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Risperidone versus olanzapine among patients with schizophrenia participating in supported employment: Eighteen-month outcomes

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Abstract

This study compares the efficacy and tolerability of olanzapine versus risperidone among patients with schizophrenia who are established in outpatient psychiatric care and entering supported employment. A multicenter, randomized, double-blind trial was conducted among 107 outpatients with schizophrenia, who were cross-titrated to flexible dose risperidone or olanzapine over 2 weeks. Clinical endpoints included time to hospitalization and persistence on assigned medication. Weight, laboratory tests, psychopathology, neurologic side effects, social adjustment and role functioning were assessed at 3–6 month intervals. Data were analyzed first by randomized treatment, and then reassessed controlling for prior medication treatment. The proportion of patients on assigned medication at 18 months was 30.9% for risperidone and 37.3% for olanzapine. Mean doses were 6.4+/−3.2 mg daily for risperidone, and 17.0+/−5.0mg daily for olanzapine. The groups did not differ significantly in time to medication discontinuation, first hospitalization or first employment. There were few differences in psychopathology, laboratory, or neurological assessments between groups at 18 months. Patients randomized to olanzapine gained modestly more weight. Controlling for pre-randomization medication suggested improvement in some aspects of psychopathology from switching medications; however, switching from olanzapine to risperidone was associated with more hospitalizations. Risperidone and olanzapine have similar efficacy and tolerability in patients with schizophrenia who are participating in supported employment. Randomization to olanzapine was associated with more weight gain, but randomization from olanzapine to risperidone appeared to be associated with a greater likelihood

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of hospitalization. Careful monitoring of metabolic effects and participation in supported employment may have contributed to minimal weight gain and metabolic effects.

Keywords

schizophrenia; antipsychotic medication; supported employment; BMI

Introduction

Guiding outpatients with schizophrenia in choosing optimal antipsychotic therapy for participating in psychosocial rehabilitation is complex and poorly understood (Salkever et al., 2006; Sungur et al., 2011). Antipsychotic medications may be associated with side effects such as sedation and EPS that can interfere with attention, learning and motor function (Kumar et al., 2013). There is some evidence that antipsychotics may have differential effects on cognitive function (Bilder et al., 2002; Keefe et al., 2007; Matsuda et al., 2014). Switching antipsychotic medications can also be disruptive and destabilizing (Takeuchi et al., 2017).

Large randomized trials such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study have demonstrated that the second-generation antipsychotics (SGAs) as a group have similar effects on psychopathology, with some advantages in treatment outcomes for clozapine, olanzapine, and risperidone (Lieberman et al., 2005; McEvoy et al., 2007, 2006; Stroup et al., 2006). However, the agents also differed in their side effects. A re-analysis of the CATIE phase 1 findings by Essock and colleagues (Essock et al., 2006) found that patients who were randomized to the same antipsychotic that they were taking before study entry tended to have better outcomes than those who were randomly assigned to take a different antipsychotic medication during the study. However, the authors did not evaluate the effects of continuing or changing antipsychotics on adverse effects. All of these medication effects were studied in isolation from any psychosocial rehabilitation that patients were receiving.

In the current trial, stable, unemployed outpatients with schizophrenia were randomly assigned to an 18-month double-blind comparison of olanzapine and risperidone at the point of initiating a supported employment program (Glynn et al., 2017). The purpose of this study was to compare two highly prescribed antipsychotic medications in the understudied clinical context of psychosocial rehabilitation. We examined the effectiveness, but also the side effects, of assigned medication treatment as a function of prior antipsychotic treatment.

Materials and methods

Study Setting and Design

We randomized 107 stable outpatients to double-blind risperidone vs. olanzapine. In addition, all participants received supported employment using the evidence-based Individual Placement and Support Program (IPS)(Becker and Drake, 1994), and half of these participants were randomly assigned to receive vocational maintenance skills training in the clinic (Glynn et al., 2017; Mueser et al., 2005). Patients were recruited from a Dartmouth-

affiliated Community Mental Health Center (NH site) and an outpatient psychiatric clinic at UCLA and a Veterans Affairs Medical Center (LA site). The study was reviewed and approved by the institutional review boards at each site.

Participants

Eligible participants were 18 – 65 years old, living in the community, not currently competitively employed and interested in finding competitive work. Participants had a diagnosis of schizophrenia or schizoaffective disorder made by a research psychiatrist using DSM-IV criteria (American Psychiatric Association, 2000), and verified by the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002). Exclusion criteria included organic brain disease, mental retardation, active substance dependence within the prior 6 months, or a chronic medical illness which would prevent employment. Concomitant antidepressants and mood stabilizers were permitted. Participants were required to be competent to provide informed consent, and to demonstrate understanding of the informed consent document on a true-false test (Wirshing et al., 1998). After complete description of the study to the subjects, written informed consent was obtained.

The IPS model of supported employment used in this study encourages inclusion of interested patients regardless of psychiatric symptom severity (Becker and Drake, 1994). Therefore, while all participants were clinically stable outpatients at the point of entry into the study, there was no exclusion for severity of psychotic symptoms.

Interventions

Cross-titration from the prior antipsychotic medication to randomized, double-blind therapy with risperidone or olanzapine was to be completed within 2 weeks. Medications were blinded using a double-dummy strategy, with 10 dose levels available. Medication was distributed to patients weekly in a medication planner, and adherence to daily doses monitored at the end of each week by recording any doses remaining in the planner. The risperidone dose range was 1–10 mg daily, with an initial target of 4 mg once daily. The olanzapine dose range was 2.5–30 mg daily, with an initial target of 12.5 mg once daily.

Outcomes

At baseline, all participants received medical, metabolic, symptom and psychosocial assessments. Participants were weighed at every clinic visit, and blood tested at baseline, 3, 6, 12, 18 and 24 months. Body Mass Index (BMI) was calculated using height measured at baseline. Psychiatric symptoms were measured every 3 months using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Schedule for the Assessment of Negative Symptoms (SANS) (Andreasen, 1990), the Symptom CheckList-90 (SCL-90) (Derogatis and Cleary, 1977), and the Hamilton Depression Scale (HAM-D) (Hamilton, 1960).

Neurologic side effects were rated every 3 months using the Abnormal Involuntary Movement Scale (AIMS) (Lane et al., 1985) the Barnes Akathisia Scale (BAS) (Barnes, 1989), The Subjective Extrapyramidal Rating Scale (SERS) (Van Putten et al., 1981), and the Modified Simpson-Angus Scale (S-A) (Simpson and Angus, 1970). Social and role

functioning were rated every 6 months using the Social Adjustment Scale (SAS) (Weissman et al., 2001) and the Quality of Life scale (QOL) (Heinrichs et al., 1984). Time on study medication, time to first hospitalization and time to competitive employment were also recorded for each subject.

Inter-rater reliability was established by training all raters to the standards of the UCLA Diagnostic Assessment Laboratory (kappa coefficient > 0.8), and maintaining regular conference calls among study raters. Regular reliability checks of study raters were conducted throughout the study via examination of video taped study assessments.

In this group of stable outpatients identifying interest in employment, we expected that risperidone and olanzapine would have similar effects on participants' continuance on assigned medication, psychiatric symptoms, likelihood of relapse and ability to obtain competitive employment. We also hypothesized that differences in side effects between the two medications would influence functional outcomes and quality of life. We evaluated continuation of assigned medication as an indicator of outcome that incorporates both efficacy and tolerability, consistent with other studies (Kahn et al., 2008; Lieberman et al., 2005). Hospitalization was used as a proxy for relapse.

Data Analysis

Demographic variables were examined for differences by both site and study medication using t-tests and chi-squared tests. Comparative analyses were performed using two sets of patient groupings: (a) assigned study medication (risperidone or olanzapine) and (b) the combination of pre-randomization and assigned study medication (RSP-RSP, RSP-OLZ, OLZ-RSP, OLZ-OLZ, N-RSP, N-OLZ), where RSP-RSP indicates that the participant was taking risperidone naturalistically prior to randomization and then was randomized to blinded risperidone treatment during the trial, RSP-OLZ indicates prior treatment with risperidone followed by randomization to olanzapine, and so forth. N indicates the subject was on a medication other than risperidone or olanzapine prior to randomization, which primarily was a first generation antipsychotic. Subjects who were on both risperidone and olanzapine pre-randomization were grouped with the olanzapine subjects. We made this decision based on an assumption that a patient's metabolic status was more likely to be related to olanzapine rather than risperidone. The purpose of the second set of analyses was to determine whether subjects who switched medications during the study had different outcomes than those who were randomized to continue on their prior medication.

Continuation on assigned study medication, time to relapse (hospitalization) and time to obtain employment were analyzed by estimating survival curves stratified by medication group using all available data for each subject (SAS PROC LIFETEST). Subjects who remained on their randomized medication or who failed to relapse until they left the study were considered censored. Median survival times are reported to avoid bias incurred in the mean due to censoring in the longest continuing subjects. Overall comparisons were made using the log-rank test for equality over strata and 18-month survival rates were compared using Z-tests. For subjects who obtained a job, the median number of weeks worked is also reported. The primary analytic tool for other outcomes was mixed effects regression with site, medication group, time, and a medication group by time interaction as fixed effects and

random intercept and slope effects within subjects to account for the repeated measures. Data were used only for those time points during which patients remained on their assigned study medication. The mixed model approach automatically handles missing observations, producing unbiased parameter estimates as long as values are missing at random. All models were fit with SAS PROC MIXED using REML estimation and an unstructured covariance matrix. The primary tests of interest were the time by medication interactions and between medication group contrasts.

Results

Randomized Medication Group Analysis (Two Groups)

The demographic composition of the sample is presented in Table 1. There were no differences in any of the demographic variables between the two randomized treatment groups. There was a significant difference in pre-randomization medication by site, with patients recruited in LA more often taking risperidone, and patients recruited in NH more often taking olanzapine. There were also site differences in race, gender, education and prior psychiatric hospitalizations (Glynn et al., 2017). Therefore, we included an indicator for site in the mixed effects models.

Persistence on study medication: The mean daily dose of study medication at 18 months was 6.4 ± 3.2 mg for risperidone and 17.0 ± 5.0 mg for olanzapine. Overall, 42 (39.6%) of the 107 patients remained on assigned medication and in the study at one year and 36 (34.0%) at 18 months (Fig 1). In the risperidone group 20 (36.4%) of 55 patients remained on study medication at 1 year and 17 (30.9%) remained on study medication at 18 months. In the olanzapine group, 22 (43.1%) of 51 patients remained on study medication at 1 year, and 19 (37.3%) at 18 months. Kaplan-Meir survival rates were 0.49 for risperidone and 0.57 for olanzapine at 18 months. Reasons for medication discontinuation in participants who continued the vocational portion of the study included lack of efficacy (RSP 6/OLZ 8), intolerable side effects (RSP 7/OLZ 7), participant decision (RSP 6/OLZ 2) and poor adherence (RSP 0/OLZ 1). Side effects that led to termination of risperidone included weight gain, lipid elevation, cognitive slowing, priapism, seizure and neuroleptic malignant syndrome. Side effects that led to termination of olanzapine included weight gain, anxiety, restlessness and insomnia. There was no evidence of a significant difference in persistence on study medication by group (Overall log rank test: $X^2 = 0.92$, NS; difference in 18-month survival rate: Z = 0.77, NS; Fig 2*a*), nor in reasons for discontinuation.

Effectiveness

Psychopathology: There were no significant differences between the risperidone and olanzapine groups in the rate of change (i.e. medication by time interaction) on the BPRS or any of its subscales, nor on the SANS or any of its subscales (Table 2). The risperidone group demonstrated a greater rate of improvement on the SCL-90 somatization subscale up to 18 months (medication by time interaction $p < 0.05$). There were no other between groups differences on the remaining SCL-90 subscales, nor in depression as measured by the HAM-D. There was significant improvement over time but no medication effect (time p's < .05, negative slope; medication and interaction terms NS) on the BPRS psychosis and

suspiciousness subscales and on the SANS avolition subscale. There were site differences indicating that participants in NH had lower mean BPRS total, BPRS psychosis and SANS alogia subscale scores, but higher SANS affective flattening subscales scores relative to their counterparts in LA after adjusting for other factors in the model.

Relapse: Twenty-eight of the 107 participants were hospitalized at some point during their study participation, 4 at the Los Angeles site and 24 at the New Hampshire site for a total of 50 hospital admissions. Sixteen of these subjects were in the group randomized to risperidone versus 12 to olanzapine. Twenty-three of these subjects experienced their first hospitalization within the first 18 months. Forty-five of these admissions occurred while patients were receiving double-blind study medications. There was no significant difference in time to first hospitalization between the risperidone and olanzapine groups (Overall log rank test: $X^2 = 1.46$, NS; difference in 18 month survival rate $Z = 1.20$, NS). However the difference in hospitalization rates between the two sites was significant ($X^2 = 4.91$, $p < .05$)

Side effects

Adverse effects: Patients randomized to olanzapine had an estimated rate of *increase* of .650 BMI points/year while those randomized to risperidone had an estimated rate of *decrease* of 1.095 BMI points/year, a statistically significant difference (Table 2). There were no significant interactions between medication group and time for any measures of neurological side effects. Applying Schooler-Kane criteria to the AIMS data, we identified 6 cases of treatment-emergent tardive dyskinesia (all of mild severity) during the 18-month assessment period, 3 of whom were in the risperidone group and 3 in the olanzapine group (NS). This represents a treatment-emergent tardive dyskinesia rate of 3.6%/year for risperidone, and 3.8%/year for olanzapine. There were site differences indicating that participants in NH had higher mean BMI scores and lower mean AIMS scores than their counterparts in LA after adjusting for other factors in the model.

Serious adverse events: There was one death in the risperidone group due to respiratory arrest and 1 death in the olanzapine group due to brain hemorrhage, both while on assigned study medication. There were no suicide attempts or completed suicides during study participation.

Lab measures: There were no significant differences in the rate of change in any laboratory studies by medication group over the course of the study (Table 2). The olanzapine group had higher mean total cholesterol levels overall. Eliminating observations when subjects were on concurrent lipid-lowering medications revealed no systematic differences in the findings. There was a trend towards increasing HDL in both groups over time. Patients at the NH site had significantly higher mean triglycerides and HDL levels than those at the LA site after adjusting for other factors in the model.

Functional outcomes

Social and role functioning: There were no significant differences in either mean or rate of change between the medication groups in terms of social adjustment or overall quality of life (Table 2). However, there was significant improvement over the 18-month study period on

the QOL total score (time p-value < .05). There was also a significant difference between the LA and NH sites, with subjects in LA having better average scores on the SAS general adjustment scale.

Employment: Sixty-seven of the 107 subjects obtained competitive employment during the study period (Glynn et al., 2017). Thirty-two of these subjects were in the group randomized to olanzapine and 35 were in the group randomized to risperidone. All but one of the subjects who obtained jobs had done so by 18 months, and the corresponding the Kaplan-Meier estimates of employment rates at 18 months were .73 for the olanzapine group and .80 for the risperidone group. There were no significant differences in time to first employment by medication group (Overall log rank test: $X^2 = 0.31$, NS; difference in 18-month employment rate: Z = 0.44, NS). The estimated median time to obtain a job was 182 days (mean 216.4 +/− 21.9 days) in the olanzapine group and 225 days (mean 274.2 +/− 24.3 days) in the risperidone group (Z = 0.74, NS). Among subjects who did obtain competitive employment the median number of weeks during the two-year follow-up with at least some work hours was 43 in both medication groups.

Pre-randomization By Randomized Medication Group Analysis (Six Groups)

To account for potential differences between subjects who switched medications and those who were randomized to remain on their prior medication, we reran the above analyses using a 6-class pre-post randomization medication grouping. There were no statistically significant differences in demographic variables among these groups, except for ethnic composition. This was attributable to the fact that the New Hampshire site had both a higher proportion of white subjects and a higher prevalence of olanzapine use pre-randomization. Overall 12 subjects switched from risperidone to olanzapine (RSP-OLZ), 20 switched from olanzapine to risperidone (OLZ-RSP), 33 subjects remained on their pre-randomization medication (12 RSP-RSP and 21 OLZ-OLZ) and 40 subjects were placed on risperidone or olanzapine for the first time at randomization (23 N-RSP, 17 N-OLZ). While sample sizes for the 6 group analyses are small, limiting our power to detect group by time interactions in the mixed models with high confidence, the repeated measures give us enough information to identify some suggested areas of interest. Specific details are given below.

Persistence on study medication: Median survival time on assigned medication was similar across the 6 medication groups to 18 months, and there was no statistically significant difference in survival rate across treatment groups (Log rank test: $X^2 = 6.00$, NS; Fig 2*b*). Visually, the RSP-OLZ, N-OLZ and N-RSP groups clustered together, followed by the OLZ-OLZ, RSP-RSP, and OLZ-RSP groups.

Effectiveness

Psychopathology: There were suggestions of significant differences in response among the groups on several psychopathology variables using the 6-group model (Table 3). However, none of them were strong enough to survive correction for multiple testing. Measures with possible medication by time interactions were the BPRS psychosis subscale (favoring the OLZ-RSP and RSP-OLZ groups) and SCL-90 total score (favoring the OLZ-OLZ, OLZ-RSP and N-RSP groups). See Table 3 for details.

Relapse: The OLZ-RSP group had a significantly higher rate of hospitalization than the remaining 5 groups (59.5% by 18 months as compared to 12.5–28.9% for the other groups, Log rank test: $X^2 = 12.23$ p=0.03). In contrast to the other groups, no participant in the OLZ-RSP group remained in the study and on their assigned study medication without a hospitalization for 600 days or longer, and the majority were hospitalized or dropped out in under a year. As subjects at the NH site were more likely to be on olanzapine prior to randomization and there was also a lower threshold for hospitalization at that site, we reran the analyses comparing only participants who entered the study on olanzapine (OLZ-OLZ vs. OLZ-RSP groups, total n=41). The OLZ-RSP group appeared to again have a shorter time to first hospitalization, although the difference did not quite achieve statistical significance (Log rank test: $X^2 = 2.99$, p = .0838; Rate difference at 18 months: Z = 1.62, p = .1052).

Side Effects—There was a trend towards pre-randomization medication influencing change in BMI in response to randomized medication in the expected direction, with those who were randomized to the same medication that they were taking pre-randomization showing the least change in BMI (p = .0737). There were no significant differences in the rate of change in the side effect scales by medication group in the 6-group analysis. The only laboratory measures with suggested effects were triglyceride levels (group effect, no interaction) and HDL cholesterol (group-by-time interaction, with decreasing HDL only in the N-OLZ group and the largest increase in HDL in the N-RSP group.) Eliminating observations when subjects were on concurrent lipid-lowering medications again revealed no systematic differences. See Table 3 for details.

Functional outcomes

Social adjustment and role functioning: Again, there were no significant differences in rate of change in the social adjustment and role functioning subscales by medication group in the 6 group analyses. There was again borderline evidence of improvement over time on the QOL total score, and of better general social adjustment at the LA site. See Table 3 for details.

Employment: Median time to employment was similar across the 6 medication groups to 18 months, and there was no statistically significant difference in employment rates (Overall log rank test: $X^2 = 0.93$, NS).

Discussion

The primary analysis comparing the 2 randomized treatment groups confirmed our hypothesis that risperidone and olanzapine have similar effectiveness in the context of supported employment. The low 18-month assigned medication continuation rates, consistent with those found in CATIE phase-1 (Lieberman et al., 2005), are somewhat surprising in this study where participants were actively involved in psychosocial rehabilitation. Study physicians were actively working with rehabilitation staff to reinforce obtaining and maintaining competitive employment. We might have expected stable outpatients who are focused on achieving vocational goals to be less reliant on medication

manipulation to achieve satisfactory illness management. This finding may reflect the continual churn in medication many prescribers and patients undergo to find the elusive optimal trade-off between functioning, symptoms, and side effects. It may also simply reflect the difficulty study participants have in sustaining blinded, randomized treatment.

Our finding of differences in BMI change is consistent with the finding of greater weight gain during olanzapine treatment relative to other first-line SGAs from several other studies (Pagsberg et al., 2017; Zhao et al., 2016). However, we found substantially less weight gain than CATIE (where patients on olanzapine gained approximately 2 pounds per month). Moreover, we did not find the changes in lipids that appeared in other studies (Grootens et al., 2011; Patel et al., 2009). We also found no support for our hypothesis that differences in the effects of the two medications would influence functional outcomes and quality of life. This may be related to the careful monitoring of metabolic effects that took place during this study (Marder et al., 2004). It may have also been related to increased physical activity among this unique population that was participating in supported employment. We have previously reported that reversal of antipsychotic-associated weight gain was associated with vocational activity (O'Keefe et al., 2003). Finally, olanzapine and risperidone may be too similar in their effects on functional outcomes and quality of life to result in differences in employment parameters that are apparent beyond the robust effect of supported employment.

Our findings of significant improvement in thought disorder, suspiciousness, avolitional symptoms, and quality of life across both medication groups over time are intriguing, leading to several potential explanations. This could result from both risperidone and olanzapine being more effective than previous antipsychotic treatment, however, less than 40% of the sample entered the study on medications other than risperidone or olanzapine, and the 6-group analyses demonstrated little advantage for patients switched from other antipsychotics to these agents. It could also result from more frequent or effective psychiatric care during the study relative to previous care, although recruitment took place among patients in case management services in well-organized clinics. Finally, it is possible that involvement in supported employment was helpful in reducing symptom levels, potentially by engaging patients attention outside of their internal thought processes for significant periods of time (Jäckel et al., 2017). The latter explanation, together with the finding of attenuated changes in weight and positive changes in lipids, would be consistent with synergistic interactions between medication and rehabilitation (Kane et al., 2016; Noordsy et al., 2000).

We found rates of treatment-emergent tardive dyskinesia are higher than previously reported with risperidone and olanzapine (Mari et al., 2004; Schooler et al., 2005), but consistent with the findings of recent analyses among patients in maintenance treatment (Carbon et al., 2017; Yoshida et al., 2014). While our study was not powered for detection of treatment-emergent tardive dyskinesia, this finding should remind clinicians to remain vigilant for signs of tardive dyskinesia even among stable patients in maintenance treatment.

The secondary analysis comparing the 6 pre-randomization-by-randomized treatment groups suggested that patients who were changed from olanzapine to risperidone had a significantly shorter time to first hospitalization, consistent with the Essock reanalysis of the CATIE data

(Essock et al., 2006). There was also a weak trend towards those who were randomized to the same medication that they were taking pre-randomization showing the least change in BMI. These findings suggest that clinical practice may result in medication selection that is better matched to patient specific responses than random assignment. However, they also suggest a dilemma for clinicians who are managing patients who are clinically stable on olanzapine, but who are also overweight, insulin resistant, or have elevated lipids. That is, changing medication is associated with a risk of psychotic exacerbation.

Limitations

We lacked a more distinct control medication such as clozapine or a first-generation antipsychotic medication, which are challenging to implement in controlled trials. Sample size may have also limited our power to detect differences between the medication treatment groups. All of the above findings must be considered exploratory given the fact that we did not correct for multiple comparisons. They should be considered most generalizable to patients who are established in psychiatric care and interested in competitive employment. Dropout from assigned medication condition was substantial over time. While there was no evidence of a differential rate of dropout among treatment groups, only a third of patients remained on their assigned medication at 18 months, creating potential for biases due to dropouts who were poor responders or had difficulty tolerating their assigned medication.

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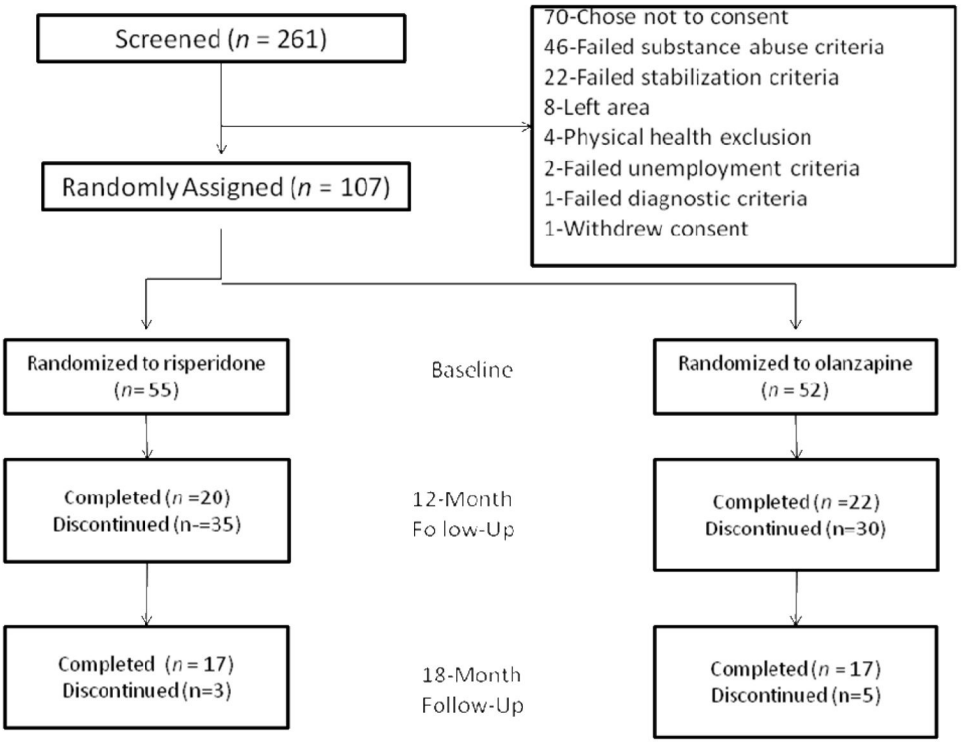
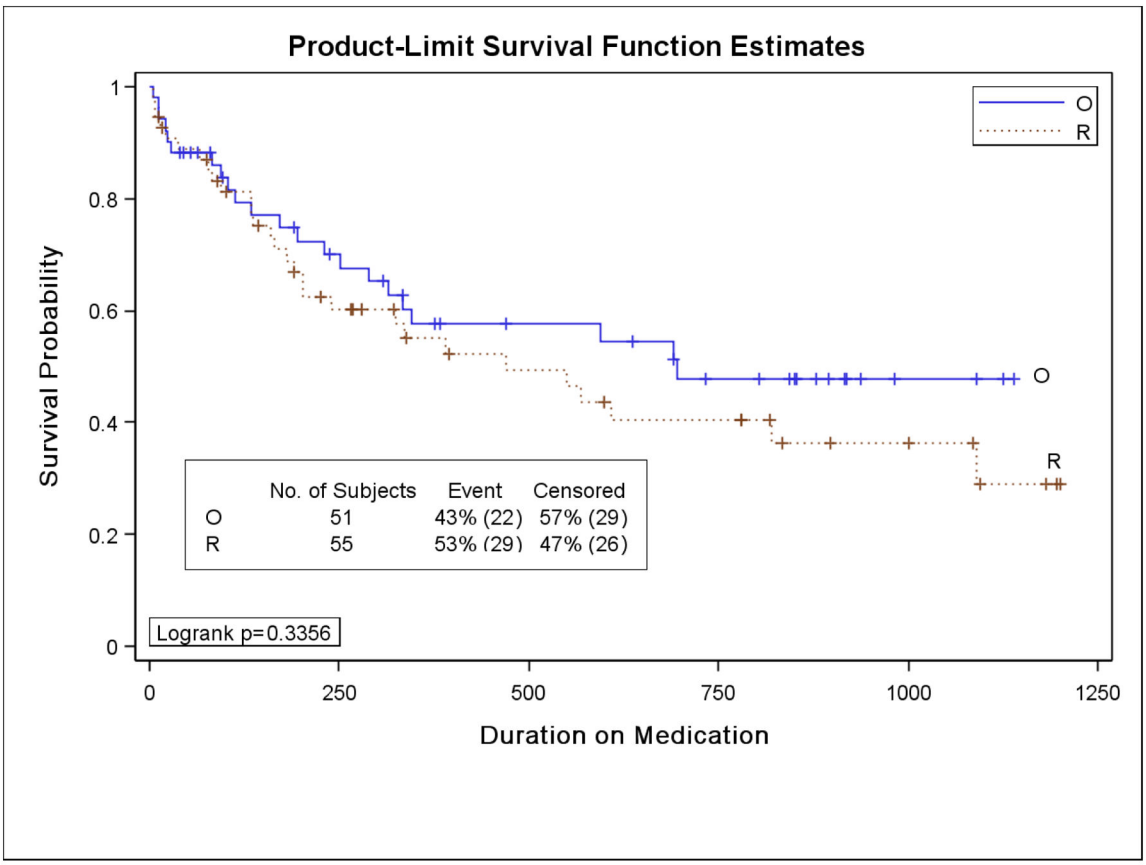


Figure 1.
Flow Diagram of Participants in the Randomized Control Trial



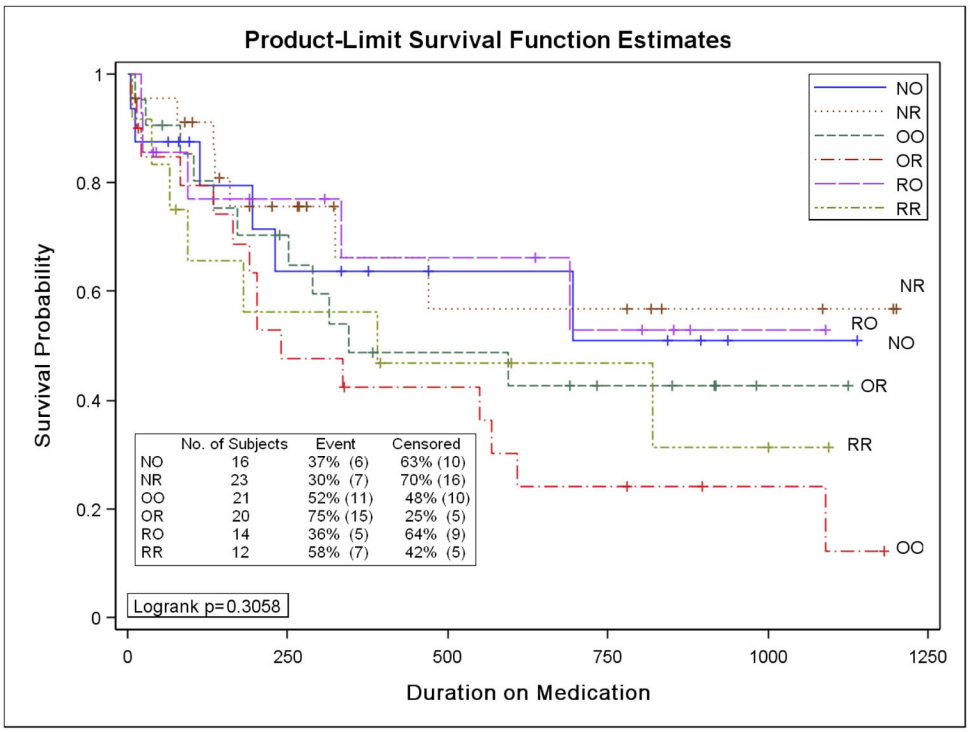


Figure 2.

Figure 2*a*. 18-month survival on study medication (2 group analysis)

X^2 = .9271, df = 1, p-value .3356

R = risperidone, O = olanzapine

Figure 2*b*. 18-month survival on study medication by pre-randomization medication (6 group analysis)

X^2 = 6.0042, df = 5, p-value .3058

R = risperidone, O = olanzapine, N = other antipsychotic medication

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Table 1

Demographic variables at baseline by site and medication assignment

Variable	LA (N=45)	NH (N=62)	p	RSP[1] (N=55)	OLZ[2] (N=52)	p	Total (N=107)
Education (yrs)	13.4	11.6	<.0001	12.4	12.4	n.s.	12.4
Age of onset (N=102, yrs)	26.8	23.5	.0526	24.0	25.9	n.s.	24.9
Prior Hospitalizations (N=100)	5.5	8.6	.0448	7.6	6.9	n.s.	7.3
Age (yrs)	42.2	41.9	n.s.	41.8	42.2	n.s.	42.0
Illness duration (N=102, yrs)	15.4	18.5	n.s.	17.9	16.5	n.s.	17.3
Ethnicity N((%)			<.0001			n.s.	
White	23 (51.1%)	60 (96.8%)		40 (72.7%)	43 (82.7%)		83 (77.6%)
Latino	2 (4.4)	0 (0)		1 (1.8)	1 (1.9)		2 (1.9)
Asian	3 (6.7)	0 (0)		1 (1.8)	2 (3.9)		3 (2.8)
Black	15 (33.3)	1 (1.6)		10 (18.2)	6 (11.5)		16 (15.0)
Other	2 (4.4)	1 (1.6)		3 (5.5)	0 (0)		3 (2.8)
Gender N(%)			.0105			n.s.	
Male	42 (93.3%)	46 (74.2%)		45 (81.8%)	43 (82.7%)		88 (82.2%)
Female	3 (6.7)	16 (25.8)		10(18.2)	9 (17.3)		19 (17.8)
Marital status N(%)			n.s.			n.s.	
Never	28 (62.2%)	30 (49.2%)		30 (54.6%)	28 (54.9%)		58 (52.4%)
Divorced	6 (13.3)	8 (13.1)		7 (12.7)	7 (13.7)		14 (13.3)
Married	11 (24.4)	23 (37.7)		18 (32.7)	16 (31.4)		34 (32.4%)
Pre-randomization medication			<.0001			n.s.	
RSP[1]	18(40%)	8 (13%)		12(22%)	14(27%)		26 (24%)
OLZ[2]	6 (13)	35 (56)		20 (36)	21 (40)		41 (38)
Other	21 (47)	19 (31)		23 (42)	17 (33)		40 (37)

[1]RSP = risperidone

[2]OLZ = olanzapine

Table 2

Eighteen-month psychopathology, side effect, laboratory and social outcomes, adjusted for site and medication adjustment period (2 group analysis)

Variable	Time[1]	Group	Group x Time
Pyschopathology Measures			
Brief Pyschiatric Rating Scale (BPRS)[2]	n.s.	n.s.	n.s.
BPRS-D (Depression)	n.s.	n.s.	n.s.
BPRS-S (Thought Disturbance)	.0442	n.s.	n.s.
BPRS-R (Retardation)	n.s.	n.s.	n.s.
BPRS-P (Paranoid Suspiciousness)	.0001	n.s.	n.s.
Negative Symptoms (SANS)	.0802	n.s.	n.s.
Affect Flattening	n.s.	n.s.	n.s.
Alogia	.0982	n.s.	n.s.
Avolition	.0089	n.s.	n.s.
Anhedonia	n.s.	n.s.	n.s.
Symptom Checklist (SCL)-90 Somatization	.0073	n.s.	.0396[3]
Hamilton Depression Scale (HAM-D)	n.s.	n.s.	n.s.
Side Effect Measures			
Body Mass Index (BMI)	n.s.	n.s.	0.0176[4]
Abnormal Involuntary Movement (AIMS)	n.s.	n.s.	n.s.
Barnes Akathisia Scale (BAS)	n.s.	n.s.	n.s.
Simpson-Angus Scale (SA)	n.s.	n.s.	n.s.
Subjective Extrapyramidal Rating Scale (SERS)	n.s.	n.s.	n.s.
Laboratory Measures			
Glucose	n.s.	n.s.	n.s.
HbA1c	n.s.	n.s.	n.s.
Cholesterol	n.s.	0.0339[5]	n.s.
Triglycerides	n.s.	n.s.	n.s.
LDL Cholesterol	n.s.	n.s.	n.s.
HDL Cholesterol	0.0812	n.s.	n.s.
Social Adjustment and Quality of Life Measures			
SAS: General Adjustment	n.s.	n.s.	n.s.
QOL: Total Score	.0314	n.s.	n.s.

[1] All changes over time are in the direction of improvement.

[2] BPRS and SANS totals are sums; Subscale scores are averages of their respective items.

[3] The model estimates a rate of decrease of .077 points/year on the SCL-90 SOM scale in the OLZ group and a rate of decrease of .292 points/year in the RSP group.

[4] Patients randomized to OLZ had an estimated rate of *increase* of .650 BMI points/year while those randomized to RSP had an estimated rate of *decrease* of 1.095 points/year.

[5] Average cholesterol scores of OLZ subjects are 18.673 points higher than RSP subjects.

Table 3

Eighteen-month psychopathology, side effect, laboratory and social outcomes, adjusted for site and medication adjustment period (6 group analysis)

Variable	Time[1]	Group	Group x Time
Pyschopathology Measures			
Brief Pyschiatric Rating Scale (BPRS)[2]	n.s.	.0833	n.s.
BPRS-D (Depression)	n.s.	.0484	n.s.
BPRS-S (Thought Disturbance)	.0850	n.s.	.0488
BPRS-R (Retardation)	n.s.	n.s.	n.s.
BPRS-P (Paranoid Suspiciousness)	.0004	n.s.	n.s.
Negative Symptoms (SANS)	.0758	n.s.	n.s.
Affect Flattening	n.s.	n.s.	n.s.
Alogia	.0678	n.s.	n.s.
Avolition	.0113	n.s.	n.s.
Anhedonia	n.s.	n.s.	n.s.
Symptom Checklist (SCL)-90 Positive Symptoms	n.s.	n.s.	.0142
Hamilton Depression Scale (HAM-D)	n.s.	n.s.	n.s.
Side Effect Measures			
Body Mass Index (BMI)	n.s.	n.s.	0.0737
Abnormal Involuntary Movement (AIMS)	n.s.	n.s.	0.0664
Barnes Akathisia Scale (BAS)	n.s.	0.0435	n.s.
Simpson-Angus Scale (SA)	n.s.	n.s.	n.s.
Subjective Extrapyramidal Rating Scale (SERS)	n.s.	n.s.	n.s.
Laboratory Measures			
Glucose	n.s.	n.s.	n.s.
HbA1c	n.s.	n.s.	n.s.
Cholesterol	n.s.	n.s.	0.0699
Triglycerides	n.s.	0.0195	n.s.
LDL Cholesterol	n.s.	n.s.	n.s.
HDL Cholesterol	n.s.	n.s.	0.0300
Social Adjustment and Quality of Life Measures			
SAS: General Adjustment	n.s.	n.s.	n.s.
QOL: Total Score	.0538	n.s.	n.s.

[1] All changes over time are in the direction of improvement.

[2] BPRS and SANS totals are sums; Subscale scores are averages of their respective items.