One-Year Treatment Continuation in Patients Prescribed Risperidone Long-Acting Injection in New Zealand: A Retrospective Study

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Abstract

Objective: Treatment discontinuation is a major problem in routine clinical settings and is associated with poorer outcomes for conditions like schizophrenia. Risperidone long-acting injection (RLAI) has shown low discontinuation and good tolerability in long-term clinical trials. This retrospective study investigated RLAI continuation in a naturalistic clinical setting in New Zealand. **Methods:** Those starting publicly funded RLAI between October 1, 2005 and October 31, 2006 in five public mental health services were included in the study. Data were retrospectively collected for 443 patients 12 months pre- and post-RLAI initiation. Patient demographics, diagnosis, antipsychotic treatment and treatment setting were obtained from clinical files and patient information systems. **Results:** Patients were mostly male (64%), the mean age was 35.9 years, and were predominantly European (43%) or Māori (29%). Most started RLAI due to adherence issues (77%). Adverse events due to RLAI were reported by 39%; most commonly, extrapyramidal side effects. Fifty-eight percent of patients continued treatment 12 months after starting; patient choice (either refusal or failure to turn up) was the most common reason for discontinuation (54%), followed by lack of efficacy (29%). Alternative antipsychotic treatment was prescribed for 79% of those who discontinued. Regression analysis found continuation was more common for people started in the community, on a compulsory treatment order, with a dose of >25 mg and for non-Māori. **Conclusions:** RLAI appears well-tolerated and over half the patients continued treatment for one year or more. Using treatment continuation as an indicator of effectiveness, RLAI appears to be an effective treatment for people with adherence problems in this real world practice setting.

Key Words: Risperidone Long-Acting Injection, Schizophrenia, Naturalistic, Duration of Treatment

Introduction

Most clinical practice guidelines recommend second-generation antipsychotic (SGA) agents as first-line treatment for schizophrenia and related disorders, including those of the National Institute for Health and Clinical Excel-

lence (NICE), the American Psychiatric Association (APA), the Royal Australian and New Zealand College of Psychiatrists (RANZCP), and the Canadian Psychiatric Association (CPA) (1-4). The introduction of SGA agents has not been without debate as regards their benefits compared with those of the first-generation antipsychotic (FGA) agents. The anticipated advantages of SGA agents in routine clinical practice are reduction in negative symptoms, improved cognition, tolerability, medication adherence and quality of life for people with schizophrenia and related disorders (5, 6).

Nonadherence or discontinuation of antipsychotic treatment has been associated with more negative outcomes in enduring disorders like schizophrenia, primarily because of increased rates of relapse and subsequent hospitalization (7, 8). Long-acting injectable (LAI) first-generation antipsychotics (FGAs) have been associated with improved outcomes (relapse and recurrence prevention) and lower treatment discontinuation rates than oral formulations (7-10).

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Clinical Implications

This study provides important insights into clinical outcome and patient characteristics predicting continuation of risperidone long-acting injection (RLAI) treatment. A continuation rate of 58.3% at one year is indicative of an effective treatment that was generally acceptable for many patients. This effectiveness outcome found in real world, public clinical practice supports the efficacy results found in experimental conditions. Treatment continuation with RLAI was better for those who started treatment in the community, were treated compulsorily, who were of European/Other and/or Pacific ethnicity and had a starting dose of more than 25 mg. The importance of the collaborative relationships between clinician and patient for successful re-engagement in treatment is indicated by the increased likelihood of continuation at one year for those starting RLAI treatment in an outpatient setting and with the support of a compulsory treatment order. Further investigation into the reasons for ethnic differences in continuation rates will provide useful insights into the social and cultural factors influencing treatment adherence.

While LAIs ensure that medication is being taken, they cannot prevent patients from discontinuing treatment. Antipsychotics such as SGAs that are better tolerated (lower risk of extrapyramidal side effects, particularly tardive dyskinesia) and more effective than the older FGAs would be expected to have better continuation rates and improved health outcomes.

The development of LAI formulations of SGA agents was proposed to be a solution to this treatment quandary and, almost a decade after the introduction of oral risperidone, the first LAI SGA agent, risperidone long-acting injection (RLAI), became available. RLAI has demonstrated better efficacy in placebo and equal efficacy in oral risperidone-controlled studies (11, 12). RLAI has also been shown to be as efficacious as another oral SGA agent, olanzapine, in a 12-month controlled study (13). The long-term clinical trials of RLAI have shown low discontinuation rates and good tolerability (13-16), both of which would be expected to translate into improved long-term adherence in routine practice.

More recently, large pragmatic clinical trials such as Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (14), Comparison of Atypicals for First-Episode Psychosis (CAPE) (15), and the European First-Episode Schizophrenia Trial (EUFEST) (16) have been undertaken to investigate effectiveness of oral antipsychotic treatment in schizophrenia under real world conditions. These pragmatic trials used continuation of treatment or time to discontinuation for any reason as the primary outcome measure of effectiveness rather than traditional efficacy criteria such as improvement on scales rating psychopathological symptoms. Overall, relatively short-treatment duration was found for the oral antipsychotics used in these clinical studies, supporting the dilemma facing most clinicians that treatment discontinuation rates are a major problem.

Therefore, duration of continuous drug therapy would seem to be a key tangible measure for health services to investigate when evaluating the effectiveness of new treatments in routine clinical practice, especially as the costs for new medicines increases. To date, there have been few studies examining the effectiveness of RLAI in routine clinical

practice and these have shown variable impact on treatment continuation (20-25).

Risperidone was registered in New Zealand in late 1993, but its use was restricted until February 1999 when, in an attempt by the New Zealand Ministry of Health to meet patient access targets for the new antipsychotics, it gained full government prescription funding subsidy. (Note: in New Zealand, PHARMAC is the Crown entity that manages the pharmaceutical budget on behalf of public district health boards, and decides which medicines are funded by the Government.) In 2003, the LAI formulation of risperidone was licensed in New Zealand. It was not government funded until October 2005 and, therefore, access to this treatment varied throughout the country depending on levels of discretionary health board funding.

The aim of this study was to evaluate likelihood of achieving twelve months of continuous treatment with RLAI in naturalistic clinical settings. These practice settings provided care to a large sample of secondary-care patients who started on RLAI treatment the first year that the medication was government funded in New Zealand. The study was undertaken across five District Health Boards (DHBs) within New Zealand.

Methods

Patients and Setting

This study was set in the Mental Health Services of the three District Health Boards (DHBs) serving the greater Auckland region, and two DHBs serving the area north of Auckland and central Wellington. These five services are referred to as DHB-A, DHB-B, DHB-C, DHB-D and DHB-E in this paper and, in total, provide mental health services to a resident population of approximately 1.6 million (2006 NZ Census [17]). The study received approval from the Ministry of Health and Disability Regional Ethics Committees to be undertaken as an observational audit of practice.

This study retrospectively investigated RLAI treatment continuation for all patients who were approved government funding between October 1, 2005 and October 31, 2006 in

each of the five District Health Boards ($n=627$). The files for each patient were reviewed to confirm that first-time RLAI treatment was started prior to June 1, 2007. This restriction was applied to ensure that 12-month follow-up data were available for all patients at the time of data collection.

All patients who started RLAI while incarcerated (e.g., forensic inpatient setting or prison) or while resident in a long-stay facility (e.g., rest home or rehabilitation unit) were excluded from the study, as these long-term settings were likely to influence treatment continuation as an outcome. Patients who had started RLAI at another DHB in New Zealand or overseas were also excluded.

Data Collection

Study data were extracted by trained researchers from the paper and/or electronic clinical file used in each service and from each DHB's patient electronic information management system. Data were entered directly into a custom-designed SPSS database (Version 15), with predetermined response options used wherever possible to ensure data quality and to facilitate analysis.

The data collection included initiation (time of starting RLAI= T_0), demographics (gender, age, and ethnicity), principal diagnosis (*DSM-IV* [18]), comorbid conditions and duration of mental illness (time, in years, from first contact with a treatment provider). Ethnicity was collected as it was recorded in the patient's clinical file. The principal Axis I diagnosis documented at time of starting RLAI (T_0) was recorded as the major mental disorder. Axis I and II comorbidities were similarly recorded. Documented physical health comorbidities were recorded and also extrapolated from medications prescribed concurrently. At initiation previous treatment history, including oral risperidone, FGA LAIs, and clozapine trials or any documentation of treatment-resistance were recorded. The national clozapine registration database was used to verify that patients had a previous trial of clozapine.

Treatment data (RLAI and all other antipsychotic medication, total daily dose and route of administration) were recorded for the twelve months after RLAI initiation ($T_1=3$ months post-RLAI, $T_2=6$ months post-RLAI and $T_3=12$ months post-RLAI). Reasons for starting RLAI (and for any subsequent discontinuation) were also collected from the patient's clinical notes. If this information was not recorded in the notes, then the researchers attempted to contact either the prescriber or key worker to obtain this information wherever possible. RLAI discontinuation was defined as any break in treatment during the 12-month period where ≥ 3 injections were not administered continuously (pharmacokinetics of RLAI would predict that almost all risperidone would have been eliminated after 6 weeks [19]). Any adverse effects associated with RLAI were

recorded in the 12 months post-RLAI or at discontinuation.

The clinical information was extracted from summaries, case reviews, discharge plans and the multi-disciplinary progress notes. All antipsychotic prescription and RLAI data were recorded from the medication chart and verified in the body of the clinical notes or with duplicate copies of outpatient prescriptions wherever possible. Resource utilization (including cost) outcomes and an explicit review of prescribing practice were also undertaken and are reported elsewhere (20, 21).

Data Analysis

Multiple logistic regression was used to investigate factors associated with the binary outcome variable of RLAI treatment continuation or not at twelve months (T_3) when controlling for other variables in the model. Variables identified in the literature as being associated with continuation were included in the model together with other measured variables found to be associated using univariate tests. The final model included demographic (gender, age, ethnicity), service (DHB) and clinical covariates (primary diagnosis, duration of illness, previous clozapine treatment, previous FGA LAI treatment, treatment setting, compulsory status and RLAI starting dose).

Chi-square and Kruskal-Wallis tests were used to investigate differences in adverse events, reasons for discontinuation, final dose and treatment after discontinuation between continuation groups and ethnic groups. Data analyses were conducted using SPSS (Version 15).

Results

A total of 489 patients from the funding cohort of 627 had medical records documenting that they had started on RLAI treatment (114 did not start RLAI, 19 were missing medical records and 5 had duplicate identifiers). However, 46 were subsequently excluded (42 started RLAI while in a long-stay residential facility, at another DHB, or outside New Zealand, and 4 had potentially started on RLAI as part of a double-blind trial comparing RLAI with paliperidone long-acting injection) leaving a study population of 443 (see Table 1). Most had a diagnosis of schizophrenia, were inpatients at initiation and were being treated compulsorily. They had been unwell for a median of 8 years, and one-third (33.6%) had a documented history of treatment resistance. The most commonly recorded reason for starting RLAI was concern about adherence with medication ($n=343$; 77.4%). RLAI treatment was started with a first dose of 25 mg for the majority of patients ($n=363$; 81.9%).

Continuation of Risperidone Long-Acting Injection

In total, 253 people continued on RLAI treatment for

a minimum of one year. Five patients were transferred to another health service not included in the study while prescribed RLAI, and 4 died while prescribed RLAI; therefore, these nine patients are not included in any further analysis, leaving an evaluable study population of 434. Overall, there

was a continuation rate of 58.3% ($n=253/434$).

Over the 12-month follow-up period, 181 people stopped treatment: 67 (15.4%) stopped in the first 3 months, 47 (10.8%) stopped between 3–6 months, and 67 (15.4%) stopped between 6–12 months.

Table 1 Continuation versus Discontinuation of Risperidone Long-Acting Injection: Comparison of Population

	TOTAL N=443 N	Continuation N=253 N (%)	Discontinuation N=181 [†] N (%)	Logistic Regression Analysis: Continuation at T3 (12 months post-RLAI)	
				Odds Ratio [‡] (95% CI)	P Value
Gender					p=0.067
Male	285	171 (60.6)	111 (39.4)	1	
Female	158	82 (53.9)	70 (46.1)	0.65 (0.41–1.0)	
Age (years)					
Mean (95% CI)	35.9 (12.4)	37.4 (35.9–38.9)	34.0 (32.1–35.8)	1.02 (1.00–1.04)	p=0.112
Median (range)	34 (16–80)	36 (16–79)	32 (17–80)		
Ethnicity					p=0.007**
European/Other	241	150 (62.5)	90 (37.5)	1	
NZ Māori	127	53 (43.8)	68 (56.2)	0.51 (0.30–0.85)	
Pacific Peoples	75	50 (68.5)	23 (31.5)	1.33 (0.72–2.46)	
DHB					p=0.137
DHB-A	118	75 (64.1)	42 (35.9)	1	
DHB-B	98	49 (51.6)	46 (48.4)	0.48 (0.26–0.88)	
DHB-C	97	52 (55.3)	42 (44.7)	0.56 (0.30–1.05)	
DHB-D	80	53 (67.1)	26 (32.9)	0.85 (0.44–1.63)	
DHB-E	50	24 (49.0)	25 (51.0)	0.63 (0.30–1.34)	
Primary Diagnosis					p=0.133
Schizophrenia	298	175 (59.9)	117 (40.1)	1	
Schizoaffective	61	41 (67.2)	20 (32.8)	1.35 (0.72–2.55)	
Bipolar	25	13 (52.0)	12 (48.0)	0.65 (0.26–1.62)	
Other Disorders	59	24 (42.9)	32 (57.1)	0.54 (0.28–1.03)	
Duration of Illness (years)					
Mean (95% CI)	11.7 (9.9)	12.8 (11.5–14.1)	10.4 (9.1–11.8)	1.00 (0.97–1.04)	p=0.749
Median (range)	8 (1–50)	10 (1–50)	7 (1–39)		
Previous Clozapine Treatment					p=0.394
No	348	202 (59.2)	139 (40.8)	1	
Yes	95	51 (54.8)	42 (45.2)	0.80 (0.48–1.34)	
Previous FGA Depot Treatment[§]					p=0.560
No	241	130 (53.9)	111 (46.1)	1	
Yes	192	122 (63.5)	70 (36.5)	1.14 (0.73–1.80)	
Compulsory Treatment at Initiation					p=0.043*
No	109	58 (55.2)	47 (44.8)	1	
Yes	334	195 (59.3)	134 (40.7)	1.87 (1.02–3.43)	
Treatment Setting at Initiation					p=0.001**
Inpatient	301	162 (54.7)	134 (45.3)	1	
Community	142	91 (65.9)	47 (34.1)	2.57 (1.44–4.61)	
RLAI Dose at Initiation					p=0.023*
25 mg or less	368	200 (55.4)	161 (44.6)	1	
37.5 mg or more	75	53 (72.6)	20 (27.4)	2.04 (1.11–3.78)	

[†]Nine patients who moved out of area or who died are excluded; all Odds Ratios (OR) are adjusted for other variables in the model;

[§]one person with missing information is excluded from analysis; ^{||}RLAI-initiation doses ranged between 12.5–50 mg/2 weeks;

**p<0.01; *p<0.05; RLAI=risperidone long-acting injection; FGA=first-generation antipsychotic; DHB=district health board; CI=confidence interval

Table 1 compares the demographic and clinical profile of the group of patients who continued on RLAI for 12 months or more and those that discontinued earlier than 12 months. This table contains the variables that were included in the logistic regression. Other variables analyzed but not included in the model were: previous oral risperidone treatment (82.2% continuation vs. 84.0% discontinuation; $p=0.630$), adherence issues as primary reason for initiation (76.7% continuation vs. 79.0% discontinuation; $p=0.566$), Axis II comorbidity (12.6% continuation vs. 13.8% discontinuation; $p=0.723$), and physical health issues (65.6% continuation vs. 57.5% discontinuation; $p=0.08$).

Logistic regression analysis was conducted to investigate the factors associated with RLAI continuation at 12 months (T3) after controlling for other variables in the model (see Table 1). Ethnicity, treatment setting, compulsory status and RLAI dose at initiation were the only variables that remained significant in the analysis. Therefore, Māori, those started in an inpatient setting, those started informally (not under a compulsory treatment order) and on a dose of 25 mg or less were less likely to continue treatment with RLAI for 12 months or more. Age and duration of illness variables, which were found to differ between the two treatment groups in univariate analysis, did not remain significant in the logistic regression model.

A total of 172 people treated with RLAI (39.6%) had an adverse effect that was attributed to RLAI documented in their clinical file: extrapyramidal side effects 18%; hyperprolactinemia 6%; weight gain 5.9%; sexual dysfunction 2.3% and other 7.6%. "Other" adverse effects included pain at injection site, lethargy/sedation, headache, nausea, hypotension, bradycardia, seizure, constipation and subjective complaints of general intolerability. There was no difference in the proportion of adverse effects reported between those that continued on RLAI and those that discontinued treatment before 12 months ($\chi^2=3.73$, $df=5$, $p=0.590$).

Table 2 outlines the reason for discontinuation recorded in the clinical file; patient and/or family refusal to continue RLAI was the most common reason followed by lack of efficacy. Other reasons included three patients moving overseas where either RLAI was not available or it was too expensive, and two patients who developed medical issues and a clinical decision was made to withhold RLAI (pregnancy and cerebrovascular accident). There was no difference between ethnic groups for the main reasons for discontinuation of RLAI treatment: patient choice (refusal or failure to attend), poor response or intolerability ($\chi^2=5.12$, $df=4$, $p=0.275$).

Treatment Duration and Dose of Risperidone Long-Acting Injection

The overall distribution of two weekly doses for RLAI treatment at three time points after treatment initiation (3,

Table 2 Reasons for Discontinuing Risperidone Long-Acting Injection (N=181)

Reason	N (%)	Mean Final 2 Weekly Dose (95% CI)	Mean Duration of Treatment (95% CI)
Refusal	79 (41.6)	33.4 mg (31.0–35.8)	21.1 weeks (18.0–24.1)
Poor response/ineffective	55 (28.9)	40.9 mg (37.3–44.6)	20.2 weeks (16.8–23.7)
Intolerability/adverse effects	24 (12.6)	31.8 mg (25.5–38.0)	23.8 weeks (17.3–30.3)
Lost to follow-up	18 (9.5)	36.8 mg (31.8–41.8)	21.3 weeks (12.7–29.9)
Other	5 (2.6)	30.0 mg (21.5–38.5)	26.1 weeks (14.6–37.6)

CI=confidence interval

6 and 12 months) is shown in Figure 1. The average dose increased from 36.0 mg at T1 (3 months) to 39.3 mg at T2 (6 months) and 41.5 mg every two weeks at T3 (12 months).

For those that discontinued RLAI ($n=181$), the mean duration of treatment was 21.3 weeks (95% CI=19.3–23.4 weeks). The mean final dose at treatment cessation varied significantly according to the four main reasons for discontinuation, with those stopping because of inadequate response having the highest dose (Kruskal-Wallis, $p<0.001$) (see Table 2). There was no difference between the discontinuation groups for mean duration of treatment (Kruskal-Wallis, $p=0.829$).

The final two weekly doses were significantly higher for those who continued RLAI treatment until 12 months than for those who had discontinued treatment earlier: mean dose was 41.5 mg, 95% CI=39.7–43.2 mg/2 weeks for continuers versus a mean final dose of 35.7 mg, 95% CI=33.9–37.5 mg/2 weeks for discontinuers (Mann-Whitney U, $p<0.001$). There was also a difference in final dose between ethnic groups: average dose Māori=41.4 mg/2 weeks, Pacific peoples=39.9 mg/2 weeks, and European/other 37.6 mg/2 weeks (Kruskal-Wallis, $p=0.025$).

Treatment after Risperidone Long-Acting Injection Discontinuation

Antipsychotic treatment prescribed after RLAI discontinuation is described in Table 3. Although 41.7% of the population discontinued RLAI within 12 months, most were switched to alternative antipsychotics, one-third to oral risperidone. For the largest discontinuation group—refusal to continue with RLAI—only 21.5% ($n=17/79$) refused to take any form of antipsychotic treatment and the majority switched to an oral antipsychotic agent ($n=50$; 63.3%), primarily oral risperidone ($n=36$; 45.6%). Of those who

stopped because RLAI was ineffective, over half switched to clozapine ($n=31/55$; 56.4%).

Discussion

In this naturalistic, retrospective study of RLAI treatment, outcome for 443 patients treated in 5 different mental health services across New Zealand was examined for up to 12 months. Overall 58.3% of the evaluable patients continued RLAI treatment for at least one year. The majority had been started because of treatment adherence issues and, in those that stopped, the main reason was patient choice not to continue (over half either actively refused or failed to turn up). Multivariate analysis found that continuation was more likely for those who started RLAI in the community setting (OR 2.56), those who started RLAI under a compulsory treatment order (OR 1.87), those who started RLAI on a dose of 37.5 mg or more (OR 2.04), and less likely for those of Māori ethnicity than those of European/other ethnicity (OR 0.51). Unexpectedly, despite a high rate of treatment resistance (21.4% previously treated with clozapine) in the population who started RLAI, this factor did not predict one-year continuation as a treatment outcome in the study.

Continuing treatment in the longer term was more likely when RLAI was started when the patient was stable or not

Figure 1 Risperidone Long-Acting Injection Dose Distribution (N=434)

Table 3 Treatment Prescribed after Risperidone Long-Acting Injection Discontinuation (N=181)

	Treatment Post-RLAI Discontinuation N (%)
No Antipsychotic	38 (21.0)
Risperidone	58 (32.0)
Olanzapine	29 (16.0)
Quetiapine	10 (4.0)
Clozapine	36 (19.9)
Amisulpride	1 (0.6)
Ziprasidone	1 (0.6)
FGA Oral	5 (2.8)
FGA LAI	19 (10.5)
ECT	1 (0.6)
Poly-antipsychotics	25 (13.8)

RLAI=risperidone long-acting injection; FGA=first-generation antipsychotic; LAI=long-acting injection; ECT=electroconvulsive treatment

so severely unwell that they required inpatient hospitalization. Therefore, it is possible that despite a history of poor adherence to medication, positive re-engagement in treatment and recovery planning is more likely in the community setting. It would also appear that using the Mental Health Act in this population was a positive factor to reinforce treatment continuation. However, understanding the association of continuation and ethnicity requires further investigation. The lesser likelihood of Māori continuing at 12 months is of concern; but in the absence of any other antipsychotic continuation studies conducted in a New Zealand population it is not possible to directly attribute this finding to RLAI alone. While there is no evidence in the literature to suggest differences in antipsychotic efficacy between ethnic groups, and the reasons recorded for discontinuation in this study were no different between ethnic groups, more in-depth qualitative investigation into why patients choose to stop treatment may help with understanding this observation.

Initiating treatment higher than the recommended dose (more than 25 mg) was also associated with continuation at 12 months. Starting RLAI with 25 mg/2 weeks is recommended in the regulatory data sheet with dosage adjustments to be made no more frequently than every four weeks (19). RLAI maintenance dose is still a controversial issue with clinical trials lacking evidence to support therapeutic benefit above 25 mg/2 weeks (12, 22), but the data sheet suggests that patients stabilized on oral risperidone more than 4 mg/day may benefit from doses of 37.5 mg or 50 mg/2 weeks after a trial of 25 mg/2 weeks (19). In this study we found that clinicians were escalating the dose of RLAI over time

(see Figure 1), and that those who continued had higher final doses at 12 months than those who discontinued earlier.

A U.K. observational study reporting high attrition rates at six months and three years (52.8% and 84% discontinuation, respectively) found that patients receiving maximum RLAI doses of 25 mg/2 weeks during treatment were more likely to discontinue (23, 24). The authors suggested that treatment doses higher than 25 mg/2 weeks may improve outcome. Furthermore, Viala et al., who found continuation rates (59.5% at 12 months) similar to our study, reported that the majority of patients received a starting dose of 50 mg (81%) and proposed that higher starting doses may be beneficial to continuation of treatment (25). The association we have found may also indicate that higher starting doses may be more effective, but further work examining outcome with different starting and maintenance treatment doses is required.

Continuation rates reported in the literature with RLAI vary: an early, open-label clinical trial in schizophrenia ($n=615$) found 65% continuation at 12 months (22), and another open-label clinical trial in people with recent-onset psychosis ($n=50$) found higher continuation rates of 72% at two years (26). In comparison, observational studies in the U.K. have reported 58% continuation at 6 months in one service ($n=50$) (27), another reported only 32.4% continuation at 12 months ($n=250$) (28), and a third found 58% at 12 months ($n=67$) (29). One of the U.K. studies recently reported continuation rates at three years from the original cohort; this reduced from 32.4% at one year (28) to 16% at year 3 (23). This New Zealand study found an overall continuation rate of 58.3%, which compares favorably with the higher continuation rates reported by Niaz et al. in a psychiatric service in northern England (29), and by Viala et al. in a psychiatric service in France (25). One-year continuation rates in the five New Zealand services varied between 49–67%, but the regional variation was not statistically significant.

Our continuation rates also support practice recommendations that this form of administration of an SGA agent can be an effective way of maintaining treatment in schizophrenia when compared to the risk of discontinuation and short-treatment duration associated with oral SGA agents (14, 15, 30). In the only other large published observational investigation of oral SGA discontinuation, Mullins et al. (using a pharmacy claims database; $n=5,898$ patients) found that the majority (90%) of patients had discontinued their treatment at one-year follow-up with no difference between individual SGA agents (30).

Overall, RLAI seems to have been well tolerated and extrapyramidal side effects were the most commonly documented problem. When adverse effects were reported they only led to intolerability-associated discontinuation in a

small proportion of patients. It is important to note that the low rate of recorded adverse effects may be a reflection of poor documentation in the clinical notes. It was beyond the scope of the study to investigate reasons why patients refused to continue RLAI. Therefore, it is possible that adverse effects experienced by patients led to their decision to stop RLAI treatment or not comply with follow-up.

A number of limitations need to be considered. Firstly, the study was undertaken as a retrospective review of information recorded in patients' case notes. Reliance on the degree, extent, accuracy and validity of the information recorded and on the expertise of the original clinicians who provided the information in their assessments and summaries was inherent in the study design. Every effort was made to ensure that the data collected were as complete and accurate as possible, but this remains a limitation of the study findings. While a prospective study that gathers data by interviewing patients using validated questionnaires can collect more specific information, this design limits a study to smaller numbers of patients and potential biases in the patient group who consent to participate in the study (i.e., patients with time to participate may be those who are less likely to have a regular occupational activity and may represent a more complex and/or treatment-resistant group). Additionally, treatment may not represent "real world" practice in such a study because the clinical team is aware that the interventions and outcomes are being reviewed.

The focus of this study was to examine real world prescribing and outcome with RLAI treatment. The strengths of the study include the large sample size and ethnic diversity of the study population. The study was conducted in five large public mental health services providing free care to patients and is likely to be representative of the population of people with a serious mental illness such as schizophrenia. In addition, the findings reflect the treatment practices of more than fifty psychiatrists, medical officers and psychiatric registrars. The study findings may not be generalizable to other mental health services outside New Zealand, particularly as it is not possible to take into account differences in the way healthcare is delivered and of the impact of non-pharmacological interventions.

Conclusions

This study provides important insights into clinical outcome and patient characteristics predicting continuation of RLAI treatment. A continuation rate of 58.3% at one year is indicative of an effective treatment that was generally acceptable for many patients. This effectiveness outcome found in real world, public clinical practice supports the efficacy results found in experimental conditions.

Treatment continuation with RLAI was better for those who started treatment in the community, were treated

compulsorily, who were of European/Other and/or Pacific ethnicity and had a starting dose of more than 25 mg. The importance of the collaborative relationships between clinician and patient for successful re-engagement in treatment is indicated by the increased likelihood of continuation at one year for those starting RLAI treatment in an outpatient setting and with the support of a compulsory treatment order. Further investigation into the reasons for ethnic differences in continuation rates will provide useful insights into the social and cultural factors influencing treatment adherence. Research examining the clinical outcome of different starting doses is also necessary.

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