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Long-Acting Injectable vs Oral Risperidone for Schizophrenia and Co-Occurring Alcohol Use Disorder: A Randomized Trial

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ABSTRACT

Objective: Alcohol use disorders worsen the course of schizophrenia. Although the atypical antipsychotic clozapine appears to decrease alcohol use in schizophrenia, risperidone does not. We have proposed that risperidone's relatively potent dopamine D_2 receptor blockade may partly underlie its lack of effect on alcohol use. Since long-acting injectable (LAI) risperidone both results in lower average steady-state plasma concentrations than oral risperidone (with lower D_2 receptor occupancy) and encourages adherence, it may be more likely to decrease heavy alcohol use (days per week of drinking 5 or more drinks per day) than oral risperidone.

Method: Ninety-five patients with *DSM-IV-TR* diagnoses of schizophrenia and alcohol use disorder were randomized to 6 months of oral or LAI risperidone between 2005 and 2008. Explanatory (efficacy) analyses were carried out to evaluate the potential benefits of LAI under suitably controlled conditions (in contrast to real-world settings), with intent-to-treat analyses being secondary.

Results: Explanatory analyses showed that heavy drinking in the oral group worsened over time ($P = .024$) and that there was a statistical trend toward significance in the difference between the changes in heavy drinking days in the oral and LAI groups ($P = .054$). Furthermore, the 2 groups differed in the mean number of drinking days per week ($P = .035$). The intent-to-treat analyses showed no difference in heavy drinking but did show a difference in average drinking days per week similar to that obtained from the explanatory analyses ($P = .018$). Neither explanatory nor intent-to-treat analyses showed any between-group differences in alcohol use as measured by intensity or the Alcohol Use Scale. The plasma concentrations of the active metabolite 9-hydroxyrisperidone were significantly lower in patients taking LAI ($P < .05$), despite their significantly (overall) better treatment adherence ($P < .005$).

Conclusion: For the population considered here, schizophrenia patients with alcohol use disorder appear to continue drinking some alcohol while taking either form of risperidone. Nonetheless, our data suggest that injectable risperidone may be a better choice than the oral form for these dual diagnosis patients.

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Alcohol use disorder is 3 times more common in schizophrenia than in the general population and is known to increase symptoms and worsen the functional course of schizophrenia.[1,2] Integrated psychosocial treatment programs for both the psychotic illness and the alcohol use disorder provide limited short-term effectiveness for these dual diagnosis patients, but few patients respond, and those who do are at a high risk of relapse.[3,4] Data regarding the ability of most antipsychotics to limit alcohol and other substance use in patients with schizophrenia are mixed and not overly promising.[5] An exception is the atypical antipsychotic clozapine; preliminary data suggest that clozapine limits alcohol and other substance use in patients with schizophrenia.[6–12] Unfortunately, however, clozapine's substantial side-effect profile has continued to limit its use to a small percentage of patients who have treatment-resistant psychosis.

We have proposed that the effects of clozapine on alcohol use in these dual diagnosis patients may relate to its broad-spectrum pharmacologic effects (ie, its weak antagonism at the dopamine D_2 receptor and its potent blockade of the noradrenergic α_2 receptor, coupled with its ability to release norepinephrine in the brain) that result in an amelioration of a brain reward circuit deficiency in these patients.[12] This neurobiological formulation further suggests that although the atypical antipsychotic risperidone appears not to limit alcohol use in dual diagnosis patients,[13] it might be able to do so if its potent dopamine D_2 receptor blockade were decreased (since, like clozapine, risperidone is also a potent noradrenergic α_2 receptor antagonist). Thus, we hypothesized that the long-acting injectable (LAI) form of risperidone might be more likely to decrease alcohol use for 2 reasons: (1) a therapeutic dose of the injectable form is likely to produce a somewhat lower average steady-state plasma concentration and thus a lower dopamine D_2 receptor occupancy than a therapeutic dose of the oral form,[14] and

(2) the injectable form is likely to ensure greater adherence with treatment. We initiated a 6-month study to compare the effects of these 2 forms of risperidone on alcohol drinking and related measures in dual diagnosis patients, with the primary hypothesis that patients using LAI risperidone will have less alcohol use as measured by heavy drinking days than patients taking oral risperidone.

Clinical Points

- Alcohol use disorder worsens the course of schizophrenia.
- While neither long-acting injectable risperidone nor oral risperidone decreased drinking in this study, long-acting injectable risperidone may be a better choice than oral risperidone for patients with schizophrenia and co-occurring alcohol use disorder.

METHOD

Study Group

The study was a proof-of-concept, 4-site (New Hampshire, South Carolina, Florida, and Missouri), randomized 6-month study to evaluate the efficacy of treatment with LAI risperidone compared to oral risperidone in 95 patients with schizophrenia or schizoaffective disorder and current alcohol use disorder. The design was powered to detect effects expected under suitably controlled conditions, rather than the smaller effects typical of heterogeneous real-world settings. The study was approved by Dartmouth's Committee for the Protection of Human Subjects, as well as by each research site's institutional review board. The study group was recruited from adults (age 18–65 years) who presented for evaluation and treatment at community mental health and Veterans Affairs clinics. All participants gave written informed consent prior to initiating study activities. The study was registered at ClinicalTrials.gov and assigned NCT00130923.

Diagnostic inclusion criteria included schizophrenia or schizoaffective disorder and current alcohol use disorder (abuse or dependence) as assessed using the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version, Patient Edition (SCID-I/P[15]), with use of alcohol on at least 5 days during the 4 weeks prior to randomization (based on the Timeline Follow-Back procedure[16]). Other current substance use disorders were allowed (Table 1). Participants were required to be psychiatrically stable and taking antipsychotic medication without a change of psychotropic medications for the past 30 days. Patients were excluded from participation if they were (1) being treated with clozapine, 2 or more concurrent antipsychotics, or any LAI antipsychotic; (2) being treated with agents that may curtail substance use (eg, disulfiram, naltrexone, valproic acid, topiramate, acamprosate, opiate replacement therapy, or benzodiazepines); (3) currently pregnant or unwilling to use an acceptable form of birth control; (4) currently residing in a residential program designed to treat substance use disorders; or (5) intolerant of or allergic to oral or LAI risperidone.

Study Procedures

Consenting, eligible participants were randomly assigned between 2005 and 2008 to take either LAI risperidone every 2 weeks or daily oral risperidone. Randomization was stratified by use of oral risperidone at recruitment (see Table 1) to control for effects such as expectations of improvement (or lack thereof). Participants attended study visits every 2 weeks for 6 months. At these visits, unblinded study investigators assessed participants for overall response to treatment and adverse events; and trained, blinded raters assessed participants for alcohol and other substance use, psychiatric symptoms, and treatment utilization. Experienced study raters were trained and certified prior to rating study patients and recertified yearly. Psychosocial treatment for psychosis and substance use was measured monthly. Participants were given a $25 gift card at the completion of each study visit for their time and travel expenses.

Study participants who were randomized to the LAI risperidone group were started on a dose of 25 mg given intramuscularly (IM) every 2 weeks. The dose was titrated up to a target dose of 37.5 mg IM, with injections given every 2 weeks. Most people reached 37.5 mg at the second injection, and some increased or decreased thereafter depending upon tolerability, reaching their final dose by 6 weeks. Participants who were randomized to take oral risperidone were titrated over 2 weeks up to a target dose of 4 mg/d. For both groups, the prestudy antipsychotic was gradually lowered and discontinued by week 6, except for those patients taking oral risperidone at recruitment and randomized to the oral risperidone group. Study medication was prescribed open label, although raters remained blinded to the study medication. Study physicians adjusted the risperidone doses based on psychiatric symptom response. The maximum dose of LAI risperidone was 50 mg every 2 weeks, and the maximum daily dose of oral risperidone was 6 mg. Concomitant psychotropic medications were maintained without changes, whenever possible. While use of any antipsychotic medication in addition to study risperidone (oral or long-acting) was avoided, olanzapine was allowed on a short-term basis for symptom exacerbation during the switch period, eg, during the initial 6 weeks of the study.

At the second study visit, participants viewed a 30-minute alcohol education videotape, were given a list of local self-help groups, and were encouraged to continue with psychosocial treatment at their clinic as before. Participants who required acute hospitalization during the 6-month study period remained on their study medication unless their treatment providers deemed that a switch of antipsychotic medication was necessary. If the prescribing psychiatrist stopped the study medication because of lack of efficacy or side effects, he/she prescribed the subject an alternate antipsychotic medication based on clinical judgment, with input from both the patient's clinical treatment team and the patient. Whenever possible, subjects who stopped their study medication were followed for the full 6-month study period. After 6 months of treatment, participants were transitioned back to clinical care.

Table 1. Baseline Characteristics of Patients Taking Oral or LAI Risperidone

Characteristic	Total Group N = 95	Oral Risperidone n = 46	LAI Risperidone n = 49
Age, mean ± SD, y	41.73 ± 10.7	41.72 ± 11.5	41.73 ± 10.1
Male gender, n (%)	73 (76.8)	36 (78.3)	37 (75.5)
Race, n (%)			
White	49 (51.6)	24 (52.2)	25 (51.0)
African American	42 (44.2)	22 (47.8)	20 (40.8)
Education, mean ± SD, y	11.0 ± 1.7	11.2 ± 1.4	10.9 ± 2.0
Ever employed, n (%)	92 (96.8)	45 (97.8)	47 (95.9)
Marital status (single), n (%)	48 (50.5)	25 (54.3)	23 (46.9)
Diagnosis schizophrenia (vs schizoaffective disorder), n (%)	46 (48.4)	23 (50.0)	23 (46.9)
Lifetime hospitalizations, mean ± SD	7.5 ± 15.9	6.9 ± 14.9	8.1 ± 16.9
Alcohol dependence (vs abuse), n (%)	80 (84.2)	41 (89.1)	39 (79.6)
Drinks/wk, mean ± SD	23.99 ± 23.1	24.4 ± 22.7	23.6 ± 24.5
Drinking days/wk, mean ± SD	3.6 ± 1.8	3.7 ± 1.8	3.6 ± 1.9
Heavy drinking days/wk, mean ± SD	2.0 ± 2.3	2.2 ± 2.1	1.8 ± 1.9
Days cannabis use/wk, mean ± SD	1.1 ± 2.0	1.1 ± 2.1	1.1 ± 1.9
Days other drug use/wk, mean ± SD	0.3 ± 0.8	0.3 ± 0.6	0.4 ± 0.9

Abbreviations: LAI = long-acting injectable, SD = standard deviation.

Assessments

Researchers ensured participant eligibility during the screening phase. A SCID-I/P[15] interview was used to establish diagnoses of schizophrenia or schizoaffective disorder and alcohol and other substance use disorder. A physical examination and laboratory assessment confirmed medical stability. Interviewers used the Timeline Follow-Back procedure[16] at screening and baseline to determine the amount of recent alcohol and substance use.

Blinded raters assessed the level of alcohol and other substance use every 2 weeks with the Timeline Follow-Back procedure,[16] which included a standardized interview with a calendar and memory prompts, as well as data obtained from the breathalyzer (using the alcoHAWK-Pro, Q3 Innovations, Independence, Iowa) and urine drug screens (using the ACON 6 Panel Multiline Test Device, San Diego, CA [detecting tetrahydrocannabinol to 50 ng/mL]). Blinding was maintained by ensuring that raters did not participate in the treatment aspects of the study, and patients were asked not to discuss the details of their treatment with raters. Raters were trained and certified to conduct Timeline Follow-Back interviews, and taped interviews were monitored yearly for quality. Lastly, clinician ratings of the Alcohol Use Scale[17] were collected at baseline, 3 months, and 6 months. Using all of this information, a blinded research assistant established a global Alcohol Use Scale rating at baseline, 3 months, and 6 months.

Trained raters assessed psychopathology monthly with the Positive and Negative Syndrome Scale (PANSS; 30 items, severity scale 1 to 7),[18] the Clinical Global Impressions (CGI; severity scale 1 to 7),[19] and the Global Assessment of Functioning (GAF).[20] Medication adherence was assessed by weekly pill count or documentation of injections (delivered by research medical staff). Study investigators assessed concomitant medications with a medication review every 2 weeks. Raters utilized a substance use treatment services questionnaire to assess the amount of services patients received to address their alcohol use disorder.

Study investigators conducted a clinical assessment of medication effectiveness, side effects, and vital signs every 2 weeks for the first 2 months and then every 4 weeks. Plasma concentrations of risperidone (and 9-hydroxy [OH] risperidone) were obtained at 8, 16, and 24 weeks.[21]

Neurologic side effects were assessed by study physicians monthly and scored on the Simpson Angus Scale,[22] the Abnormal Involuntary Movement Scale (AIMS),[23] and the Barnes Akathisia Rating Scale (BARS).[24]

Statistical Analysis

Longitudinal random-effects models[25] were used to investigate potential differential treatment effects over time on alcohol use. Explanatory (efficacy) analyses were carried out to evaluate differences between groups using data (complete or partial) obtained while subjects were still taking their assigned medication; intent-to-treat analyses were secondary. The main outcome was days of heavy drinking, eg, 5 or more drinks per day. Intensity of drinking as measured by the number of drinks per week was also an outcome. Analyses were conducted using weeks 5 (to ensure that steady blood levels were reached in the LAI group) through 23 (to avoid end of study effects on drinking behavior); the use of these weeks was decided prior to viewing the data. For the explanatory analyses, data for a patient were censored for the rest of the study (1) once the study medication was stopped or a prohibited medication was used or (2) if a subject was in the hospital or otherwise incarcerated for more than 4 days (to control for carryover effects due to forced abstinence). For the intent-to-treat analyses, data were censored (1) for the rest of the study if a subject was given clozapine or received a medication thought to decrease alcohol use or (2) for every week that a subject was in the hospital or otherwise incarcerated for more than 4 days during that week. We note that the use of partial data whenever possible according to rules for censoring distinguishes our approach from that of a completer analysis.

Because the data distributions of plasma concentrations of risperidone and 9-OH risperidone were heavily skewed, we used the Mann-Whitney nonparametric test to compare groups at each time point for these measures.

RESULTS

Characteristics of Study Participants

Of the 150 patients who consented to participate in the study, 95 met study criteria and proceeded with the study. The study participants were primarily men with moderate symptoms whose average age was 41.7 years (Table 1). Most study participants had alcohol dependence (rather than abuse) and reported, on average, 2 heavy drinking days per

Table 2. Treatment Characteristics of Patients Taking Oral or LAI Risperidone

Characteristic	Total Group N = 95	Oral Risperidone n = 46	LAI Risperidone n = 49
Retained 6 months, n (%)	68 (71.6)	32 (69.6)	36 (73.5)
Weeks on study medication, mean ± SD	17.3 ± 8.0	17.1 ± 8.1	17.6 ± 7.9
Medication dose, mean ± SD, mg	NA	4.3 ± 1.5	33.8 ± 9.0
Patients ending medication early, n (%)	36 (38)	21 (46)	14 (29)
Good adherence,[a] n (%)	71 (75)	28 (61)	43 (88)
Counseling sessions per week, mean ± SD	0.5 ± 1.0	0.6 ± 1.2	0.6 ± 0.8
Alcoholics Anonymous sessions per week, mean ± SD	0.3 ± 1.0	0.4 ± 1.3	0.2 ± 0.6

[a]*Good adherence* is defined as taking medication at least 75% of the days in the treatment period; $P < .005$.
Abbreviation: LAI = long-acting injectable.

week and minimal drug use. Demographic, diagnostic, and substance use characteristics did not differ between groups.

Sixty-eight patients (71.6% of the randomized sample) remained in the study for 6 months; 36 (38% of the randomized sample) stopped assigned medication at some point during follow-up. Eight participants (2 on LAI, 6 on oral) switched to a different antipsychotic medication but completed the study. Moreover, 3 participants took other prohibited medication (1 on LAI, 2 on oral). Study retention and length of time on study medication did not differ between the oral and the injectable groups (Table 2). Participants engaged in a minimal amount of psychosocial treatment during the study period, which did not differ between the groups.

Alcohol Outcomes

Explanatory analyses (using weeks 5–23) showed that heavy drinking in the oral group worsened over time ($t_{67} = 2.31$, $P = .024$) and that there was a statistical trend toward significance in the difference between the changes in heavy drinking days in the oral and LAI groups (Figure 1; $t_{63.5} = -1.96$, $P = .054$). The estimated change (decrease, on average) in the LAI group after steady blood levels were reached was −0.11 heavy drinking days/wk ($t_{82} = 0.12$, $P > .9$), compared to an increase of 0.68 heavy drinking days/wk in the oral group during that same period ($t_{67} = 2.31$, $P = .024$). Trends between the 2 groups were not significantly different for the intent-to-treat analysis.

We further investigated the number of drinking days per week as a secondary outcome. For explanatory analyses, there was a significant curvilinear trend over time in the 2 groups ($t_{1382} = 2.65$, $P < .01$). The 2 groups differed in mean number of drinking days per week ($t_{88} = -2.14$, $P = .035$), but between-group differences did not significantly vary over time. The estimated change over time for the entire sample was −0.95 drinking days/wk. The intent-to-treat results were similar: a significant curvilinear trend ($t_{1624} = 3.11$, $P < .002$), a significant main effect due to treatment ($t_{87} = 2.42$, $P = .018$), and an estimated change of −1.16 drinking days/wk (for the entire sample).

Finally, intensity of use (number of drinks per week) and the global Alcohol Use Scale scores did not differ between groups over time for either explanatory or intent-to-treat comparisons. There were also no significant trends in either measure.

Treatment Adherence

Medication adherence (defined as taking medication at least 75% of the days in the treatment period) was significantly worse among participants assigned to oral risperidone (61% vs 88%; $\chi^2_1 = 9.08$, $P = .003$).

Plasma Risperidone Concentrations

Risperidone and plasma metabolite concentrations are reported in Table 3. Between-group differences reached significance for 9-OH risperidone at every time point (weeks 8, 16, 24) and for risperidone at week 8.

Symptoms and Functioning

Longitudinal random-effects models that controlled for baseline scores showed no differences in symptoms (total PANSS) scores between groups. Similarly, there were no significant between-group differences in GAF and CGI scores. Psychiatric symptom exacerbation occurred in 36 participants (37.9%): 20 (21.1%) were hospitalized, 16 (16.8%) were not. Rates did not differ between groups.

We also investigated the relationship of symptoms to drinking behavior in 2 ways. First, we considered the symptom score at baseline as a predictor in the longitudinal models for alcohol outcomes; symptoms did not have a significant (time invariant) effect on alcohol outcomes during follow-up. Second, we considered the correlation between changes in symptoms over time with changes in drinking over time. Because symptoms and alcohol outcomes were measured with different frequency, it was necessary to average the drinking outcomes for each subject between time points for symptoms. We looked specifically at heavy drinking days per week for the LAI group because this outcome was fairly stable for those subjects, and such averages were deemed meaningful for that group. Although the correlation between heavy drinking and symptoms in the LAI group was significant, it was weak and not clinically relevant: a 1-point increase in symptom score was associated with an increase of 0.018 heavy drinking days per week ($t_{199} = 2.43$, $P = .016$).

Safety

An adverse event occurred in 75 participants (79%). Forty-five participants (47.4%) experienced side effects that were deemed possibly or probably related to study medication. The frequency of side effects did not differ between the oral and the LAI risperidone groups. The most common adverse events included pain 11/95 (11.6%), upper respiratory tract infection 5/95 (5.3%), drooling 5/95 (5.3%), nausea or stomach discomfort 6/95 (6.3%), diarrhea 6/95 (6.3%), vomiting 5/95 (5.3%), other digestive or hepatic problems 8/95 (8.4%), and drooling 5/95 (5.3%). Finally,

Figure 1. Heavy Drinking Days per Week in Patients Taking Oral Risperidone vs Long-Acting Injectable (LAI) Risperidone: Explanatory and Intent-to-Treat (ITT) Analyses

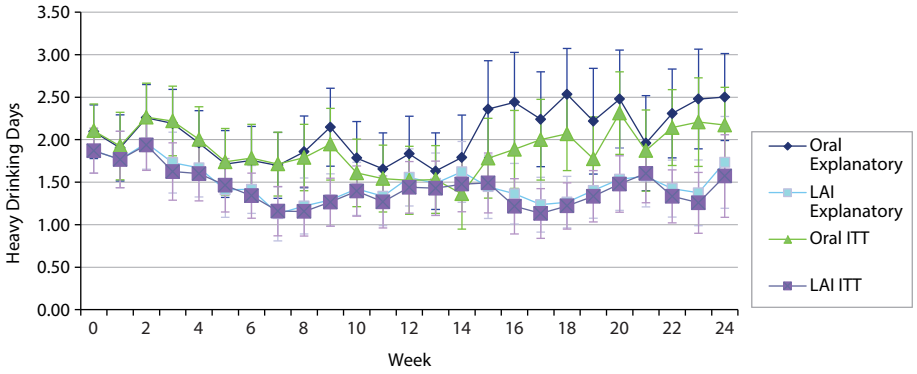

Table 3. Risperidone Dose and Plasma Concentrations in Patients Taking Oral or LAI Risperidone

	Week 8		Week 16		Week 24	
Variable	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
Medication dose, mg						
Oral	4.3 (1.6)		4.4 (1.4)		4.3 (1.6)	
Injectable	32.6 (8.7)		33.2 (8.4)		33.1 (9.2)	
Plasma risperidone concentration, μg/L[a]						
Oral	15.2 (26.2)	0.646	20.1 (27.5)	10.8	23.3 (27.2)	12.0
Injectable	12.5 (19.6)	9.3	13.7 (18.1)	7.9	14.2 (22.7)	8.7
Plasma 9-OH risperidone concentration, μg/L[b]						
Oral	15.8 (13.7)	11.8	28.5 (31.0)	18.3	26.5 (30.1)	18.3
Injectable	13.5 (21.0)	7.7	16.8 (17.7)	11.4	15.6 (21.5)	9.6

[a]The plasma risperidone concentrations for oral vs LAI are significantly different at week 8 ($P < .05$).
[b]The plasma 9-OH risperidone concentrations for oral vs LAI are significantly different at weeks 8, 16, and 24 ($P < .05$).
Abbreviations: LAI = long-acting injectable, OH = hydroxy.

scores on the neurologic side effects scales (Simpson Angus, AIMS, and BARS) did not differ over time between the oral and the LAI groups.

DISCUSSION

In this randomized, controlled 6-month trial of risperidone for alcohol drinking in patients with schizophrenia and co-occurring alcohol use disorder, explanatory (efficacy) analyses showed that there was a significant increase in heavy drinking in the oral group over the course of the study, but not in the LAI group. However, a decrease in heavy drinking in the LAI group was not clearly found. Between-group differences in changes in heavy drinking trended toward statistical significance in the explanatory analyses, but not in the intent-to-treat comparison. Analysis of other drinking outcomes provided mixed results. The 2 groups did differ significantly in mean number of drinking days per week, in both explanatory and intent-to-treat analyses, but did not in alcohol use (as measured by intensity and the Alcohol Use Scale). In our study, there was only a weak association in symptom changes over time with changes in drinking in the LAI group that were not clinically relevant. Thus, the apparent beneficial effect on drinking derived from the use of the injectable medication largely occurred independently of an effect on psychiatric symptoms.

Given that lack of adherence to treatment is characteristic of patients with schizophrenia and co-occurring substance use disorders,[26] it is perhaps not surprising that LAI antipsychotics have often been used to treat psychosis in these patients,[27] although data on the efficacy of these medications for this indication are sparse. In this study, patients who were assigned to LAI risperidone were more adherent to their medication. Since nonadherence to prescribed medication dosing regimens is an all too common cause for relapse in patients with schizophrenia, the enhanced adherence with LAI risperidone versus oral risperidone in this sample of patients with co-occurring alcohol use disorder is noteworthy.

The mean doses of both the injectable (33.7 mg/2 wk) and the oral (4.3 mg/d) form of risperidone were moderate, although the injectable dose was slightly below the target dose for the study, and the oral dose was slightly above the target. Median risperidone levels were most likely low due to very low adherence in some participants taking oral risperidone. The mean plasma concentrations for the 2 groups were similar to concentrations reported in previous studies[28]; further, the increasing mean plasma concentration over time (that occurred despite a stable mean medication dose) is also similar to previous reports.[29] Interestingly, as others have reported,[14] the plasma concentrations of risperidone (as well as the active metabolite 9-OH risperidone) were lower in patients treated with the LAI risperidone as compared to the oral form, possibly resulting in a lower dopamine D_2 receptor occupancy in these patients.[14,30] This occurred despite increased adherence among subjects in the LAI group.

The finding of an increase in days of heavy drinking among patients taking oral (but not injectable) risperidone is consistent with our published neurobiological formulation of the basis of the effect of clozapine in this population: that a pharmacologic profile of relatively weak dopamine D_2 receptor antagonism and potent norepinephrine α_2 receptor antagonism may reduce problematic alcohol drinking among patients with schizophrenia and alcohol use disorders through improvement in signal detection capacity in dopamine-mediated brain reward circuits.[12] Our animal studies have shown that increasing the dopamine D_2 receptor antagonism of clozapine, by adding the potent dopamine D_2 receptor antagonist raclopride limits the ability of clozapine to decrease alcohol drinking.[31] The ability to obtain an antipsychotic effect with LAI risperidone at a somewhat lower plasma concentration of risperidone and 9-OH risperidone than with oral risperidone, thus avoiding a potent dopamine D_2 receptor blockade in the presence of a continued, albeit lower, norepinephrine α_2 receptor blockade, may contribute to its difference from oral risperidone (regarding alcohol drinking) in this population. Of course, as in any efficacy finding, it is possible that greater adherence to assigned medication among patients taking the injectable form of risperidone may also be related to the beneficial effect we have detected for LAI risperidone. However, because improved treatment adherence in the LAI group was (overall) accompanied by lower, rather than higher, plasma levels, there is support in our data for the importance of the role played by the lessened dopamine D_2 receptor blockade in patients treated with LAI risperidone.

This study was designed as a proof-of-concept clinical trial. Thus, it is limited by a relatively small sample size, as well as by the loss of power for our explanatory analysis of days of heavy alcohol drinking due to the fact that patients stopped their assigned medication. Moreover, although we stratified randomization for patients entering the study taking oral risperidone, the presence of such subjects, who might have continued on the same treatment during the study, is another potential limitation. Also, the open-label nature of the study could have potentially led to biases in the way subjects were treated and the way in which they reported outcomes. And lastly, although research interviewers were blinded to treatment assignment, we did not conduct an assessment to confirm that they remained blinded throughout the study. Nonetheless, given the difficulties involved in implementing studies in patients with schizophrenia and co-occurring alcohol use disorder, this is, to our knowledge, the largest randomized, controlled medication trial in this population. The strengths of the present study include the 6-month duration of treatment, the strong subject retention rate, the comprehensive diagnostic and evaluative procedures (including serial Timeline Follow-Back assessment using several sources to assess alcohol and substance use), the blinded rater assessments, and the longitudinal collection of plasma antipsychotic levels in this patient sample. Additionally, the treatment groups were well matched for baseline characteristics (including alcohol use), thereby facilitating informative comparisons over the duration of this 6-month clinical trial. Lastly, our use of statistical analyses appropriate to issues of the study (hospitalization, deviations from protocol) enabled a meaningful assessment of the efficacy effect of these medications on alcohol drinking and other outcomes in this population.

In conclusion, this study suggests that patients with schizophrenia and co-occurring alcohol use disorders continue some drinking despite treatment with either LAI risperidone or oral risperidone. Our data, however, also suggest that the injectable form of risperidone may be a better choice than the oral form for these difficult-to-treat dual diagnosis patients.

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Role of the sponsor: The sponsor had no role in the study itself. The investigators requested information from the sponsor regarding clinical use of LAI risperidone.

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