Clinical and Psychopharmacologic Factors Influencing Family Burden in Refractory Schizophrenia

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Background: This study compares the effect of clozapine and haloperidol and identifies other factors related to family burden as experienced by relatives of patients with refractory schizophrenia (DSM-III-R).

Method: Of 423 patients participating in a multisite randomized clinical trial, 221 identified a family member who was actively involved in their care and who agreed to complete a standardized measure of family burden at 6 weeks and 3, 6, 9, and 12 months after randomization, simultaneous with comprehensive patient assessments.

Results: Patient factors most consistently correlated with greater family burden were symptom severity, days living in the community (i.e., not in the hospital), and frequency of family contact. Among family members, clozapine was associated with significantly ($p = .048$) greater reduction in feelings of dissatisfaction related to providing support to the patient, but not in objective measures of support, amount of worry the patient engendered, or days of missed employment or household activity. Although clozapine reduces symptoms, thus lowering family burden, it also increases days living in the community, which tends to increase family burden, perhaps canceling out the benefit to families of reduced symptoms.

Conclusion: Clozapine has a small but significant effect on the experience of families of patients. This is the first study to demonstrate that effective pharmacotherapy may be of some benefit to families as well as to patients.

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Increasing attention has been paid in recent years to the strains experienced by families in which a member has severe mental illness and to the impact of such family experiences on patient outcomes.[1–4] The term *family burden*, although criticized by some as too general or too negative, has been increasingly used to refer to a broad range of experiences that include (1) providing support around routine community adjustment and coping with symptomatic behavior, (2) experiencing personal stress and dissatisfaction as a result of these efforts, (3) worrying about the safety and well-being of the affected family member, and (4) having to take time away from work or household responsibilities to provide assistance to a family member with serious mental illness.[5] Studies have shown that substantial family burden is experienced both by families who do not live with their mentally ill member and by those who do[6] and that the degree of burden increases with both clinical severity and family members' belief that the patient can control his or her behavior.[4]

As managed care and other cost-cutting efforts reduce the availability of inpatient care for people with severe mental illness,[7,8] responsibility for managing both routine daily care and acute exacerbations for people with severe mental illness increasingly falls on family members and other unpaid caregivers. If managed care initiatives, new medications, or innovative psychosocial treatments such as Assertive Community Treatment, for example, successfully reduce hospital use and therefore save inpatient expenditures, it is important to determine whether the overall burden or cost of care has been reduced or merely redistributed away from the health care system and onto families who must spend increasing amounts of time, economic resources, and emotional energies on the care of their family member.

While many recent studies have identified clinical and sociological factors that influence family burden,[4,5,9] there have been few reports on the impact of newer pharmacologic or psychosocial treatments on family burden.[2] Over the past 10 years, novel atypical antipsychotic medications such as clozapine and, to a lesser extent, risperidone, olanzapine, and quetiapine have been shown in randomized prospective clinical trials to be significantly more ef-

ficacious than conventional antipsychotic medication, to have markedly fewer extrapyramidal side effects, and, in some instances, to reduce hospital utilization.[10–14] In a few studies, these medications seem to result in enhanced participation in psychosocial treatment and improved quality of life.[11–15] These findings raise the possibility that novel antipsychotic medications may also have a notable effect of reducing family burden.

This study examines data on family burden from participants in a 12-month randomized clinical trial of clozapine and haloperidol that demonstrated significant advantages of clozapine as compared with haloperidol in reducing symptoms, side effects, and hospital utilization and improving quality of life.[5] In the current study, we first seek to determine whether patient factors (involving both clinical status and physical proximity to their families) that are affected by clozapine are associated with increased or decreased family burden and whether clozapine significantly reduces family burden compared with haloperidol.

METHOD

Data for this study are from a double-blind trial in which patients at 15 Veterans Affairs (VA) medical centers were randomly assigned to clozapine or haloperidol and treated for 12 months.

Entry Criteria

Hospital use criteria. Trial eligibility was limited to patients with treatment-refractory schizophrenia and a history of high inpatient use, defined as 30 to 364 days of hospitalization for schizophrenia during the previous year.

Clinical criteria. Patients were required to meet 4 clinical eligibility criteria: (1) DSM-III-R diagnostic criteria for schizophrenia on the Semistructured Clinical Interview for Diagnosis[16]; (2) refractoriness criteria that included persisting psychotic symptoms despite adequate treatment trials involving 2 different neuroleptic drugs at dosages equivalent to or greater than 1000 mg/day of chlorpromazine for at least 6 weeks, or lower dosage if the patient was unable to tolerate 1000 mg/day of chlorpromazine equivalents; (3) symptom severity criteria that included a total score on the Brief Psychiatric Rating Scale (BPRS)[17] of at least 45, a minimum score on the Clinical Global Impressions-Severity scale (CGI-S) of at least 4 (moderately ill),[18] BPRS scores of at least 4 (moderate) on 2 of the following 4 items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content; and (4) criteria of serious social dysfunction for the previous 2 years.

After providing written informed consent to participate in the study and completing baseline assessments, patients were randomly assigned to a treatment condition, and treatment was initiated.

Treatment

The protocol required weekly clinic visits after random assignment to double-blind treatment with either clozapine (100–900 mg/day) or haloperidol (5–30 mg/day). Haloperidol-treated patients also received benztropine mesylate (2–10 mg/day) for prophylactic control of extrapyramidal side effects, and clozapine patients received a matching benztropine placebo. Haloperidol patients participated in the same weekly blood counts required for clozapine treatment. The required clozapine blood monitoring protocol was followed. Therefore, all patients received their weekly prescription of medication only after their blood had been drawn for a white blood cell count.

A broad range of adjunctive psychotherapeutic and rehabilitative treatments were offered to study subjects and were standardized across participating sites with a case management system that used a structured treatment planning module based on a comprehensive menu of locally available services.[15]

Assessment of Family Burden

A brief questionnaire based on work by Tessler and colleagues[5,19] was developed to assess family burden and was used to generate 4 subscales. Because pilot testing suggested that respondents had difficulty responding to anchors based on the number of times they had various experiences of family burden each week, we used a series of Likert-type scales, described below.

Objective support. First, 16 questions were asked concerning practical community support provided by the family member to the patient in the previous month. Data were obtained on both concrete tasks (e.g., "During the past month, how much support did you give your son/daughter/relative with preparing meals, doing household chores, using leisure time, etc.?") and coping with illness (e.g., "How much support did you give for talk or threats of suicide and/or excessive use of drugs or alcohol?"). Respondents rated their answers on a 1-to-4 scale where 1 = none, 2 = little, 3 = some, and 4 = much (range, 16–64) ($\alpha = 0.86$).

Dissatisfaction. A second part of each of the 16 objective support questions asked, "How did this make you feel?" to which family members responded on a 1-to-3 scale where 1 = satisfied/content, 2 = resigned, and 3 = dissatisfied (range, 16–48) ($\alpha = 0.88$).

Burden of worry. A second set of 2 questions asked about how much worry the caregiver had experienced with respect to the patient in the past year and past month on a 1-to-4 scale where 1 = not at all, 2 = minor worry, 3 = some worry, 4 = great worry (range, 2–8) ($\alpha = 0.75$).

Days of missed work or household activity. A third set of 2 questions asked how many days in the past month the relative was absent from work or was unable to perform household responsibilities because of caring for the patient (range, 0–30).

The questionnaire was completed by interview (in person or by telephone). Family members were included in the study only if the patient identified a family care provider at baseline and the baseline questionnaire was completed. If the family member refused the baseline interview, another contact was sought. If the family member was interviewed at baseline but refused follow-up interviews, no substitution was made. Thus, the same person who was interviewed at baseline completed all follow-up interviews.

At baseline, the intercorrelations among subscales were moderately high for the objective support and dissatisfaction subscales (r = 0.69), and lower between those 2 subscales and the burden of worry subscale (r = 0.42, 0.43). These 3 subscales were only weakly correlated with nonproductive days for the family (r = 0.26–0.30).

Family Proximity

An item from the Lehman quality of life interview[20] was used to indicate family proximity; i.e., how frequently patients had contact with their families (daily, weekly, monthly, less than monthly).

Assessment of Clinical Status

Symptom outcomes were assessed with the structured clinical interview for the Positive and Negative Syndrome Scale (PANSS) for schizophrenia.[21] Social functioning and quality of life were evaluated with the Heinrichs-Carpenter Quality of Life Scale (QLS), a clinician-rated scale.[22] Medication side effects were assessed with the Simpson-Angus Scale for extrapyramidal side effects,[23] the Barnes Akathisia Scale for akathisia,[24] and the Abnormal Involuntary Movement Scale (AIMS) for tardive dyskinesia.[25]

In addition, 4 items from the Lehman scale[20] documented how satisfied the patients were with their family relationships on a 7-point scale ranging from delighted to terrible. These items were averaged to generate a subjective family quality-of-life score. All assessments were conducted at 6 weeks and at 3, 6, 9, and 12 months after randomization.

Statistical Analysis

First, we compared the subsample that had a participating family member with the subsample that lacked a participating family member to better characterize veterans with family members. Within the sample that included a participating family member, we then compared patients assigned to haloperidol and clozapine on key baseline measures.

Second, we used random effects regression models[26] to replicate our previous findings, which demonstrated clozapine's superiority to haloperidol,[11] in the subsample of patients with family members. We then analyzed the relationship between various clinical factors and family proximity and the 4 measures of family burden using data from all timepoints. Random effects models were used for these analyses because they accommodate correlations among repeated observations for the same individual.

Third, we determined whether there had been significant change in family burden measures over the year of the study, regardless of treatment assignment, again using random effects modeling to evaluate the effect of time on each measure of family burden.

Finally, we tested the significance of differences in change in family burden between treatment conditions. Specifically, we compared a model that included the effects of time, time-squared, and treatment condition on each measure of family burden. The quadratic term (time-squared) was included to address possible nonlinear effects that may occur in a long-term study and was included where it significantly improved the goodness-of-fit as evaluated by the –2 log likelihood test. The group by time interaction is the primary hypothesis of interest.

Because there is little room for improvement when there are low levels of family burden to begin with, we repeated this analysis with a subsample that demonstrated especially high levels of family burden at the baseline interview. This subsample was defined as having levels of family burden that were above the sample median.

All analyses were conducted using PROC MIXED from the statistical computer package SAS version 6.12 (SAS Institute, Cary, N.C.).

RESULTS

Sample

Approximately half of the patients participating in the study provided the name of a family care provider who also subsequently agreed to participate (221/423; 52%). Comparisons of demographic and clinical characteristics of patients who did and did not have a participating family member (Table 1) show that patients with a family member were younger, were less likely to be male, had a briefer duration of illness, and were less likely to be separated or divorced than patients without a participating family member. They also had significantly higher quality-of-life ratings, fewer hospital days in the previous year, and lower health care costs in the previous 6 months.

Within the group with a participating family member, there were no significant differences at baseline on sociodemographic or clinical measures between patients assigned to clozapine and patients assigned to haloperidol.

Family Contact During the Study

At baseline, when all patients were hospitalized, only 9% of patients reported seeing their families every day, 43% saw them weekly, and 48% less than weekly. At the 1-year follow-up, family contact was far more frequent, with 31% reporting seeing their families every day, 33%

weekly, and 36% less than weekly. There were no significant differences between treatment groups in the frequency of family contact at any timepoint.

Impact of Clozapine

In the family subsample that is the focus of this report, as in previous reports from the full sample that participated in the trial,[11,15] intention-to-treat analysis showed that patients treated with clozapine had significantly greater reduction than controls in symptoms ($t = –3.31$, $df = 378$, $p = .001$) and side effects ($t = –3.45$, $df = 369$, $p = .0006$), a nonsignificantly greater improvement in quality of life ($t = 2.52$, $df = 379$, $p = .11$), and significantly fewer hospital days during the last 6 months of the trial ($t = –1.97$, $df = 218$, $p < .05$).

Clinical Determinants of Family Burden

Analysis of determinants of family burden is presented in Table 2. The factors most consistently correlated with the 4 measures of family burden are symptom severity, days living in the community (i.e., not in the hospital), and frequency of family contact. Furthermore, akathisia was associated with greater dissatisfaction, and both akathisia and extrapyramidal side effects were associated with increased worry; higher patient quality of life as measured by the QLS (which emphasizes interpersonal relationships and adaptive functioning) was associated with reduced worry. Patient satisfaction with family relationships was associated with reduced days lost from work or from household responsibilities for the family member, but not with any of the other measures of family burden.

Changes in Family Burden and Impact of Clozapine

Significant reductions in family burden were observed across the duration of the study for objective support, dissatisfaction, and burden of worry, and marginally significant for days of missed work or household activity (Table 3).

A significant relationship between assignment to clozapine and change in family burden was observed for only 1 subscale, dissatisfaction ($\beta = –.46$, $t = 1.97$, $df = 632$, $p = .048$), but not for other measures. Although at baseline families of patients assigned to clozapine expressed more dissatisfaction with their support activities than families of patients assigned to haloperidol, they were less dissatisfied at 4 of 5 follow-up timepoints. However,

Table 1. Comparison of Patients With Family Burden Data and Patients Without Family Burden Data[a]

	No Family (N = 202)		Family (N = 221)			
Variable	N	%	N	%	χ^2	p Value
Gender						
Male	200	99.0	212	95.9	3.96	.05
Race						
White	133	65.8	147	66.5	5.69	.13
Black	64	31.7	61	27.6		
Hispanic	4	2.0	13	5.9		
Other	1	0.5	0	0.0		
Marital status						
Married	9	4.5	22	10.0	8.82	.032
Never married	111	55.0	133	60.2		
Separated/divorced	76	37.6	63	28.5		
Widowed	6	3.0	3	1.4		
Lifetime comorbidity						
Alcohol abuse	134	66.3	144	65.2	1.15	.28
Drug abuse	98	48.5	103	46.6	0.25	.61
	Mean	SD	Mean	SD	t test	p Value
Age, y	44.8	8.0	42.9	7.9	2.3	.02
Duration of illness, y	22.4	7.5	20.3	8.1	2.55	.01
Lehman Quality of Life Scale score	36.0	17.3	41.3	16.4	3.19	.002
PANSS total score	90.7	14.6	92.4	14.9	1.14	.25
Clinical Global Impressions-Severity score	4.7	0.7	4.8	0.7	0.87	.38
AIMS (tardive dyskinesia) score	3.7	4.3	3.6	3.7	0.409	.68
Simpson-Angus Scale score (extrapyramidal side effects)	5.2	5.1	5.1	4.2	0.87	.38
Barnes Akathisia Scale score	3.5	3.7	3.2	3.1	1.05	.29
Hospital days, previous year	78.0	52.4	66.0	46.7	2.39	.02
Health care costs (past 6 mo)	$28,469	$19,487	$24,897	$15,153	2.09	.04

[a]Abbreviations: AIMS = Abnormal Involuntary Movement Scale, PANSS = Positive and Negative Syndrome Scale.

Table 2. Clinical Correlates of 4 Measures of Family Burden[a]

Clinical Measure	Objective Support	Dissatisfaction	Worry Burden	Days Absent
Contact with family[b]	1.57***	0.70***	0.12	0.27*
PANSS score	0.07***	0.06***	0.02**	0.01
QLS score	–0.0009	–0.003	–0.02**	0.00
Simpson-Angus Scale score (pseudoparkinsonism)	0.07	0.08	0.04**	0.03
AIMS (tardive dyskinesia) score	0.00	0.02	0.01	0.02
Barnes Akathisia Scale score	0.00	0.14*	0.06*	–0.02
Days living outside of a hospital	0.01***	0.01***	0.003***	0.001
Family quality-of-life score	–0.03	–0.05	–0.004	–0.06**

[a]Abbreviations: AIMS = Abnormal Involuntary Movement Scale, PANSS = Positive and Negative Syndrome Scale, QLS = Quality of Life Scale. Regression coefficients from multiple random regression models (df = 768, 774, 774, 770) using data from all timepoints.
[b]Range from 4 (one per day) to 1 (less than once per month).
*p < .05.
**p < .01.
***p < .001.

Table 3. Measures of Family Burden Among Patients Assigned to Clozapine (N = 114) and Haloperidol (N = 107)

Burden and Group	Baseline Mean	Baseline SD	6 Weeks Mean	6 Weeks SD	3 Months Mean	3 Months SD	6 Months Mean	6 Months SD	9 Months Mean	9 Months SD	12 Months Mean	12 Months SD	Effect for Time[a] t	df	p	Effect for Time × Condition[b] t	df	p
Support burden																		
Haloperidol	25.8	8.0	22.7	6.5	23.5	6.5	23.5	7.6	23.3	6.6	24.3	6.5	2.7	223	.008	1.2	641	.23
Clozapine	25.7	9.4	21.9	5.7	23.3	7.7	23.9	7.2	23.2	6.3	23.2	6.3						
Dissatisfaction																		
Haloperidol	20.8	6.2	18.7	5.7	19.9	5.7	18.6	4.9	19.3	5.6	18.9	5.2	–3.7	223	.0003	1.97	632	.048
Clozapine	21.8	7.4	18.4	4.5	18.7	5.1	18.9	4.3	18.4	3.8	18.7	4.3						
Worry burden																		
Haloperidol	9.7	2.9	9.3	2.9	9.4	2.9	9.0	2.8	8.6	2.5	8.6	2.5	8.6	223	.0001	–.065	641	.52
Clozapine	9.7	2.7	9.1	2.3	8.9	2.5	8.6	2.4	8.1	2.3	7.9	2.3						
Days absent																		
Haloperidol	1.4	4.1	1.5	6.1	0.8	2.6	0.8	3.5	0.8	4.0	1.0	4.0	1.8	223	.08	0.50	641	.62
Clozapine	0.8	2.5	0.3	1.3	0.5	1.9	0.2	1.0	0.5	1.9	0.2	1.0						

[a]Separate random effects model evaluating change over time.
[b]Separate random effects model evaluating interaction of time and treatment condition.

these differences were small—typically less than 1 point (5%). It is perhaps also notable that although distress due to worrying about the patient was the same for both treatment groups at baseline, it was lower for the clozapine group at each successive timepoint; however, this difference did not reach statistical significance.

Although the sample sizes were smaller, findings were somewhat more consistent in the subsample whose baseline levels of family burden were greater than the median. In this subsample, treatment by time effects were marginally significant for both objective support ($t = –1.80$, $df = 253$, $p = .07$) and dissatisfaction ($t = –1.72$, $df = 264$, $p = .09$).

DISCUSSION

The analyses presented here demonstrate that, as suggested by other studies,[4] clinical factors, especially severity of symptoms and, to a lesser extent, overall quality of life and extrapyramidal side effects, are associated with increased family burden. Indicators of family proximity such as frequency of patient-family contact and days out of the hospital are also associated with increased burden. This last observation is important because it suggests that, other things being equal, as inpatient lengths of stay decline and patients are discharged earlier and with higher symptom levels, the burden on their families is likely to increase. Strategies that improve the efficiency of the service system thus seem to be implemented at the expense of increased effort and distress for families.

Direct analysis of the impact of clozapine on family burden showed a small but significant difference on 1 of 4 measures. Family members of patients treated with clozapine showed a slightly greater reduction in dissatisfaction than controls. However, if we make a Bonferroni correction for the fact that we evaluated 4 measures of family burden, thus lowering our α threshold to .0125, this finding is no longer statistically significant.

The weakness of the relationship between clozapine and reduced family burden may be due to the fact that some of clozapine's benefits are likely to increase family burden whereas others are likely to decrease it. Since clozapine is associated with both reduced symptoms, which may reduce family burden, and increased days out of the hospital, which may increase burden, its net effect could approach zero because these 2 factors cancel each other out by both lowering symptoms and increasing family responsibility.

It is also possible that the magnitude of clozapine's impact on symptoms, only a 5% to 10% improvement in mean symptom levels in this study, is insufficient to produce a substantial reduction in family burden. One of the major questions that remains unanswered in psychiatric effectiveness research concerns how much symptom improvement is clinically meaningful. A previous analysis of data from this study suggested that the improvement observed here is clinically detectable on average,[27] but a barely detectable improvement might not be sufficient to change the level of family burden.

A third possibility is that medications may affect family burden only in families that have high levels of burden. We repeated the analyses with the subsample of subjects whose baseline level of family burden was greater than the median, with marginally significant but similar results to those observed with the full sample.

Several methodological limitations must also be noted. First, since random assignment was not stratified across patient subsamples according to whether they had a family participant, it is possible that our findings are confounded by unmeasured differences between patients assigned to clozapine and haloperidol within the subsample with participating family members. Furthermore, since detailed data are not available on the identity of the family participants, it is possible that the groups had quite different family relationships to start with. Although this possibility cannot be ruled out entirely, it seems unlikely, be-

cause the group with participating family members is a subsample of a randomized trial, and no differences were observed between the groups in frequency of family contact at baseline, in average patient-rated quality of family relationships, or in any patient characteristic.

Second, because this was an opportunistic study of patients recruited into a randomized clinical trial, it involves a highly selected patient sample that may not include families with the greatest experience of family burden. Clozapine might have a more beneficial effect in families for whom burden is an especially serious problem.

Third, our measures may have been insensitive to important areas of change, and there may have been other, unmeasured, benefits of clozapine for family members, such as the instillation of increased hope. Furthermore, these measures were administered to only 1 family member (who remained consistent during the course of the trial), and this family member may have lacked knowledge about some areas of family experience.

CONCLUSION

This study is the first to suggest that novel antipsychotic medications may have beneficial effects on family members as well as patients, although the effects were small in magnitude and affected only 1 of 4 measures of family burden.

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

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