

Long-term functional improvements in the 2-year treatment of schizophrenia outpatients with olanzapine long-acting injection

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Background: Little is known about the long-term changes in the functioning of schizophrenia patients receiving maintenance therapy with olanzapine long-acting injection (LAI), and whether observed changes differ from those seen with oral olanzapine.

Methods: This study describes changes in the levels of functioning among outpatients with schizophrenia treated with olanzapine-LAI compared with oral olanzapine over 2 years. This was a secondary analysis of data from a multicenter, randomized, open-label, 2-year study comparing the long-term treatment effectiveness of monthly olanzapine-LAI (405 mg/4 weeks; n=264) with daily oral olanzapine (10 mg/day; n=260). Levels of functioning were assessed with the Heinrichs–Carpenter Quality of Life Scale. Functional status was also classified as “good”, “moderate”, or “poor”, using a previous data-driven approach. Changes in functional levels were assessed with McNemar’s test and comparisons between olanzapine-LAI and oral olanzapine employed the Student’s *t*-test.

Results: Over the 2-year study, the patients treated with olanzapine-LAI improved their level of functioning (per Quality of Life total score) from 64.0–70.8 ($P<0.001$). Patients on oral olanzapine also increased their level of functioning from 62.1–70.1 ($P<0.001$). At baseline, 19.2% of the olanzapine-LAI-treated patients had a “good” level of functioning, which increased to 27.5% ($P<0.05$). The figures for oral olanzapine were 14.2% and 24.5%, respectively ($P<0.001$). Results did not significantly differ between olanzapine-LAI and oral olanzapine.

Conclusion: In this 2-year, open-label, randomized study of olanzapine-LAI, outpatients with schizophrenia maintained or improved their favorable baseline level of functioning over time. Results did not significantly differ between olanzapine-LAI and oral olanzapine.

Keywords: antipsychotics, functioning, olanzapine long-acting injection, quality of life, schizophrenia

Introduction

Schizophrenia is often a chronic and severe illness characterized by impairment in thinking, feeling, and behavior; it is accompanied by impaired functioning, low levels of productivity, and high rates of unemployment.^{1,2} According to the consensus guidelines for the treatment of patients with schizophrenia, antipsychotics are the cornerstone in the treatment of the illness; maximizing patient quality of life and adaptive functioning are the primary treatment goals.^{3–7}

Prior antipsychotic research has shown that olanzapine in an oral tablet formulation is associated with favorable functional improvements in the acute and maintenance treatment of patients with schizophrenia.^{8–11} Olanzapine is also available in long-acting injection formulation (LAI, depot), which was shown to significantly improve patient

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level of functioning compared with placebo in an 8-week, acute-phase study of schizophrenia.¹² Practice guidelines for schizophrenia management recommend depot antipsychotics for patients who are nonadherent with their medication.⁴ Up to one-third of outpatients are reported to be nonadherent, and another third are reported to be only partially adherent.¹³ Furthermore, patient adherence has been found to deteriorate over time, with up to three-fourths of patients demonstrating only partial adherence after 2 years of treatment.¹⁴ Medication adherence has been previously shown to predict relapse and hospitalization,¹⁵ which tend to signal patients' growing difficulties to function in the community.¹⁶

Although there is evidence supporting the effectiveness of olanzapine-LAI^{17,18} and the associated short-term improvements in patient functioning and quality of life,¹² little is known about long-term changes in the level of functioning in schizophrenia patients receiving maintenance therapy with olanzapine-LAI, and whether observed changes differ from those seen with oral olanzapine.

The primary objective of the present analysis was to describe the changes in the level of functioning among schizophrenia patients receiving long-term maintenance therapy with olanzapine-LAI, using data from a 2-year, randomized, open-label maintenance study of outpatients with schizophrenia that compared monthly olanzapine-LAI therapy with daily oral olanzapine therapy. As a secondary objective of this analysis, observed functional changes were compared between patients treated with olanzapine-LAI or oral olanzapine.

Materials and methods

Study design and participants

This was a secondary analysis of data from a multicenter, randomized, open-label, 2-year study comparing the long-term treatment effectiveness and safety of olanzapine-LAI with that of daily oral olanzapine in schizophrenia outpatients (ClinicalTrials.gov registration number: NCT00320489; code: F1D-MC-HGLQ).¹⁹

Participants were aged 18–65 years, with a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition or Fourth Edition-Text Revision diagnosis of schizophrenia, with a Positive and Negative Syndrome Scale (PANSS) total score <70 and a Clinical Global Impression–Severity (CGI-S) scale rating of ≤4, who had not been hospitalized in the 8 weeks before study inclusion, and who were at risk for relapse as demonstrated by at least two episodes of clinical worsening in the past 24 months (2 years) (ie, the patient was hospitalized or required an increased level of

care surrounding the episode). Exclusion criteria included: significant suicidal or homicidal risk; pregnancy or breastfeeding; acute, serious, or unstable medical conditions; or substance dependence (except nicotine or caffeine) within the past month.

The study design consisted of two periods – a screening phase during which the patients were screened for eligibility (in visit one and in visit two) and an open-label treatment phase lasting up to 104 weeks. Patients were randomly assigned in a 1:1 ratio to receive olanzapine-LAI (405 mg/4 weeks, n=264) or oral olanzapine (10 mg/day, n=260). Dosing was flexible following the initial randomization dose (150–405 mg/4 weeks for olanzapine-LAI, and 5–20 mg/day for oral olanzapine).

No oral antipsychotic supplementation was allowed after week 8. Concomitant medications with primarily central nervous system activity were prohibited, except for benzodiazepines and sedative-hypnotics as sleep aids (≤2 mg/day lorazepam equivalents) and any antidepressants that the patient was already taking (except for fluvoxamine, which was prohibited).

The study protocol was approved by institutional review boards at each site. After receiving a complete description of the study, all patients and/or their authorized legal representatives provided written informed consent before participation.

Measures

Level of functioning was measured with the Heinrichs–Carpenter Quality of Life Scale (QLS).²⁰ The QLS is a clinician-rated scale used to assess the impact of schizophrenia on occupational, social, and psychological functioning in patients with schizophrenia. The scale consists of 21 items rated on a 7-point scale from normal or unimpaired functioning (scores of 5 or 6) to impaired functioning (scores of 0 and 1). The QLS items assess four domains: intrapsychic foundation; interpersonal relations; instrumental role; and common objects and activities. The QLS scale was administered at baseline, at 22 weeks, at 46 weeks, and at 70 weeks thereafter and at endpoint (104 weeks or at the discontinuation visit). Patient functioning was also classified using cut-off points developed using the QLS.²¹ Patients were considered to have: a “good” level of functioning if the QLS total score was ≥84.5; a “moderate” level if the QLS total score was <84.5, and the QLS Intrapsychic foundation score was ≥15.5; and a “poor” level of functioning if the QLS total score was <84.5 and the QLS intrapsychic foundation score was <15.5. In addition to levels of functioning, symptom

Table 1 Baseline sociodemographic and clinical characteristics, by treatment

Characteristic	Olanzapine-LAI	Olanzapine	P ^a
Number of patients	(n=264)	(n=260)	
Female, n (%)	89 (33.7)	83 (31.9)	0.66
Age at study entry (years), mean (SD)	41.7 (10.9)	40.1 (10.8)	0.09
Age at onset (years), mean (SD)	25.9 (9.2)	26.5 (8.7)	0.28
CGI-S score, mean (SD)	3.2 (0.8)	3.3 (0.7)	0.82
PANSS total score, mean (SD)	56.7 (9.8)	56.6 (8.7)	0.43
In paid employment, n (%)	56 (21.3)	48 (18.5)	0.43
Living independently, n (%)	67 (25.5)	56 (21.6)	0.29

Note: ^aP-value comparing olanzapine-LAI with oral olanzapine.

Abbreviations: LAI, long-acting injection; SD, standard deviation; CGI-S, Clinical Global Impression–Severity; PANSS, Positive and Negative Symptom Scale.

severity was assessed using the 30-item PANSS²² and the CGI-S scale.²³

Statistical methods

The patients included in the analyses were those randomized patients with at least one postbaseline assessment; the last observation carried forward methodology was employed. A total of 524 patients were included; 264 (50.4%) received olanzapine-LAI, and 260 (49.6%) received oral olanzapine. Changes in the level of functioning from baseline during the study were assessed with McNemar's test, and comparisons between olanzapine-LAI and oral olanzapine on level of functioning per QLS total score employed the Student's *t*-test. All analyses were performed using SAS, version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

The baseline sociodemographic and clinical characteristics of the patients in the two treatment groups are shown in Table 1. There were no significant differences between the

olanzapine-LAI and the oral olanzapine groups. About one-third of the patients in both groups were women. Mean age at study entry was about 41 years, and the mean time since the onset of schizophrenia was about 26 years. Baseline illness severity was within the mild range and similar across the two groups; the mean CGI-S score was 3.2 for olanzapine-LAI and 3.3 for oral olanzapine, indicating that these patients were mildly ill. Similarly, the total PANSS scores were about 57 for both groups, a score consistent with being mildly ill with regard to symptomatology.²⁴ Roughly 20% of the patients were unemployed, and about one-fourth were living independently. There were no group differences in the proportion of patients who discontinued before the end of the study.

Over the 2-year study, patients treated with olanzapine-LAI improved their level of functioning (QLS total score) from a mean of 64.0–70.8 ($P<0.001$) (Table 2). Patients taking oral olanzapine increased their QLS total score from 62.1–70.1 ($P<0.001$).

At baseline, 19.2% of the olanzapine LAI-treated patients were identified as having a “good” level of functioning,

Table 2 Change in level of functioning per QLS total and QLS subscale scores from baseline to last observation, by treatment group

QLS score/visit	Olanzapine-LAI ^a	P ^b	Oral olanzapine	P ^b
QLS total score, mean (SD)				
Baseline	64.0 (21.2)	<0.001	62.1 (18.8)	<0.001
Last observation years	70.8 (22.9)		70.1 (22.4)	
QLS common objects and activities, mean (SD)				
Baseline	6.6 (2.6)	<0.001	6.5 (2.5)	<0.001
Last observation	7.3 (2.6)		7.1 (2.6)	
QLS intrapsychic foundation, mean (SD)				
Baseline	21.9 (7.9)	<0.001	21.6 (6.9)	<0.001
Last observation	24.1 (8.7)		23.9 (8.4)	
QLS intrapersonal relation, mean (SD)				
Baseline	21.0 (10.0)	<0.001	20.0 (9.3)	<0.001
Last observation	24.2 (10.2)		23.9 (10.0)	
QLS instrumental role, mean (SD)				
Baseline	14.1 (3.6)	<0.001	13.9 (3.2)	<0.001
2 years	14.8 (3.9)		14.8 (3.8)	

Notes: ^aThere were no statistical differences between olanzapine-LAI and oral olanzapine in any of the ratings. ^bP value; change from baseline to endpoint.

Abbreviations: LAI, long-acting injection; SD, standard deviation; QLS, Quality of Life Scale.

Table 3 Proportion of patients with “good”, “moderate”, and “poor” levels of functioning at baseline and last observation, by treatment group

Visit/functioning cluster	Olanzapine-LAI	Oral olanzapine	Total	P ^a
Baseline, n (%)				0.11
“Good”	50 (19.2)	37 (14.2)	87	
“Moderate”	150 (57.5)	172 (66.2)	322	
“Poor”	61 (23.4)	51 (19.6)	112	
2 years, n (%)				0.26
“Good”	66 (27.5)	56 (24.5)	122	
“Moderate”	125 (52.1)	136 (59.4)	261	
“Poor”	49 (20.4)	37 (16.2)	86	

Note: ^aP value comparing the proportion of patients in each cluster between olanzapine-LAI and oral olanzapine.

Abbreviation: LAI, long-acting injection.

which increased to 27.5% following up to 2 years of therapy (Table 3). There was a numerical, but not a statistically significant, decrease in the proportion of patients with a “moderate” level of functioning (from 57.5%–52.1%) and in the proportion of patients with a “poor” level of functioning (from 23.4%–20.4%). Results were not significantly different between the oral olanzapine and the olanzapine-LAI treatment groups.

Baseline characteristics of the patients in the “good”, “moderate”, and “poor” functional clusters are shown in Table 4. There were significant differences between the groups for CGI-S score, PANSS total score, and functioning parameters, but not between the groups in the proportion of females, age at study entry, and time since illness onset.

The proportion of patients in the “good”, “moderate”, and “poor” functioning clusters at endpoint, by their baseline functional cluster and treatment group, are shown in Table 5. Although there was some variability within each group, there was a consistent trend toward an increase in the proportion of patients in the “good” functioning cluster.

Discussion

In this 2-year, randomized, open-label maintenance study, schizophrenia patients who were treated with olanzapine-LAI

experienced a significant improvement in their level of functioning over time. The improvements were observed in the total QLS score and in each of its four functional domains: interpersonal; instrumental (occupational); intrapsychic (motivational); and in common objects and activities (a domain that may reflect a patient’s ability to function in the community). Moreover, when using the functional categories of “good”, “moderate”, and “poor” to assess change in functional levels, most patients (73.5%–76.1%) maintained their “good” baseline level of functioning, and some moved from “moderate” and “poor” to the “good” functional category. More specifically, of the patients treated with olanzapine-LAI, 18.8% moved from “moderate” to “good” levels of functioning and 9.1% moved from “poor” to “good”. Of patients treated with oral olanzapine, a similar proportion of patients moved from “moderate” to “good” levels of functioning (19.6%) but a numerically smaller proportion (2.4%) moved from “poor” to “good”. Overall, the observed improvements in QLS scores and in the proportion of patients in the “good” functional category did not differ significantly between patients treated with monthly olanzapine-LAI and daily oral olanzapine.

The current assessment of levels of functioning in the long-term maintenance study of patients with schizophrenia

Table 4 Baseline characteristics of the patients in the “good”, “moderate”, and “poor” functional clusters (all patients, n=524)

Characteristic	Functioning cluster			P ^a
	“Good”	“Moderate”	“Poor”	
Number of patients	(n=87)	(n=322)	(n=112)	
Female, n (%)	33 (38)	102 (32)	36 (32)	0.5367
Age at study entry (years), mean (SD)	39.2 (11.4)	40.8 (10.7)	42.7 (10.9)	0.0928
Time since onset (years), mean (SD)	13.9 (11.2)	14.6 (10.2)	15.8 (10.7)	0.2367
CGI-S score, mean (SD)	2.7 (0.9)	3.3 (0.7)	3.5 (0.6)	<0.0001
PANSS total score, mean (SD)	50.0 (10.5)	57.1 (8.4)	60.3 (7.9)	<0.0001
In paid employment, n (%)	39 (45)	59 (18)	6 (5)	<0.0001
Living independently, n (%)	25 (29)	84 (26)	13 (12)	0.0032

Note: ^aP value comparing the three clusters.

Abbreviations: SD, standard deviation; CGI-S, Clinical Global Impression-Severity; PANSS, Positive and Negative Symptom Scale.

Table 5 Proportion of patients in the “good”, “moderate”, and “poor” functioning clusters at last observation, by baseline functional cluster and treatment group

Treatment/functioning cluster at baseline	Functioning cluster at endpoint			Total, n
	“Good”	“Moderate”	“Poor”	
Olanzapine-LAI, n (%)				
“Good”	35 (76.1)	11 (23.9)	0 (0.0)	46
“Moderate”	26 (18.8)	93 (67.4)	19 (13.8)	138
“Poor”	5 (9.1)	20 (36.4)	30 (54.5)	55
Total, n (%)	66 (27.6)	124 (51.9)	49 (20.5)	239
Oral olanzapine, n (%)				
“Good”	25 (73.5)	8 (23.5)	1 (2.9)	34
“Moderate”	30 (19.6)	110 (71.9)	13 (8.5)	153
“Poor”	1 (2.4)	18 (42.9)	23 (54.8)	42
Total, n (%)	56 (24.5)	136 (59.4)	37 (16.2)	229

Notes: There were no statistical differences between the change from baseline to endpoint for each of the functioning clusters when comparing olanzapine-LAI and oral olanzapine. Percentages may not =100, due to rounding.

Abbreviation: LAI, long-acting injection.

provides valuable information for patients, clinicians, and other health care decision makers about the value of antipsychotic therapy, and – specifically – about olanzapine therapy in depot or oral formulations, to enhance the patients’ functional status, and thus their potential ability to achieve greater reintegration into society. While antipsychotic medications play an important role in achieving this goal, it appears that a patient’s level of functioning depends on a host of factors, including his or her symptom severity level, various social and environmental factors,^{25,26} and the level of cognitive deficits.²⁷

Our findings are consistent with a previous study showing that patients receiving another long-acting atypical antipsychotic (risperidone-LAI) also experience improvements in functioning over the course of maintenance treatment, although our findings apply to a longer period of time^{28,29} and provide a relevant comparison group (the oral counterpart of the depot formulation) that is typically missing from prior research efforts.

Limitations

Current findings need to be evaluated in the context of the study limitations. First, the present study included a patient population that was clinically stable on oral olanzapine at baseline, manifested a relative low level of symptom severity, and had a substantial proportion of patients whose level of functioning was deemed to be “good”. These relatively favorable baseline patient characteristics may have created a ceiling effect that curtailed the ability to find marked improvements from baseline and may have also reduced the ability to differentiate between the two treatment groups. Second, as with other randomized clinical trials of schizophrenia

patients,³⁰ this randomized trial included mostly adherent patients. In such an adherent patient population, it is difficult to differentiate between oral and depot therapy, although differences between these formulations are likely to manifest in real world practice where long-acting injections are often reserved for nonadherent patients. Third, in this study, the highest possible dose of olanzapine-LAI was 405 mg/4 weeks, which is comparable to 15 mg/day of oral olanzapine. However, patients randomized to oral olanzapine could receive a higher dose – up to 20 mg/day. Therefore, it is possible that patients treated with oral olanzapine (but not patients treated with olanzapine-LAI) could be rescued with a higher dose of the medication, if needed. Thus, although the two treatment groups did not differ significantly on functional outcomes, the difference in the maximum daily dose may have placed the olanzapine-LAI treatment group at a relative disadvantage to oral olanzapine. Last, level of functioning was assessed only at five points of time over the 2-year study. This prevented the ability to describe the detailed course of change in level of functioning over time.¹⁹

Conclusion

In this 2-year open-label, randomized study of patients with schizophrenia treated with olanzapine-LAI, most patients either maintained their favorable baseline level of functioning or further improved it over time. Although results did not differ significantly between the olanzapine-LAI and the oral olanzapine treatment groups, the lack of differentiation may have been driven by the fact that most patients who enrolled in this study were adherent and mildly ill, and are not patients who are typically treated with depot antipsychotics in usual care.

Author contributions

All of the authors contributed to the design of the analysis of the study. All authors were involved in the interpretation of data. Jordan Bertsch and Josep Maria Haro conducted the statistical analysis. All authors contributed to development of the manuscript, revised it critically for important intellectual content, and gave their approval of this version to be published.

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