Olanzapine in Treatment-Refractory Schizophrenia: Results of an Open-Label Study

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Background: Clozapine is currently the treatment of choice for neuroleptic-resistant schizophrenia. Olanzapine is a new antipsychotic drug that has shown efficacy against positive and negative symptoms of schizophrenia, with minimal extrapyramidal side effects. However, the effectiveness of olanzapine has not yet been reported among treatment-refractory schizophrenic patients.

Method: A total of 25 schizophrenic patients (DSM-IV criteria) with documented lack of response to two conventional antipsychotic drugs entered this 6-week prospective, open-label treatment trial with olanzapine 15 to 25 mg/day. An optional extension up to 6 months was provided.

Results: As a group, the olanzapine-treated patients showed statistically significant improvement ($p < .05$) in both positive and negative symptoms by the end of 6 weeks of therapy. Overall, 9 of the patients (36%) met the a priori criteria for treatment-response (≥ 35% decrease in Brief Psychiatric Rating Scale [BPRS] total score, plus posttreatment Clinical Global Impression-Severity ≤ 3 or BPRS total < 18). Only one patient discontinued treatment because of an adverse event during the study. Despite the relatively high dosages of olanzapine used, there were no reports of parkinsonism, akathisia, or dystonia, and no patients required anticholinergic medication.

Conclusion: This open study suggests that olanzapine may be effective and well tolerated for a substantial number of neuroleptic-resistant schizophrenic patients. Further blinded, controlled trials are needed to confirm our results.

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Despite the efficacy of antipsychotic drugs in the treatment of schizophrenia, there are a group of schizophrenic patients who demonstrate very little improvement while taking these drugs and exhibit significant residual psychopathology. These patients are generally known as treatment-refractory or treatment-resistant schizophrenics.[1]

The proportion of schizophrenic patients that could be considered neuroleptic-resistant depends to a great extent on the criteria used. Turkelsen and Grosser[2] estimate that between 18% and 24% of schizophrenic patients receive clozapine due to their treatment-refractory status. The general consensus is that between 5% to 25% of schizophrenic patients could be considered treatment resistant.[1]

The empirical approach to apparent treatment-resistance has been to increase doses, to prolong treatment duration, or to switch to a different neuroleptic drug class. An alternative step has been to use non-neuroleptic drugs, such as lithium, carbamazepine, or valproate, usually as adjuvants.[3–5] Benzodiazepines, antidepressants, and electroconvulsive therapy have been used successfully as well.[6] Nevertheless, these drugs have not been studied in adequate numbers of patients to permit firm conclusions regarding their efficacy.

Clozapine has shown efficacy superior to conventional neuroleptics in treating neuroleptic-refractory schizophrenic patients. Between 30% and 40% of schizophrenic patients strictly defined as treatment refractory achieved clinical response with clozapine.[7,8] However, the use of clozapine has been limited by the increased risk of leukopenia and agranulocytosis relative to other antipsychotics.[9]

Therefore, the treatment of refractory patients is still not optimal. Untreated psychosis may have deleterious biological effects that might further impair potential for response.[10]

Currently, the development of several novel or atypical antipsychotics provides promising alternatives for the treatment of schizophrenia. Risperidone is a new antipsychotic that is effective for treating positive and negative symptoms of schizophrenia. Efficacy of risperidone in treating schizophrenic symptoms nonresponsive to conventional neuroleptics has been studied, but results are still inconclusive.[11,12] A recently published paper[13] reported response to open-label risperidone treatment in 9 of 25 treatment-refractory schizophrenic and schizoaffective patients; concomitant use of antidepressants, valproic acid, lithium, and occasional intramuscular antipsychotics was allowed during risperidone treatment. Olanzapine is a thienobenzodiazepine with a broad in vitro affinity for serotonergic, cholinergic, α_1-adrenergic, as well as dopaminergic receptors.[14] In placebo- and haloperidol-controlled clinical trials, which included schizophrenic patients not selected for their history of lack of response, olanzapine has been shown to be effective in treating positive and negative symptoms of schizophrenia, with minimal extrapyramidal side effects.[15,16]

Thus, we postulated that olanzapine might be effective in treating schizophrenic patients who are refractory to conventional neuroleptic drugs.

METHOD

We conducted a 6-week prospective, open-label, multicenter pilot clinical trial, with an optional 26-week extension of treatment for those patients who showed an initial response. Patients were inpatients at five psychiatric research units in general hospitals affiliated with the Spanish National Health Service. The protocol was approved by the Institutional Review Board at each participating site and by the Spanish Ministry of Health. All patients (or their legal representatives) gave their written informed consent to participate in the trial, and the investigation was conducted according to the Declaration of Helsinki and the European Good Clinical Practice Guidelines.

To be included in the study, patients had to meet DSM-IV[17] criteria for schizophrenia, have a documented treatment-refractory status as defined by absence of clinically significant improvement with at least two different antipsychotics (except clozapine) from different chemical classes during a minimum treatment period of 4 weeks each at adequate doses (equivalent to 750 mg/day of chlorpromazine or 15 mg/day of haloperidol), and have evidence of inadequate social functioning for the past 2 years. Additionally, patients had to show psychotic symptoms at baseline as defined by a minimum normalized (0–6 scoring) Brief Psychiatric Rating Scale (BPRS) score (extracted from the Positive and Negative Syndrome Scale [PANSS]) of 24 points; a rating of at least moderately ill on the Clinical Global Impression-Severity of Illness scale; plus either (1) at least 4 points on any two of the following items on the PANSS: hallucinatory behavior, suspiciousness, unusual thought content, grandiosity, and conceptual disorganization or (2) 4 points on one of the PANSS items mentioned previously plus a PANSS negative subscore of at least 21.

Patients with clinically significant organic disorders, substance dependence disorders, or documented resistance to clozapine were excluded from the study.

A total of 25 treatment-refractory schizophrenic patients were sought. Patients were inpatients at baseline except for 2 who were kept at home under close familial and professional supervision. All patients were treated with olanzapine after a washout period of 4 to 9 days. Baseline scores were obtained at the end of this washout period. The treatment phase consisted of 6 weeks of olanzapine treatment plus an optional extension up to 6 months. To enter the extension phase, patients had to show at least some benefit at the end of the initial 6-week period, defined by at least a 5% decrease in BPRS total score and a 1-point decrease in CGI-S score.

Patients were evaluated weekly during the initial 6 weeks and monthly thereafter using the following efficacy rating scales: PANSS,[18] in its Spanish-validated version by Peralta and Cuesta[19,20]; the normalized BPRS (0–6 score range), extracted from the PANSS[18]; the Clinical Global Impression-Severity of Illness (CGI-S) and -Improvement (CGI-I)[21] scales; and the Patient Global Impression of Improvement (PGI).[21] Extrapyramidal symptoms were assessed through the following scales: Abnormal Involuntary Movement Scale (AIMS),[22] Simpson-Angus scale,[23] and Barnes Akathisia Scale (BAS).[24] For the categorical analysis of extrapyramidal symptom rating scales, clinically significant akathisia was defined as a score ≥ 2 points on the BAS and clinically significant parkinsonism as a score > 3 on the Simpson-Angus scale. In addition to EPS rating scales, all adverse events, including extrapyramidal symptoms, were collected through nondirected questioning and clinical examination and coded according to the *Coding Symbols for Thesaurus of Adverse Drug Reaction Terms* (COSTART) dictionary.[25]

Prior to the start of the study, all investigators took part in a meeting to establish an agreement on the use of rating scales and inclusion criteria. Training in the use of the PANSS included the rating of two videotaped patient interviews by the investigators, followed by discussion of rating guidelines and potential disagreements. All discrepancies of more than one point on each individual item were discussed thoroughly.

Olanzapine therapy was initiated at 15 mg/day as a single daily dose from Day 1. Dosing could be adjusted afterward within the range of 10 to 25 mg/day. All patients were treated with doses equal to or above 15 mg/day (initial dose). Compliance was confirmed by measuring plasma olanzapine levels after 6 weeks and 6 months of olanzapine treatment. Patients did not receive any additional antipsychotics, antidepressants, or mood stabilizers during participation in the study. Prescription of benzodiazepines was permitted for the treatment of preexisting or treatment-emergent conditions such as insomnia or anxiety.

Response to treatment was defined, according to previous literature,[7] as a baseline to endpoint decrease in normalized BPRS ≥ 35% (extracted from the PANSS), plus an endpoint score of either < 18 for the BPRS total or ≤ 3 (moderately ill) for the CGI-S.

Statistical Analysis

Data management and analysis were done using SAS, Version 6.10 (SAS Institute. Cary, N.C.). The description of the sample was done by means of SAS PROC means, univariate, and tabulate programs.

The analyses of evolution was carried out by deriving at Visit 8 (6 weeks of treatment) and at the end of the study (6 months of treatment) the scores for the different scales with respect to baseline. The last-observation-carried-forward convention was used to determine the end of 6 weeks and end of study values. The analysis of the 6-week data observed an intent-to-treat approach. The 6-month study analysis included only those patients who completed the 6-month extension period. Within-group analyses of efficacy for all rating scales were done by using 95% confidence intervals (CIs), with the same SAS PROC programs.

RESULTS

A total of 25 patients (18 men) entered the active treatment trial. The mean ± SD age of the patients was 32 ± 9.3 years, and the mean age at onset was 20 ± 4.1 years. Schizophrenia subtype was paranoid in 18 patients, disorganized in 4, and undifferentiated in the remaining 3 patients. A total of 24 patients (96%) completed the initial 6-week treatment period; 1 dropped out owing to worsening of psychosis at Week 3. Eight more patients were discontinued from the study at the end of the initial 6-week period of treatment due to lack of efficacy (did not meet minimum improvement criteria, as defined in the protocol), and the remaining 16 patients entered the 6-month extension. During the extension period, 2 more patients were discontinued due to lack of efficacy, 2 due to noncompliance, and 1 due to depression. The discontinuation due to depression and 1 discontinuation due to noncompliance actually occurred at the end of the extension period; therefore, a total of 13 patients completed the 13 visits included in the protocol. Modal daily dose was 15 mg/day for 1 patient (4%), 20 mg/day for 8 patients (32%), and 25 mg/day for 16 patients (64%).

Table 1. Mean Improvement From Baseline in Psychopathology Rating Scales After 6 Weeks of Olanzapine Treatment*

	Baseline Score		Change in Score		95% CI of Mean Change	
Scale	Mean	SD	Mean	SD	Lower Limit	Upper Limit
BPRS total	38.68	11.82	–13.88	18.59	–6.21	–21.55
PANSS						
Total	102.88	19.55	– 24.28	31.53	–11.27	–37.29
Positive	24.56	6.49	–4.92	8.27	–1.51	–8.33
Negative	28.96	6.66	–8.04	9.47	–4.13	–11.95
General	49.36	10.36	–11.32	15.98	–4.72	–17.92
CGI-S	5.72	0.54	–1.28	1.37	–0.71	–1.85

*Last observation carried forward. N = 25.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness, CI = confidence interval, PANSS = Positive and Negative Syndrome Scale.

Efficacy

As a group, the olanzapine-treated patients improved significantly. Within-group analyses revealed a significant mean decrease in rating scales from baseline to endpoint during the 6-week acute therapy phase (Table 1). As shown by the 95% CIs, within-group improvements on all efficacy rating scales were statistically significant at the level of $p < .05$.

At the end of 6 weeks, 9 (36%) of 25 patients met previously defined criteria for treatment response. The 95% CI (exact) for response rate is 17.97% to 57.48%.

Improvement was also evident through physician- and patient-rated global evaluations of improvement using the CGI and PGI improvement scales. At endpoint evaluation of the initial 6-week period of the study, 11 patients (44%) were rated as much better or very much better on the CGI-I scale, 5 (20%) as a little better, 4 (16%) as no change, and 5 patients (20%) as worse (a little, much, or very much worse).

A total of 13 patients completed the extension phase. Those patients experienced further improvements in psychopathology as shown in Table 2. At the 6-month endpoint evaluation, a total of 12 patients (48%) met criteria for treatment response. The exact 95% CI for this response rate is 27.79% to 68.69%.

Table 2. Mean Improvement From Baseline in Psychopathology Rating Scales After 6 Months of Olanzapine Treatment for Patients Who Completed the Treatment Extension Period (N = 13)

	Change in Score		95% CI of Mean Change	
Scale	Mean	SD	Lower Limit	Upper Limit
BPRS total	–29.85	13.75	–21.54	–38.15
PANSS				
Total	–49.46	24.18	–34.85	–64.07
Positive	–12.54	5.49	–9.22	–15.85
Negative	–13.00	8.08	–8.12	–17.88
General	–23.92	14.00	–15.46	–32.38
CGI-S	–2.69	0.75	–2.24	–3.15

Table 3. Incidence of Spontaneously Reported Treatment-Emergent Adverse Events That Appeared in More Than 1 Patient*

Event	Event N	Incidence %
Anxiety	9	36
Hallucinations	5	20
Delusions	4	16
Insomnia	3	12
Personality disorder[a]	3	12
Schizophrenic reaction[b]	3	12
Agitation	2	8
Cough increased	2	8
Depression	2	8
Fever	2	8
Hostility	2	8
Hyperkinesia	2	8
Weight gain	2	8

*N = 25 patients treated with olanzapine 15–25 mg/day for up to 6 months. Event terms are classification terms from the COSTART dictionary.[25]
[a]Personality disorder is the COSTART codification term for nonviolent behavior disturbance.
[b]Schizophrenic reaction is the COSTART codification term for exacerbation of schizophrenia.

Safety

Overall, olanzapine at single daily doses between 15 and 25 mg/day was well tolerated. No patients required dose reductions below 15 mg/day. The adverse events experienced by at least 2 patients are shown in Table 3. Only 1 treatment-associated event required discontinuation of olanzapine, and that was depression. None of the adverse events reported by only 1 patient were associated with treatment discontinuation.

Extrapyramidal Side Effects

No cases of treatment-emergent parkinsonism, dystonia, or akathisia were reported. Two patients reported cases of hyperkinesia (COSTART coding term). One of these patients experienced psychomotor restlessness throughout the study duration; nevertheless, scores on the BAS were 0 at all evaluations. The other patient with hyperkinesia showed psychomotor agitation, probably reflective of psychotic worsening; this patient was discontinued after 3 weeks of treatment due to worsening of symptoms.

One patient presented treatment-emergent ocular dyskinesia that appeared in acute episodes during olanzapine treatment. The patient had shown similar symptoms with some, but not all, antipsychotic drugs received in the past. The ocular dyskinesia disappeared after olanzapine discontinuation. No patient required treatment with an anticholinergic during the study. There were no significant changes from baseline to endpoint on the Simpson-Angus scale or the BAS. This included no cases of treatment-emergent akathisia (BAS score ≥ 2). Two subjects with akathisia at baseline experienced reductions in their BAS scores. Significant parkinsonism (Simpson-Angus score > 3) was present in 4 patients at baseline, and 2 of them did not have significant parkinsonism at endpoint; the other 2 still maintained scores over 3. Of the 20 patients without significant parkinsonism at baseline, none presented Simpson-Angus scores > 3 at endpoint. It is important to remember that the Simpson-Angus scale is more efficient in assessing rigidity than akinesia; however, the lack of reported cases of akinesia, hypokinesia, tremor, or parkinsonism, based on nondirected questioning and clinical examination, is consistent with the absence of parkinsonian syndrome as assessed by this scale.

Weekly laboratory tests during the first 6 weeks and monthly thereafter revealed no clinically significant changes. At endpoint, 1 patient had an SGOT level and 3 patients had CPK levels above the upper limit of the reference range, but without clinical consequences.

Patients treated with olanzapine had a mean ± SD increase in weight from baseline to endpoint of 3.27 ± 6.10 kg. No clinically significant baseline to endpoint changes in vital signs or electrocardiogram parameters were evident.

DISCUSSION

The results of the present investigation revealed that a substantial portion of schizophrenic patients who have not responded to conventional neuroleptics may respond to olanzapine with minimal drug-induced extrapyramidal side effects. However, the open nature of this study limits its interpretation. Without a parallel and blinded control group, it is difficult to know the comparative response rate under these study conditions. The increased medical attention that patients included in a research protocol receive may be a possible source of nonpharmacologic effect. Part of the symptomatic improvement seen in this study may also be attributed to spontaneous fluctuations in disease symptomatology over time. Nevertheless, the chronicity and lack of response to neuroleptics that characterize this particular group of patients argue against a substantial contribution of spontaneous fluctuations. No

other antipsychotics, antidepressants, or mood stabilizers were administered concomitantly, in contrast to study designs in other recently published works[13]; therefore, a substantial component of improvement in our patients should be attributed to olanzapine.

Despite being treatment-refractory schizophrenics, patients were required to show some degree of cooperativeness in order to enter the investigation. Therefore, the generalizability of our results to regular treatment-refractory schizophrenics is limited. Exclusion of patients with concomitant substance dependence disorders should be taken into account in this regard.

As shown by the CGI-I scores, a small percentage of patients (20%) actually worsened upon discontinuation of previous antipsychotic therapy and initiation of olanzapine treatment. This finding argues against an investigator bias in our open design. Despite having been evaluated as treatment nonresponders, some subjects were probably receiving some marginal symptomatic benefit from their previous treatments.

Treatment response was not dose or concentration dependent, but a fixed-dose design was not used here. In a majority of patients, the olanzapine dose was maximized per protocol limitations. We do not know whether lower olanzapine doses would yield similar results.

The positive safety profile exhibited by olanzapine in this small study is consistent with other larger and controlled studies using 5- to 20-mg daily doses of the compound.[15,16] The absence of treatment-emergent dystonia, parkinsonism, and akathisia, both spontaneously reported or collected through rating scales, suggests that even high doses of olanzapine are virtually free from extrapyramidal side effects.

Most treatment-associated events reported reflect lack of efficacy rather than a specific undesirable effect of medication, e.g., hallucinations, delusions, personality disorder, schizophrenic reaction, and hostility. Other adverse events, such as anxiety, insomnia, agitation, and depression, are unlikely to be related to study medication, but a causal relationship may not be completely ruled out.

In conclusion, olanzapine has demonstrated efficacy in treating a wide variety of schizophrenic patients through well-controlled clinical trials. Our pilot study suggests that olanzapine might also be useful (effective and well tolerated) for schizophrenic patients with a historical lack of response to conventional antipsychotics. Controlled and blinded prospective clinical trials that compare olanzapine with other antipsychotics in treatment-refractory schizophrenia are awaited.

Drug names: carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal), valproic acid (Depakene and others).

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