Efficacy and Tolerability of Olanzapine in Patients with Schizophrenia in Lithuania: A 13-Week, Multicenter, Open-Label, Nonrandomized Study

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ABSTRACT

Background: The atypical antipsychotic olanzapine has been approved for the treatment of schizophrenia in Europe since 1996 but has been used primarily as a second-line treatment to the less expensive typical agents. However, similar to other atypical antipsychotic drugs, olanzapine has a lower risk of inducing extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, and sexual dysfunction compared with the typical antipsychotic drugs.

Objective: The aim of this study was to determine whether patients with schizophrenia who have a poor response to their present antipsychotic therapy would show improvement when switched to olanzapine.

Methods: This 13-week, multicenter, open-label, nonrandomized trial was conducted at 5 centers in Lithuania. Patients were started on oral olanzapine 10-mg tablets once daily, which could be adjusted by 5 mg/d in the dosing range of 5 to 20 mg/d. The primary efficacy measure was the total score on the Brief Psychiatric Rating Scale (BPRS), which was extracted from the Positive and Negative Syndrome Scale (PANSS). Efficacy response rate was defined a priori as the percentage of patients achieving $\geq 40\%$ improvement in the BPRS total score. Secondary assessments included the PANSS total and BPRS and PANSS subscales and scores on the Clinical Global Impression–Severity of Illness (CGI-S), the CGI–Global Improvement (CGI-I), and the Patient Global Impression–Improvement (PGI-I) tests. Tolerability was primarily measured by

This article was presented as a poster at the IXth International Congress on Schizophrenia Research, Colorado Springs, Colorado, March 29–April 2, 2003.

Accepted for publication January 7, 2004.

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0011-393X/04/\$19.00

assessing the incidence of treatment-emergent adverse events (AEs) according to the Udvalg fuer Kliniske Undersogelser (UKU) Side Effect Rating Scale and laboratory analyses.

Results: Twenty-four patients (13 men [54.2%]; mean [SD] age, 32.4 [8.1] years) entered the study. Twenty-three (95.8%) of the 24 patients completed the study. The mean (SD) daily dosage of olanzapine was 11.40 (2.18) mg/d. The total mean (SD) BPRS score improved significantly from 37.8 (7.9) to 19.5 (13.7) ($P < 0.001$). The response rate was 58.3% (14/24 patients). The mean positive and negative BPRS scores and the mean total and subscale PANSS scores all improved significantly from baseline ($P < 0.001$). The mean (SD) CGI-S score improved significantly from 4.8 (0.8) at baseline to 3.5 (1.1) at end point ($P < 0.001$). Twenty-two patients (91.7%) showed improvement on the CGI-I scale. Similar improvement was found on the PGI-I scale. Treatment-emergent AEs occurred in 7 patients (29.2%). Improvement was found on 31 of the 48 UKU scale items; no change was shown on 15 items; and slight worsening was shown on 2 items. No clinical abnormalities were detected during the study.

Conclusion: In this study of Lithuanian patients with schizophrenia, significant improvement was shown in all efficacy measures. In addition, olanzapine was well tolerated in these patients. (*Curr Ther Res Clin Exp.* 2004;65:57–69) Copyright © 2004 Excerpta Medica, Inc.

Key words: olanzapine, schizophrenia, antipsychotic, tolerability, psychopathology.

INTRODUCTION

Although the atypical antipsychotic drugs have generally been shown to be more effective and tolerable than the older typical antipsychotic drugs, the majority of patients with schizophrenia in Europe are presently being prescribed a typical antipsychotic, such as haloperidol or fluphenazine hydrochloride. The atypical antipsychotic olanzapine has been approved for the treatment of schizophrenia in Europe since 1996 but has been used primarily as a second-line treatment to the less expensive typical agents. However, similar to other atypical antipsychotic drugs, olanzapine has a lower risk of inducing extrapyramidal symptoms,^{1–3} tardive dyskinesia,^{4–6} neuroleptic malignant syndrome,^{7,8} and sexual dysfunction^{9,10} compared with the typical antipsychotic drugs. Olanzapine and the atypical antipsychotics in general have been shown to be more effective than typical antipsychotics in treating negative symptoms, mood disturbances, and cognitive deficits.^{11–14} In their meta-analysis comparing the head-to-head trials of olanzapine versus haloperidol, Davis and Chen¹⁵ found that olanzapine was significantly better than haloperidol on all 5 factors of the Positive and Negative Syndrome Scale¹⁶ (PANSS), including positive symptoms.

Atypical antipsychotic drugs are clearly more expensive than the typical antipsychotics, especially the generic formulations of these drugs. However, drug treatment constitutes only a small portion of the total costs, which may include such direct costs as hospitalization and such indirect costs as long-term social support.^{17–20} Several of the atypical antipsychotic drugs, including olanzapine,²¹ risperidone,²² ziprasidone,²³ quetiapine,²⁴ and aripiprazole,²⁵ have demonstrated superiority to typical antipsychotics in maintaining response or preventing relapse in patients with schizophrenia. This reduction in relapses, and therefore fewer hospitalizations,²⁶ would be a cost benefit for patients taking atypical antipsychotic drugs.¹⁸ Indeed, most studies show a total cost savings for patients taking atypical antipsychotics compared with typical antipsychotics.^{24,27–30} However, 2 studies^{31,32} showed no savings advantage for atypical antipsychotics compared with typical antipsychotics.

This study was designed to determine whether patients with schizophrenia who were being treated with typical antipsychotic drugs but were still experiencing severe symptomatology would show improvements in psychopathology and tolerance after initiating olanzapine treatment.

PATIENTS AND METHODS

Patients

Male and female patients aged 18 to 65 years with *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*³³ (DSM-IV)-defined schizophrenia who were inpatients or outpatients were recruited from 5 sites in Lithuania. To be included in this study, patients were required to have a Clinical Global Impression–Severity of Illness^{34*} (CGI-S) score of ≥ 3 both before and after the washout periods (visits 1 and 2). To participate in this study, all patients or their legal representatives provided written informed consent after the study was described in detail.

Study Design

This was a 13-week, multicenter, open-label, nonrandomized study. Local ethics review boards approved the study protocol. Study period 1 was the screening and washout portion of the study (2–9 days). Visit 1 consisted of the CGI-S, psychiatric and physical examinations, and patient history, all performed by the clinical investigator and other medical personnel. Patients with a history of a serious, unstable medical illness; leukopenia; narrow-angle glaucoma; jaundice; severe allergies; multiple adverse drug reactions; DSM-IV-defined substance abuse or dependence within the 3 months prior to the study; or judged to be a serious suicidal risk were not eligible for the study. Patients having

*Clinical Global Impression–Severity of Illness scale: 1 = normal/not at all ill, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, or 7 = among the most extremely ill patients.

≥ 1 seizure without a clearly resolved cause or treatment with an injectable depot neuroleptic within <1 dosing interval prior to visit 2, those participating in a clinical trial of another investigational drug within 30 days prior to study entry, and those taking any other concomitant medication with primarily central nervous system activity, as well as pregnant, possibly pregnant, or lactating patients, were excluded. Women of childbearing age were required to use an effective method of birth control throughout the study. Study period 2 consisted of 13 weeks of open-label therapy.

Patients were assessed at weeks 1, 3, 6, and 13 after starting olanzapine treatment. At visit 2, patients were initiated on 10-mg olanzapine tablets self-administered once daily. The daily dosage could then be adjusted upward or downward by 5-mg increments within the allowed 5- to 20-mg/d dosage range. The use of benzodiazepines was permitted during the study, but was not to exceed the equivalent of diazepam 60 mg/d. Trihexyphenidyl hydrochloride, benzotropine mesylate, or biperiden could be given up to 6 mg/d throughout the study if extrapyramidal symptoms (EPS) appeared. The continued use of anticholinergic medication was allowed, but once symptoms resolved the dosage was to be reduced as much as possible. The use of anticholinergic medication as prophylaxis for EPS was prohibited.

Compliance was determined by medical personnel using pill counts. Outpatients were to return bottles containing pills and the remaining pills were counted. If he or she was an inpatient, his or her nurse was responsible for the pill count.

Patients were considered noncompliant with study drug and were discontinued from the trial if they missed 5 consecutive days of medication use or if they were taking more than the prescribed amount of medication on a regular basis, based on the discretion of the individual investigator.

Assessments

The primary efficacy measure was the change from baseline to end point in the total score on the Brief Psychiatric Rating Scale³⁵ (BPRS) extracted from the PANSS.¹⁶ Efficacy response rate was defined a priori as the percentage of patients who showed a $\geq 40\%$ improvement in the BPRS total score. Secondary efficacy assessments included the BPRS positive and negative subscales, the PANSS total score, and the PANSS positive, negative, general psychopathology, and mood subscale scores. The PANSS mood subscale consists of 4 items (somatic concern, anxiety, guilt feelings, and depression). The CGI-Global Improvement* (CGI-I), CGI-S, and Patient Global Impression-Improvement* (PGI-I) scales were also assessed in this study.³⁴

*Clinical Global Impression-Global Improvement and Patient Global Impression-Improvement scales: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse.

Tolerability was primarily measured by assessing the incidence of treatment-emergent adverse events (AEs) (defined as AEs that occurred for the first time or that worsened in severity while olanzapine therapy was being received) according to the Udvalg fuer Kliniske Undersogelser (UKU) Side Effect Rating Scale.^{36*} Clinical laboratory testing (including clinical chemistry, hematology, and urinalysis) was performed at visit 1 and when the patient completed or discontinued from the study.

Statistical Analysis

All statistical analyses were performed on an intent-to-treat basis, and all end point analyses employed either a last-observation-carried-forward or an observed-cases method. To be included in analyses of change from baseline to end point, the patient must have had both a baseline score (visit 2, unless missing, then visit 1) and ≥ 1 postbaseline score. Changes from baseline to end point and within-group analyses were assessed using the paired *t* test. A separate analysis of variance was performed at each study visit for the last observation and for observed cases; 5 observed case analyses were performed (for each of the 5 visits after baseline) and 5 last-observation analyses were performed (for each of the 5 visits after baseline). Analyses were performed using 2-sided tests with a significance level of 0.05. SAS software version 6.08 (SAS Institute Inc., Cary, North Carolina) was used in the statistical analysis.

RESULTS

Of the 27 patients initially screened during study period 1, 24 (88.9%) were enrolled in the study. All patients were white and 13 (54.2%) were male (**Table I**).^{16,35} The mean (SD) age was 32.4 (8.1) years (range, 18.0–52.9 years). The mean (SD) baseline BPRS total score was 37.8 (7.9).

Prior to entering the study, 12 (50.0%) of the patients were receiving non-neuroleptic medication, 8 patients (33.3%) were receiving a benzodiazepine, and 1 patient (4.2%) was receiving an anticholinergic drug.

Twenty-three (95.8%) of the original 24 patients completed the study. Physician decision (not specified) was the reason for the 1 patient (4.2%) being discontinued from the study.

The mean (SD) modal daily dosage of olanzapine was 9.79 (1.02) mg/d. The mean (SD) daily dosage of olanzapine was 11.40 (2.18) mg/d. The modal dosage

*On the 48-item UKU scale, the physician or patient rates the items on a 4-point scale (0 = none, 1 = mild, 2 = moderate, or 3 = pronounced). The UKU was administered at each visit, and the score was calculated using baseline to end point (23 of 24 were end of study; 24 was last visit). Based on the UKU score, a patient improved or worsened by 0 to 3 points. For example, if at baseline a patient had a mild headache (score = 1), he or she could improve no more than 1 point (no headache; score = 0; change from baseline = -1) but could worsen by 1 point (moderate headache; score = 2; change from baseline = +1) or 2 points (pronounced headache; score = 3; change from baseline = +2) or have no change (mild headache; score = 1; change from baseline = 0). So, if improved, the score would be -1; if worsened to moderate headache, then scored +1; if worsened to pronounced headache, then +2.

Table I. Baseline demographic and clinical characteristics of the study patients (N = 24).

Characteristic	Value
Age, y	
Mean (SD)	32.4 (8.1)
Range	18.0–52.9
Sex, no. (%)	
Men	13 (54.2)
Women	11 (45.8)
Schizophrenia type, no. (%)	
Paranoid	19 (79.2)
Residual	4 (16.7)
Disorganized	1 (4.2)
No. of previous hospitalizations	
Mean (SD)	6.1 (5.1)
Range	1–20
Duration of illness, mean (SD), y	8.8 (6.6)
BPRS ³⁵ total score, mean (SD)	37.8 (7.9)
PANSS ¹⁶ total score, mean (SD)	99.2 (16.4)

BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale.

distribution included 1 patient (4.3%) receiving 5 mg/d and 23 patients (95.8%) receiving 10 mg/d. Maximum daily dosages included 4 patients (16.7%) receiving 20 mg, 8 (33.3%) receiving 15 mg, and 12 (50.0%) receiving 10 mg. All 24 patients (100.0%) were compliant with the study drug.

Fourteen patients (58.3%) received ≥ 1 dose of a non-neuroleptic medication during the study. The most common medications were the benzodiazepines (clonazepam, 6 patients [25.0%]; diazepam, 4 patients [16.7%]); and the anticholinergic trihexyphenidyl hydrochloride (4 patients [16.7%]).

The mean (SD) BPRS total score significantly decreased from 37.8 (7.9) at baseline to 19.5 (13.7) at end point ($P < 0.001$). The rate of response ($\geq 40\%$ decrease in BPRS total score) was 58.3% (14/24 patients). The mean BPRS positive and negative subscales also significantly improved (both $P < 0.001$). The mean PANSS total score and all of the mean PANSS subscale scores significantly improved from baseline to end point (all $P < 0.001$). The mean (SD) CGI-S score significantly improved from 4.8 (0.8) (markedly ill) at baseline to 3.5 (1.1) (mildly/moderately ill) at end point ($P < 0.001$) (**Table II**).^{16,34,35}

Twenty-two patients (91.7%) showed improvement on the CGI-I, including 15 patients (62.5%) being much or very much improved. Twenty-two patients (91.7%) also showed improvement on the PGI-I scale, with 17 patients (70.8%) being much or very much improved (**Table III**).³⁴

Treatment-emergent AEs occurred in 7 (29.2%) patients (**Table IV**). Most of the AEs were considered treatment related. The most common AEs were akathisia (4 patients [16.7%]) and hypertonia/rigidity, hypokinesia, and tremor

Table II. Mean (SD) change in efficacy measures from baseline to end point (last observation carried forward) (N = 24).

Efficacy Measure	Baseline	End Point*	Change
BPRS ³⁵ total	37.8 (7.9)	19.5 (13.7)	– 18.3 (12.0)
Positive	10.6 (4.0)	4.5 (3.5)	– 6.1 (5.0)
Negative	7.9 (2.3)	4.5 (2.8)	– 3.4 (2.5)
PANSS ¹⁶ total	99.2 (16.4)	66.6 (23.4)	– 32.6 (21.3)
Positive	22.7 (5.2)	13.8 (5.5)	– 9.0 (6.9)
Negative	26.0 (6.2)	18.0 (6.8)	– 8.0 (4.9)
General psychopathology	50.4 (8.4)	34.8 (12.4)	– 15.6 (10.9)
Mood	11.9 (3.9)	8.4 (3.7)	– 3.5 (3.0)
CGI-S ^{34†}	4.8 (0.8)	3.5 (1.1)	– 1.3 (1.0)

BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale; CGI-S = Clinical Global Impression–Severity of Illness.

*All $P < 0.001$ versus baseline.

†CGI-S scale: 1 = normal/not at all ill, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, or 7 = among the most extremely ill patients. A patient with a CGI-S score of 4.8 would be considered markedly ill.

Table III. Clinical Global Impression–Global Improvement^{34*} (CGI-I) and Patient Global Impression–Improvement^{34*} (PGI-I) scores at end point.

Scale	No. (%) of Patients (N = 24)	Cumulative %
CGI-I		
Very much improved	3 (12.5)	12.5
Much improved	12 (50.0)	62.5
Minimally improved	7 (29.2)	91.7
No change	1 (4.2)	95.8
Minimally worse	1 (4.2)	100.0
Much worse	0 (0.0)	100.0
PGI-I		
Very much improved	3 (12.5)	12.5
Much improved	14 (58.3)	70.8
Minimally improved	5 (20.8)	91.7
No change	1 (4.2)	95.8
Minimally worse	0 (0.0)	95.8
Much worse	1 (4.2)	100.0

*CGI-I and PGI-I scales: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse.

Table IV. Treatment-emergent adverse events (AEs) reported by $\geq 5\%$ of patients (N = 24).

	No. (%) of Patients
None	17 (70.8)
≥ 1 AE	7 (29.2)
AE*	
Akathisia	4 (16.7)
Hypertonia/rigidity	3 (12.5)
Hypokinesia	3 (12.5)
Tremor	3 (12.5)
Hypotension	2 (8.3)
Sleep disorder	2 (8.3)
Urinary tract disorder	2 (8.3)

*All of these AEs were considered treatment related except urinary tract disorder. None of the AEs were serious or resulted in study withdrawal.

(3 patients [12.5%] each). No serious AEs occurred during the study. No clinical laboratory abnormalities were detected during the 13 weeks of olanzapine therapy.

Improvement was shown on 31 items on the UKU scale; no change was shown on 15 items; and slight worsening was found on 2 items. For all patients, the Global Assessment of Side Effects on the UKU scale was ≤ 2 , which suggests mild AEs that do not interfere with a patient's performance at all assessed time points, including the end of the study. On 10 UKU items, $\geq 20\%$ patients showed improvement from baseline to end point (**Table V**).³⁶ Only 2 UKU items—headache (2 patients [8.3%] worsened, 21 [87.5%] showed no change, 1 [4.2%] improved) and headache, other forms (1 patient [4.2%] worsened, 23 [95.8%] showed no change, 0 [0.0%] improved)—showed more patients worsening than improving at study completion.

DISCUSSION

This moderately to markedly ill patient population at study entry significantly improved on all efficacy measures (all $P < 0.001$), including the primary measure of the BPRS total score, and all patients were considered mildly ill at study completion. Importantly, the patients also perceived that they considerably improved after 13 weeks of olanzapine treatment. Patient self-rating on the PGI-I scale was nearly identical to the physician rating on the CGI-I. In addition, few treatment-emergent AEs, and no serious AEs, occurred. The tolerability of olanzapine was corroborated, in that nearly all of the UKU items remained unchanged or improved at the end of the study.

The improvements observed in this trial are similar to the results from an open-label olanzapine switch trial,³⁷ in which patients were primarily receiving

Table V. Items of Udvalg fuer Kliniske Undersogelser (UKU) Side Effect Rating Scale^{36*} in which $\geq 20\%$ of patients showed improvement. (Values are presented as no. [%] of patients [N = 24].)

Item	<div style="text-align: center;"> </div>						
	-3	-2	-1	0	1	2	3
Concentration difficulties	0 (0.0)	0 (0.0)	9 (37.5)	14 (58.3)	1 (4.2)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	9 (37.5)	14 (58.3)	1 (4.2)	0 (0.0)	0 (0.0)
Sleepiness	0 (0.0)	0 (0.0)	5 (20.8)	19 (79.2)	0 (0.0)	0 (0.0)	0 (0.0)
Failing memory	0 (0.0)	1 (4.2)	4 (16.7)	19 (79.2)	0 (0.0)	0 (0.0)	0 (0.0)
Depression	0 (0.0)	1 (4.2)	7 (29.2)	15 (62.5)	1 (4.2)	0 (0.0)	0 (0.0)
Tension/inner unrest	1 (4.2)	3 (12.5)	9 (37.5)	11 (45.8)	0 (0.0)	0 (0.0)	0 (0.0)
Reduced duration of sleep	0 (0.0)	1 (4.2)	4 (16.7)	18 (75.0)	1 (4.2)	0 (0.0)	0 (0.0)
Increased dream activity	0 (0.0)	1 (4.2)	4 (16.7)	19 (79.2)	0 (0.0)	0 (0.0)	0 (0.0)
Emotional indifference	0 (0.0)	0 (0.0)	7 (29.2)	17 (70.8)	0 (0.0)	0 (0.0)	0 (0.0)
Hypokinesia/akinesia	0 (0.0)	3 (12.5)	5 (20.8)	15 (62.5)	1 (4.2)	0 (0.0)	0 (0.0)

*On the 48-item UKU scale, the physician or patient rates the items on a 4-point scale (0 = none, 1 = mild, 2 = moderate, or 3 = pronounced). The UKU was administered at each visit, and the score was calculated using baseline to end point (23 of 24 were end of study; 24 was last visit). Based on the UKU score, a patient improved or worsened by 0 to 3 points. For example, if at baseline a patient had a mild headache (score = 1), he or she could improve no more than 1 point (no headache; score = 0; change from baseline = -1) but could worsen by 1 point (moderate headache; score = 2; change from baseline = +1) or 2 points (pronounced headache; score = 3; change from baseline = +2) or have no change (mild headache; score = 1; change from baseline = 0). So, if improved, the score would be -1; if worsened to moderate headache, then scored +1; if worsened to pronounced headache, then +2.

typical antipsychotic drugs before initiation of olanzapine treatment. In that 6-week trial, PANSS total (18-point decrease) and subscale scores significantly improved from baseline ($P < 0.001$). Interestingly, and similar to the switch trial, a nearly identical decrease in the PANSS total score occurred in olanzapine-treated patients in the international, double-blind, 6-week trial of olanzapine versus haloperidol.³ In addition, and similar to our findings, the mean CGI-S score in the switch trial improved from moderately ill to mildly ill, and a relatively low incidence of treatment-emergent AEs was found. These kinds of improvements in patients treated with olanzapine have been reported numerous times in the literature, thus supporting the validity of the present findings.³⁸⁻⁴¹

Some investigators believe that cognition may be the most important factor or a correlate in the improvement of psychosocial functioning.^{42,43} Olanzapine has been shown to significantly improve various aspects of cognition in patients with schizophrenia.^{12,44,45} It is worth noting that several of the UKU items that showed the most improvement are related to cognition. Concentration

difficulties and failing memory showed improvement in 38% and 20% of patients, whereas tension (1 of 7 items placed in the cognitive factor by Bell et al⁴⁶) showed the most improvement for all UKU items (54%). Unfortunately, psychosocial outcomes were not measured in our study, but olanzapine has been shown to significantly improve these outcomes in other studies.^{47–50}

This study has several limitations. It was an open-label study and included only 24 patients. However, improvements in psychopathology are similar to findings from the larger double-blind studies.^{38–41} It would have been informative to have included a comparator drug, particularly a typical antipsychotic, because these drugs are used more commonly in Lithuania and Europe than in the United States. Inclusion of a scale measuring EPS, such as the Abnormal Involuntary Movement scale³⁴ or the Simpson-Angus scale,⁵¹ would have better demonstrated the potential effectiveness of olanzapine in improving these syndromes than can be shown with the UKU scale. In addition, change in body weight was not captured in this study. Weight gain is common with the use of olanzapine and several of the other atypical antipsychotics. Interestingly, on the UKU item of “weight gain,” only 1 patient (4.2%) was recorded to have a worsening in this item at end point.

CONCLUSIONS

In this study of Lithuanian patients with schizophrenia, significant improvement was shown in all efficacy measures. In addition, olanzapine was well tolerated in these patients. These results suggest that olanzapine may be an effective and tolerable therapeutic option for patients with schizophrenia having continued severe psychopathology while receiving typical antipsychotic therapy.

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