness, and victimization. The chronic nature of this disease requires continuous management.

Schizophrenia is characterized by a high rate of relapse. Once relapse occurs, hospitalization is usually required to bring symptoms under control. Relapses typically result in poorer mental health outcomes, including higher probability of relapse, reduced or delayed likelihood of recovery, and treatment refractoriness for the patient.

Health care costs in schizophrenia are disproportionately high. Although the illness affects ~1% of the population, it accounts for up to 3% of health care expenditure. The high economic cost of schizophrenia is due to the nature of the disease, with its early onset, lifetime duration, and, in particular, the high rate of hospitalization. Seventy-nine percent of the direct costs
of schizophrenia result from hospitalization or other residential care,\textsuperscript{9} while medications represent only a small fraction (1\%-6\%) of the total cost.\textsuperscript{10} In Canada, the total direct and indirect costs for 1 year (1996) were estimated to be Can $2.35 billion.\textsuperscript{5} Patients who do not adhere to antipsychotic medication have high rates of relapse.\textsuperscript{1-13} Within 2 years of nonadherence, the relapse rate in patients rises to >80\%.\textsuperscript{14} Risk of relapse over a period of 6 months to 2 years has been quantified in a review\textsuperscript{15} of 7 studies of patients with schizophrenia. In that study, patients who were nonadherent to medication relapsed at a rate 2.7 times higher than those patients who were adherent. Clearly, one of the consequences of relapse is hospitalization; the 1-year rehospitalization rate for nonadherent patients with schizophrenia is \~80\%.\textsuperscript{13,16,17}

Relapses have an impact on future long-term prognosis and a profound impact on a patient’s quality of life.\textsuperscript{18-20} Each time a patient relapses and becomes acutely psychotic, they are unable to return to the same level of functioning they experienced before the exacerbation.\textsuperscript{21} In addition, with each subsequent psychotic episode, the time to remission has been found to increase substantially.\textsuperscript{22} Consequently, treatment is aimed at preventing acute episodes or relapses.\textsuperscript{20,23} However, many factors impact relapse prevention, including the effectiveness of the drug treatment, the tolerability of the drug treatment, and medication adherence.\textsuperscript{15}

Risperidone long-acting injection* (RLAI) is the first injectable, long-acting, atypical antipsychotic drug marketed in Canada.\textsuperscript{24} The drug is administered intramuscularly to the gluteal muscle at a starting dose of 25 mg and may be increased to 37.5 mg or 50 mg biweekly. A therapeutic amount of the medication is released steadily over several weeks. The efficacy of RLAI with respect to cognitive functioning (Clinical Global Impression-Improvement [CGI-I] Scale,\textsuperscript{25} Positive and Negative Symptom Scale\textsuperscript{26}), adverse events (Extrapyramidal Symptom Scale),\textsuperscript{27} and resource utilization (rehospitalization rates, length of stay) has been reported in both long- and short-term clinical trials.\textsuperscript{10,28-32}

RLAI has been used at the Vancouver Community Mental Health Organization (VCMHO) since the summer of 2005. This pilot study was intended to avoid some of the limitations of a tightly controlled clinical trial to provide a preliminary assessment of RLAI by retrospectively examining clinical improvement and hospitalization rates in our institution. Its purpose was to aid decision makers in pursuing efficient and effective treatment of individuals with schizophrenia, schizoaffective disorder, or schizophreniform disorder. We hypothesized that treatment with RLAI would be effective in reducing hospitalization rates and improving clinical symptoms.

*Trademark: Risperdal\textsuperscript{©} Consta\textsuperscript{©} (Janssen LP, Titusville, New Jersey).
PATIENTS AND METHODS
The study protocol was approved by the VCMHO’s research advisory committee and ethical approval was received. The study was conducted in accordance with the Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki.

In this naturalistic, retrospective, non-randomized, within-patient study, patients served as their own controls. The intervention was the introduction of the atypical antipsychotic medication RLAI. Patient demographic characteristics collected included age, gender, diagnosis, and number of previous psychiatric admissions.

Data were collected via a retrospective chart review of current outpatients treated by 1 of the 8 mental health teams in the VCMHO in Vancouver, British Columbia, Canada, between August 1, 2006 and September 30, 2006. Male and female patients aged 19 to 65 years who were outpatients were eligible for the study if they had a diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. In addition, they had to have been started on RLAI treatment during their last hospital inpatient admission and had to have continued RLAI treatment for >90 days.

We used 4 sources of data for the chart review: (1) the physical chart maintained by the patient’s mental health team; (2) the patients’ case-manager interviews; (3) the patient care information system; and (4) the primary access regional information system (PARIS). These data sources contained case histories, hospitalizations, registrations, referrals, assessments, case notes, care plans, and scheduling of ongoing treatment information. The last 2 sources of data are electronic databases maintained by Vancouver Coastal Health (Vancouver, British Columbia, Canada) and the VCMHO.

The overall severity of symptoms before and after RLAI treatment and the improvement in symptoms during treatment were gauged by the CGI-Severity (CGI-S) Scale (1 = not ill to 7 = extremely ill) and the CGI-I Scale (1 = very much improved to 7 = very much worse), respectively. All ratings were completed by a single rater with CGI Scale certification who, because of the nature of this retrospective chart review, was not blinded to the patients’ treatment. Patients were rated according to the assessment and follow-up notes written by the treating psychiatrist that were found in the PARIS database, in their medical charts, and in their case-manager interviews.

Data Collection
A patient medication and history instrument was developed. The instrument contained separate sections for the following: (1) frequency, location, and duration of institutional care; (2) discharge and relapse rates; (3) demographic variables (age, sex, ethnicity, socioeconomic status); (4) diagnosis history (primary diagnosis, secondary diagnosis, comorbid conditions); (5) RLAI medication history (date of first injection, injection frequency, date of last injection); and (6) previous and concurrent antipsychotic medications.
The PARIS database was used to generate a list of patients who had received RLAI in the VCMHO. The data were collected by a trained research assistant and entered into an Access database (Microsoft Corporation, Seattle, Washington). As the selection criteria for inclusion in the review were a diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder and treatment with RLAI, data could not be collected in a blind manner. However, all identifying data were extracted, with each patient's chart being issued a unique code number and all information gathered from the chart being identified by this number.

If a significant number of patients had extended psychiatric histories compared with the length of RLAI treatment, comparing these unequal periods could lead to erroneous conclusions. Therefore, a comparison of hospitalization rates during identical periods before and after treatment was calculated.

Statistical Analysis
The data were analyzed using a paired Student t test and z score for proportion, depending on the nature and distribution of the data. All data were screened for normality, homogeneity of variance, and outliers. Statistical significance was set at P < 0.05. All statistical analyses were conducted using SPSS version 14.0 (SPSS Inc., Chicago, Illinois). As this was a preliminary pilot study, no power calculation was performed. All data are reported as mean (SD).

RESULTS
Forty-four patients were identified as having received treatment with RLAI, and 19 (10 men, 9 women) of these met the inclusion criteria. The mean (SD) age at time of chart audit was 36.7 (11.7) years. The mean age at primary diagnosis of schizophrenia was 23.6 (7.4) years, with most patients being white (10 [53%]) or Asian (6 [32%]). The majority of patients were diagnosed with schizophrenia (13 [68%]), followed by schizoaffective disorder (5 [26%]), and schizophreniform disorder (1 [5%]) (Table I).

Figure 1 shows the percentage of patients taking other drugs, by drug category, before and after treatment with RLAI. Before initiation of RLAI, the majority of patients (78%) had been treated with an antipsychotic medication, followed by mood stabilizers (39%), antidepressants (28%), sedatives (17%), and anticholinergic drugs (28%). The percentage change for each drug category before and after commencing RLAI was not found to be significantly different. The most common medications prescribed prior to RLAI treatment were oral risperidone (77%), quetiapine (47%), zuclopenthixol (43%), olanzapine (43%), and loxapine (17%).

The mean (SD) RLAI treatment period was 235.6 (162.6) days (Table I). At the time of the chart audit, all 19 patients were still receiving RLAI. The number of patients receiving 25 mg, 37.5 mg, or 50 mg as a function of their initial dose versus final study dose is shown in Figure 2. The majority of patients were
Table I. Demographic and clinical characteristics (N = 19).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of chart audit, y</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>36.7 (11.7)</td>
</tr>
<tr>
<td>Range</td>
<td>18–54</td>
</tr>
<tr>
<td>Age at primary diagnosis, y</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>23.6 (7.4)</td>
</tr>
<tr>
<td>Range</td>
<td>16–44</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10 (52.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>6 (31.6)</td>
</tr>
<tr>
<td>American Indian</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Primary diagnosis, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>13 (68.4)</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Schizophreniform disorder</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Duration of RLAI therapy, d</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>235.6 (162.6)</td>
</tr>
<tr>
<td>Range</td>
<td>94–771</td>
</tr>
</tbody>
</table>

RLAI = risperidone long-acting injection.

receiving a dose of 25 mg at both initial treatment and final study treatment. Although there was a shift in the number of patients receiving differing initial and final doses of RLAI, the differences were not statistically significant.

Pretreatment initiation and posttreatment initiation RLAI CGI-S Scale scores were examined using a paired t test. Two patients were excluded from the analysis due to insufficient case notes to calculate a CGI-S or CGI-I score. The mean (SD) CGI-S score declined significantly from 5.29 (1.3) to 3.05 (1.0) (t16 = 7.36; P < 0.001), indicating a movement from the severe range to the mild range (Figure 3). Mean CGI-I score suggested an overall improvement (2.58 [0.71]). Using a categorical definition of CGI-I of ≤3, 16 of the 17 patients (94%) showed improvement (z = 8.8; P < 0.001).

Treatment with RLAI was well tolerated, and no serious adverse events (AEs) were observed. Three patients (15.8%) experienced AEs (sedation [1 patient], impotence [1], and akathisia [1]). Prolactin concentration, Abnormal Involuntary Movement Scale (AIMS) scores, and weight measurements were not available at the time of the chart audit.

A significant number of patients (84%) had extended psychiatric histories in comparison to the length of their RLAI treatment. Because comparison of
Figure 1. Percentage of patients with a schizophrenia spectrum illness receiving treatment with other drugs prior to and during treatment with risperidone long-acting injection (RLAI) (N = 19).

Figure 2. Initial and final doses in patients with a schizophrenia spectrum illness treated with risperidone long-acting injection (N = 19).
these unequal periods might have led to erroneous results, a comparison of hospitalization rates during identical periods before and after treatment was calculated. For each patient, the duration of the pre-RLAI assessment period was defined by the duration of treatment with RLAI. The hospitalization data were examined using a paired Student t test. The mean (SD) duration of hospitalization decreased from 15.7 (19.7) to 2.4 (6.0) days ($t_{18} = 2.78; P < 0.05$). Similarly, the mean number of psychiatric hospitalizations decreased from 2.0 (1.8) before RLAI treatment to 0.5 (1.3) after RLAI treatment ($t_{18} = 2.89; P < 0.01$) (Table II).

<table>
<thead>
<tr>
<th>Duration of psychiatric hospitalizations, mean (SD), d</th>
<th>Pre-RLAI (n = 19)</th>
<th>Post-RLAI (n = 19)</th>
<th>$t_{18}$</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric hospitalizations, mean (SD), no.</td>
<td>15.7 (19.7)</td>
<td>2.4 (6.0)</td>
<td>2.78</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>2.0 (1.8)</td>
<td>0.53 (1.3)</td>
<td>2.89</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

RLAI = risperidone long-acting injection.  
*Paired 2-tailed Student t test.
DISCUSSION
In a systematic chart review of all patients with a clinical diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder treated with RLAI in the VCMHO, we found a moderate response in controlling symptoms in the majority of these patients. There were clinically relevant and statistically significant improvements in disease state and functioning, as measured by the CGI-S and CGI-I Scale scores. Pretreatment initiation and posttreatment initiation CGI-S ratings for RLAI treatment suggested a statistically significant movement from the severe (5.29 [1.3]) to the mild (3.05 [1.0]) range and were consistent with previously published studies. Similarly, CGI-I scores showed an overall positive result (mean score, 2.58 [0.71]), with 94% of patients scoring ≤3. The clinical improvement was also noted by case managers and considered to be high quality.

The number of hospitalizations and the duration of hospitalization have been suggested to be indicators of relapse. During treatment with RLAI, the total mean duration of hospitalization decreased from 15.7 (19.7) days to 2.4 (6.0) days and the mean number of hospitalizations decreased from 2.0 (1.8) to 0.53 (1.3). Despite the limited total mean duration of RLAI treatment (235.6 [162.6] days), these findings suggest that there was a reduction in patient relapse.

RLAI treatment was well-tolerated, with no reports of serious AEs. The most common AEs were sedation, impotence, and akathisia, reported in 1 patient each. Sedation was considered mild and well-tolerated. The severity of AEs, as measured by AIMS or Extrapyramidal Side Effect Rating Scale, were unavailable, as were the relationship of AEs to dose. Although weight gain is generally modest in patients taking RLAI, it can be significant in a minority of these patients. Unfortunately, in the present review, weight was not adequately quantified to allow for analysis.

Limitations
The data presented were derived from a retrospective chart review and, as such, were subject to observation and assessment bias. In addition, 22% of patients had not been treated with an antipsychotic drug prior to RLAI treatment. This might have exaggerated the positive effects of RLAI treatment. Other limitations include a lack of AE data and CGI ratings that were calculated by only 1 rater, which might have introduced single-rater bias. Despite the inherent limitations of chart reviews, such data are needed to begin to formulate hypotheses regarding the potential therapeutic use of new treatment approaches, such as RLAI for schizophrenia, in a community mental health setting. The results were cautiously encouraging and indicated the need for more prospective controlled trials with RLAI.

The data presented in this study suggest that the majority of patients initiated on RLAI remained on stable doses with high continuation rates along with concomitant medication. Long-term data with larger sample size are being accrued to further explore these outcomes over time.
CONCLUSIONS
The results of this pilot study suggest that use of the atypical antipsychotic medication RLAI significantly decreased duration and rates of hospitalization, compared with baseline, in these VCMHO patients with schizophrenia spectrum illnesses.

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