An Exploratory, Open-Label, Randomized Trial Comparing Risperidone Long-Acting Injectable with Oral Antipsychotic Medication in the Treatment of Early Psychosis

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Abstract

Few studies have examined effectiveness and tolerability of risperidone long-acting injections (RLAI) in the early phase of a schizophrenia spectrum (SS) disorder using a randomized controlled trial (RCT) design. Eighty-five patients in early phase of an SS disorder were randomized to receive either oral second-generation antipsychotics (SGAs; n=41) or RLAI (n=44) over two years. Analyses were conducted on eligible participants (n=77) for the stabilization (maximum 18 weeks) and maintenance phases (up to Week 104) on primary outcome measures of time to stabilization and relapse, change in symptoms and safety, and comparisons made across the two groups. Both groups showed improvement on Positive and Negative Syndrome Scale (PANSS) scores and Clinical Global Impression-Severity (CGI-S) scores. There were no time X group interactions on any of the primary outcome measures. Post hoc examination revealed that the RLAI group showed greater change on CGI-S and PANSS negative symptom scores during the stabilization phase, while the oral group reached the same level of improvement during the maintenance phase. The current exploratory study suggests that—within an RCT design—RLAI and oral SGAs are equally effective and have similar safety profiles in patients in the early phase of SS disorders. Thus, RLAI offers no advantage to patients in early phase of SS disorders, but is likely to be effective and safe for those who may have problems with adherence and may either choose to take it or be prescribed under conditions of external control such as community treatment orders.

Key Words: Risperidone, Early Psychosis, RCT

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Introduction

Antipsychotics—drugs that block dopamine D2 receptors—attenuate positive symptoms in schizophrenia, and

Clinical Implications

The objectives of this investigation were to explore the efficacy, safety, and tolerability of risperidone long-acting injection (RLAI) relative to standard oral second-generation antipsychotic (SGA) treatment in patients with recent onset of schizophrenia spectrum (SS) psychotic disorder. Our results show oral SGAs and RLAI to be equally effective (efficacy with positive and negative symptoms and tolerability) within an open-label randomized controlled trial (RCT) design. This is somewhat similar to data reported by Emsley (34) in first-episode psychosis patients.

Our findings of comparable efficacy of an SGA/LAI compared to oral SGAs are especially important for people being recently diagnosed with a psychotic disorder, since evidence suggests the first five years of psychotic illness represent a critical period that has significant consequences for symptoms and functioning throughout the lifespan (25, 37). Hence, the benefits of antipsychotic medications can be made available to patients in the early phase of the illness with SGA/LAI medications as safely as with oral SGAs. This may assist in overcoming hesitation among clinicians in prescribing LAIs to patients with a recent diagnosis (40, 41) who are generally at a high risk of nonadherence. On the other hand, patients willing to take oral SGAs are likely to gain little from taking LAIs.

help improve outcomes, especially in the early stages of illness (1, 2). Their efficacy in treating acute episodes of psychotic disorders, as well as preventing relapses, is now well established. Relatively substantial proportions of patients, however, show poor adherence to oral antipsychotic medication and this problem may be particularly prevalent in the early phase of treatment. For example, data from 2,588 first-episode patients revealed that only 58% collected their prescription during the first 30 days of hospital discharge, and only 46% continued their initial treatment for 30 days or longer (3).

Few interventions have been shown to be specifically effective in improving the modest rates of adherence (4), nor has the introduction of oral second-generation antipsychotics (SGAs) altered these rates significantly (5). Long-acting antipsychotics (LAIs), administered through an intramuscular (IM) route, have been regarded as one method of assuring that patients actually receive these medications. The benefits of this method of administering medications have been demonstrated in some trials, including randomized control trials (RCTs), although several studies using RCT designs have shown no clear advantages (6). The benefits are likely to be greater for patients who would otherwise not have taken oral medications, and such patients are also unlikely to be included and sign informed consent in order to be enrolled in RCTs.

The use of LAIs declined following the introduction of oral SGAs, most likely under the false assumption that a large part of nonadherence was attributable directly to neurological side effects with first-generation antipsychotics (FGAs). Several years ago, risperidone long-acting injectable (RLAI) in a microspheres formulation was approved for use in schizophrenia and related psychotic disorders (7, 8). A number of studies with stable patients have concluded that RLAI is effective (9-11), safe and well-tolerated (12-14), linked to lower rates of hospitalization (15) and reduced relapse rates (15, 16), as well as higher rates of remission when compared to oral medication. There is also evidence that RLAI-treated inpatients exhibit significantly fewer side effects compared to oral risperidone (17, 18). On the other hand, a recent trial by Rosenheck and colleagues (19) found no difference in hospitalization rates (but more side effects) among unstable schizophrenia inpatients randomized to RLAI versus those randomized to mixed oral antipsychotics.

All initial studies for the efficacy, effectiveness and tolerability of RLAI were conducted in patients with several years of illness. Few studies have examined outcomes among patients with a first-psychotic episode (FEP) (11, 20) or in the early course of a psychotic disorder (21), and most randomized control trials have been reported on more chronically ill patient populations (19, 22). This is particularly noteworthy in the context of rates of nonadherence to medication being especially high in the early phase of psychosis (23, 24) and the potential advantages of preventing relapse early in the course of illness (25, 26).

Here we report the results of an exploratory, multisite, randomized, open-label and controlled efficacy study comparing RLAI with oral SGAs in a sample of early-phase schizophrenia spectrum (SS) psychotic disorders. The primary objective of this study was to explore the comparative efficacy, safety and tolerability of RLAI relative to oral SGAs in patients with a recent onset of an SS psychotic disorder.

Method

Participants

Eighty-five (male: 69; female: 16) participants, who had recently received a diagnosis for an SS psychotic disorder and were in voluntary treatment, were recruited for the study at twelve sites across Canada between 2004 and 2006. Partici-

pants were either medication naive or had been taking oral risperidone, olanzapine or quetiapine. Enrollment ranged from 3 to 16 participants per site. The mean time between diagnosis and study entry was 9 (SD=.88) months. Participants were included if they were between 18 and 30 years of age; had a Positive and Negative Syndrome Scale (PANSS) total score between 60 and 120 at screening; and, received a *DSM-IV-TR* diagnosis for schizophrenia, schizophreniform or schizoaffective disorder based on the Structured Clinical Interview for *DSM-IV* (SCID-IV) no longer than three years prior to study entry. In addition, females were required to be surgically sterile or engaging in effective birth control methods. Participants were randomly assigned to one of two treatment conditions: RLAI or oral therapy with SGA medications.

Participants were excluded if their primary axis-I diagnosis was not within SS *DSM-IV-TR* categories; if they were receiving mood stabilizers or antidepressants *at the time of entering the study*; displayed current drug or alcohol dependence; were treated with depot antipsychotics within three months of study entry; had or were suspected of a history of hypersensitivity or allergy to risperidone; were risperidone nonresponders; failed to respond to two or more adequate treatment trials of antipsychotics; had a clinically significant laboratory abnormality or a serious unstable and untreated medical illness; were at significant risk of suicide or violence at study entry; required electroconvulsive treatment within three months of study entry; received or used an experimental drug or device within thirty days before study entry; had previous treatment with clozapine; or, if they were in a conflict of interest with the investigation. The institutional review boards of each enrollment site approved this study, and participants gave informed consent before being enrolled in the study.

Procedure

This two-year, open-label, two-arm randomized controlled study consisted of two phases: stabilization and a maintenance phase. Eligible patients were randomly assigned to one of two treatment conditions. The experimental group received RLAI injections every two weeks while the control group continued with the oral SGAs they were already taking (e.g., risperidone, olanzapine, or quetiapine) upon study entry. Drug naive patients were started on oral risperidone prior to randomization.

The study began with an 18-week stabilization phase, which was followed by an 86-week maintenance phase for both arms. Clinical stability was defined as at least 4 weeks of improved or stable values (≤4) on the Clinical Global Impression-Severity Scale (CGI-S) (27). Patients stable within 18 weeks of baseline were eligible to continue the trial in the maintenance phase. Patients not stable at Week 18 were withdrawn from the study. Patients were stabilized on oral SGAs in the oral group and RLAI in the RLAI group. However, all patients in the RLAI group received oral risperidone (2–6 mg) for the first three weeks following the initial injection as per guidelines for the use of RLAI. Subjects on RLAI visited their respective clinics every two weeks throughout the trial to receive their injection while patients on oral medication—with prescriptions given every 4 weeks—visited their respective clinics as determined necessary by their clinicians. Procedures used were in accordance with internationally accepted principles.

Study assessment visits were conducted every four weeks from Visit 3 to Visit 8 (Week 22), then one visit after 6 weeks (Visit 9, Week 28), then every 12 weeks until Visit 14 (Week 88) and a final visit at Week 104.

Primary Outcome Measures

Psychotic symptoms were measured using the Positive and Negative Syndrome Scale (PANSS) (28). Global clinical severity was measured with the CGI-S (27). Neurological side effects were assessed using the Abnormal Involuntary Movement Scale (AIMS) (29), the Simpson-Angus Scale (SAS) (30), and the Barnes Akathisia Rating Scale (BARS) (31). Patients' attitude toward their medications was assessed with the Drug Attitude Inventory (DAI). No direct measure of medication adherence was used (32).

Criteria for Relapse

Relapse was defined according to the criteria proposed by Csernansky and colleagues (33). Participants met criteria for relapse if they required psychiatric hospitalization; needed an increase in psychiatric care and experienced a significant increase in PANSS scores; demonstrated much worse or very much worse scores on the CGI-S; engaged in deliberate self-injury or experienced suicidal or homicidal ideation; or, participated in violent behavior resulting in injury to a person or destruction of property.

Dosage and Administration

The permitted RLAI dose was between 25–50 mg administered by deep IM gluteal injections every two weeks. Dose increases of RLAI or oral treatments were permitted if participants received medications for a minimum of 6 weeks. Increases during the stabilization phase were allowed if participants had a CGI-S score ≥4 (moderately ill or worse) and a CGI-I score of >4 (no change or worse). The dose of RLAI could be increased by increments of 12.5 mg to a maximum dose of 50 mg.

During the maintenance phase, the dosage could be increased by the same increments if the subject experienced

a worsening of psychotic symptoms (defined as a 25% increase in the total PANSS score, or a 20% increase in the psychosis subscale [P1 Delusions, P2 Conceptual disorganization, P3 Hallucinations, and P6 Suspiciousness/persecution]), to a maximum dose of 50 mg. The dose of oral atypical antipsychotics was permitted to be changed using the same criteria as for RLAI and was required to be below the maximum daily Compendium of Pharmaceuticals and Specialities (CPS) guidelines (risperidone 6 mg, olanzapine 20 mg, quetiapine 800 mg). Dose reduction was permitted if a previous increase did not result in the anticipated improvement. If participants were already receiving the maximum dosages allowed and required a higher dose, they were withdrawn from the study due to lack of efficacy. Furthermore, if significant side effects were experienced which could not be treated, the participant was withdrawn due to lack of tolerability. RLAI was provided by the study sponsor (Janssen) and the costs of oral medication were reimbursed on site.

Data Analyses

This was an exploratory study; no formal sample size calculations were performed. All randomized subjects were included in the analysis of the safety, demographic, and baseline characteristic data. The study was not powered to detect differences between study arms. Statistical tests were performed only for primary outcome measures (efficacy and safety), as the sample size did not allow enough power to conduct multiple comparisons for secondary outcomes. A Bonferroni correction was applied to the analyses for the primary outcome measures and all other analyses were considered exploratory.

Efficacy

For efficacy outcomes, the main analysis was defined as per protocol to include all subjects who had received at least three injections of RLAI or 6 weeks of oral antipsychotic treatment and had at least one postbaseline efficacy assessment. The change from the screening/baseline score was summarized by group at each visit and at endpoint.

Time to Stabilization and Relapse: An estimate of likelihood ratio between the treatment groups and its 95% confidence interval was calculated. A Kaplan-Meier analysis of time to stabilization provided the cumulative distribution function of the study period. For each group, Kaplan-Meier estimates of risk (probability) of relapse and 95% confidence interval at the end of the trial were calculated. Furthermore, differences in the time to relapse between groups were calculated from the start of the maintenance period to the date of relapse as defined above. Both analyses were evaluated with Log-rank tests.

Symptom Outcomes: Raw changes from baseline to the study endpoint, from baseline to stabilization visit, and from stabilization to the study endpoint were computed. Values presented for within-treatment tests indicated the average amount of change in scores that occurred over a measurement period, while values for between-treatment tests indicated the average difference between treatments. Comparisons across time on PANSS and CGI-S scores were analyzed using scores at baseline, stabilization visit, and the last reported visit for both groups using t-tests, while group comparisons were computed using ANOVAs. Confidence intervals (95%) were also calculated for between-group analyses. Analyses were conducted while correcting for first assessments (e.g., analyses at stabilization visit were conducted while correcting for baseline scores).

Safety

Adverse Effects and Hospitalization Rates: Descriptive analyses were conducted to show how many participants experienced spontaneous adverse effects as reported from each site and/or were admitted to hospital.

Neurological Side Effects: Changes in neurological side effects between and within groups were examined using scores from the AIMS and SAS using ANOVAs and t-tests. Fisher's Exact Test was used to discern group differences on mild or moderate symptoms on the BARS before and after stabilization.

Weight Change: Changes in weight were evaluated at Weeks 10, 18, 52 and 104. At each time point, the percentage of participants in both treatment groups who had experienced at least a 7% increase in weight was calculated.

Attitudes toward Medication: Group differences on the DAI were tested at baseline, stabilization, and the study endpoint using ANOVAs. Within-group differences were measured using t-tests. For all other secondary measures, no formal statistical tests were performed.

Results

One hundred and one patients were screened at twelve Canadian centers; 85 of these subjects were randomized (see Figure 1). One participant withdrew consent after randomization, but prior to baseline evaluation. Seven additional participants were excluded prior to first usable baseline assessment and, therefore, from any analyses (except safety analyses) due to a protocol violation (n=1); being lost to follow-up (n=2); withdrawing consent (n=3); and, being withdrawn by the investigator (n=1). Seventy-seven randomized participants (RLAI n=42, oral SGA n=35), who received at least three doses of RLAI (n=42; 54.5%) or six weeks of oral antipsychotic therapy (n=35; 45.4%), in addition to having at least one postbaseline efficacy assessment,

Figure 1 Trial Design

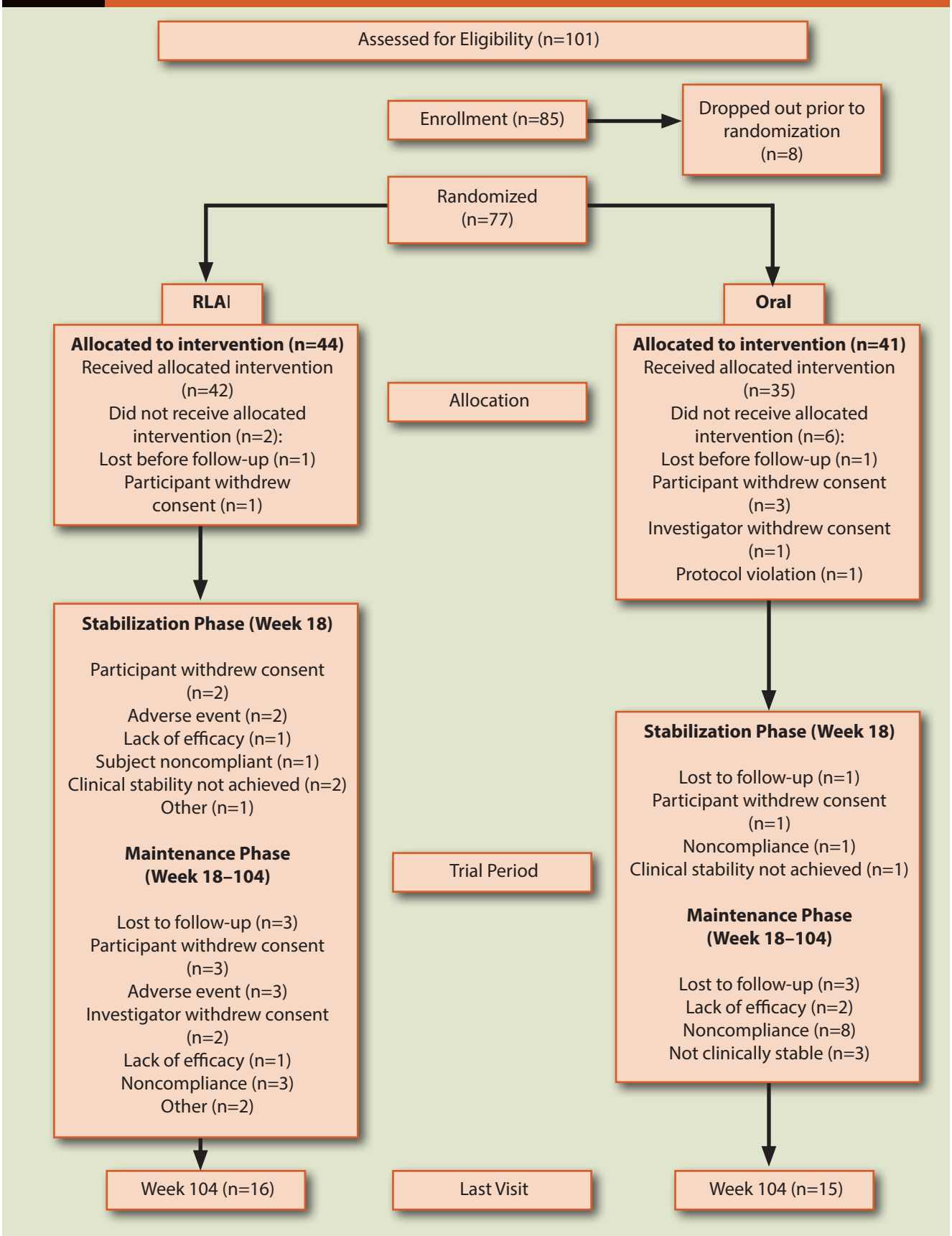


Table 1 Concomitant Medications Used Throughout the Trial

Medication Name	Treatment			
	RLAI		Oral	
	N	%	N	%
Atomoxetine	6	13.6		
Citalopram	2	4.5	4	10
Clonazepam	8	18.2	2	5
Benztropine	6	13.6	1	2.5
Venlafaxine	12	27.3	5	12.5
Escitalopram			4	10
Haloperidol	4	9.1		
Procyclidine	1	2.3	1	2.5
Loxapine	1	2.3		
Oxazepam	1	2.3	1	5
Propanolol			1	2.5
Trazodone	1	2.3		
Fluvoxamine	2	4.5		

were included in an intent-to-treat analysis (ITT). As shown in Table 1, the RLAI and oral groups had similar baseline demographic and clinical characteristics. Participants in both groups had previous psychiatric histories, which included personality (n=4), developmental (n=4), neurological disorders (n=3), as well as problems with substance abuse (n=15). All patients, except one, had received antipsychotic monotherapy prior to being randomized. Eight patients with active alcohol or drug abuse but not dependence (two in the RLAI group and six in the oral group) were included in the ITT group.

Thirty-one patients completed the entire study (104 weeks; n=31); 33 dropped out before the end of the two-year study (RLAI: 17; median weeks to dropout: 35; oral: 16; median weeks to dropout: 36.15). Reasons for dropout among those who reached stabilization included adverse events (n=3); noncompliance (n=11); being lost to follow-up (n=6); lack of efficacy (n=3); participants (n=3) or investigators (n=2) withdrawing consent; as well as other reasons (n=5). Thirteen participants (RLAI: 9; oral: 4; median time to dropout: 11 weeks) dropped out before the end of the stabilization period. Reasons for dropout among participants who had not stabilized included adverse events (n=2); noncompliance (n=2); being lost to follow-up (n=1); lack of efficacy (n=1); participants withdrawing consent (n=3); not being stable by Week 18 (n=3); as well as other reasons (n=1).

Medications and Dosage

During the stabilization phase, the mean dose of RLAI was 30.5 mg. The mean dosage for RLAI during the maintenance phase was 31.75 mg (SD=8.82; median: 31.3; mode: 32.8; range: 25–50 mg). Oral concomitant antipsychotic medication was prescribed for a mean period of 47 days for the entire study period, including the three weeks during the stabilization phase.

For the oral group, 10 participants received olanzapine, 2 quetiapine, and 20 risperidone. Mean doses during the stabilization phase were 15.5 mg for olanzapine (SD=5.87; median: 17.5; mode: 14.60; range: 15–20 mg), 400 mg for quetiapine (SD=141.42; median: 400; mode: 400; range: 300–500 mg) and 3.7 mg for risperidone (SD=1.34; median: 3.8;

Table 2 Characteristics of Participants Who Were Randomized

	RLAI N=42		Oral N=35		All N=77	
	N/ Mean	%/ SD	N/ Mean	%/ SD	N/ Mean	%/ SD
Age	22.5	3.12	23	2.93	22.7	3.02
Gender						
Male	33	78.6	32	91.4	65	84.4
Female	9	21.4	3	8.6	12	15.6
Race						
White	34	81	26	74.3	60	77.9
Black	4	9.5	4	11.4	8	10.4
Asian	1	2.4	2	5.7	3	3.9
Aboriginal	1	2.4	1	2.9	2	2.6
Other	2	4.8	2	5.7	4	5.2
Diagnosis						
Schizophrenia	36	85.7	33	94.3	69	89.6
Schizoaffective	4	9.5	1	2.9	5	6.5
Schizophreniform	2	4.8	1	2.9	3	3.9
Other Psychiatric History						
No	19	45.2	10	28.6	29	37.7
Yes	23	54.8	25	71.4	48	62.3
CGI-Severity						
Mild	5	11.9	7	20	12	15.6
Moderate	22	52.4	17	48.6	39	50.6
Marked	13	31	7	20	20	26
Severe	2	4.8	4	11.4	6	7.8

%/SD=Percentage or standard deviation

mode: 3.2; range: 1–6 mg). During the maintenance phase, mean doses were 15.5 mg for olanzapine (SD=5.39; median: 17.5; mode: 14.60; range: 15–20 mg), 400 mg for quetiapine (SD=141.42; median: 400; mode: 400; range: 400–500 mg) and 3.82 mg for risperidone (SD=1.87; median: 3.9; mode: 3.2; range: 1–6 mg).

Concomitant medications that were used throughout the study are listed in Table 2. These included antidepressants (RLAI: n=22; oral: n=13), antipsychotics (RLAI: n=4; oral: n=0), hypnotics (RLAI: n=11; oral: n=4), and antiparkinsonian (RLAI: n=7; oral: n=2) medications. Concomitant medications prescribed were recorded even if only one dose was given. It is likely that patients were not maintained on all medications throughout the trial.

Symptom Outcomes

Efficacy

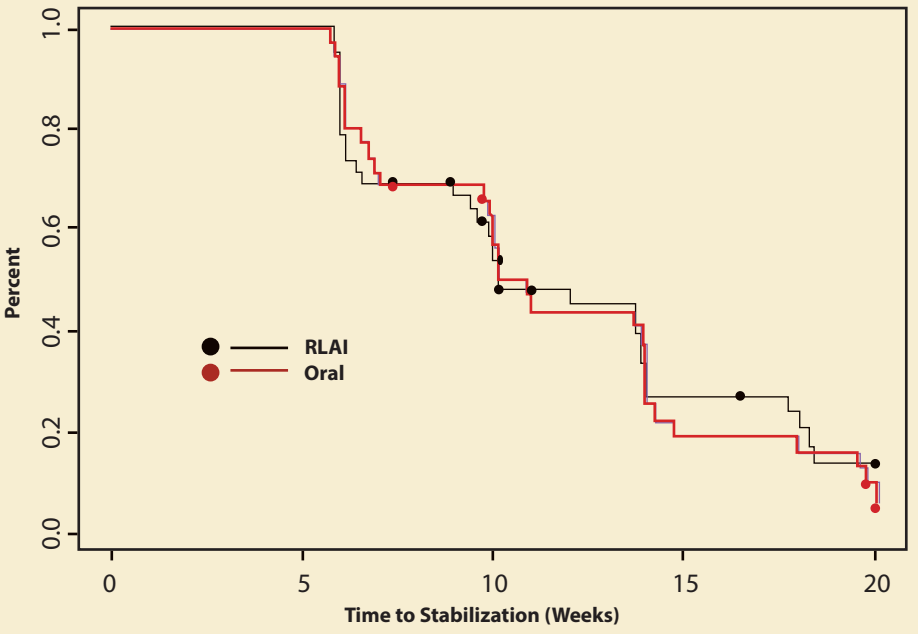
PANSS Total Scores (see Table 3): Scores decreased significantly for both the RLAI (M=-19.4, SD=13.13) and oral (M=-11.4, SD=10.09) groups between baseline and stabilization. Significant differences in total PANSS scores between baseline and the study endpoint for both RLAI (M=-18.1, SD=22.48) and oral (M=-17.7, SD=16.45) were found. No other effects were observed.

Table 3 PANSS Positive, Negative and Total Scores

Measurement	Group	N	Mean	SD	Group Difference
PANSS Total Scores					
Change from Baseline to Last Reported Visit	RLAI	42	-18.1*	22.48	-0.3
	Oral	34	-17.7*	16.45	
Change from Baseline to Stabilization Visit	RLAI	32	-19.4*	13.13	-7.5
	Oral	31	-11.4*	10.09	
Change from Stabilization to Last Reported Visit	RLAI	32	0.5	21.95	8
	Oral	29	-7.2	17.4	
PANSS Positive Symptom Factor Scores					
Change from Baseline to Last Reported Visit	RLAI	42	-6.1*	7.17	-0.6
	Oral	34	-5.4*	5.49	
Change from Baseline to Stabilization Visit	RLAI	32	-5.9*	4.17	-0.5
	Oral	31	-5.2*	4.66	
Change from Stabilization to Last Reported Visit	RLAI	32	-0.2	6.41	0.7
	Oral	29	-0.3	6.49	
PANSS Negative Symptom Factor Scores					
Change from Baseline to Last Reported Visit	RLAI	42	-6.2*	8.42	-0.3
	Oral	34	-5.7*	6.6	
Change from Baseline to Stabilization Visit	RLAI	32	-6*	5.31	-3.7
	Oral	31	-1.9	4.26	
Change from Stabilization to Last Reported Visit	RLAI	32	-1.1	7.31	3.8
	Oral	29	-4.2*	5.9	

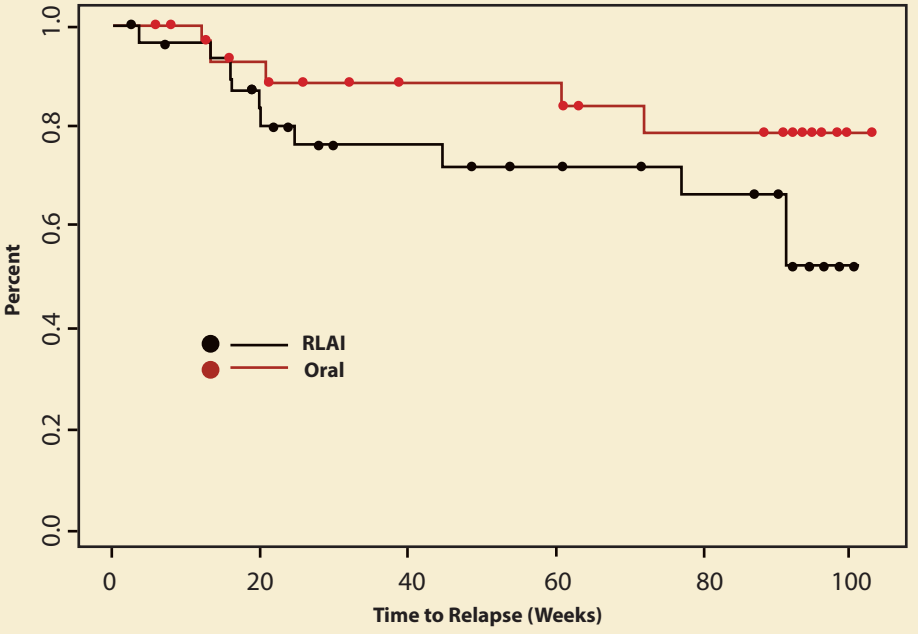
*=p<.05

Figure 2 Survival Curve on Time to Stabilization



Likelihood ratio=.07, p=.79

Figure 3 Survival Curve on Time to Relapse



Likelihood ratio=2.57, p=.15

PANSS Positive Symptoms Factor (see Table 3): A decrease in scores was observed for both groups (RLAI: M=-5.9, SD=4.17; oral: M=-5.2, SD=4.66) between baseline and stabilization, with no differences between groups. Both groups also reported a decrease in scores (RLAI: M=-6.1, SD=7.17; oral: M=-5.4, SD=5.49) from baseline to the study endpoint, and no differences were observed between groups. No other significant differences were observed.

PANSS Negative Symptoms Factor: Significant differences were observed for the negative symptoms factors over time (see Table 3). A decrease in scores was observed between baseline and stabilization in the RLAI (M=-6, SD=5.31) but not in the oral group, and this difference was significant. Furthermore, a decrease in scores was present from stabilization to the study endpoint, but only for the oral (M=-4.2, SD=5.9) group and this group difference was also significant. Scores decreased between baseline and the study endpoint for both groups (RLAI: M=-6.2, SD=8.42; oral: M=-5.7, SD=6.6), with no differences between groups.

Clinical Global Improvement: CGI scores decreased among participants in the RLAI (M=-1.2, SD=.82) and oral (M=-.7, SD=.77) groups from baseline to stabilization. Between-group tests revealed no significant differences across all periods.

Time to Stabilization (see Figure 2): The Kaplan-Meier analysis on time to stabilization did not reveal any differences in time to stabilization between the RLAI and oral groups (likelihood ratio=.07; 95% CI=.651–1.75).

Time to Relapse (see Figure 3): A total of 16 participants relapsed: 11 from the RLAI group and 5 from the oral group. The analysis comparing time to relapse between groups produced a likelihood ratio of 2.57 (i.e., a shorter time to relapse in the RLAI group) that did not reach statistical significance (see Figure 2; 95% CI=.151–1.25).

Drug Attitude Inventory: No significant differences between or within groups were observed across any period of the study.

Safety and Tolerability

Hospitalization and Adverse Effects: Eight RLAI and four oral group participants were admitted to hospitals over the entire study. Reasons for hospitalization included exacerbation of symptoms, relapse, or adverse events. The latter included alcohol dependence syndrome (n=1), a depressive state marked by suicidal ideation (n=1) in participants receiving RLAI; lacerations to the face (n=1), nausea and thrombocytopenia (n=1) for those receiving oral SGAs.

Weight Gain: Overall, almost half the participants (RLAI: n=20/42, 47.6%; oral: n=17/35, 48.6%) met criteria for significant weight gain (>7%) at some point during the study. The proportion increased over time from Week 10 (RLAI: 15.2%; oral: 15.5%) to Week 104 (37.1% and 39.3%), respectively.

Extrapyramidal Side Effects: No significant change was observed on AIMS or SAS scores in either group across the entire period of the study. However, 7 patients in the RLAI group and 2 in the oral group were prescribed anticholinergic medications (benztropine: RLAI=6, oral=1; procyclidine: 1 in each group). Data for the BARS revealed that a small number of patients experienced akathisia both during (RLAI: n=7 [5.64%]; oral: n=9 [10.25%]) and following (RLAI: n=10 [7.72%]; oral: n=10 [9.23%]) stabilization, with no between-group differences observed.

No differences were observed on anxiety, depression or manic symptoms between the groups across any periods of treatment.

Discussion

The objectives of this investigation were to explore the efficacy, safety, and tolerability of RLAI relative to standard oral SGA treatment in patients with recent onset of SS psychotic disorder. Our results show oral SGAs and RLAI to be equally effective (efficacy with positive and negative symptoms and tolerability) within an open-label RCT design. This is somewhat similar to data reported by Emsley (34) in first-episode psychosis patients.

Although a greater proportion (11/42) in the RLAI group relapsed compared to the oral group (5/35), there were no significant differences regarding the time to achieve stabilization or the time to relapse. Participants in both groups experienced weight gain as well as other side effects and adverse events (relatively infrequent) to the same degree. Lack of differences in safety or tolerability is consistent with other studies conducted with patients in later stages of the illness (8, 12, 35, 36).

While, although on post hoc examination of outcome, patients in the RLAI group achieved greater reduction in negative symptoms and CGI during the stabilization phase, no such differences were observed at the end of the study or at the last assessment carried out during the maintenance phase. Macfadden and colleagues (37) reported similar results for the stabilization phase. This may also be related to lower fluctuations to maximize efficacy associated with LAIs (38). Furthermore, patients receiving RLAI may have been more adherent to medication earlier on than those in the SGA group. However, scores on DAI—often considered a proxy measure of medication adherence—showed no differences over any period of the study, which is consistent with similar findings reported elsewhere (39). The apparent difference in outcome on negative symptoms during the stabilization phase may also be accounted for by a somewhat higher use of antidepressants in the RLAI group, as there was no attempt made to distinguish primary from secondary negative symptoms.

The lack of differences observed on the DAI also implies patients may not harbor more negative beliefs about LAI medication than they do about oral medications, as is often believed (40, 41). Evidence for equal adherence between groups is further suggested by similar EPS and akathisia levels between groups.

The relatively higher proportion of patients relapsing in the RLAI group may indicate the effect of restriction on increasing the dose of RLAI beyond 50 mg. In fact, the modal dose used by the investigators was 32.6 mg; only 11 patients were prescribed 50 mg at any time during the study and only 4 received supplemental oral antipsychotics poststabilization. It is possible that increasing the dose beyond 50 mg—or even having a higher proportion of patients receiving 50 mg in the event of an impending relapse—may have avoided a full relapse. Alternatively, a decrease in medication adherence over time may also account for higher relapse rates (42). Patients in the oral group were permitted to receive the maximum dose for each medication.

It is somewhat surprising that the hypothesized adherence benefits of RLAI did not translate into better relapse prevention in the present study. However, the effect of hypothesized nonadherence on efficacy may have been minimized because nonadherent patients tend not to be included in RCT designs as they are likely to refuse to sign consent and that patients in the oral group are likely to have been equally adherent.

The current study is one of the few reports on efficacy of SGA LAIs in the early phase of psychosis, when patients are most vulnerable to relapse and the trajectories of long-term outcome are likely to be established (11, 39). However, there are several limitations to this study. For example, medication adherence was not measured systematically, either in the stabilization or the follow-up phase. A second limitation is that patients in the oral group were treated with several different SGAs, thus adding statistical noise to the analyses. The overall dropout rate of around 50%, while restricting the interpretation of findings, was relatively modest considering the duration of the study and comparable to most long-term randomized controlled studies. However, the higher dropout rate during the stabilization phase in the RLAI group may reflect the effect of change in antipsychotic medications used by the patient. Lastly, the sample size of this largely exploratory efficacy study did not have enough power to detect small, but significant, differences in time to relapse between the two treatment groups. One of the major limitations in evaluating differential efficacy of LAIs within an RCT design is the fact that patients most likely to benefit from LAIs in clinical practice (nonadherent, involuntary, acutely ill and refusing treatment, etc.) are unlikely to sign consent to participate in an RCT, even if it is not blinded.

Despite these limitations, our findings of comparable efficacy of an SGA/LAI compared to oral SGAs are especially important for people being recently diagnosed with a psychotic disorder, since evidence suggests the first five years of psychotic illness represent a critical period that has significant consequences for symptoms and functioning throughout the lifespan (25, 37). Hence, the benefits of antipsychotic medications can be made available to patients in the early phase of the illness with SGA/LAI medications as safely as with oral SGAs. This may assist in overcoming hesitation among clinicians in prescribing LAIs to patients with a recent diagnosis (40, 41) who are generally at a high risk of nonadherence. On the other hand, patients willing to take oral SGAs are likely to gain little from taking LAIs.

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