Comparative Efficacy of Risperidone and Clozapine in the Treatment of Patients With Refractory Schizophrenia or Schizoaffective Disorder: A Retrospective Analysis

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Background: Clozapine is effective in up to 60% of patients with refractory schizophrenia, whereas the efficacy of risperidone remains unknown. This retrospective study examined the relative efficacy of these drugs in chronically institutionalized patients refractory to conventional antipsychotic agents.

Method: A total of 24 patients who at different time periods had received adequate trials of both clozapine and risperidone and met our inclusion criteria for minimum dose and duration of each trial were included; for clozapine, a minimum dose of 300 mg/day had to be maintained for at least 12 weeks, and for risperidone, a minimum dose of 6 mg/day for at least 6 weeks. Information obtained from systematic retrospective chart review was blindly rated by 2 psychiatrists using the 7-point Clinical Global Impressions-Improvement (CGI-I) scale on overall clinical state and along specific symptom domains of positive symptoms, negative symptoms, and aggressive behavior.

Results: The mean ± SD dose was 520 ± 94 mg/day for clozapine and 7.5 ± 2.2 mg/day for risperidone. Fourteen patients (58%) were classified as responders to clozapine, while 6 (25%) responded to risperidone (CGI-I score of 1 or 2); on specific symptom domains, response rates to clozapine were 38% (9/24) on positive symptoms, 29% (7/24) on negative symptoms, and 71% (12/17) on aggressive behavior. For risperidone, response rates were 17% (4/24) on positive symptoms, 8% (2/24) on negative symptoms, and 41% (7/17) on aggressive behavior.

Conclusion: The results of this study support the utility of first giving a risperidone trial in a treatment algorithm for refractory patients because of its better risk/benefit profile compared with clozapine. Clozapine, however, remains our gold standard in the management of these patients.

(J Clin Psychiatry 2000;61:498–504)

Received Aug. 26, 1999; accepted April 19, 2000. From the Schizophrenia Research Unit, Creedmoor Psychiatric Center (Drs. Sharif and Raza); Columbia University College of Physicians and Surgeons (Drs. Sharif and Raza); and Elmhurst Hospital Center, Queens, New York, N.Y. (Dr. Ratakonda).

Supported in part by National Alliance for Research on Schizophrenia and Affective Disorders Young Investigator Award (Dr. Sharif) and National Institute of Mental Health grant 5P20-MH50727 (Developing Schizophrenia Research Center grant; Jack Gorman, M.D., principal investigator).

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Refractoriness to antipsychotic treatment remains a significant problem in the clinical management of patients with schizophrenia, with up to 30% of patients demonstrating suboptimal symptom response to adequate trials of conventional antipsychotic agents. Treatment refractoriness in schizophrenia extends beyond positive symptoms to include negative symptoms, aggressive behavior, cognitive impairment, and comorbid mood symptoms. Clozapine, the first atypical antipsychotic, is the only agent with proven efficacy in the treatment of refractory patients. It is effective in producing significant symptom attenuation in 30% of patients at 6 weeks of treatment[1] and up to 60% of patients with longer treatment periods.[2,3] However, because of the small but significant risk of agranulocytosis, this drug remains a second-line agent. Additionally, its unfavorable side effect profile, including high anticholinergic activity, sedation, seizures, weight gain, sialorrhea, and orthostasis, further limits its use by affecting patient acceptance and compliance.

With the introduction of the next atypical antipsychotic, risperidone, the obvious question arose regarding its efficacy in treatment-refractory patients. A few studies[4–7] suggest that risperidone may have efficacy similar or somewhat inferior to that of clozapine in refractory patients. Small et al.[4] conducted sequential trials (minimum 6-week duration) of risperidone and clozapine in 20 treatment-refractory hospitalized patients with schizophrenia. Twelve patients demonstrated some improvement on clozapine treatment compared with 13 on risperidone treatment, although robust responses were seen

more frequently with clozapine. Daniel et al.,[5] in a randomized, crossover, 6-week study, also found no difference in clinical efficacy measures with the 2 drugs. However, this study was conducted in outpatients who were successfully treated and maintained on clozapine treatment, and therefore conclusions about relative efficacy are limited. Bondolfi et al.[6] compared the 2 agents in a controlled, double-blind, 8-week trial and found that approximately two thirds of patients achieved at least a 20% reduction in total Positive and Negative Syndrome Scale score with either agent. However, the maximum clozapine dose allowed was 400 mg/day, and the study included patients who were refractory to or intolerant of adequate doses of conventional antipsychotics. Breier et al.[7] reported on a prospective 6-week, double-blind trial comparing risperidone with clozapine in patients with refractory schizophrenia and found a response rate for clozapine of 36% compared with 20% for risperidone. Lindenmayer et al.,[8] in a 12-week, open, nonrandomized trial comparing clozapine and risperidone in severely ill refractory patients, found that both drugs demonstrated efficacy on a broad range of symptomatology with no statistically significant between-group differences, although clozapine was numerically superior to risperidone on all outcome measures.

In summary, the literature suggests a substantial efficacy profile for risperidone in this patient population, although it does not appear to achieve the frequency or robustness of clinical response seen with clozapine. An important factor in treatment outcome may be the degree of treatment refractoriness of the study population, since treatment response and refractoriness are not dichotomous but rather lie on a continuum. The studies clearly differed in the degree of refractoriness of the patient population, and this difference may have contributed to the variable results reported.

The goal of this retrospective chart review study was to compare the relative efficacy profiles of clozapine and risperidone in a group of the most refractory, chronically institutionalized patients, similar to those in the trial by Kane et al.[1] To be included in the sample, patients had to have failed at least 2 adequate conventional antipsychotic trials, be chronically institutionalized, and at different time periods have received adequate trials of both clozapine and risperidone. The specific goal was to identify superiority (or lack thereof) of either agent on global clinical outcome as well as on specific symptom domains, including positive symptoms, negative symptoms, and aggressive behavior, compared with a baseline of conventional antipsychotic treatment.

METHOD

The study was conducted at Creedmoor Psychiatric Center, a long-term treatment facility of the New York State Office of Mental Health affiliated with Columbia University. For patient selection into the study, 2 lists were generated from computerized pharmacy records: all patients who had received clozapine since its introduction at Creedmoor in early 1990 through December 1995, and a second list of all patients who had received risperidone from introduction at Creedmoor in February 1994 through December 1995. These lists were then cross-matched to identify patients who had received trials of both medications but at different times. This initial cross-matched list contained 43 patients. Information was gathered from the medical records of these patients to determine adequacy of prior conventional antipsychotic trials as well as the adequacy of the risperidone and clozapine trials. To be included in the study, patients had to meet the following criteria for adequacy of antipsychotic trials: failure of at least 2 trials of at least 6 weeks each of conventional antipsychotic agents from different chemical classes at a minimum dose of 1000 mg of chlorpromazine equivalent; in the clozapine trial, a minimum dose of 300 mg/day maintained for at least 12 weeks followed by a 4-week period that was used for clinical rating; and in the risperidone trial, a minimum dose of 6 mg/day maintained for at least 6 weeks followed by a 4-week rating period. The most recent 4-week period of conventional antipsychotic treatment was used as a baseline for comparison with the clozapine- and risperidone-treatment periods. Of the 43 patients, 1 patient was excluded because the indication for treatment with a novel agent was severe extrapyramidal symptoms with conventional antipsychotics and not treatment refractoriness, and 18 patients were excluded for inadequate dose or duration of one or both trials (clozapine and/or risperidone). This yielded a total of 24 patients who met our inclusion criteria for the minimum dose and duration criteria for each trial and constituted the study sample.

The medical records of these patients were reviewed in detail. Information collected included demographics, diagnoses, number of prior hospitalizations, age at first hospitalization, duration of hospitalization, and concomitant medications taken during the clozapine and risperidone trials. For each atypical antipsychotic trial, the date of initiation, time in weeks from initiation to achieve target dose (300 mg/day for clozapine, 6 mg/day for risperidone), mean dose of antipsychotic during the rating period, and maximum dose administered were obtained. To assess symptom domain response, the medical records of these patients were reviewed by one research assistant, trained in chart review by Z.A.S., utilizing a structured format that gathered information on patient symptomatology during several rating periods: a 4-week baseline period on treatment with a conventional antipsychotic immediately preceding the atypical antipsychotic trial, a 4-week period after 12 weeks of clozapine treatment at a minimum dose of 300 mg/day, and a 4-week period after 6

Table 1. Reasons for Exclusion (N = 19)

Reason for Exclusion	N
Was treatment intolerant to conventional agents, not treatment refractory	1
Responded to atypical antipsychotic at less than threshold levels for dose and/or duration	4
Noncompliance with risperidone	1
Developed side effects with clozapine or noncompliant with blood monitoring. One patient responded to risperidone at 4 mg/day	5
Trial terminated at below-threshold levels by clinical team secondary to lack of efficacy	8

weeks of risperidone treatment at a minimum dose of 6 mg/day. Data were collected along several dimensions: group attendance and participation, privilege level, 1:1 observations, seclusion/restraint, verbal aggression, assaults on peers or staff, destruction of property, administration of p.r.n. medications, presence and severity of psychotic symptoms, level of social and verbal interaction with others, hygiene and grooming, and discharge or transfer to a less (or more) restrictive setting. Information was obtained from medical record documentation of all disciplines including professional staff as well as mental health aides. Whenever possible, verbatim quotations were documented.

After completion of data, collection copies were made of the symptom description sections of the structured rating forms, and all information that could potentially divulge the identity of the trial (i.e., clozapine or risperidone) including side effects was obliterated with a black marker. The research assistant then randomly designated each trial for any given patient as trial "X" or trial "O" such that for any given patient, trial "X" could be a clozapine trial or a risperidone trial. These blinded forms that now contained only information on patients' clinical state during the rating periods were independently rated by 2 research psychiatrists (Z.A.S., S.S.R.) using the 7-point Clinical Global Impressions-Improvement (CGI-I) scale[9] along the psychopathology domains of positive symptoms, negative symptoms, aggressive behavior, and a global clinical improvement rating. Each atypical trial was compared with the baseline of conventional antipsychotic treatment. Ratings for improvement in aggression were only given for patients who were felt to demonstrate significant aggressive behavior at baseline. This was defined as one or more of the following: assault on others, property destruction, need for seclusion/restraint, or 1:1 monitoring to prevent assaults. After completion of ratings, the results were compared and where there were differences, the 2 raters arrived at a consensus rating. All ratings were finalized prior to breaking the blind about the identity of the trials. A CGI-I rating of 1 or 2 ("very much improved" or "much improved" compared with baseline) was required to classify a patient as a responder on any symptom domain or on the global rating.

Table 2. Patient Characteristics

Variable	N	Mean ± SD	Range
Age, y	24	35.9 ± 6.3	25–46
Sex			
Male	13		
Female	11		
Race			
White	15		
Black	5		
Hispanic	3		
Asian	1		
Age at first hospitalization, y		18.5 ± 4.1	10–25
No. of previous hospitalizations		8 ± 5	4–27
Duration of hospitalization, mo		61 ± 56	1–248
Diagnosis			
Schizophrenia	16		
Schizoaffective disorder	8		
No. of previous antipsychotic trials			
2 (minimum criteria)	24		
3	16		

RESULTS

The reasons for not meeting inclusion criteria in the 19 patients excluded from the study sample are shown in Table 1. The demographics and clinical characteristics of the patient sample (N = 24) are shown in Table 2. In 10 patients, a stable conventional antipsychotic treatment period preceded each novel antipsychotic trial and was used as baseline for that trial. In the remaining 14 patients, there was only one baseline comparison period with a conventional agent, since the patient proceeded directly from risperidone to clozapine (8 patients) or clozapine to risperidone (6 patients). In these 14 patients, the reasons for switching from one atypical to another were lack of efficacy in 10 patients, noncompliance with blood work for clozapine (1 patient), and low white blood cell count on clozapine treatment in 1 patient. In 2 patients, no clear reason for the switch was indicated.

The mean ± SD clozapine dose during the 4-week rating period was 520 ± 94 mg/day, while for risperidone, it was 7.5 ± 2.2 mg/day. The duration of treatment (mean ± SD) to the beginning of the rating period was 17.0 ± 2.6 weeks for clozapine and 8.1 ± 1.9 weeks for risperidone. Therefore, it took a mean of 5 weeks to reach the 300-mg/day minimum dose required for clozapine, and a mean of 2 weeks to reach 6 mg/day of risperidone.

A maximum of 8 CGI-I ratings could be given for each patient, 4 per trial (positive symptoms, negative symptoms, aggressive behavior, and a global rating); however, only 17 of the 24 patients demonstrated significant aggressive behavior at baseline. This yielded a total of 178 possible CGI-I ratings in the study by each rater. There was exact agreement between the 2 raters on 154 of the total of 178 ratings (86.5%); in 22 (12.4%), there was only a 1-point difference between the raters; and in 2 ratings (1.1%), there was a 2-point difference. In

Table 3. Response Rates to Risperidone and Clozapine[a]

	Risperidone Trial		Clozapine Trial	
Symptom Domain	N	%	N	%
Global rating	6	25	14	58
Positive symptoms	4	17	9	38
Negative symptoms	2	8	7	29
Aggressivity[b]	7	41	12	71

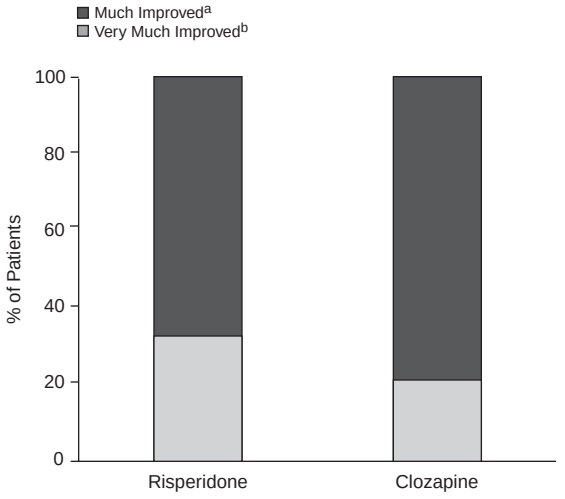
[a]Clinical Global Impressions-Improvement score ≤ 2.
[b]At baseline, 17 of 24 patients demonstrated significant aggressive behavior.

instances where there was not an exact agreement, a consensus rating was arrived at before the blind was broken.

The response rates (rating of "much improved" [CGI-I score = 2] or "very much improved" [CGI-I score = 1] compared with conventional antipsychotic baseline) on overall clinical state as well as specific symptom domains are shown in Table 3. Fourteen patients (58%) were classified as clear responders to clozapine, and 6 (25%) were responders to risperidone on global improvement. Aggressive behavior had the highest response rate (71% for clozapine vs. 41% for risperidone), followed by psychotic symptoms (38% for clozapine vs. 17% for risperidone), with least efficacy evident on negative symptoms (29% for clozapine vs. 8% for risperidone). The response rate was greater in clozapine-treated patients compared with risperidone-treated patients in global improvement, positive symptoms, negative symptoms, and aggressive behavior. Response to one agent did not necessarily predict response to the other. Four patients responded to both drugs, 10 responded to clozapine but not risperidone, and 2 responded to risperidone but not clozapine. Eight (33%) had no response to either agent. Two patients were rated as worse during the risperidone trial compared with the conventional antipsychotic baseline measurements versus none for clozapine.

To further explore the potential impact of order of drug administration, we examined response in the subgroups of patients in which a conventional antipsychotic baseline preceded each atypical antipsychotic trial (N = 10) and that in which patients had only one conventional antipsychotic baseline and proceeded directly from risperidone to clozapine (N = 8) or clozapine to risperidone (N = 6). In the first group (N = 10), 3 patients (30%) responded to risperidone, 5 (50%) to clozapine, and 4 (40%) to neither drug. In patients proceeding directly from risperidone to clozapine (N = 8), 2 (25%) responded to risperidone, 6 (75%) to clozapine, and 2 (25%) to neither drug. In patients who proceeded from clozapine to risperidone (N = 6), 1 (17%) responded to risperidone, 3 (50%) to clozapine, and 2 (33%) to neither drug. These proportions are comparable with the parent sample as a whole, in which risperidone resulted in significant improvement in 25% of patients (N = 6), clozapine in 58% of patients (N = 14); neither drug was successful in 33% of patients

Figure 1. Degree of Clinical Improvement in Responders to Risperidone and Clozapine



[a]Clinical Global Impressions-Improvement (CGI-I) score = 2.
[b]CGI-I score = 1.

(N = 8). (Note: for any group, the total may be more than 100% since individual patients could have responded to both clozapine and risperidone.) We also explored if the degree of improvement in responders was different between the 2 drugs (Figure 1). Three (21%) of 14 responders to clozapine were rated as very much improved (CGI-I score = 1), while 79% (N = 11) were given a rating of much improved (CGI-I score = 2). With risperidone, 2 of the 6 responders (33%) were rated as very much improved (CGI-I score = 1), while 67% (N = 4) were rated as much improved (CGI-I score = 2). These observations do not suggest a substantial impact of order of drug administration or any difference in the robustness of clinical response once it occurred.

Other pertinent clinical information included 3 patients who demonstrated evidence of compulsive water drinking at baseline. All these patients demonstrated unequivocal improvement in this behavior on clozapine treatment compared with none on risperidone treatment. All 3 patients were also rated as responders to clozapine in psychotic symptoms, while none of them were classified as responders on this symptom domain with risperidone.

Eight patients had no concomitant medication during either trial. Of the remaining 16 patients, 5 were being treated with a mood stabilizer (lithium, valproic acid, or carbamazepine) prior to initiation of either trial medication, and the mood stabilizer was maintained during the trial; 1 patient received lorazepam during both trials; 9 patients had different concomitant medication during the trials, but these were not felt to contribute to the clinical response because either there was no improvement noted during the respective trials or the outcomes assessed were

not target symptoms of the concomitant medication. This left 1 patient in whom there was a potential contributing role for concomitant medication. In this patient, lithium and valproic acid were initiated during the risperidone trial and significant improvement was noted on aggressivity.

DISCUSSION

The main finding in this study was that in treatment-refractory, institutionalized patients with schizophrenia or schizoaffective disorder, the global response rate to risperidone was 25%, which is clearly superior to the 0% to 4% response rate to conventional antipsychotics in a similar patient population.[1,10] Fourteen (58%) of 24 patients were classified as unequivocal responders to clozapine. The response rate to clozapine in this study is exactly in line with that demonstrated in prospective clozapine trials in similar patient populations with this duration of treatment[3,11,12] and provides validity to the data. Further confirmation was obtained of the broader spectrum of efficacy of both drugs compared with conventional antipsychotics. Superior efficacy of risperidone compared with conventional antipsychotics (which were the baseline treatment) was evident on positive symptoms as well as on chronic aggressive behavior. Similarly, clozapine demonstrated greater efficacy compared with conventional agents on positive symptoms, negative symptoms, and aggressive behavior. The finding of a broader spectrum of efficacy is consistent with previously published literature on both agents.[1,13–17] Clozapine was superior to risperidone in the probability of therapeutic success in all symptom domains examined; however, among responders, the robustness of clinical improvement was quite comparable for both drugs.

A recent study by Bondolfi et al.[6] reported equivalent response rates of clozapine and risperidone (approximately 65%) in an 8-week randomized double-blind trial comparing the 2 drugs in treatment-refractory or intolerant patients with schizophrenia. The response rate to clozapine in this study after only 8 weeks of treatment is significantly higher than that reported in other trials and is probably accounted for by the inclusion of patients who were treatment intolerant to conventional antipsychotics. This subgroup of patients has been shown to have response rates to clozapine approaching 80%.[2] Despite this limitation, the study by Bondolfi et al.[6] also supports the superior efficacy of risperidone in refractory patients compared with conventional antipsychotic agents. Breier et al.[7] reported on a prospective 6-week double-blind trial comparing risperidone with clozapine in patients with refractory schizophrenia and found a response rate of 36% for clozapine compared with 20% for risperidone. Categorical response rates in the prospective study by Lindenmayer et al.[8] were not reported. In the recent prospective double-blind study by Wirshing et al.,[18] risperidone was superior to haloperidol at the end of the 4-week fixed-dose phase, but not after another 4 weeks of treatment in which there was flexible dosing of both agents. Response rates at the end of the fixed-dose phase were 24% for risperidone and 11% for haloperidol. This probability of success with risperidone is identical to our conclusion from this study.

The efficacy of both agents in the treatment of chronic aggressive behavior is intriguing. The improvement in aggressive behavior in most instances appeared independent of improvement in psychotic symptoms with either drug. In the risperidone-treatment phase, 7 of the 17 patients with aggressive behavior at baseline demonstrated improvement in this domain, but only 2 also had improvement in psychosis ratings; in the clozapine-treatment phase, of the 12 patients with significant improvement in aggressive behavior, only 5 demonstrated improvement in psychosis. This finding suggests a unique efficacy of these agents on chronic aggressive behavior. Others have also reported a salutary role for both clozapine (reviewed in reference 17) and risperidone[14] in the treatment of chronic aggressive behavior in patients with schizophrenia or schizoaffective disorder.

Another observation of interest in this study was the efficacy of clozapine in the reduction of compulsive water drinking. Clozapine has demonstrated efficacy in this clinical syndrome.[19] Risperidone was not effective in reducing compulsive water drinking in our study, although the number of patients is too small to draw conclusions. The etiology and pathophysiology of compulsive water intake in schizophrenic patients is unknown. Goldman et al.[20] demonstrated that compulsive water intake was preceded by exacerbation of psychotic symptoms induced by a pharmacologic challenge, suggesting a possible relationship between these domains of pathology. All 3 patients who improved on this clinical domain with clozapine were also classified as responders on psychotic symptoms, whereas none of the 3 patients improved with risperidone in either compulsive water drinking or psychosis. Although speculative, our results are consistent with the notion that the mechanism of action of clozapine on reducing compulsive water intake may be through its superior antipsychotic effect.

It is conceivable that the shorter treatment period for risperidone compared with clozapine (8.1 ± 1.9 weeks vs. 17 ± 2.6 weeks) might have placed risperidone at a disadvantage. The shorter treatment period requirement for risperidone was chosen for several reasons. First, most of the improvement in risperidone-treated patients in the North American Risperidone trial occurred in the first 4 weeks of treatment[21]; secondly, the response rate in that 8-week trial did not differ in patients who were acutely admitted (< 1 week in the hospital) versus the more chronic patients who had been hospitalized for greater than 6 months,[16]

i.e., the more chronic patients did not appear to need a longer time to respond. However, none of the patients in the above studies were formally defined as treatment refractory, and these observations may be of limited relevance to this study population. The primary reason for the choice of a 6-week treatment period for risperidone was the fact that clinicians are, in general, more likely to abandon a risperidone trial in nonresponding patients earlier than a clozapine trial, simply because clozapine is perceived as a drug of last resort. If we had selected a minimum duration of treatment of 12 weeks for risperidone, our sample size would have been smaller, and a natural selection for responders to risperidone would have occurred. The possibility remains, however, that a longer treatment period with risperidone to match the clozapine-treatment period might have resulted in a higher response rate with risperidone than that observed. Despite this potential bias, risperidone demonstrated clearly superior efficacy compared with the predicted response rates from conventional agents in this severely ill patient population.

Various factors could have potentially influenced the treatment outcomes in this study. First is the order in which the 2 drugs were received. One specific concern is the phenomenon of cholinergic rebound upon rapid discontinuation of clozapine. Because of the high anticholinergic activity of clozapine, a patient going directly from clozapine to risperidone without a gradual taper period might be expected to have a higher likelihood of clinical deterioration and a high dropout rate compared with patients who went from risperidone to clozapine. However, these patients would probably have had an early relapse and, because of the minimum duration of treatment requirement, would have been excluded from the study. It remains a possibility that a patient might have been maintained on risperidone treatment despite clinical worsening. In fact, 1 of the 2 patients in the study rated as worse on the risperidone trial proceeded directly from clozapine to risperidone. However, as mentioned earlier, the order of drug administration did not have a significant impact on the proportion of responders or nonresponders to each drug.

Another possible confound could be the differences between the groups in concomitant medications such as mood stabilizers administered during each trial. In the 5 patients who were maintained with a mood stabilizer during each trial as well as during baseline conventional antipsychotic treatment, all 5 were responders to clozapine and 3 were responders to risperidone; this is about the same ratio of response to the 2 agents in the entire sample and suggests that concomitant mood stabilizer treatment did not differentially affect the response rate to the 2 agents. In 1 patient, lithium and valproic acid were initiated during the risperidone trial, and significant improvement in aggressivity was noted. Whether this improvement was due to risperidone, mood stabilizer, or the combination is impossible to discern.

This study included only those patients who met a priori criteria of adequate dose and duration of treatment. On further examination, the 18 patients who were excluded because they did not meet these criteria represented a mixed group. Fourteen patients clearly had inadequate trials of one or both drugs. However, 3 patients did not satisfy the time criterion because they were clinically improved and were discharged, and in 1 patient the clozapine dose judged by the treatment team to be the optimal dose for the patient (250 mg/day) was less than our minimum of 300 mg/day. If we accept the obvious clinical reality that there are patients who respond at lower doses and in shorter time periods, and that the minimum dose/duration cut-offs were necessary only to ensure adequacy of a trial to make the determination of nonresponse, this subsample could be included in the larger data set. The medical records of these 4 patients were also reviewed using the same methodology described above and all were rated as much or very much improved on all relevant symptom domains and global rating in both trials. If these patients are included in the total sample, then the overall response rates are 36% for risperidone and 64% for clozapine. Again, the response rate for clozapine is consistent with reports in the literature while the risperidone response rate, although not as high as that of clozapine, is substantial and impressive.

The strength of this study lies in each patient receiving adequate trials of both drugs and the several strategies that improved the quality of data. These included data collection by a single individual using a structured format and blind ratings of outcomes. The overall response rate to clozapine in this study was identical to published response rates in prospective clozapine trials, which provides validity to our database and methodology. A substantial response rate was evident with risperidone in this severely ill cohort. The results of this study give an estimate of the probability of therapeutic success with each of these drugs in a treatment-refractory population who have received long and adequate dose trials of each agent. This design naturally selects for patients who are able to tolerate the medications. The results do not tell us the probability of treatment failure secondary to noncompliance related to intolerability. Clozapine is clearly the more toxic and less tolerated of the 2 drugs. The choice of which drug to use first in a given patient is always a risk/benefit consideration for that individual. The results of this study would support the utility of first giving a risperidone trial in patients with treatment-refractory schizophrenia because of its better side effect profile compared with clozapine. However, in certain patients with severe symptomatology in whom maximum probability of therapeutic success is the primary consideration, clozapine would be the drug of first choice. Despite its limitations, clozapine remains our standard in the management of patients with treatment-refractory schizophrenia.

Drug names: carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), lorazepam (Ativan and others), risperidone (Risperdal), valproic acid (Depakene).

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