

Negative Symptoms: A Path Analytic Approach to a Double-Blind, Placebo- and Haloperidol-Controlled Clinical Trial With Olanzapine

Gary D. Tollefson, M.D., Ph.D., and Todd M. Sanger, Ph.D.

Objective: The authors investigated whether primary negative symptoms of schizophrenia are enduring or treatment-responsive. **Method:** Previously, a double-blind, random-assignment trial of the novel antipsychotic olanzapine (in low, medium, and high dose ranges), placebo, or haloperidol (10–20 mg/day) for 335 schizophrenic inpatients was conducted for up to 52 weeks. Changes in the treatment groups from baseline to endpoint in summary scores on the Scale for the Assessment of Negative Symptoms (SANS) and several secondary measures were compared. This article describes a path analysis to determine to what extent the total treatment effect on negative symptoms was direct or indirect (i.e., mediated by differential effects on positive symptoms, extrapyramidal symptoms, or mood). **Results:** Significantly greater improvement was achieved with high-dose olanzapine than with placebo or haloperidol. Olanzapine had a significantly greater direct effect than placebo on all SANS dimensions except anhedonia-asociality. Olanzapine also demonstrated a significantly greater direct effect than haloperidol on negative symptoms, especially on the dimensions of affective flattening and avolition-apathy. Olanzapine's superior effects were replicated in a subgroup with SANS-defined prominent negative symptoms ($N=116$) and a subgroup with a BPRS-defined cross-sectional proxy for the deficit state ($N=117$). **Conclusions:** These results suggest that the negative symptoms of schizophrenia are directly responsive to treatment. The significantly greater direct and indirect effects of olanzapine than of haloperidol on negative symptoms are likely related to olanzapine's pleotrophic pharmacology, which includes dopaminergic, serotonergic, muscarinic, and adrenergic activities. The results contribute to the hypothesis that negative symptoms may be under the influence of several neurotransmitters within one or more neuroanatomic circuits.

(Am J Psychiatry 1997; 154:466–474)

Schizophrenia has recently been characterized as “polythetic” (1), that is, phenomenologically heterogeneous and inclusive of multiple psychological domains. One domain commanding substantial attention is negative (or deficit) symptoms (2, 3), as characterized in the DSM-IV criteria for schizophrenia. The importance of the negative symptom complex includes the implication for long-term outcome (e.g., a relative resistance to conventional antipsychotics) (4). This clinical relevance has spurred greater attention toward the accurate recognition and longitudinal assessment of negative features. Arndt et al. (5) suggested that negative symptoms have an “independent pattern of evolution” that merits special focus in clinical treatment studies.

To a greater extent than assessment of positive symptoms, assessment of negative symptoms depends on a complex observer judgment. The work of Carpenter and colleagues (6) has highlighted the inherent difficulties in distinguishing between primary (disease-specific) negative symptoms and secondary negative symptoms (attributable to comorbid features and/or conventional neuroleptic side effects). While improvement in any negative symptom likely contributes to better functional well-being of the patient, it is of heuristic interest to demonstrate whether primary negative symptoms are indeed “enduring” or, alternatively, have appeared to be because of the therapeutic limitations of conventional neuroleptics.

From the data set used in the present report, a double-blind comparison of olanzapine with placebo and/or haloperidol (7) showed that the response of positive symptoms to the unique pharmacologic profile of olanzapine (8) was comparable, and the acute re-

Received June 20, 1996; revision received Nov. 18, 1996; accepted Nov. 26, 1996. From Lilly Research Laboratories. Address reprint requests to Dr. Tollefson, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Drop Code 0538, Indianapolis, IN 46285.

sponse of negative symptoms was significantly superior. These significant differences were seen on the Scale for the Assessment of Negative Symptoms (SANS) (9) composite and summary scores (7, table 5). In light of these between-treatment differences, the present article, with the application of a path analytical statistical approach, explores three key questions. First, it examines whether differences in negative symptom treatment encompassed direct and/or indirect improvement in negative components. Second, we repeated analyses across a five-dimensional model of the SANS to explore whether specific SANS dimensions accounted for direct improvement in negative features. Third, we hypothesized that if any selective advantages of negative symptom treatment were evident with olanzapine, they should be replicable in a subgroup with a prominent negative symptom presentation.

METHOD

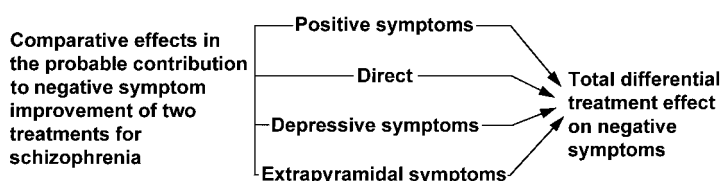
The study on which these analyses were based was a double-blind, placebo- and comparator-controlled trial. Eligible subjects included both male and female inpatients, between 18 and 65 years of age, who met the DSM-III-R criteria for schizophrenia (diagnoses 295.1–295.3 and 295.9) and were experiencing an acute exacerbation of their illness (residual type, 295.6, excluded). Initial severity of illness scores on the Brief Psychiatric Rating Scale (BPRS) (10) had to equal or exceed 24 (item scores based on a rating scale of 0–6). The Clinical Global Impression (CGI) (11) severity rating also had to be at least moderate (score ≥ 4). Subjects were further required to have a level of education and degree of understanding such that they were able to provide informed consent. All subjects gave written informed consent after a full explanation of the elements contained in the research protocol.

Patients were excluded from the trial if they were pregnant or lactating; were experiencing serious concomitant medical illnesses; had a history of leukopenia without a clear etiology; reported a history of severe allergies or multiple adverse drug reactions; had a history of lack of response to standard neuroleptic treatment; were drug- or alcohol-dependent or had a history of drug abuse (including alcohol abuse) within the preceding 3 months; had received treatment with a depot neuroleptic within the preceding 6 weeks or an oral neuroleptic within the preceding 2 days (48 hours); or had participated in a clinical trial of an investigational drug within the preceding month.

Following a 1-week placebo lead-in period, subjects were required to have sustained a BPRS total score of at least 24 and not to have achieved a reduction of 25% or more from their initial screening score. Blind random assignment was made to one of five study treatment arms: placebo, low-dose olanzapine (mean=5 mg/day, SD=2.5), medium-dose olanzapine (mean=10 mg/day, SD=2.5), high-dose olanzapine (mean=15 mg/day, SD=2.5), or haloperidol (10–20 mg/day). The period of randomly assigned acute treatment was 6 weeks. Patients were permitted to continue their blind treatment into a 46-week maintenance period if they had responded to acute treatment as evidenced by a BPRS total score of 18 or less and/or had achieved at least a 40% improvement in BPRS total score at the end of week 6.

The primary evaluations of efficacy for negative symptoms were based on patients' baseline-to-endpoint improvement on the SANS. The scale contains 24 items and uses a 0 (none) to 5 (severe) symptom rating range. The sum of the five global ratings comprised the SANS summary score and was the primary measure of negative symptoms. Assessments were completed at each scheduled visit during the 6 weeks of the acute treatment phase. The negative item factor from the BPRS was used to corroborate SANS data. To best calculate whether patients met percent improvement criteria, a rating system of 0 (nor-

FIGURE 1. A Model of Path Analysis



mal) to 6 (extremely ill) was used in the analysis of data from the 18-item BPRS. A CGI improvement rating was also obtained at the conclusion of the study. Extrapyramidal side effects were assessed by the first seven items of the Simpson-Angus rating instrument (12). Akathisia was evaluated with the global assessment item from the Barnes scale (13).

Concomitant medications with primary CNS activity were not allowed during the study. If a medication for sleep or agitation was clinically indicated, lorazepam could be given during the placebo lead-in period and for up to a maximum of 21 cumulative days of treatment. If extrapyramidal side effects occurred, benztropine mesylate was permitted up to a maximum dose of 6 mg/day.

Patients' compliance was determined by a regular capsule count at each visit. Patients who missed 5 consecutive days of at least one dose of study medication were discontinued.

A total of 335 inpatients with DSM-III-R schizophrenia diagnoses were randomly assigned to the study treatments: placebo, N=68; low-dose olanzapine, N=65; medium-dose olanzapine, N=64; high-dose olanzapine, N=69; haloperidol, N=69. Each of six study sites contributed a minimum of 25 patients.

All data analyses were performed on an intent-to-treat basis, meaning that the data of all patients were included for analysis of the treatment groups to which they were randomly assigned. For the analysis of change from baseline to endpoint, the data of all patients with a baseline measurement and at least one postbaseline measurement were included (N=326). All analyses were conducted with SAS software (14).

We used analysis of variance (ANOVA) (15) to compare treatment groups with regard to change from baseline to endpoint in BPRS total, positive symptom, and negative symptom scores, SANS summary score, and CGI severity score. The ANOVA model contained the terms for treatment, investigator, and treatment-by-investigator interaction. For all analyses, main effects were tested at a two-sided alpha level of 0.05, and treatment-by-investigator interactions were tested at an alpha level of 0.10 to increase the power to detect such interactions. Pairwise comparisons with no correction for multiplicity were performed for all treatment groups with the use of least squares means. In the analysis of the five SANS dimensions, the sum of the individual item scores in each dimension was analyzed instead of the global item score.

The modal maintenance dose was defined as the dose prescribed most often for the patients who completed at least 3 weeks of double-blind therapy. Predictors of baseline negative symptoms and predictors of negative symptom response were investigated with the use of stepwise linear regression with alpha=0.15.

We used path analysis (16, 17) to determine whether a differential efficacy for negative symptoms favoring either olanzapine, haloperidol, or placebo was due to direct and/or indirect therapeutic effects. Figure 1 shows a generic path model illustrating the relationships between direct effects and indirect effects (from positive, depressive, and extrapyramidal symptoms) on negative symptoms. Improvement in negative, positive, depressive, and extrapyramidal symptoms was measured by using change from baseline to endpoint (last observation carried forward) in SANS summary score, BPRS positive symptom subscale score, BPRS item 9 (depressive mood) score, and Simpson-Angus scale total score, respectively. The treatment effect denotes the additional change in scores of olanzapine-treated subjects relative to that of subjects who received either placebo or haloperidol. In path analysis, the direct effect on negative symptoms is defined as the treatment effect remaining after covarying for improvement in secondary

TABLE 1. Endpoint Change in SANS Dimensions (Last Observation Carried Forward) of Schizophrenic Patients Given Placebo, Olanzapine, or Haloperidol

SANS Dimension	Change in Score									
	Placebo Group (N=65)		Olanzapine Groups						Haloperidol Group (N=68)	
			Low Dose (N=65)		Medium Dose (N=63)		High Dose (N=65)			
Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Affective flattening	-1.03	6.75	-3.09	6.54	-1.90	7.23	-4.95 ^a	7.33	-2.06	7.04
Alogia	-0.20	3.80	-2.09 ^a	3.92	-1.81 ^b	3.46	-2.52 ^a	3.58	-1.60	3.55
Anhedonia-asociality	-0.40	4.54	-1.02	3.13	-0.73	4.41	-1.78	4.15	-1.18	4.32
Attention	-0.15	2.68	-0.94 ^b	2.09	-0.48	2.76	-1.86 ^a	2.94	-1.03	2.65
Avolition-apathy	-0.32	3.72	-1.82 ^b	2.95	-1.40	3.16	-2.51 ^{a,c}	3.85	-0.69	2.80

^aVersus placebo, $p \leq 0.01$ (t test on least squares means).

^bVersus placebo, $p < 0.05$ (t test on least squares means).

^cVersus haloperidol, $p = 0.004$ (t test on least squares means).

negative symptoms, including positive, depressive, and extrapyramidal symptoms, according to the linear regression. The indirect effect (e.g., through positive symptoms) is the product of the coefficient of the positive symptom covariate in the above model and the treatment effect on positive symptoms. Thus, total effect on negative symptoms is the sum of both the direct effect and the indirect effects. This total effect is essentially the unadjusted treatment effect that is commonly used. We hypothesize that this direct effect on negative symptoms may represent an improvement in primary, or deficit, negative symptoms.

RESULTS

The mean age of the subjects was 36 years ($SD=9$), and most were Caucasian (68.7%) and male (87.8%). The paranoid subtype of schizophrenia was diagnosed in 59.4% of the subjects, and 90.7% had a chronic course with an acute exacerbation. The mean age at onset of psychosis was 22 years ($SD=6$). The mean length of the current episode was 91 days ($SD=336$). Slightly over one-half (50.8%) of the patients had had fewer than 10 previous episodes. At baseline, the BPRS mean total score was 39.7 ($SD=10.5$) for the placebo group, 41.2 ($SD=11.7$) for the low-dose olanzapine group, 42.8 ($SD=10.0$) for the medium-dose olanzapine group, 42.6 ($SD=10.9$) for the high-dose olanzapine group, and 41.8 ($SD=11.4$) for the haloperidol group. There were no significant between-group differences on any of the key characteristics of illness or baseline severity scores. Just under one-half ($N=139$) of the patients completed the acute phase of the protocol. Early terminations due to an adverse event were numerically more frequent with placebo, low-dose olanzapine, and haloperidol than with medium-dose or high-dose olanzapine (7, table 7).

The mean modal maintenance doses for patients with at least 3 weeks of therapy were 6.6 mg/day ($SD=1.4$) for low-dose olanzapine, 11.6 mg/day ($SD=1.5$) for medium-dose olanzapine, 16.3 mg/day ($SD=1.6$) for high-dose olanzapine, and 16.4 mg/day ($SD=4.0$) for haloperidol. The primary efficacy analysis for the acute phase was the last-observation-carried-forward comparison of mean change from baseline to endpoint in

rank-transformed BPRS total score. As described in our earlier work (7), the total improvement according to the BPRS in both the medium-dose olanzapine and high-dose olanzapine groups was significantly greater than in the placebo group. With respect to BPRS core positive symptoms, both the medium-dose olanzapine and high-dose olanzapine treatment groups also demonstrated significantly greater improvement than the placebo group. These improvements included last-observation-carried-forward mean change from baseline and an analysis through the visit at which 70% or more of the patients still remained in each treatment group. A summary of the outcome across the primary and secondary measures has been given by Beasley et al. (7).

Do Disease Characteristics or Changes in Psychopathology Predict Negative Symptoms at Baseline?

The following factors that may predict baseline negative symptoms were investigated with the use of stepwise regression: age, age at onset, duration of current episode, number of previous episodes, gender, race, history of schizophrenia in the immediate family, history of psychotic disorder in the immediate family, type of schizophrenia, and course of schizophrenia. The best predictive model accounted for only 10% of the total variability in baseline SANS scores; type of schizophrenia ($F=9.30$, $df=2$, 268, $p<0.001$) and duration of the current episode ($F=4.37$, $df=1$, 268, $p<0.04$) were the only significant predictors of baseline negative symptom severity. Patients with undifferentiated schizophrenia manifested the highest level of baseline negative symptoms, followed by the disorganized and then the paranoid subtypes. The longer the duration of the current episode, the greater the likelihood that the patient would exhibit a higher level of baseline negative symptoms. The length of the disease course was only a marginally significant predictor of baseline negative symptoms ($F=2.36$, $df=2$, 268, $p<0.10$), with chronic schizophrenic patients tending to manifest more negative symptoms at baseline than subchronic patients.

No significant relationships emerged between pa-

TABLE 2. Correlations Between Change in Negative Symptoms (SANS Ratings) and Positive, Depressive, and Extrapyramidal Symptoms in Schizophrenic Patients Given Olanzapine, Haloperidol, or Placebo

Measure	Correlation (r)					
	SANS Summary Score	Affective Flattening Rating	Alogia Rating	Avolition-Apathy Rating	Anhedonia-Asociality Rating	Attention Rating
BPRS positive symptom score	0.56 ^a	0.37 ^a	0.41 ^a	0.48 ^a	0.48 ^a	0.45 ^a
BPRS depressive symptom score	0.31 ^a	0.29 ^a	0.22 ^a	0.28 ^a	0.27 ^a	0.21 ^a
Simpson-Angus extrapyramidal symptom scale total score	0.13 ^b	0.14 ^b	0.11	0.11	0.05	0.07

^ap<0.002 (t test on Pearson correlation).^bp<0.02 (t test on Pearson correlation).

tients' SANS summary scores at baseline and change from baseline to endpoint BPRS total, BPRS positive symptom, and CGI severity scores. In contrast, an improvement in BPRS depressive mood (item 9) score was negatively related to SANS baseline score ($r=-0.12$, $N=326$, $p<0.03$), whereas improvement in BPRS negative features was positively related to baseline SANS summary score ($r=0.14$, $N=326$, $p<0.01$).

Comparative Negative Symptom Outcomes

For the SANS summary score, the last-observation-carried-forward analyses of the mean change from baseline to endpoint indicated that the effects of both low-dose olanzapine and high-dose olanzapine were significantly superior to the effects of placebo. Furthermore, the effect of high-dose olanzapine was significantly superior to that of haloperidol. Use of the BPRS negative symptom score in a last-observation-carried-forward analysis of mean change from baseline to endpoint corroborated the high-dose olanzapine group's superior performance relative to that of both the placebo group and the haloperidol group (7).

The unidimensional model described above has been shown to fit SANS data generated in a large group of schizophrenic subjects. However, it has been proposed that a five-dimensional model, corresponding to each SANS dimension or subscale (affective flattening, alogia, avolition-apathy, anhedonia-asociality, and attention), provides an even better fit (18). Accordingly, we also conducted analyses on each of these five SANS dimensions. Between-group comparison of treatment results demonstrated that high-dose olanzapine was significantly superior to placebo for affective flattening; low-, medium-, and high-dose olanzapine for alogia; low- and high-dose olanzapine for attention; and low- and high-dose olanzapine for avolition-apathy (table 1). No significant difference was evident for the dimension of anhedonia-asociality. In marked contrast, there were no significant differences between haloperidol treatment and placebo on any of the five dimensions. Negative symptom improvement with high-dose olanzapine included effects superior to those of haloperidol on the dimension of avolition-apathy. Haloperidol did not outperform olanzapine on any SANS dimension.

Andreasen and Grove (19) have suggested that SANS item 6 (inappropriate affect) should be deleted from the

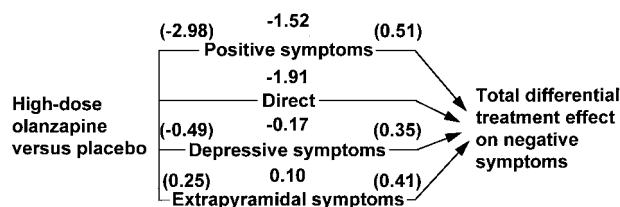
affective flattening dimension, since it may better reflect positive symptom response. In a reanalysis of our data set, exclusion of this item did not materially affect the results; however, the analyses deleting it were more robust in favor of olanzapine. High-dose olanzapine was significantly more effective than placebo with item 6 included ($F=6.73$, $df=1$, 226 , $p=0.01$) or excluded ($F=8.13$, $df=1$, 226 , $p=0.005$). Similar results were seen in the comparison with haloperidol, where high-dose olanzapine was marginally significantly more effective for affective flattening ($F=3.63$, $df=1$, 226 , $p<0.06$) and significantly more so without item 6 included ($F=3.93$, $df=1$, 226 , $p<0.05$).

Distinguishing Between Direct and Indirect Improvement in Negative Symptoms

Improvement in negative symptoms was correlated with improvement in positive, depressive, and extrapyramidal symptoms (table 2). To explore further the existence of a direct therapeutic effect on primary negative symptoms, we again analyzed data with a path analysis technique (16, 17). Application of this technique permitted determination of a direct treatment effect on negative symptoms after accounting for secondary differences in positive, depressive, and/or extrapyramidal symptoms.

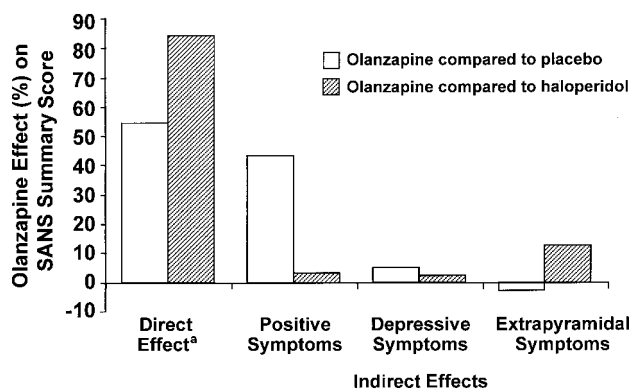
Path analysis of last-observation-carried-forward endpoint change in SANS summary scores indicated that treatment with high-dose olanzapine was associated with a response superior to the response to placebo after adjustment for change in positive, depressive, and extrapyramidal symptoms. The high-dose olanzapine group achieved a 3.51-point greater improvement in SANS summary score than the placebo group (figure 2). The direct therapeutic effect of treatment with high-dose olanzapine relative to placebo accounted for 55% of the olanzapine advantage (figure 3) (1.91 of 3.51 points difference in SANS summary score); this direct effect was also significant. The other major contributor to negative symptom improvement was the indirect benefit of improved positive symptom control, which accounted for 43% of the olanzapine advantage over placebo (figure 3) (1.52 of 3.51 points difference in SANS summary score). The indirect contributions of lower levels of depression (5%) and extrapyramidal side effects (–3%) were minimal in this comparison (figure 3).

FIGURE 2. Estimated Path Coefficients for the Comparison of Effects of High-Dose Olanzapine With Those of Placebo for Schizophrenic Patients^a



^aThe numbers in parentheses are the coefficients of the intermediate paths. The coefficients for the entire indirect path can be obtained by multiplying the coefficients of the intermediate paths.

FIGURE 3. Direct Effect on Negative Symptoms and Indirect Effect Through Secondary Positive, Depressive, and Extrapyramidal Symptoms of High-Dose Olanzapine Compared With Placebo and Haloperidol for Schizophrenic Patients

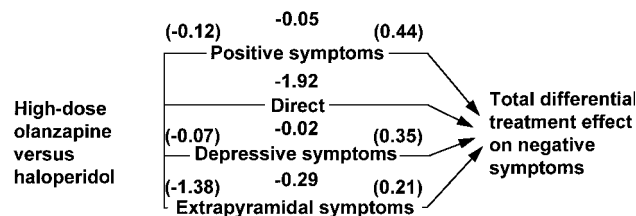


^aFor olanzapine compared with placebo, $t=-2.75$, $df=121$, $p=0.007$; for olanzapine compared with haloperidol, $t=-2.58$, $df=125$, $p=0.01$.

Path analyses were also conducted for effects on each of the five SANS dimensions. The superior direct effect on negative symptoms of high-dose olanzapine over placebo was principally made up of change in affective flattening ($t=-1.90$, $df=121$, $p=0.06$), alogia ($t=-2.85$, $df=121$, $p=0.005$), attention ($t=-2.31$, $df=121$, $p=0.02$), and avolition-apathy ($t=-2.20$, $df=121$, $p=0.03$). The change in anhedonia-asociality was almost exclusively through positive symptom improvement (78%).

In the comparison of high-dose olanzapine and haloperidol, the high-dose olanzapine group had a 2.28-point greater improvement in SANS summary score than their haloperidol counterparts (figure 4). The superior effect on SANS summary scores of high-dose olanzapine over haloperidol was principally attributable to a direct effect of treatment on presumably primary negative symptoms (84% of the olanzapine advantage, 1.91 of 2.28 points) (figures 3 and 4). This direct olanzapine treatment advantage was statistically significant. The indirect effect gained through improvement of extrapyramidal side effects was 13% of the to-

FIGURE 4. Estimated Path Coefficients for the Comparison of Effects of High-Dose Olanzapine With Those of Haloperidol for Schizophrenic Patients^a



^aThe numbers in parentheses are the coefficients of the intermediate paths. The coefficients for the entire indirect path can be obtained by multiplying the coefficients of the intermediate paths.

tal high-dose olanzapine advantage in total symptom change, while change in positive and depressive symptoms accounted for 2% and 1%, respectively, of the high-dose olanzapine advantage (figure 3). Path analysis of the five dimensions revealed especially large direct olanzapine effects on affective flattening ($t=-1.93$, $df=125$, $p<0.06$) and avolition-apathy ($t=-3.49$, $df=125$, $p<0.001$).

In the comparison of haloperidol and placebo, haloperidol treatment produced a 1.23-point greater improvement in SANS summary score than placebo (figure 5), although the difference was not statistically significant. This advantage was mainly attributable to the indirect effect through positive symptoms (figures 5 and 6). The direct effect was negligible. Path analysis of the five dimensions yielded a similar pattern.

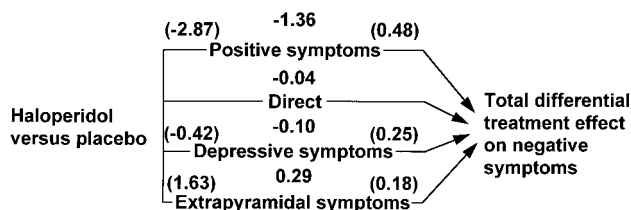
Prediction of Negative Symptom Response

The following factors that may predict the magnitude of response of negative symptoms were investigated by using stepwise regression: age, age at onset, duration of current episode, previous number of episodes, gender, race, history of schizophrenia in the immediate family, history of psychotic disorder in the immediate family, type of schizophrenia, and course of schizophrenia. Age at onset, while of limited magnitude as a predictor ($R^2=0.07$), was the only feature correlated significantly with negative symptom response ($F=5.01$, $df=4$, 269 , $p<0.001$). These results suggest that the later the age at onset, the greater the response of negative symptoms.

Treatment Response in Subgroups With Prominent Negative Symptom Presentations

In an effort to corroborate the path analytic results from the entire study group, we separated the patients into a negative symptom subgroup and a nonnegative symptom subgroup. They were placed in the negative symptom subgroup if they had at least two "marked" ratings on the SANS global items at baseline, as previously proposed by Andreasen and Olsen (2). The negative symptom subgroup contained 116 patients

FIGURE 5. Estimated Path Coefficients for the Comparison of Effects of Haloperidol With Those of Placebo for Schizophrenic Patients^a

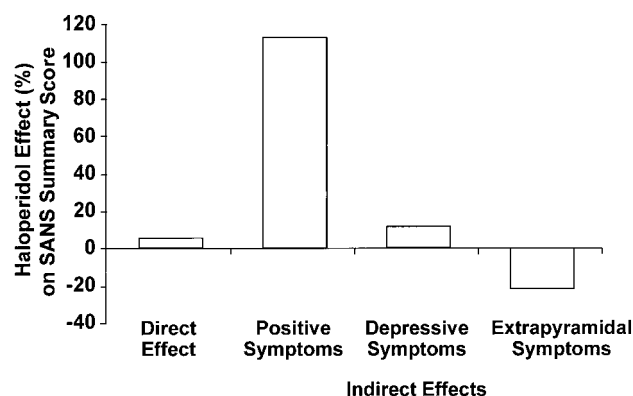


^aThe numbers in parentheses are the coefficients of the intermediate paths. The coefficients for the entire indirect path can be obtained by multiplying the coefficients of the intermediate paths.

and the nonnegative symptom group 219 patients. By definition, the ability to show a significant treatment effect on negative symptoms among those with negligible baseline negative features would be unlikely. However, in the negative symptom subgroup, only high-dose olanzapine (and not haloperidol) was superior to placebo for change in SANS summary score ($F=10.44$, $df=1$, 86 , $p=0.002$). High-dose olanzapine was significantly superior to placebo for every SANS dimension except anhedonia-asociality. The effects of haloperidol did not separate from those of placebo on any dimension. In the comparison of olanzapine and haloperidol, high-dose olanzapine was also superior to haloperidol on change in SANS summary score ($F=11.27$, $df=1$, 86 , $p=0.001$). Across individual dimensions, high-dose olanzapine outperformed haloperidol for affective flattening ($F=5.20$, $df=1$, 86 , $p<0.03$), attention ($F=11.80$, $df=1$, 85 , $p<0.001$), avolition-apathy ($F=7.55$, $df=1$, 86 , $p=0.007$), and alogia ($F=3.34$, $df=1$, 86 , $p=0.07$).

Kirkpatrick and colleagues (20) described a validated and stable model derived from the BPRS to cross-sectionally identify deficit and nondeficit subjects. This proxy for the deficit syndrome comprises the sum of scores on BPRS items 2 (anxiety), 5 (guilt feelings), 9 (depressive mood), and 10 (hostility) subtracted from the score on item 16 (blunted affect). Deficit patients exhibited higher proxy-for-deficit-syndrome scores than their nondeficit counterparts. Applying this analogue to our entire study group, we defined a subgroup of 117 deficit patients on the basis of a proxy-for-deficit-syndrome score of 7 or more. We chose this cutoff point in order to produce a deficit symptom subgroup similar in size to our SANS-defined negative symptom subgroup. It is interesting that only 46 patients were common to both subgroups. In the proxy-for-deficit-syndrome subgroup, high-dose olanzapine and haloperidol were superior to placebo for SANS summary score change from baseline ($F=14.14$, $df=1$, 95 , $p<0.001$, and $F=4.03$, $df=1$, 95 , $p<0.05$, respectively). High-dose olanzapine was significantly superior to placebo for every SANS dimension, including anhedonia-asociality. Haloperidol was significantly superior to placebo only for attention. High-dose olanzapine was

FIGURE 6. Direct Effect on Negative Symptoms and Indirect Effect Through Secondary Positive, Depressive, and Extrapyramidal Symptoms of Haloperidol Compared With Placebo for Schizophrenic Patients



superior to haloperidol for alogia ($F=3.92$, $df=1$, 95 , $p=0.05$) and avolition-apathy ($F=4.51$, $df=1$, 95 , $p<0.04$).

Safety Experience

Review of the adverse events reported in the acute phase indicated that few study patients discontinued any treatment because of an adverse event (across the three olanzapine conditions, 10 patients, or 5.1%; haloperidol, six patients, or 8.7%; placebo, seven patients, or 10.3%). In the acute phase, the most common treatment-emergent adverse events across all five treatment groups were psychomotor slowing (somnolence, asthenia) and psychomotor activation (agitation, nervousness, insomnia, anxiety). Among these events, only somnolence showed a significant pattern of relatedness to olanzapine dose. Analyses of the Simpson-Angus scale scores (extrapyramidal side effects) and Barnes akathisia scale scores demonstrated that mean scores from baseline to endpoint were decreased in all olanzapine treatment groups and in the placebo group (no significant differences). Among the haloperidol-treated subjects, significant increases in both Simpson-Angus and Barnes scale scores (relative to scores of the olanzapine and placebo groups) were evident (7, table 9). This occurred despite a significantly higher rate of use of benztropine among the haloperidol subjects and no significant differences between treatment groups with respect to use of benzodiazepines.

DISCUSSION

Evidence suggests that when typical neuroleptics are initially effective, they may appear to reduce both the positive and negative symptoms of schizophrenia (21–26). However, conventional neuroleptics reportedly fail to provide a sustained reduction in primary or deficit negative symptoms for the majority of patients (27). Even the apparent acute improvement in negative

symptoms is limited to secondary (nondeficit) features. Antithetically, neuroleptic drugs may actually worsen negative symptoms (e.g., through a liability to extrapyramidal side effects). In 1980 Crow (4) suggested the general resistance of negative symptoms to neuroleptics. An alternative hypothesis is that conventional drugs, principally the by-product of dopamine D₂ receptor screening programs, possess pharmacologic limitations, that is, limited pharmacologic potential to have an impact on negative symptoms. Thus, those limitations may have promoted the concept that primary negative symptoms are enduring.

A superior negative symptom outcome is a principal objective in novel antipsychotic drug development (28). This result could be realized through one or both of the following scenarios: 1) a reduction in secondary negative symptoms (e.g., those associated with positive symptoms, depression, and extrapyramidal side effects) through an improved efficacy for positive symptoms and/or an improved side effect profile possibly coupled with benefits for associated mood features; 2) a direct therapeutic effect on primary negative symptoms.

The atypical antipsychotic clozapine has been reported to be superior to chlorpromazine in reducing both the positive and negative features of schizophrenia (29). However, a direct effect on primary negative symptoms has been challenged by evidence that a subset of patients with predominantly negative symptoms were less responsive than their paranoid (positive symptom) counterparts (30). Thus, clozapine's apparent advantage for negative symptoms in that study group may have been attributable to the superior control of positive symptoms, which only secondarily (indirectly) influenced negative symptom ratings. Several other groups of investigators have suggested that clozapine's apparent advantage for negative symptoms may actually relate to a relatively lower incidence of extrapyramidal side effects (6, 31, 32) as well as its superior efficacy for positive symptoms (6, 30, 31). Accordingly, it can be argued that clozapine may reduce secondary negative features only through its broader spectrum of positive antipsychotic activity coupled with a lower incidence of extrapyramidal side effects. This effect would be expected to be attenuated or nonexistent among patients with predominantly negative symptoms or when a change in primary negative symptoms is being specifically targeted.

However, it is equally plausible that evidence for a direct clozapine effect on primary negative symptoms has been confounded by limitations in method, study group size, conventional data analyses, and so on. Unfortunately, the published literature addressing these two differing perspectives has been limited principally to open-label studies (33, 34). The present investigation contained several important methodologic improvements: 1) the trial was blind, 2) it contained both an active-drug and a placebo comparison group, 3) the dosing permitted flexibility within a range in order to optimize each individual's dose, 4) the protocol excluded or controlled for other concomitant drug use, 5) it did

not permit concurrent nonpharmacologic treatments, and 6) the data analysis strategy included a novel statistical method to differentiate direct versus indirect (or secondary) change in negative symptoms across the randomly assigned treatment groups.

A previous study by Miller et al. (35) illustrates the value in the design of our current trial. That group of investigators, in a 6-week uncontrolled study of 29 treatment-resistant patients, reported that clozapine-associated change in negative symptoms was correlated with improvements in extrapyramidal side effects, depression, psychosis, and disorganization. These data could be interpreted as having shown that improvement in negative symptoms was indirect and related to improvements in positive symptoms, extrapyramidal side effects, or mood. The uncontrolled nature of the trial did not permit clarification of whether a direct treatment effect on primary negative symptoms had occurred. In contrast, the present study demonstrated that high-dose olanzapine was significantly superior to placebo and/or haloperidol in both directly and indirectly reducing negative symptoms. This could be explained by olanzapine's superior efficacy for positive symptoms, lower propensity to elicit extrapyramidal side effects, and/or greater treatment impact on secondary mood symptoms, as well as a presumptive treatment effect on primary or deficit features as contained within the direct improvements.

In an in-depth review of clozapine, Carpenter et al. (6) hypothesized that a superior effect on positive symptoms might explain apparent change in negative symptoms. The present study demonstrated comparable improvements in BPRS positive symptom scores for olanzapine and haloperidol (although improvements with olanzapine were numerically greater) by the end of the acute treatment period. This comparability argues against the premise that olanzapine's efficacy for negative symptoms occurred among a group of subjects whose positive features had previously failed to respond to a conventional neuroleptic drug. Furthermore, if change in negative symptoms was only secondary to initial improvement in acute positive symptoms, it would be expected that the two active treatment groups would have demonstrated similar magnitudes of negative symptom improvement. In contrast, significant differences between olanzapine and haloperidol for negative symptoms were evident (table 1). The use of the path analytic approach permitted further testing of this hypothesis. Not only did high-dose olanzapine exhibit a significantly greater total effect on SANS scores than either placebo or haloperidol, but this advantage was principally accounted for by a significant direct benefit of treatment (figure 3). Thus, while not belittling olanzapine's indirect advantage for negative symptoms, we found that change in BPRS positive symptom score alone was insufficient to account for the observed improvement in negative symptoms.

In this trial, a correlation between change in negative symptoms and extrapyramidal side effects was evident. However, the path analysis revealed that the relatively

low incidence of extrapyramidal side effects related to olanzapine in comparison with those related to haloperidol was only a minor indirect contributor to overall improvement in SANS score. The same was true for improvement in mood. The overall data permit the conclusion that a relationship between changes in primary and secondary negative symptoms does exist. However, while olanzapine was associated with fewer secondary symptoms than haloperidol, a significant and robust direct therapeutic effect was also seen. This confirms the two-compartment model of negative symptoms: primary and secondary.

Several properties may account for the preferential differences in treatment. Olanzapine exhibits a 5-HT₂-to-D₂ binding ratio in excess of 1; it is also active at muscarinic cholinergic and α_1 adrenergic sites (8). Even within dopaminergic receptor systems, olanzapine exhibits a higher binding affinity for the D₁ and D₄ subpopulations than haloperidol. This pharmacologic profile would be expected to bestow a broader profile of symptom response and lower risk of extrapyramidal side effects than conventional D₂ antagonists. Electrophysiologic studies have shown that olanzapine exhibits mesolimbic (A10) selectivity relative to striatal (A9) dopamine systems (36). In vivo behavioral testing has demonstrated that 5-HT-mediated behaviors occur at smaller doses than those required for manifesting dopamine-related effects (37). Experience with positron emission tomography in studies of humans further confirmed an atypical binding profile in which striatal D₂ occupancy with olanzapine, 10 mg p.o., was less than that observed with haloperidol while comparable to that with clozapine (38). Similar results from a study that used single photon emission computed tomography among schizophrenic patients who responded to treatment distinguished the D₂ binding of clozapine and olanzapine in vivo from that of risperidone/haloperidol (39). On the basis of this atypical pharmacologic profile (i.e., one not solely based on conventional D₂ receptor antagonism), it seems apparent that a broader-based neurotransmitter profile makes direct and indirect improvement in negative symptoms an achievable therapeutic objective.

If such a direct treatment effect on primary negative features is possible, a validation strategy would be confirmation of the effect in a study group with prominent negative symptoms. In several previous studies (40, 41), it was reported that subgroups with predominantly negative symptoms experienced little improvement in deficit symptoms while receiving clozapine. The separation of our study group into a subgroup of 116 patients with negative symptoms corroborated the superior improvement in global and dimensional SANS ratings with high-dose olanzapine relative to both placebo and haloperidol. A second validation strategy, a cross-sectional application of select BPRS items (20), is a proxy for the deficit state. With this cross-sectional model, we observed that in a subgroup with deficit symptoms (N=117), olanzapine outperformed both placebo and haloperidol. Both of these approaches go beyond any exist-

ing data on clozapine relative to conventional neuroleptic drugs in establishing the therapeutic advantages of olanzapine in the pharmacotherapy of negative symptoms.

CONCLUSIONS

This controlled trial in schizophrenic patients provided evidence that negative symptoms are directly responsive to treatment. That is, there were improvements in negative features that were not attributable to effects on other schizophrenic symptoms. Whether these were true deficit features or not is uncertain. Within the context of improvement in symptoms, a positive correlation between changes in positive and negative symptoms exists. However, improvement in positive symptoms alone was neither required for nor explanatory of the majority of observed improvements in the negative domain. The evidence also supported a positive relationship between change in negative symptoms and change in the secondary variables of mood and extrapyramidal side effects. However, this again did not explain all of the observed treatment benefits for negative symptoms. Specifically, the path analytic method revealed that the superior olanzapine-related improvements included both direct and indirect improvements in negative symptoms. Confirmation of these treatment effects in a negative symptom subgroup and in a cross-sectional model for the deficit state illustrated that olanzapine was a clinically more effective intervention than placebo or haloperidol.

The data gathered in this trial were from patients with chronic schizophrenia who had been hospitalized for an acute exacerbation. Most exhibited both positive and negative features. It is not known what their negative symptom histories were and, in turn, whether they exhibited a chronic deficit state before this index admission. However, it is likely that these results could be generalized to patients in a chronic deficit state who are not in an acute exacerbation of schizophrenia.

These study results further suggest that the unique and broad pharmacologic profile of olanzapine contributed to a significantly greater therapeutic benefit for negative features relative to treatment with haloperidol or placebo. This highlights several intriguing avenues for future biological studies in the pathophysiology of negative symptoms. Furthermore, the profound impairment that negative symptoms bestow upon individual productivity and independence (and the related caregiver burden) encourages continued efforts to demonstrate that treatment alternatives contribute to a patient's functional well-being and social reintegration. Such studies in the future will serve to strengthen further the value of the present study observations.

REFERENCES

1. Andreasen NC, Arndt S, Alliger R, Miller D, Flaum M: Symptoms of schizophrenia: methods, meanings, and mechanisms. *Arch Gen Psychiatry* 1995; 52:341-351

2. Andreasen NC, Olsen S: Negative v positive schizophrenia: definition and validation. *Arch Gen Psychiatry* 1982; 39:789-794
3. Eaton WW, Thara R, Federman B, Melton B, Liang K: Structure and course of positive and negative symptoms in schizophrenia. *Arch Gen Psychiatry* 1995; 52:127-134
4. Crow TJ: Molecular pathology of schizophrenia: more than one disease process? *BMJ* 1980; 280:66-68
5. Arndt S, Andreasen NC, Flaum M, Miller D, Nopoulos P: A longitudinal study of symptom dimensions in schizophrenia: prediction and patterns of change. *Arch Gen Psychiatry* 1995; 52:352-360
6. Carpenter WT Jr, Conley RR, Buchanan RW, Breier A, Tamminga CA: Patient response and resource management: another view of clozapine treatment of schizophrenia. *Am J Psychiatry* 1995; 152:827-832
7. Beasley CM Jr, Tollefson G, Tran P, Satterlee W, Sanger T, Hamilton S, Olanzapine HGAD Study Group: Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology* 1996; 14:111-123
8. Bymaster FP, Calligaro DO, Falcone JF, Marsh RD, Moore NA, Tye NC, Seeman P, Wong DT: Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology* 1996; 14:87-96
9. Andreasen NC: Scale for the Assessment of Negative Symptoms (SANS). Iowa City, University of Iowa, 1983
10. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. *Psychol Rep* 1962; 10:799-812
11. Guy W (ed): ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976
12. Simpson GM, Angus JWS: A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl* 1970; 212:11-19
13. Barnes TR: A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989; 154:672-676
14. SAS/STAT User's Guide, version 6, 4th ed, vols 1, 2. Cary, NC, SAS Institute, 1990
15. Snedecor GW, Cochran WG: Statistical Methods, 7th ed. Ames, Iowa University Press, 1980
16. Möller HJ, Müller H, Borison RL, Schooler NR, Chouinard G: A path-analytical approach to differentiate between direct and indirect drug effects on negative symptoms in schizophrenic patients. *Eur Arch Psychiatry Clin Neurosci* 1995; 245:45-49
17. Retherford RD, Kim Choe MK: Path analysis, in *Statistical Models for Causal Analysis*. New York, John Wiley & Sons, 1993, pp 93-99
18. Peralta V, Cuesta MJ: Negative symptoms in schizophrenia: a confirmatory factor analysis of competing models. *Am J Psychiatry* 1995; 152:1450-1457
19. Andreasen NC, Grove WM: Evaluation of positive and negative symptoms in schizophrenia. *Psychiatrie et Psychobiologie* 1986; 1:108-121
20. Kirkpatrick B, Buchanan R, Breier A, Carpenter W: Case identification and stability of the deficit syndrome of schizophrenia. *Psychiatry Res* 1993; 47:47-56
21. Goldberg SC: Negative and deficit symptoms in schizophrenia do respond to neuroleptics. *Schizophr Bull* 1985; 11:453-456
22. Meltzer HY, Sommers AA, Luchins DJ: The effect of neuroleptics and other psychotropic drugs on negative symptoms in schizophrenia. *J Clin Psychopharmacol* 1986; 6:329-338
23. Opler LA, Albert D, Ramirez PM: Psychopharmacologic treatment of negative schizophrenic symptoms. *Compr Psychiatry* 1994; 35:16-28
24. Tandon R, Goldman RS, Goodson J, Greden JF: Mutability and relationship between positive and negative symptoms during neuroleptic treatment. *Biol Psychiatry* 1990; 27:1323-1326
25. Tandon R, Ribeiro SCM, DeQuardo JR, Goodman RS, Goodson J, Greden JF: Covariance of positive and negative symptoms during neuroleptic treatment in schizophrenia: a replication. *Biol Psychiatry* 1993; 34:495-497
26. van Kammen DP, Hommer DW, Malas KL: Effect of pimozide on positive and negative symptoms in schizophrenic patients: are negative symptoms state dependent? *Neuropsychobiology* 1978; 18:113-117
27. Kane J, Mayerhoff D: Do negative symptoms respond to pharmacologic treatment? *Br J Psychiatry* 1989; 55(suppl 7):115-118
28. Kirkpatrick B, Carpenter WT: Drug development and the deficit syndrome of schizophrenia. *Biol Psychiatry* 1995; 38:277-278
29. Kane J, Honigfeld G, Singer J, Meltzer H: Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; 45:789-796
30. Honigfeld G, Patin J: Predictors of response to clozapine therapy. *Psychopharmacology (Berl)* 1989; 99:564-567
31. Tandon R, Goldman R, DeQuardo JR, Goldman M, Perez M, Jibson M: Positive and negative symptoms covary during clozapine treatment in schizophrenia. *J Psychiatr Res* 1993; 27:341-347
32. Lieberman JA, Safferman AZ, Pollack S, Szymanski S, Johns C, Howard A, Kronig M, Boodstein P, Kane JM: Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. *Am J Psychiatry* 1994; 151:1744-1752
33. Meltzer HY, Bastani B, Kwon KY, Ramirez LF, Burnett S, Sharpe J: A prospective study of clozapine in treatment-resistant schizophrenic patients, I: preliminary report. *Psychopharmacology (Berl)* 1989; 99(suppl):S68-S72
34. Meltzer HY: Clozapine: pattern of efficacy in treatment-resistant schizophrenia, in *Novel Antipsychotic Drugs*. Edited by Meltzer HY. New York, Raven Press, 1992, pp 33-46
35. Miller DD, Perry PJ, Cadoret RJ, Andreasen NC: Clozapine's effect on negative symptoms in treatment-refractory schizophrenics. *Compr Psychiatry* 1994; 35:8-15
36. Stockton ME, Rasmussen K: Olanzapine, a novel atypical antipsychotic, reverses d-amphetamine-induced inhibition of mid-brain dopamine cells. *Psychopharmacology* 1996; 124:50-56
37. Moore NA, Calligaro DO, Wong DT, Bymaster F, Tye NC: The pharmacology of olanzapine and other new antipsychotic agents. *Curr Opin Invest Drugs* 1993; 2:281-293
38. Nyberg S, Farde L, Halldin C: A PET study of 5-HT₂ and D₂ dopamine receptor occupancy induced by olanzapine in healthy subjects. *Neuropsychopharmacology* 1997; 16:1-7
39. Pilowsky LS, Busatto GF, Taylor M, Costa DC, Sharma T, Sigmundsson R, Ell PJ, Nohria V, Kerwin RW: Dopamine D₂ receptor occupancy in vivo by the novel atypical antipsychotic olanzapine—a ¹²³I IBZM single photon emission tomography (SPET) study. *Psychopharmacology (Berl)* 1996; 124:148-153
40. Breier A, Buchanan RW, Kirkpatrick B, Davis OR, Irish D, Summerfelt A, Carpenter WT Jr: Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. *Am J Psychiatry* 1994; 151:20-26
41. Conley R, Gounaris C, Tamminga C: Clozapine response varies in deficit versus non-deficit schizophrenic subjects. *Biol Psychiatry* 1994; 35:746-747