Profile of olanzapine long-acting injection for the maintenance treatment of adult patients with schizophrenia

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Abstract: Olanzapine long-acting injection (OLAI) is a crystalline salt composed of olanzapine and pamoic acid, which permits a depot intramuscular formulation of olanzapine. The half-life of olanzapine pamoate is 30 days, and its steady state is reached approximately at 12 weeks. Oral supplementation of olanzapine is not required during OLAI initiation, according to Eli Lilly recommendations, although a study indicated that $60\%$ of $D_2$ receptor occupancy was reached only by the fifth injection cycle. To date, a short-term, placebo-controlled study of 8 weeks in acutely ill patients and a long-term, controlled trial of 24 weeks in stabilized patients have been conducted. In both the studies, efficacy and safety were similar to those of oral olanzapine, with the exception of an acute adverse effect, the so-called inadvertent intravascular injection event, which occurred 1–3 hours after the injection with an incidence rate of 0.07% per injection. It consisted of symptoms that are similar to those reported in cases of oral olanzapine overdose. The most significant studies published to date, on the use of olanzapine pamoate in schizophrenia, are reviewed in this article. The pharmacodynamic and pharmacokinetic profile and related side effects of OLAI are reported.

Keywords: olanzapine pamoate long-acting injection, efficacy, safety

Introduction

Schizophrenia is characterized by disorganized behavior and thought, positive (delusions and hallucinations) and negative symptoms (eg, anhedonia, affective flattening, alogia, avolition) that induce dysfunction in many areas, such as interpersonal relations, work, and self-care,1,2 and, in most cases, progressive deterioration of personality and social skills.3 It is a chronic disorder with frequent exacerbations that often require hospitalization. Schizophrenia constitutes an economic burden for society due to both the patient’s inability to work and the need for assistance.4 To date, antipsychotic medication remains the cornerstone of current therapeutic interventions for schizophrenia, but approximately one-third of schizophrenic patients are treatment-resistant and approximately 50% of patients are noncompliant with antipsychotic treatment.5–6

Long-acting antipsychotic drugs

The first long-acting antipsychotic agents were developed in the 1960s in order to assure a constant delivery of the drug and to enhance therapeutic compliance.7 Using a long-acting antipsychotic drug may improve patient outcome by offering good efficacy and tolerability of an antipsychotic drug at the lowest effective dose without “first-pass metabolism” and hematic peaks. Long-acting drug therapy also combines these pharmacological advantages with an improvement in therapeutic compliance since it

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provides the opportunity for regular contacts between patient and therapeutic teams. Many data from clinical trials and meta-analyses show that long-acting antipsychotic treatments reduce relapses and hospitalizations and favor rehabilitation and psychosocial programs, which have a positive influence on such clinical outcomes as medication compliance, and symptom and relapse reduction.

Conventional long-acting agents are associated with similar side effects to the equivalent oral doses of typical antipsychotic drugs, especially extrapyramidal symptoms and hyperprolactinemia. During the past 15 years, atypical antipsychotic agents have been introduced. The group of atypical antipsychotic drugs is heterogeneous but is characterized by similar clinical efficacy on both negative and cognitive symptoms with low risk of extrapyramidal side effects (EPS). Consequently, many patients were switched from conventional long-acting therapies to oral atypical antipsychotic drugs, a practice that, interestingly, has never been evaluated scientifically.

In 1997, the American Psychiatric Association guidelines for the treatment of patients with schizophrenia highlighted the need for a long-acting formulation of atypical antipsychotic drugs and indicated 3 primary goals in the treatment of schizophrenia: (1) sustained relief from psychotic symptoms, (2) reduced relapse rates, and (3) improved functioning and quality of life.

Long-acting injectable risperidone, constituted by biodegradable polymers, was the first available long-acting atypical antipsychotic drug. It is a newly developed intramuscular depot formulation of olanzapine, whose oral form was commercialized in 1996 in the United States; olanzapine pamoate was approved by US Food and Drug Administration (FDA) on November 12, 2009 for adult patients affected by schizophrenia.

Methods
First, we review the pharmacodynamic profile and the effectiveness of oral olanzapine according to the most relevant and recent studies, with the aim of highlighting the benefits and the risks of this drug, which has been largely used in a rapid-release formulation during the past 15 years. Then we analyze the chemical characteristics and pharmacokinetic profile of olanzapine pamoate, according to technical details of Eli Lilly, and positron emission tomography (PET) and plasma concentration studies. Then we describe the short- and long-term clinical studies conducted and published to date in order to define the efficacy and safety profile of this new formulation. We favor data published in scientific journals over those in poster and oral communications to congresses.

Data sources

Pharmacodynamic profile of olanzapine
Olanzapine, a dibenzothiazepine structurally similar to clozapine, shares higher affinity to 5-HT\textsubscript{2A} receptors than D\textsubscript{2} receptors (high 5-HT\textsubscript{2A}/D\textsubscript{2} ratio).\textsuperscript{11,16} In comparison to the other atypical neuroleptics, olanzapine presents high affinity for serotonergic 5-HT\textsubscript{2A}, 5-HT\textsubscript{2C}, 5-HT\textsubscript{3}, and 5-HT\textsubscript{1A} receptors,\textsuperscript{17} medium affinity for dopaminergic D\textsubscript{1}, D\textsubscript{2}, D\textsubscript{3}, D\textsubscript{4}, and muscarinic M\textsubscript{1}–M\textsubscript{5} receptors,\textsuperscript{18} low affinity for adrenergic \\textalpha\textsubscript{1} and \textalpha\textsubscript{2} receptors, and the highest affinity for histamine H\textsubscript{1} receptors (olanzapine is the most potent histamine H\textsubscript{1} antagonist known).\textsuperscript{19,20} Olanzapine selectively reduced the activity of dopaminergic mesolimbic (A10) neurons but not dopaminergic striatal (A9) neuron fire and, in animal studies, counteracted conditioned avoidance behavior (test of antipsychotic efficacy) at a dose that was not sufficient to induce catalepsy (test of motor side effect).\textsuperscript{21} More recently, preclinical studies showed that olanzapine efficacy on psychotic and cognitive symptoms of schizophrenia may be represented by its facilitating effect on N-methyl-D-aspartic acid, which can favor brain derived neurotrophic factor (BDNF) expression.\textsuperscript{22,23} According to another study, treatment with olanzapine markedly restored the reduction of both BDNF and TrkB receptors in hippocampus, associated with previous treatment with haloperidol.\textsuperscript{24} Other studies mentioned that olanzapine efficacy on negative and depressive symptoms of schizophrenia might be related to inhibition of norepinephrine transporter\textsuperscript{25} and modulation of cytokine plasma level, as interleukin-2 declined after 8-week olanzapine treatment.\textsuperscript{26}

Side effects of olanzapine
Olanzapine usually is a well-tolerated drug. Among its main side effects, bodyweight gain is the most significant, and it is especially marked in children and adolescents.\textsuperscript{27–29} According to data of Eli Lilly, the frequency of \textgeq 7% bodyweight gain was 22.2% in adult patients and 40.6% in adolescent patients treated for a mean period of 47 days; during long-term treatment with olanzapine of 21–48 weeks, the increase in bodyweight was more relevant.\textsuperscript{30} Olanzapine, like clozapine but not conventional antipsychotic agents, increases...
insulin release and induces a metabolic syndrome more frequently than the other first- or second-generation antipsychotic drugs, also in the acute treatment of first psychotic episode.

EPS, including akathisia, can be induced only by high doses, whereas tardive dyskinesia can be improved by olanzapine treatment, as reported in some cases. Olanzapine rarely induces seizure or neuroleptic malignant syndrome.

An influence on blood pressure, like hypotension, was observed only in the elderly (>65 years), and myocardial conduction alterations were rarely observed during olanzapine treatment. Although olanzapine possesses direct cardiac electrophysiological effects similar to those of class III antiarrhythmic drugs, it is less potent than other antipsychotic drugs (haloperidol, risperidone, sertindole) in lengthening the QT interval. Only under some conditions of impaired drug elimination, such as renal or hepatic insufficiency, coadministration of CYP1A2 substrate inhibitors or after drug overdose, could a QT-prolonging effect during olanzapine treatment be observed. Despite its affinity for muscarinic M1–M5 receptors shown in in vitro studies, its anticholinergic symptoms (dry mouth and constipation) are moderate. Olanzapine has a favorable profile in terms of prolactin-sparing compared with first-generation antipsychotic drugs in adults but not in children and adolescents (a relevant prolactin elevation was observed in 47.4% of the pediatric population).

Antipsychotic efficacy of olanzapine
Olanzapine effectiveness in the treatment of schizophrenia is indirectly shown by its extensive clinical use and is noted by many studies, and further confirmed by meta-analyses, such as that conducted by Davis et al. and large effectiveness studies, such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and the European First Episode Schizophrenia Trial. Oral olanzapine has received regulatory approvals for the treatment of bipolar mania and, in combination with fluoxetine, for bipolar depression. A rapid-acting, nondepot intramuscular preparation of olanzapine is also available and approved for the treatment of agitation associated with schizophrenia and bipolar mania.

The CATIE study found that olanzapine had the lowest discontinuation rates compared with the other 5 antipsychotic drugs over the 18-month treatment period. In a meta-analysis including 16 studies, patients treated with olanzapine were found to have a lower all-cause discontinuation rate than those treated with other antipsychotic drugs.

Olanzapine pamoate monohydrate: chemical structure and pharmacokinetic profile
Olanzapine long-acting injection (OLAI) is a crystalline salt, whereas long-acting risperidone is a compound polymerized through a physical process in order to be slowly released, and conventional antipsychotic long-acting injections (fluphenazine decanoate, haloperidol decanoate, perphenazine enanthate, zuclopenthixol decanoate) are esterified compounds. OLAI is composed of olanzapine and pamoic acid in the form of micron-sized crystals suspended in water, which permits a depot intramuscular formulation of olanzapine. When injected into the muscle, the salt slowly dissolves and dissociates into separate molecules of olanzapine and pamoic acid at the site of injection; both these components enter into systemic circulation. The rate of dissolution of the crystalline salt is slow and regular, resulting in the absorption of olanzapine over a period of 4 weeks (steady state is approximately reached at 12 weeks). The oral supplementation of olanzapine is not required during OLAI initiation, according to Eli Lilly recommendations. The half-life of olanzapine pamoate is 30 days (vs oral olanzapine 33 hours). The absorption and distribution of olanzapine pamoate are rapid and completed 6–8 months after the last injection. Ninety-three percent of olanzapine pamoate is bound to albumin and α1-acid-glycoprotein. In impaired renal functioning, a significant reduction of clearance and half-life of oral olanzapine (57% of metabolized olanzapine is excreted into urine) is not observed, whereas in mild impaired hepatic functioning, both clearance (18 L/h) and half-life (39.3 hours) of oral olanzapine increased. OLAI has not been studied in these pathological situations, likewise in the elderly or in the pediatric and adolescent population, and it is not indicated for these conditions. Olanzapine is principally metabolized by CYP1A2, so that carbamazepine and cigarette smoke could induce its metabolism, but the reduction of olanzapine concentration when combined with these agents is clinically mild. Fluvoxamine and ciprofloxacin have shown a relevant inhibitor action on CYP1A2 olanzapine metabolism, increasing its hematic concentration. The pharmacokinetic variation related to gender and smokers is not superior to the inter-individual variability.
Olanzapine pamoate monohydrate: dose-finding studies

Plasma olanzapine concentrations were sampled periodically in a subset of 346 patients who had participated in a 24-week maintenance study of olanzapine pamoate in order to discover the equivalent dose to oral olanzapine (Table 1).45

The percentage of patients who experienced relapse by 24 weeks ranged from 1.5% (when switched from 10 mg/d oral olanzapine to 300 mg/2 wk of olanzapine pamoate) to 18.8% (from 20 mg/d oral olanzapine to 150 mg/2 wk of olanzapine pamoate). In order to minimize the risk for exacerbation of psychosis, the authors recommended to start with the equivalent dose of olanzapine pamoate and then, 2 months later, to evaluate the maintenance dose, which would remain at 300 mg/2 wk for patients who had previously been stabilized with 20 mg/d of oral olanzapine.

Oral olanzapine has shown a dose-dependent striatal D₂ receptor occupancy of 60%–80% at usual clinical doses.46 With the aim of determining whether the long-acting olanzapine pamoate depot provided sustained D₂ receptor occupancy, an open-label PET study was conducted in 14 patients (9 males, 5 females) with schizophrenia and schizoaffective disorder treated with an intramuscular injection of olanzapine pamoate 300 mg every 4 weeks for 6 months (6 injection cycles).47 During the first 4 injection cycles, 7 patients needed a supplementation with oral olanzapine due to the worsening of psychotic symptoms, as shown by the Brief Psychiatric Rating Scale (BPRS). No patients received an oral supplementation at the time of PET scanning, which reflected only the OLAI D₂ receptor occupancy. The need for oral olanzapine supplementation decreased when occupancy with OLAI reached ≥60%, which represents a sufficient percentage for antipsychotic efficacy of most antipsychotic drugs. During the fifth injection cycle, the D₂ receptor occupancy resembled the baseline occupancy level of oral olanzapine (84%). Dopamine D₂ receptor occupancy and plasma olanzapine concentrations were significantly correlated (r = 0.76; P = 0.001) during the 6-month period. As suggested by the authors, these data could indicate that supplementation with oral olanzapine, or a higher dose (eg, 400 mg/4 wk) or an increased frequency of depot dosing for the first 3 months, may be required to maintain adequate therapeutic response during the first injection cycles.47

Olanzapine pamoate: clinical studies

In order to conform to FDA requirements, the parent pharmaceutical company conducted 2 studies: a short-term, placebo-controlled study48 and a long-term, controlled trial.49

A third study of long-term treatment with olanzapine pamoate is available online (http://www.fda.gov), and has been reported in a review.50

Another long-term study (ClinicalTrials.gov Identifier: NCT00320489) of 2 years was completed in September 2009, but the results are not published yet. In this clinical trial, primary outcome measures consisted of the assessment of the difference between olanzapine pamoate (405 mg intramuscular followed 4 weeks later by 150–405 mg flexible dosing every 4 weeks for 96 weeks) and oral olanzapine (10 mg/d for 4 weeks followed by 5–20 mg flexible dosing, oral tablets, once daily, for 100 weeks) in time to all-cause discontinuation in outpatients with schizophrenia at risk for relapse.51

Data for OLAI comparison with other antipsychotic long-acting injections are not available because, to date, such a study has not been conducted and comparison among results of different depot trials may be scientifically inaccurate.

Olanzapine pamoate: efficacy

1) The first double-blind placebo-controlled study was conducted for a period of 8 weeks in acutely ill patients affected by schizophrenia.48 The primary efficacy measure was represented by mean change from baseline to end point in Positive and Negative Syndrome Scale (PANSS) total score. The second outcome was represented by change from baseline to end point in the Clinical Global Impression-Improvement (CGI-I) scale score. The acutely ill patients (n = 404) affected by schizophrenia were randomly assigned to olanzapine pamoate of 300 mg/2 wk, 405 mg/4 wk, and 210 mg/2 wk or placebo without any antipsychotic drug supplementation. All the 3 doses were found to be statistically significant superior to placebo (P < 0.001): the mean changes from baseline to end point in PANSS total score were −26.32, −22.57, and −22.49, respectively, compared with −8.51 for placebo. All the

| Table 1 Doses of oral olanzapine and olanzapine pamoate and their plasma concentrations at steady state |
|----------------------------------|----------------------------------|
| **Doses** | **Plasma concentrations at steady state (ng/mL)** | **Doses** | **Plasma concentrations at steady state (ng/mL)** |
| 10 mg/d | 13–48 | 150 mg/2 wk | 5–41 |
| 15 mg/d | 21–63 | 210 mg/2 wk | 8–51 |
| 20 mg/d | 21–85 | 300 mg/2 wk | 7–73 |
3 doses induced a statistically significant difference from placebo at PANSSE score by 7 days, but the doses 300 mg/2 wk and 405 mg/4 wk induced a more rapid improvement at only 3 days from the starting of treatment. All OLAI treatment groups showed a statistically significant improvement ($P < 0.001$) compared with placebo group at end-point CGI-I scale score ($\geq 3$).

2) A 24-week, double-blind randomized study, designed to assess the efficacy of olanzapine pamoate as maintenance treatment for outpatients affected by schizophrenia, investigated whether clinically stable patients already treated with other antipsychotic drugs would remain stable when switched to olanzapine pamoate.

Patients enrolled were first switched to open-label, oral olanzapine monotherapy over a period of 4–8 weeks. Only patients stabilized ($n = 1065$) for 4 consecutive weeks (no dose change of oral olanzapine, CGI-I = 4, BPRS positive symptom score = 4) were randomized to receive olanzapine pamoate at high dose (405 mg/4 wk), medium dose (300 mg/2 wk), low dose (150 mg/2 wk), very low dose (45 mg/4 wk), or to remain on their oral olanzapine up to 24 weeks. The first 3 doses of olanzapine pamoate corresponded to oral olanzapine 10, 15, and 20 mg, whereas the low subtherapeutic dose of 45 mg/4 wk was included as a comparator for the 3 therapeutic doses and could be considered a possible placebo equivalent. No supplementation with oral antipsychotic therapy was permitted after randomization. Two primary measures were rate and time of exacerbation. Exacerbation was defined as either the worsening of positive symptoms (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) at BPRS or the need for hospitalization due to the worsening of positive psychotic symptoms since randomization.

At the end point, the 3 groups treated with therapeutic doses of olanzapine pamoate showed a statistically significant superior period of time without psychotic exacerbation in comparison to the dose of 45 mg/4 wk ($P < 0.001$, $P < 0.001$, and $P = 0.006$, respectively). These observations were confirmed by the PANSSE total scores, which showed that the 3 therapeutic doses of olanzapine pamoate were effective in maintaining a response throughout all the study periods, whereas the 45 mg/4 wk group showed a statistically significant worsening of total PANSSE scores over the 24 weeks ($P < 0.001$). In addition, the noninferiority analysis demonstrated the equivalent efficacy of pooled 2-week depot doses (150 mg/2 wk and 300 mg/2 wk) of oral olanzapine in terms of exacerbation rate after 24 weeks of maintenance treatment (the cumulative nonexacerbation rate was 90% for the pooled 2-week regimen and 93% for the oral olanzapine group).

The population ($n = 1065$) of this study was further investigated in order to compare patients’ quality of life between oral and long-acting injectable formulations of olanzapine: clinician-rated and patient-reported outcomes were evaluated by means of the Heinrichs–Carpenter Quality of Life Scale (QLS), the Short Form Health Survey (SF36), and the Drug Attitude Inventory (DAI). Over the course of the 24-week study, subjects remained stable and experienced an increase in quality of life regardless of assignment to OLAI or oral olanzapine, suggesting a comparable effect of OLAI with equivalent doses of oral olanzapine on this parameter.

Adult patients with schizophrenia or schizoaffective disorder ($n = 931$), who participated in the 24-week study, were enrolled in an open-label extension trial of OLAI.

A total of 880 patients were included, and results showed that there was a statistically significant decrease in PANSSE total score ($P = 0.013$) from 56.28 to 54.90 and CGI-Severity scores (range, 2.91–2.78), indicating patient improvement that remained stable throughout all periods of the study. The all-cause discontinuation rate, a widely accepted measure of treatment effectiveness, was found to be 34% at 18 months.

Olanzapine pamoate: safety

Data of all patients ($n = 1778$, June 2006) treated with OLAI were collected from 2 controlled studies and 6 open-label studies (number of injections on average: 11.31) and were integrated in to a unique database.

In this population, discontinuation rate was inferior to 6% due to adverse effects (weight gain, sedation/somnolence, and increased hepatic enzymes) or inefficient control of psychotic symptoms; 3 deaths occurred that were not apparently related to the drug.
As shown in Table 2, in the short-term study,\textsuperscript{48} the incidence of bodyweight gain $\geq 7\%$ of baseline was significantly greater for all the olanzapine groups relative to placebo ($P = 0.046$). The increase in fasting total cholesterol was significantly higher in all patients treated with OLAI compared with placebo ($P = 0.015$) and, in particular, a significant difference in fasting cholesterol was found between the patients treated with 210 mg/2 wk and 405 mg/4 wk ($P = 0.16$). Incidence of sedation and increased appetite were significantly higher for 300 mg/2 wk OLAI compared with placebo ($P < 0.05$).

As shown in Table 3, in the long-term study,\textsuperscript{49} bodyweight gain was significantly greater for high dose than low dose ($P = 0.04$), but the incidence of weight gain $\geq 7\%$ from the randomization time in all the OLAI groups was not significantly different from that of the oral olanzapine groups. Patients in both OLAI and oral olanzapine groups had significantly higher levels of low-density lipoprotein and cholesterol relative to the comparative group (OLAI 45 mg/4 wk). The metabolic parameters (fasting glucose and lipid levels) of all OLAI groups overlapped those of oral olanzapine groups. Only the higher dose OLAI induced an increase of prolactin and a significantly higher level of triglycerides relative to the other doses of olanzapine pamoate. In this study, extrapyramidal and cardiovascular effects were not observed. Two patients experienced sedation and delirium consistent with inadvertent intravascular (IAIV) injection event.

These studies did not show any statistically significant difference in adverse events between oral olanzapine and the depot formulation, with the exception of a new potential safety risk that emerged in clinical trials, known as IAIV injection event, or postinjection delirium sedation syndrome (PDSS) as it was formerly defined, which initially led the FDA not to approve this preparation. This came to light when an unanticipated degree of sedation was observed in a small number of patients after an injection. Although sedation is a common adverse effect in olanzapine treatments, the extent of sedation appeared relevant. As of September 30, 2007, 25 excessive sedation events were reported in 24 patients (1.2\% of patients, 0.07\% of injections).\textsuperscript{54,55} As of May 31, 2008, the incidence of PDSS with olanzapine pamoate was 29 events in 28 patients, per $>40,000$ injections, for an incidence rate of 0.07\% of injections.\textsuperscript{56}

This adverse event consists of sedation, confusion, dizziness, altered speech/dysarthria, and somnolence, symptoms that are consistent with those reported in case of oral olanzapine overdose. The severity of sedation ranged from drowsiness to deep coma (2 cases of coma, 2 patients intubated, 2 cases of delirium, and 2 cases of tonic-clonic convulsions were reported). In all the cases but one, who presented high blood pressure, the cardiovascular function remained unaltered. These effects usually occur within 1 hour of injection, but the median time ranged from 20 minutes to 3 hours postinjection. PDSS typically begins with milder symptoms (feeling of weakness, dizziness, irritability, or general malaise), which can then progressively worsen (delirium, heavy sedation). Seventy-nine percent of patients who presented this adverse event needed to be hospitalized in order to observe and give them supportive medical care. To date, all patients have recovered fully from this adverse event, usually within 3–72 hours, without permanent damage, and approximately 70\% of these continued to receive the depot injections.

Since an unpredictable pattern of IAIV injection events occurrence was observed, without any relationship with concomitant medications, substances, organic diseases or repeated OLAI injections, it has been hypothesized that a rapid release of free olanzapine into the bloodstream could

### Table 2 Metabolic side effects in a short-term study$^{48}$ evaluated at the end point (8 weeks)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Mean change from baseline (kg)</th>
<th>% patients with weight gain ($\geq 7%$)</th>
<th>% patients with increased triglycerides (&gt;200 mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12.4</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>210 mg/2 wk</td>
<td>23.6</td>
<td>12.8</td>
<td>12.8</td>
</tr>
<tr>
<td>405 mg/4 wk</td>
<td>27.0</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>300 mg/2 wk</td>
<td>35.4</td>
<td>14.3</td>
<td>14.3</td>
</tr>
<tr>
<td>Oral olanzapine</td>
<td>(mean dose, 14.3 mg/d)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3 Metabolic side effects in a long-term study$^{49}$ evaluated at the end point (24 weeks)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Mean change from baseline (kg)</th>
<th>% patients with weight gain ($\geq 7%$)</th>
<th>% patients with increased triglycerides (&gt;200 mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 mg/4 wk</td>
<td>−0.95</td>
<td>8</td>
<td>3.4</td>
</tr>
<tr>
<td>150 mg/2 wk</td>
<td>0.67</td>
<td>15</td>
<td>6.5</td>
</tr>
<tr>
<td>405 mg/4 wk</td>
<td>0.89</td>
<td>16</td>
<td>9.8</td>
</tr>
<tr>
<td>300 mg/2 wk</td>
<td>1.70</td>
<td>21</td>
<td>24.5</td>
</tr>
<tr>
<td>Oral olanzapine</td>
<td>(mean dose, 14.3 mg/d)</td>
<td></td>
<td>13.8</td>
</tr>
</tbody>
</table>
have occurred.\textsuperscript{37} Data on elevated plasma concentration of olanzapine measured during the event can confirm this hypothesis. The solubility of olanzapine pamoate monohydrate in plasma is \textasciitilde 167 times higher (0.5 mg/mL in plasma, 0.003 mg/mL in aqueous buffer) than that in an aqueous medium. If the salt comes into contact with a considerable amount of blood or plasma, as occurs if the needle punctures a vessel or enters a rich capillary bed during administration, it dissolves more quickly, releasing free olanzapine. This dissolution can occur over a period of minutes to hours in the bloodstream, whereas when it takes place in muscle tissue, it requires a period of days to weeks. Other factors are believed to affect the dissolution rate of the pamoate salt, such as the amount of olanzapine pamoate suspension, the volume and rate of blood flow, and the degree of vascular injury secondary to injection. In order to decrease the risk of accessing a major nerve or blood vessel, the injection recommendations of OLAI should ensure that no blood is visible in the syringe after the aspiration for approximately 5 seconds and to place it deeply only into the gluteal muscle at a ventrogluteal site. Until now, data on OLAI injection in other parts of body, like deltoid muscle, are not available.\textsuperscript{56}

Eli Lilly recommend a postinjection observation period of at least 1 hour up to 3 hours in a healthcare facility and require advising patients not to drive or operate heavy machinery and to be vigilant for signs and symptoms of potential IAIV injection events in the 24 hours after OLAI injection.

Conclusions
As highlighted by Citrome,\textsuperscript{57} olanzapine pamoate demonstrated efficacy both in acutely ill and stabilized patients affected by schizophrenia, with low risk for extrapyramidal or vascular effects but high risk for metabolic syndrome. OLAI showed a pharmacological profile overlapping that of oral olanzapine, with the exception of a new acute adverse effect represented by an IAIV injection event, which has worried physicians and pharmacologists, delaying registration and clinical use of this new preparation. Although it has been interpreted as a type of acute overdose of olanzapine due to a relatively high hematic solubility of olanzapine pamoate salt, it could represent an unbalanced effect of this atypical antipsychotic agent due to its complex action on different central receptors. This effect has not yet been completely clarified. It could resemble the paradoxical worsening of psychotic symptoms which commonly occurs in some patients when optimal titration of an atypical antipsychotic drug has not been completely reached. We need to take account that evidence from clinical experience shows that a paradoxical excitement reaction with worsening of psychotic symptoms occurs during the first 24 hours postinjection of a typical antipsychotic depot, according to the information referred to in the sheet of drugs, which could be interpreted as a sulpiride-like action of antipsychotic drugs that act as an antidepressant agent when their hematic concentration is very low. Nevertheless, this acute adverse effect has not been observed in such a severe clinical form during other long-acting antipsychotic treatments probably for pharmacokinetic reasons: other typical antipsychotic depot are fat-soluble compounds with a slow dissolution rate and risperidone RP is a polymer compound that needs a long period of absorption. Only postmarketing data will indicate the real incidence and risk of OLAI IAIV injection event.

According to the pharmacokinetic profile (the absorption of OLAI occurs over a period of 4 weeks and steady state is approximately reached at 12 weeks)\textsuperscript{30} and the D\textsubscript{2} receptors occupancy data (only by the fifth injection cycle of 300 mg/4 wk of OLAI, the D\textsubscript{2} receptor occupancy resembled the baseline occupancy level of oral olanzapine),\textsuperscript{47} a supplementation of oral olanzapine during the first injection cycle could be indicated in order to maintain a sufficient and stable hematic concentration, especially for patients who have previously required high doses of oral olanzapine. The prudent recommendation by the manufacturer, which does not advise any oral olanzapine supplementation, needs to be confirmed by real-world clinical use since the most severely affected patients are often excluded from controlled clinical trials because of ethical issues.

As cited above, nonadherence to treatment represents one of the most important reasons for relapse in schizophrenia, which progressively favors the worsening of disease course and the deterioration of patient skills. Unmedicated schizophrenia patients relapse at a rate of approximately 10\% per month, whereas maintenance treatment with antipsychotic medications can reduce this rate dramatically.\textsuperscript{61} Consistent treatment can improve the patient’s quality of life and lead to an overall reduction in the cost of care,\textsuperscript{58} by preventing or delaying relapse, which, if repeated, could induce neuronal apoptosis, so favoring progressive clinical deterioration, according to some authors.\textsuperscript{59}

As indicated by many authors,\textsuperscript{60} one of the best strategies to overcome poor compliance may be long-acting injection therapy, although to date it has not yet been well accepted by physicians probably due to the availability of only few typical antipsychotic drug depots and also because of personal resistance that leads the physician to consider depot as a type of invasive instrument for a patient.\textsuperscript{61} If the physician identifies poor compliance as a symptom of psychosis, they use depot
as a necessary therapeutic instrument to overcome it so that they can foster their relationship with the patient in order to support the patient in therapeutic and rehabilitation care.

The general safety profile of olanzapine pamoate, which is similar to that of oral olanzapine with a comparable low rate of neurological side effects, can further improve compliance and adherence to treatment. The positive effect of olanzapine on neurotoxic factors and its nonrelevant action on the seizure threshold can support the use of this drug as an option for some clinical situations. Otherwise, in OLAI treatment, the risk for metabolic syndrome, which appeared related to the higher doses of olanzapine pamoate also in short-term treatment, can represent a severe side effect because it could predispose patients to a premature death, especially in chronic treatment, according to most studies.62–64

The availability of atypical antipsychotic depot, like olanzapine pamoate, permits maintenance treatment in non-adherent therapy patients who have previously shown a good response only to these oral drugs, as in cases characterized by negative, cognitive, or depressive symptoms, which are not ameliorated by typical antipsychotic drugs. Because olanzapine has demonstrated a good efficacy on affective symptoms the oral preparation has been approved for the treatment of bipolar mania, and, in combination with fluoxetine, for the treatment of bipolar depression. In future, if clinical studies confirm this indication, olanzapine pamoate might represent an important therapeutic option for bipolar disease, which is characterized by very low compliance.

Finally, many other postmarketing clinical trials supported by clinical experience are necessary to better identify the antipsychotic effectiveness of “an old drug in a new look”, such as olanzapine pamoate.

Disclosure

The authors report no conflicts of interest in this work.

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