Supplementary Online Content


eAppendix. Additional Methods and Results

This supplementary material has been provided by the authors to give readers additional information about their work.
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Methods

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Additional Study Inclusion and Exclusion Criteria

1) 18 to 45 years of age;
2) no evidence of a known neurological disorder;
3) no evidence of significant and habitual drug abuse or alcoholism in the 6 months prior to hospitalization and no evidence that the psychosis was accounted for by substance abuse;
4) no premorbid mental retardation;
5) sufficient acculturation and fluency in the English language to avoid invalidating research measures;
6) residence within commuting distance of the UCLA Aftercare Research Program; and
7) treatment with risperidone was not contraindicated.

Randomized Treatment with Either Oral Ris or RLAI Medication, Additional Details

Randomization did not occur until the patients finished an assessment battery that was completed a few hours at a time at weekly clinic visits and were judged able to meaningfully participate in the 2-day/week psychosocial treatment program, resulting in a median duration between study enrollment and randomization of 4.8 months (mean=5.5 months, SD=0.4). Although patients had typically achieved clinical stability prior to beginning randomized treatment, clinical stability was not a requirement for randomization. The most common reason for participants dropping out after enrollment but prior to randomization was poor awareness of having a disorder requiring psychiatric treatment. Following randomization, if an inadequate response to risperidone or intolerable side effects were observed, study psychiatrists prescribed a different second-generation antipsychotic medication, at which point the RCT treatment was considered to have concluded. Introduction of a second, adjunctive antipsychotic medication other than risperidone also concluded an individual’s RCT medication protocol. Adjunctive oral risperidone was very rarely used in the RLAI condition beyond the first 3 weeks after the first injection.

Randomized Psychosocial Treatment: Cognitive Remediation (CR), Additional Details

Patients in CR participated in a series of 23 cognitive training exercises, each of which involved a computer-based task with graduated levels of difficulty, conducted in a group “computer lab” setting at the clinic with cognitive trainers (see 16 for further details). A one-hour “Bridging Group” met weekly throughout CR to facilitate connections between the training and work/school performance 17,18.
Measurement of Medication Nonadherence

A dimension of adherence to risperidone across the long-acting injectable and oral groups was also evaluated so that medication adherence effects could be directly examined. Each patient’s adherence was rated on a 1-5 scale (1= excellent adherence, 5=very poor adherence) based on timeliness of injections for injectable medication, and on pill counts, patient reports, plasma levels, Medication Event Monitoring System (MEMS™) data, and psychiatrist judgments for oral medication. Pill counts, patient self-report, and clinician judgments were obtained every 1-2 weeks. Plasma risperidone and 9-hydroxyrispidone (9-OH) levels were assayed every four weeks in the oral Ris condition, and typically at weeks 8 and 12 for RLAI. Weekly adherence ratings were made for all sources of information available during a given rating period. Periods of partial or full medication nonadherence for patients who continued to attend clinic visits were recorded as study data and not considered to be protocol discontinuation or withdrawal from treatment. Adherence ratings and symptom ratings were rated by different staff members, and BPRS ratings and relapse data were not reviewed when making the adherence ratings. Ratings of nonadherence for RLAI were based on estimates that a stable plasma concentration lasts 4-5 weeks after the last injection, and then decreases with a 5-day average half-life over the following 2-3 weeks. Beginning 10 days after a missed injection, nonadherence was rated at gradually increasing levels of severity, with any day more than 49 days since the last injection rated at the highest level of nonadherence. The average level of nonadherence was computed for the entire time that RLAI treatment was intended (until a medication changed occurred, the patient withdrew from the protocol, or the 12-month point was reached).

Primary Outcome: Psychotic Exacerbation/Relapse, Additional Details

Symptoms were rated by the patient’s case manager who was not blinded to treatment group. Quality was assured through the use of a semi-structured rating scale, clear anchor points for each rating within items, and review of difficult item ratings by the quality assurance director without consideration of medication assignment. In addition, we believe that clinicians who meet with the patient frequently and have established a therapeutic alliance are well suited to identify subtle changes in the patient’s condition. Further, the BPRS data were computer scored many months after being collected, so categorization of exacerbations and relapses was not fully known at the time of symptom ratings.
Secondary Outcomes

Psychotic Symptom Control, Additional Details

We utilized the frequent symptom ratings throughout the 12 months to evaluate psychotic symptom control, a common and important clinical goal of maintenance antipsychotic medication treatment. The average level of these symptoms over the follow-through period was also used as an indicator of psychotic symptom control. An advantage of both of these measures, breakthrough and average symptom control, is that they are measured throughout the protocol, as opposed to a first relapse “event,” and provide a continuous index of symptom control for relapsing and non-relapsing patients alike.
Results

Sample Characteristics, Additional Details

Racial and ethnic backgrounds appeared typical of the Los Angeles metropolitan region. Participants in the two medication conditions did not differ significantly on any of these demographic variables. Only five patients (6%) had had an additional psychotic episode subsequent to their first psychotic episode prior to study entry (N=2 in the oral risperidone group, and N=3 in the RLAI group). Also, patients who entered the study but withdrew prior to group randomization were not statistically different at study entry than patients who were randomized in BPRS Thought Disturbance (mean of Unusual Thought Content, Hallucinations, and Conceptual Disorganization) (F(1,121)=0.1, p=.71), total time since onset of the first psychotic episode (F(1,115)=0.3, p=.57), education (F(1,118)=0.7, p=.41), sex (χ²(1)=.49, p=.48), race (χ²(5)=2.9, p=.72), or ethnicity (χ²(1)=.03, p=.87). However, patients who withdrew prior to randomization were significantly older (F(1,116)=4.7, p=.03) and had higher levels of negative symptoms (BPRS Withdrawal-Retardation factor (mean of Blunted Affect, Motor Retardation, and Emotional Withdrawal)) (F(1,121)=4.4, p=.04). Most patients who withdrew prior to randomization did so because of poor awareness of having a psychotic disorder, or did so in order to seek treatment at a location closer to their homes or in a non-research setting that involved minimal clinic visits.

Dosage of oral risperidone was based on psychiatrist choice for optimal dose. For RLAI, one participant’s dosage was subsequently lowered to the 12.5 mg dosage for 8 injections, and 10 participants required a switch to the 37.5 dosage (10.4% of the injections given) at some point during the 12-month protocol (one of whom was subsequently treated with the 50 mg dosage for 3 injections (0.4% of injections).

Primary Outcome: Psychotic Exacerbation/Relapse, Completers Analyses

For the 57 participants who completed the 12-month medication study, there was no interaction between medication and psychosocial conditions (χ²(1)=0.0, p=.97). RLAI was associated with a much lower risk of psychotic exacerbation or relapse (2/30=6.7%) compared to oral Ris (10/27=37.0%, χ²(1)=7.6, p<.01, Relative Risk Reduction = 81.9%). The rate of psychotic exacerbation/relapse was comparable in the two psychosocial groups (χ²(1)=0.1, p=.73).

We examined the rate of exacerbation/relapse over time in a Cox Regression survival analysis for participants who completed the 12-month medication protocol. The risk of exacerbation/relapse
over time was significantly lower for the RLAI group than the Oral Ris group ($\beta=2.1$, Wald(df=1)=6.5, $p=.01$).

**Secondary Outcomes**

**Psychiatric Hospitalizations, Additional Details.** Only 6 of the 16 (37.5%) psychotic exacerbation/relapses required inpatient psychiatric treatment, so hospitalizations were examined as a separate outcome variable. There were 10 psychiatric hospitalizations, all occurring within the first 6 months following randomization (mean 94.7 days, SD=50.9). There were no significant effects of the psychosocial conditions or interaction effects between the psychosocial and medication conditions, so main effects of the medication condition are reported. The analyses conducted with the study completers yielded results that were similar to the analyses conducted with all randomized patients, albeit nonsignificant, for the proportion hospitalized (Hierarchical LogLinear Model, RLAI=3.3% versus oral Ris=14.8%, $\chi^2(1)=2.4$, $p=.12$) and fewer hospital days for RLAI ($t(28)=1.8$, $p=.08$).

**Control of Psychotic Symptoms during Follow-Through, Additional Details.** At the time of the entry diagnostic assessment, the participants were usually psychotic and many had negative symptoms. At the outpatient randomization point these patients, on average, had obtained relative clinical stability. The patients later randomly assigned to the two medication conditions were not significantly different on the BPRS Thought Disturbance or Withdrawal-Retardation factor scores at either the entry ($t(81)=-0.9$, $p=.35$, and $t(81)=-1.1$, $p=.27$, respectively) or randomization points ($t(81)=1.1$, $p=.28$, and $t(81)=-0.6$, $p=.56$, respectively). Treatment with RLAI, as opposed to oral Ris, was nonsignificantly associated with shorter total duration of hallucinations and delusions (standardized regression coefficient beta ($\beta)=-0.2$, $t(80)=-1.6$, $p=.12$).

For medication protocol completers, the above regression analyses yielded comparable, albeit fully significant, findings (i.e., breakthrough symptom duration ($\beta=-0.3$, $t(54)=-2.1$, $p<.05$); mean level of reality distortion, ($\beta=-0.28$, $t(54)=-2.9$, $p<.05$). There were no significant effects of the psychosocial condition or interaction effects of the psychosocial and medication conditions for either duration or mean levels of reality distortion.

**Drug Discontinuation, Additional Details.** Randomized treatment was discontinued due to lack of clinical efficacy for six participants, due to intolerable side effects for 11 participants, and due to both
for 2 participants. Six other participants withdrew from treatment altogether prior to completing the 12-month protocol, typically due to poor insight into the need for continued treatment.

**Side Effects**

Using a General Linear Mixed Model (GLMM) with the medication condition, the psychosocial condition, and their interaction as predictor variables, we find that despite more consistent medication delivery with RLAI, treatment with RLAI was not associated with significantly increased involuntary movements (F(1,54)=1.2, p=.29), assessed with the AIMS, or increased akathisia (F(1,35)=1.1, p=.31, assessed with the Barnes Rating Scale for Akathisia) (Table 2). Prior to beginning the randomized medication treatment phase the two medication groups were not different in the use of adjunctive medications to treat EPS-related side effects (F(1,81)=.008, p=.93), but the oral Ris patients were more frequently prescribed side effect medication during the randomized medication protocol than were the RLAI patients (F(1,75)=9.3, p<.01). Higher 12-month average plasma Ris+9OH levels were associated with the use of medications to treat EPS-related side effects (r=.43, N=56, p<.01). Twelve-month average Ris+9OH levels were not associated with EPS severity (r=.14, N=44, p=.44) or with akathisia severity (r=.07, N=33, p=.70). Further, treatment with RLAI compared to oral Ris was not differentially associated with increased Body Mass Index (BMI; (F(1,94)=.40, p=.53), Body Weight (F(1,94)=.87, p=.35), total cholesterol (F(1,54)=1.4, p=.24), hemoglobin A1c (F(1,68)=1.0, p=.31), prolactin (F(1,41)=.01, p=.97), or with systolic (F(1,110)=.16, p=.69) or diastolic blood pressure (F(1,117)=.29, p=.59).

**Dimension of Medication Adherence**

**Primary Outcome: Psychotic Exacerbation/Relapse**

To examine the extent to which medication adherence was a key underlying factor, we examined the relationship of the medication adherence rating to clinical outcome across medication groups. There were no effects of the psychosocial condition or psychosocial X adherence interaction effects on exacerbation/relapse, so only the main effects of medication adherence are reported.

The logistic regression finding for the main effect of medication adherence on exacerbation/relapse was similar to the analyses involving all randomized participants when only completers were examined (β=1.5, Wald(df=1)=9.6, p<.01). When the medication group assignment was entered into the logistic regression after the adherence variable, the main effect of the medication
condition was not statistically significant ($\beta=-0.9$, Wald (df=1)=0.6, $p=.43$). This suggests that the effect of the medication conditions (oral Ris versus RLAI) on relapse for patients who were successfully maintained on the assigned medication can be accounted for by differences in adherence between the two conditions.

As with the analyses including all randomized participants, analyses involving only protocol completers showed that the rate of relapse over time was significantly associated with adherence ($\beta=1.1$, Wald (df=1)=15.8, $p<.001$).

**Secondary Outcomes**

**Relationships to Plasma Medication Levels**

The relationships among medication plasma levels and positive symptoms were examined using GLMM analyses, controlling for the length of the pre-randomization period. The analyses were completed separately for each medication condition because dosages levels for oral and IM medications cannot be collapsed across conditions.

**Oral Ris Condition**

Higher plasma levels of Ris+9OH did not appear to be associated with either the 12-month duration of breakthrough reality distortion symptoms ($t (25)=1.3$, $p=.20$), 12-month mean level of reality distortion ($t (25)=1.3$, $p=.20$), or relapse risk ($t (25)=-.5$, $p=.64$). These relationships continued to be nonsignificant after controlling for adherence and dosage.

**RLAI Condition**

Higher levels of Ris+9OH were not associated with duration of reality distortion symptoms ($t (28)=.5$, $p=.64$), 12-month mean level of reality distortion ($t (25)=1.3$, $p=.20$), or relapse risk ($t (27)=0.7$, $p=.49$). These relationships continued to be nonsignificant after controlling for adherence and dosage.