Incidences of Extrapyramidal Symptoms in Patients with Schizophrenia after Treatment with Long-Acting Injection (Depot) or Oral Formulations of Olanzapine

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Abstract

Background: The incidence of extrapyramidal symptoms (EPS) has been shown to be generally low among patients with schizophrenia receiving oral olanzapine. A long-acting injection (LAI) of olanzapine has recently been approved for the treatment of schizophrenia in a number of countries. Accordingly, the objective of the current analyses was to compare the incidences of EPS during treatment with olanzapine LAI versus oral olanzapine. **Methods:** The incidences of treatment-emergent EPS were examined in adults with schizophrenia receiving olanzapine LAI or oral olanzapine for up to 3 years. Short-term data were obtained from two double-blind studies of olanzapine LAI: one included a placebo comparator, and the other included oral olanzapine as an active comparator. Long-term data were obtained from an open-label extension study for olanzapine LAI and from an integrated database for oral olanzapine. **Results:** The short-term incidence of EPS was 5.6% during treatment with olanzapine LAI (45–405 mg every 2–4 weeks) and 5.0% with oral olanzapine (5–20 mg/day). Akathisia (2.6% LAI, 1.2% oral), and Parkinson-like symptoms (1.8% LAI, 3.7% oral) were similar between treatment groups. The incidence of EPS for long-term treatment was 9.2% for olanzapine LAI. Incidences of EPS events were not significantly different between patients receiving olanzapine LAI or oral olanzapine for up to 3 years. **Conclusions:** These findings suggest that EPS profiles are similar for olanzapine LAI and oral olanzapine.

Key Words: Drug Therapy, Extrapyramidal Symptoms, Olanzapine, Safety, Schizophrenia, Tolerability

Introduction

Extrapyramidal symptoms (EPS) are manifestations of dopamine-depleting defects in the basal ganglia. These symptoms are sometimes painful and disabling to patients and represent a major challenge to their clinicians, who must contend with the largely heterogeneous and unpredictable nature of EPS (1, 2). Observed with antipsychotic therapies for >50 years (3), EPS are either acute (for example, dystonias or akathisia), occurring within hours or days of treatment, or tardive (for example, tardive dyskinesia [TD]), typically developing only after sustained medication exposure (≥30 days) (2). EPS can narrow the therapeutic index of antipsychotics by compromising medication adherence, limiting medication doses, or being associated with suboptimally tolerated adjunctive (for example, cholinergic) therapies, all of which may lead to schizophrenic relapse (4-6).

While the incidence of EPS has been shown to be lower with atypical compared with typical antipsychotics (7-10), there is still some risk for EPS in patients receiving atypical antipsychotics (11, 12). The risk for EPS, though, is not consistent across the atypical class (7, 10), with risperidone showing the highest risk and clozapine and quetiapine the lowest risk (13).

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Clinical Implications

Based on the present analysis, olanzapine long-acting injection (LAI) has a similar treatment-emergent EPS profile to that of oral olanzapine. The incidence of treatment-emergent EPS events was not significantly higher among patients receiving olanzapine LAI compared with those receiving oral olanzapine, based on our exploratory data analysis. No new or unusual EPS events were detected with olanzapine LAI as compared with what has been observed with oral olanzapine.

The severity of EPS—as measured by the Simpson-Angus Scale (SAS), the Barnes Akathisia Rating Scale (Barnes), and the Abnormal Involuntary Movement Scale (AIMS)—was low at baseline in the olanzapine LAI studies. Nevertheless, in Study HGKA (25), patients on all doses of olanzapine LAI showed numerically greater improvement on the SAS compared with oral olanzapine. Olanzapine LAI doses showed similar improvements on the Barnes and AIMS scales. Moreover, the incidence of EPS was very low (2 to 5%) in both olanzapine LAI and oral olanzapine, which was likely due to the initial 4- to 8-week stabilization phase. In contrast, Study HGJZ patients taking olanzapine LAI had an EPS incidence in the range of 8 to 13%, which is similar to EPS rates found in an integrated analysis of acute trials of oral olanzapine (7).

Potential limitations of the present analysis include differences in study durations and study/analysis designs (for example, fixed vs. flexible dose; open label vs. double blind; clinical trial vs. integrated safety database), dampening the validity of possible statistical comparison. As with all cross-study comparisons—because potential differences may occur between study populations such as ethnicity, age, duration of illness, and previous antipsychotic exposure—one should exhibit caution in the interpretation of these results.

Long-acting injections (LAIs) of atypical antipsychotics may improve patient outcomes because of more continuous medication delivery, with overall lower plasma drug concentrations and smaller peak/trough fluctuations (14-18). Indeed, previous studies suggest that patients receiving depot formulations were more adherent to these regimens and were less likely to experience relapse and rehospitalization compared with patients taking oral formulations (17-22). Limited information is available regarding the relative safety profiles of antipsychotic medications' oral and intramuscular formulations. However, studies have shown that, although EPS are lower with risperidone LAI compared with oral risperidone (15, 17), depot formulations of typical antipsychotics tend to have worse EPS compared with the oral forms (14, 23), although this could be due to a dose or adherence effect.

An LAI formulation of olanzapine (olanzapine pamoate monohydrate) was approved by the U.S. Food and Drug Administration in December 2009 and in the European Union in November 2008. The present study sought to evaluate the incidence of EPS during treatment with olanzapine LAI (that is, depot) or oral olanzapine in adults with schizophrenia.

Methods

Study Design

In this exploratory analysis of data from an open-label, Phase 3 extension study of olanzapine LAI (Study F1D-MC-HGKB), patients aged 18–74 years (mean, 39.2 years) with schizophrenia or schizoaffective disorder (n=931) received flexibly dosed olanzapine LAI 45–405 mg at injection intervals of 2, 3, or 4 weeks for up to about 3 years. Patients could enter this trial within 10 days after having completed 1 of 3 previous studies: a Phase 3, 8-week, randomized, double-blind, controlled study of olanzapine LAI 210 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks (n=306) compared with placebo (n=98) in acutely ill patients (Study F1D-MC-HGJZ) (24); a 24-week, double-blind, maintenance-of-effect study in which patients with schizophrenia who were stable on oral olanzapine 10–20 mg/day for 4–8 weeks were randomly assigned to either remain on their stabilized dose of oral olanzapine (n=322) or to olanzapine LAI 45 mg/4 weeks, 150 mg/2 weeks, 405 mg/4 weeks, and 300 mg/2 weeks (n=743) (Study F1D-MC-HGKA) (25); or, a Phase 1 pharmacokinetic study of olanzapine LAI 405 mg (single dose), n=134 (schizophrenia, n=106; schizoaffective disorder, n=28) (Study F1D-EW-LOBS) (26). Data on the incidence of EPS during treatment with olanzapine LAI were compared with an historical integrated clinical database, comprising 26 trials of oral olanzapine (modal dose, 15.1 mg; range, 0–50 mg) in the treatment of patients with schizophrenia. The minimum modal dose was 0 mg because one study allowed subjects to opt out of study medication and yet remain in the study and complete assessments (all patients who opted out received study medication for at least a portion of the study). All patients (mean age, 37.8; range, 18–86 years) were required to have at least 48 weeks of exposure to oral olanzapine to be included in the analyses. In addition, the incidences of EPS events in the acute phase of the double-blind studies (HGJZ and HGKA) were assessed.

Table 1 Incidences of Treatment-Emergent EPS Events during Treatment with Olanzapine Long-Acting Injection, Oral Olanzapine, or Placebo

EPS Category	Olanzapine LAI* 45–405 mg/every 2–4 weeks (N=1,049) N (%)	Oral Olanzapine† 10, 15, or 20 mg/day (N=322) N (%)	Placebo (IM)/every 2 weeks‡ (N=98) N (%)
Any EPS event	59 (5.6)	16 (5.0)	8 (8.2)
Akathisia	27 (2.6)	4 (1.2)	6 (6.1)
Akathisia	14 (1.3)	2 (0.6)	3 (3.1)
Hyperkinesia	0	0	0
Psychomotor hyperactivity	3 (0.3)	0	1 (1.0)
Restlessness	11 (1.0)	3 (0.9)	2 (2.0)
Dyskinesia	4 (0.4)	0 (0)	0 (0)
Athetosis	0	0	0
Dyskinesia	3 (0.3)	0	0
Oculogyric crisis	1 (0.1)	0	0
Tardive dyskinesia	0	0	0
Dystonia	11 (1.0)	1 (0.3)	1 (1.0)
Muscle contractions, involuntary	0	1 (0.3)	0
Muscle spasms	7 (0.7)	0	1 (1.0)
Muscle tightness	2 (0.2)	0	0
Posturing	2 (0.2)	0	0
Parkinson-like	19 (1.8)	12 (3.7)	2 (2.0)
Bradykinesia	2 (0.2)	0	0
Bradyphrenia	1 (0.1)	0	0
Dysphonia	0	0	1 (1.0)
Gait disturbance	2 (0.2)	0	0
Hypertonia	0	1 (0.3)	0
Hypokinesia	1 (0.1)	1 (0.3)	0
Muscle rigidity	1 (0.1)	0	0
Parkinsonism	1 (0.1)	3 (0.9)	0
Tremor	11 (1.0)	7 (2.2)	1 (1.0)
Nonspecific	5 (0.5)	0 (0)	1 (1.0)
Extrapyramidal disorder	5 (0.5)	0	0
Muscle twitching	0	0	0
Tic	0	0	1 (1.0)

*Data from acute phase of studies HGKA, and HGJZ; †data from study HGKA only; ‡data from study HGJZ only.
EPS=extrapyramidal symptoms; IM=intramuscular injection; LAI=long-acting injection; N=number randomized.

Statistical Analysis

Using the *Medical Dictionary for Regulatory Activities*® version 12.0, treatment-emergent EPS events were defined as newly appearing events, or worsening of pre-existing symptoms, on treatment. EPS were also measured using the Barnes Akathisia Rating Scale (Barnes) (27), the Abnormal Involuntary Movement Scale (AIMS) (28-30), and the Simpson-Angus Scale (SAS) (31).

For the acute and maintenance studies, baseline was defined as the lead-in period before treatment. For the open-

Table 2 Incidences of Treatment-Emergent EPS Events during Treatment with Olanzapine Long-Acting Injection

EPS category	Olanzapine LAI* 45–405 mg/every 2–4 weeks (N=931) N (%)
Any EPS event	86 (9.2)
Akathisia	24 (2.6)
Akathisia	14 (1.5)
Hyperkinesia	0
Psychomotor hyperactivity	1 (0.1)
Restlessness	9 (1.0)
Dyskinesia	15 (1.6)
Athetosis	1 (0.1)
Dyskinesia	9 (1.0)
Oculogyric crisis	1 (0.1)
Tardive dyskinesia	4 (0.4)
Dystonia	15 (1.6)
Muscle contractions, involuntary	0
Muscle spasms	13 (1.4)
Muscle tightness	1 (0.1)
Posturing	1 (0.1)
Parkinson-like	33 (3.5)
Bradykinesia	1 (0.1)
Bradyphrenia	0
Dysphonia	1 (0.1)
Gait disturbance	0
Hypertonia	4 (0.4)
Hypokinesia	1 (0.1)
Muscle rigidity	8 (0.9)
Parkinsonism	5 (0.5)
Tremor	16 (1.7)
Nonspecific	16 (1.7)
Extrapyramidal disorder	13 (1.4)
Muscle twitching	3 (0.3)
Tic	0

*Data from Study HGKB. EPS=extrapyramidal symptoms; LAI=long-acting injection; N=number randomized.

label extension study and the integrated oral olanzapine database, treatment-emergent EPS events were assessed at 0 (end of prior randomized trial) to ≤6 months; >6 months to ≤1 year; >1 year to ≤2 years; >2 years to ≤3 years; and, >3 years. The baseline definition was from beginning of study prior to the specific period under study. For the acute and maintenance studies, Fisher's exact test was used for pairwise comparisons between different olanzapine LAI dose groups, between oral and LAI olanzapine, and between olanzapine LAI and placebo.

The oral olanzapine database includes long-term, multicountry clinical studies with patient treatment exposure of at least 48 weeks. Twenty-six studies were taken from the database and used in the present analyses. For the open-label extension study and the integrated oral olanzapine database analyses, summary statistics were provided, because there was only one treatment group. To assess potential dose-response relationships between olanzapine LAI therapy and the incidence of EPS, we performed Cochran-Armitage trend tests across different olanzapine LAI dose groups. All statistical tests were two-sided at α=.05.

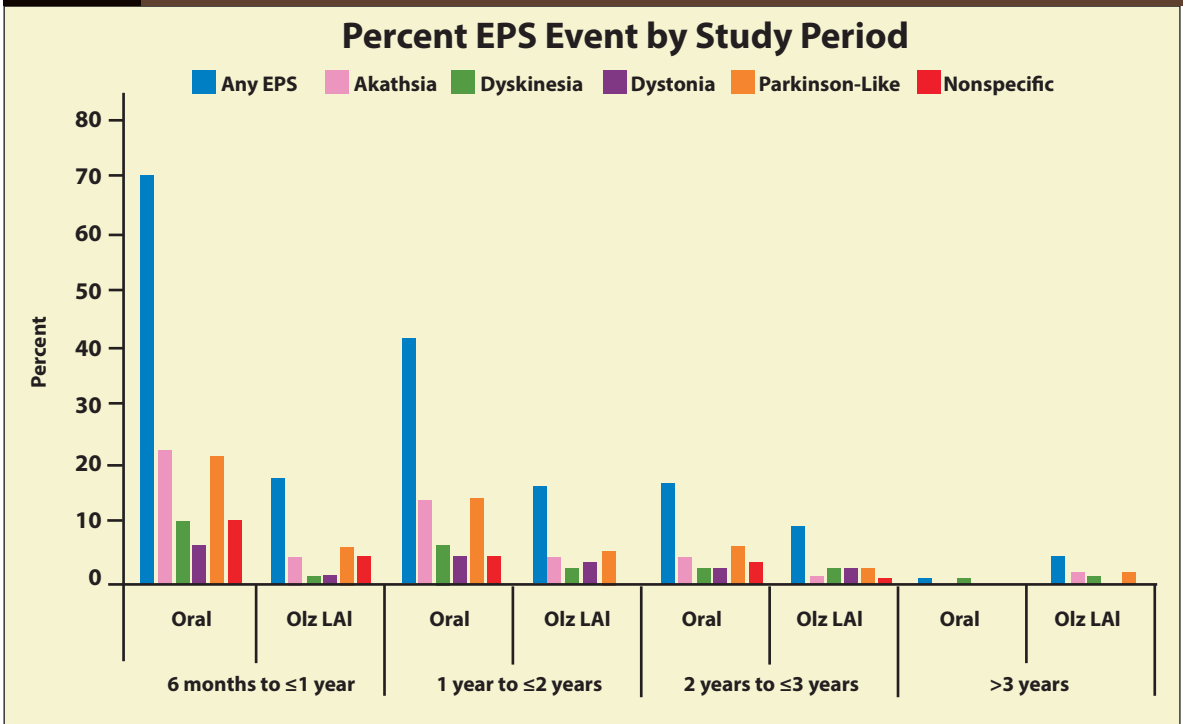
Results

The mean (standard deviation [SD]) baseline age in the olanzapine LAI studies ranged from 37.7 (10.5) to 41.5 (11.1) years, and the mean Positive and Negative Syndrome Scale (PANSS) total score ranged from 54.3 (15.3) to 102.6 (15.6). The mean (SD) baseline scores for the SAS, Barnes, and AIMS scales in the olanzapine LAI studies ranged from 0.88 (1.65) to 1.65 (2.79), 0.19 (0.53) to 0.37 (0.73), and 0.49 (1.35) to 1.12 (1.97), respectively.

In the acute phase of the double-blind studies (HGJZ and HGKA), a total of 59 (5.6%) of 1,049 patients receiving olanzapine LAI experienced EPS events. In comparison, in the integrated oral database, 16 (5.0%) of 322 receiving oral olanzapine experienced EPS events (see Table 1). The most frequent EPS seen with olanzapine LAI was akathisia (LAI, 2.6%; oral, 1.2%). Moreover, small, nonsignificant decreases in EPS severity generally occurred in patients receiving olanzapine LAI as measured by the Barnes, AIMS, and SAS scales (24, 25). In the open-label study of olanzapine LAI, 86 (9.2%) patients experienced treatment-emergent EPS (see Table 2). The most common events experienced by patients were tremor (1.7%) and akathisia (1.5%).

In study HGKA—a direct test of olanzapine LAI versus oral olanzapine that is included in the previous up-to-3-year comparison—29 (3.9%) and 16 (5.0%) patients (p=.36), respectively, experienced an EPS event during the 24 weeks. Also included in the overall comparison is 8 weeks of treatment with olanzapine LAI or placebo, during which 30 olanzapine LAI (9.8%) and 8 placebo patients (8.2%) experienced an EPS event (p=.61). In both studies, no significant differences occurred between olanzapine LAI and the other treatments groups for any individual EPS. There was no significant dose-response effect in the incidence of EPS events as a function of increasing olanzapine dose (data not

Figure 1 **Proportions of Patients with Treatment-Emergent EPS Events by Treatment Interval with Olanzapine LAI (n=931) in Study HGKB (Long-Term, Open-Label, Extension Study) and Oral Olanzapine (n=941) in the Integrated Clinical Database**



Number of patients per time period: 6 months to ≤1 year (oral, 939; LAI, 765); 1 year to ≤2 years (oral, 818; LAI, 677); 2 years to ≤3 years (oral, 471; LAI, 562); >3 years (oral, 165; LAI, 344). EPS=extrapyramidal symptoms. Olz LAI=olanzapine long-acting injection.

shown). However, it is unclear whether this may have been due to a lack of statistical power, as the incidence of EPS events was very low.

EPS events with olanzapine LAI in the long-term extension study (HGKB) were, in general, less frequent than observed with oral olanzapine in the integrated database. In particular, the incidence of TD within the time intervals with olanzapine LAI was 0–0.3% compared with 0–1.3% for oral olanzapine in the integrated database. The incidence of EPS events did not increase over time with either olanzapine LAI or oral olanzapine; in fact, these incidences tended to decrease from the interval of 6 months to >3 years (see Figure 1).

Discussion

Based on the present analysis, olanzapine LAI has a similar treatment-emergent EPS profile to that of oral olanzapine. The incidence of treatment-emergent EPS events was not significantly higher among patients receiving olanzapine LAI compared with those receiving oral olanzapine, based on our exploratory data analysis. No new or unusual EPS events were detected with olanzapine LAI as compared with what has been observed with oral olanzapine.

The severity of EPS, as measured by the SAS, Barnes, and AIMS scales, was low at baseline in the olanzapine LAI studies. Nevertheless, in Study HGKA (25), patients on all doses of olanzapine LAI showed numerically greater improvement on the SAS compared with oral olanzapine. Olanzapine LAI doses showed similar improvements on the Barnes and AIMS scales. Moreover, the incidence of EPS was very low (2 to 5%) in both olanzapine LAI and oral olanzapine, which was likely due to the initial 4- to 8-week stabilization phase. In contrast, Study HGJZ patients taking olanzapine LAI had an EPS incidence in the range of 8 to 13%, which is similar to EPS rates found in an integrated analysis of acute trials of oral olanzapine (7).

The incidence rates of EPS events and changes in the severity of EPS with LAIs of other antipsychotics have been compared with the same drug given orally. In a small study (n=50), patients with schizophrenia who had been stabilized for at least 3 months on oral risperidone were randomly assigned to treatment with either risperidone LAI or oral risperidone for 12 weeks of treatment (15). Patients on risperidone LAI showed similar mean baseline-to-endpoint changes on the SAS, Barnes, and AIMS scales compared with patients receiving oral risperidone. In the somewhat larger

6-month StoRMi (Switch to Risperidone Microspheres) trial (32), symptomatically stable patients transitioned from oral risperidone to its LAI formulation in fact showed a highly significant improvement in EPS severity. Similar findings that suggest a favorable EPS tolerability profile for the LAI formulation of olanzapine have been obtained in another study (24), with measures of extrapyramidal symptoms showing no significant difference from the effects of placebo. In contrast, comparison of intramuscular formulations of the first-generation antipsychotics with their oral formulations has been somewhat less encouraging (14). For example, in a 1-year relapse study of remitted patients with schizophrenia, significantly more patients on fluphenazine decanoate discontinued because of akinesia compared with patients receiving oral fluphenazine (23). Unfortunately, few other studies make a direct head-to-head comparison between oral and intramuscular formulations of antipsychotics with respect to their EPS profiles.

Potential limitations of the present analysis include differences in study durations and study/analysis designs (for example, fixed vs. flexible dose; open label vs. double blind; clinical trial vs. integrated safety database), dampening the validity of possible statistical comparison. As with all cross-study comparisons—because potential differences may occur between study populations such as ethnicity, age, duration of illness, and previous antipsychotic exposure—one should exhibit caution in the interpretation of these results.

Conclusions

Incidences of EPS in patients receiving olanzapine LAI were low and not significantly different from those among patients receiving either oral olanzapine or placebo. Additional prospective, randomized, controlled trials in larger and more heterogeneous patient populations followed-up for longer periods are needed to assess the potential effects of switching from oral olanzapine to olanzapine LAI.

Study ID and Registration Numbers

Study ID	Clinical Trials Identifier	URL	Date Accessed
F1D-MC-HGKA	NCT00088491	http://clinicaltrials.gov/ct2/show/NCT00088491	June 30, 2010
F1D-MC-HGKB	NCT00088465	http://clinicaltrials.gov/ct2/show/NCT00088465	June 30, 2010
F1D-MC-HGJZ	NCT00088478	http://clinicaltrials.gov/ct2/show/NCT00088478	June 30, 2010
F1D-EW-LOBS	NCT00094640	http://clinicaltrials.gov/ct2/show/NCT00094640	June 30, 2010

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