Maintenance Treatment With Long-Acting Injectable Risperidone in First-Episode Schizophrenia: A Randomized Effectiveness Study

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ABSTRACT

Background: Because long-acting injectable (LAI) antipsychotics are largely reserved for persistently ill patients, little is known about the use of LAIs early in the course of illness for first-episode outpatients.

Method: A prospective, open-label, randomized controlled trial was conducted in which outpatients with first-episode *DSM-IV* schizophreniform disorder, schizophrenia, or schizoaffective disorder were enrolled from December 2004 to March 2007. Participants were randomly assigned at a 2:1 ratio to a recommendation of changing to LAI risperidone microspheres (RLAI) (n = 26) or continuing oral antipsychotic treatment (n = 11) for up to 104 weeks. Primary outcomes were time until initial nonadherence (medication gap of ≥ 14 days) and medication attitudes as assessed with the Rating of Medication Influences scale. Patients randomly assigned to an RLAI recommendation could decline the recommendation, so analysis defined treatment groups by intent-to-treat and as-actually-treated.

Results: Eighty-one percent of patients (30/37) stopped medication within 104 weeks. There was a trend toward an initial adherence benefit favoring RLAI acceptors at 12 weeks ($P = .058$), but no significant difference between RLAI and oral antipsychotic treatment in time to initial nonadherence during the overall study ($P = .188$). Medication attitudes did not differ between groups.

Conclusions: Acceptance of RLAI was associated with an initial adherence benefit that was not sustained over time. Early introduction of LAI therapy did not adversely affect adherence attitudes. The small size of the study and low power limit interpretation, but the few patients who remained adherent into a second year were all receiving RLAI. Nonadherence was almost universal in our first-episode cohort, but nonadherence was more easily detected among first-episode patients treated with LAI therapy than it was with oral antipsychotics.

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Maintenance antipsychotic treatment is as important for first-episode schizophrenia patients as it is for patients with more established diagnoses. However, most first-episode patients do not stay on antipsychotic medication for very long. While clinicians think about duration of antipsychotic therapy in terms of how many years until discontinuation is recommended, many first-episode patients think of their duration of treatment in terms of *days,* not years.

Long-acting injectable (LAI) antipsychotics are often recommended for schizophrenia patients identified as being at high risk of nonadherence.[1] Certainly, a recently diagnosed first-episode patient embarking on maintenance antipsychotic treatment for the first time is at very high risk for nonadherence.[2–4] Nonetheless, despite its apparent advantages, LAI therapy is generally not considered to be a first-line approach during the early phases of schizophrenia. For example, the 2004 American Psychiatric Association guidelines suggest waiting until patients show patterns of "recurrent relapses related to partial or full nonadherence."[5] At least in the United States, if LAI therapy is used at all during the early phases of illness, it is only after the "revolving door" pattern has already been established.

Even for the "revolving door" patient, LAI therapy is underused, in large part because of clinician ambivalence about, or reluctance toward, using it.[6,7] Because the literature on physician barriers to LAI therapy pertains to persistently ill patients, there is virtually no research on physician attitudes toward LAI medication for first-episode populations. However, informal discussions with experienced clinicians indicate that—compared to "revolving door" patients—there is even less enthusiasm about recommending LAI to patients early in the illness course, shortly after a diagnosis of schizophrenia is established. From these informal discussions, we have noted some common concerns voiced by clinicians about recommending LAI therapy for recently diagnosed patients. Reasons for hesitation include the belief that a recommendation of LAI medication would be rejected out of hand, that suggesting injections could jeopardize the therapeutic relationship, and that first-episode patients would be particularly likely to experience medication by LAI as more stigmatizing or demeaning than oral therapy. Furthermore, there are few prospective studies evaluating the effectiveness of LAI therapy in first-episode patient cohorts treated in "real world" settings.[8]

We conducted a prospective randomized controlled trial (RCT) of maintenance antipsychotic treatment in a cohort of recently stabilized, first-episode schizophrenia patients who were embarking on their initial maintenance outpatient treatment. Eligible patients were randomly assigned to a clinical recommendation of staying on their current oral second-generation antipsychotic (ORAL) versus changing to long-acting injectable risperidone microspheres (RLAI). The initial acceptance and 12-week adherence outcomes have been reported.[9] We now report the results of the PREvent First-Episode Relapse (PREFER) study for the full 2-year trial regarding the primary outcomes of adherence behavior and adherence attitudes.

METHOD

Study Design

This is a randomized, open-label, parallel-group maintenance treatment study comparing patients who remained on their current oral second-generation antipsychotics to those who changed to RLAI. The study included patients who experienced their first acute psychotic episode; met diagnostic criteria for schizophreniform disorder, schizophrenia, or schizoaffective disorder confirmed by the Structured Clinical Interview for *DSM-IV* Axis I Disorders[9]; and had limited lifetime prior exposure to antipsychotic medication. Details of the initial phases of the study and subjects have been reported[10] and are briefly summarized here. The study was registered at ClinicalTrials.gov (identifier: NCT00220714).

- Most recently diagnosed, first-episode schizophrenia patients stop their antipsychotic medication within the first year of outpatient treatment.
- Early initiation of long-acting antipsychotic therapy seems to delay but not prevent the onset of nonadherence in this patient population.
- Nonadherence to oral therapy was usually not recognized in "real time" by the treating clinician. Given the likelihood of unrecognized nonadherence in first-episode patients, long-acting therapy offers an "information advantage" regarding efficacy and safety of the prescribed antipsychotic.

Clinical Points

Study Population

Participants were enrolled from December 2004 to March 2007 from 2 affiliated sites: SUNY Downstate Medical Center and Kings County Hospital Center (Brooklyn, New York). Institutional review board approval was obtained at each site. Seventy-four patients with a first episode of psychosis consented to an evaluation phase; 46 patients who met diagnostic criteria for schizophrenia or schizoaffective or schizophreniform disorder were eligible for the RCT. In addition to diagnosis, the following inclusion criteria were met: long-term maintenance antipsychotic treatment was clinically indicated; clinical response to oral antipsychotic medication was demonstrated; a history of recent willingness to attend outpatient treatment services; and completion of at least 1 dedicated psychoeducation session that, when possible, included a key family member. Thirty-eight subjects consented, and 37 were randomized.

Procedures

Subjects were randomized to a *recommendation* of either (1) remaining on treatment with oral medication (ORAL group) or (2) changing from oral medication to RLAI (RLAI group). Randomization to the RLAI or ORAL recommendation was in a 2:1 ratio. Study duration was up to 2 years after randomization. Patients who discontinued antipsychotic medication were encouraged to return for monthly monitoring visits and assessments. Patients randomly assigned to RLAI continued to receive RLAI whenever possible, including starting or restarting RLAI for those who refused or discontinued their RLAI after randomization.

Setting and Provision of Care

The treatment service setting was a specialty program for treatment of first-episode schizophrenia patients located at the outpatient service of Kings County Hospital Center, a busy inner-city public psychiatry outpatient clinic.

Pharmacologic Intervention

General approach for entire sample. Antipsychotic dosing philosophy was consistent with the first-episode psychopharmacology literature, which is to dose at the lower end of therapeutic dosage range (eg, a target dose of 3 mg/d of oral risperidone or its equivalent, or 25 mg every 2 weeks for RLAI). Most other commonly used adjunctive psychiatric medications (eg, valproate, lithium, lorazepam) were allowed. Conventional antipsychotics and combination antipsychotics (except during antipsychotic crossovers) were not permitted. Subjects assigned to the oral recommendation were not allowed to receive any LAI during the study period.

Treatment after randomization. For subjects assigned to the RLAI recommendation, actual treatment status depended on RLAI acceptance. RLAI acceptors received an initial 25-mg injection with overlap of oral risperidone for at least 3 weeks. The maintenance target dose for RLAI was 25 mg every 2 weeks, with an allowable dose range between 25 and 50 mg every 2 weeks as per clinician judgment. After the crossover, oral supplementation was permitted for acute exacerbations of positive symptoms, but long-term use (>4 weeks) of ongoing combination oral antipsychotic with RLAI was not permitted. Injections were given at a treatment room onsite, usually by a nurse practitioner. Those who refused RLAI continued on their current oral antipsychotic.

Subjects assigned to ORAL continued with their recommended oral regimen. They were given a written prescription to be filled at the central pharmacy located in the hospital complex. For both conditions, there were no direct medication out-of-pocket costs (eg, medication copays). Also, patients did not receive any payment to attend clinical appointments, and there was no active outreach prior to scheduled medication management visits.

Assessments

Major assessments were completed at randomization and 12, 36, 52, 78, and 104 weeks postrandomization by independent raters blinded to randomization and to actual treatment status. Subjects received $10 for each of these research assessment study visits. Symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS)[11] and the Clinical Global Impressions-Severity of Illness scale (CGI-S).[12] Adverse event monitoring was done by treating clinicians who were not blinded. Assessments used included

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the Abnormal Involuntary Movement Scale (AIMS),[12] the Barnes Akathisia Rating Scale (BAS),[13] the Simpson-Angus Scale (SAS)[14] for extrapyramidal side effect (EPS)–related adverse events, and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[15] adverse event scale for other common adverse events associated with antipsychotic medication.

Definition of nonadherence behavior. Nonadherence behavior was defined as a medication gap of ≥ 14 consecutive days of complete discontinuation of all antipsychotic medication (GAP). Adherence tracking data came from a multisource approach known as the All Source Verification (ASV).[16] The ASV approach takes information from various sources on adherence behavior in parallel and integrates these information sources into a single summary outcome. The ASV generates a running record of adherence behavior at a day-to-day level, with each day defined as either "adherent" or "nonadherent." The primary source for patients prescribed oral antipsychotics was the pharmacy refill records; for those receiving RLAI, it was the injection records. These sources were supplemented by patient report, family report, and clinicians' notes. The reasons for medication discontinuation were assessed using the CATIE all cause discontinuation measure.[15]

Assessment of adherence attitude. The primary adherence attitude outcome used a standardized interview developed to assess adherence influences to antipsychotic medication for persons with schizophrenia, the Rating of Medication Influences (ROMI),[17] which was conducted at each major assessment point except baseline. The first ROMI was done at week 12 to ensure that all subjects had adequate duration of time on antipsychotic medication. Two a priori item clusters (Denial of Illness and Medication Affinity) and 4 post hoc clusters (Relapse Prevention, Influence of Others, Life Goals, and Rejection of Label) were identified for between-group analysis. A secondary adherence attitude outcome was distress from problems attributed to the antipsychotic medication based on self-reported distress and influence on future adherence from the CATIE side effect assessment interview.[15]

Data Analyses

Treatment status grouping. Treatment groups were defined a priori in 2 ways: by initial randomization status (intent-to-treat [ITT]) and by initial acceptance status (as-actually-treated [AAT]).[10] The AAT grouping compared RLAI acceptors to all ORAL subjects, including those who were randomly assigned to stay on oral treatment and those who were randomly assigned to, but who refused, RLAI. Both groupings were used for primary outcomes of adherence behavior and attitudes. Only AAT was used for secondary adherence outcomes, symptoms, and adverse events.

Baseline characteristics. Comparisons were made for all variables using both ITT and AAT groupings. For continuous variables, means were compared using the 2-sample *t* test. Categorical variables were compared using χ^2 analysis or Fisher exact test if an expected cell value was less than 5.

Adherence behavior. The primary outcome of time until nonadherence used Kaplan-Meier product limit survival methods between groups defined according to both ITT and AAT, using the log-rank test of differences between groups, for up to 2 years' follow-up. Secondary analyses included a 2×2 contingency table with Fisher exact test for proportions of patients meeting GAP criteria, proportion of nonadherent days (adjusted for days in study), and time until rehospitalization using Kaplan-Meier survival.

Adherence attitudes. ROMI cluster scores were compared between groups at 5 timepoints (12, 36, 52, 78, and 104 weeks). Intraclass correlation coefficients using a 2-way mixed model and a consistency definition of agreement were computed to evaluate test-retest reliability of the 6 ROMI cluster scores, adjusting for any consistent change over time. A generalized mixed linear model was constructed to predict each of these outcomes; fixed factors were treatment arm–defined in separate analyses according to ITT and AAT status and time (12, 36, 52, 78, and 104 weeks). An unstructured intrasubject covariance matrix was modeled. Normal distribution was assumed and verified by inspection of model residuals for each outcome other than the Rejection of Label cluster, which, due to extreme skewness, was dichotomized as zero vs > zero. Satterthwaite corrections were made to denominator degrees of freedom. SAS 9.2 statistical software (SAS Institute; Cary, North Carolina) was used. No adjustment was made for multiplicity.

The secondary analysis of distress attributed to antipsychotic side effects used the CATIE distress/nonadherence item with the criterion of a score of at least moderate distress at any follow-up assessment. Because these ratings were obtained by clinicians who were aware of the prescribed treatment status, only AAT groups were compared, and no statistical tests were done.

Symptoms. PANSS scores were analyzed using the 5-factor model for PANSS (negative symptoms, positive symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression).[18] All other symptom scales used total scores.

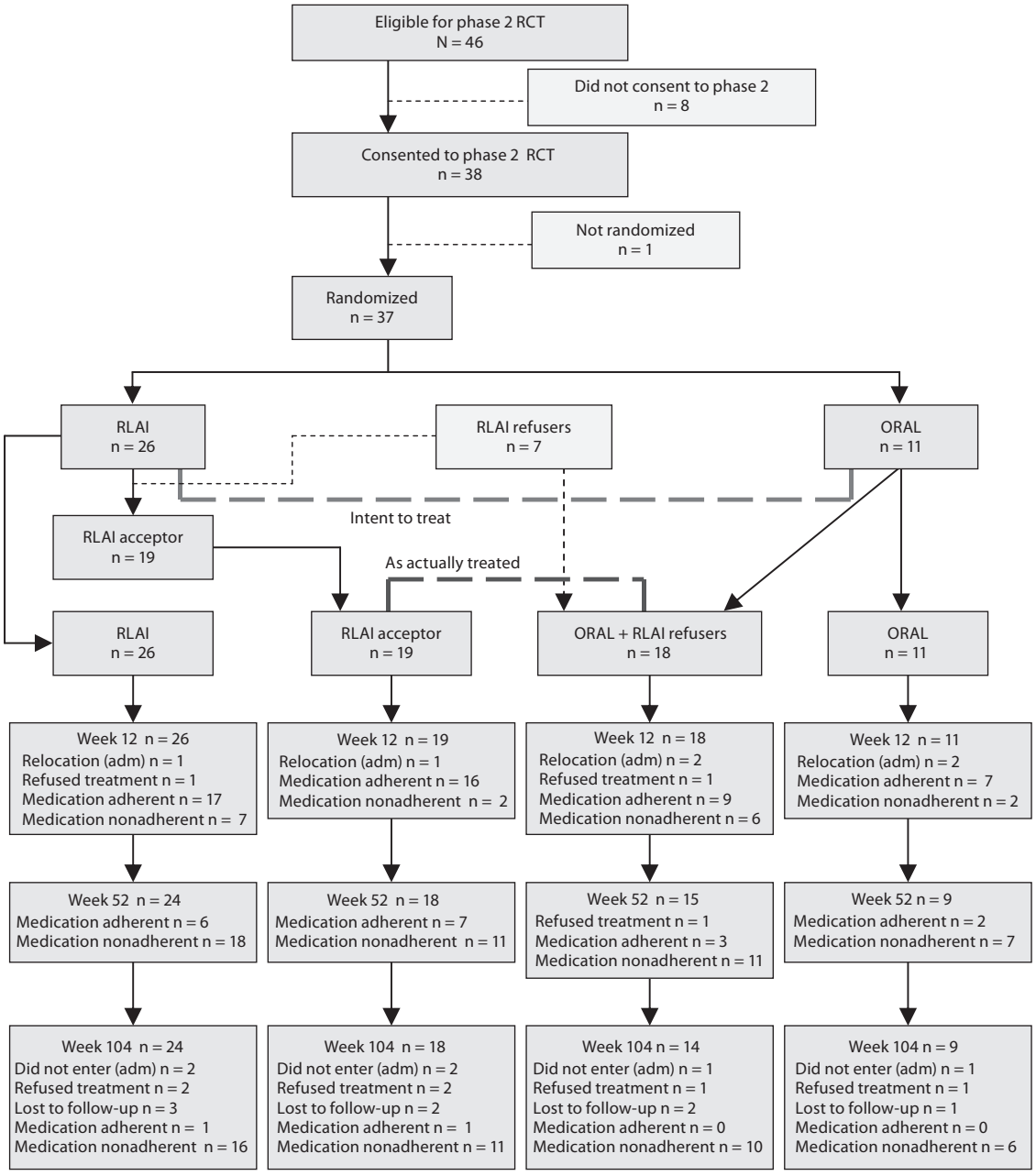
Adverse events. Ratings of moderate or severe on the CATIE adverse event scale[15] are presented at baseline (whole cohort) and after baseline by AAT group. In the postbaseline summary, each subject is counted only once and only if a rating of moderate or severe was recorded. The mean BAS, SAS, and AIMS scores were summarized by AAT group using the same criteria. No statistical tests were conducted because these measures were completed by nonblinded clinicians.

RESULTS

Characteristics of the Sample

As shown in Figure 1, of the 37 randomized patients, 26 were randomized to a recommendation of RLAI and 11, to ORAL. Seventy-six percent of subjects were male, 38% were African American and 62% were of Afro-Caribbean origin, their mean age at first hospitalization for psychosis and at the time of recruitment was 25.3 (SD = 6.6) years, and 95%

Figure 1. Participant Flow (CONSORT chart) for PREFER RCT



Abbreviations: adm = administrative reasons, ORAL = oral antipsychotic, PREFER = PREvent First-Episode Relapse study, RCT = randomized controlled trial, RLAI = long-acting injectable risperidone microspheres.

were single. Virtually all of the patients lived with family, predominantly parents or other lineal relatives (76%), and their mean number of years of education was 11.5 (SD = 1.8). There were no baseline differences in demographic, illness, or symptom variables between groups defined by either ITT or AAT criteria.

Acceptance of RLAI Recommendation

Figure 1 also shows acceptance of RLAI; 19 of 26 accepted RLAI within 6 weeks of receiving the recommendation, with an additional subject accepting RLAI after a relapse. The cumulative acceptance of RLAI recommendation was 77%.

Adherence Behavior

A Kaplan-Meier survival analysis of the entire cohort (N = 37) using time until GAP shows that most (81%; n = 30) had a GAP by 104 weeks, with most of these (76%; n = 28) occurring within 52 weeks (Figure 2A).

For the ITT analysis of initial group assignment (Figure 2B), 22 of 26 subjects assigned RLAI (85%) reached a GAP compared with 8 of 11 (73%) in the ORAL group (Fisher exact test, $P = .403$). Median time to GAP event was 23 weeks (95% CI, 11–49) in the RLAI group and 44 weeks (95% CI, 0.7–49) in the ORAL group (log-rank test, $\chi^2_1 = 0.14$, $P = .709$).

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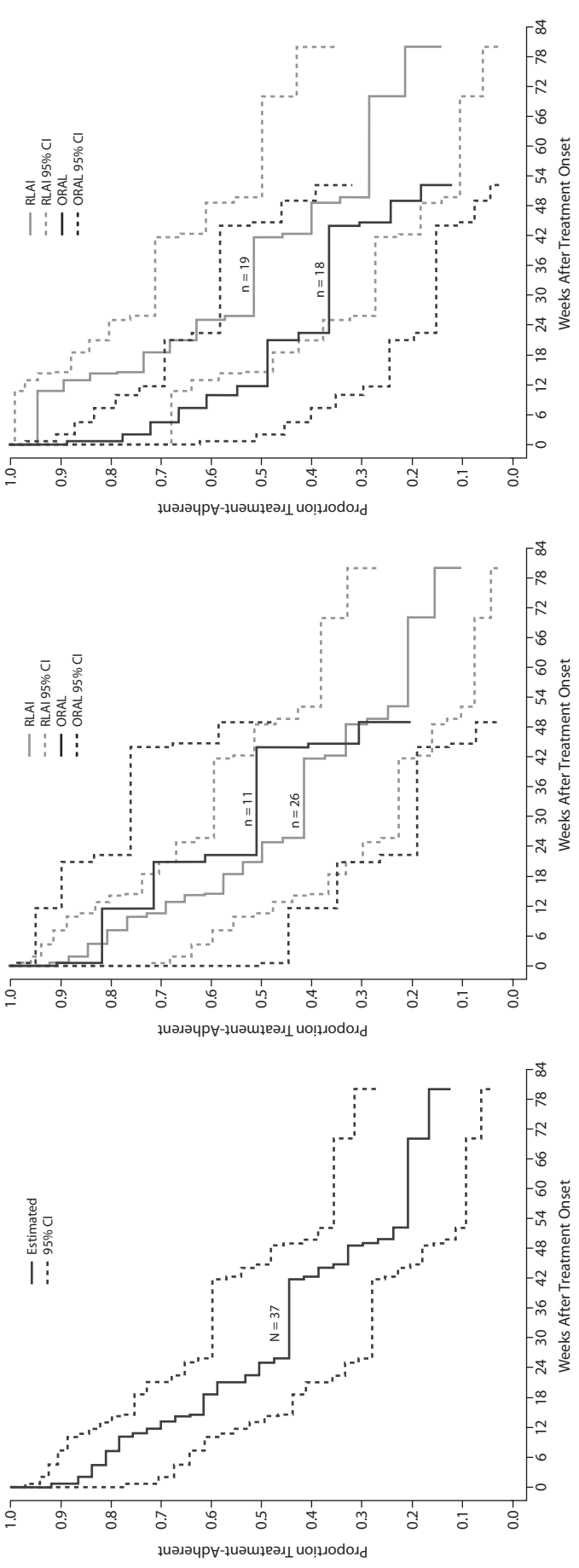

Figure 2. Time to Initial Medication Gap[a]

[a]At least 14 consecutive days of complete discontinuation of all antipsychotic medication.
Abbreviations: AAT = as actually treated, ITT = intent to treat, ORAL = oral antipsychotic, RLAI = long-acting injectable risperidone microspheres.

For the AAT analysis (Figure 2C), 15 of 19 (79%) of the RLAI acceptors reached a GAP event, compared with 15 of 18 (83%) in the ORAL group (Fisher exact test, $P = 1.000$). Median time to GAP event was 42 weeks (95% CI, 15–50) for the RLAI group and 12 weeks (95% CI, 2–45) for the ORAL group (log-rank test, $\chi^2_1 = 1.73$, $P = .188$). We also used proportional hazards regression to estimate (in a single model) the hazard ratio between the 2 groups for each of the 3 time intervals (interval 1 = < 12 weeks, interval 2 = 12–36 weeks, and interval 3 = 36–52 weeks). Numbers were too small to allow examination of later periods. This analysis shows the hazard ratio for ORAL relative to RLAI to be 4.6 ($P = .058$) for the first interval, 0.7 ($P = .630$) for the second interval, and 1.1 ($P = .879$) for the third interval. A comparison of the hazard ratios for intervals 1 and 2 yields $P = .080$; for intervals 1 and 3, $P = .205$; and for intervals 2 and 3, $P = .664$. A test of whether any differences exist among the 3 hazard ratios yields $P = .202$.

For secondary adherence behavior outcomes, there was no difference in proportion of nonadherent days between groups. Rehospitalization estimates (Kaplan-Meier) were 26% (5/19) for RLAI and 23% (4/18) for ORAL at 52 weeks and 58% (11/19) for RLAI and 72% (13/18) for ORAL at 104 weeks.

Dosing and Reasons for Medication Changes

Dosing of the RLAI and ORAL groups is shown in Table 1. The most frequent modal dose of RLAI (58% of cases) was 25 mg every 2 weeks. Modal doses for oral medications were at the lower end of the labeled ranges for risperidone (3 mg), aripiprazole (10 mg), and quetiapine (200 mg) and at the higher end for olanzapine (20 mg) and ziprasidone (160 mg). In addition to nonadherence, we evaluated reasons for discontinuation of specific medications; clinician decision was not considered nonadherence. Fifteen of 18 ORAL patients stopped their antipsychotic before 52 weeks. All 15 were categorized as "patient decision" (using CATIE discontinuation criteria), and all 15 (100%) subsequently met GAP criteria for nonadherence.

Of the 15 RLAI discontinuations, 12 were categorized as "patient decision," 2 were tolerability-related (clinician decision), and 1 was efficacy-related (clinician

Table 1. Medication Dosages[a]

Treatment Group	Modal Dose, % of Patients	Maximum Dose, % of Patients	
RLAI group[b] (n = 19)			
25 mg/2 wk (n = 19)	57.9	36.8	
37.5 mg/2 wk (n = 11)	31.6	36.8	
50 mg/2 wk (n = 6)	10.5	26.3	
ORAL group[c] (n = 18)[d]	Modal Dose (mg/d)	Maximum Dose (mg/d)	Dose Range (mg/d)
Risperidone (n = 18)	3	8	0.5–8
Aripiprazole (n = 3)	10	30	5–30
Olanzapine (n = 2)	20	20	5–20
Quetiapine (n = 1)	200	600	100–600
Ziprasidone (n = 3)	160	160	40–160

[a]Using as-actually-treated grouping.
[b]Patients who switched to long-acting injectable risperidone microspheres (RLAI) during the maintenance period.
[c]Patients who continued taking oral antipsychotics (ORAL) during the maintenance period.
[d]Ns for individual oral medications are more than the total group N because patients may have received more than 1 oral antipsychotic during the course of the study.

decision). Many of the 12 subjects with RLAI "patient decision" discontinuations told the clinician at the time of the discontinuation that they would continue with an oral antipsychotic, but all 12 refused or discontinued oral antipsychotic shortly after RLAI discontinuation and met GAP criteria. Six of the 12 patients restarted RLAI after a symptom exacerbation or hospitalization. The time between stopping and resuming RLAI ranged from 3 to 33 weeks. Once resuming RLAI, these subjects then remained on their second course of RLAI from 10 to 73 weeks. The 3 clinician decision RLAI discontinuation subjects were prescribed an oral antipsychotic, and all 3 remained adherent to their oral antipsychotic for the remainder of the study duration.

Adherence Attitudes

Overall, adherence attitudes did not differ by treatment group. Only 1 of the 12 analyses (6 clusters by 2 groupings) showed significant group-by-time effects. The Relapse Prevention cluster showed a significant group-by-time interaction ($P < .05$) in the AAT grouping. Simple effects analysis (unadjusted P values are reported) for that measure suggests significantly lower ROMI Relapse Prevention scores at 12 weeks in the RLAI group ($P < .005$) than in the ORAL group. In addition, the Denial of Illness cluster showed a significant time effect ($P < .05$); scores increased (greater denial) over time in both groups.

Overall likelihood of reported distress from attributed side effects between groups is shown in Table 2 for the AAT groups (n = 34). Overall distress from any attributed problem at any time during follow-up was 73.7% (14/19) for RLAI and 53.3% (8/15) for ORAL. No statistical comparisons were made, but distress from weight gain appeared to be more frequent in the RLAI group (47.4% [n = 9] vs 6.7% [n = 1]). In contrast, ORAL patients appeared to be more distressed by sedation (20.0% [n = 3] vs 5.3% [n = 1]) and EPS-related problems (26.7% [n = 4] vs 10.5% [n = 2]).

Symptom Outcomes

There were no statistically significant differences between groups for CGI-S or the 5 PANSS factors at any timepoint.

Adverse Events

Table 3 shows the percentage of patients rated as having moderate or severe adverse events at baseline (n = 33) and at any time after baseline (n = 35) by AAT groups. The most commonly reported adverse events for RLAI and ORAL treatments were menstrual irregularity at any time after baseline (females only, 60.0% [n = 3] vs 50.0% [n = 2]), weight gain (36.8% [n = 7] vs 25.0% [n = 4]), and sexual side effects (36.8% [n = 7] vs 25.0% [n = 4]). Table 4 shows the same information for the AIMS and BAS. Depending on cutoffs used, AIMS severity criteria were met at any time after baseline by 5.3% (n = 1) of the RLAI group vs 6.7% (n = 1) (cutoff of ≥ 3) or 13.3% (n = 2) (cutoff of ≥ 2) of the ORAL group; BAS criteria were met by 5.3% (n = 1) of the RLAI group vs 13.3% (n = 2) (≥ 3) or 20.0% (n = 3) (≥ 2) of the ORAL group; and SAS severity criteria were met by 5.3% (n = 1) of the RLAI group and 6.7% (n = 1) of the ORAL group.

DISCUSSION

We report the 104-week outcome results of the PREFER study. In terms of our primary outcomes, we found that nonadherence behavior was very common in both groups. Very few patients remained adherent for the entire 2-year follow-up. Time until first medication GAP did not differ between randomized groups. Among RLAI acceptors, the median time to a medication GAP event was 42 weeks compared to only 12 weeks in the ORAL group (log-rank test, $\chi^2_1 = 1.73$, $P = .19$). The lack of statistical significance in the complete long-term follow-up contrasts with our previously published findings[10] that indicated that acceptance of RLAI was associated with significantly longer medication continuation within the first 12 weeks. Adherence attitudes also showed no consistent differences between groups throughout the follow-up period. This is consistent with our initial findings of no difference in adherence attitudes at 12 weeks.

Long-Term Effect of RLAI on Adherence Behavior

The early advantage of accepting RLAI on adherence behavior at 12 weeks was not sustained. The clearest statement of our findings is that acceptance of injections in first-episode patients delays nonadherence. As noted, although the survival times are not significantly different, the observed median time to nonadherence is 30 weeks longer in those who accept injections. Further, only RLAI acceptors were represented in the few patients who remained continuously adherent with no GAPs for the entire 2-year follow-up.

Long-Term Effect of RLAI on Adherence Attitudes

The only significant between-group difference on any of the ROMI clusters was at the initial week 12 ROMI assessment. Patients who accepted the RLAI recommendation

Table 2. Self-Reported Distress From Attributed Side Effects[a]

Attributed Side Effect	Baseline, Whole Cohort (N = 30), n (%)	After Randomization[b]		
		Whole Cohort (N = 34), n (%)	As Actually Treated	
			RLAI[c] (n = 19), n (%)	ORAL[d] (n = 15), n (%)
Any attributed side effect	9 (30.0)	21 (61.8)	14 (73.7)	8 (53.3)
Gynecomastia or galactorrhea	3 (10.0)	1 (2.9)	1 (5.3)	0 (0.0)
Sedation	6 (20.0)	4 (11.8)	1 (5.3)	3 (20.0)
Weight gain	4 (13.3)	10 (29.4)	9 (47.4)	1 (6.7)
EPS-related problem[e]	3 (10.0)	6 (17.6)	2 (10.5)	4 (26.7)
Anticholinergic problem (dry mouth, urinary hesitancy, or constipation)	2 (6.7)	6 (17.6)	3 (15.8)	3 (20.0)
Sexual difficulties[f]	1 (3.3)	4 (11.8)	3 (15.8)	1 (6.7)

[a]Includes patients for whom distress was scored as 2 (patient thinks side effect is caused by antipsychotic and side effect affects willingness to take antipsychotic, but patient is still taking antipsychotic) or 3 (patient thinks side effect is caused by antipsychotic and is not willing to take medication due to side effect) on the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[14] patient-reported distress item for rating common side effects associated with antipsychotic therapy, a 0–3 point interval scale.
[b]Distress rated ≥ 2 at any assessment point after baseline.
[c]Patients who switched to long-acting injectable risperidone microspheres (RLAI) during the maintenance period.
[d]Patients who continued taking oral antipsychotics (ORAL) during the maintenance period.
[e]Items included distress from either perceived akathisia or akinesia.
[f]Items included distress from decreased sex drive, sexual arousal, or sexual orgasm problems attributed to antipsychotic medication.
Abbreviation: EPS = extrapyramidal side effects.

Table 3. Clinician-Elicited Adverse Events[a]

Clinician-Elicited Adverse Event	Baseline, Whole Cohort (N = 33), n (%)	After Randomization[b]		
		Whole Cohort (N = 35), n (%)	As Actually Treated	
			RLAI[c] (n = 19), n (%)	ORAL[d] (n = 16), n (%)
Insomnia	1 (3.0)	2 (5.7)	0 (0.0)	2 (12.5)
Hypersomnia, sleepiness	7 (21.2)	6 (17.1)	2 (10.5)	4 (25.0)
Urinary hesitancy, dry mouth, constipation	1 (3.0)	2 (5.7)	1 (5.3)	1 (6.3)
Decreased sex drive, arousal, ability to reach orgasm	5 (15.2)	11 (31.4)	7 (36.8)	4 (25.0)
Gynecomastia, galactorrhea	2 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)
Menstrual irregularities[e]	3 (50.0)	5 (14.3)	3 (60.0)	2 (50.0)
Incontinence, nocturia	0 (0.0)	1 (2.9)	0 (0.0)	1 (6.3)
Orthostatic faintness	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
EPS-related[f]	6 (18.2)	6 (17.1)	3 (15.8)	3 (18.8)
Weight gain	3 (9.1)	11 (31.4)	7 (36.8)	4 (25.0)

[a]Includes patients for whom adverse events were scored as 2 (moderate) or 3 (severe) on the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[14] adverse event scale.
[b]Adverse event rated ≥ 2 at any point after baseline during the study.
[c]Patients who switched to long-acting injectable risperidone microspheres (RLAI) during the maintenance period.
[d]Patients who continued taking oral antipsychotics (ORAL) during the maintenance period.
[e]Percentages based on the total number of women in the study (baseline total = 6; thereafter, total = 9, as-actually-treated RLAI = 5, as-actually-treated ORAL = 4).
[f]Items included distress from perceived akathisia or akinesia.
Abbreviation: EPS = extrapyramidal side effects.

Table 4. Extrapyramidal Side Effects (EPS) Rating Scales

EPS-Related Scale	Baseline, Whole Cohort (N = 37), n (%)	After Randomization[a]		
		Whole Cohort (N = 34), n (%)	As Actually Treated	
			RLAI[b] (n = 19), n (%)	ORAL[c] (n = 15), n (%)
Abnormal Involuntary Movement Scale				
Global severity score ≥ 2	1 (2.7)	3 (8.8)	1 (5.3)	2 (13.3)
Global severity score ≥ 3	0 (0.0)	2 (5.9)	1 (5.3)	1 (6.7)
Barnes Akathisia Rating Scale				
Global score ≥ 2	3 (8.1)	4 (11.8)	1 (5.3)	3 (20.0)
Global score ≥ 3	0 (0.0)	3 (8.8)	1 (5.3)	2 (13.3)
Simpson-Angus Scale mean score ≥ 1	3 (8.1)	2 (5.9)	1 (5.3)	1 (6.7)

[a]Patients who scored the described criteria at any point after baseline during the study.
[b]Patients who switched to long-acting injectable risperidone microspheres (RLAI) during the maintenance period.
[c]Patients who continued taking oral antipsychotics (ORAL) during the maintenance period.

were more likely to report relapse prevention as a motivation for adherence than those who declined injections or were randomized to stay on oral medication treatment. We believe that this difference is unlikely to be a treatment effect but rather reflects intrinsic differences in medication attitude between those who agree to receive injectable medication and those who do not.

Neither recommendation nor acceptance of LAI therapy was associated with any long-term differences in adherence attitudes toward medication. We looked for, but did not find, any evidence to support the commonly voiced clinical concern that offering LAI too soon would disenfranchise a first-episode patient. In other words, there are far more important determinants of adherence attitudes than the recommended route of medication administration.

We describe distress due to adverse effects of medication without formal statistical evaluation. Over 60% of patients reported distress at some time during treatment. It appears that the overall likelihood of reporting a distressing side effect was somewhat higher in the RLAI acceptor group (73.7% vs 53.3%), and there were differences in specific side effects that were the source of distress. Distress-attributed weight gain was most frequent, and it was more common in RLAI acceptors than in the oral group. Patients in this group might be more likely to notice weight gain because of the somewhat longer exposure to RLAI than oral therapy. Distress about EPS and sedation was more commonly reported in patients treated with oral antipsychotics. It may be that these qualitative differences are related to greater plasma drug level fluctuation resulting from the pharmacokinetics of oral administration. Finally, we note that subjective reports are valid in their own right but cannot be directly compared to the clinicians' ratings of adverse events. Therefore, we present patient self-report and clinician ratings in separate tables.

Other Outcomes

There were no differences in symptom assessments or in rehospitalization during the study course. We did not expect to find differences in hospitalization, because a much larger sample size and longer follow-up would have been required.[19] Our findings regarding adverse events are of interest because they are comparable to those seen in patients with a more chronic course despite the generally low dosing strategies used in this first-episode sample. These findings underscore the importance of monitoring for adverse events and that high rates of perceived side effects in first-episode populations should be anticipated despite the use of relatively low doses.

Limitations

There are several limitations to the study. All subjects assigned to long-acting therapy received risperidone microspheres. In the "real world," there are other alternatives, including first-generation, conventional antipsychotics available in long-acting formulations (eg, haloperidol decanoate and fluphenazine decanoate in the United States and other formulations outside the United States). Furthermore, since the time the study was done, 2 other second-generation formulations have been approved, paliperidone palmitate and olanzapine palmoate. The current study does not provide any clinical information on the relative effectiveness of the newer versus older antipsychotics, and other studies are needed to address this very important question.

It is easier to monitor adherence to injections than to oral medications. We could always identify a medication gap for the LAI patients by reviewing their appointment and injection records. This was certainly not the case for those prescribed oral antipsychotics. Differential measurement error might therefore bias these results toward the null (eg, showing no advantage of LAI when in fact one exists). We think this is an unlikely explanation of the lack of adherence differences in the ITT analyses because we did observe a significant effect favoring those who accepted injections at 12 weeks in the AAT analysis. However, we did replicate in a first-episode sample[16] the now well-documented finding in persistently ill patients that clinicians are not very accurate at identifying nonadherence to oral medication.[20–22] In our study, the 12-week adherence difference favoring RLAI acceptors would not have been detected if we had relied only on clinician report of adherence. We believe that our multisource tracking method for oral adherence largely addresses this potential problem.

Of more concern is that this RCT was underpowered. Our final randomized sample of 37 was less than 50% of the sample we projected would be needed to detect a difference between groups in adherence. It seems, though, that the 1-year finding that virtually all subjects become nonadherent regardless of initial recommendation or acceptance of RLAI is unlikely to be explained by lack of statistical power ($P = 1.0$). However, there is a suggestion that acceptance of long-acting antipsychotic delays nonadherence. While not statistically significant, the median time until nonadherence was only 12 weeks for those who remained on oral therapy compared to 42 weeks for those who accepted RLAI ($P = .188$). Also, a hazard ratio analysis of 3 follow-up points showed that those accepting RLAI were 4.6 times more likely to still be adherent than the ORAL group; however, this result narrowly missed statistical significance ($P = .058$). It is our belief that this would have reached significance if we had adequate sample size, but we cannot be sure. Therefore, we feel that the sample size limitation may have attenuated the statistical significance of our finding of initial adherence benefits, and, more importantly, leads to the conundrum of how to interpret a seemingly very meaningful delay in time until nonadherence (12 weeks for RLAI acceptors vs 42 weeks for ORAL patients) that does not meet statistical significance ($P = .188$). We are more confident that the sample size limitation did not compromise our finding that LAI does not prevent nonadherence from happening eventually, at least in our treatment setting.

Other limitations include that the study was done at a single facility, which is a public hospital treating patients predominantly of first- or second-generation immigrant minority status. Our subjects' demographics were a reflection

of the larger treatment services environment. However, our cohort was not at all favorably inclined toward injections over oral medication, and patients' families did not readily accept this recommendation either. Therefore, we feel that our finding of feasibility of acceptance of LAI medication in first-episode patients is probably generalizable to other first-episode patients who are initially hesitant to accept LAI medication, with the important caveat that this finding applies only to the subgroup of first-episode patients who accept some form of outpatient treatment after discharge.

Clinical Implications

The literature on the relative effectiveness of LAI medications compared to oral antipsychotics remains difficult to assess. Meta-analyses[8,23] of relapse prevention favor LAIs, but recent large studies[24,25] have not shown benefits of LAI on relapse prevention. The present study was not designed to assess differences in relapse; nonadherence was the primary outcome measure, and, in contrast to the studies just cited, our study focused on patients early in the course of illness. The potential effectiveness of LAI over oral medication may depend on the reasons for using LAI medication. In our cohort, LAI medication delayed but did not prevent nonadherence and aided in adherence assessment.

The potential benefits of LAI medication relative to oral medication can be divided into adherence tracking benefits and direct improvement of adherence behavior. In this study, LAI medication provided some direct benefits for adherence behavior during the first few months of outpatient treatment for first-episode schizophrenia patients starting maintenance antipsychotic treatment. However, these short-term adherence benefits were not sustained, suggesting that early initiation of LAI therapy may *delay* but not *prevent* initial nonadherence in first-episode patients. Our clinical interpretation is that the clinical factors driving premature medication cessation in a first-episode patient population are usually related to an active decision to stop medication. LAI therapy might delay but will not stop an active choice.

The other clinical benefit of LAI therapy is adherence tracking. We were able to track the accuracy of clinicians' assessment of adherence with oral antipsychotic therapy by comparing their ratings with the ASV. The ASV is labor intensive and not practical in routine clinical care. Using the ASV, we found that clinicians overestimated medication adherence for patients on oral antipsychotic therapy. Whereas discontinuing LAI medication was always recognized by the clinician, over 50% of medication gaps from oral therapy were not recognized at the time of the discontinuation. This finding was not predicted a priori, but poor recognition of oral adherence problems by clinicians is consistent with studies of more persistently ill schizophrenia patients taking oral antipsychotics.

A theoretical advantage of LAI therapy is that the longer half-life of LAI medication may attenuate the clinical impact of a temporary medication gap. Another possible advantage is that discontinuation of LAI therapy is always recognized as a medication gap, whereas oral discontinuation may be covert. This may lead to differences in what the patient chooses to disclose to the clinician and also improves the clinician's quality of information about the efficacy and safety of the regimen. This study was not powered to determine whether these theoretical benefits translated to outcome differences.

We did not observe an effect of route of administration on attitudes toward medication and adherence. This suggests to us that recommending an LAI medication during the initial outpatient treatment period for first-episode patients neither helps nor hurts key subjective adherence factors such as stigma or therapeutic alliance. We conclude that it is not whether the medication is given by pills or injections that matters in terms of attitude toward medication. This is consistent with research suggesting that acceptance of medication and treatment depends on many other factors such as therapeutic alliance, family attitudes, and awareness of medication benefit.

CONCLUSION

To our knowledge, this is the first randomized controlled study comparing LAI and oral antipsychotics in first-episode patients. LAI medication is usually accepted by those first-episode patients starting outpatient treatment who accept—even transiently—oral antipsychotic medication. Contrary to widely held clinician beliefs that offering LAI medication early in the course of illness would be stigmatizing or hurt the therapeutic relationship, we found no adverse psychological impact from offering LAI treatment. We found improvements in adherence behavior by those patients who accepted RLAI at 12 weeks, but these improvements were not sustained. Nonadherence to oral medication was often missed by clinicians, and adherence tracking was much more accurate for patients receiving their medication as an LAI. We conclude that LAI therapy is a feasible intervention during early phases of maintenance treatment. It appears that RLAI may delay but does not prevent initial nonadherence in this patient population, although firm conclusions about later follow-up results are limited by inadequate sample size. The adherence tracking advantages associated with LAI therapy for more persistently ill patients were also seen in this first-episode study.

Drug names: aripiprazole (Abilify), haloperidol (Haldol and others), lithium (Lithobid and others), lorazepam (Ativan and others), olanzapine (Zyprexa), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal, Consta, and others), ziprasidone (Geodon).

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