A Randomized Controlled Trial of Olanzapine Versus Haloperidol in the Treatment of Primary Negative Symptoms and Neurocognitive Deficits in Schizophrenia

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Objective: Primary negative symptoms are intrinsic to the pathology of schizophrenia and are associated with significant deficits in motivation, verbal and nonverbal communication, affect, and cognitive and social functioning. Overall, atypical antipsychotic medications have been found to be more efficacious than conventional antipsychotics in the treatment of negative symptoms, based on studies with acute patients. Results have been confounded by concomitant improvements in positive, depressive, and extrapyramidal symptoms. This 12-week, double-blind, controlled study aimed to examine the effects of the atypical antipsychotic olanzapine versus haloperidol on persistent, primary negative symptoms and neurocognitive functions in stable schizophrenic patients with the deficit syndrome and low levels of concomitant positive, depressive, and extrapyramidal symptoms.

Method: Thirty-five patients with DSM-IV-TR schizophrenia and predominant negative symptoms were randomly assigned in a 12-week double-blind study to either olanzapine (15–20 mg/day) or haloperidol (15–20 mg/day). Patients taking haloperidol received additional blinded benztropine. Inclusion criteria were Positive and Negative Syndrome Scale (PANSS) negative score of ≥ 20, PANSS positive score < 20, and fulfilling the criteria for the Schedule for the Deficit Syndrome. The PANSS, Clinical Global Impressions, Hamilton Rating Scale for Depression (HAM-D), Simpson-Angus Scale, and Abnormal Involuntary Movement Scale were assessed at regular subsequent intervals. A neuropsychological battery examining declarative verbal learning memory, attention and processing speed, executive functioning, and simple motor functioning domains of cognition was assessed at baseline and endpoint. The study ran from September 1998 through May 2005.

Results: Clinical Results: There was a statistically significant difference for PANSS negative symptoms ($F = 5.44$, $df = 1,15$; $p \leq .05$), with an 8.63-point decrease in the olanzapine group ($t = 5.66$, $df = 1,33$; $p \leq .05$), and PANSS total score ($t = 9.304$, $df = 1,33$; $p \leq .05$). Linear mixed model for repeated measures indicated that the olanzapine group showed a statistically significant change in negative symptom scores ($F = 9.70$, $df = 1,15$; $p \leq .05$). There were no significant differences for change in PANSS positive score, PANSS general psychopathology score, and HAM-D score. Using a criterion of 40% decrease in the PANSS negative subscale score, 31.25% of patients were classified as responders in the olanzapine group, while only 10.53% were responders in the haloperidol group. There were no significant between-treatment differences in the incidence of extrapyramidal side effects. Olanzapine-treated patients experienced more weight gain than the haloperidol-treated group ($F = 7.044$, $df = 1,33$; $p \leq .05$). Neuropsychological Results: Significant differences in change from baseline to endpoint for the olanzapine-treated group were seen for declarative verbal learning memory ($F = 11.499$, $df = 1,14$; $p = .021$) and the motor functioning domain ($F = 4.405$, $df = 1,31$; $p = .044$).

Conclusions: The results of this study suggest that olanzapine treatment was associated with significant improvement in primary negative symptoms, overall symptomatic improvement as measured by the PANSS total score, and improvement in some areas of neurocognition as compared with haloperidol/benztropine mesylate treatment.

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Primary negative symptoms are intrinsic to the pathology of schizophrenia and are associated with significant deficits in motivation, verbal and nonverbal communication, interest in socialization, affect, and social functioning.[1,2] Negative symptoms are better predictors of social functioning, particularly in comparison with positive symptoms.[3] Overall, atypical antipsychotic medications (second-generation antipsychotics [SGAs]) have been found to be more efficacious than first-generation antipsychotics (FGAs) in the treatment of negative symptoms.[4–6] Atypical antipsychotics, as compared with FGAs, have also produced improvements in depression[7] and in cognitive dysfunction.[8,9]

Despite extensive research, it has not been fully established whether this superior anti–negative symptom effect of atypical antipsychotics is due to indirect effects, such as an ameliorating or sparing effect on extrapyramidal symptoms, or is due to a direct effect on primary negative symptoms. Primary negative symptoms reflect the inherent and enduring pathology of schizophrenia itself. Secondary negative symptoms may be artifacts of concomitant depression, extrapyramidal symptoms, or environmental understimulation (e.g., depressive anhedonia, paranoid social withdrawal, neuroleptic-induced akinesia, anergia due to sedation).[10,11] Although significant anti–negative symptom effects have been reported for olanzapine, these studies included predominantly acutely psychotic schizophrenic patients[12,13] or chronic symptomatic patients with prior suboptimal response,[14] which fails to support the argument that olanzapine has a direct beneficial effect on primary negative symptoms.[15] The ameliorative effect on negative symptoms in such studies can be explained in part by effects on secondary negative symptoms, such as fewer extrapyramidal symptoms, improvement of concomitant depressive symptoms, or a superior effect on positive symptoms. The rating scales used in these studies do not allow for a clear differentiation between primary and secondary negative symptom effects. Three strategies have been used in such studies to assess direct effects on negative symptoms: correlational, covariance, and path analyses have been used to identify secondary effects on negative symptom measures.[15] These approaches are not entirely satisfactory, as they are based on the assumption that the degree of unexplained variance reflects a direct anti–negative symptom effect. Due to such methodological limitations, a clear conclusion as to whether the improvement of negative symptoms is predominantly in primary or secondary negative symptoms cannot be drawn from these studies.[16]

In order to remedy these inherent methodological difficulties, the study design should include a patient population with a significant degree of primary negative symptoms and a comparator FGA dosed at a level so as not to induce secondary negative symptoms. The comparator FGA should be used together with concomitant anticholinergic medication in order to minimize the emergence of extrapyramidal symptoms during treatment. Further, only patients who are low on positive symptoms, depression, and extrapyramidal symptoms should be included in the study sample, and patients should also satisfy the criteria for the Schedule for the Deficit Syndrome (SDS),[17] which will assure that included negative symptoms are stable- rather than unstable-state manifestations. Despite agreement that the primary/secondary distinction is theoretically sound, there has been concern that this distinction cannot be made with good reliability. A semistructured instrument for diagnosing deficit versus nondeficit groups, the SDS was developed for the purpose of studying primary, enduring negative symptoms. The deficit/nondeficit categorization can be made with good interrater reliability.[17–19] Finally, the duration of the trial has to be long enough to allow for a possible change in negative symptoms, which tend to take longer to show improvement.

Negative symptoms and cognitive dysfunction have been found in some studies to be correlated with each other.[20,21] Given our aim of examining the effects of atypical antipsychotics on primary negative symptoms, we were therefore also interested in examining possible effects on neurocognitive measures. Several studies have reported improvements in cognitive symptoms after switching subjects from FGAs to SGAs[22–25] or improvements in cognitive symptoms with SGAs when compared in double-blind controlled studies to an FGA.[8,9,26–31]

The primary aim of this double-blind, controlled, parallel-design study was to compare olanzapine with haloperidol for primary negative symptoms in a study population of stable patients with schizophrenia with high levels of primary negative symptoms and low levels of positive symptoms, depression, and extrapyramidal symptoms. The comparator FGA (haloperidol) was administered together with concomitant, blinded anticholinergic medication in order to minimize the emergence of extrapyramidal symptoms during treatment. The secondary aim was to investigate the effect of olanzapine compared with haloperidol on neurocognitive deficits in patients with primary negative symptoms. The implication of a finding of a superior effect in these 2 related areas of schizophrenia deficits could be associated with improvements in patients' participation in active rehabilitation programs and with the promotion of higher levels of social functioning.

METHOD

Study Population

Participants were male and female, 18- to 60-year-old inpatients and outpatients at a state psychiatric hospital in New York who met DSM-IV-TR criteria for schizophrenia. Staff psychiatrists were asked to refer stable patients with predominant negative symptoms for screening for the present study, which ran from September 1998 through May 2005. Patients were required to have a Positive and Negative Syndrome Scale (PANSS)[32] total score of ≥ 50, with a PANSS negative subscale score of ≥ 20. The negative symptom score was required to contain at least 3 out of 7 negative item scores of ≥ 3. All patients fulfilled the criteria for the SDS. The PANSS depression-item score (exclusion level ≥ 4) was used to exclude patients with significant levels of depression as a secondary negative symptom. Patients were also excluded if they had (1) a PANSS positive subscale score of ≥ 20; (2) a Simpson-Angus Scale (SAS)[33] akinesia-item score of ≥ 2; the SAS defines akinesia as the absence, loss, or

impairment of voluntary movement; (3) a history of treatment failure on antipsychotics (persistent positive symptoms after 8 weeks of treatment with adequate dosages of 1 or more antipsychotics); (4) a significant medical disorder; or (5) positive substance-abuse diagnosis in the last 3 months. Patients on antipsychotic decanoate preparations prior to the study were converted to oral tablets at equivalent doses at least 3 weeks before study entry. Use of mood stabilizers was allowed provided that the dosage was stable throughout the study and that patients had been on a stable dose for at least 2 months prior to randomization. Pregnant or breastfeeding women and women of childbearing age not using adequate contraception were excluded. The sample consisted of stable inpatients and outpatients. The continued hospitalization of stable inpatients was due to the lack of available community beds after discharge.

The study was approved by the local institutional review board of the participating center in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent prior to the start of the study. Of the 36 patients enrolled in the study, 35 were randomly assigned to haloperidol or to olanzapine. One patient did not receive study treatment due to withdrawal of consent.

Study Design

This was a parallel, double-blind, 12-week study design in which patients were randomly assigned (1:1 ratio) to a fixed dose of either olanzapine 15 mg daily or haloperidol 15 mg daily for the first 6 weeks after 1 week of cross-titration from previous antipsychotic medication. The fixed-dose period was followed by a 6-week, double-blind, flexible-dose phase. The dose of the study medication could be increased or decreased in a blinded fashion by 5 mg at 2-week intervals during this second phase to a maximum of 20 mg daily for both groups, based on the discretion of the physician.

Study-dose change was based on lack of improvement in PANSS negative symptom ratings. The aim was (1) to find the most effective dose for negative symptom improvement and (2) to keep the study medication dose as low as possible. This latter point is related to the finding that the best response for negative symptoms in olanzapine trials was seen at doses of 12.5 to 17.5 mg daily.[5]

Patients randomly assigned to haloperidol received additional blinded, active benztropine mesylate 2 mg PO b.i.d., while patients randomly assigned to olanzapine received benztropine mesylate placebo tablets. If significant extrapyramidal symptoms persisted despite benztropine treatment, the dose of study drug was first lowered. If this was not helpful, 2 mg of benztropine mesylate could in all cases (for blinded olanzapine or haloperidol) be added to the study benztropine mesylate. The comparably high dose of benztropine mesylate for the haloperidol group was chosen in order to assure that the blinding of study drug would be fully maintained by minimizing any occurrence of extrapyramidal symptoms and to match the anticholinergic effects of olanzapine.

Clinical assessments consisted of the PANSS and the Clinical Global Impressions-Severity of Illness (CGI-S)[34] and Clinical Global Impressions-Improvement (CGI-I)[34] scales at baseline, week 1, and biweekly thereafter and the Hamilton Rating Scale for Depression (HAM-D)[35] at baseline and week 12; all ratings were performed by trained raters who obtained an interrater reliability correlation on the PANSS of at least 0.85. The SDS for all patients was rated by an experienced, trained psychiatrist (for more information on SDS rating, see Amador et al.[19]). Safety was assessed by patient reports of adverse events throughout the study period and by physical examination at baseline and endpoint. Additionally, changes in weight, vital signs, laboratory values, and prolactin level were assessed. Extrapyramidal symptoms were assessed by the SAS and the Abnormal Involuntary Movement Scale (AIMS),[34] performed at screening and at weeks 1, 2, 4, 6, 8, 10, and 12.

Neurocognitive Assessment

The neurocognitive assessment was designed to include a range of reliable and validated tests frequently used in similar studies.[8] The tests were grouped into 4 domains as outlined in principle-components analysis by Bilder and colleagues[8] and by Wagner and colleagues.[36] The domains included executive functioning, declarative verbal learning memory, attention and processing speed, and motor functioning. The test battery was administered at screening (prior to the start of study medication) and at endpoint (week 12).

Executive functioning. We administered the computerized 128-card Wisconsin Card Sorting Test.[37] The amount of perseverative errors and correct responses was the dependent variable. To assess global verbal fluency, we administered the Controlled Oral Word Association (COWA) category/semantic fluency and COWA letter fluency tests.[38] The respective fluency scores were summed to a global fluency score, which was the dependent variable. The Letter-Number Span was also used to measure executive functioning.[39]

Declarative verbal learning memory. The Rey Auditory-Verbal Learning Test was used as a measure of verbal learning memory.[40] The number of words correct was the dependent variable. The Letter-Number Sequencing Task was used to measure verbal working memory.[39] The sum of correct trials was the dependent variable. In addition, we used the Verbal Learning Test recognition form[39]; the discrimination value (correct recognitions + false positives/50) was the dependent variable.

Attention and processing speed. The Trailmaking Tests A and B[41] and the Visual Digit Coding Task[42] were used to

assess visuomotor speed. The dependent variable for both tests was the time required to complete the tests. To assess vigilance, the distractibility task[43] was administered, with the total number of correct responses, commissions, and omissions as the dependent variables. The Tapping Forward Test[44] was also administered, with the total score used as the dependent variable.

Motor functioning. For the assessment of motor functioning, the Finger-Tapping Test[45] was used. The mean of the first 5 trials was used as the dependent variable. We also computed a global cognitive index score as the mean of z scores on all 12 individual neurocognitive variables.

Data Analysis

Before analysis of clinical and neuropsychological data, we examined demographic variables and severity of illness as well as neuropsychological test performance at baseline. All continuous dependent variables were examined for linearity and normality. If normality was not present, appropriate transformations were applied. All clinical and neuropsychological baseline variables were analyzed by t tests for continuous variables and χ^2 or Fisher exact test for categorical variables to determine if baseline differences existed between the 2 treatment groups. For all patients who did not complete the entire 12-week study, a likelihood-based repeated-measures model (mixed models repeated measures [MMRM]) was applied.[46] Last observation carried forward (LOCF) was applied to PANSS data only if patients completed ≥ 8 weeks of the study.

For the post hoc analysis, the primary efficacy variable was specified a priori as the negative symptoms subscale score as derived from the PANSS. Additionally, the PANSS positive symptom score and total score were evaluated as secondary efficacy variables. Neurocognitive variables were grouped into 4 domains and were considered secondary efficacy measures.

For those measures with repeated observations, changes from baseline scores were analyzed with the general linear mixed model-repeated measures (GLMM-RM) analysis[47] using a model that included fixed class effects of visit week, treatment, and random components of all patients. The GLMM-RM uses methods of maximum likelihood and restricted maximum likelihood estimation and can handle missing values.[47(p139)] The linear mixed-effects models procedure in Statistical Package for the Social Sciences, Version 13.0, fits models more general than those of the general linear model (GLM) procedure, and it encompasses all models in the variance components procedure. The major capabilities that differentiate GLMM-RM from GLM are that GLMM-RM handles correlated data and unequal variances, which are very common in studies with repeated measures. In a linear mixed-effects model, responses from a subject are thought to be the sum (linear) of the fixed and random effects. If an effect, such as a treatment of olanzapine or haloperidol, affects the population mean, it is fixed. If an effect is associated with a sampling procedure (e.g., subject effect), it is random. The linear mixed-model analyses utilized all available data once the patient had completed at least 8 weeks of treatment.

Efficient estimation of the fixed effects of mean change is dependent in specifying an appropriate variance-covariance structure.[48] The following covariance models were specified: unstructured, diagonal, and first-order autoregressive for the PANSS negative and positive subscale and total scores and the HAM-D, SAS, and AIMS scores. The covariance models were compared using the fit statistics, which included a nested χ^2 based on the model likelihood, Akaike's information criterion, and Bayesian information criterion.[49] Based on the fit statistics, the unstructured covariance model had the best fit for PANSS negative symptom score (the primary efficacy variable), which included fixed effects for treatment (olanzapine vs. haloperidol) and for HAM-D, SAS, and AIMS. Each subject's outcome between baseline and week 12 visits was summarized with a linear regression line defined by a subject-specific intercept α_i and slope β_i. The subject-specific intercept α_i was assumed to depend on the subject's PANSS subscale scores at baseline and on treatment group, while the subject-specific slope β_i was assumed to depend on the treatment group. Because regression to the mean can often lead to erroneous conclusions in analyses, the analysis method employed adjusts for regression-to-the-mean bias and provides a more realistic estimate of the effects. Because the reference group available for use in this study is small, the procedure approximates the amount of regression-to-the-mean bias in the data set, and selection of the unstructured covariance model provides goodness of fit.

A total of 12 variables were extracted from the neuropsychological tests for each of the 2 test sessions (baseline and endpoint). Only patients who completed both baseline and endpoint neurocognitive evaluations were included in the analysis; the neurocognitive data were standardized with reference to the mean and standard deviation of the entire sample. Signs were adjusted so that negative values reflected impairment. The z metric[50] allows for an integration of single variables into cognitive domains and into a global cognitive index, which was used as a primary measure for confirmatory testing. Analysis of treatment effect in each of the 4 cognitive domains and the global index used the linear regression model approach with baseline and endpoint scores as dependent variables, time as a within-subject measure, and treatment group as a between-subjects fixed factor (2-fold). Frequency data (gender, dropout rates) were analyzed using Fisher exact model. Interrelations between cognitive and clinical improvement were tested by

Table 1. Demographic and Clinical Characteristics of Patients With Primary Negative Symptoms Participating in a 12-Week Trial of Haloperidol Compared With Olanzapine

Characteristic	Haloperidol (N = 19)	Olanzapine (N = 16)	Difference Between Treatments, p Value[a]
Age, mean (SD), y	39.77 (9.49)	39.02 (10.48)	.828[b]
Gender, N (%)			.119[c]
Male	19 (100)	14 (87.5)	
Female	0 (0)	2 (12.5)	
Race, N (%)			.161[c]
White	1 (5.26)	1 (6.25)	
African American	12 (63.16)	15 (93.75)	
Hispanic	5 (26.32)	0 (0)	
Other	1 (5.26)	0 (0)	
End-of-study mean (SD) modal dose, mg/d	17.11 (3.84)	18.44 (2.39)	.140[b]

[a]Significance level: $p \leq .05$.
[b]From type III sum of squares F statistic for analysis of variance, including terms for treatment.
[c]Fisher exact test.

Table 2. Prior Antipsychotic Treatment by Haloperidol and Olanzapine Groups

	Haloperidol		Olanzapine	
Prior Antipsychotic	N	Dose, Mean (SD), mg/d	N	Dose, Mean (SD), mg/d
Haloperidol	4	16.25 (2.50)	2	10.00 (0.00)
Thiothixene	1	20.00 (NA)	1	40.00 (NA)
Olanzapine	2	15.00 (7.07)	0	–
Risperidone	8	4.75 (2.05)	10	5.30 (1.77)
Thioridazine	1	300.00 (NA)	0	–
Fluphenazine	2	17.50 (10.61)	2	22.50 (3.54)
Aripiprazole	1	40.00 (NA)	0	–
Ziprasidone	1	160.00 (NA)	0	–
Quetiapine	2	550.00 (353.55)	1	400.00 (NA)
No previous antipsychotic	0	–	1	NA

Abbreviation: NA = not applicable, if only 1 patient was observed.

Pearson product moment correlation. The confirmatory statistical comparisons of all data were carried out at a significance level of $p \leq .05$, 2-tailed.

To minimize the problem of spurious significant results, differences in subscales or individual items were considered important only when total-scale means differed between treatments. Incidence rates for adverse events and discontinuation due to adverse events or any other reason were identified. These rates were based on all randomized patients, who by a priori definition received at least 1 dose of study medication, in accordance with the intent-to-treat principle. The distribution of mean modal doses during the flexible-dose phase was determined via a univariate analysis. All data were analyzed using Statistical Package for the Social Sciences, Version 13.0.[51]

RESULTS

Subject Characteristics

Thirty-six patients (33 inpatients, 3 outpatients) qualified to participate in the study. However, 35 subjects entered the study and were randomly assigned to treatment; 1 subject did not enter the trial due to withdrawal of consent and was therefore excluded from the analysis. The predominance of inpatients enrolled was a result of inadequate community resources, such as housing and available community beds, leading to prolonged inpatient stays. The mean length of time for inpatients to obtain community housing after having been deemed appropriate for discharge at the New York State hospital from which inpatients were selected is approximately 28.80 (SD = 6.36) weeks. Demographic and clinical characteristics by treatment group are described in Table 1. Nineteen patients were randomly assigned to the haloperidol group and 16 patients were randomly assigned to the olanzapine group. Of the 3 outpatients, 2 were randomly assigned to olanzapine and 1 to haloperidol. Subjects who completed the entire 12-week study were 84.2% of patients in the haloperidol-treated group and 93.8% of patients in the olanzapine-treated group. Four patients (11.4%) did not complete up to week 8 of the study and were not included in the analyses. Reasons for discontinuation included suicidal ideation (N = 2, one from each treatment group), patient decision (N = 1, haloperidol treatment group), and violent behavior (N = 1, haloperidol treatment group). A large percentage of subjects (94.3%) were male, 77.1% were African American, 14.3% were Hispanic, 5.7% were white, and 2.9% were from other racial groups. The mean age was 39.77 (SD = 9.49) years for the haloperidol group and 39.02 (SD = 10.48) years for the olanzapine group. At baseline, 2.9% of subjects (N = 1) had never received antipsychotic treatment, 71.4% had been treated with an atypical antipsychotic, and 37.1% had been treated with typical antipsychotics. For specific prestudy drugs, see Table 2. For those subjects receiving prior antipsychotic treatment, the median duration was 128.00 days for the haloperidol group and 136.50 days for the olanzapine group. The mean chlorpromazine equivalency dose for prior antipsychotic treatment (i.e., the antipsychotics from which the patients were switched) for the haloperidol group was 376.32 (SD = 282.08) mg/day, with a median dose of 300.00 mg/day; for the olanzapine group, the mean chlorpromazine equivalency dose prior to study medication was 356.25 (SD = 250.91) mg/day, with a median dose of 300.00 mg/day (for more information on chlorpromazine equivalency doses, please see Woods[52] and Kane et al.[53]). No patients were on long-acting injections prior to study entry. Ten patients were on mood stabilizers for the duration of the study period; of these, 5 were randomly assigned to the haloperidol group and 5 to the olanzapine group. Two-group t tests revealed no baseline differences between groups for PANSS subscale scores, extrapyramidal-symptom measures, or laboratory measures.

Table 3. Baseline and Endpoint Last-Observation-Carried-Forward (LOCF) Efficacy Measures for Clinical Assessments for Patients With Primary Negative Symptoms Participating in a 12-Week Trial of Haloperidol Compared With Olanzapine

	Haloperidol (N = 19)[a]		Olanzapine (N = 16)[a]		Difference Between
Measure	Baseline	Endpoint[b]	Baseline	Endpoint[b]	Treatments, p Value[c]
PANSS					
Positive	13.05 (3.12)	14.16 (4.99)	14.13 (4.15)	12.06 (4.07)	.884
Negative	26.16 (4.73)	22.58 (6.54)	26.88 (3.40)	18.25 (4.42)	.031*
General	31.58 (5.68)	30.89 (8.90)	32.44 (7.85)	26.75 (5.29)	.420
Total	70.79 (9.86)	67.58 (17.70)	71.25 (17.46)	57.25 (11.73)	.020*
SAS total	0.95 (1.22)	0.89 (1.15)	1.63 (2.22)	1.00 (1.37)	.523
AIMS total	0.74 (2.75)	0.53 (1.47)	0.38 (1.50)	0.94 (2.57)	.894
HAM-D	5.58 (3.13)	5.74 (4.00)	6.81 (3.33)	4.50 (3.23)	.778
Laboratory values					
Weight, lb	197.05 (48.68)	194.08 (47.67)	194.91 (47.67)	203.28 (41.62)	.012*
Cholesterol, mg/dL	170.11 (27.95)	156.28 (35.62)	153.55 (73.42)	135.18 (46.81)	.099
Glucose, mg/dL	84.44 (8.28)	83.22 (7.16)	100.73 (29.99)	94.00 (17.49)	.031*
Triglycerides, mg/dL	135.94 (61.56)	126.72 (83.25)	184.91 (42.57)	168.64 (32.83)	.529

[a]Values are shown as mean (SD).
[b]LOCF was applied to endpoint measures for patients who completed at least 8 weeks of the trial; for patients terminated early from the study, an attempt was made to perform all endpoint procedures.
[c]F statistic testing equality of linear slope coefficients from a linear mixed model with an unstructured covariance structure. Information criteria used: –2 restricted likelihood ratio.
*Significant at $p \leq .05$.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, HAM-D = Hamilton Rating Scale for Depression, PANSS = Positive and Negative Syndrome Scale, SAS = Simpson-Angus Scale.

The mean modal endpoint dose was 18.44 mg/day of olanzapine and 17.11 mg/day of haloperidol (see Table 1). After the fixed-dose phase, 9 patients had their dose lowered or remain the same, while 10 patients had their dose raised. Three patients (15.7%) from the haloperidol group and 1 patient (6.3%) from the olanzapine group received supplemental benztropine mesylate 2 mg/day in addition to their concomitant, blinded benztropine mesylate. While the olanzapine group showed a higher mean value in extrapyramidal symptoms as measured by the SAS at baseline, these differences were not statistically significant (Table 3).

Efficacy Analysis

Descriptive statistics indicated that all clinical assessments were normally distributed except for PANSS positive symptoms; therefore, the square root of PANSS positive symptoms was used as the normalizing transformation for all the analyses. Table 3 shows the mean values and standard deviations for PANSS subscale and total scores for both groups.

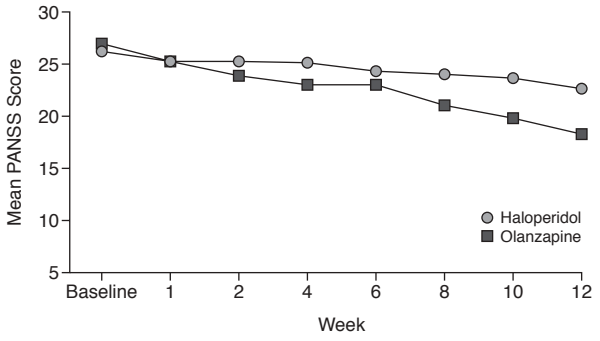
Table 3 indicates that estimated regression lines demonstrated statistically significant differences for change of PANSS negative symptoms between the 2 groups ($t = 5.66$, $df = 1,33$; $p \leq .05$, global tests of intercepts and slopes). The olanzapine group had an 8.63-point decrease from baseline to week 12 ($F = 5.44$, $df = 1,15$; $p \leq .05$). The covariance parameter for the random effect showed a significance value (Wald $z = 33.32$, $p = .000$), indicating the random effect contributed enough to be kept in the model. Estimated regression lines demonstrated statistical significance between the 2 groups for PANSS total score ($t = 9.304$, $df = 1,33$; $p \leq .05$, global tests of intercepts and slopes); analysis indicated that the olanzapine group had a statistically significant change in scores from baseline to week 12 ($F = 9.70$, $df = 1,15$; $p \leq .05$). Table 3 indicates mean values and standard deviations for all PANSS and extrapyramidal-symptom measures. For PANSS positive and general symptom scores and HAM-D scores, the linear slopes for the olanzapine and haloperidol groups did not differ significantly. There were no significant differences for change in PANSS positive score ($F = 0.021$, $df = 1,33$; $p > .05$, linear slope [–1.75, SE = 0.95]) and PANSS general psychopathology ($F = 0.668$, $df = 1,33$; $p > .05$, linear slope [1.53, SE = 1.88]). Similarly, there was no significant change in the HAM-D score ($F = 0.081$, $df = 1,32$; $p > .05$). Change in PANSS negative, positive, and total symptom scores from baseline to endpoint for all completed patients taking olanzapine and haloperidol is presented in Figures 1 through 3.

Examining improvement using a categorical response criterion of 20% decrease of the PANSS negative subscale score (baseline and endpoint difference), 43.75% of patients were responders in the olanzapine group, while 31.58% of patients met this criterion in the haloperidol group. Using a 40% decrease in the PANSS negative subscale score, 31.25% of patients were classified as responders in the olanzapine group, while only 10.53% of patients met this criterion in the haloperidol group.

Safety Assessments

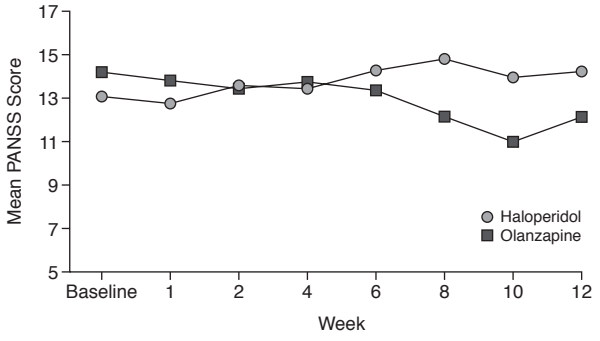
There were no significant between-treatment differences in the incidence of extrapyramidal side effects as

Figure 1. Change in Positive and Negative Syndrome Scale (PANSS) Negative Symptom Score From Baseline to Endpoint by Treatment Group[a]



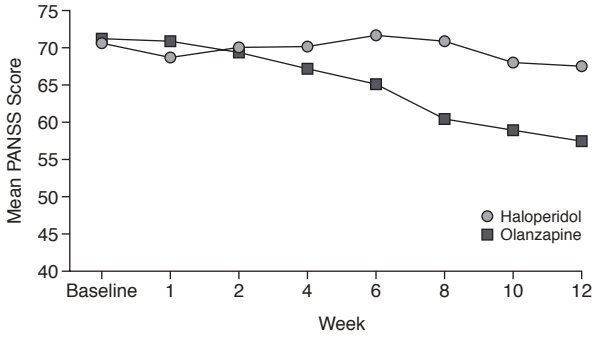
[a]Week 12: N = 16 for haloperidol, N = 15 for olanzapine; week 8: N = 19 for haloperidol, N = 16 for olanzapine (t = 5.66, df = 1,33; p ≤ .05).

Figure 2. Change in Positive and Negative Syndrome Scale (PANSS) Positive Symptom Score From Baseline to Endpoint by Treatment Group[a]



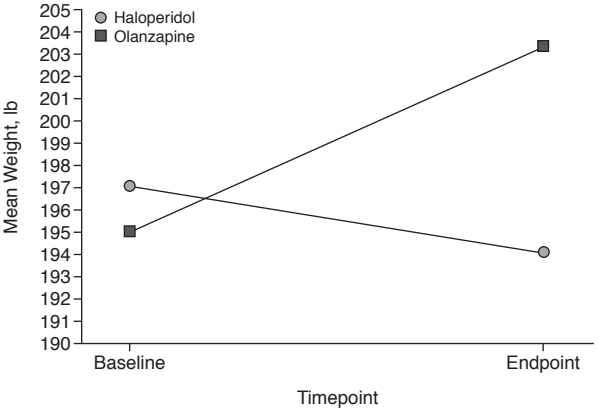
[a]Week 12: N = 16 for haloperidol, N = 15 for olanzapine; week 8: N = 19 for haloperidol, N = 15 for olanzapine.

Figure 3. Change in Positive and Negative Syndrome Scale (PANSS) Total Score From Baseline to Endpoint by Treatment Group[a]



[a]Week 12: N = 16 for haloperidol, N = 15 for olanzapine; week 8: N = 19 for haloperidol, N = 16 for olanzapine.

Figure 4. Change in Weight (lb) From Baseline to Endpoint for Haloperidol (N = 19) and Olanzapine (N = 16) Groups[a]



[a]Endpoint N = 36 (last observation carried forward).

reflected by change in scores on the SAS (F = 0.417, df = 1,33; p > .05) and the AIMS (F = 0.018, df = 1,33; p > .05). The olanzapine-treated patients experienced more weight gain than the haloperidol-treated group (F = 7.044, df = 1,33; p ≤ .05), with the olanzapine group showing a mean increase of 8.37 lb compared with a mean decrease of 2.97 lb in the haloperidol group (Figure 4).

In terms of glucose level, the olanzapine group showed a small but significant decrease in glucose level to 94.00 (SD = 17.49) mg/dL at endpoint (F = 5.164, df = 1,27; p ≤ .05). There were no significant changes in cholesterol and triglyceride levels between treatment groups, and despite the 9.22- and 16.27-point reductions in the triglyceride levels of the haloperidol and olanzapine groups, respectively, there were no trends for decrease observed in the analysis.

Neurocognitive Results

Four domain scores were constructed on the basis of the results of a 4-factor principal-components analysis of neuropsychological tests in a similar patient population[8]: declarative verbal learning memory, attention and processing speed, executive functioning, and simple motor functioning, plus a global cognitive index score. Internal reliability of the resulting domain scores was evaluated by computing coefficient alpha and resulted in satisfactory values: global score = 0.79, declarative verbal learning memory = 0.70, attention and processing speed = 0.61, executive functioning = 0.88, and motor functioning = 0.73. There was no significant difference for the change from baseline to endpoint for the olanzapine-treated group (t = –2.63, df = 3, p = .076) or the haloperidol-treated group (t = –0.319, df = 3, p = .770) in terms of

Table 4. Neurocognitive Global and Domain z Scores and Scores on Individual Neuropsychological Tests at Baseline and Week 12 (Endpoint)

Measure	Haloperidol			Olanzapine			Difference Between Treatments, p Value[b,c]
	Baseline, Mean (SD)	Endpoint,[a] Mean (SD)	N	Baseline, Mean (SD)	Endpoint,[a] Mean (SD)	N	
Global cognitive index[d]	–0.18 (0.33)	–0.09 (0.25)		–0.02 (0.39)	0.13 (0.47)		.081
Neurocognitive domain scores[e]							
Declarative verbal learning memory	0.04 (0.80)	–0.44 (0.73)	18	0.48 (0.31)	0.70 (0.74)	15	.021
Attention and processing speed	–0.20 (0.46)	–0.01 (0.51)	9	–0.18 (0.52)	0.07 (0.38)	12	.373
Executive functioning	0.09 (0.59)	–0.07 (0.51)	13	0.08 (0.69)	0.21 (0.55)	12	.303
Simple motor functioning	–0.64 (1.08)	0.16 (0.85)	18	–0.45 (0.88)	–0.45 (0.98)	15	.044
Neuropsychological test scores[f]							
Declarative verbal learning memory							
Rey Auditory Verbal Learning Test, sum of trials 1–5, words	25.29 (10.89)	21.29 (12.75)		33.60 (5.15)	40.90 (13.95)		
Rey Auditory Verbal Learning Test, recognition form, words	0.87 (0.14)	0.71 (0.32)		0.89 (0.06)	0.98 (0.29)		
Attention and processing speed							
Trailmaking Test A, s	72.67 (27.06)	122.29 (90.38)		114.62 (101.70)	84.72 (51.97)		
Trailmaking Test B, s	189.70 (91.97)	231.00 (68.48)		192.90 (90.58)	153.70 (95.95)		
Visual Digit Coding Task, s	21.29 (7.45)	15.43 (9.48)		26.60 (15.35)	26.00 (10.47)		
Distractibility task, no. correct	9.86 (9.19)	6.57 (4.99)		12.90 (10.47)	8.90 (10.57)		
Executive functioning							
Letter-Number Span	7.86 (5.11)	7.29 (4.96)		7.40 (5.52)	9.30 (5.04)		
WCST, perseverative errors	0.16 (0.06)	0.27 (0.11)		0.24 (0.14)	0.22 (0.22)		
COWA, letter fluency	22.71 (9.23)	19.57 (11.76)		19.70 (13.23)	22.60 (10.86)		
COWA, category/semantic	22.57 (6.75)	18.57 (8.02)		24.40 (13.35)	23.70 (8.11)		
Simple motor functioning							
Finger tapping left, no. taps	32.04 (13.36)	34.40 (11.27)		42.06 (10.67)	42.83 (12.99)		
Finger tapping right, no. taps	34.26 (12.61)	38.14 (11.44)		50.80 (12.67)	45.73 (19.29)		

[a]Endpoint results are actual endpoints and not estimated endpoint results.
[b]Significance level: $p \leq .05$.
[c]Only the global cognitive index and neurocognitive domains were analyzed statistically, using analysis of variance.
[d]Equally weighted mean of z scores for 12 test variables.
[e]Mean of z scores of contributing neuropsychological test scores.
[f]Mean values of actual test scores.
Abbreviations: COWA = Controlled Oral Word Association, WCST = Wisconsin Card Sorting Test.

the global cognitive index score (Table 4). For declarative verbal learning memory scores, post hoc tests revealed that olanzapine treatment showed greater improvement over time than did haloperidol treatment ($F = 11.499$, $df = 1,14$; $p = .021$). For the motor functioning domain, treatment with olanzapine resulted in greater improvement over time than did treatment with haloperidol ($F = 4.405$, $df = 1,31$; $p = .044$). There were no significant main effects for factor time for the haloperidol-treated group. There were no significant main effects for attention and processing speed ($F = 0.836$, $df = 1,18$; $p = .373$), or for executive functioning ($F = 1.114$, $df = 1,22$; $p = .303$), between treatment groups.

In order to compare the effect sizes of the present study with that of others, the actual effect sizes were calculated by using Cohen's d[50] and were somewhat large for some domains, since the standard deviations of the composite scores were approximately ≤ 1.0. The greatest effect sizes were seen for the olanzapine group for attention and processing speed and the global cognitive index, and for the haloperidol group, for declarative verbal learning memory and simple motor functioning, with effect sizes of 0.53, 0.72, 0.61, and 0.81, respectively. Medium effect sizes were seen for the olanzapine-treated group for change in declarative verbal learning memory (–0.38) and the global cognitive index (–0.35), and in the haloperidol-treated group, for change in the global cognitive index, attention and processing speed, and executive functioning, with effect sizes of 0.30, –0.39, and –0.29, respectively. Effect sizes were small for the olanzapine group on simple motor functioning (–0.001) and executive functioning (0.21).

Additional analyses examined the correlation between change in negative symptom scores and change in cognitive domain measures. The change scores for each neurocognitive domain were used as time-varying covariates in a mixed-model repeated-measures analysis of variance. Results indicate that there was no association between the change in negative symptoms and neurocognitive domain change. Interrelations were also examined using Pearson product moment correlations, and no associations were found between negative symptom improvement and change in neurocognitive domains.

DISCUSSION

The main findings of this study are that olanzapine treatment was associated with better outcomes in negative symptoms and in some areas of neurocognition as compared with haloperidol/benztropine mesylate treatment. There were no significant changes seen in positive, depressive, and extrapyramidal symptoms. The lack of change in the 3 latter measures allows us to conclude that the effect on negative symptoms was most likely a direct effect, rather than an indirect effect through the improvement of secondary negative symptoms.

While there is significant evidence that SGAs show superior effects on negative symptoms as compared with FGAs,[12,13,54–56] these effects were primarily found in the context of improvement in the treatment of acutely psychotic schizophrenic patients, making it difficult to differentiate between effects on primary or secondary negative symptoms. Our study followed recommendations made by Möller et al.[57] suggesting that trials of pharmacologic treatment of negative symptoms not be performed in the acute phase of the illness. Therefore, we included only stable patients with low levels of positive, depressive, and extrapyramidal symptoms, which could act as potential confounds.

A study with similar inclusion criteria comparing olanzapine and risperidone in stable patients with predominantly negative symptoms and with low levels of positive symptoms[58] showed that both treatments significantly reduced the Scale for the Assessment of Negative Symptoms (SANS) global, total, and composite scores. However, this study was open-label and did not compare these 2 atypical compounds to an FGA. In contrast to our findings, Möller et al.[59] found that zotepine, another dopamine D_2/serotonin $(5\text{-HT})_{2a}$ antagonist with a similar receptor profile to other atypical antipsychotics, was not superior to placebo in reducing primary negative symptoms. The study by Möller et al.[59] had similar design features to ours and investigated the effect of zotepine on primary negative symptoms in an 8-week, double-blind, placebo-controlled study, with patients showing a high level of negative symptoms and a low level of positive symptoms at baseline. These results suggest that not all atypical antipsychotics may have a significant anti–negative symptom effect.

In contrast to our findings, 2 recent studies examining the effects of olanzapine and haloperidol combined with benztropine found no significant differences for positive or negative symptoms in schizophrenia.[60,61] Buchanan and colleagues[60] found no significant differences between olanzapine (20.3 mg/day) and haloperidol (18.3 mg/day) combined with benztropine (4 mg/day) in outpatients with partially responsive schizophrenia. Rosenheck and colleagues[61] found almost complete equivalent effects of haloperidol compared with olanzapine in most of their outcome measures. The conflicting results are probably due to differences in the definitions of the study samples. Our study took pains to enrich the sample with patients with primary negative symptoms and excluded possible confounds.

Another important feature of the present study is that all included patients were assessed as showing the deficit syndrome. Kirkpatrick et al.[62] reported that deficit schizophrenia is found among 15% of first-episode individuals and among 25% to 30% of patients with chronic schizophrenia. The presence of a deficit syndrome suggests that negative symptoms in these patients are enduring, trait-like characteristics and that they are therefore unlikely to change. In contrast to these expectations, 31% of the olanzapine group showed a significant response, with a 40% drop in negative symptom score. In contrast to our study, a 12-week, open-label study by Kopelowicz and colleagues[63] assessed the effects of olanzapine on primary negative versus secondary negative symptoms and found that olanzapine (mean dose, 18.5 mg/day) was effective in treating secondary negative symptoms, while primary negative symptoms did not respond. It should be noted that the Kopelowicz et al.[63] results for the deficit group are based on a much smaller sample size (N = 13) than the present sample.

Similar to our findings on improvements in declarative verbal learning memory and motor function, a number of other studies with SGAs have demonstrated significant ameliorative effects in areas of neurocognitive deficits when compared with FGAs.[8,27] Meltzer and McGurk[30] observed similar improvements in declarative learning and memory with olanzapine compared with typical and other atypical antipsychotics. Even when a very low dose of haloperidol had been used (mean modal dose of 4.6 mg/day) in comparison with olanzapine, the latter had a beneficial effect on neurocognitive function in patients with a first episode of psychosis, although with a small beneficial difference in favor of olanzapine.[64] Specific domains of cognitive functioning have concurrent and predictive relationships with functional outcomes in patients with schizophrenia.[3] These deficits tend not to be very responsive to treatment with FGAs[30] and have been demonstrated to interfere with successful participation in psychiatric rehabilitation.[3,65]

Our finding of olanzapine-mediated cognitive improvement is also noteworthy as other ameliorative, indirect effects on neurocognitive improvement could be ruled out, such as improvement in positive and depressive symptoms and avoidance of extrapyramidal symptoms. We cannot, however, rule out interference by anticholinergic effects due to the concomitant benztropine treatment in the haloperidol group. These effects have been reported to possibly mediate impairments in neurocognitive functions in patients treated with concomitant anticholinergic compounds.[66–69] Results of McGurk and colleagues[70] also

found that the relative benefits of the SGA risperidone on spatial working memory performance were largely explained by differential benztropine treatment for the haloperidol-treated subjects. However, Purdon and colleagues,[27] in a 12-month trial, randomly assigned patients to haloperidol at 5 to 20 mg/day (73.3% of subjects received anticholinergic medications), olanzapine at 5 to 20 mg/day (45% received anticholinergic medications), or risperidone at 4 to 10 mg/day (15% received anticholinergics); they examined cognitive effects and found olanzapine to be superior to both risperidone and haloperidol in global cognitive measures. A stratification based on anticholinergic use within each treatment group showed no significant differences on the general cognitive index, nor on any of the individual cognitive domains, between subgroups receiving or not receiving anticholinergic treatment. In addition, our own group,[8] in a double-blind, 14-week trial comparing clozapine (mean endpoint dose, 498.4 mg/day), haloperidol (26.8 mg/day) plus benztropine (4–6 mg/day), olanzapine (30.0 mg/day), and risperidone (11.3 mg/day), found improvements in global neurocognitive function with olanzapine and risperidone that were superior to the haloperidol/benztropine combination without statistical association of anticholinergic blood levels with memory change, comparable to findings by Green and colleagues.[71] These results support a limited impact of anticholinergic effects for the haloperidol group. Other studies, which minimized the use of concomitant anticholinergics with FGA treatment, have also reported a lack of change on neurocognitive measures in subjects treated with haloperidol.[68,72,73] Another factor underlying the comparative advantage of olanzapine in our study may have been due to the relatively high dose of haloperidol. The negative effects of haloperidol may be related to a direct impairment of neurocognitive functions.[74]

In contrast to prior research,[8] there was no association of neurocognitive change with psychopathology symptom ratings. Our findings support the observation that treatment-related modulation of neurocognitive deficits and psychopathologic symptoms may progress with significant independence.

The effect sizes of cognitive improvement in the present study are similar to those reported by Harvey and Keefe[31] and Bilder and colleagues.[8] Harvey and Keefe[31] found effect sizes between 0.13 (immediate memory) and 0.43 (verbal fluency) for studies of 4 to 8 weeks' duration in which the amount of improvement was seen by switching patients from typical to atypical antipsychotics, while Bilder and colleagues[8] reported effect sizes between 0.74 (olanzapine treatment for attention and processing speed) and –0.08 (haloperidol treatment for global cognitive index) for a 14-week trial. The present study found the greatest effect sizes in the olanzapine group for global cognitive index and in the haloperidol group for simple motor functioning, with effect sizes of 0.72 and 0.81, respectively, and found small to moderate effect sizes for cognitive improvements across 12 weeks (0.01–0.61 for the entire sample), equivalent to those of other studies.[8]

Neurologic safety was excellent for both olanzapine and haloperidol; the latter treatment was supplemented by use of an anticholinergic. The neurologic-scale scores (SAS and AIMS) were low at baseline and did not increase during the study, thus demonstrating that neither drug generated a significant level of extrapyramidal symptoms. These findings confirm that the addition of benztropine mesylate in the haloperidol group was effective in protecting against extrapyramidal symptoms and, therefore, against secondary negative symptoms.

Olanzapine-treated patients gained a mean of 8.37 lb in 12 weeks, reflecting a similar occurrence as seen in patients in other studies.[75] In contrast, there was a significant, but very small, decrease in glucose levels in the olanzapine-treated group, which is difficult to interpret. The lack of glucose increase with olanzapine is similar to the results of our cross-sectional study examining changes in glucose, lipids, and leptin in patients with schizophrenia who were treated with typical or atypical antipsychotics.[76] These findings may suggest that some of the reported metabolic changes with olanzapine[75] are caused by mechanisms independent from those linked with weight change.

There are several potential limitations of the current study. First, the number of subjects included in our study was relatively small, which could lead to an unreliable estimate of the real effect size. Even with the present sample size, it appears that our effect size estimate is valid, based on concordance with other studies of olanzapine with a similar magnitude of neurocognitive improvement. Second, our study excluded patients who had demonstrated lack of response to olanzapine in the past, which we were able to ascertain as olanzapine had been more recently introduced. On the other hand, we could not exclude with complete certainty patients who may have had a prior exposure to haloperidol with limited response. This might have biased the findings in the direction of showing less improvement in the haloperidol group. Third, an important issue is the comparability of dosages of haloperidol and olanzapine. We used in the present study a dose of 15 mg/day of olanzapine and 15 mg/day of haloperidol for the fixed-dose phase. It could be argued that the haloperidol dose was too high and could have interfered with a potential improvement in negative symptoms. We used the present dose levels to reflect the naturalistic practice patterns in treatment settings of patients with chronic schizophrenia. The mean dose of olanzapine used in our study is similar to doses of 18.6 mg/day used in New York State hospitals.[77,78] Haloperidol mean dose was 17.11 mg/day in the present study, which is within the range of mean daily haloperidol doses used for schizophrenic

patients from 1998 (19.1 mg/day) to 2005 (15.0 mg/day) in New York State facilities, from which the present sample was drawn (L. Citrome, M.D., M.P.H., personal e-mail correspondence, Nov. 29, 2005).[78] It should also be noted that our results showed no difference in extrapyramidal side effects between the 2 groups. A meta-analysis of 7 studies investigating haloperidol concentration and therapeutic effects concluded that the optimum therapeutic response for haloperidol was achieved by dosing patients within a range of 5 to 18 ng/mL.[79] This range of haloperidol level corresponds to a dose range of 4 to 16 mg/day.[14] Olanzapine/haloperidol dosing similar to that used in our study has also been used by other recent studies[27,60,61] comparing olanzapine to haloperidol. Rosenheck and colleagues[61] found almost complete equivalent effects of haloperidol compared with olanzapine in their outcome measures (PANSS, functional, and neurocognitive measures) at a final mean daily dosage of haloperidol of 14.3 mg and of olanzapine at 15.8 mg. In addition, our concomitant and systematic use of benztropine in the haloperidol group may have further reduced the potential dose effect on negative symptoms in the haloperidol group. In support of this hypothesis is the lack of difference in extrapyramidal symptoms in the 2 treatment groups, which was also shown in the Rosenheck et al. study.[61]

In summary, the results of this 12-week, double-blind treatment study comparing olanzapine and haloperidol add to the relatively limited literature on the treatment response to atypical antipsychotics by patients with primary negative symptoms. The present results suggest that olanzapine has superior therapeutic effects for primary negative symptoms, declarative verbal learning memory, and motor functioning in patients with the deficit syndrome. However, olanzapine was associated with greater weight gain. An improvement in these specific deficits may also have a positive impact on vocational functioning in schizophrenia, including the ability to benefit from psychiatric rehabilitation, and on the degree of independent living.

Drug names: aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others), fluphenazine (Prolixin and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), ziprasidone (Geodon).

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