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Olanzapine vs. Risperidone in Patients with First-Episode Schizophrenia and a Lifetime History of Cannabis Use Disorders: 16-Week Clinical and Substance Use outcomes

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Abstract

The purpose of this study is to compare the efficacy of olanzapine and risperidone for the acute treatment of first-episode schizophrenia patients with cannabis use disorders. This secondary analysis of a previously published study included forty-nine first-episode patients with a diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder and a co-occurring lifetime diagnosis of cannabis use disorders randomly assigned to treatment with either olanzapine (n=28) or risperidone (n=21) for 16 weeks. The olanzapine group did not differ significantly from the risperidone group for initial response rates of positive symptoms, and rates of cannabis use or alcohol use during the study. Positive symptoms and SANS global asociality-anhedonia improved over time but did not differ between study medications. In both groups, cannabis use during the study was higher in patients who used cannabis within 3 months of the admission. Thus, our results suggest that olanzapine and risperidone had a similar initial efficacy on psychotic symptoms and substance use in first-episode patients with co-occurring cannabis use disorders. If clinicians are choosing between olanzapine versus risperidone treatment for this population, their decision should be based upon factors other than symptom response and short-term substance misuse.

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Keywords

psychosis; marijuana; atypicals; alcohol; negative symptoms; positive symptoms

1. Introduction

Cannabis is the most common illicit drug used among individuals presenting with a first episode of schizophrenia with lifetime prevalence ranging from 13% to 64% (Linszen et al., 1994; Hambrecht and Hafner, 1996; Kovasznay et al., 1997; Cantwell et al., 1999; Sevy et al., 2001; Buhler et al., 2002; Barnes et al., 2006; Wade et al., 2006; Barnett et al., 2007). Despite the prevalence of cannabis use disorders (abuse or dependence) among patients presenting for treatment for a first episode of schizophrenia, there are little data to guide clinicians about the choice of the initial antipsychotic for treating an acute episode in these patients. To the best of our knowledge, previous studies have focused on substance use outcomes in non-acute patients. The only study (van Nimwegen et al., 2008) in the literature examining second generation antipsychotic treatment with patients with recent-onset schizophrenia and cannabis use is a randomized, double-blind comparison of subjects treated with either olanzapine (n=63) or risperidone (n=65). No differences between subjects treated with olanzapine or risperidone on measures of subjective well-being and craving for cannabis were found. However, the study did not address several important issues for guiding clinicians about initial medication choice for patients with first episode schizophrenia and cannabis use disorders: the study did not report clinical outcomes; it only addressed very short-term outcomes (6 weeks); it did not exclude subjects with substance-induced psychosis, and it did not specify whether subjects had previous psychotic episodes and antipsychotic treatment. Data from comparative trials with patients with multi-episode schizophrenia and cannabis use disorders are also limited. Green et al. (2003) reported that 31 patients with schizophrenia or schizoaffective disorder on clozapine were more likely to be sober for alcohol and marijuana than 8 patients on risperidone after one year of treatment. Potvin et al. (2004) reported a decrease in cannabis use after 6 months of treatment with quetiapine in 8 psychotic patients dependent on cannabis, but did not report other clinical outcomes. Akerele and Levin (2007) conducted a randomized, double-blind study comparing schizophrenia patients with cocaine and/or cannabis use disorders treated with either olanzapine (n=14) or risperidone (n=14) for 10 weeks. They found a reduction in marijuana-positive urine drug screens for both groups and a greater decrease in marijuana craving with olanzapine compared to risperidone. They also report improved positive and depressive symptoms over the course of the study, but no differences between groups. The degree to which these limited data with multi-episode patients generalize to treatment with first episode patients is unknown.

Although the prevalence of schizophrenia is high, the incidence is low. This makes recruitment of an adequate number of subjects for comparative trials with first episode patients challenging. Adding the inclusion criteria of subjects with cannabis use disorders increases recruitment difficulties. A dedicated definitive study with these challenges would require large amounts of resources. In the absence of such a trial, we report the results of a secondary analysis of data from a previously published prospective study comparing olanzapine and risperidone treatment for subjects with first-episode schizophrenia (Robinson et al., 2006). Although not designed to study subjects specifically with cannabis use disorders, the study sample included 49 subjects with first episode schizophrenia-spectrum disorders and a history of cannabis use disorders that are the focus of this report. We were particularly interested in examining the outcomes of these subjects as previous studies suggest that the most promising atypical antipsychotic for decreasing psychotic symptoms and substance use is clozapine (McEvoy et al., 1995, 1999; Drake et al., 2000; Brunette et

al., 2006). Because olanzapine is closely related in chemical structure to clozapine and shares many common receptor binding characteristics (binding affinities for D2, HT2a, HT2c, alpha2, M1 receptors) (Bymaster et al., 1996), we hypothesized that olanzapine might be better than risperidone as an antipsychotic treatment among the 49 subjects with first-episode schizophrenia and co-occurring cannabis use disorders.

2. Methods

2.1. Overview

The present study is a secondary analysis of data from the acute treatment phase of a prospective, randomized trial comparing risperidone and olanzapine for the treatment of first-episode subjects with a diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder. Details of the original study have previously been described (Robinson et al., 2006). The original study consisted of an acute treatment phase (lasting 4 months) followed by a longitudinal follow-up phase of 32 months. A previous assessment indicated that first episode subjects would be reluctant to take blinded medication for a total of 3 years, so the study was designed as an open-label treatment with masked assessment of psychopathology. The present study focused on the first sixteen weeks because it was an adequate timeframe to determine an acute treatment response in a first-episode sample, and it was long enough to assess the efficacy of the study medications.

The study was conducted under the guidelines of the Institutional Review Boards (IRBs) of the North Shore - Long Island Jewish Health System (New York) and the Bronx-Lebanon Hospital (Bronx, NY). It was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.2. Subjects

All new patients referred to psychiatric acute care at the Zucker Hillside Hospital and Bronx-Lebanon Hospital were screened for this study. Adult subjects provided written informed consent. For subjects less than 18 years old, written parental consent and written subject assent were obtained. Eligible subjects were between the age of 16 and 40, had a current diagnosis of DSM-IV schizophrenia, schizophreniform disorder, or schizoaffective disorder with less than 12 weeks of lifetime cumulative antipsychotic medication treatment, and demonstrated either current positive or negative symptoms as evidenced by a rating of 4 or more on the Schedule for Affective Disorders and Schizophrenia - Change Version with psychosis and disorganization items (SADS-C+PD) *or* on the affective flattening, alogia, avolition, or anhedonia global items of the Hillside Clinical Trials version (Robinson et al., 2000) of the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1989). All subjects for this secondary analysis also met DSM-IV criteria for a lifetime history of cannabis abuse or dependence. Although these subjects met criteria for cannabis use disorders, they also met criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. Thus, subjects whose psychotic symptoms occurred solely in the context of a substance-induced psychotic disorder were not included in the parent study or this secondary analysis.

2.3. Treatment protocol

In the original study subjects were stratified by sex, pre-treatment current (within the last month) DSM-IV-defined substance abuse or dependence (excluding nicotine and caffeine), and site. They were randomly assigned to the treatment conditions according to a computer pre-generated block randomization list provided by the Department of Biostatistics and only accessible to the biostatisticians and dedicated research coordinators. For the current

analysis, all subjects from the original study with lifetime DSM-IV diagnoses of cannabis abuse or dependence were included.

The treatment goal of the original study was to find the lowest effective dose to treat the initial acute psychotic episode. The initial daily dose was 2.5 mg for olanzapine and 1 mg for risperidone. A slowly increasing titration schedule was used: after week 1, dose increases occurred at intervals of 1-3 weeks until the subject improved or reached a maximum daily dose of 20 mg of olanzapine or 6 mg of risperidone. Lorazepam was given for agitation requiring pharmacological treatment. Subjects with persistent mood symptoms unresponsive to antipsychotic treatment were prescribed sertraline for depression or divalproex sodium for manic symptoms. Motor side effects were treated with antipsychotic dose reduction or, if this was ineffective, benztropine for extrapyramidal symptoms and lorazepam or propranolol for akathisia. Because of concern about maintaining psychotic subjects for 16 weeks on an ineffective treatment, subjects who did not achieve Clinical Global Impression (CGI) ratings of at least minimal improvement of psychotic symptoms by 10 weeks were terminated from controlled treatment. At each site, subjects were seen by a social worker who was assigned to the project. All subjects received psychoeducation about schizophrenia, its treatment and the importance of abstinence from cannabis and other substances of abuse. Subjects were seen on a regular basis by the social workers during their entire study participation. Subjects also had access to the ancillary treatment services available from two large departments of psychiatry.

2.4. Measures

Diagnosis and psychopathology assessments were performed by masked (“blind”) assessors. To increase uniformity of assessments, a central rating team performed the masked assessments at both sites. The same raters performed assessments with individual subjects throughout that subject's study participation. Subject diagnoses were evaluated at study entry using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) (First et al., 1998). Assessments for psychopathology were done weekly for the first four weeks, then bi-weekly. Psychopathology was assessed with the SADS-C+PD, CGI, and Hillside Clinical Trials version of the SANS. Since changes in body weight have been well described for atypical antipsychotics (Lieberman et al., 2003; Schooler et al., 2005), we also measured body weight and body mass index (BMI—weight in kilograms/height in meters^2) throughout the study.

2.5. Substance use

Lifetime and current (the last three months) substance use was assessed at study entry using the alcohol and substance abuse sections of the SCID interview. Sources of information about substance use during the study included collateral information from health care providers, case managers, family members, friends, and housemates when available. Subjects were diagnosed conservatively with cannabis abuse when the differentiation between cannabis abuse and dependence was unclear. Psychometricians questioned subjects about substance use at each rating session. At The Zucker Hillside Hospital site, a Substance Use Questionnaire (available on request) was administered by a research nurse. Of note, the study design allowed subjects to admit cannabis use without jeopardizing continued study participation. Urine drug screens were done when the subject appeared intoxicated or when there was a strong suspicion of substance use which the subject denied. These information sources were used to make the best estimate of substance use since the last study visit. For some subjects, the extent of substance use only became known after study entry. Thus, substance use classifications for the present study are the best assessments of substance use using all data sources at baseline and during follow-up.

2.6. Statistical Analysis

We used two-sample t-tests to compare the treatment groups at baseline for continuous variables and Chi-square or Fisher's exact tests for categorical variables.

The parent study defined a priori a positive symptom treatment response as 1) a rating of mild or better on all the SADS-C+PD items severity of delusions, severity of hallucinations, impaired understandability, derailment, illogical thinking, and bizarre behavior; and 2) a concurrent rating of very much improved or much improved on the CGI. The response criteria required that substantial improvement be maintained for two consecutive visits. Cumulative rates of response were computed and compared using standard survival analysis methods, i.e., Kaplan-Meier product-limit method and the log-rank test. Time to treatment response was coded as the first of the two visits meeting substantial improvement criteria. The relationships between the positive and the negative symptom responses over time and the effect of treatment group were explored with multivariate repeated measures analysis of covariance (RMANCOVA) with site entered as a covariate. We first entered the time by group interaction term into the analyses but since it was never significant, we report the results without the interactions.

Analysis of data from the original study revealed that olanzapine compared with risperidone treatment was associated with more weight gain (Robinson et al, 2006). Hence, we wished to examine weight changes with treatment among the subjects in the current subsample. Changes in BMI were examined using repeated measures ANCOVA models with divalproex sodium treatment utilized as a covariate. Divalproex was included in the model given its effects on weight gain that were revealed in analyses of the parent study sample.

To examine cannabis and alcohol use during the study, we compared usage in the olanzapine and risperidone groups during the last eight weeks of the study, necessitating the use of only treatment completers since dropouts did not have these data. This time point was chosen because the vast majority of subjects were hospitalized for clinical reasons at study entry and thus had no access to cannabis. We wished to examine substance use during periods when subjects would have potential access to cannabis and alcohol. We also compared substance use between subjects who met for current (i.e., within 3 months of admission) cannabis abuse/dependence at the start of the study and those who had stopped cannabis misuse earlier than 3 months before randomization.

3. Results

3.1. Subject sample

Data for this report were collected from November 1998 to November 2004. Subject flow for the parent study is described elsewhere (Robinson et al., 2006). Briefly, 474 subjects were assessed for eligibility. Of these, 282 did not meet inclusion criteria, 64 declined study participation and 8 did not enter for miscellaneous reasons. One hundred twenty subjects were randomly assigned to either olanzapine or risperidone, but eight of these subjects were not included in the final parent study sample because 1) they refused all study medication or assessments after randomization; or 2) it was detected after randomization that a subject met a study exclusion criteria. Forty-nine subjects (28 subjects randomized to olanzapine and 21 subjects randomized to risperidone) met DSM-IV criteria for cannabis use disorders either prior to or at the time of study entry and compose the sample for the current analyses. Among them, 19 subjects also met lifetime criteria for alcohol use disorders (abuse n=12, dependence n=7) and seven subjects had other lifetime substance use disorders (cocaine n=5, hallucinogens n=2, opiates n=1, inhalants n=1).

At baseline, 17 (65%) subjects in the olanzapine group for the current analysis and 12 (75%) subjects in the risperidone had been using cannabis within 3 months of the admission. The other subjects stopped using cannabis more than 3 months prior to admission. There were no significant differences between current and past users for demographic or clinical variables at the start of the study, and no differences between current and past users for rates of alcohol abuse or dependence.

Baseline demographic characteristics of the olanzapine and risperidone groups are presented in Table 1. Both groups were mostly male, had the onset of cannabis use disorders around age 17, and the onset of positive symptoms about two years later. Subjects assigned to olanzapine and risperidone did not differ on any socio-demographic measure or on any measure of baseline symptoms (Table 2).

3.2. Treatment received

Rates of completion of the 16 weeks of acute treatment for subjects assigned to olanzapine and risperidone did not differ (75% for olanzapine and 76% for risperidone treated subjects, χ^2=0.02, p=0.90). Subjects who did not complete 16 weeks either dropped out from the study or were removed from controlled treatment earlier than 16 weeks because they were too ill to continue for 16 weeks on their randomized medication. The mean modal daily dose was 15 mg ± 6 (SD) for olanzapine and 4 mg ± 2 (SD) for risperidone.

3.3. Treatment response

Results of the survival analyses indicated that response rates did not differ between treatment groups. The median survival time until achieving treatment response for the risperidone group was 14 weeks; the olanzapine group had not reached the median at the end of the 16 weeks. The number of responders at 16 weeks were 13 (45%, 95% CL 25-65%) for the olanzapine group and 11 (54%, 95% CL 29-79%) for the risperidone group, which were not significantly different (χ^2=0.17, p=0.68).

Results of the MANCOVAs for positive and negative symptoms are reported in Table 2. There were no significant differences between the treatment groups for either the positive symptoms total or subscale scores, or for negative symptoms. Both treatment groups improved over time for scores on the positive symptoms total and subscale scores. Among the negative symptoms, only Asociality-Anhedonia improved over time.

3.4. Substance Use

Among subjects who completed 16 weeks of treatment, data on cannabis use were available for 21 subjects on olanzapine and 16 subjects on risperidone. Ten subjects (48%) on olanzapine and 6 subjects (38%) on risperidone used cannabis during weeks 8 to 16 of the study. This was not statistically significant (χ^2=0.38, p=0.54). The rates of alcohol use during weeks 8 to 16 of the study were also similar (11 (52%) in the olanzapine group and 6 (38%) in the risperidone group; χ^2=0.81, p=0.37). The majority (17 in the olanzapine group and 13 in the risperidone group) were concordant for alcohol and cannabis during the study. Among subjects who used cannabis within three months of entering the study and completed the study (11 in the olanzapine group and 9 in the risperidone group), 7 (64%) in the olanzapine group and 5 (56%) in the risperidone group used cannabis during weeks 8 to 16. Among subjects who did not use within three months of admission, 3 (30%) in the olanzapine group and 1 (14%) in the risperidone group used during weeks 8 to 16. Combining the two medication groups, the Fisher's Exact comparing current use at study entry and use during the study was significance (χ^2=3.46, p=0.049).

3.5. Weight gain

Baseline mean weight in the olanzapine and risperidone groups (155 lbs. ± 29 (SD) and 140 lbs. ± 24, respectively) and BMI (23 ± 4 and 22 ± 4) were significant increased at week 16 (weight: 180 lbs. ± 34 in the olanzapine group vs. 151 lbs ± 41 in the risperidone group and BMI: 26 ± 4 in the olanzapine group vs. 25 ± 5 in the risperidone group). There was a time main effect for weight and BMI ($F=8.11$; $p<0.001$), but no effect of the covariate (divalproex sodium), nor time by group or time by group by divalproex sodium treatment interactions.

4. Discussion

Contrary to our original hypothesis, we did not find any indications that olanzapine is superior to risperidone for the treatment of patients with first-episode schizophrenia and co-occurring cannabis use disorders. Both medications improved positive and negative symptoms and some negative symptoms (asociality-anhedonia). The improvement of symptoms in the group with cannabis use disorders is similar to the improvement of symptoms observed in the parent study that included both subjects with and without substance use disorders (Robinson et al., 2006).

We did not find statistically significant differences between treatment groups for the proportion of subjects using alcohol or cannabis during the study. However, the use of cannabis during the study was substantial in both treatment groups and was higher in subjects who used cannabis within 3 months of admission compared with subjects who had stopped cannabis use earlier than 3 months before study entry. Future studies will need to identify other risk factors associated with increased substance use during treatment and develop interventions targeting them.

The main limitation of this study is the small sample size and the subsequent lack of statistical power. Because of the paucity of studies comparing atypical antipsychotics in first-episode patients with cannabis use disorders, we believe that it is important to report these results even if the statistical power is low. This secondary analysis of a prospective trial was a unique opportunity to compare the effectiveness of two widely used antipsychotics with this patient group and to provide information for future studies in this field. Other limitations include the lack of accurate measures of the amount and frequency of substance use. The parent study was not a substance abuse trial and it would require a dedicated substance use study to quantify substance use adequately. Likewise, we did not assess craving.

In conclusion, olanzapine and risperidone have a similar initial efficacy on psychotic symptoms and substance use outcomes in first-episode patients with a lifetime diagnosis of cannabis use disorders. Our results suggest that if clinicians are choosing between olanzapine versus risperidone treatment for this population the decision should be based upon factors other than symptom response and short-term substance misuse, for which both medications have equal efficacy.

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Table 1
Comparison of demographics in the olanzapine and risperidone groups

	Olanzapine	Risperidone	Statistics
Males/females	24/4	16/5	Fisher's Exact p=0.50
Site (site1/site2)	22/6	14/7	χ^2=0.9, p=0.35
Age at study entry	21.7 (2.6)*	21.7 (4.8)*	t=-0.03, p=0.97, df=47
Age at onset of psychosis	19.8 (3.4)*	19.8 (5.2)*	t=-0.02, p=0.98, df=47
Age at onset of cannabis use disorders	16.9 (1.7)*	17.1 (3.9)*	t=-0.25, p=0.80, df=44
Cannabis abuse/dependence	8/20	8/13	χ^2=0.5, p=0.55

*mean (standard deviation)

Table 2

Comparison of baseline and 16 week positive and negative symptoms between the olanzapine and risperidone groups

	Olanzapine		Risperidone		Mixed Model Results					
	Baseline	Week 16	Baseline	Week 16	Olanzapine vs. Risperidone		Time (0-16 weeks)		Site	
Positive symptoms	**n=28**	**n=21**	**n=21**	**n=16**	**F**	**P**	**F**	**P**	**F**	**P**
Delusions	5.5 (0.6)*	2.7 (1.6)	5.4 (0.6)	2.6 (1.7)	0.54[a]	0.47	10.34[b]	<0.0001	0.53[a]	0.47
Hallucinations	4.6 (1.6)	2.0 (1.6)	5.0 (0.9)	1.8 (1.2)	1.49[a]	0.23	9.62[b]	<0.0001	2.52[a]	0.12
Thought disorder+	7.3 (3.5)	4.5 (2.6)	6.6 (3.7)	3.6 (0.8)	0.47[a]	0.49	6.60[b]	<0.0001	2.96[a]	0.09
Total¶	19.8 (4.3)	10.6 (4.3)	19.2 (4.7)	9.1 (2.9)	0.04[a]	0.84	18.97[b]	<0.0001	1.70[a]	0.20
Baseline Negative symptoms	n=28	n=22	n=21	n=17	F	P	F	p	F	P
Affective flattening/blunting	2.0 (1.1)	2.0 (1.0)	2.1 (1.3)	2.5 (1.1)	2.46[a]	0.12	1.25[c]	0.25	7.01[a]	0.01
Alogia	2.0 (1.0)	1.8 (0.8)	1.8 (1.1)	2.2 (1.1)	0.11[a]	0.75	0.46[c]	0.93	9.61[a]	0.003
Avolition-apathy	3.1 (1.2)	3.0 (1.1)	3.0 (1.3)	2.9 (0.9)	0.06[a]	0.81	1.29[c]	0.52	0.42[a]	0.52
Asociality-anhedonia	3.1 (1.1)	2.7 (1.1)	3.3 (1.0)	2.6 (1.1)	0.46[a]	0.50	3.35[c]	0.0002	6.14[a]	0.02

*Mean (standard deviation)

[a]df=1.46;

[b]df=11,387;

[c]df=11,371.

+A composite score that includes derailment, illogical thinking, and impaired understanding;

¶Total score includes delusions, hallucinations, thought disorder, and bizarre behavior.