A Comparative Effectiveness Study of Risperidone and Olanzapine in the Treatment of Schizophrenia

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Background: Risperidone and olanzapine have each been demonstrated to be efficacious and safe in the treatment of patients with chronic schizophrenia. To evaluate their relative effectiveness, and to better understand the advantages and limitations of each neuroleptic during actual clinical use, we compared one directly against the other.

Method: Forty-two subjects with DSM-IV schizophrenia had received open-label treatment with either risperidone or olanzapine. Symptoms, global functioning, and extrapyramidal side effects before and after acute treatment were compared within and across groups. At 6-month follow-up, the relative effectiveness of these 2 atypical neuroleptics on symptoms and quality of life were further evaluated.

Results: Following an average of 4 weeks of acute treatment, both risperidone and olanzapine were effective in reducing negative, psychotic, and disorganized symptoms. Although both neuroleptics were associated with low occurrence of treatment-emergent parkinsonism, risperidone was more likely to induce akathisia. The measures for parkinsonism were no different across treatment groups, even after taking into account the higher rate of anticholinergic use in the risperidone group. Following 6 months of treatment with these 2 atypical neuroleptics, there was a significantly greater reduction in psychotic symptoms among risperidone-treated subjects. Otherwise, risperidone and olanzapine appear to be equally effective in reducing disorganized and negative symptoms and in improving the quality of life.

Conclusion: Risperidone and olanzapine were equally effective as acute treatments. Risperidone was more effective for treatment of psychotic symptoms at 6 months, but otherwise the 2 medications were equally effective in the routine clinical care of patients with schizophrenia. If low (< 6 mg/day) doses of risperidone are used, the 2 medications have comparable rates of parkinsonian side effects.

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The reintroduction of clozapine has stimulated the development of a new generation of neuroleptic medications that attempt to mimic its pharmacologic characteristics. Risperidone and olanzapine were the first among these atypical or novel neuroleptics to become available for clinical use in the United States. Each has been demonstrated in clinical studies[1–6] to be efficacious in the acute treatment of patients with schizophrenia.

However, those studies were conducted under strict experimental conditions and examined outcome after 6 to 8 weeks of treatment. Furthermore, only a select group of patients were involved, i.e., mostly subjects who had been ill for long periods of time and who did not have comorbid medical or psychiatric conditions. With these limitations, the finding of therapeutic efficacy in such studies might not generalize to effectiveness in actual clinical practice.[7] Hence, studies that reflect real-world conditions, involve representative samples, and evaluate effectiveness after longer periods of treatment are much needed.

There is also a need for studies that directly compare these 2 atypical neuroleptics. Such head-to-head comparisons can add to our understanding of the advantages as well as the limitations of each neuroleptic. This may, in turn, assist the clinician in selecting the more appropriate neuroleptic medication for a given patient.

With these goals in mind, we examined a cohort of subjects who had been treated with risperidone or olanzapine under actual clinical practice conditions over a 6-month period. We were interested to see if one atypical neuroleptic may be better than the other in reducing symptoms, causing fewer extrapyramidal side effects, and improving quality of life.

METHOD

Subjects

All subjects in this study met DSM-IV criteria for schizophrenia and had been inpatients at the Mental Health Clinical Research Center, University of Iowa. At the time of admission to the center, the subjects had not been on neuroleptic treatment either because (1) they had been neuroleptic-naive and were being evaluated for a first episode of psychosis, (2) they had discontinued neuroleptic treatment prior to hospitalization at the center, or (3) they had consented to be withdrawn from neuroleptic medication as part of a positron emission tomography study. These subjects were subsequently started on either risperidone or olanzapine treatment while in the center. Approximately half of these subjects also participated in the ongoing Iowa Prospective Longitudinal Study of Recent-Onset Psychoses.[8]

Inpatient Assessment

During hospitalization, the subjects underwent evaluation using the Comprehensive Assessment of Symptoms and History (CASH)[9] assessment and the Psychiatric Status You Currently Have-Baseline Version (PSYCH-BASE)[10] instrument. The PSYCH-BASE is a structured interview instrument with items designed to evaluate quality of life, previous treatments, and course of illness at intake. All possible sources of information, including the subject, family members, hospital records, and observations during the hospitalization, were used in completing the CASH and PSYCH-BASE. The Scale for the Assessment of Negative Symptoms (SANS)[11] and the Scale for the Assessment of Positive Symptoms (SAPS)[12] are included in the CASH and PSYCH-BASE.

Each subject's symptoms and extrapyramidal side effects (EPS) were evaluated by the same research nurse on a weekly basis throughout the duration of the inpatient hospitalization. These research nurses underwent extensive training in administering standardized rating scales. They also received ongoing weekly training sessions to reduce intrarater drift.

For this study, measures of effectiveness included the SANS, SAPS, Brief Psychiatric Rating Scale (BPRS),[13] Global Assessment Scale (GAS),[14] and quality-of-life measures. We divided symptoms into 3 dimensions of psychopathology. The *negative dimension* is defined as the sum of alogia, anhedonia, avolition, and affective flattening global ratings in the SANS. The *psychotic dimension* is defined as the sum of the delusions and hallucinations global ratings in the SAPS. The *disorganized dimension* is defined as the sum of the bizarre (disorganized) behavior, positive thought disorder, and inappropriate affect global ratings in the SAPS. Total SANS/SAPS score is the sum of these 3 dimensions.

EPS were assessed with the Simpson-Angus Scale[15] and the Barnes Akathisia Scale.[16] *Baseline ratings* of symptoms and EPS refer to those obtained in the week prior to initiation of atypical neuroleptic treatment, whereas *at-discharge ratings* reflect the measurements assessed during the last week of inpatient hospitalization.

Eight measures of quality of life were assessed during the week prior to hospitalization using the PSYCH-BASE: occupational impairment, financial dependence, impairment in performance of household duties, relationships with family members, relationships with friends, enjoyment of recreational activities, satisfaction with life, and overall level of psychosocial functioning. These 8 measures of quality of life are described in detail on the PSYCH-BASE. The degree of "relationship impairment with family members" is the average of the levels of interpersonal relationships between the subject and each family member.

Follow-Up Assessment

Subjects who participated in the Iowa Prospective Longitudinal Study of Recent-Onset Psychoses were evaluated at 6-month intervals. At each follow-up visit, the subjects' levels of symptoms during the preceding week and quality of life during the preceding month were evaluated using the PSYCH-UP, the longitudinal follow-up version of the PSYCH-BASE. Subjects who were not in our longitudinal study were contacted and invited to participate in a follow-up interview to assess their symptoms and quality of life. Since we were interested in assessing the comparative effectiveness of these 2 atypical neuroleptics at 6 months following initiation of treatment, only subjects who had been started on olanzapine or risperidone treatment in the center between June 26, 1997, and December 26, 1997, were contacted. As with the intake assessment, information from all available sources was used to complete the PSYCH-UP at the follow-up interview.

Neuroleptic Treatment

All subjects were started on either risperidone (N = 21) or olanzapine treatment (N = 21) while in the center. The choice of neuroleptic was the treating psychiatrist's decision, except in 6 patients (2 in the risperidone group and 4 in the olanzapine group), where participation in a particular research protocol determined the type of neuroleptic. The dose of neuroleptic was uncontrolled and was adjusted by the treating psychiatrist based on clinical considerations, including the patient's response, tolerability of side effects, and the manufacturer's recommendations. Anticholinergic medications were used to treat EPS if clinically indicated. After discharge, each subject continued treatment outside of the center. Neuroleptic dose adjustments, anticholinergic medication treatment, and any decisions to alter neuroleptic treatment were left to the treating psychiatrist. Thus, neuroleptic treatment in this study may be considered to reflect actual clinical practice.

Table 1. Sociodemographics, Baseline Psychopathology, and Neuroleptic Treatment of Sample[a]

Variable	Olanzapine Group	Risperidone Group	Statistic t (df = 40)	Statistic p
Sociodemographics				
Sample size (breakdown[b])	21 (6/3/12)	21 (6/7/8)		
Male, N (%)	16 (76.2)	16 (76.2)		
Educational achievement, y	12.9 (2.06)	12.9 (2.50)	0.0	1.00
Age, y	33.5 (10.6)	29.6 (10.4)	1.20	.24
Age at first outpatient care, y	26.6 (10.1)	24.7 (8.8)	0.65	.52
Baseline psychopathology scores				
Negative symptom dimension	11.2 (4.5)	10.3 (3.2)	0.71	.48
Psychotic symptom dimension	5.5 (3.0)	6.5 (2.3)	–1.28	.21
Disorganized symptom dimension	3.5 (2.8)	4.5 (3.3)	–1.01	.32
Total SANS/SAPS	20.2 (7.5)	21.3 (5.2)	–0.57	.57
Total BPRS	43.9 (13.5)	46.3 (10.1)	–0.65	.52
Neuroleptic treatment at discharge				
Dose, mg/d	14.4 (4.8)	5.7 (1.7)		
Duration of treatment, wk	4.3 (1.7)	3.6 (2.4)	1.18	.24
Anticholinergic use, N (%)	0 (0)	6 (28.6)		.02[c]
Neuroleptic treatment at follow-up				
Sample size	13	13		
Dose, mg/d	13.8 (7.6)	4.5 (2.3)		
Duration of follow-up, mo	5.2 (1.6)	5.2 (1.5)	–0.13[d]	.90
Anticholinergic use, N (%)	1 (7.7)	5 (38.5)		.16[c]

[a]Values are presented as mean (SD) unless otherwise indicated. Abbreviations: BPRS = Brief Psychiatric Rating Scale, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.
[b]Broken down by reasons for not having been on neuroleptic treatment at time of admission (neuroleptic-naive/noncompliance/medication withdrawal).
[c]Fisher exact test (2-tailed).
[d]df = 22.

Statistical Analysis

Differences between the treatment groups in baseline variables were compared by means of independent t tests and the Fisher exact test. Within-group comparisons of symptoms between baseline and discharge and between baseline and follow-up were made using paired t tests. Since the data on EPS and quality-of-life measures were not normally distributed, the Wilcoxon signed rank test was used in these within-group comparisons. Differential effects of the 2 atypical neuroleptics at discharge and at follow-up were examined using an analysis of covariance (ANCOVA). The dependent measures were symptoms, GAS score, EPS, and quality-of-life measures following treatment, with each corresponding baseline measure as the covariate. For the EPS and quality-of-life measures, ranked data were used in the ANCOVA.[17,18] All tests of significance were 2-tailed.

RESULTS

A total of 42 subjects, with 21 in each treatment group, had been started on olanzapine or risperidone treatment at our center. There was no preferential assignment to one treatment group over the other based on the reasons for not having been on neuroleptic treatment at the time of admission to the research center (χ^2 test of independence = 2.4, df = 2, $p < .30$). In the olanzapine group, the subjects had stopped neuroleptic medication for a median period of 22 days (interquartile range [IQR] = 21) before starting olanzapine treatment. For the risperidone group, the median duration was 25 days (IQR = 14). None of the subjects had been on treatment with a depot neuroleptic during the 6 months prior to starting atypical neuroleptic treatment.

The sociodemographics, baseline psychopathology, and neuroleptic treatment at discharge and at follow-up are summarized in Table 1. Sociodemographics and baseline psychopathology were not different between the 2 groups. The subjects had received approximately 4 weeks of atypical neuroleptic treatment by the time of discharge from the center. Six subjects in the risperidone group received concomitant benztropine treatment (mean ± SD dose = 1.83 ± 0.98 mg/day), and this difference between the 2 groups in anticholinergic treatment was statistically significant. When each treatment group was broken down according to the reasons for not having been on neuroleptic treatment at the time of admission, the levels of baseline psychopathology and neuroleptic doses at discharge in the 3 subgroups were comparable.

Since we were interested in the comparative effectiveness of these 2 neuroleptics at 6 months following initiation of treatment, data on only approximately two thirds of the sample were available at follow-up. These included 22 participants (9 in the olanzapine group and 13 in the risperidone group) in our longitudinal study and 6 nonparticipants in our longitudinal study (5 olanzapine, 1 risperidone) who had initiated atypical neuroleptic treatment in the center during the specified period. Among the latter, 2 declined to be interviewed when contacted (1 olanzapine, 1 risperidone). The mean ± SD doses of neuroleptic medication at discharge for the 13 olanzapine- and 13 risperidone-treated subjects who had follow-up were 13.7 ± 4.85 mg/day and 6.0 ± 1.15 mg/day, respectively. The mean dose of risperidone at follow-up (see Table 1) was lower than that at discharge. Although there were still more subjects in the risperidone-treated group receiving concomitant benztropine, the difference was not statistically significant.

Within-Group Comparison

The within-group mean differences in symptoms, GAS score, and EPS before treatment and at time of discharge are summarized in Table 2. Symptoms and GAS score improved significantly following treatment with olanzapine and risperidone. Parkinsonism side effects following treatment with either neuroleptic did not become significantly worse. Subjects in the risperidone group had significantly more akathisia at the time of discharge than before the initiation of risperidone treatment.

Table 2. Within-Group Mean Differences and Differential Effects of Risperidone and Olanzapine at Discharge[a]

Scale	Olanzapine Group Mean Difference (SE)	Olanzapine Group t (p)[b]	Risperidone Group Mean Difference (SE)	Risperidone Group t (p)[b]	Effect of Neuroleptic Type F (p)[c]
Symptom scores					
Negative symptom dimension	–2.8 (0.76)	–3.66 (.002)	–1.8 (0.61)	–2.96 (.008)	0.5 (.49)
Psychotic symptom dimension	–1.3 (0.55)	–2.33 (.03)	–1.9 (0.53)	–3.57 (.002)	0.1 (.82)
Disorganized symptom dimension	–1.8 (0.68)	–2.58 (.02)	–2.1 (0.77)	–2.79 (.01)	0.2 (.67)
Total SANS/SAPS	–5.8 (1.58)	–3.67 (.002)	–5.9 (1.46)	–4.01 (.0007)	0.2 (.69)
Total BPRS	–9.0 (2.91)	–3.11 (.006)	–6.5 (2.47)	–2.62 (.02)	2.3 (.14)
GAS score	8.9 (2.18)	4.06 (.0006)	6.2 (1.40)	4.44 (.0002)	3.1 (.09)
Extrapyramidal side effects scores		S (p)[d]		S (p)[d]	F Value Using Ranked Data (p)[e]
Simpson-Angus Scale	0 (0.19)	0 (1.00)	0.4 (.56)	10 (.36)	1.08 (.31)
Barnes Akathisia Scale	–0.1 (0.15)	–1.51 (.75)	0.6 (.20)	28.5 (.009)	14.6 (.001)

[a]Differences between baseline and discharge. Abbreviation: GAS = Global Assessment Scale.
[b]df = 20.
[c]df = 1,41.
[d]Wilcoxon signed rank test.
[e]df = 1,35.

Table 3. Within-Group Mean Differences and Differential Effects of Risperidone and Olanzapine at Follow-Up[a]

Scale	Olanzapine Group (N=13) Mean Difference (SE)	Olanzapine Group (N=13) t (p)[b]	Risperidone Group (N=13) Mean Difference (SE)	Risperidone Group (N=13) t (p)[b]	Effect of Neuroleptic Type F (p)[c]
Symptom scores					
Negative symptom dimension	–1.5 (0.94)	–1.63 (.13)	–1.5 (1.18)	–1.30 (.22)	0.04 (.84)
Psychotic symptom dimension	–1.4 (0.50)	–2.77 (.02)	–3.9 (0.64)	–6.18 (.0001)	5.0 (.03)
Disorganized symptom dimension	–0.8 (0.70)	–1.10 (.29)	–3.2 (1.10)	–2.86 (.01)	0.9 (.36)
Total SANS/SAPS	–3.7 (1.23)	–3.00 (.01)	–8.6 (2.39)	–3.60 (.004)	1.1 (.30)
GAS score	8.8 (4.01)	2.19 (.05)	13.9 (2.43)	5.72 (.0001)	0.4 (.52)
Quality of life scores		S (p)[d]		S (p)[d]	F Value Using Ranked Data (p)
Occupational impairment	–0.5 (0.43)	–2 (.50)	0.5 (0.27)	5 (.13)	3.9 (.06)
Financial dependence	0.7 (0.27)	14.5 (.05)	0.7 (0.26)	15 (.05)	0.5 (.49)[e]
Impairment in performance of household duties	–0.7 (0.24)	–10.5 (.03)	–0.6 (0.40)	–8 (.27)	0.01 (.91)
Relationship impairment					
With family members	–0.01 (0.27)	1 (.93)	–0.4 (0.20)	–9.5 (.13)	1.3 (.27)
With friends	–0.4 (0.29)	–10.5 (.26)	–0.2 (0.25)	–2 (.50)	0.8 (.37)
Enjoyment of recreational activities	–0.8 (0.36)	–16 (.06)	–0.3 (0.38)	–6 (.55)	0.1 (.77)
Satisfaction	–0.5 (0.22)	–14 (.06)	–0.8 (0.30)	–15 (.05)	0.2 (.67)
Overall psychosocial functioning	–0.7 (0.31)	–11.5 (.08)	–1.15 (0.22)	–33 (.01)	1.5 (.24)

[a]Between baseline and follow-up.
[b]df = 12.
[c]df = 1,25.
[d]Wilcoxon signed rank test.
[e]df = 1,23.

At follow-up, the global measures of psychopathology (total SANS/SAPS score and GAS score) were significantly improved as compared with intake in both groups (Table 3). Although there was reduction in negative symptoms in both groups, these differences were not significantly lower than at baseline. In the risperidone group, the reduction in psychotic and disorganized symptoms was statistically significant. With olanzapine treatment, no statistically significant differences in the disorganized symptoms were found. Two indices of quality of life in the risperidone group (satisfaction with life and overall psychosocial functioning) and 1 index in the olanzapine group (impairment in performance of household duties) were significantly improved at the time of follow-up. Another 3 indices of quality of life in the olanzapine group (enjoyment of recreational activities, satisfaction with life, and overall psychosocial functioning) showed a trend toward significant improvement. In both treatment groups, the subjects became more reliant on social service agencies for financial support.[19]

Between-Group Comparison

The differential effects of the 2 atypical neuroleptics at the time of discharge and at follow-up are summarized in Tables 2 and 3, respectively.

At discharge, the only difference between the 2 groups was in akathisia ratings. When compared with olanzapine, risperidone treatment had a significant effect on inducing akathisia. There were no differential effects in neuroleptic type on symptoms, GAS score, or parkinsonism side ef-

fects. However, the risperidone group had more anticholinergic use during the inpatient treatment phase. Concomitant anticholinergic treatment may have moderated the Simpson-Angus ratings in this group. We further explored this by entering anticholinergic use as an additional covariate in the model. After statistically controlling for the effects of benztropine, the subjects in the risperidone treatment group still did not appear to have significantly more parkinsonism side effects ($F = 1.50$, $df = 1,34$; $p < .23$) than the olanzapine group.

At follow-up, the effect of risperidone on reduction of psychotic symptoms was significantly greater than that of olanzapine. There was a trend toward significant difference in occupational impairment between the 2 treatment groups, with olanzapine-treated subjects having less impairment. However, there were no differential effects on the other 7 quality-of-life measures, nor were there differential effects on negative symptoms, disorganized symptoms, total SANS/SAPS score, or GAS score.

DISCUSSION

In this study, we were most interested in the comparative effectiveness of risperidone and olanzapine. We found that during acute treatment, the 2 atypical neuroleptics had comparable effectiveness in the reduction of negative, psychotic, and disorganized symptoms in patients with schizophrenia. Although both neuroleptics were associated with low occurrence of treatment-emergent parkinsonism, risperidone was more likely to induce akathisia. The measures for parkinsonism were no different across treatment groups, but this lack of difference could have been masked by concomitant benztropine treatment in the risperidone group. However, when we statistically controlled for this potential confounding factor, risperidone still did not appear to be more likely than olanzapine in inducing parkinsonism.

Following approximately 6 months of treatment with these 2 atypical neuroleptics (when information was available on two thirds of the original sample), risperidone was more effective than olanzapine in reducing psychotic symptoms. A potential clinical implication of this finding could be that for patients with severe delusions and hallucinations, risperidone may be preferable over olanzapine. This greater antipsychotic effectiveness for risperidone was observed even when the mean dose had decreased from 5.7 mg/day at discharge to 4.5 mg/day at 6-month follow-up. Beyond this difference in antipsychotic effectiveness, one neuroleptic did not appear to be superior to the other in the reduction of disorganized or negative symptoms or in the improvement in quality of life.

Although the experimental conditions, including pharmacotherapy, in our study may reflect actual clinical practice, there are several limitations to this study. These include the small sample size, nonrandomized open-label design, and a relatively short treatment period when the subjects were assessed at the time of discharge from the center. In addition, some investigators have advocated that *effectiveness* research studies, such as ours, should not be the answer to the serious limitations of *efficacy* studies.[20] Therefore, our findings should be considered preliminary, and the clinical implications of our results will require replication.

There has been only one published randomized control study comparing olanzapine with risperidone.[21] The group at the Lilly Research Laboratories has reported a 28-week, multicenter, double-blind comparison of olanzapine and risperidone involving 339 subjects with schizophrenia or related disorders.[21] Like our study, their subjects in both treatment groups improved from baseline to endpoint. However, those investigators found that a greater proportion of patients in the olanzapine group experienced at least 40% improvement in symptoms (37% vs. 27%). Survival analysis also indicated that patients treated with olanzapine more often maintained their clinical response. Risperidone-treated patients were found to experience more side effects, including EPS. However, this study has received several criticisms, including that a 1-tailed statistical test was used for its primary efficacy analysis, that no correction for multiple comparisons was conducted, and that the rate of titration and the relatively high dose of risperidone used may have contributed to more EPS.[22–27]

The optimal dose of risperidone has been much debated in the literature. Conceptually, the optimal dose of a medication is the dose that confers the greatest benefits with the least side effects. In addition, the optimal dose for a given patient needs to be individualized. The original clinical trials comparing risperidone against haloperidol and placebo suggested an optimal dose of risperidone of 4 to 8 mg/day.[1–3] However, there has been a trend by clinicians to use lower doses of risperidone during actual clinical practice in more recent years. Our study, as well as data from the state of Maryland,[28] reflects this trend, which is important to patients with respect to EPS.

Risperidone-induced EPS, both parkinsonism and akathisia, appear to be dose-related.[1,2,29] Higher doses of risperidone (10 and 16 mg/day) cause higher rates of EPS than lower doses (2 and 6 mg/day). The prevalence of EPS among patients receiving less than 6 mg/day of risperidone is comparable to that in patients receiving placebo. If 7.2 mg/day of risperidone is considered a high dose, an important question would be: Can lower doses of risperidone still produce effectiveness comparable with olanzapine and yet not result in higher EPS rates? The findings from our study suggest that this is possible. In our study, subjects received lower doses of risperidone (5.7 mg/day at discharge), and yet effectiveness comparable with that of olanzapine was achieved without an increase in parkinsonism side effects.

The risperidone-treated subjects in our study still had higher rates of akathisia at discharge. Neuroleptic-induced parkinsonism and akathisia are often associated with one another, and may occur concurrently. These 2 distinct syndromes have traditionally been classified under the rubric of EPS, even though each has a different pathogenesis.[30] Although both syndromes appear to be dose related, they may require different threshold doses of risperidone to manifest. Our findings suggest that the threshold for the emergence of akathisia may be lower than that for parkinsonism. With lower doses of risperidone used at follow-up (mean = 4.5 mg/day), one could expect even lower rates of akathisia among the risperidone-treated subjects.

Future comparative trials with olanzapine and risperidone will need to further explore how different doses of risperidone, including doses below what has been touted as its optimal dose, affect the comparative rates of treatment-emergent parkinsonism and akathisia.

CONCLUSION

In this comparative effectiveness study of 2 of the most widely used atypical neuroleptics, both were equally effective at the time of discharge, but olanzapine was associated with less akathisia. At 6 month follow-up, risperidone was more effective for the treatment of psychotic symptoms. Otherwise, these 2 atypical neuroleptics appear to be more or less equal in effectiveness when used in the routine clinical care of patients with schizophrenia.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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