Clinical Predictors of Response to Clozapine Treatment in Ambulatory Patients With Schizophrenia

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Background: Despite the advent of new atypical antipsychotics, clozapine remains an important option in the treatment of patients with poor response to conventional antipsychotics. Clinicians would be well served if clinical characteristics could be identified that predict a favorable response to clozapine. A few studies addressing this issue have reported inconsistent results.

Method: The association of clinical characteristics with a sustained response was investigated in 37 partially treatment-refractory outpatients with a DSM-III-R diagnosis of chronic schizophrenia who had been assigned to clozapine treatment in a double-blind, haloperidol-controlled, long-term (29-week) study of clozapine. Response was defined as a 20% decrease of the Brief Psychiatric Rating Scale (BPRS) psychosis factor score sustained over 2 consecutive ratings. Differences between responders and nonresponders with regard to selected baseline variables were analyzed with t tests and χ^2 tests. In addition, Cox regression analyses were performed to identify variables that best predicted a response to clozapine treatment.

Results: Clozapine responders were rated as less severely ill, showed a lesser degree of negative symptoms, and demonstrated fewer extrapyramidal side effects at baseline as compared with nonresponders. In addition, higher BPRS total scores—after controlling for the effects of the other variables—were associated with a response.

Conclusion: In a cohort of partially treatment-refractory outpatients, a favorable response to clozapine was associated with characteristics describing less severely ill patients. The history of patients did not affect their response to clozapine.

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The atypical antipsychotic clozapine has now been well established as the treatment of choice for severely ill schizophrenic patients refractory to treatment with conventional antipsychotics.[1] In addition, in ambulatory schizophrenic patients who are partially refractory to conventional antipsychotics, clozapine has also been proven to be superior to conventional antipsychotics.[2,3] With the advent of new antipsychotics such as risperidone, olanzapine, and quetiapine, clinicians have now more alternatives to treatment with conventional antipsychotics at their disposal.

Despite these welcome additions to the treatment choices, clozapine remains a mainstay in the treatment of severely ill treatment-refractory patients. Clinicians would be well served in their choice of antipsychotic agents if patient characteristics could be identified that predict a favorable response to clozapine. In recent years, several studies[4–11] have investigated this question. High levels of symptoms,[9,10] higher extrapyramidal symptom (EPS) scores,[4] a greater decrease of EPS during treatment with clozapine,[4,6] and a paranoid subtype of schizophrenia[4,9] have been reported to predict good response to clozapine. In addition, earlier[11] as well as later[4] age at illness onset have been found to be associated with favorable outcome of clozapine treatment. Overall, the results of these studies have been inconsistent and, to some extent, contradictory.

Most of these studies have used a specific decrease in symptomatology during a specific time interval as response criterion. This leaves open the possibility that some of the responders did not sustain the initial improvement and thus would not be counted as responders in a clinical setting. In addition, these studies were either short-term or open-label studies. Each of these study designs creates specific problems in identifying responders. In short-term studies, patients who would have fulfilled response criteria after 3 or 4 months are missed. In open-label studies the unblinded design introduces a potential bias in ratings, artificially inflating the response rate. Lastly, some studies[4,6] also included patients who were treatment intolerant, but not necessarily refractory, potentially obscuring or inflating the association of certain clinical characteristics with treatment response. The study, which is the basis of this report on clinical predictors of response to clozapine, avoided all of these potential pitfalls: it included only patients who met strictly defined criteria of partial treatment nonresponse, utilized a long-term, double-blind and controlled design, and applied a response criterion that required the presence of a sustained clinical improvement.

SUBJECTS AND METHOD

The 37 subjects of this report were outpatients with partially treatment-refractory schizophrenia who participated in a double-blind, 29-week treatment study comparing clozapine with haloperidol treatment. Patients were randomized to clozapine treatment. The study was conducted at the Research Department, Hillside Hospital; the North Shore–Long Island Jewish Health System, Glen Oaks, N.Y.; the Department of Psychiatry, West Los Angeles Veterans Affairs Medical Center, Los Angeles, Calif.; and the Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, Pa. The study was approved by the institutional review boards of all institutions. The main results of this study have been reported elsewhere.[3] All patients were fully informed about the benefits, risks, and potential side effects involved in participating in this study and signed informed consent. Inclusion criteria were (1) a DSM-III-R diagnosis of schizophrenia or schizoaffective disorder established by a structured clinical interview (Structured Clinical Interview for DSM-III-R [SCID], Patient Version[12]); (2) age 20–55 years; (3) clinically manageable in the community despite continuing psychotic symptoms; (4) documented failure on trials of 2 neuroleptic drugs at dosages equivalent to or greater than 600 mg/day chlorpromazine for at least 6 weeks and 1 trial of a neuroleptic at doses equivalent to 250–500 mg/day chlorpromazine for at least 4 weeks; (5) presence of persistent psychotic symptoms as evidenced in a rating of moderate (4 or more) on at least 1 of the 4 psychosis items (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content) of the Brief Psychiatric Rating Scale (BPRS).[13]

After baseline assessments of patients, all psychotropic medications were tapered and double-blind study medication was titrated over a period of 5 weeks. The titration schedule aimed at reaching 500 mg/day of clozapine at the end of 5 weeks. If patients showed intolerable side effects, the titration could be slowed down or stopped at a lower dose. The minimum dose that had to be reached was 250 mg/day of clozapine. If clinically indicated, the dose could be further increased up to a maximum of 850 mg/day of clozapine.

Assessments of psychopathology were performed with the BPRS - Anchored Version[14] (severity scale 1–7), the Scale for the Assessment of Negative Symptoms (SANS),[15] and the Clinical Global Impressions-Severity of Illness (CGI-S) and Change scales.[16] The premorbid functioning of patients was assessed using a questionnaire covering education and work history and categorized as "very well," "moderately well," and "poorly."

Acute EPS were assessed with the Simpson-Angus Scale[17] and the Barnes Akathisia Scale.[18]

Assessments of psychopathology and side effects were performed weekly for the first 5 weeks, every 2 weeks until week 17 of the study, and subsequently at weeks 23 and 29.

Treatment response was defined as a reduction of the BPRS psychosis factor (sum of items "conceptual disorganization," "suspiciousness," "hallucinatory behavior," and "unusual thought content") of 20% or more that was sustained over at least 2 consecutive ratings.

The following variables were evaluated with respect to their association with treatment response to clozapine: sex, age, age at first psychiatric symptom, age at first hospitalization, duration of illness (defined as time since first hospitalization), premorbid functioning, and psychopathology and extrapyramidal side effects at study baseline. The measures of psychopathology were the BPRS total score, the BPRS psychosis factor score, the score on the suspiciousness/paranoia item of the BPRS, the SANS total score (sum of the 4 global ratings), and the CGI-S score. As a measure of acute EPS we used (1) the sum of the scores on the items gait, arm dropping, cogwheeling, and rigidity of the Simpson-Angus Scale (referred to as EPS score) and (2) the global score on the Barnes Akathisia Scale.

The association of the selected variables with treatment was assessed by comparing responders and nonresponders with regard to the baseline values of the selected variables with the help of t tests for continuous and chi-square tests for categorical data, respectively ($\alpha = 0.05$, 2-tailed).

RESULTS

A total of 37 patients (26 male/11 female) were assigned to the clozapine treatment group. Their mean ± SD

Table 1. Baseline Characteristics of 37 Chronically Psychotic Outpatients With Schizophrenia[a]

Characteristic	Total Sample (N = 37)	Responders (N = 22)	Non-responders (N = 15)	Significance
Sex	26M/11F	13M/9F	13M/2F	< .10
Age, mean ± SD, y	41.1 ± 10.2	41.1 ± 9.7	41.1 ± 11.2	NS
Level of premorbid functioning, %[b]	69/31	67/33	73/27	NS
Age at first symptom, mean ± SD, y	21.9 ± 5.0	22.1 ± 4.2	21.7 ± 6.1	NS
Age at first hospitalization, mean ± SD, y	24.3 ± 6.7	23.2 ± 3.8	25.8 ± 9.4	NS
Duration of illness, mean ± SD, y	19.2 ± 10.9	19.0 ± 10.3	19.4 ± 12.1	NS
CGI-S scale score, mean ± SD	4.9 ± 0.8	4.7 ± 0.8	5.3 ± 0.9	< .05
BPRS total score, mean ± SD	47.4 ± 10.3	47.8 ± 10.0	46.8 ± 11.1	NS
BPRS psychosis factor score, mean ± SD	16.3 ± 3.9	15.9 ± 3.8	17.0 ± 4.2	NS
BPRS suspiciousness/ paranoia item, mean ± SD	4.1 ± 1.9	4.1 ± 1.7	4.1 ± 2.2	NS
SANS total score, mean ± SD	10.3 ± 3.5	9.2 ± 3.0	11.8 ± 3.5	< .05
EPS score, mean ± SD[c]	1.5 ± 2.0	0.9 ± 1.0	2.4 ± 2.7	< .10
Barnes Akathisia Scale global score, mean ± SD	0.8 ± 1.1	0.8 ± 1.2	0.8 ± 0.8	NS

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness, EPS = extrapyramidal symptoms, NS = nonsignificant, SANS = Scale for the Assessment of Negative Symptoms.
[b]Sum of items: gait, arm dropping, cogwheeling, and rigidity.
[c]"Very good" or "moderately good" versus "poor."

age was 41 ± 10 years and their age at first hospitalization 24 ± 7 years. Further characteristics are given in Table 1.

Twenty-two patients (59%) met our response criterion. At baseline, i.e., before starting clozapine treatment, these 22 responders were rated as significantly less ill on the CGI-S and demonstrated a significantly lower level of negative symptoms as assessed by the SANS total score than patients who never met the response criterion (see Table 1). Responders also tended to have lower levels of acute EPS at baseline than nonresponders. Among female patients the response rate was higher than in men, although this difference failed to reach significance (see Table 1). With regard to all other variables, responders and nonresponders did not differ significantly.

In order to further explore our results, we entered the variables that were found to differentiate between responders and nonresponders at a significance level of 0.1 into a Cox regression analysis (Table 2). A Cox regression analysis permits assessment of the unique predictive power of both continuous and categorical variables while controlling for the contributions of all others. The variables entered into the Cox regression analysis were sex, CGI-S score, SANS total score, and EPS score. The overall

Table 2. Cox Regression Analysis[a]

Variable	Wald χ^2	Hazard Ratio	% Change in Hazard[b]	Significance
CGI-S score	8.74	0.231	–77	< .01
EPS score	5.44	0.578	–42	< .05
SANS total score	4.47	0.831	–17	< .05
BPRS total score	5.64	1.092	9	< .05
Sex	2.12	0.462	...	...

[a]Overall $\chi^2 = 19.04$, df = 5, $p < .005$. Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness, EPS = extrapyramidal symptoms, SANS = Scale for the Assessment of Negative Symptoms.
[b]The estimated change of the hazard that a subject is a responder when the associated variable changes by 1 point. For instance, for a 1-point increase of the CGI-S score, the hazard of responding to clozapine decreases by 77%.

regression analysis was significant ($\chi^2 = 13.15$, df = 4, $p < .05$). Of the 4 variables, only the CGI-S score and the EPS score were individually significant predictors of responder/nonresponder status ($p < .05$). For both variables, increased scores were associated with a reduced likelihood of responding to clozapine. Although the Cox regression analysis using these variables provided a good fit of the data, additional models were explored using different combinations of variables. We thus found that adding the BPRS total score as a predictor to the 4 variables previously included in the Cox regression analysis, the best fit of the data was achieved ($\chi^2 = 19{,}04$, df = 5, $p < .005$; see Table 2). In this model, the CGI-S score was significant at the $p < .01$ level, while the BPRS total score, the EPS score, and the SANS total score were significant at the $p < .05$ level. Again, gender was not significant. Thus, after accounting for effects of all other variables in the regression analysis, increases in CGI-S scores, SANS total score, and EPS score individually predicted a smaller chance of responding to clozapine, whereas a higher BPRS score was associated with a higher likelihood to respond. In practical terms, an increase of 1 point on the CGI-S scale reduced the chance of being a responder by approximately 77%. Similarly, an increase of 1 point in the EPS score was associated with a decrease of the chance to respond by about 42% (see Table 2).

DISCUSSION

In this study, the association of specific clinical characteristics of chronically psychotic and partially treatment-refractory schizophrenic patients with response to clozapine was investigated. A lower severity of illness, a lesser degree of negative symptoms, and fewer EPS during treatment with typical antipsychotics were associated with a favorable response to clozapine treatment. In contrast to these variables, which describe patient characteristics just prior to initiation of clozapine treatment, none of the variables providing information about the patients' history of illness differentiated responders from nonresponders. In

particular, neither age at onset of symptoms nor age at first hospitalization was associated with response to clozapine as has been observed in previous studies.

The main finding of our study is that among patients who have only partially responded to treatment with conventional agents, those who are considered less ill overall and show fewer negative symptoms respond better to clozapine. This finding contrasts with results of other studies that reported higher Positive and Negative Syndrome Scale (PANSS)[19] and BPRS scores to be associated with more improvement after 10 to 12 months of treatment with clozapine.[9] This discrepancy may be due to the different patient groups investigated. While these studies included mostly patients with a high use of inpatient services, our patients were functioning on an outpatient basis.[10] However, some, albeit indirect, support of an association of treatment response with higher symptom levels at baseline is given by our finding that a higher BPRS total score was associated with a greater likelihood of responding to clozapine, after the effects of illness severity, negative symptoms, and EPS were statistically controlled for. Although this may be a chance finding, it may relate to the fact that more items in the BPRS assess positive symptoms and complaints than negative symptoms. This finding would thus indicate that for any given level of illness severity, patients with more positive symptoms, as reflected in a higher BPRS total score, were more likely to respond to clozapine.

We could not confirm that clozapine responders show higher EPS at baseline.[4] In contrast, in our sample higher EPS scores at baseline were associated with a decreased likelihood of responding to clozapine. This discrepancy between our findings and those reported by earlier studies is most likely attributable to differences in patient selection since the prior studies that reported such an association also included patients with intolerance to conventional treatment. Such an inclusion criterion also selects patients who are not necessarily true nonresponders. Thus, the reported association of EPS and treatment response in the studies may just reflect the fact that patients intolerant to treatment with conventional antipsychotics demonstrate a greater response to clozapine than patients who are truly refractory to conventional treatment. However, our finding of lower EPS prior to clozapine treatment in responders to clozapine is in agreement with the results of studies of conventional antipsychotics in which worse outcome was demonstrated in patients who developed EPS.[20–24] Moreover, it supports earlier suggestions that the occurrence of acute EPS may identify subgroups of patients with subtle differences in the pathophysiology underlying their disease[25] and affecting treatment outcome. However, it is also conceivable that those patients who showed more EPS were receiving higher doses of typical antipsychotics prior to enrolling in the study because they were more refractory to treatment. This hypothesis could not be tested directly in our analysis.

In an analysis of the patient sample of the original study by Kane et al.,[1] Honigfeld and Patin[8] found that among 46 variables investigated, only the diagnosis of a paranoid subtype of schizophrenia, a low score on the grandiosity item of the BPRS, and more past hospitalizations predicted outcome. Other studies have also reported an association of paranoid features with treatment response.[4,9] Again, in our patient sample such an association was not observed.

This study is limited by the rather moderate sample size. Thus, our failure to replicate findings of previous studies may also be the result of the limited power of this study.

CONCLUSION

In conclusion, in a methodologically rigorous long-term study of chronically psychotic schizophrenic outpatients, patients who responded to clozapine were less ill at baseline as demonstrated by lesser severity of illness and lower negative symptoms and exhibited less EPS. These findings suggest that factors similar to those determining response to conventional antipsychotics are also associated with response to clozapine. However, the observed differences between responders and nonresponders, albeit statistically significant, were small. Thus, while our findings may influence the clinician's hope of seeing a response in a given patient, trial and error still remain the best option to find out which patient will benefit from clozapine.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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REFERENCES

1. Kane JM, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789–796
2. Breier A, Buchanan RW, Kirkpatrick B, et al. Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. Am J

Psychiatry 1994;151:20–26
3. Kane JM, Marder SR, Schooler NR, et al. Clozapine and haloperidol in moderately refractory schizophrenia: a 6-month randomized and double-blind comparison. Arch Gen Psychiatry 2001;58:965–972
4. Lieberman JA, Safferman AZ, Pollack S, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. Am J Psychiatry 1994;151:1744–1752
5. Owen RR, Beake BJ, Marby D, et al. Response to clozapine in chronic psychotic patients. Psychopharmacol Bull 1989;25:253–256
6. Pickar D, Owen RR, Litman RE, et al. Clinical and biologic response to clozapine in patients with schizophrenia: crossover comparison with fluphenazine. Arch Gen Psychiatry 1992;49:345–353
7. Breier A, Buchanan RW, Irish D, et al. Clozapine treatment of outpatients with schizophrenia: outcome and long-term response patterns. Hosp Community Psychiatry 1993;44:1145–1149
8. Honigfeld G, Patin J. Predictors of response to clozapine therapy. Psychopharmacology (Berl) 1989;99(suppl):S64–S67
9. Meltzer HY, Bastani B, Young Kwon K, et al. A prospective study of clozapine in treatment-resistant schizophrenic patients. Psychopharmacology (Berl) 1989;99(suppl):S68–S72
10. Rosenheck R, Lawson W, Crayton J, et al, for the Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. Predictors of differential response to clozapine and haloperidol. Biol Psychiatry 1998;44:475–482
11. Buchanan RW, Breier A, Kirkpatrick B, et al. Positive and negative symptom response to clozapine in schizophrenic patients with and without the deficit syndrome. Am J Psychiatry 1998;155:751–760
12. Spitzer RL, Williams JBW, Gibbon M, et al. Structured Clinical Interview for DSM-III-R, Patient Version. Washington, DC: American Psychiatric Press; 1999
13. Overall JE, Gorham DR. Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
14. Woerner MG, Mannuzza S, Kane JM. Anchoring the BPRS: an aid to improved reliability. Psychopharmacol Bull 1988;24:112–117
15. Andreasen NC. The Scale for the Assessment of Negative Symptoms in Schizophrenia (SANS). Iowa City, Ia: University of Iowa; 1983
16. Guy W. Clinical global impressions. In: ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
17. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;45(suppl 212):11–19
18. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
19. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–271
20. Alpert M, Diamond F, Kesselman M. Correlation between extrapyramidal and therapeutic effects of neuroleptics. Compr Psychiatry 1977;18:333–336
21. Alpert M, Diamond F, Weisenfreund J, et al. The neuroleptic hypothesis: study of the covariation of extrapyramidal and therapeutic drug effects. Br J Psychiatry 1978;133:169–175
22. Hogan TP, Awad AG. Pharmacotherapy and suicide risk in schizophrenia. Can J Psychiatry 1983;28:277–281
23. Levinson DF, Simpson GM, Singh H, et al. Fluphenazine dose, clinical response, and extrapyramidal symptoms during acute treatment. Arch Gen Psychiatry 1990;47:761–768
24. Kinon BJ, Kane JM, Chakos M, et al. Possible predictors of neuroleptic-resistant schizophrenic relapse: influence of negative symptoms and acute extrapyramidal side effects. Psychopharmacol Bull 1993;29:365–369
25. Umbricht DS, Kane JM. Understanding the relationship between extrapyramidal side effects and tardive dyskinesia. In: Kane JM, Möller H-J, Awouters F, eds. Serotonin in Antipsychotic Treatment. New York, NY: Marcel Dekker; 1996:221–251