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Clozapine and Risperidone in Moderately Refractory Schizophrenia: A 6-Month Randomized Double-Blind Comparison

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ABSTRACT

Objective: Clozapine remains the only medication indicated for refractory schizophrenia. As new antipsychotic drugs become available, their efficacy compared to clozapine, particularly in moderately ill patients, is of great clinical interest. We compared risperidone, the first of these, to clozapine in partially responsive patients. Further, since participation of patients usually excluded from clinical trials is increasingly important, we broadened inclusion to a wider patient population.

Methods: We compared clozapine (n = 53) to risperidone (n = 54) in a randomized, double-blind, 29-week trial in schizophrenia patients (diagnosed using *DSM-IV*) at 3 research outpatient clinics. Randomization was stratified by "narrow" or "broad" inclusion criteria. The study was conducted between December 1995 and October 1999. Time to treatment discontinuation for lack of efficacy and time to 20% improvement in the Brief Psychiatric Rating Scale psychotic symptom cluster were the primary outcome measures.

Results: There were no differences in all-cause discontinuation; clozapine-treated participants were significantly less likely to discontinue for lack of efficacy (15%) than risperidone-treated participants (38%) (Wilcoxon $\chi^2_1 = 6.10$, $P = .01$). Clozapine resulted in significantly more global improvement ($F_{2,839} = 6.07$, $P < .01$) and asociality improvement ($F_{2,315} = 6.64$, $P < .01$) than risperidone. There was no difference in proportions meeting an a priori criterion of psychosis improvement (risperidone: 57%; clozapine: 71%). Significant adverse effect differences in salivation ($F_1 = 4.05$, $P < .05$) ($F_1 = 12.13$, $P < .001$), sweating ($F_1 = 5.07$, $P < .05$), and tachycardia ($F_1 = 6.51$, $P < .05$) favored risperidone.

Conclusions: Clozapine-treated partially responsive patients were less likely to discontinue treatment for lack of efficacy and improved more globally than those treated with risperidone, although psychotic symptoms did not differ. These findings suggest that clozapine should not be restricted to the most severely ill, treatment-refractory patients; it should be considered as an alternative for patients who have some response to other antipsychotics, but still experience troubling symptoms.

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Clozapine remains the standard of care for schizophrenia patients who are nonresponsive to other antipsychotic medications. Kane et al[1] found significant and substantial clinical benefit of clozapine for patients who by history and prospective evaluation failed other antipsychotic medications. Other well-designed, randomized controlled trials[2–5] have confirmed and extended the finding that clozapine provides advantages over first-generation antipsychotics, although the extent of the advantage is often qualified.

Currently, patients with refractory schizophrenia are being treated with a new generation of antipsychotic medications: risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, iloperidone, asenapine, and lurasidone. Some argue that these newer medications share some receptor characteristics with clozapine.[6] However, the key *clinical* question is whether they share efficacy for treatment-refractory schizophrenia.

Because risperidone was the first so-called second-generation drug (after clozapine) licensed in the United States and Europe, it was also the first compared to clozapine in short-term trials (28 days to 14 weeks).[7–13] In 2 of the trials,[7,12] clozapine had significantly better outcomes; in others,[8,9,11,13] there was no statistically significant advantage. Two longer, but not fully blinded trials[14,15] also provide relevant data. In phase 2 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), 99 patients who discontinued in phase 1, primarily due to lack of efficacy, were randomly assigned to open treatment with clozapine or blinded treatment with olanzapine, quetiapine, or risperidone.[14] Time to discontinuation for lack of efficacy was significantly longer for clozapine than the comparators, and Positive and Negative Syndrome Scale (PANSS) total scores decreased significantly more with clozapine than risperidone or quetiapine, but not olanzapine. The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study 2 (CUtLASS 2) found a significantly greater reduction in PANSS total score with clozapine compared to risperidone, quetiapine, olanzapine, or amisulpride in patients with poor clinical response to 2 or more antipsychotics.[15]

Clinical Points

- Treatment with clozapine should not be limited to the most severely ill schizophrenia patients but should be offered to patients who show a limited response to other antipsychotics.
- This study identifies a further advantage of clozapine—greater improvement seen in longer term treatment compared to risperidone.
- Higher clozapine dose was associated with better response.

We previously completed a 6-month study in community-based, partially refractory patients with schizophrenia that compared haloperidol to clozapine.[4] We found longer time to all-cause and lack-of-efficacy discontinuation and greater improvement in psychotic symptoms with clozapine. There are, to our knowledge, no long-term, double-blind, randomized clinical trials comparing clozapine and risperidone. The present study, conducted at the same 3 research centers (University of California–Los Angeles [UCLA]; The Zucker Hillside Hospital, Glen Oaks, New York; and Western Psychiatric Institute and Clinic [WPIC], Pittsburgh, Pennsylvania) and following similar procedures, compares risperidone to clozapine. In addition, in order to enhance generalizability, we enrolled 2 groups. The first group comprises patients traditionally included in trials: subjects who do not require concomitant medications, are not abusing substances, and have never received the experimental treatments. The second group met at least 1 of these exclusion criteria. Treatment efficacy in this second population is of great clinical importance, but fewer data are available to guide clinicians.

METHODS

The study was a 29-week, double-blind, prospective, random-assignment trial comparing clozapine (target dose 500 mg/d) to risperidone (target dose 6 mg/d) that was conducted between December 1995 and October 1999. In order to assess medication efficacy in a range of patients with schizophrenia, enrollment included subjects who have been excluded from many clozapine clinical trials. Randomization was carried out within 2 strata: narrow and broad inclusion groups.

Subjects

Inclusion criteria for all subjects (N = 107) were *DSM-IV* schizophrenia or schizoaffective disorder diagnosis by 1 of the authors using a diagnostic check-list; age 18 to 60 years; and living in the community. *Partial* or *poor response* was defined by failure in at least 1 trial of first-generation antipsychotic medication at a dose equivalent to or greater than 600 mg/d of chlorpromazine for 6 weeks (high-dose qualification) and failure at a dose equivalent to 250–500 mg/d for 4 weeks (low-dose qualification). To insure that too high dosage was not the reason for lack of clinical response, we reviewed patient charts to document a low-dose trial. If a low-dose trial was not documented, patients received prospective dose reduction for 4 weeks (or less if clinical worsening was seen). Score of at least "moderate" on 1 of 4 Brief Psychiatric Rating Scale (BPRS) items (conceptual disorganization, suspiciousness, hallucinatory behavior, or unusual thought content) or 1 of 4 global ratings on the Scale for Assessment of Negative Symptoms (SANS) (affective flattening, alogia, avolition-apathy, or asociality-anhedonia) was required.[16–18]

Exclusion criteria for all subjects were neuroleptic malignant syndrome with recurrence upon rechallenge; central nervous system disorder history (eg, epilepsy or brain tumor); bone marrow suppression; blood dyscrasia; glaucoma; history of significant cardiovascular, renal, or hepatic disease; current treatment with medications for medical conditions that have psychotropic effects, interfere with drug absorption or metabolism, or have the potential to suppress bone marrow function; total white blood count below 3,500/mm^3; pregnancy; and mental retardation that precluded understanding study participation or assessment procedures.

Exclusion criteria for the narrow inclusion criteria stratum included prior treatment with clozapine or risperidone for 3 weeks or longer, history of poor medication compliance, dependence on drugs of abuse or alcohol within the past 6 months, and receipt of mood stabilizers or antidepressants that could not be discontinued. Potential subjects who met any of these exclusion criteria were enrolled in the broad inclusion criteria stratum, resulting in 2 distinct groups.

The study protocol and informed consent form were approved by institutional review boards at all sites. All subjects were judged competent to provide written informed consent. Competency was assessed by asking a series of true/false questions that tapped elements of the informed consent form (eg, "The doctor will know which medicine I'm getting" [false]). Potential subjects who were unable to appreciate the risks, benefits, or discomforts of the study were ineligible.

Patients receiving fluphenazine or haloperidol decanoate received oral medication for 2 injection cycles before beginning double-blind dosage titration.

Treatment Implementation

Dosage titration. Medication was administered under double-blind conditions. Because matching tablets for risperidone and clozapine were unavailable, we employed a "double-dummy" design. Clozapine was started at 12.5 mg/d and titrated to 500 mg/d by day 28. Risperidone was started at 1 mg/d and titrated to 6 mg/d by day 15. Dosage titration could be slowed or stopped if subjects could not tolerate the titration schedule. Simultaneously, other antipsychotic medication was gradually decreased. To maintain blinding, all subjects had a weekly blood draw.

Double-blind treatment continued for up to 29 weeks. After 5 weeks, dosage could be increased to 800 mg/d (clozapine) or 16 mg/d (risperidone).

Table 1. Demographic and Psychiatric History Characteristics of Trial Participants[a,b]

Characteristic	Risperidone (n = 54)	Clozapine (n = 53)
Site, no. of participants		
Zucker Hillside Hospital	16	14
University of California–Los Angeles	22	24
Western Psychiatric Institute and Clinic	16	15
Broad-narrow inclusion criteria, % broad	70	77
Diagnosis, %		
Schizophrenia	87.5	86.2
Schizoaffective disorder	12.5	13.7
Gender, % male	80	77
Race, % white[c]	61	52
Age, mean (SD), y[d]	42 (9)	42 (8)
Marital status, % never married	76	69
Living arrangement, %[d]		
Parental	20	25
Conjugal/alone/collateral	31	14
Structured environment	48	61
Education, %[d]		
Beyond high school	37	43
Completed high school	33	35
Less than completed high school	30	22
Level of premorbid functioning, %[e]		
Very well	36	40
Moderately well	56	46
Poorly	8	14
Highest occupation, %		
Clerical, skilled manual, administrative, and above	38	43
Semiskilled or less or never worked	62	57
Longest employment in months, mean (SD)	49 (69)	46 (44)
Age at which functioned well, mean (SD), y[d]	21 (8)	22 (6)
Age at first psychiatric illness, mean (SD), y[d,f]	22 (7)	23 (7)
Age at first hospitalization, mean (SD), y[d,f]	25 (8)	24 (7)
Years since first hospitalization, mean (SD)[d,f]	18 (7)	17 (8)
Number of prior hospitalizations, mean (SD)	10 (9)	9 (9)
Months of hospitalization, mean (SD)	32 (43)	18 (18)
Months of neuroleptic exposure, mean (SD)[d,f]	169 (87)	184 (152)
EPS in conjunction with neuroleptic treatment, %		
Never/rarely/sometimes	43	36
Frequently	57	64
Use of antiparkinsonian medication in conjunction with neuroleptic treatment, %		
Never/rarely/sometimes	30	43
Frequently	70	57
Prior exposure to study medications, %		
Risperidone	44	45
Clozapine	22	28

[a]Site, treatment, and site × treatment effects were tested for all variables. Analyses of continuous variables utilized ANOVA, while categorical variables were analyzed with either logistic or multinomial regression.
[b]No significant main effects for treatment were found for any variables, except race.
[c]Drug effect for race: $\chi^2_1 = 5.47$, $P < .05$.
[d]Site effect significant.
[e]Unable to include site in analyses due to small cell sizes.
[f]Site × drug effect significant.
Abbreviations: ANOVA = analysis of variance, EPS = Extrapyramidal Side Effects–Hillside version.

Outcome Measures

Psychopathology was assessed with the BPRS, scaled from 1 to 7,[16,17] the modified SANS,[19] and the Clinical Global Impressions scale (CGI).[20] Adverse effects were monitored with the Simpson-Angus Scale for Extrapyramidal Side Effects–Hillside version (EPS),[21] Barnes Akathisia Scale (BAS),[22] and the Treatment Emergent Symptom Scale (TESS).[23] The Hillside version of the EPS substitutes "head rotation" for "head dropping." Weight was measured at each visit. Full assessments were completed at baseline and weeks 5, 11, 17, and 29. The BPRS, CGI, and TESS were also completed at weeks 1, 2, 3, 4, 7, 15, and 23.

Data Analysis

Demographic and psychiatric history characteristics were evaluated with analysis of variance for continuous variables and logistic or multinomial regression for categorical variables, including terms for treatment, site, and site × treatment interaction.

Time to treatment discontinuation for lack of efficacy was based on consensus clinical judgment at the site. This criterion and time to 20% improvement in the BPRS psychotic symptom cluster (defined as a 20% decrease from baseline for 2 consecutive assessments) were the primary outcome measures. Survival analysis was also used to evaluate time to all-cause discontinuation. Subjects who discontinued treatment for lack of efficacy were withdrawn from the at-risk sample at discontinuation. Remission, defined by 20% improvement criterion and no psychotic symptom worse than "mild," was also assessed. These outcome measures are the same as those in our earlier study.[4] We also evaluated time to a 30% and 40% improvement criterion.

Each psychopathology measure was included as the dependent variable in a mixed-model regression analysis (SAS version 8.2, SAS Institute, Inc, Cary, North Carolina). Supplementary eTable 1 (available at PSYCHIATRIST.COM) lists the measures. The model included treatment, site, site × treatment, week, treatment × week, dosage at each evaluation point, and treatment × dosage. Dose was converted to a percentage of the target dose (clozapine: 500 mg; risperidone: 6 mg). In this metric, dose ranged from 2.5% for the 12.5-mg starting dose of clozapine to 267% for a 16-mg dose of risperidone. Mixed-model regression analyses were fit with random intercepts and slopes using a covariance structure in which correlations decreased with increasing distance between time points (ie, first-order autoregression).

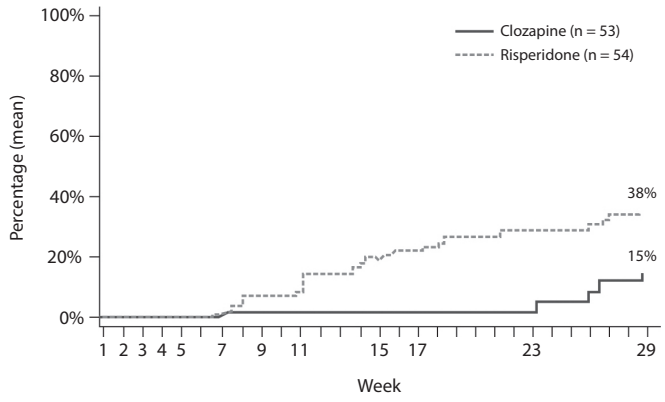
The EPS, BAS, TESS, and weight measures taken at 5 week or at the last available earlier assessment were evaluated using a general linear model of covariance analysis that included baseline as the covariate and terms for treatment, site, and site × treatment interaction. The α level in all analyses was .05 (2-tailed).

RESULTS

Sample Characteristics

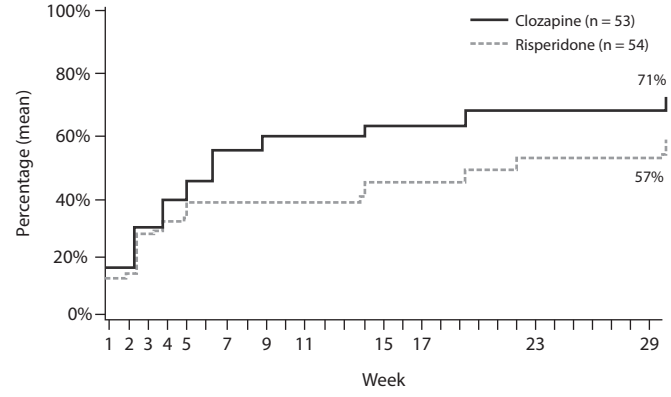
Table 1 displays demographic and psychiatric characteristics by treatment. Fifty-four subjects were randomly assigned to risperidone; 53 to clozapine. The majority of patients qualified for the study under broad inclusion criteria; 70% risperidone, 77% clozapine. Although 86% of subjects met negative symptom inclusion criteria, all but 4 also had psychotic symptoms. The only significant treatment difference was for race: 61% of risperidone and 52% of clozapine subjects were white ($\chi^2_1 = 5.47$, $P < .05$).

Figure 1. Time to Discontinuation of Study Medication by Treatment for Lack of Efficacy[a]



[a]Wilcoxon $\chi^2_1 = 6.10$, $P = .01$.

Figure 2. Time to First of 2 Consecutive Ratings of 20% Improvement on the Brief Psychiatric Rating Scale Psychosis Cluster[a]



[a]Wilcoxon $\chi^2_1 = 1.49$, $P = .22$.

Mean age was 42 years. Eighty percent of risperidone and 77% of clozapine subjects were male; 76% of risperidone and 69% of clozapine subjects had never been married.

Table 1 shows treatment × site effects (as well as site main effects) for variables reflecting chronicity: age at first psychiatric illness and hospitalization, years since first hospitalization, and months of prior neuroleptic exposure.

Dose

Mean daily doses were as follows. Risperidone dose was 3.3 mg (SD = 0.8) at week 1; 5.6 mg (SD = 1.5) at week 5; 6.6 mg (SD = 1.6) at week 11; 7.4 mg (SD = 2.4) at week 17; and 6.8 mg (SD = 1.7) at week 29. Clozapine dose was 152.1 mg (SD = 74.1) at week 1; 340.7 mg (SD = 140.2) at week 5; 427.9 mg (SD = 164.3) at week 11; 440.9 mg (SD = 151.8) at week 17; and 456.7 mg (SD = 123.7) at week 29.

To compare dosage between treatments, dosage was converted to levels 1 to 18. The target dose (level 12) corresponded to 500 mg of clozapine and 6 mg of risperidone. There was a significant site effect at week 1 ($F_2 = 42.71$, $P < .0001$; means: Zucker Hillside = 6.76, UCLA = 4.66, WPIC = 4.38). Initial dose titration was somewhat faster at The Zucker Hillside Hospital.

Duration of Study Participation

Figure 1 shows the cumulative proportion of subjects discontinued for lack of efficacy; by week 29, 38% of risperidone- compared to 15% of clozapine-treated patients discontinued, a 23% difference (Wilcoxon $\chi^2_1 = 6.10$, $P = .01$). All-cause time to discontinuation did not differ. By week 29, 57% of risperidone- and 47% of clozapine-treated patients had discontinued treatment (Wilcoxon $\chi^2_1 = 0.055$, $P = .82$).

Psychotic Symptoms

Figure 2 shows time to 20% improvement on the 4-item BPRS psychosis cluster. By 29 weeks, 57% of risperidone-treated patients met the criterion compared to 71% of clozapine-treated patients (Wilcoxon $\chi^2_1 = 1.49$, $P = .22$). Inspection of Figure 2 suggests that rate of response diverges after 4 weeks. However, the log-rank statistic, which gives greater emphasis to later time points, was not significant either (log-rank $\chi^2_1 = 2.16$, $P = .14$).

Using 30% improvement, the response curves for the treatment groups became even more similar. By week 29, 62% of the clozapine-treated patients reached the 30% improvement criterion as compared with 56% of risperidone-treated patients (Wilcoxon $\chi^2_1 = 1.42$, $P = .23$). Similarly, using 40%, 44% of the clozapine-treated patients achieved the criterion by week 29 as compared with 40% of risperidone-treated patients (Wilcoxon $\chi^2_1 = 0.57$, $P = .45$). These criteria are based on change from baseline and do not reflect symptom absence. This outcome represents "improvement" rather than "remission."

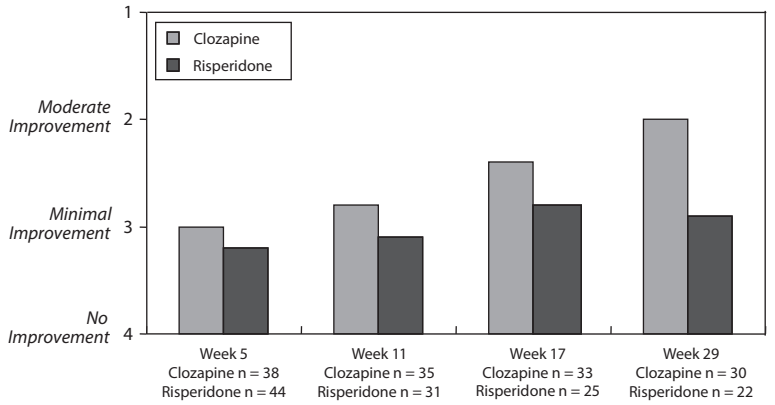
Twenty-four percent of risperidone- and 26% of clozapine-treated patients were judged remitted by study conclusion, defined by the 20% improvement criterion and no symptom in the BPRS psychosis cluster rated greater than "mild" ($\chi^2_1 = 0.12$, $P = .73$).

Symptoms of Psychopathology

Supplementary eTable 1 presents means and standard deviations for observed cases over time by treatment for all measures. Results of the mixed-model analyses indicated no significant treatment main effects. (Model χ^2 values were significant at the $P < .0001$ level.) There were significant treatment by time effects for CGI-Improvement ($F_{2,839} = 6.07$, $P < .01$) and for modified SANS asociality ($F_{2,315} = 6.64$, $P < .01$) and a trend level effect for BPRS total score ($F_{2,777} = 2.62$, $P < .10$). In all cases, the difference between clozapine and risperidone increased over time, indicating greater improvement with clozapine (Figure 3; CGI-Improvement).

Significant site effects were seen for BPRS anergia and modified SANS variables. In all cases, the UCLA site had higher negative symptom scores compared to the other 2 sites. A significant time effect was seen

Figure 3. Doctors' Ratings of Improvement (mean scores on CGI): Clozapine Versus Risperidone Over Time[a]



[a]Treatment × week: $F_{1,839} = 12.02$, $P < .001$.
Abbreviation: CGI = Clinical Global Impressions scale.

Table 2. Treatment-Emergent Adverse Effects by Treatment at Fifth Week of Observation[a]

Adverse Effect	Risperidone (n = 54)	Clozapine (n = 53)
Barnes Akathisia Scale		
Global clinical assessment	0.50 (0.97)	0.30 (0.57)
Simpson Angus Scale		
Rigidity of major joints (overall)	0.22 (0.57)	0.19 (0.40)
Tremor (overall)[b]	0.31 (0.54)	0.33 (0.55)
Salivation[b,c]	**0.13 (0.48)**	**0.42 (0.89)**
Akinesia[b]	0.39 (0.63)	0.62 (0.74)
Treatment Emergent Symptom Scale (TESS)		
Insomnia	1.57 (0.80)	1.32 (0.59)
Drowsiness	1.66 (0.73)	1.98 (0.84)
Dry mouth	1.45 (0.67)	1.34 (0.66)
Nasal congestion	1.53 (0.80)	1.38 (0.67)
Blurred vision	1.38 (0.56)	1.52 (0.79)
Constipation	1.23 (0.58)	1.34 (0.63)
Excess salivation[d]	**1.42 (0.63)**	**1.96 (0.78)**
Sweating[e]	**1.15 (0.41)**	**1.46 (0.84)**
Nausea/vomiting/indigestion/abdominal pain	1.19 (0.56)	1.26 (0.56)
Diarrhea[f]	1.19 (0.56)	1.10 (0.30)
Hypotension	1.15 (0.53)	1.16 (0.47)
Syncope/dizziness/light-headedness on standing	1.45 (0.67)	1.58 (0.73)
Tachycardia[b,g]	**1.13 (0.34)**	**1.34 (0.66)**
Fever	1.04 (0.19)	1.00 (0.00)
Dermatologic/rash	1.09 (0.30)	1.06 (0.42)
Anorexia/decreased appetite	1.08 (0.27)	1.14 (0.45)
Weight, lb[h]	185 (42)	190 (35)

[a]Site, treatment, site × treatment effects were tested for all variables using analysis of covariance (baseline included). Means (standard deviations) are presented. Significant drug effects are given in boldface. If data were not available at week 5, data from the last prior observation were used. Number of participants is 103 for TESS variables and 76 for weight. Higher scores on all scales indicate greater severity.
[b]Site effect: significant; test and *P* values unavailable.
[c]Drug effect: $F_1 = 4.05$, $P < .05$.
[d]Drug effect: $F_1 = 12.13$, $P < .001$.
[e]Drug effect: $F_1 = 5.07$, $P < .05$.
[f]Drug × site interaction: significant; test and *P* values unavailable.
[g]Drug effect: $F_1 = 6.51$, $P < .05$.
[h]No significant effects were found with or without gender in the analysis.

for CGI-Severity ($F_{1,883} = 3.71$, $P = .054$); severity decreased over time in both groups.

For all BPRS and CGI measures, the target dose percent was highly significant ($P < .001$); as dose increased, psychopathology decreased. Significant interactions of target dose percent by treatment were found for psychosis, thought disturbance, hostile suspiciousness, and BPRS total score. In all cases, higher dose was associated with greater symptom improvement for clozapine than for risperidone. Target dose percentage was not related to any modified SANS measures.

Adverse Effects

Seven patients receiving clozapine were discontinued for adverse effects; significant main effects for salivation, sweating, and tachycardia favored risperidone. A trend for insomnia favored clozapine ($F_{1,94} = 3.93$, $P = .0506$). Means and standard deviations associated with these effects are presented in Table 2.

DISCUSSION

This study helps to place risperidone and clozapine along a continuum of treatment for patients who are poor or partial responders. Those receiving clozapine were less likely to discontinue treatment for lack of efficacy and showed greater improvement over time reflected in psychiatrists' global and asociality ratings. Secondary measures of all-cause discontinuation, psychosis, and thought disturbance and the primary outcome measure of time to improvement in psychosis were not significantly different. These effects held even when site and dose were included in the analyses that examined effects over time.

The study was conducted at sites with extensive clozapine experience and a cadre of clinical investigators comfortable initiating clozapine treatment under double-blind conditions. Despite our plan to include equal numbers of patients who met narrow and broad inclusion criteria, over 70% of patients in this trial would not have entered under more restrictive standards. If we had restricted enrollment to our narrow stratum, the trial would not have been feasible. The numbers in the 2 strata were too small to allow statistical analysis of response differences between patients who met strict

inclusion criteria and those who did not. The patients in our study had demographic and treatment history characteristics similar to those in other studies comparing clozapine and risperidone. Further, dosage did not differ between the strata, suggesting that dosage recommendations do not need to be altered to account for concomitant medications or characteristics such as substance abuse. Including patients with prior exposure to clozapine and those who receive antidepressants or mood stabilizers in the trial suggests that our results apply to these patients as well as to a more narrowly defined patient population.

This trial was substantially longer than earlier ones. If it had been 6 rather than 29 weeks long, we would have concluded that only 54% of clozapine and 38% of risperidone patients met the 20% BPRS response improvement criterion and would have presented a more limited picture of differential efficacy. We would have agreed with Bondolfi and colleagues[8] and Klieser and colleagues[9] in not finding differences between the 2 treatments. Instead, we see increasing differences over time in CGI, although not in specific measures of psychopathology, favoring clozapine. These findings are suggestive, but not conclusive. We note that clinicians (and family members) report improvements over time with clozapine that may not be captured with symptom rating scales. Even in our substantially longer trial, in agreement with Volavka and colleagues' study[13] we do not find differences in overall time to discontinuation; the difference favoring clozapine is seen only in discontinuation for lack of efficacy.

We used a slow cross-titration strategy, and titration was slower for clozapine than for risperidone. Subjects randomized to risperidone reached the 6-mg target by day 15; those randomized to clozapine reached the 500-mg target by day 28. Despite this apparent handicap for clozapine, the rate of response during the early weeks of the trial did not favor risperidone. The mean clozapine dose was slightly less than the target (420 mg at week 5), but higher than in other trials. The modal dose in the study by McEvoy et al[14] was 332 mg/d, and the mean dose in the study by Lewis and colleagues[15] was 333 mg/d. Further, higher clozapine dose in our study was associated with greater symptom improvement. These data should encourage clinicians to titrate to doses that may result in increased response.

The adverse effect profiles of the 2 drugs at 5 weeks are generally consistent with other trials. When there are significant differences between the 2 treatments in salivation, sweating, and tachycardia, they favor risperidone. We included early terminated subjects using last observation carried forward analysis, which may overestimate differences.

The study strengths include a double-blind design, relatively high doses of clozapine, duration, and inclusion of a broad range of patients. Weaknesses include a relatively small sample size and the absence of assessment of prolactin, lipids, and sexual side effects.

Clozapine has now been available for over 20 years. Despite the marketing of many newer antipsychotic medications and the side effect burden of clozapine, it remains the standard of care for individuals who are treatment refractory to other antipsychotics and for those with suicidal ideation. The results of this study, taken in conjunction with our earlier clozapine-haloperidol comparison[4] and the results of CATIE[14] and CUtLASS 2,[15] suggest that clozapine should not be restricted to the most severely ill, treatment refractory patients. Rather, it should be considered as an alternative for patients who do have some response to other antipsychotics, but still experience troubling psychotic symptoms.

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Drug names: aripiprazole (Abilify), asenapine (Saphris), clozapine (Clozaril, FazaClo, and others), iloperidone (Fanapt), lurasidone (Latuda), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

Potential conflicts of interest: **Dr Schooler** is a consultant for Alkermes, Forum, and Shire; is on speaker/advisory boards for Abbott, Amgen, Eli Lilly, Janssen, Lundbeck, and Shire; has received grant support from Otsuka; and has received honoraria from Abbott, Amgen, Alkermes, Eli Lilly, Forum, Janssen, Lundbeck, Shire, and Sunovion. **Dr Marder** is a consultant for Abbott, Allergan, Amgen, Boehringer Ingelheim, Genentech, Lundbeck, Otsuka, PsychoGenics, Roche, Sunovion, and Takeda; has received grant support from Forum; and is a stockholder in MedAvante. **Dr Petrides** has received grant support from Ai-Cure, AstraZeneca, Corcept, the National Institute of Mental Health (NIMH), Proteus, and St Jude Medical. **Dr Wirshing** has received honoraria from Alkermes, Otsuka, and Sunovion and is on speaker/advisory boards for Bristol-Myers Squibb, Otsuka, and Sunovion. **Dr Baker** is a full-time employee of and stock/shareholder in Eli Lilly. **Dr Umbricht** is a full-time employee and stockholder of F. Hoffman La Roche. **Dr Kane** is a consultant for Alkermes, Amgen, BMS, Eli Lilly, Forum, Forest, Genentech, Lundbeck, Intracellular Therapies, Janssen, Johnson & Johnson, Merck, Novartis, Otsuka, Pierre Fabre, Reviva, Roche, Sunovion, and Teva; has received honoraria from Genentech, Janssen, Lundbeck, and Otsuka for lectures; and is a stock/shareholder in MedAvante and Vanguard Research Group. **Drs Ames, Chengappa, McMeniman,** and **Parepally** report no conflicts.

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Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Clozapine and Risperidone in Moderately Refractory Schizophrenia: A 6-Month Randomized Double-Blind Comparison

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List of Supplementary Material for the article

1. **eTable 1** Symptom Ratings by Time and Treatment: Observed Cases Only

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1: Symptom ratings by Time and Treatment: Observed cases only										
	Baseline		***Week 5***		***Week 11***		***Week 17***		***Week 29***	
Measure	CLZ (N=53) Mean (SD)	RSP (N=54) Mean (SD)	CLZ (N=38) Mean (SD)	RSP(N=44) Mean (SD)	CLZ(N=35) Mean (SD)	RSP (N=31) Mean (SD)	CLZ (N=33) Mean (SD)	RSP(N=25) Mean (SD)	CLZ (N=30) Mean (SD)	RSP (N=22) Mean (SD)
BPRS Variables										
Anxiety/ Depression	2.3(1.1)	2.3(1.0)	1.9 .9)	1.9 (.8)	1.8(.8)	2.0(1.2)	1.7(.9)	1.9(1.1)	1.7(.8)	1.7(.7)
Anergia	2.3(.9)	2.2 (.8)	2.0(.7)	1.9(.7)	1.9(.6)	1.8(.8)	1.8(.8)	1.8(.5)	1.8(.7)	1.8(.6)
Thought Disturbance	3.6(1.1)	3.4(1.0)	2.7(1.0)	2.9(1.1)	2.6(1.1)	2.4(1.0)	2.4(1.0)	2.3 (.9)	2.2(1.0)	2.3 (.9)
Activation	1.8(.7)	1.8(.7)	1.6(.7)	1.5(.6)	1.4(.4)	1.3(.5)	1.4(.6)	1.4(.4)	1.2(.4)	1.3(.4)
Hostile-Suspiciousness	2.4(.9)	2.3(.9)	1.9(.8)	2.0(1.0)	1.9(.7)	1.6(.6)	1.6(.7)	1.7(.8)	1.6(.6)	1.4(.6)
Psychosis Cluster	4.0(1.1)	3.8(1.0)	2.8(1.1)	3.1(1.2)	2.8(1.0)	2.6(1.1)	2.5(1.0)	2.4(1.0)	2.5 (.9)	2.4(1.0)
Total	45.1 (9.6)	43.9 (8.4)	36.3 (9.0)	37.3 (10.2)	34.6 (8.3)	33.7 (9.1)	32.6 (9.4)	33.2 (7.8)	31.5 (7.9)	31.3 (6.5)
CGI Severity of Illness	4.9(.9)	4.8(.7)	4.3(.9)	4.2(.8)	4.1(.9)	4.0(.8)	3.8(1.1)	3.9 (.9)	3.4(.8)	3.7(.9)

Improvement	NA	NA	3.0(.9)	3.2(1.1)	2.8(.8)	3.1(1.2)	2.4(.8)	2.8(1.1)	2.0(1.1)	2.9(1.4)
SANS Globals										
Affective Flattening	2.8(1.1)	2.5(1.1)	2.4(1.0)	2.5(1.1)	2.3 (.9)	2.3(1.1)	2.1 (.9)	2.3 (.9)	2.2 (.8)	2.3 (1.0)
Alogia	2.4(1.0)	2.2(1.0)	2.3 (.9)	2.1(1.1)	2.2(1.0)	2.0(1.1)	1.9(1.0)	2.1(1.1)	2.0 (.8)	2.0 (1.1)
Avolition/ Apathy	3.4(1.1)	3.0(1.0)	3.4(1.1)	2.8(1.1)	2.9(1.2)	2.7(1.3)	3.0(1.1)	2.6(1.0)	2.6(1.0)	2.7 (1.3)
Asociality/ Anhedonia	3.2(1.2)	3.0(1.2)	3.0(1.2)	2.9(1.3)	2.9(1.2)	2.6(1.2)	2.9(1.0)	2.8(1.2)	2.5(1.1)	2.8 (1.2)

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions, SANS = Scale for the Assessment of Negative Symptoms, NA = Not applicable