

Evidence for the Effectiveness of Olanzapine Among Patients Nonresponsive and/or Intolerant to Risperidone

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Background: This multicenter, open-label study evaluated the efficacy and safety of olanzapine in patients with schizophrenia who had been nonresponsive or intolerant to a course of risperidone (mean duration of risperidone treatment = 46.3 days). **Method:** A total of 34 patients with DSM-III-R and ICD-9 schizophrenia entered this trial. Twenty-five patients were nonresponsive to previous risperidone treatment, 6 patients were intolerant to the risperidone treatment, and 3 patients listed both reasons for discontinuation of risperidone. Patients were treated across a dose range of 5 to 25 mg/day of olanzapine. The primary efficacy variable was baseline to endpoint change in Positive and Negative Syndrome Scale (PANSS) score. Safety was assessed using the Clinical Global Impressions-Severity of Illness scale. **Results:** Improvement from baseline PANSS score (mean \pm SD PANSS score = 119.4 \pm 26.9) was evident at the week-6 midpoint (-22.2 ± 19.5) and at the week-14 endpoint (-28.7 ± 22.3). On average, severity ratings were reduced from baseline by 25% after 14 weeks of olanzapine therapy. Twenty olanzapine-treated patients (58.8%) achieved the a priori-defined response criterion of $\geq 20\%$ reduction in PANSS total score. Among patients who met the response criterion, 50% (10/20) had done so by the fourth week. These clinical improvements occurred across a broad range of symptom domains and included reductions in PANSS positive, negative, general psychopathology, and mood subscores. No statistically significant differences were found on any efficacy measure at any visit between the patients who were nonresponsive to risperidone compared with those who were intolerant to risperidone. Olanzapine was well tolerated, with no subject discontinuing early owing to an intolerable adverse event that could be conclusively linked to olanzapine. **Conclusion:** The results of this open-label study suggest that olanzapine may be an effective alternative for schizophrenic patients who are nonresponsive and/or intolerant to risperidone treatment. Moreover, the results underscore the differential pharmacology that exists among the newer antipsychotic agents. (J Clin Psychiatry 2001;62[suppl 2]:28-34)

Both risperidone and olanzapine are examples of novel therapeutic approaches for the treatment of schizophrenia; however, they are distinguished on the basis of quite different pharmacologic profiles.¹

Risperidone is principally a dopamine-2 (D₂) and serotonin-2 (5-HT₂) receptor antagonist. According to the U.S. label, risperidone has a maximal effect generally seen

in the dose range of 4 to 6 mg/day; however, in the clinical trials conducted by Peuskens and colleagues,² a maximal effect in the range of 4 to 8 mg/day was found. At the lower end of the risperidone dose range, the incidence of extrapyramidal symptoms (EPS) is similar to that seen with placebo. However, with increased doses, the extrapyramidal profile of risperidone appears more like that of haloperidol.^{3,4}

Olanzapine is a novel antipsychotic agent of the thienobenzodiazepine class. In addition to potent 5-HT_{2A/2C}, 5-HT₃, and 5-HT₆ receptor antagonism, olanzapine further exhibits affinity for dopamine D₁, D₂, D₃, and D₄ receptors and selective muscarinic binding sites.⁵ This novel pharmacologic profile may explain the broad spectrum of efficacy reported with olanzapine⁶⁻⁸ and the low incidence of EPS⁶⁻⁹ and hyperprolactinemia.¹⁰

Recently, Tran et al.¹¹ reported the results of a trial with direct comparisons between olanzapine and risperidone in patients with schizophrenia and other related disorders.

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Both agents exhibited similar baseline-to-endpoint improvement according to the Positive and Negative Syndrome Scale (PANSS). Acute 8-week responders (defined as at least a 20% improvement in PANSS total score and Clinical Global Impressions-Severity of Illness scale¹² [CGI-S] score ≥ 3 at the end of 8 weeks) were subsequently followed on a continued double-blind basis for a total treatment duration of 28 weeks. The olanzapine-treated patients demonstrated a statistically significantly lower probability for a clinical relapse than their risperidone-treated counterparts (olanzapine, 12.1%; risperidone, 32.3%; $p = .001$). Other differences between the 2 treatment groups included a significantly lower incidence of EPS (as measured by objective rating scales) and hyperprolactinemia, and significantly superior symptomatic improvement in negative symptoms (as measured by the Scale for the Assessment of Negative Symptoms) and mood features in the olanzapine-treated group. The mean doses used for olanzapine and risperidone were 17.2 mg/day and 7.2 mg/day, respectively.

Such a head-to-head trial does not answer the question of whether one compound is effective among nonresponders to another compound. The present open-label study evaluated the efficacy and safety of olanzapine in schizophrenic patients previously defined as nonresponsive or intolerant to risperidone treatment.

METHOD

The study was conducted in accordance with the Declaration of Helsinki, good clinical practice guidelines, and the laws and regulations applicable in the country of study conduct. All patients gave written informed consent before entry to the study. A total of 43 schizophrenic patients (aged 18–65 years) were entered into 7 study centers. Women of childbearing potential using medically accepted contraception were included, but patients found to be pregnant or lactating were excluded. All patients had DSM-III-R¹³ and ICD-9¹⁴ diagnoses of schizophrenia, made by 2 independent assessors. Twenty-five patients had discontinued risperidone owing to lack of efficacy (efficacy defined as $< 20\%$ reduction in total Brief Psychiatric Rating Scale [BPRS] score [scale of 1–7]¹⁵ after a minimum of 4 consecutive weeks of treatment within the range of 4–12 mg/day of risperidone), and 9 patients had discontinued because of treatment intolerance (3 patients experienced both lack of efficacy and intolerance to treatment). Patients nonresponsive and some of the patients intolerant to risperidone treatment had received the drug in an open-label, multicenter trial performed in Israel. Some of the patients who were intolerant to treatment had received risperidone under a compassionate-use protocol. Following discontinuation of risperidone, patients could be treated with other antipsychotics before they were enrolled in the present open-label study. Patients were enrolled after discontinuation of antipsychotics and a minimum washout pe-

riod of 4 days. All patients had sufficient understanding to communicate intelligently with the investigator, nurse, and study coordinator and agreed to cooperate with all trial assessments.

Exclusion criteria included the following: serious unstable illness; leukopenia or history of leukopenia; DSM-IV¹⁶ substance (alcohol or other drugs) abuse; 1 or more seizures without a clear etiology; serious suicidal risk; treatment with lithium, anticonvulsants, benzodiazepines, antidepressants, psychostimulants, reserpine, guanethidine, or guanadrel within 1 week before the start of active treatment; treatment with irreversible monoamine oxidase inhibitors within 2 weeks, fluoxetine within 4 weeks, or remoxipride within 6 months (180 days) of active treatment; any other concomitant medication with primary central nervous system activity; depot neuroleptic therapy in which the last dose interval was shorter than the patient's dosing interval before study entry; uncorrected hypothyroidism or hyperthyroidism; myasthenia gravis; narrow-angle glaucoma; current jaundice; and history of severe allergy or multiple drug reactions. Patients were also excluded if they had any prior exposure to olanzapine, had been treated with clozapine within 8 weeks of the start of active treatment, or had participated in a clinical trial of another investigational drug (except risperidone).

Study Procedures

Study period 1 (screening and washout) evaluated the patients' psychiatric and physical status (including clinical laboratory results) and provided a baseline for subsequent efficacy and safety assessments. Patients not satisfying the entry criteria were discontinued at visit 2. Study period 2 was the open-label active treatment period lasting 14 weeks. During this period, the efficacy and safety of olanzapine were assessed weekly for the first 6 weeks of treatment and monthly thereafter. Treatment was started at a dose of 10 mg/day of olanzapine and was adjusted up or down by 5-mg (1 tablet) increments within the range of 5 to 25 mg/day. Patients intolerant to the minimum olanzapine dose of 5 mg/day were removed from the study. Dosage increases were not permitted within 7 days of the last dosage increase and were allowed only if CGI-S¹² score was > 1 and if CGI-S score worsened or had not improved from baseline. Patients who improved only marginally (7 to 6 or 6 to 5 on the CGI-S) were also eligible for dosage increase. Dosage decreases due to adverse events were allowed at any time. Study period 3 was an open-label extension period that lasted until registration of olanzapine; only safety exposure data were collected. This report will be restricted to the results from study periods 1 and 2.

The primary efficacy variable, defined a priori, was the baseline-to-endpoint (14-week) change in PANSS¹⁷ total score. Additionally, the a priori definition of response was a $\geq 20\%$ improvement in PANSS total score. Positive and Negative Syndrome Scale and BPRS (extracted from the

Table 1. Summary of Patient Demographic Characteristics

Characteristic	N (%)
Sex	
Male	25 (73.5)
Female	9 (26.5)
Age, mean \pm SD, y	33.9 \pm 9.4
Duration of risperidone therapy, mean \pm SD, d	46.3 \pm 31.8
Reason for stopping risperidone ^a	
Nonresponse only	25 (73.5)
Adverse events only	6 (17.7)
Both nonresponsive and adverse events	3 (8.8)

^aPatients could give both reasons for stopping risperidone therapy; for analyses, the 3 patients who listed both nonresponse and adverse events were included in the nonresponse group.

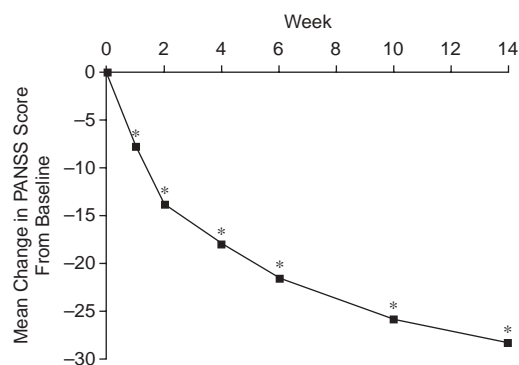
PANSS) scores were assessed at visit 1 (study period 1) and at visits 2, 3, 4, 6, 8, 9, and 10 (study period 2). Clinical Global Impressions assessments were made at all study visits. At screening (study period 1, visit 1), patients' medical histories were taken, and a physical examination, including electrocardiography (ECG), was performed. The physical examination and ECG were repeated after 6 weeks of open-label therapy and if a patient discontinued olanzapine therapy.

Patients were monitored for the occurrence of EPS at each visit during study periods 1 and 2 using the Extrapyramidal Symptom Rating Scale (ESRS).¹⁸ Vital signs (blood pressure, pulse rate, body weight, and body temperature) were measured at each study visit. Blood pressure and pulse rate were taken in the supine (after the patient had been resting for 5 minutes) and standing (after the patient had been standing for 2 minutes) positions.

Clinical laboratory investigations (clinical chemistry, electrolytes, hematology, and urinalysis) were performed at visits 1 and 2, at any time a patient completed or discontinued from the study, and where clinically indicated. Measures of hepatic status, including aspartate transaminase, alanine transaminase, total bilirubin, alkaline phosphatase, and γ -glutamyl transferase, were performed weekly during the first 6 weeks of open-label therapy, monthly for the remainder of the first 12 months of therapy, and once every 2 months thereafter.

Data Analysis

According to whether the data were normally distributed, either the paired t test or the Wilcoxon signed rank test was used to ascertain whether there were within-group changes from baseline to endpoint in the primary measure (PANSS total score), secondary measures (BPRS total score, CGI-S scores, and PANSS subscale scores), and EPS. Similarly, the 2-sample t test or Wilcoxon rank sum test was performed to ascertain whether there were differences between the responder and nonresponder groups. Patients were included in the analysis only if they had both a baseline and postbaseline score. Data were analyzed using a last-observation-carried-forward (LOCF) methodology.

Figure 1. Weekly Mean Change in PANSS Total Score From Baseline to Endpoint (LOCF)^a

^aAbbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.
* $p \leq .05$.

The incidence of treatment-emergent adverse events was recorded together with the changes from baseline (latest available results of visits 1 and 2) to endpoint in vital signs and laboratory test parameters. Data were summarized descriptively.

RESULTS

Forty-three patients were screened, of whom 34 (79.0%) were eligible to be enrolled. Table 1 presents a summary of the demographic characteristics of the patients enrolled. Twenty-five patients (73.5%) had discontinued from the risperidone study because of nonresponse to risperidone (response defined as a $\geq 20\%$ improvement in BPRS total score after a minimum of 4 weeks of treatment), and 6 patients (17.7%) discontinued because of intolerance to risperidone. Three patients (8.8%) reported both reasons for discontinuation, and for purposes of all of the analyses, these patients will be considered in the nonresponsive group. The average duration of risperidone therapy was 46 days. Prior to receiving risperidone, and before entry into this trial, the 3 most commonly used antipsychotics in this population were haloperidol (88.2% of patients), chlorpromazine (76.5%), and fluphenazine (61.8%).

Thirty-four patients entered study period 2. During study period 2, nine patients discontinued treatment, leaving 25 (73.5%) to complete this period. Two patients were withdrawn because of lack of efficacy, 2 were withdrawn because of adverse events (worsening of psychosis, suicide attempt), 2 were withdrawn by the investigator, 1 was lost to follow-up, 1 violated the entry criteria, and 1 was withdrawn by the treating physician owing to a protocol violation (i.e., use of an excluded concomitant medication). The mean \pm SD daily olanzapine dose adminis-

Table 2. Baseline-to-Endpoint (LOCF) Change in PANSS Total, Positive, Negative, Psychopathologic, and Mood Scores and BPRS Total Score (N = 34)^a

Measure	Baseline		Week 1 (visit 3)		Week 2 (visit 4)		Week 4 (visit 6)		Week 6 (visit 8)		Week 10 (visit 9)		Week 14 (visit 10)	
	Mean	SD	Mean Change	SD	Mean Change	SD	Mean Change	SD	Mean Change	SD	Mean Change	SD	Mean Change	SD
PANSS														
Total score	119.4	26.9	-7.8	9.7	-13.8	15.5	-18.0	16.0	-22.2	19.4	-26.0	21.8	-28.7	22.3
Positive subscale score	27.4	8.8	-2.3	3.7	-4.2	5.6	-5.7	5.5	-6.8	6.4	-7.5	7.4	-8.4	7.4
Negative subscale score	33.3	7.3	-1.1	2.3	-2.6	3.6	-3.9	4.2	-5.1	5.1	-6.4	5.8	-6.9	6.4
General psychopathology score	58.7	14.8	-4.4	5.3	-7.0	8.4	-8.4	8.6	-10.4	10.4	-12.2	11.6	-13.5	11.4
Mood score	11.5	5.0	-1.4	2.2	-1.9	2.9	-2.2	2.4	-2.4	2.9	-3.0	3.0	-3.1	2.9
BPRS														
Total score	46.4	16.8	-5.1	6.5	-9.1	9.7	-11.4	9.6	-13.5	11.3	-15.5	12.8	-17.17	12.6

^aAbbreviations: BPRS = Brief Psychiatric Rating Scale, LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale. All changes from baseline significant on a $p \leq .05$ level.

tered during the 14-week open-label treatment period was 15.7 ± 4.3 mg.

Efficacy

Figure 1 presents the weekly mean change from baseline to endpoint (LOCF) in the PANSS total score. This measure showed a reduction in symptom severity that was evident and statistically significant beginning at the end of the first week of pharmacotherapy and continuing through the week-14 endpoint. The mean \pm SD change from baseline to endpoint in PANSS total score was -28.7 ± 22.3 ($p < .05$) (Table 2). In addition, the other efficacy measures (PANSS positive subscale, negative subscale, general psychopathology, and mood scores and BPRS total score) showed statistically significant changes that were evident at week 1 ($p \leq .05$).

Similar changes from baseline to endpoint were also evident for PANSS positive and negative subscale scores, PANSS general psychopathology score, and PANSS mood score (mood items measured: somatic concern, anxiety, guilt feelings, and depression) (see Table 2); the mean \pm SD overall changes from baseline to the week-14 endpoint for these scales were -8.4 ± 7.4 , -6.9 ± 6.4 , -13.5 ± 11.4 , and -3.1 ± 2.9 , respectively. No statistically significant differences were found at any visit on any efficacy measure for the patients who were nonresponsive to risperidone treatment ($N = 28$) versus those who were intolerant to risperidone treatment ($N = 6$).

Based on the a priori definition of response, $\geq 20\%$ decrease in PANSS total score, 20 patients (58.8%) achieved a response to olanzapine treatment by week-14 endpoint. Fifty percent of patients (10/20) meeting this response criterion met it by the fourth week of treatment. The weekly mean change scores were analyzed for the patients who met the response criterion ($N = 20$) and for those who did not ($N = 14$) (Table 3). Responders demonstrated statistically significant improvements over nonresponders by week 1 on the BPRS total score ($p = .0178$) and PANSS total and general psychopathology scores ($p = .0430$ and $p = .0263$,

respectively), by week 2 on the PANSS negative subscale score ($p = .0042$), and by week 4 on the PANSS positive subscale and mood scores ($p = .0135$ and $p = .0132$, respectively).

For the 28 patients who were nonresponsive to risperidone treatment, we applied the definition of response used in the risperidone trial: $\geq 20\%$ decrease in BPRS total score with at least 4 weeks of treatment. Nineteen (67.9%) of the 28 patients achieved a response by the fourth week of treatment. There was already a statistically significant difference between the patients who responded, based on the BPRS definition, starting at week 1 on the PANSS total score (Figure 2).

Clinical Global Impressions-Improvement scale (CGI-I) scores at the week-14 endpoint showed that "minimal" or greater improvement was achieved by 70.6% of patients ($N = 24$) and that the remainder of the patients either experienced no change (17.6%; $N = 6$) or their CGI-I score worsened (11.8%; $N = 4$).

Safety

All 34 patients who received olanzapine were included in the safety analysis. Of these patients, 17 (50%) reported no treatment-emergent adverse events, and 17 (50%) reported ≥ 1 treatment-emergent adverse event. The most frequently reported adverse events were abnormal liver function test (3 patients) and weight gain (3 patients). Two adverse events led to drug discontinuation: one patient attempted suicide, considered not to be causally related to olanzapine, and 1 patient experienced worsening of psychotic symptoms, considered to be possibly related to olanzapine (Table 4). Extrapyramidal symptoms were evaluated using the ESRS total score. Mean values fell from 2.8 at baseline to 0.6 ($p < .001$) at the week-14 endpoint. The CGI-S for adverse events demonstrated that the functioning of 97.1% of patients ($N = 33$) was either "not affected" or "not significantly affected" by olanzapine treatment.

No clinically relevant changes in electrocardiograms, clinical laboratory parameters, blood pressure, or pulse

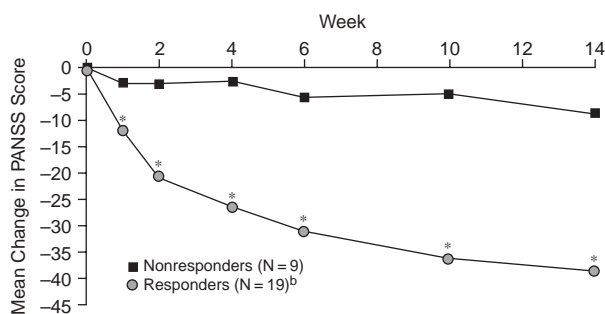
Table 3. Visitwise Mean Change Efficacy Measures: Responders to Olanzapine (N = 20) Versus Nonresponders (N = 14)^a

Measure	Baseline Mean (SD)	Week 1 (visit 3) MC (SD)	Week 2 (visit 4) MC (SD)	Week 4 (visit 6) MC (SD)	Week 6 (visit 8) MC (SD)	Week 10 (visit 9) MC (SD)	Week 14 (visit 10) MC (SD)
PANSS							
Total score							
Responders	115.2 (22.3)	-10.4 (10.4)	-18.9 (16.4)	-25.8 (14.4)	-32.1 (18.0)	-39.3 (15.8)	-43.4 (15.5)
Nonresponders	125.5 (32.2)	-4.1 (7.5)	-6.5 (10.8)	-7.0 (11.0)	-8.0 (11.1)	-7.1 (13.7)	-7.8 (10.4)
Between-group p value	.2755	.0430 ^b	.0189	.0003	.0001	.0001	.0001
Positive subscale score							
Responders	25.4 (8.5)	-2.9 (3.9)	-5.5 (6.3)	-7.8 (5.8)	-9.2 (6.6)	-11.1 (6.4)	-12.2 (6.3)
Nonresponders	30.4 (8.5)	-1.6 (3.3)	-2.3 (3.7)	-2.8 (3.6)	-3.3 (4.1)	-2.4 (5.5)	-2.9 (5.1)
Between-group p value	.1018	.3298 ^b	.0981	.0135 ^b	.0058	.0003	.0001
Negative subscale score							
Responders	33.0 (4.4)	-1.5 (2.5)	-4.1 (3.7)	-5.8 (4.3)	-7.7 (4.9)	-9.5 (5.3)	-10.6 (5.6)
Nonresponders	33.8 (10.3)	-0.5 (2.1)	-0.6 (2.4)	-1.2 (2.0)	-1.4 (2.6)	-1.9 (2.7)	-1.6 (2.3)
Between-group p value	.1854	.2104 ^b	.0042	.0009	.0010 ^b	.0001	.0001
General psychopathology score							
Responders	56.8 (13.2)	-6.1 (5.4)	-9.4 (8.2)	-12.3 (7.5)	-15.3 (9.5)	-18.7 (8.4)	-20.7 (8.6)
Nonresponders	61.4 (17.1)	-2.0 (4.1)	-3.6 (7.7)	-3.0 (7.2)	-3.4 (7.3)	-2.9 (8.9)	-3.2 (5.5)
Between-group p value	.5327	.0263 ^b	.0490	.0011	.0004	.0001	.0001
Mood score							
Responders	11.5 (4.3)	-2.1 (2.4)	-2.4 (2.7)	-3.1 (2.1)	-3.2 (2.4)	-4.4 (2.6)	-4.6 (2.6)
Nonresponders	11.6 (6.1)	-0.5 (1.5)	-1.3 (3.1)	-1.0 (2.4)	-1.1 (3.1)	-1.0 (2.4)	-1.0 (2.0)
Between-group p value	.9683	.0238 ^b	.0513 ^b	.0132	.0383	.0005	.0001
BPRS total score							
Responders	43.4 (15.0)	-7.0 (7.0)	-12.0 (10.1)	-15.8 (8.8)	-18.9 (10.8)	-23.0 (9.3)	-25.3 (8.8)
Nonresponders	11.6 (6.1)	-2.4 (4.8)	-4.9 (7.6)	-5.3 (7.0)	-5.7 (6.7)	-4.9 (9.2)	-5.6 (7.0)
Between-group p value	.2051	.0178 ^b	.0356	.0008	.0003	.0001	.0001

^aAbbreviations: BPRS = Brief Psychiatric Rating Scale, MC = mean change, PANSS = Positive and Negative Syndrome Scale. Responders based upon the a priori definition of response of $\geq 20\%$ reduction in PANSS total score baseline to endpoint (last observation carried forward).

^bWilcoxon rank sum test.

Figure 2. Weekly Mean Change in PANSS Total Score: Responders to Risperidone Treatment Versus Nonresponders^a



^aAbbreviations: BPRS = Brief Psychiatric Rating Scale, PANSS = Positive and Negative Syndrome Scale.

^bResponse defined as a $\geq 20\%$ decrease in BPRS total score from baseline to week 4 (last observation carried forward) for patients originally categorized as nonresponsive to risperidone treatment.

*p values: week 1 = .0240; week 2 = .0047; week 4 = .0001; week 6 = .0008; week 10 = .0001; week 14 = .0003.

rate were associated with olanzapine treatment. Body weight increased by a mean \pm SD of 1.28 ± 3.45 kg over the 14 weeks of therapy.

Concomitant Medication

Of 34 patients, 11 (32.4%) did not use concomitant anticholinergic medication during either risperidone or olanzapine treatment. Twenty-two patients (64.7%) received

Table 4. Treatment-Emergent Adverse Events (incidence $\geq 5\%$)

Event	N	%
Patients with no treatment-emergent adverse event	17	50
Patients with ≥ 1 treatment-emergent adverse event	17	50
Abnormal liver function test	3	8.8
Weight gain	3	8.8
Akathisia	2	5.9
Anxiety	2	5.9
Asthenia	2	5.9
Headache	2	5.9
Insomnia	2	5.9

anticholinergics during risperidone treatment, whereas only 12 patients (35.3%) received anticholinergics during olanzapine therapy. Of the 12 patients who received anticholinergics during olanzapine treatment, only 3 patients started the anticholinergic medication during olanzapine treatment, and 8 patients had begun continued use prior to the olanzapine open-label study.

DISCUSSION

This open-label trial investigated the efficacy and tolerability of olanzapine in schizophrenic patients nonresponsive or intolerant to open-label risperidone (mean duration of risperidone treatment = 46.3 days). An inadequate response to risperidone had been defined a priori as a reduction of $\leq 20\%$ in BPRS total symptom score after a mini-

mum of 4 consecutive weeks of treatment at dosages of risperidone within the range of 4 to 12 mg/day. Forty-three patients were screened, of whom 34 were eligible to be enrolled. These patients had been participants in an open-label trial of risperidone or had taken risperidone under a structured compassionate-use protocol.

Thirty-four patients satisfied the entry criteria and were given between 5 and 25 mg/day of olanzapine (mean daily dose = 15.7 mg). Nine of the patients were intolerant to risperidone treatment, and 28 were nonresponsive to risperidone treatment during the risperidone trial (3 patients cited both reasons for discontinuation of risperidone). Patients experienced a mean reduction of 25% in PANSS total score after olanzapine treatment. Interestingly, there were no statistically significant differences on any efficacy measure between patients who were nonresponsive or treatment-intolerant to risperidone. The open-label risperidone trial defined response as a $\geq 20\%$ reduction in BPRS total score, and therefore, for comparison purposes, we also analyzed response using BPRS total score for patients who were classed as nonresponsive in the risperidone trial. Applying the definition of response used in the risperidone study, 19 (67.9%) of 28 patients who were nonresponsive to risperidone treatment responded to olanzapine treatment in our open-label study. Twenty-four (70.6%) of these previously nonresponsive or treatment-intolerant patients showed at least minimal improvement on the CGI-I (2.9% [N = 1], very much improved; 29.4% [N = 10], much improved; and 38.2% [N = 13], minimally improved), while 29.4% (N = 10) either experienced no change or deteriorated (17.6% [N = 6], no change; 5.9% [N = 2], minimally worse; 2.9% [N = 1], much worse; and 2.9% [N = 1], very much worse). Moreover, 58.8% of patients (N = 20) showed a reduction of least 20% in PANSS total score at endpoint. These results suggest that olanzapine may be an effective alternative in the treatment of patients nonresponsive or intolerant to risperidone.

Similar reductions in PANSS subscale scores were also of interest, including a mean positive subscale score reduction from baseline of 30%, negative subscale score reduction of 20%, general psychopathology score reduction of 23%, and mood score reduction of 24%. These results demonstrated that olanzapine exhibited a broad spectrum of activity even within a nonresponding group of patients with schizophrenia. These data suggest that when a novel agent is effective, the spectrum of symptomatic improvement may be similar among patients with varied histories of response to more conventional agents.

Weekly analyses of all olanzapine-treated patients demonstrated that on all efficacy measures (PANSS total, positive, negative, general psychopathology, and mood scores and BPRS total score) there were statistically significant improvements after 1 week of treatment. Not surprisingly, responders, based on our a priori definition of

response of $\geq 20\%$ reduction in PANSS total score, demonstrated statistically significant improvements over nonresponders very early in the trial. Statistically significant differences between responders and nonresponders were noted for BPRS total score and PANSS total and general psychopathology scores at week 1, for PANSS negative subscale score at week 2, and for PANSS positive subscale and mood scores at week 4. These findings are important from a clinical perspective, as they suggest that response to olanzapine may occur quite rapidly and across all of the symptom domains. However, it is important to consider that while 50% (10/20) of the patients who met the a priori response criterion met it by the fourth week of treatment, 40% of patients (8/20) who met the criterion met it during the last 4 weeks (30% [6/20] by the tenth week and 10% [2/20] by the fourteenth week).

Olanzapine was well tolerated and was not associated with EPS. No clinically significant hematologic changes were encountered. Weight gain was consistent with previously published reports. Only 1 patient worsened on the global assessment of patient functioning.

While this study was not a double-blind comparison, it clearly has strengths beyond a historical report. Study participants were enrolled after a prior open-label study with risperidone. In addition, the BPRS, PANSS, and structured assessment were completed by the same investigative staffs who participated in the risperidone study. A very high proportion of eligible risperidone nonresponders were recruited. Risperidone was newly available in Israel for the risperidone study, and thus the subsequent response to olanzapine is less likely to be due to placebo factors.

What to do when a subject has failed to benefit from a course of a novel antipsychotic agent is an important contemporary clinical question. The present data suggest that the broad pharmacologic profile of olanzapine may offer additional treatment advantages beyond the tandem of 5-HT₂/D₂ receptor blockade. Future schizophrenia studies of this nature with crossover evaluation among the various novel agents may shed further light on the mechanisms underlying this disabling psychiatric disorder.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), fluoxetine (Prozac), guanadrel (Hylafrel), haloperidol (Haldol and others), olanzapine (Zyprexa), reserpine (Serpasil and others), risperidone (Risperdal).

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