ORIGINAL ARTICLE

# Depressive Signs and Symptoms in Schizophrenia

## *A Prospective Blinded Trial of Olanzapine and Haloperidol*

*Gary D. Tollefson, MD, PhD; Todd M. Sanger, PhD; Yili Lu, PhD; Martha E. Thieme*

**Background:** Depressive signs and symptoms during the course of schizophrenia are common and have been associated with impaired recovery and a higher risk of self-harm. Novel antipsychotic agents introduce new pharmacological avenues that may differentially affect schizophrenic signs and symptoms, including depression.

**Methods:** This was a 17-country investigation of 1996 patients with schizophrenia or a related diagnosis randomly assigned to a blinded, comparative trial of the novel antipsychotic agent olanzapine (5-20 mg/d) or the conventional $D_2$ antagonist haloperidol (5-20 mg/d). Patients were evaluated with the Positive and Negative Syndrome Scale, the Montgomery-Asberg Depression Rating Scale, and the Simpson-Angus Rating Scale. The trial consisted of a 6-week and a 46-week masked responder maintenance period.

**Results:** At least moderate depressive signs and symptoms (Montgomery-Asberg Depression Rating Scale score, ≥16) were seen in slightly more than half of this sample. Although both treatments were associated with short-term baseline-to-end point improvement on the Montgomery-Asberg Depression Rating Scale, olanzapine-associated improvements were significantly superior to those observed with haloperidol ($P$=.001). Furthermore, the response rate for the group receiving olanzapine (≥50% improvement on the Montgomery-Asberg Depression Rating Scale after at least 3 weeks of treatment) was also significantly higher ($P$=.008). Analysis demonstrated that improvement in positive, negative, and/or extrapyramidal symptoms was associated with mood improvement (indirect effect); however, most of the olanzapine treatment effect on mood was a primary direct effect (57%) that alone was significantly greater than that seen with haloperidol treatment ($P$<.001).

**Conclusions:** Depressive signs and symptoms in schizophrenia are responsive to treatment. The pleotrophic pharmacological features of olanzapine, through 1 or more non–$D_2$-mediated pathways, likely contribute to its superior treatment effect. Better control of the mood disorders accompanying schizophrenia holds the possibility for improved patient outcomes.

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*From the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Ind.*

SCHIZOPHRENIA IS a heterogeneous disorder with classic domains including positive, negative, and disorganized features.[1] This triad is well recognized as the primary target in contemporary treatment studies. Mood disorders are conventionally viewed as nosologically distinct from schizophrenia, yet depressive signs and symptoms (DSS), as noted by Bleuler,[2] are evident during the course of schizophrenia. Although comorbid DSS in schizophrenia were initially interpreted through analytic constructs of despair, denial, or loss,[3] recent findings highlight that in schizophrenia they are common and often severe, pursue a distinct course, compromise functional well-being, and adversely affect the course of recovery. It is now recognized that patients with schizophrenia with comorbid DSS also display a distinct morbidity and mortality profile, including higher rates of relapse[4] and suicide.[5]

Siris[6] summarized about 30 studies of DSS in schizophrenia. Estimates of DSS range from 7% to 65%, with a modal rate of 25%.[7,8] They do not appear to be exclusively a reaction to the course of chronic schizophrenia because they are also common among patients having a first episode.[9]

The evaluation of DSS is challenging and encompasses a differential diagnosis that includes organic factors (eg, drug abuse), environmental reactions, negative symptoms, and, more importantly, ad-



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## METHODS

This was a double-blind, controlled clinical trial comparing the use of olanzapine with that of haloperidol for up to 52 weeks of treatment.[14] Eligible patients had a diagnosis based on criteria of the *DSM-III-R*[13] of schizophrenia or schizoaffective or schizophreniform disorder and a $BPRS_{0-6}$ (as extracted from the Positive and Negative Symptom Scale[17]) screening score of 18 or higher and/or intolerance to their last neuroleptic treatment. BPRS items were scored from 0 to 6. Inpatient status was not required, and patients were medically stable. No other primary Axis I diagnosis was permitted. Additional outcome instruments were the MADRS,[16] the Clinical Global Impression-Severity Scale[18] for efficacy, and the Simpson-Angus Scale[19] and the Barnes Akathisia Scale[20] for safety. In addition, vital signs and laboratory analyses were screened regularly. Following a screening assessment, a minimum washout of 3 days from oral antipsychotic agents or 1 cycle from a depot neuroleptic agent was required.

All patients provided written informed consent. Randomization was 2 persons receiving olanzapine treatment to every 1 person receiving treatment with haloperidol. All study patients began taking either olanzapine or haloperidol at 5 mg/d for the first 7 study days. Thereafter, titrations by 5 mg to a maximum of 20 mg/d were permitted at the discretion of the investigator. The need for centrally acting concomitant medications was exclusionary, with the exception of benztropine mesylate (maximum of 6 mg/d) or lorazepam (maximum of 12 mg/d) as necessary for extrapyramidal syndromes or agitation. Study patients were evaluated weekly through the first 6 visits. Responders (≥40% improvement in BPRS score) were evaluated monthly through 52 study weeks.

In this study, a statistical software package (SAS, version 6.07, running under version 4.2) was used to perform all statistical analyses.[21] Analysis of variance with a type III sum of squares was used to evaluate continuous datausing a general linear model procedure. The model generally included terms for treatment, country, and treatment-by-country interaction. For analysis of proportions, the Pearson $\chi^2$ test, using a distributive procedure within SAS, was generally used for treatment comparisons. Fisher exact confidence intervals (CIs) were constructed for differences in response rates. For all analyses, main effects were tested at a 2-sided $\alpha$ level of .05, and treatment-by-investigator interactions were tested at an $\alpha$ level of .10.

All total scores from rating scales and subscales were derived from the individual items. If any of the individual items were missing, the total score was treated as missing. When a change in the last observation carried forward from baseline to end point was assessed, patients were included in the analysis only if a patient had a baseline and at least 1 postbaseline measure. Unless otherwise defined, a baseline measure was the visit at which randomized treatment began; if data were missing, the baseline measure was the initial screening observation. Unless otherwise defined, a short-term end-point measure was the last measure obtained during the initial phase (weeks 1-6 of randomized treatment).

A path analysis[22] was used to determine if a differential efficacy on DSS emerged favoring the use of either olanzapine or haloperidol and to equate unexplained DSS treatment effect after covarying for presumed confounders as a primary (direct) therapeutic effect. In path analysis, the direct effect on DSS was defined as the treatment effect remaining after covarying for secondary (indirect) effects, including positive, negative, and extrapyramidal symptoms via a linear regression. Conversely, a secondary effect, eg, through positive symptoms, was the product of the coefficient of the positive symptom covariate in the above model and the treatment effect on positive symptoms. **Figure 1** and shows a "path" model illustrating the relationships between positive, negative, depressive, and extrapyramidal symptoms. Thus, the total effect on DSS was the sum of the primary and the secondary effects. This total effect was the same as the more commonly cited unadjusted treatment effect. Thus, the path analysis assumed that a direct effect on DSS represented an improvement in the core mood exclusive of secondary factors.

verse events. The existence of multiple contributors to DSS in patients with schizophrenia highlights the importance of baseline and periodic mood assessments. Despite the prevalence, severity, prognostic importance, and psychosocial consequences of DSS, relatively few treatment studies appear in the literature. With the introduction, however, of a new generation of putative antipsychotic agents exhibiting novel pharmacological properties beyond the $D_2$ receptor, a unique opportunity to address this issue exists.[10] Each of these neurotransmitter systems has been implicated in mood disturbance.[11] Olanzapine exhibits pharmacological activity within these systems and, thus, is an interesting candidate to investigate for its effect on DSS.[12]

In a 17-nation, double-blind, comparator-controlled study of 1996 patients with *DSM-III-R*[13] criteria for schizophrenia or related conditions,[14] we hypothesized that the use of the conventional $D_2$ antagonist haloperidol would be a less effective treatment of DSS in schizophrenia than that of olanzapine. The following additional questions were posed:

- What is the prevalence of DSS in this large multinational cohort?
- How do DSS relate to the overall psychosis, negative symptoms, extrapyramidal syndromes, and treatment outcome?
- Do certain patients experience a treatment-associated worsening of mood, and, if so, are there between-treatment differences?
- What is the role of anticholinergic or benzodiazepine drugs in the course of mood symptoms?
- Does the treatment outcome differ between patients with schizophrenia and those with schizoaffective depression?



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• Is there a concordance between a Brief Psychiatric Rating Scale (BPRS)[15] depression factor and scores on the Montgomery-Asberg Depression Rating Scale (MADRS)[16]?

• Within a treatment assignment, does the dose necessary to achieve an antipsychotic response differ based on the presence or absence of comorbid DSS?

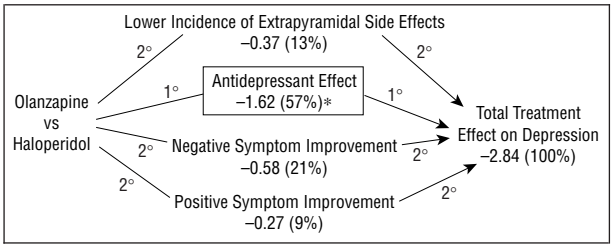


**Figure 1.** *Exhibit of the "path-analytic" model illustrating the relationships between positive, negative, extrapyramidal, and mood symptoms and their relative contributions to Montgomery-Asberg Depression Rating Scale score changes. The majority and a significant change is attributable to a primary or "direct" effect on mood. Asterisk indicates* P<*.001,* t*=3.645,* df*=1, 456.*

## RESULTS

### OVERALL POPULATION AND DISPOSITION

At baseline, 1996 patients were randomly assigned to the 2 treatment arms, 1336 to receive olanzapine and 660 to receive haloperidol. A total of 1948 patients were evaluable, ie, they had at least 1 postbaseline assessment. At baseline, patient characteristics (**Table 1**) and severity of illness (**Table 2**) were comparable. The MADRS scores were collected only at baseline and the last visit at week 6 of the study. Thus, total change scores for the last-observation-carried-forward MADRS were available on 1481 patients. Most patients (95%) had histories of previous neuroleptic therapy. An analysis of patients with and without such a history revealed no substantial baseline DSS differences. Patient disposition (**Table 3**) included statistically significantly more olanzapine-treated than haloperidol-treated patients completing the 6-week study ($P<.001$).

**Table 1. Patient Characteristics**

| Variable | Treatment Group: Olanzapine (n=1336) | Treatment Group: Haloperidol (n=660) | Total (N=1996) | *P* |
|---|---|---|---|---|
| Sex, No. (%) | | | | |
| Male | 869 (65.0) | 427 (64.7) | **1296** (64.9) | .88* |
| Race or ethnicity, No. (%) | | | | |
| White | 1078 (80.7) | 523 (79.2) | **1601** (80.2) | |
| African descent | 138 (10.3) | 81 (12.3) | **219** (11.0) | |
| Asian | 29 (2.2) | 16 (2.4) | **45** (2.3) | .76* |
| Hispanic | 56 (4.2) | 27 (4.1) | **83** (4.2) | |
| Other | 35 (2.6) | 13 (2.0) | **48** (2.4) | |
| Age, y | | | | |
| Mean (SD) | 38.73 (11.58) | 38.27 (11.13) | 38.58 (11.43) | .40† |
| Diagnosis, No. (%) | | | | |
| Schizophrenia | | | | |
| Catatonic | 14 (1.0) | 9 (1.4) | **23** (1.2) | |
| Disorganized | 81 (6.1) | 39 (5.9) | **120** (6.0) | |
| Paranoid | 662 (49.6) | 327 (49.5) | **989** (49.5) | |
| Undifferentiated | 288 (21.6) | 138 (20.9) | **426** (21.3) | .95* |
| Residual | 67 (5.0) | 33 (5.0) | **100** (5.0) | |
| Schizophreniform | 28 (2.1) | 10 (1.5) | **38** (1.9) | |
| Schizoaffective | 196 (14.7) | 104 (15.8) | **300** (15.0) | |
| Schizophrenia course, No. (%)‡ | | | | |
| Unspecified | 30 (2.7) | 18 (3.3) | **48** (2.9) | |
| Chronic/subchronic | 706 (63.5) | 333 (61.0) | **1039** (62.7) | .74* |
| Chronic/subchronic with AE | 368 (33.1) | 193 (35.3) | **561** (33.8) | |
| In remission | 8 (0.7) | 2 (0.4) | **10** (0.6) | |
| Age at onset of psychosis, y§ | | | | |
| Mean (SD) | 24.16 (7.90) | 23.37 (6.70) | 23.90 (7.53) | .03† |
| Length of current episode, d‖ | | | | |
| Mean (SD) | 1062.78 (2226.20) | 1212.66 (2435.07) | 1111.55 (2296.58) | .22† |
| Previous episodes, No. (%)¶ | | | | |
| <10 | 939 (71.4) | 442 (68.5) | **1381** (70.5) | |
| 10 to <30 | 235 (17.9) | 126 (19.5) | **361** (18.4) | .76* |
| ≥30 | 141 (10.7) | 77 (11.9) | **218** (11.1) | |

**Frequencies are analyzed using a $\chi^2$ test.*
*†Means are analyzed using a type III sum of squares analysis of variance.*
*‡Includes only those patients with a diagnosis of schizophrenia: olanzapine, n=1112; haloperidol, n=564. AE indicates acute exacerbation.*
*§Olanzapine, n=1332; haloperidol, n=657.*
*‖Olanzapine, n=1105; haloperidol, n=533.*
*¶Olanzapine, n=1315; haloperidol, n=645.*



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**Table 2. Baseline Severity of Illness**

| Test* | Treatment Group: Olanzapine (n=1312) | Treatment Group: Haloperidol (n=636) | Total (N=1948) | P |
|---|---|---|---|---|
| BPRS total | 33.05 (10.58) | 34.09 (11.03) | 33.39 (10.74) | .02† |
| PANSS total | 90.11 (19.15) | 92.10 (19.99) | 90.76 (19.44) | .01† |
| PANSS positive | 21.23 (6.05) | 21.53 (6.04) | 21.33 (6.05) | .49† |
| PANSS negative | 24.02 (6.83) | 24.47 (7.11) | 24.17 (6.92) | .07† |
| PANSS general psychiatric | 44.85 (10.42) | 46.11 (11.12) | 45.26 (10.66) | .003† |
| CGI-S‡ | 4.68 (0.93) | 4.73 (0.93) | 4.70 (0.93) | .05† |
| MADRS total§ | 16.62 (8.87) | 16.70 (8.69) | 16.64 (8.82) | .55† |
| BPRS depression cluster | 11.04 (4.89) | 11.56 (5.20) | 11.21 (5.00) | .03† |

*BPRS indicates the Brief Psychiatric Rating Scale; PANSS, the Positive and Negative Syndrome Scale; CGI-S, the Clinical Global Impression Severity Scale; MADRS, the Montgomery-Asberg Depression Rating Scale. Data are given as mean (SD).

†Means are analyzed using a type III sum of squares analysis of variance using a general linear model procedure that included terms for investigator, treatment, and interaction.

‡Olanzapine, n=1318; haloperidol, n=640.

§Olanzapine, n=1053; haloperidol, n=428.

**Table 3. Patient Disposition**

| Reason for Discontinuation | No. (%) Treatment Group: Olanzapine (n=1336) | No. (%) Treatment Group: Haloperidol (n=660) | No. (%) Total (N=1996) | P* |
|---|---|---|---|---|
| Completed study | 887 (66.4) | 309 (46.8) | **1196** (59.9) | <.001 |
| Adverse event | 60 (4.5) | 48 (7.3) | **108** (5.4) | .01 |
| Lack of efficacy | 277 (20.7) | 212 (32.1) | **489** (24.5) | <.001 |
| Lost to follow-up | 15 (1.1) | 11 (1.7) | **26** (1.3) | .31 |
| Patient decision | 48 (3.6) | 49 (7.4) | **97** (4.9) | <.001 |
| Criteria not met/compliance | 44 (3.3) | 29 (4.4) | **73** (3.7) | .22 |
| Sponsor decision | 4 (0.3) | 2 (0.3) | **6** (0.3) | .99 |

*Frequencies are analyzed using a $\chi^2$ test.

## FREQUENCY OF MODERATE DEPRESSION AT BASELINE

To estimate the frequency of at least moderate DSS, the sample was stratified a priori by a baseline MADRS score of 16 or higher. By this a priori criterion, 1047 persons, or 53% of the overall sample, were at least moderately depressed (olanzapine treatment group, 694; haloperidol treatment group, 353). A secondary definition, requiring only a MADRS item 1 (apparent sadness) mood score of 2 or higher, yielded a similar prevalence estimate. Another a priori secondary definition, a cluster of BPRS "depression" items (somatic concern, anxiety, guilt feelings, depression, tension, and motor retardation), defined moderate DSS as a cluster score of 10 or higher. This definition characterized 61% of the total sample (olanzapine treatment group, 811; haloperidol treatment group, 414). This modified factor was chosen, in contrast to the more conventional BPRS anxiety-depression factor (which excludes item 6, tension, and item 13, motor retardation), to include a psychomotor continuum, a frequent part of the depressive symptom constellation.

## ANTIDEPRESSANT RESPONSE

### All Patients

During the initial study phase, the mean (±SD) modal daily dosages of olanzapine and haloperidol were approximately 13±15 mg and 12±10 mg per day, respectively. No meaningful difference was detected between the moderate-DSS and non-DSS strata.

In the present study, both agents demonstrated an improvement in the initial 6-week study phase by baseline-to-end point change on the MADRS (last observation carried forward). Olanzapine, however, exhibited a significantly greater treatment effect ($F=10.60$; $df=1, 1439$; $P=.001$) among all patients. Olanzapine-treated patients (n=1053) experienced a mean (±SD) change of −5.97±8.69 in the MADRS total scores vs −3.06±8.78 points for haloperidol-treated patients (n=428). Hence, olanzapine-treated patients had a 2.92-point greater improvement in MADRS total scores than haloperidol-treated patients (95% CI, 1.93-3.90). These differences were consistent across countries, with the results from 13 of 17 countries favoring the use of olanzapine. Within



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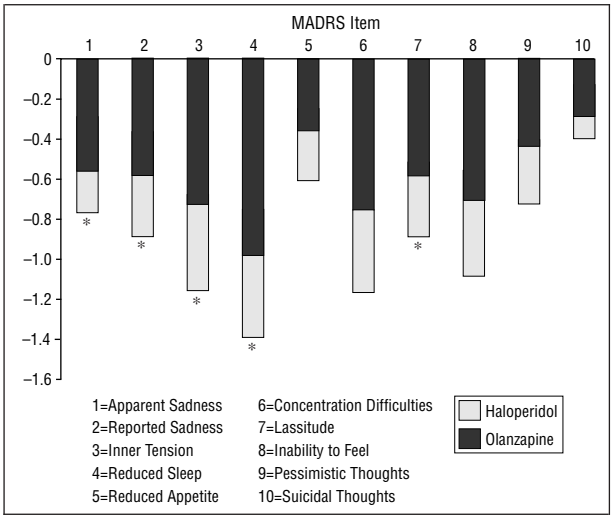


**Figure 2.** *The individual Montgomery-Asberg Depression Rating Scale (MADRS) item contributions to the total score change. Those with an asterisk represent significant between-treatment differences (items 1-4 and 7), which all favored olanzapine. Asterisk indicates* P<*.05, F test of treatment effect using analysis of variance.*

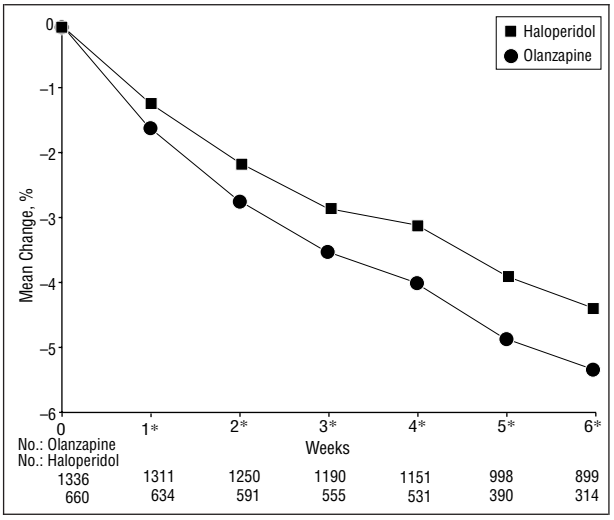


**Figure 3.** *A plot of weekly (observed case) change between treatments on the Brief Psychiatric Rating Scale depression cluster scores. Weekly change, beginning at week 1, favored olanzapine during the 6-week phase of the study. Asterisk indicates* P<*.05, F test of treatment in analysis of variance model.*

the MADRS total score change, item 1 (apparent sadness) improvement also favored the use of olanzapine over haloperidol (F=12.71; *df*=1, 1441; *P*<.001). **Figure 2** illustrates that all 10 MADRS items demonstrated greater improvement with the use of olanzapine than with haloperidol. The BPRS 6-item depression cluster demonstrated a baseline-to-end point change that also significantly favored the use of olanzapine (n=1312; –4.11±4.98) over haloperidol (n=636; –2.75±5.11; F=5.94; *df*=1, 1906; *P*=.02), a difference of 1.35 points (95% CI, 0.89-1.82). Among the individual 6 BPRS cluster items, scores for both the depression and motor retardation items demonstrated significantly greater improvement with the use of olanzapine than with haloperidol (F=11.85; *df*=1, 1906; *P*=.01; F=4.56; *df*=1, 1906; *P*=.03, respectively). A more stringent definition of response, ie, 50% or greater improvement from the baseline MADRS total score (on those patients completing at least 3 weeks of the treatment), demonstrated a significantly higher response rate among 950 olanzapine-treated (46%) than 350 haloperidol-treated (35%) patients ($\chi^2_1$=12.02; *P*=.001). The 95% CI on the difference-in-response rates was 5% to 17%.

Weekly BPRS depression cluster scores (observed case) were analyzed (**Figure 3**). The difference between the 2 treatments significantly favored the use of olanzapine beginning at week 1 (F=4.62; *df*=1, 1944; *P*=.03) and throughout the remainder of the initial 6-week phase.

### Depression Outcome by Stratification

When the same analyses were conducted on the MADRS score stratum of 16 or higher at baseline, the MADRS between-treatment effects were magnified to a mean (±SD) score of –9.69±9.02 for olanzapine-treated patients (n=538) vs –5.66±8.96 for haloperidol-treated patients (n=229). This treatment-effect difference of 4.03 points (95% CI, 2.64-5.42) also significantly favored the olanzapine-treated patients (F=11.00; *df*=1, 725; *P*=.001) and was about twice as large as that seen among the haloperidol-treated patients. In a conversation, Stuart Montgomery, MD (June 15, 1996), stated to one of us (G.D.T.) that a 4-point difference between 2 active therapies on the MADRS is clinically meaningful. Of note, a significant MADRS treatment benefit was also still evident in the less depressed group baseline (MADRS score, <16), favoring the use of olanzapine (–2.08±6.32; n=515) over haloperidol (–0.06±7.55; n=199; F=8.63; *df*=1, 675; *P*=.003). This difference was 2.03 points (95% CI, 0.94-3.12). Depressive response rates in both groups favored the use of olanzapine (DSS: olanzapine, 48.3%; haloperidol, 36.9%; $\chi^2_1$=6.93, *P*=.008; 95% CI difference, 2.8%-20.1%; non-DSS: olanzapine, 42.7%; haloperidol, 32.7%; $\chi^2_1$=5.20, *P*=.02, 95% CI difference, 1.2%-18.7%).

### DEPRESSIVE SYMPTOM RELATIONSHIPS

The overall correlation was strongly and positively correlated between initial 6-week change scores in the last-observation-carried-forward MADRS total and the following rating scales: BPRS total, BPRS depression cluster, Positive and Negative Syndrome Scale (PANSS), positive PANSS and negative subscales(**Figure 4**).

Among patients with a predominant negative or mixed negative symptom presentation[17] (n=913), the change in the MADRS scores with the use of olanzapine (–6.4±8.9) was significantly greater than that seen with haloperidol (–3.4±9.0; F=8.00; *df*=1, 873; *P*=.005). The magnitude of the change in the MADRS scores was less among patients with predominantly positive symptoms but still significantly favored the use of olanzapine (olanzapine treatment group, –5.8±8.1; haloperidol treatment group, –2.6±7.9; F=7.93; *df*=1, 256; *P*=.005).

To better assess whether the improvement in the MADRS scores was a direct effect of therapy or the product of better control of the patient's psychotic episode, a



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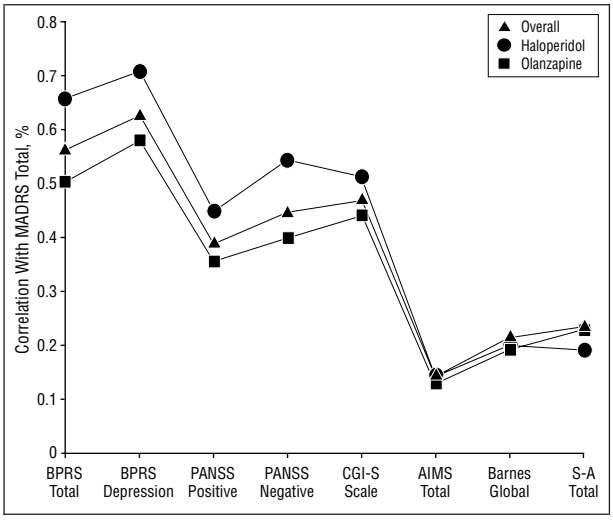


**Figure 4.** *The respective correlation between treatment-associated change on several rating instruments, relevant subscales, and the Montgomery-Asberg Depression Rating Scale (MADRS). All correlation values displayed are positive. BPRS indicates Brief Psychiatric Rating Scale; PANSS, Positive and Negative Symptom Scale; CGI-S, Clinical Global Impression-Severity Scale; AIMS, Abnormal Involuntary Movement Scale; and S-A, Simpson-Angus Scale.*

path analysis was conducted. This analysis demonstrated that the early improvement in MADRS scores was not solely related to an antipsychotic response that was either positive-and/or negative-symptom based (Figure 1). Rather, the majority (57%) of the treatment effect was directly on depressive symptoms. This direct effect alone was significantly greater with the use of olanzapine ($t_{1456}$=–3.65, $P$<.001). When extrapyramidal syndromes, as indirect contributors to mood change, were assessed, only 13% of the difference in the MADRS scores was attributable to olanzapine's more favorable effect on these syndromes.

## SCHIZOAFFECTIVE SUBGROUP

A separate analysis of schizoaffective patients with depressed mood (n=134) revealed a similar benefit on mood symptoms favoring the use of olanzapine (MADRS scores change, –9.2±11.2) relative to haloperidol (MADRS scores change, –2.6±10.5; $F_{1, 116}$=9.06; $P$=.003). After adjusting for the variation caused by the diagnostic type through an analysis of covariance, the use of olanzapine remained significantly superior to that of haloperidol on the change in MADRS scores ($F_{1, 1433}$=5.03; $P$=.03).

## EFFECT OF CONCOMITANT AGENTS

Significantly fewer olanzapine-treated (35%) than haloperidol-treated (46%) patients received 1 or more doses of benzodiazepine hydrochloride in the 2 weeks preceding their final initial-phase evaluation ($\chi^2$1=15.09, $P$<.001). Among those not receiving a benzodiazepine (olanzapine treatment group, 680; haloperidol treatment group, 230), olanzapine-treated patients demonstrated greater improvement in mean (±SD) MADRS scores of –6.5±8.3 scale points vs haloperidol's mean (±SD) scores of –4.0±8.4 (F=4.25; $df$=1, 868; $P$=.04). Among those receiving a benzodiazepine (olanzapine treatment group, 373; haloperidol treatment group, 198), the olanzapine-treated patients (–5.1±9.3) again outperformed the haloperidol-treated patients (–2.1±9.2) on total MADRS score improvement (F=3.77; $df$=1, 531; $P$=.05). When benzodiazepine use was adjusted for in the analysis of the mean change in MADRS total scores by analysis of covariance, patients treated with olanzapine continued to demonstrate a superior improvement in mood (F=8.10; $df$=1, 1399; $P$=.005).

When anticholinergic use in the 2 weeks before the final MADRS assessment was reviewed, significantly more haloperidol-treated patients (37%) than olanzapine-treated (10%) were noted to have received at least 1 dose ($\chi^2_1$=156.53, $P$<.001). Among the olanzapine-treated patients either with anticholinergic use (F=4.46; $df$=1, 231; $P$=.04) or without (F=8.07; $df$=1, 1177; $P$=.005), olanzapine treatment was associated with a significantly greater mean improvement in MADRS total scores than haloperidol treatment. When concomitant anticholinergic use was adjusted for, the mean change in the MADRS total score showed a superior olanzapine treatment effect (F=8.82; $df$=1, 1408; $P$=.003).

## TREATMENT-ASSOCIATED WORSENING

A treatment-associated worsening of DSS was defined a priori as a 50% or more increase in the MADRS total score from baseline at any time during the initial phase. By this criterion, a significantly higher rate of treatment-associated mood worsening was seen among haloperidol-treated (13%) than olanzapine-treated (9.0%) patients ($\chi^2_1$=6.08, $P$=.01).

## MAINTENANCE OF INITIAL TREATMENT EFFECTS

A total of 933 initial treatment responders were eligible to move into the masked extension phase (olanzapine treatment group, 718; haloperidol treatment group, 215). **Figure 5** illustrates the 52-week course of DSS among the olanzapine- and haloperidol-treated patients. This observed case plot reveals that the initial therapeutic benefits on mood from the use of olanzapine were retained during long-term maintenance. The large attrition rate that led to a small number of haloperidol-treated patients reaching the latter stages of the trial leaves the relative long-term-maintenance benefit of haloperidol unclear.

## SAFETY SUMMARY

As previously reported,[14] treatment with olanzapine was well tolerated, with significantly fewer olanzapine-treated patients discontinuing early because of an adverse event ($\chi^2_1$=6.68, $P$=.01). A detailed discussion of events has been reported previously.[14]

## COMMENT

Aspects of this study design, size, and analyses presented several strengths relative to previous studies. Study



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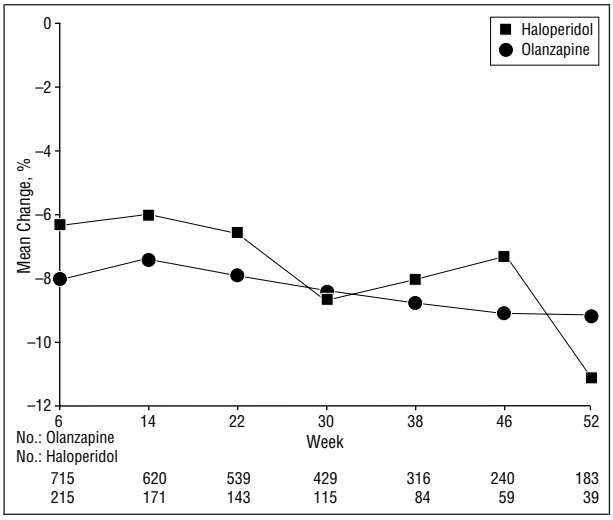


**Figure 5.** *An observed case plot of Montgomery-Asberg Depression Rating Scale change during 46 weeks of additional treatment in a double-blind, extension phase. Only initial treatment responders, defined as a 40% or greater Brief Psychiatric Rating Scale improvement and at least 3 weeks of initial treatment, were eligible.*

groups were comparable at baseline. Raters were unaware of the randomized treatment, minimizing bias. Among the 1996 study participants, about 1 of every 2 patients exhibited at least a moderate mood disturbance at baseline (MADRS score, ≥16). Given the relatively brief prestudy washout, some residual DSS from a previous therapy was possible; however, such effects should have been equally distributed between the 2 study arms.

The present trial compared 2 chemically distinct antipsychotic therapies for their respective antidepressive properties. The use of olanzapine was statistically significantly superior to that of haloperidol in the early improvement of DSS. Substantial advantages were evident on 5 of the 10 MADRS items, including core mood (items 1 and 2). While an improvement in mood was related to a change in both positive and negative symptoms, it further appeared to be a separate dimension of the schizophrenic disease.

This study incorporated reliable and validated tools for the assessment of treatment-associated changes in mood. The MADRS, initially developed from the Comprehensive Psychopathological Rating Scale,[23] has been shown to be both sensitive and reliable.[24,25] Montgomery[26] previously reported that the MADRS was a valid instrument for assessing mood in patients with schizophrenia.

Despite a broad heterogeneity in methods, previous studies have confirmed the presence of DSS during the course of schizophrenia. Burrows and Norman[27] reported a modal rate between 25% and 50%. In the present study, the presence and severity of comorbid, nonprimary DSS were based on the MADRS total score. Slightly more than half the sample exhibited a baseline MADRS score of 16 or higher. This rate also agrees with rates obtained by Knights et al[28] (Present State Examination, 54%), Johnson[29] (Hamilton Rating Scale for Depression (24%-50%), Martin et al[30] (Feighner criteria, 57%), and Leff et al (Present State Examination, 45%).[31]

Several researchers[32-36] have suggested that there is no substantial difference in the dose necessary for the control of psychosis when comparing patients with schizophrenia with or without concurrent DSS. We evaluated the mean modal daily dosages of olanzapine and haloperidol stratified by the presence of DSS (MADRS score, ≥16) and saw no dose difference based on the DSS.

Most conventional neuroleptic agents, as represented by haloperidol, have been the product of $D_2$-receptor screening programs.[10] In his review, Nelson[37] commented, "There is considerable evidence that neuroleptics are useful in the treatment of depression." Paradoxically, however, $D_2$ antagonists block receptor populations throughout the brain, including frontal reward pathways.[38] The consequence of attenuating reward or pleasure has raised the concern that treatment with conventional neuroleptic agents could be responsible for the emergence or intensification of DSS. This phenomenon has been referred to as neuroleptic-induced dysphoria. Although DSS are described in neuroleptic-naive schizophrenic patients having a first episode,[9] patients receiving conventional antipsychotic drugs may have higher rates.[39,40] Several lines of evidence suggest that neuroleptic-induced dysphoria may not encompass full criteria for a depressive disorder,[41] but nonetheless may adversely affect functional well-being.[42,43] In our investigation, the absence of a placebo arm prevented the determination of the disease-associated base rate of treatment-emergent DSS. Treatment-associated worsenings (at any time) were observed, however. The incidence was significantly more frequent among haloperidol-treated patients ($\chi^2_1$=6.08, $P$=.01).

In previous studies of DSS in schizophrenia, a reported confounding factor was the possible effect of concomitant treatments, eg, anticholinergic agents. VanPutten and May[44] reported depressive features among neuroleptic-treated patients who manifest extrapyramidal syndromes. They furthermore observed a positive mood response to anticholinergic treatment. Galdi[40] has referred to this as "pseudo-parkinsonian depression." In the present study, an analysis of concomitant treatment records did not support anticholinergic drug use as a substantial confounder.

The superior mood improvement during monotherapy with olanzapine was unexpected in light of the vast majority of previous DSS treatment studies using combination strategies (eg, neuroleptic and cyclic antidepressant). Such studies have generated mixed results[6,27]; however, they suffered from methodologic limitations.[6] Several better-designed studies have established that DSS are treatment responsive with a combined drug approach. Singh et al[45] studied 60 patients who received phenothiazine therapy for at least 6 weeks. Those randomly selected to receive trazodone hydrochloride (300 mg/d) outperformed their counterparts who received a placebo in mood improvement (Hamilton Rating Scale for Depression/Clinical Global Impression), but not psychosis (BPRS). Hogarty et al[46] observed that the use of desipramine hydrochloride relieved some symptoms of chronic anxiety and mood and required less frequent dose increases in patients' neuroleptic agents. Prusoff and colleagues[47] administered perphenazine



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(16-48 mg/d) plus amitriptyline hydrochloride (100-200 mg/d) or placebo to 35 patients. During a 6-month follow-up, a greater improvement in depression ratings, social well-being, and overall response characterized the adjunctively treated group. In a study of 33 patients with schizophrenia or schizoaffective disorder as determined by the *Research Diagnostic Criteria for a Selected Group of Functional Disorders*,[48] Siris et al[49] added imipramine hydrochloride (150-200 mg/d) to a stable dose of fluphenazine decanoate and reported after 6 weeks that the combination was superior to placebo on clinical global and mood assessments. After 6 months of successful open treatment with imipramine (100-300 mg/d) and fluphenazine decanoate (n=24), patients underwent a blinded randomization to either continued maintenance imipramine therapy or placebo substitution. During the next year, significantly more of the placebo-assigned patients experienced either or both a DSS relapse and psychotic exacerbation. Although the present study did not use a rerandomization, the maintenance of short-term DSS improvement was also evident.

The modest augmentation benefit of the use of cyclic antidepressant medications may reflect the limits of reuptake inhibition rather than that DSS are a relatively "refractory element" of schizophrenia. Olanzapine exhibits a broad affinity for receptor sites for 5-hydroxytryptamine $(5\text{-HT})_{2A,C}$, $5\text{-HT}_3$, $5\text{-HT}_6$, $\text{dopamine}_{1\text{-}5}$, muscarinic $\text{cholinergic}_{1\text{-}5}$, $\alpha_1$-noradrenergic, and histamine-1 receptor sites.[12] Whether 1 or more of these systems is implicated in the pathogenesis of DSS is unknown. In light of the recent interest, however, in $5\text{-HT}_2$ binding sites in both depression[50] and schizophrenia,[51] it is tempting to implicate this site.

Previous investigators[44,52-58] have noted an interrelationship between changes in DSS and psychotic symptoms. In our trial, the early stabilization of psychosis (both positive and negative features) occurred in conjunction with DSS improvement. This phenomenon leads to the question of whether DSS improvement is merely a secondary phenomenon. In a recent study of DSS in patients with their first episode, Koreen and colleagues[9] reported that the change in the Hamilton Rating Scale for Depression score correlated with both the positive ($r$=0.69) and negative ($r$=0.62) schizophrenic symptom changes. These latter 2 dimenions were assessed by the Schedule for Affective Disorders and Schizophrenia and the Scale for the Assessment of Negative Symptoms, respectively. Controlling for negative symptoms "reduced but did not eliminate the correlations between extracted Hamilton Rating Scale for Depression and positive symptoms." Although correlations between positive psychotic and depressive symptoms were observed, the present path-analytic approach demonstrated that olanzapine treatment-associated benefits in mood that were due to positive symptom change accounted for only 9% of the total benefits. Conversely, positive symptom change explained most of haloperidol's benefit.

In a recent article, Sax et al[59] investigated patients with either schizophrenia or psychotic major depression. Mood symptoms correlated with anhedonia or asociality and avolition or apathy in both groups. Others have suggested a relationship between DSS and the negative or deficit syndrome.[60,61] Kibel et al,[62] however, observed that 5 of 10 MADRS items (reported sadness, inner tension, reduced sleep, pessimistic thought, and suicidal thoughts) were not significantly correlated with negative symptoms. Prosser et al[63] reported that certain DSS (eg, activities) were correlated with the negative symptom subscale of the BPRS. In contrast, cognitive features (eg, core mood disturbance, suicidality, and guilt) were not. In our study, a positive correlation also existed between Positive and Negative Syndrome Scale-negative and MADRS symptom change; however, path analysis showed that this correlation accounted for less than 21% of the differential olanzapine advantage on the MADRS. In contrast, a significant proportion of MADRS score improvement (57%) was through a direct effect ($t_{1456}$=−3.65, $P$<.001). Thus, these analyses suggest that the olanzapine-associated improvement in DSS was not simply the negative symptom improvement. A relationship between DSS and akinesia has been previously discussed as well.[59-63] Siris[6] noted that neuroleptic-induced akinesia "can at times produce a rather exact phenocopy of depression." In the present study, the use of path-analytic techniques also demonstrated that only a small amount (13%) of the olanzapine-associated MADRS improvement came from an extrapyramidal syndrome advantage.

## CONCLUSIONS

This study demonstrated that DSS were common in a multinational outpatient sample with schizophrenia or closely related conditions. Furthermore, the mood disturbance appeared to represent a separate dimension of schizophrenia, as previously suggested in the literature.[27] The baseline-to-end point change in the MADRS score provided evidence that DSS were treatment responsive. Such improvements appeared sustainable for at least 52 weeks.

Of interest, while both agents were associated with mood improvement, only olanzapine exhibited a significant direct effect on the MADRS separate from positive or negative symptom change. This difference may relate to the respective pharmacological profiles of olanzapine and haloperidol. Whereas haloperidol is a relatively selective $D_2$ antagonist, olanzapine exhibits nanomolar affinities for a variety of neurotransmitter receptors. To what degree one or more of these systems participate in the pathogenesis of DSS, however, awaits additional investigation.

As stated by Hogarty et al,[46] the presence of DSS coupled with a drug's adverse effects are 2 factors "that are most likely to improve clinical outcomes and are most closely associated with quality-of-life for schizophrenic patients." In both respects, innovative antipsychotic agents such as olanzapine appear to offer promise in improving clinical outcomes in schizophrenia.

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*Reprints: Gary D. Tollefson, MD, PhD, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Drop Code 0538, Indianapolis, IN 46285.*



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## Correction

**Error in Figure.** In the article titled "Depressive Signs and Symptoms in Schizophrenia: A Prospective Blinded Trial of Olanzapine and Haloperidol," published in the March 1998 issue of the ARCHIVES (1998;55:250-258), an error appeared in Figure 2 on page 254. The bars for olanzapine and haloperidol should have been separated, the lighter bar representing haloperidol-associated change, and the darker bar, olanzapine-associated change. Figure 2 is reprinted correctly here.

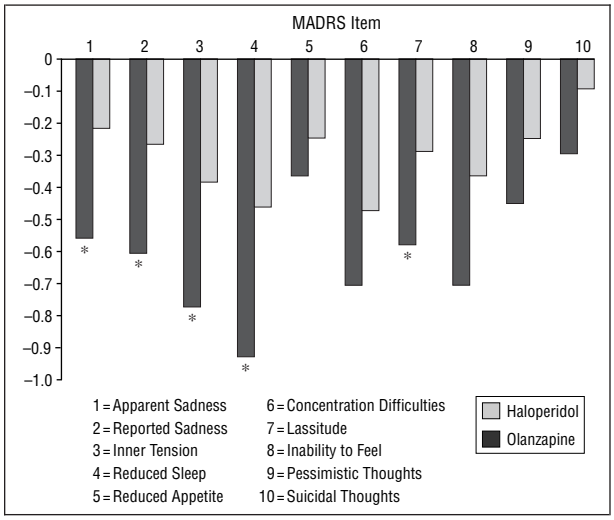


**Figure 2.** *The individual Montgomery-Asberg Depression Rating Scale (MADRS) item contributions to the total score change. Those with an asterisk represent significant between-treatment differences (items 1-4 and 7), which all favored olanzapine. Asterisk indicates* P<*.05, F test of treatment effect using analysis of variance.*



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