Effects of Atypical Antipsychotics on the Syndromal Profile in Treatment-Resistant Schizophrenia

Jean-Pierre Lindenmayer, M.D.; Pal Czobor, Ph.D.; Jan Volavka, M.D., Ph.D.; Jeffrey A. Lieberman, M.D.; Leslie Citrome, M.D., M.P.H.; Brian Sheitman, M.D.; Joseph P. McEvoy, M.D.; Thomas B. Cooper, M.A.; and Miranda Chakos, M.D.

Background: There has been considerable support for the observation that atypical antipsychotics have a broader range of therapeutic effects than traditional antipsychotics. We are exploring whether this expanded clinical efficacy can also be seen in patients with treatment-resistant schizophrenia.

Method: The subjects were 157 treatment-resistant inpatients diagnosed with DSM-IV schizophrenia or schizoaffective disorder. They were randomly assigned to treatment with clozapine, olanzapine, risperidone, or haloperidol in a 14-week double-blind trial and rated with a standard measure of clinical antipsychotic efficacy (Positive and Negative Syndrome Scale [PANSS]). Factor analysis at baseline and endpoint together with changes in 5 PANSS-derived factors were examined. Data were gathered from June 1996 to December 1999.

Results: The underlying PANSS factor structure, as indicated by the factor loadings, was essentially identical at baseline and endpoint. At baseline, the excitement factor was followed by the positive, negative, cognitive, and depression/anxiety factors, explaining 49.4% of the total variance. At endpoint, the positive factor was followed by the negative, excitement, cognitive, and depression/anxiety factors, explaining 55.5% of the total variance. The endpoint data indicated statistically significant ($p < .05$) improvements over time on the positive factor for all 3 atypicals, but not for haloperidol. The negative factor showed significant improvement for clozapine and olanzapine, with significant worsening for haloperidol. Clozapine, olanzapine, and risperidone were superior to haloperidol on the negative factor, while clozapine was also superior to risperidone. The cognitive factor showed significant improvement for all atypicals, as did the depression/anxiety factor. Only clozapine showed improvement on the excitement factor and was superior to both haloperidol and risperidone.

Conclusions: Treatment with atypical antipsychotics did not substantially change the underlying PANSS 5-factor structure. However, antipsychotic treatment with all 3 atypical medications was associated with significant improvements on 3 of 5 syndromal domains (positive, cognitive, and depression/anxiety) of schizophrenia. Clozapine and olanzapine also showed improvement on the negative factor. Only clozapine was associated with improvement on the excitement domain. This finding confirms that atypicals are associated with improvement of an expanded spectrum of symptoms in treatment-resistant patients.

(J Clin Psychiatry 2004;65:551–556)

Received July 3, 2003; accepted Oct. 6, 2003. *From the Nathan Kline Institute, Orangeburg, N.Y. (Drs. Lindenmayer, Czobor, Volavka, and Citrome and Mr. Cooper); New York University, New York (Drs. Lindenmayer, Czobor, Volavka, and Citrome and Mr. Cooper); Manhattan Psychiatric Center, Wards Island, N.Y. (Dr. Lindenmayer); the University of North Carolina, Chapel Hill (Drs. Lieberman, Sheitman, and Chakos); Dorothea Dix Hospital, Raleigh, N.C. (Drs. Sheitman and Chakos); Duke University, Durham, N.C. (Dr. McEvoy); John Umstead Hospital, Butner, N.C. (Dr. McEvoy); and New York State Psychiatric Institute at Columbia University, New York, N.Y. (Mr. Cooper).*

Grant R10 MH53550 from the National Institute of Mental Health, Bethesda, Md., provided the principal support for this project. Janssen Pharmaceutica Research Foundation, Titusville, N.J.; Eli Lilly and Company, Indianapolis, Ind.; Novartis Pharmaceuticals Corporation, East Hanover, N.J.; and Merck and Co., Inc., West Point, Pa., provided medications. Eli Lilly and Company contributed supplemental funding. However, overall experimental design, data acquisition, statistical analyses, and interpretation of the results were implemented with no input from any of the pharmaceutical companies.

Financial disclosure appears at the end of this article.

The authors acknowledge Linda Kline, R.N., M.S., C.S., who was the chief coordinator of the entire project.

Corresponding author and reprints: Jean-Pierre Lindenmayer, M.D., Manhattan Psychiatric Center, Wards Island, NY 10035 (e-mail: lindenmayer@nki.rfmh.org).

There has been considerable support for the observation that atypical antipsychotics have a broader range of therapeutic effects than traditional antipsychotics. Specifically, they appear to be superior in terms of improvement of negative, cognitive, and affective symptoms in patients with schizophrenia.[1–7] However, most of these findings have been derived from studies of patients who were predominantly treatment responsive. We were interested to know whether this expanded clinical efficacy is also seen in patients with treatment-resistant schizophrenia. A related question is whether atypical antipsychotics change the underlying syndromal structure of schizophrenic phenomenology in such patients. The use of factor analytically derived syndromal domains of psychopathology is a helpful strategy to examine both of these questions. Lindenmayer et al.[8] have described a 5-factor model based on a factor analytic study using the Positive and Negative Syndrome Scale (PANSS),[9] resulting in negative, positive, cognitive, excitement, and depression/anxiety components. Other authors have found a comparable PANSS-derived multifactorial structure using confirmatory factor analyses conducted on different samples of patients with schizophrenia.[10–12] This 5-factor model has also been exten-

sively validated in a number of studies using demographic, course, and neurocognitive variables.[12–14]

The present study used data from a prospective, double-blind, randomized 14-week trial in which 157 patients with DSM-IV schizophrenia or schizoaffective disorder and prior documented treatment resistance were assigned to clozapine, olanzapine, risperidone, or the typical comparator haloperidol.[15] We first conducted 2 PANSS-based factor analyses, one at baseline and the other at endpoint of the trial, including all patients randomly assigned to receive one of the 4 antipsychotic medications, and we examined changes in the underlying factor structure between baseline and endpoint. We then investigated changes in any of the 5 syndromal domains associated with the 4 antipsychotic medications.

METHOD

The data included in the present study are based on a prospective, double-blind, randomized 14-week trial in which inpatients at 4 psychiatric state hospitals (2 in New York and 2 in North Carolina) were randomly assigned to clozapine, olanzapine, risperidone, or haloperidol (for details, see Volavka et al.[15]). All subjects met DSM-IV criteria for schizophrenia or schizoaffective disorder and were between the ages of 18 and 60 years, with a minimum PANSS severity score of at least 60 at baseline. Treatment resistance was defined by 2 criteria, both of which had to be present at baseline: (1) persistent positive symptoms (hallucinations, delusions, or marked thought disorder) after treatment for at least 6 contiguous weeks, presently or documented in the past, with 1 or more typical antipsychotics at dosages equivalent to or greater than 600 mg/day of chlorpromazine, and (2) a poor level of functioning over the past 2 years. After complete description of the study to the subjects, written informed consent was obtained, conforming to each institution's review board guidelines (for further details, see Volavka et al.[15]). Data were gathered from June 1996 to December 1999.

The trial consisted of period 1 (8 weeks, escalation and fixed dose) and period 2 (6 weeks, variable dose). During period 1, the doses of clozapine, olanzapine, risperidone, and haloperidol were escalated to 500, 20, 8, and 20 mg/day, respectively, and remained fixed until the end of period 1. During period 2, antipsychotic dose was allowed to vary within the following ranges (in mg/day): clozapine, 200 to 800; olanzapine, 10 to 40; risperidone, 4 to 16; haloperidol, 10 to 30. The mean ± SD dose levels (mg/day) achieved at the end of period 2 (last observation carried forward [LOCF]) were 526.6 ± 140.3 for clozapine, 30.4 ± 6.6 for olanzapine, 11.6 ± 3.2 for risperidone, and 25.7 ± 5.7 for haloperidol.

Concomitant medications were restricted to benztropine, propranolol, lorazepam, diphenhydramine hydrochloride, and chloral hydrate. All subjects randomly assigned to haloperidol received prophylactic benztropine, 2 mg b.i.d. Subjects randomly assigned to risperidone, olanzapine, or clozapine received benztropine placebo. Treating physicians were permitted to prescribe additional benztropine, which resulted in the substitution of actual benztropine for placebo, up to a maximum benztropine dose of 6 mg/day. No other adjunctive psychotropics were allowed. Trained and blinded raters performed all clinical research assessments. The PANSS total score was the principal measure of efficacy. The interrater reliability, estimated by intraclass correlation coefficient for the PANSS total score for paired ratings at the 4 sites, ranged from 0.93 to 0.98.

To examine changes in the underlying structure of the psychopathologic profile, a principal components factor analysis was conducted using the 30 PANSS items at both baseline and at endpoint. After orthogonal factor rotation, factors retained were those with Eigenvalues greater than or equal to 1.50 together with items with factor loadings above 0.40, resulting in 5 interpretable clusters of highly loading symptoms at both timepoints. Internal consistency for each of the component scores was determined by Cronbach alpha. Factor scores were calculated by averaging the individual contributing item scores.

To examine the effect of each antipsychotic medication (clozapine, olanzapine, risperidone, and haloperidol) on the 5 syndromal domains, we used random regression hierarchical linear modeling (HLM).[16–18] Repeated assessments of syndromal severity over time (i.e., PANSS factor scores at all timepoints for all subjects) served as the dependent variable. The trajectory of syndrome severity in each person was represented by 2 parameters: the trajectory's initial value (intercept) and its slope. The 2 independent factors were treatment group and time. Treatment group served as the between-subject factor. Time (in weeks) from baseline was used as the within-subject factor. Interaction between treatment group and time was included in the model.

The analysis had 2 principal objectives: (1) to assess whether a significant change over time occurred in any of the 4 treatment groups (i.e., the slope of the syndrome trajectory is significantly different from zero; this analysis is analogous to the traditional test of pre-post difference) and (2) to test whether there is a slope difference among the 4 medication groups in syndrome change trajectories over time; this analysis is analogous to the traditional test of interaction between time and treatment effects. The time effect and the slope difference (interaction) effect were tested using the F statistic. If a significant effect was detected, post hoc analyses were performed to examine the direction of changes (time effect) or the differences in change over time among the treatment groups (interaction effect). Post hoc analyses were based on linear functions (contrast variables) of parameter estimates obtained from the overall HLM model.

Table 1. Positive and Negative Syndrome Scale Factor Loadings at Baseline and Endpoint[a]

Factor	Baseline	Endpoint
Excitement	Factor B1	Factor E3
Excitement	0.49	0.56
Hostility	0.92	0.86
Uncooperativeness	0.67	0.68
Poor impulse control	0.74	0.81
Positive	Factor B2	Factor E1
Delusions	0.88	0.90
Hallucinatory behavior	0.46	0.48
Grandiosity	0.72	0.70
Unusual thought content	0.88	0.88
Suspiciousness/persecution	0.47	0.57
Negative	Factor B3	Factor E2
Blunted affect	0.72	0.64
Emotional withdrawal	0.76	0.85
Poor rapport	0.67	0.63
Passive/apathetic social withdrawal	0.78	0.83
Lack of spontaneity	0.66	0.52
Active social avoidance	0.59	0.66
Cognitive	Factor B4	Factor E4
Conceptual disorganization	0.79	0.75
Difficulty with abstract thinking	0.45	0.48
Disorientation	0.52	0.41
Poor attention	0.76	0.76
Preoccupation	0.49	0.61
Depression/anxiety	Factor B5	Factor E5
Anxiety	0.76	0.54
Guilt feelings	0.45	0.44
Tension	0.51	0.37
Depression	0.67	0.47

[a]Baseline N = 157, endpoint N = 91. Factors B1–B5 = factors 1 to 5 at baseline, factors E1–E5 = factors 1 to 5 at endpoint.

RESULTS

Demographic and Basic Descriptive Data

Data from 157 subjects are included in the present analyses. Forty subjects were assigned to clozapine; 39, to olanzapine; 41, to risperidone; and 37, to haloperidol. Their diagnoses were schizophrenia (N = 135, 86%) or schizoaffective disorder (N = 22, 14%). There were 133 men (84.7%). The mean (SD) age was 40.8 (9.2) years, mean duration of illness was 19.5 (8.4) years, and mean number of hospitalizations was 10.5 (8.3). There were no statistically significant differences among treatment arms on any demographic variable. The 14-week study was completed by 91 (58%) of the 157 subjects. The differences in the attrition rates among the 4 treatment groups were not statistically significant (log-rank test $\chi^2 = 1.52$, df = 3, p = .68). Reasons for discontinuation can be found in the original report.[15]

Factor Analysis

Separate principal component analyses at baseline and at endpoint resulted in 5 factors (negative, positive, cognitive, excitement, and depression/anxiety) with 49.4% and 55.5% of explained total variance, respectively. The excitement component emerged as factor 1, accounting for 14.4% (Eigenvalue = 8.63) of the baseline variance, followed by the positive factor, which explained 12.8% (Eigenvalue = 3.77) of the variance, and the negative factor, which explained 10.3% (Eigenvalue = 2.26) of the variance. The cognitive and depression/anxiety components emerged as factors 4 and 5, accounting for 7.9% (Eigenvalue = 1.90) and 4.0% (Eigenvalue = 1.75) of the variance, respectively. The endpoint PANSS factor analysis resulted in the same 5 factors with a total variance of 55.5%, but the respective factor variances differed slightly from those at baseline, resulting in different hierarchical positions. The largest amount of variance, 15.5% (Eigenvalue = 6.83), was explained by the positive component (factor 1), followed by the negative factor (factor 2), which resulted in 14.2% (Eigenvalue = 4.34) of the variance. The third factor, excitement, accounted for 13.5% (Eigenvalue = 2.61) of the variance. The cognitive component (factor 4) and the depression/anxiety component (factor 5) resulted in 9.3% (Eigenvalue = 2.50) and 3.0% (Eigenvalue = 1.70) of the variance, respectively. The items included in each factor are listed in Table 1. The item composition of the different factors at endpoint was very similar as compared with baseline (see Table 1). Cronbach alpha revealed good internal reliability of all 5 factors at baseline (range, 0.69–0.85) and at endpoint (range, 0.63–0.85). The negative component consistently revealed the highest internal reliability, although all components demonstrated adequate reliability.

Antipsychotic Efficacy as Measured by the 5 PANSS Factors

The baseline, endpoint, and difference values of the PANSS factor score means and standard deviations (LOCF) for each medication group are shown in Table 2.

The HLM analysis of the data for the 14-week trial indicated a statistically significant overall change over time for each of the 5 efficacy measures (for the positive factor score: $F = 17.9$, df = 1,156; $p < .0001$; negative factor: $F = 35.7$, df = 1,156; $p < .0001$; excitement factor: $F = 39.0$, df = 1,156; $p < .0001$; cognitive factor: $F = 21.7$, df = 1,156; $p < .0001$; depression/anxiety factor: $F = 79.1$, df = 1,156; $p < .0001$).

The 14-week data indicate statistically significant improvements by time on the positive factor for all atypicals, but not for haloperidol. The negative factor showed significant improvement for clozapine and olanzapine and significant worsening for haloperidol, while no change was seen for the risperidone group. Only clozapine significantly improved the excitement factor. The cognitive factor showed significant improvement for all 3 atypicals, with olanzapine showing superiority over haloperidol. Similarly, the depression/anxiety factor was significantly improved by all 3 atypicals.

HLM tests for fixed effects were used to compare the effects of the 4 treatments. The measures of efficacy of

Table 2. Positive and Negative Syndrome Scale Factor Scores: Baseline, Endpoint, and Mean Differences[a]

Factor	Baseline, Mean ± SD	Endpoint, Mean ± SD	Change, Mean ± SD	t	p
Positive					
Clozapine	4.07 ± 1.20	3.80 ± 1.27	0.28 ± 1.06	–2.32	.02
Haloperidol	3.88 ± 0.91	3.54 ± 1.11	0.34 ± 0.92	–1.80	.07
Olanzapine	4.12 ± 1.11	3.57 ± 1.30	0.55 ± 1.06	–3.14	.001
Risperidone	3.71 ± 0.93	3.40 ± 1.03	0.31 ± 0.92	–2.05	.04
Negative					
Clozapine	3.31 ± 0.93	3.08 ± 0.88	0.23 ± 1.03[b]	–3.54	.0004
Haloperidol	2.76 ± 0.86	2.94 ± 0.97	–0.18 ± 0.69	2.17	.03
Olanzapine	2.66 ± 0.74	2.46 ± 0.94	0.19 ± 0.93[c]	–2.03	.04
Risperidone	2.94 ± 1.06	2.98 ± 1.07	–0.04 ± 1.04[d]	–0.46	NS
Excitement					
Clozapine	2.57 ± 1.21	2.24 ± 1.03	0.33 ± 1.37[e]	–2.64	< .008
Haloperidol	2.33 ± 0.92	2.60 ± 1.14	–0.27 ± 1.30	NS	NS
Olanzapine	2.14 ± 0.98	2.16 ± 1.40	–0.02 ± 1.18	NS	NS
Risperidone	2.27 ± 0.98	2.39 ± 1.26	–0.12 ± 1.31	NS	NS
Cognitive					
Clozapine	3.70 ± 0.82	3.46 ± 0.80	0.24 ± 0.79	–3.17	.001
Haloperidol	3.43 ± 0.71	3.22 ± 0.70	0.21 ± 0.67	–1.38	NS
Olanzapine	3.54 ± 0.85	3.07 ± 0.98	0.47 ± 0.72[f]	–4.40	.0001
Risperidone	3.32 ± 0.85	2.99 ± 0.98	0.34 ± 0.64	–3.58	.0004
Depression/anxiety					
Clozapine	2.38 ± 0.85	2.10 ± 0.78	0.28 ± 0.92	–2.00	.04
Haloperidol	2.58 ± 0.82	2.36 ± 0.76	0.23 ± 0.92	–1.25	NS
Olanzapine	2.42 ± 0.80	2.00 ± 0.69	0.42 ± 0.70	–3.17	.001
Risperidone	2.30 ± 0.90	2.22 ± 0.86	0.08 ± 0.92	–1.90	< .05

[a]Hierarchical linear analysis was performed to investigate change in syndromal severity over time and differences in change over time among medications. Group Ns were as follows: clozapine, N = 40; haloperidol, N = 37; olanzapine, N = 39; risperidone, N = 41.
[b]Clozapine > haloperidol: t = –4.01, p < .0001 and clozapine > risperidone: t = –2.19, p < .02.
[c]Olanzapine > haloperidol: t = –2.97, p < .003.
[d]Risperidone > haloperidol: t = –1.90, p < .05.
[e]Clozapine > risperidone: t = –2.11, p < .03 and clozapine > haloperidol: t = –2.48, p < .01.
[f]Olanzapine > haloperidol: t = –2.02, p < .04.

interest were the 5 PANSS factor scores for the entire 14-week trial. There was a statistically significant interaction between medication and time for the negative and excitement factors (negative, F = 35.72, df = 1,156; p < .0001; excitement, F = 39.07, df = 1,156; p < .001). This interaction indicated a general difference in efficacy among the 4 medications. To interpret this general difference, we performed 6 post hoc tests of specific differences between pairs of treatments.

Clozapine, olanzapine, and risperidone were superior to haloperidol on the negative factor, while clozapine was superior to risperidone (see Table 2). For the excitement factor, clozapine was superior to both haloperidol and risperidone. The positive, cognitive, and depression/anxiety factors did not show differential effects from the 3 atypicals.

DISCUSSION

We found that there were 5 independent, but not mutually exclusive, domains of psychopathology, measured as negative, positive, cognitive, excitement, and depression/anxiety components. This replicates our original PANSS 5-factor structure at baseline and at endpoint supporting the generalizability of the 5-factor model of schizophrenia.[8] We and others have demonstrated specific demographic, family history, neurocognitive, and neurologic correlates of these 5 components further supporting their validity.[14,19]

Factor analysis characterizes the qualitative nature of symptoms of the assessed disorder on one hand and the clustering into underlying syndromes of the manifest symptoms on the other hand. Each factor, through its item loadings and its explained variance, indicates the breadth of its contribution to the overall psychopathology. Severity of factors is expressed by averaging the individual contributing item scores.

Five clusters of symptoms that prominently contributed to the phenomenology of treatment-resistant schizophrenia were delineated in the present study. In the present sample, the excitement factor was identified as component 1. This factor was identical to the excitement factor in the original study[15] and was composed of excitement, hostility, uncooperativeness, and poor impulse control, reflecting a significant behavioral dyscontrol syndrome at baseline. The predominance of excitement symptoms at baseline reflects these patients' poor prior antipsychotic response and may also confirm the appropriateness of our inclusion criteria. White et al.[20] similarly have demonstrated that excitement symptoms characterized patients who could not be discharged from the hospital. The positive component represented the second component at baseline, and its item composition was essentially identical to the original 5-factor model. The negative component, found presently in the third position, also contained the same items as in the original study. The items included in the cognitive factor are comparable to those in our original study as well, but were augmented here by the additional item of preoccupation at both timepoints. We did not include in the present cognitive factor the item "disturbance of volition" as we did in the original study for the following reasons. Its overall rating was low and was performance related, as it showed a high correlation with scores on poor attention. In addition, it was not correlated with the other items in this factor. As in our previous study, most of the items of the cognitive factor reflect schizophrenic thought disorder and cognitive disorganization. This domain has also been consistently recognized in Scale for the Assessment of Positive Symptoms/Scale for the Assessment of Negative Symptoms–derived factor analyses and identified as disorganization.[21,22] The additional item of preoccupation may also be an expression of thought pathology reflecting the classical autistic withdrawal. The fifth factor was an independent depression/anxiety factor, which did not

overlap with negative symptoms, pointing to the validity of this affective symptom domain in schizophrenia. This factor did not contain "preoccupation" or "somatic concern," but was otherwise identical to the corresponding factor in the original study. Both the cognitive and depression/anxiety components retained their respective positions within the total psychopathology after treatment.

The finding that certain items loaded on different factors in the present analyses as compared with the original PANSS factor loadings[8] supports the view that PANSS factors cannot be considered invariant, in that they may vary in different patient populations, disease states, and treatment timepoints.[23] We chose to conduct 2 new factor analyses (baseline and endpoint) rather than to use previously defined factors because we were specifically interested in the effects of atypical antipsychotics on syndromal profiles of treatment-refractory patients.

In comparing the PANSS factor structure at baseline and endpoint after 14-week double-blind treatment, no significant changes were seen in the PANSS factor structure. After treatment, the position of the excitement component changed to third, representing a much smaller contribution to the total psychopathology, pointing to a therapeutic effect on overt behavioral dyscontrol symptoms. Indeed, a specific antihostility effect has been demonstrated for clozapine in a separate analysis of the present data,[24] as well as by others,[25–28] and for risperidone.[29]

The stability of the PANSS factor structure was also seen by Marder et al.[1] after 8-week treatment with risperidone and haloperidol. Furthermore, when the syndrome profile of patients treated with atypicals is compared with that of patients treated in an earlier study with typical antipsychotics,[13] it is remarkable to see the high degree of similarity in the resulting symptom profiles.

Examining the quantitative effects of the 4 antipsychotic medications on the 5 factor scores, we were able to confirm and expand the effects reported in the parent study.[15] We found that all 3 atypical medications were associated with significant improvements in the positive, cognitive, and depression/anxiety domains of schizophrenia. In contrast, haloperidol had only a marginally significant effect on the positive domain and worsened the negative domain. The results for haloperidol reflect the inclusion criteria of the study, which called for patients in whom treatment with conventional antipsychotics had failed. Thus, we included patients who had failed to respond to haloperidol.

While all 3 atypicals had comparable effects on the positive domain, there were differential effects in other domains. Both clozapine and olanzapine improved the negative symptom domain in a similar manner, while risperidone did not. Clozapine was superior to risperidone in this domain. The lack of effect on the negative factor by risperidone may have been contributed by the relatively high risperidone dose used in this study. Only clozapine significantly improved the excitement domain. Clozapine was also superior to risperidone and haloperidol in the excitement domain. This finding further points to clozapine's efficacy for patients having difficulty with aggression and impulse control. In addition, it was remarkable that even in patients with prior treatment resistance, we were able to demonstrate effects by all 3 atypical antipsychotics on the cognitive and depression/anxiety domains; this points to a remaining potential of therapeutic plasticity in these areas in the present sample of patients when treated with atypical antipsychotics. Using formal neurocognitive testing, Bilder et al.[30] reported significant effects on neurocognitive test performance in the same patient sample with olanzapine and risperidone, and somewhat less with clozapine, but not with haloperidol.

Since we did not want to risk the possibility of undertreatment in this severely ill population, we used high doses of all medications. Our target dose of risperidone for the fixed-dose period was 8 mg/day; this was the modal daily dose for adult inpatients in New York State hospitals at the time when our study was designed.[15] While we did not find additional benefits with the dose increases of risperidone, clozapine, and haloperidol during the variable-dose period of the study (weeks 9–14), there seemed to be some additional improvement with the elevation of the olanzapine dose. However, the dose of risperidone during this second period of the study was probably too high, representing a limitation of our study.

A similar pattern of expanded syndromal effects was reported in treatment-responsive patients in a reanalysis of the North American risperidone data by Marder et al.[1]; however, the magnitude of reported changes was much larger given the treatment-responsive nature of the sample. The effects in the present treatment-refractory sample were much more modest and their clinical significance is limited. However, we conclude that chronic patients with a history of treatment resistance can still show a pattern of modest expanded syndromal response with atypical antipsychotics in the areas of negative, excitement, cognitive, and affective symptoms without changing the underlying syndromal structure.

Drug names: benztropine (Cogentin and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), diphenhydramine (Benadryl and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), propranolol (Inderal, Innopran, and others), risperidone (Risperdal).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, olanzapine is not recommended by the U.S. Food and Drug Administration to be administered over 20 mg daily.

In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information

received is as follows: Dr. Lindenmayer is a consultant for Janssen and Bristol-Myers Squibb; has received grant/research support from Janssen, Bristol-Myers Squibb, Eli Lilly, and AstraZeneca; has received honoraria from Novartis and Pfizer; and is on the speakers/advisory boards for Novartis, Janssen, Abbott, and Bristol-Myers Squibb. Dr. Volavka is a consultant for GlaxoSmithKline and Bristol-Myers Squibb; has received honoraria from Eli Lilly, GlaxoSmithKline, and Bristol-Myers Squibb; and is on the speakers/advisory board for Eli Lilly. Dr. Lieberman is a consultant for Upjohn Pharmacia, Bristol-Myers Squibb, Novartis, Eli Lilly, Janssen, Pfizer, and AstraZeneca; has received grant/research support from Upjohn Pharmacia, Bristol-Myers Squibb, Novartis, Eli Lilly, Janssen, Pfizer, Hoechst, and AstraZeneca; and is on the speakers bureaus for Eli Lilly and Janssen. Dr. Citrome is a consultant for Abbott, Bristol-Myers Squibb, Eli Lilly, and Pfizer; has received grant/research support from Abbott, Bristol-Myers Squibb, Eli Lilly, Janssen, and Novartis; has received honoraria from Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Novartis, and Pfizer; and is on the speakers/advisory boards for Abbott, Bristol-Myers Squibb, Eli Lilly, Novartis, and Pfizer. Dr. McEvoy has received grant/research support from Janssen and Eli Lilly and has received honoraria from Janssen. Drs. Sheitman, Czobor, and Chakos and Mr. Cooper have no significant financial relationships to disclose relative to the presentation.

REFERENCES

1. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997;58:538–546
2. Sanger TM, Lieberman JA, Tohen M, et al. Olanzapine versus haloperidol treatment in first-episode psychosis. Am J Psychiatry 1999;156:79–87
3. Tollefson GD, Beasley CM Jr, Tamura RN, et al. Blind, controlled, long-term study of comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. Am J Psychiatry 1997;154:1248–1254
4. Tollefson GD, Sanger TD, Lu Y, et al. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. Arch Gen Psychiatry 1998;55:250–258
5. Arvanitis LA, Miller BG, and the Seroquel Trial 13 Study Group. Multiple and fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol Psychiatry 1999;44:233–246
6. Csernansky J, Mahmoud R, Brenner R, for the Risperidone-USA-79 Study Group. A comparison of risperidone and haloperidol for the prevention of relapse with schizophrenia. N Engl J Med 2002;346:16–22
7. Goff D, Posever T, Herz L, et al. An exploratory haloperidol-controlled dose-fixing study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorders. J Clin Psychopharmacol 1998;18:296–304
8. Lindenmayer JP, Bernstein-Hyman R, Grochowski S. Psychopathology of schizophrenia: initial validation of a five factor model. Psychopathology 1995;28:22–31
9. Kay SR, Opler LA, Fiszbein A. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
10. Lépine JP, Piron JJ, Chapatot E. Factor analysis of the PANSS in schizophrenia patients. In: Stefanis CN, Soldatos CR, Rabavilas AD, eds. Psychiatry Today: Accomplishments and Promises. Amsterdam, the Netherlands: Excerpta Medica; 1989:828
11. Bell M, Lysaker P, Beam-Goulet J, et al. Five-component model of schizophrenia: assessing the factorial invariance of the Positive and Negative Syndrome Scale. Psychiatry Res 1994;52:295–303
12. White L, Harvey P, Opler L, et al, and the PANSS Study Group. Empirical assessment of the factorial structure of clinical symptoms in schizophrenia. Psychopathology 1997;30:263–274
13. Lindenmayer JP, Grochowski S, Hyman RB. Five factor model of schizophrenia: replication across samples. Schizophr Res 1995;14:229–234
14. Potkin SG, Anand R, Alphs L, et al. Neurocognitive performance does not correlate with suicidality in schizophrenic and schizoaffective patients at risk for suicide. Schizophr Res 2003;59:59–66
15. Volavka J, Czobor P, Sheitman B, et al. Clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia and schizoaffective disorder. Am J Psychiatry 2002;159:255–262
16. Lindley DV, Smith AFM. Bayes estimates for the linear model. J R Stat Soc 1972;series B 34:1–41
17. Bryk AS, Raudenbush SW. Hierarchical Linear Models: Applications and Data Analysis Methods. Newbury Park, Calif: Sage Publications; 1992
18. Gibbons RD, Hedeker D, Waternaux C, et al. Random regression models: a comprehensive approach to the analysis of longitudinal psychiatric data. Psychopharmacol Bull 1988;24:438–443
19. Lindenmayer JP, Bernstein-Hyman R, Grochowski S. Five-factor model of schizophrenia: initial validation. J Nerv Ment Dis 1994;182:631–638
20. White L, Parella M, McCrystal-Simon J, et al. Characteristics of elderly psychiatric patients retained in state hospitals during downsizing: a prospective study with replication. Int J Geriatr Psychiatry 1997;12:474–480
21. Liddle PF. The symptoms of chronic schizophrenia: a re-examination of the positive-negative dichotomy. Br J Psychiatry 1987;151:145–151
22. Toomey R, Kremen WS, Simpson JC, et al. Revisiting the factor structure for positive and negative symptoms: evidence from a large heterogenous group of psychiatric patients. Am J Psychiatry 1997;154:371–377
23. Czobor P, Volavka J. Dimensions of Brief Psychiatric Rating Scale: an examination of the stability during haloperidol treatment. Compr Psychiatry 1996;37:205–216
24. Citrome L, Volavka J, Czobor P, et al. Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia. Psychiatr Serv 2001;52:1510–1514
25. Ratey JJ, Leveroni C, Kilmer D, et al. The effects of clozapine on severely aggressive psychiatric inpatients in a state hospital. J Clin Psychiatry 1993;54:219–223
26. Spivak B, Mester R, Wittenberg N, et al. Reduction of aggressiveness and impulsiveness during clozapine treatment in chronic neuroleptic-resistant schizophrenic patients. Clin Neuropharmacol 1997;20:442–446
27. Volavka J, Zito JM, Vitrai J, et al. Clozapine effects on hostility and aggression in schizophrenia [letter]. J Clin Psychopharmacol 1993;13:287–289
28. Buckley P, Bartell J, Donenwirth MA, et al. Violence and schizophrenia: clozapine as a specific antiaggressive agent. Bull Am Acad Psychiatry Law 1995;23:607–611
29. Czobor P, Volavka J, Meibach RC. Effect of risperidone on hostility in schizophrenia. J Clin Psychopharmacol 1995;15:243–249
30. Bilder RM, Goldman RS, Volavka J, et al. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 2002;159:1018–1028

For the CME Posttest for this article, see pages 588–589.