Pharmacokinetics of olanzapine long-acting injection: the clinical perspective

Stephan Heres[a], Susanne Kraemer[b], Richard F. Bergstrom[c,d] and Holland C. Detke[c]

Olanzapine long-acting injection (OLAI) is a sustained-release depot antipsychotic for the treatment of schizophrenia in adults. Our objective was to explain the pharmacokinetics of OLAI to provide clinical insight. Simulation models and data from clinical trials are presented. Olanzapine concentrations were observed immediately upon injection. Half-life was ~30 days, controlled by the slow rate of intramuscular absorption rather than the 30-h elimination rate-based half-life of oral olanzapine. As each injection builds on the drug still being released from previous injections, concentrations increase gradually until a steady state is reached after ~3 months. Concentrations were similar to oral olanzapine and proportional to the dose; the average steady-state concentrations (10th–90th percentile) for the 150, 210, and 300 mg/2-week doses were 16–32, 15–55, and 20–67 ng/ml, respectively, and those for the 300 and 405 mg/4-week doses were 19–48 and 19–62 ng/ml, respectively. Peak concentrations most often occurred at 2–4 days after injection. Peak-to-trough fluctuation was greater for the 4-week dosing interval than the 2-week one, with no apparent clinical ramifications for these differences. Trough concentrations were above the lower end of the therapeutic range, even at the first injection. Long-term use up to 6 years indicated no additional accumulation. The impact of smoking and sex was similar, but less pronounced than for oral olanzapine. *Int Clin Psychopharmacol* 29:299–312 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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[a]Klinik und Poliklinik für Psychiatrie und Psychotherapie der Technischen Universität München am Klinikum rechts der Isar, München, [b]Lilly Deutschland GmbH, Klinische Forschung, Neurologie und Psychiatrie, Bad Homburg, Germany, [c]Lilly Research Laboratories and [d]Indiana University School of Medicine and Butler University College of Pharmacy and Health Sciences, Indianapolis, Indiana, USA

Correspondence to Stephan Heres, MD, Klinik und Poliklinik für Psychiatrie und Psychotherapie der Technischen Universitaet Muenchen am Klinikum rechts der Isar, Moehlstrasse 26, 81675 Muenchen, Germany
Tel: +49 89 4140 4227; fax: +49 89 4140 7339;
e-mail: s.heres@lrz.tu-muenchen.de

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Introduction

In the treatment of schizophrenia, long-term relapse prevention is a key concern (Robinson *et al.*, 2004; Gaebel and Riesbeck, 2014; National Collaborating Center for Mental Health, 2009). Use of depot antipsychotic therapies in the treatment of schizophrenia offers an option to improve adherence and minimize subsequent relapses (Camacho *et al.*, 2008; Leucht *et al.*, 2011; Tiihonen *et al.*, 2011). However, understanding how best to administer a depot medication to maximize its effectiveness and minimize the potential risk of adverse events and patient relapse is clinically essential. To increase the opportunity for successful depot treatment, clinicians must understand how the formulation sustains the antipsychotic treatment and what the pharmacokinetic characteristics of the depot antipsychotic are to maximize the medication's performance through appropriate dosing during initial use as well as throughout the course of maintenance treatment.

Olanzapine pamoate [olanzapine long-acting injection (OLAI)] is the intramuscular depot formulation of the atypical antipsychotic olanzapine. Pharmacokinetics of olanzapine following doses of both oral and OLAI formulations have been well characterized (Callaghan *et al.*, 1999; Bergstrom *et al.*, 2000; Frampton, 2010), with the major distinguishing feature between them being the prolonged intramuscular absorption of OLAI. However, it is important to understand how this formulation differs from the oral formulation in its pharmacokinetic profile. First approved in 2008 in the European Union as maintenance treatment of schizophrenia in adults, the pamoate salt of olanzapine provides a sustained-release intramuscular dosage form of olanzapine. Once injected into the gluteal muscle, the organic salt dissolves slowly, dissociating into acid and base organic molecules, olanzapine (free base), and pamoic acid (Lindenmayer, 2010). The intramuscular in-situ rate of dissolution of the olanzapine pamoate salt is slow, but the absorption of the dissociated free base olanzapine in muscle tissue is very fast. This type of sustained-release mechanism provided by the salt-based formulation differs from those achieved by either oil-based depot formulations (e.g. haloperidol decanoate) or microsphere-based depot formulations (e.g. risperidone long-acting injection). Thus, the

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Table 1 Characteristics of olanzapine long-acting injection trials included

Study ID, Phase	Key objectives	Population, Number of participants	Study design, Duration	Dosing	PK measurements	Efficacy measures, Results
F1D-EW-LOAZ Phase 1	Absorption Bioavailability PK Safety Comparison with oral Olz	Healthy adult men *N*=18 enrolled *n*=18 PK analysis	Single dose of oral Olz and single dose of OLAI with at least 7 days between oral and OLAI doses	Oral Olz: 10 mg OLAI: 10, 15, 20, 30, or 40 mg	Before and after dose: oral Olz, up to 120 h after dose; OLAI, 38 days after dose	Efficacy not assessed. Subtherapeutic doses administered to healthy individuals
F1D-EW-LOBE Phase 1b (Mitchell *et al.*, 2013)	PK Safety Compare single vs. multiple dosing, various doses, and dosing intervals	Clinically stable adults with schizophrenia *N*=281 enrolled *n*=281 PK analysis	Open-label. Randomized to single-dose (assessed at 28 days), or multiple-dose treatment for up to 6 months	Single-dose: 50–450 mg (*n*=34) Multiple dose: 100–405 mg, injections every 2, 3, or 4 weeks (*n*=223)	After OLAI, daily for the first 4 days at 0, 24, 48, 72, and 96 h after injection; then weekly at 1, 2, 3, and 4 weeks after injection until the end of the dosing interval	BPRS CGI-S Changes in BPRS and CGI-S supportive of effectiveness
F1D-EW-LOBS Phase 1b	Bioavailability PK Safety Comparison of three OLAI lots manufactured with variations in the process	Clinically stable adults with schizophrenia or schizoaffective disorder *N*=134 randomized *n*=129 PK analysis	Open-label, randomized. After 2 weeks of oral olanzapine, patients randomized to a single injection of OLAI and assessed for 26 days. Patients then received a single injection of RAIM Olz and assessed for 5 days	Oral Olz: 5–20 mg/day OLAI: 405 mg RAIM Olz: 5 mg Oral Olz: 14 days, measurements for 24 h after dose on the 14th day	Oral Olz: 24 h after dose on day 14 OLAI: 0 (predose), 2, 6, 12, 18, 24, 36, 48, 72, 120, 144, 168, 192, 216 h and 11, 13, 16, 19, 22, and 25 days after injection RAIM: 0 (predose), 0.083, 0.167, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72, 96, and 120 h after injection	CGI-S Not designed to assess changes in clinical stability; no significant change in CGI-S
F1D-MC-HGKA Phase 3 (Kane *et al.*, 2010)	Safety Efficacy Comparison with oral Olz	Clinically stable adults with schizophrenia *N*=1065 randomized *n*=346 PK analysis	Randomized, double-blind relapse-prevention study. All patients received oral Olz for 4–8 weeks, then randomized to oral Olz or OLAI fixed dose for up to 24 weeks	Oral Olz: 5–20 mg/day OLAI: 150 mg/2 weeks 405 mg/4 weeks 300 mg/2 weeks or subtherapeutic reference dose of 45 mg/4 weeks	Samples collected from the first 346 patients only Up to nine samples collected per patient over a period of up to 24 weeks	PANSS, BPRS, CGI-S, relapse Efficacy scores at therapeutic doses remained stable; relapse rates were low and noninferior to oral Olz
F1D-MC-HGKB Phase 3 (McDonnell *et al.*, 2011)	Long-term safety	Adults with schizophrenia or schizoaffective disorder *N*=931 entered *n*=377 PK analysis	Open-label extension study. Patients received flexibly dosed OLAI for up to 6 years. Supplementation with oral olanzapine allowed as needed. Patients previously completed 1 of 3 feeder studies (F1D-MC-HGKA, F1D-MC-LOBS, or F1D-MC-HGJZ)	OLAI: 45–405 mg at a 2-, 3-, or 4-week interval (maximum dose of 300 mg/2 weeks)	Samples collected from only a subset of patients once each quarter. Samples collected as soon as 5 min after and as long as 73 days after the last OLAI	PANSS, BPRS, CGI-S Efficacy scores improved during first weeks of study and subsequently remained stable over the course of study

BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impression-Severity; ID, identification; OLAI, olanzapine long-acting injection; Olz, olanzapine; PANSS, Positive and Negative Syndrome Scale; PK, pharmacokinetics; RAIM, rapid-acting intramuscular injection.

pharmacokinetic profile of OLAI may be different from other more familiar depot antipsychotics.

This publication presents clinically relevant pharmacokinetic data on the depot formulation using simulations to show the impact of slow depot release on the concentration–time profile after an OLAI dose and the actual measurements of pharmacokinetic data from clinical trials to solidify the kinetic concepts. The combination of pharmacokinetic simulation models presented in the light of pharmacokinetic data from clinical trials will be discussed from a clinical practice perspective. Topics covered include the pharmacokinetic differences of OLAI relative to oral olanzapine and the rapid-acting intramuscular (RAIM) formulation of olanzapine, the pharmacokinetic differences between the 2- and 4-week dosing intervals of OLAI, the impact of transition from oral olanzapine to OLAI, the impact of individual patient factors, the pharmacokinetic profile with long-term use and upon discontinuation of OLAI, and whether postinjection syndrome or postinjection delirium/sedation syndrome (PDSS) is related to the pharmacokinetic profile.

Materials and methods

Pharmacokinetic data were obtained from five clinical trials conducted between August 2000 and December 2010 (Table 1) including a phase 1 study in healthy adults ($N = 18$) (study LOAZ); a single-dose and multiple-dose, phase 1b, open-label study ($N = 281$) (study LOBE)

(Mitchell *et al.*, 2013); a single-dose formulation performance study ($N = 129$) (study LOBS); a 24-week randomized, oral olanzapine versus OLAI controlled maintenance study (OLAI; $N = 346$) (study HGKA) (Kane *et al.*, 2010); and an open-label study of long-term maintenance treatment evaluating the safety and efficacy of OLAI ($N = 377$) (McDonnell *et al.*, 2011). Further details of these clinical trials can be found in the clinical trial registry (*http://www.lillytrials.com/results/ZyprexaLAI.pdf*).

All patients were between 18 and 76 years of age and, with the exception of healthy individuals in the phase 1 trial, had a *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV), or DSM-IV-Text Revision diagnosis of schizophrenia or schizoaffective disorder. Most patients had a diagnosis of schizophrenia; only study LOBS enrolled a proportion of patients with schizoaffective disorder ($n = 28$). Exclusion criteria included significant suicidal or homicidal risk; pregnancy or breastfeeding; acute, serious, or unstable medical conditions; or substance dependency (except nicotine or caffeine) within the past month. All study protocols were approved by institutional review boards at each site or country. After receiving a complete description of the study, all patients and/or their authorized legal representatives provided written informed consent before participation.

Pharmacokinetic simulations and analyses

Plasma samples, derived from the blood collected prospectively during the clinical trials, were analyzed using a validated bioanalytical method based on the method of Catlow *et al.* (1995) that used high-performance liquid chromatography with electrochemical detection to quantify the concentration of olanzapine. The olanzapine plasma concentration measurements were performed by BASi (Bioanalytical Systems Inc., West Lafayette, Indiana, USA). Olanzapine plasma concentrations over time were assessed graphically and compared with a database of concentration data collected across a number of clinical trials spanning a range of oral olanzapine doses administered once daily and a range of OLAI doses administered every 2–4 weeks. The plasma concentration data were most often assessed using noncompartmental pharmacokinetic methods. However, in the population modeling analyses, the pharmacokinetic objectives were best achieved with a more complex one-compartment model with parallel zero-order and first-order absorption of olanzapine from the intramuscular depot injection site and first-order absorption and elimination after an oral dose.

Computer-simulated concentration–time profiles to illustrate basic pharmacokinetics for oral olanzapine and OLAI used a one-compartment open model (Wagner and Nelson, 1964), the difference being that oral olanzapine doses were simulated using a conventional one-compartment model, but OLAI doses were simulated using the flip-flop one-compartment model. In the flip-flop model, parameters including volume of distribution, clearance, and elimination processes of the drug as described for conventional oral dosing remain unchanged, but for OLAI, the concentration–time profile of the drug is under the control of a very slow absorption process. Specifically, for oral olanzapine administration, the simulation was based on a 20 mg oral dose for a one-compartment model [absorption rate constant (k_a) = 0.3/h; elimination rate constant (k_{el})] = 0.0231/h; volume of distribution (V_d) = 1100 L]. This model incorporates first-order absorption and elimination after an oral dose and represents typical olanzapine pharmacokinetic properties for a daily oral dose (20 mg) with an elimination half-life of 30 h and a clearance of 25 L/h. For the OLAI simulations, the parameters changed in the model were the route of administration (intramuscular), the administered dose (300 mg), the dosing frequency (every 2 weeks), and the rate constant for absorption (ka = 0.000963/h) from the intramuscular site of administration, resulting in an absorption half-life of about 30 days.

Results and clinical considerations

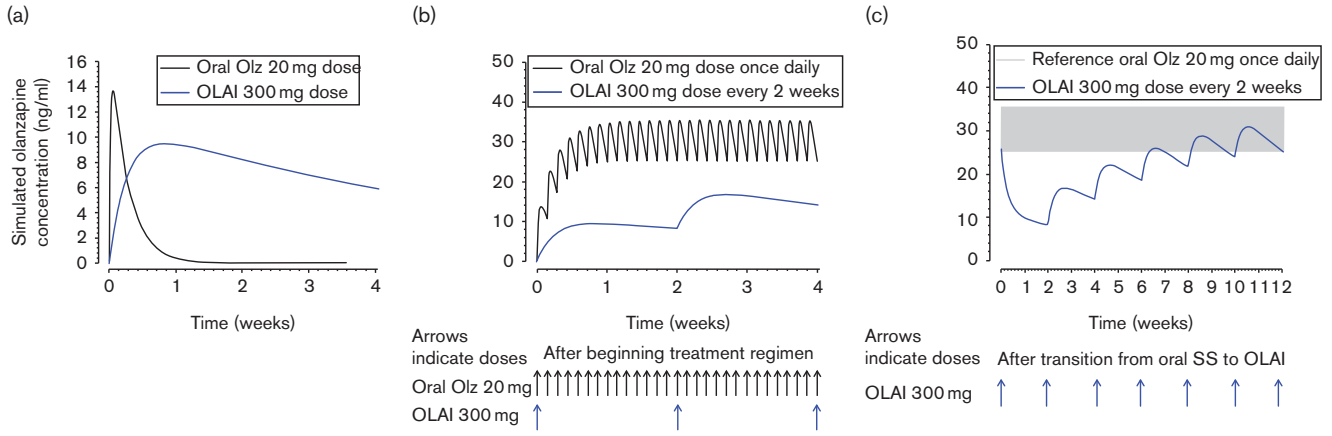
The basic pharmacodynamic and pharmacokinetic properties of OLAI are detailed by Frampton (2010), a review providing a strong pharmacokinetic underpinning. This overview provides pragmatic pharmacokinetic aspects of relevance for clinicians to facilitate an understanding of the pharmacokinetics of OLAI during clinical use. Consequently, results are presented here in a question and answer format to aid clinical understanding.

What is the basic difference in pharmacokinetic profile for oral olanzapine versus olanzapine long-acting injection?

The three panels in Fig. 1 show the basic difference between oral olanzapine and OLAI with respect to the concentration–time profile. Figure 1a shows the difference between a single 20 mg oral tablet and a single 300 mg OLAI injection. Figure 1b shows the difference over a 4-week period with consecutive dosing, and Fig. 1c shows the difference over a 12-week period of consecutive dosing after a transition from oral olanzapine.

In Fig. 1a, simulation of a single 20 mg oral dose of olanzapine predicted an $\sim$14 ng/ml maximum plasma olanzapine concentration (C_{max}) that occurred about 10 h after administration. This simulation is representative of the average profile observed after a single, oral dose of olanzapine in healthy individuals (Callaghan *et al.*, 1999). To reflect olanzapine pharmacokinetics after a 300 mg dose of OLAI, the conditions/parameters changed in the model were (a) the route of administration (intramuscular), (b) the dose administered (300 mg), and (c) the rate constant for absorption from the intramuscular site of administration. The changes resulted in a flip-flop model representing OLAI, wherein the rate

Fig. 1



Simulation of single-dose oral Olz and OLAI concentration profiles over time [(a) single-dose pattern]. Simulation of oral Olz and OLAI concentration profile for consecutive doses [(b) consecutive dosing pattern]. Transition from steady-state oral Olz to OLAI showing concentration profiles over time [(c) transition to OLAI pattern]. OLAI, olanzapine long-acting injection; oral Olz, oral olanzapine; SS, steady state.

constant for absorption (0.000963/h) was smaller than the rate constant for elimination (0.0231/h). The simulation predicted a C_{max} of ~9.5 ng/ml of olanzapine, occurring about 6 days after intramuscular injection of OLAI and a very prolonged time course of systemic concentrations lasting weeks to months. Therefore, slow absorption of a large olanzapine dose (300 mg) from an intramuscular site of injection as a suspension of a poorly soluble salt (olanzapine pamoate) is predicted to sufficiently prolong olanzapine systemic concentrations after a single OLAI dose so that an injection need only be administered every 2 or 4 weeks. The flip-flop model simulation for OLAI doses provides an olanzapine concentration–time profile consistent with the profile of observations in healthy individuals (Fig. 2) or patients with schizophrenia (Fig. 3).

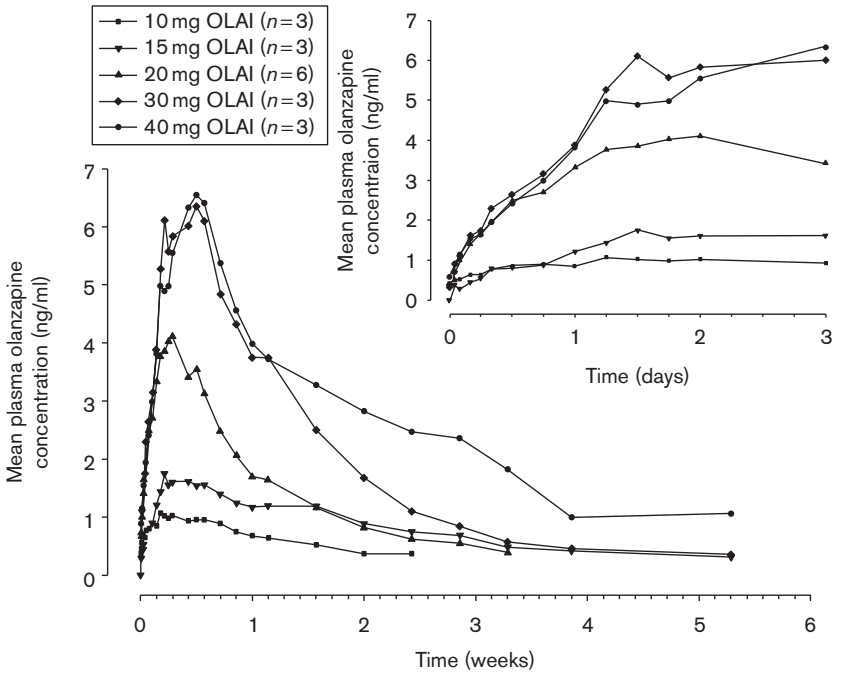
Next, the simulation model was used to predict the building pattern toward steady-state conditions (Fig. 1b) and to predict the transition profile from oral dosing under steady-state conditions to OLAI dosing (Fig. 1c). In the transition simulation (Fig. 1c), the oral dosing was immediately discontinued after beginning OLAI treatment. These simulations show that administration of a depot intramuscular dose with a prolonged absorption phase is predicted to provide a means to administer a dosage of olanzapine that, on reaching steady-state conditions, provides an olanzapine exposure that is of the same magnitude as the exposure achieved for the equivalent oral daily dose. To illustrate, a 300 mg OLAI dose injected every 14 days can be calculated to provide an approximate zero-order oral dosing rate of 20 mg/day by dividing the injected dose by the number of days in the injection interval. Therefore, in a real sense, the OLAI dosage is almost an exact replacement of the oral dosage of olanzapine once a steady state for the depot is achieved at around 12 weeks.

Real-life plasma concentration profiles do not repeat as uniformly or as consistently and are not as evenly distributed as in the simulations shown in Figs 1 and 4. Yet, these idealized simulations show the expected behavior of the depot formulation of olanzapine when injected into muscle tissue. In addition, these simulations answer several relevant questions on the use of OLAI as presented in the discussion that follows.

Why is it possible to dose olanzapine long-acting injection either once or twice a month?

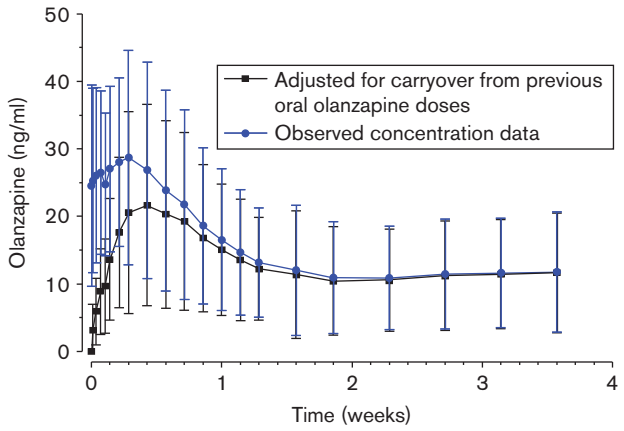
An underlying principle in repeated application of oral drugs and LAIs is the consecutive addition of every newly administered dose to the existing plasma concentration remaining from preceding applications. Even after a second injection is administered, olanzapine is still being slowly released from the intramuscular deposit of medication from the first injection, and even after the third injection is administered, olanzapine is still being released from the deposits of the first injection as well as now the second injection. This pattern continues for each injection for roughly five to six half-lives of the drug. The absorption half-life for OLAI is ~30 days. Therefore, each injection releases measurable olanzapine for ~5–6 months. A steady state is achieved when the 'stacking' of olanzapine concentrations from the repeated administration of injections over time reaches the point at which the amount of olanzapine being absorbed systemically is equal to the amount of olanzapine being eliminated from the body. In other words, at steady state, the addition of subsequent applications or doses to the systemic plasma concentration of olanzapine is balanced by the

Fig. 2



Mean plasma concentrations of olanzapine over 6 weeks after injection of small OLAI 10, 15, 20, 30, or 40 mg doses in healthy individuals (study LOAZ). Insert shows the same data on the first 3 days after the injection. OLAI, olanzapine long-acting injection.

Fig. 3

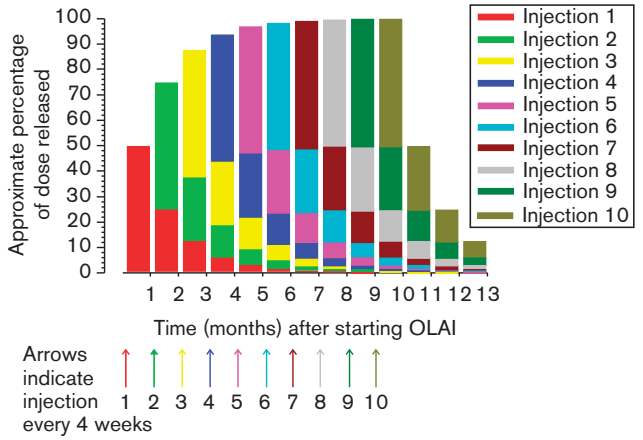


Mean (±SD) olanzapine plasma concentrations after a single, 405 mg OLAI dose (study LOBS; $N=129$ patients). The observed concentration data (●) include the contribution from previous oral olanzapine doses and OLAI. Adjusted concentration data (■) are calculated to subtract the contribution of previous oral olanzapine doses to the observed concentrations. OLAI, olanzapine long-acting injection.

eventual complete absorption and elimination of earlier OLAI applications. A similar concept applies to orally administered drugs as well, where steady-state conditions occur much more quickly owing to the shorter elimination half-life of orally administered drugs. Also, although the oral half-life is elimination rate controlled (also known as the conventional pharmacokinetic model), in the case of depot administration, the half-life is absorption rate controlled (also known as the flip-flop model).

This principle is shown for depot administration in Fig. 4, where the percentage of dose released during an injection interval eventually reaches 100% as a result of the contributions of multiple previous injections. Although Fig. 4 represents an injection frequency of every 4 weeks, the same type of principle is applicable for any consistently administered injection interval. The figure does not reflect actual patient data, and all values are approximations. With an injection every 4 weeks (every 28 days or approximately one absorption half-life), about 50% of the amount remaining to be absorbed at each injection site is released during each 4-week injection interval. As shown in Fig. 4, during the first 4-week injection interval, the amount released for absorption is 50% of the first injection. During the second 4-week injection interval, about 50% of the second injection is released and combined with 25% of the amount from the first injection. This starts the stacking of each new injection on top of decreasingly smaller incremental amounts remaining from each previous injection until the absorption is complete from each injection site and the composite of the amount released from all injections then adds up to 100% of the dose administered. Thereafter, as long as injections continue at that same

Fig. 4



Theoretical depiction of the approximate percentage of OLAI dose absorbed over time for OLAI administered once every 4 weeks (10 injections over 40 weeks). Simulation is based on a half-life of ~1 month and assumes injections of the same dose administered approximately monthly (every 4 weeks). Not actual patient data; all values are approximations. OLAI, olanzapine long-acting injection.

dose and dose interval, the composite will continue to release 100% of the dose administered, indicating that a steady state has been fully achieved.

Figure 4 also shows the slow decrease in the amount of drug released for absorption when the injections are discontinued. In this depiction, the injections were discontinued after the 10th injection. After discontinuation of the medication, deposits from the previous injections continue to release medication until each deposit is finished.

A similar principle but different numerical percentage applies when a dose of OLAI is injected every 2 weeks. In this case, ~30% of the dose remaining to be absorbed is released from each site of injection during each 2-week injection interval. As with the 4-week interval shown in Fig. 4, consecutive injections will begin to stack up over the series of bimonthly injections until the composite amount absorbed during each 2-week injection interval adds up to 100% of the administered dose. Even though the injections are administered more frequently, the kinetics of stacking solely depend on the absorption half-life. Therefore, a period of ~5 or 6 months is still required – irrespective of the dose interval – to reach the point where the systemic concentration in each dose interval reflects 100% of the intended dose.

Notably, Fig. 4 is a simplification that represents the long-acting release and absorption kinetics as a single first-order process, whereas the actual release and absorption kinetics of olanzapine after OLAI are likely much more complicated. Nonetheless, the figure reasonably shows the overlapping or stacking principle of consecutive depot injections and can serve as a practical guide to clinicians.

What happens in the first days following the initiation of olanzapine long-acting injection? Does pretreatment with oral olanzapine influence the pharmacokinetics of olanzapine long-acting injection?

The earliest pharmacokinetic measures following the injection of OLAI were performed in healthy volunteers in the LOAZ study using subtherapeutic doses. Following a single injection of 10, 15, 20, 30, or 40 mg of OLAI, olanzapine concentrations were measurable immediately after the injection and reached a maximum value between 3 and 4 days after the dose (Fig. 2). Measurable concentrations of olanzapine were detected 5 weeks after the dose. Thus, absorption of olanzapine began almost immediately after the injection, followed by slow release from the muscle.

Figure 3 presents a similar pattern when using therapeutic dosing. In the LOBS study, patients with schizophrenia or schizoaffective disorder were stabilized on oral olanzapine (5–20 mg/day) for 14 days and then administered a single injection of 405 mg OLAI. The observed mean olanzapine concentrations for 26 days after injection are shown in Fig. 3 as well as a model calculated on the basis of the same concentrations after removing the contribution of the previous oral olanzapine dosing. Because the final oral dose was administered 24 h before OLAI and blood was drawn before injecting, the first measurement in Fig. 3 (time = 0 weeks) represents the concentration of olanzapine derived from the previous oral doses and not from OLAI. After injection of OLAI, the mean observed olanzapine plasma concentration stemming from both formulations reached a peak on day 2 and olanzapine concentrations remained in all patients in the study throughout a period of 4 weeks, with mean concentrations sustained above 10 ng/ml. The wide SD bars indicate considerable interpatient variability. The variability reflects differing patterns of absorption of olanzapine after OLAI injection as well as the known large interpatient variability in olanzapine disposition (Callaghan *et al.*, 1999).

For these data, a pharmacokinetic model of oral olanzapine drug disposition was used to calculate a theoretical or an adjusted olanzapine plasma concentration–time profile that represents the concentrations attributable only to the OLAI dose. As such, the adjusted concentrations are a result of subtracting the contribution of the previous oral olanzapine doses from the observed systemic concentrations (Fig. 3). The subtraction for oral contribution only makes a meaningful difference in the concentration profile during the first week after injection. With the concentration–time profile adjusted for the oral olanzapine lead-in, the adjusted olanzapine concentrations reached a peak at day 3 and the concentration–profile remained indicative of a sustained depot release for OLAI.

What happens after the switch from stable oral olanzapine pretreatment to repeated injections of olanzapine long-acting injection?

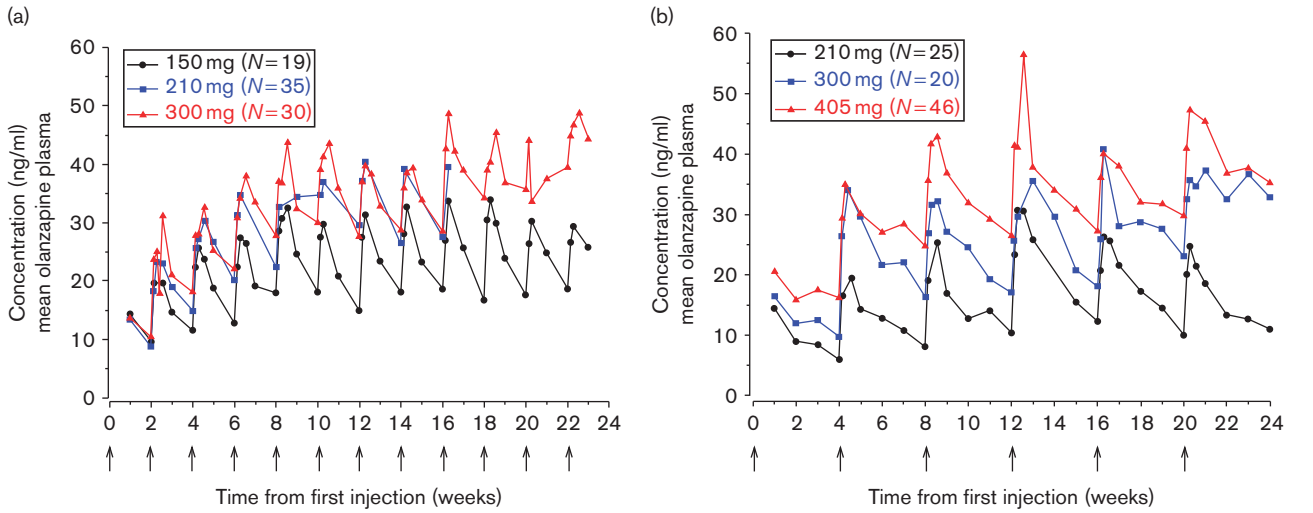
Pharmacokinetic data from two studies (Kane *et al.*, 2010; Mitchell *et al.*, 2013) provide perspectives on the switch from oral to OLAI therapies. In the first of these studies, the LOBE study, patients stabilized previously on any oral olanzapine dose (5–20 mg/day) for at least 4 weeks before study entry received repeated injections of OLAI at a fixed dose of 100, 150, 160, 210, or 300 mg every 2 weeks or 210, 255, 300, or 405 mg every 4 weeks for 24 weeks (Mitchell *et al.*, 2013). Figure 5 presents results only from those doses with sufficient numbers of patients to be adequately represented by the mean data. Steady-state conditions were reached after 3–6 months for the 2-week (Fig. 5a) and the 4-week (Fig. 5b) injection interval. The peak-to-trough concentration fluctuation index, calculated as $100 \times (C_{max}$ (maximum concentration) $- C_{min}$ (minimum concentration))$/C_{min}$, was 47% for the 2-week injection interval, indicating that peak olanzapine concentrations were ~50% higher than trough concentrations at this interval (Mitchell *et al.*, 2013). For the 4-week interval, the peak-trough concentration fluctuation index was ~76%, indicating a larger fluctuation for the 4-week interval, as would be expected (Mitchell *et al.*, 2013). Maximum olanzapine plasma concentrations and area under the curve (olanzapine concentration–time curve) were shown to be proportionate to the OLAI dose administered. Peak concentrations following OLAI were reached at day 4, and the systemic plasma concentrations decreased after the peak with a half-life that was estimated to be 30 days. The observed steady-state olanzapine concentrations after multiple injections of OLAI fell within the range of concentrations reported for oral olanzapine when administered at a dose of 5–20 mg/day (Fig. 6).

In the HGKA trial (Kane *et al.*, 2010), patients were stabilized on oral olanzapine doses of 10, 15, or 20 mg/day and then randomized to one of four different doses of OLAI (150 mg/2 weeks, 300 mg/2 weeks, 405 mg/4 weeks, and 45 mg/4 weeks) or to a maintenance dose of oral olanzapine for a treatment period of 24 weeks. The comparable dose levels (oral olanzapine mg/day vs. OLAI mg/weeks) are assumed to be 10 mg/day versus 150 mg/2 weeks, 15 mg/day versus 405 mg/4 weeks, and 20 mg/day versus 300 mg/2 weeks. The dose of OLAI 45 mg/4 weeks is subtherapeutic and approximately equivalent to an oral dose of 1.6 mg/day. Figure 7 shows olanzapine plasma concentrations for the corresponding (comparable) oral and OLAI doses over 24 weeks of treatment. Although there was an initial decrease in olanzapine concentration during the first weeks of each OLAI dose, the olanzapine concentration ranges were similar between oral and OLAI treatment by 11 or 12 weeks. Thus, for each of the OLAI dosing regimens, the olanzapine plasma concentrations appear to achieve steady-state conditions by 3 months of treatment, with concentrations remaining at these levels throughout the rest of the 6-month study.

What individual factors influence olanzapine plasma concentrations during olanzapine long-acting injection treatment?

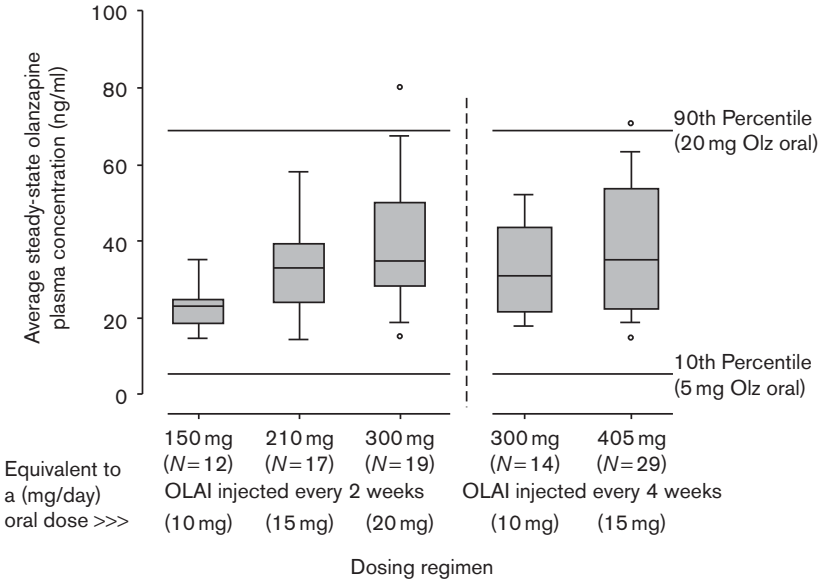
Smoking is known to increase the clearance of olanzapine, resulting in lower average steady-state plasma concentrations

Fig. 5



Mean plasma olanzapine concentration versus time profiles for the (a) 2-week and (b) 4-week injection intervals. The figures show the major dosing groups (Bergstrom *et al.*, 2000). Patients in the 210 mg dose group were administered either 200 or 210 mg injections. The small (5%) difference between a 200 and a 210 mg dose is not clinically or pharmacokinetically meaningful, given the variability. *N*, number of patients or participants. Figures (a) and (b) mean values were plotted when there were sufficient data. Arrows indicate injections.

Fig. 6



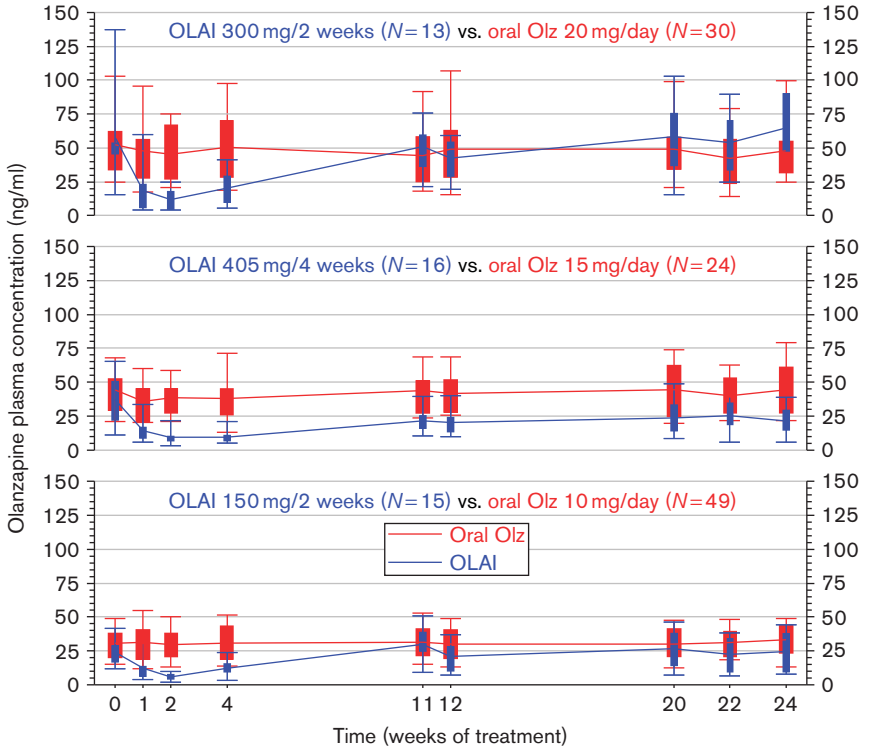
Distribution of average steady-state plasma Olz concentrations for OLAI dosing regimens compared with a range of oral Olz plasma concentrations for the 2 and 4-week injection intervals. *N*, number of patients or participants; OLAI, olanzapine long-acting injection; Olz, olanzapine. Note that the boxes show the median and the 25th–75th percentiles. The bars show the 10th–90th percentiles. Open circles show the 5th–95th percentiles when they could be estimated. Horizontal reference lines show the 10th (5 ng/ml for 5 mg dose) to 90th (69 ng/ml for 20 mg dose) percentiles for oral Olz doses.

(Fulton and Goa, 1997; Carrillo *et al.*, 2003; Gex-Fabry *et al.*, 2003; de Leon, 2004; Skogh *et al.*, 2011). Figure 8 shows the distribution of olanzapine plasma concentrations in smokers versus nonsmokers in the 24-week OLAI study for patients randomized to different doses of OLAI (Fig. 8b) or oral olanzapine (Fig. 8a). Olanzapine concentrations were higher in nonsmokers than in smokers, irrespective of the mode of administration of olanzapine, although the effects of smoking were somewhat less pronounced in the OLAI patients than in the oral patients. However, notably, there is a very large interindividual variability in steady-state olanzapine plasma concentrations, and this variability reflects a variety of factors. Therefore, solely the impact of smoking is not predictive of the absolute magnitude of plasma concentrations for an individual patient. Similarly, small differences in the distribution of concentrations were observed between female and male patients (data not shown) and consistent with previous findings of women typically showing a shift toward a higher distribution of steady-state olanzapine concentrations (Callaghan *et al.*, 1999). These results suggest that the typical steady-state plasma concentration of olanzapine resulting from doses of either oral olanzapine or OLAI may be higher for women or nonsmokers than the typical olanzapine plasma concentration for men or smokers. Additional subanalyses comparing the olanzapine plasma concentrations in obese and nonobese patients, White and non-White patients, and patients less than or equal to 40 years versus patients more than 40 years did not show a clinically meaningful difference in the distribution of olanzapine concentrations between these subgroups.

Does accumulation occur with long-term use after achieving a steady state and how long is olanzapine measurable in the systemic circulation after the last olanzapine long-acting injection?

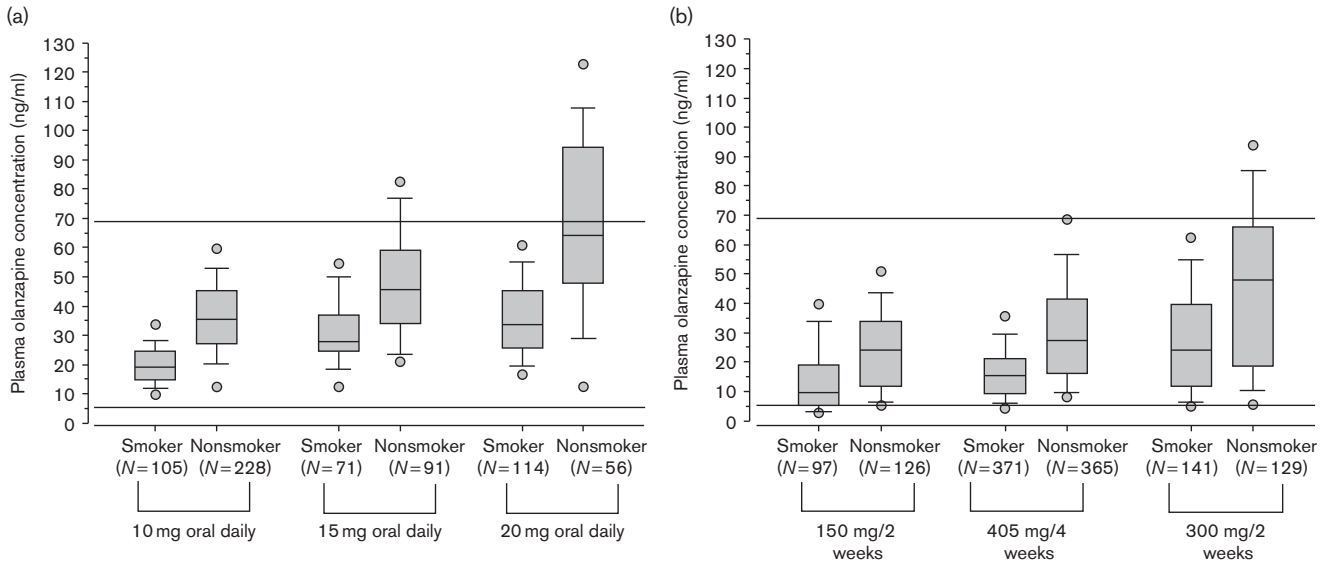
Steady-state olanzapine plasma concentrations remained consistent over time, with no evidence of continuing accumulation over the course of 6 years of treatment in an open-label extension study (McDonnell *et al.*, 2011) (data not shown). Because this was a flexibly dosed study and doses could be increased or decreased at any time, the analysis of consistency of plasma concentrations over time required the use of dose normalization to control for changes in dose. Steady-state olanzapine concentrations were normalized by dividing an individual's measured olanzapine concentration by their dose (mg/day) of olanzapine. Results showed that the median dose-normalized olanzapine plasma concentrations did not change markedly (no trend of an increase or decrease) over the period of 6 years with a measurement of olanzapine concentration made every 3 months. The median dose-normalized olanzapine concentration was 2.25 (ng/ml)/(mg/day), ranging from 1.01 (ng/ml)/(mg/day) (10th percentile) to 4.26 (ng/ml)/(mg/day) (90th percentile). This median and range of dose-normalized

Fig. 7



Olz plasma concentration for OLAI (150 mg/2 weeks, 405 mg/4 weeks, and 300 mg/2 weeks) and oral Olz dose (10, 15, and 20 mg). The distribution of Olz plasma concentration at each study visit for OLAI and oral Olz doses (Kane *et al.*, 2010). *N*, number of patients; OLAI, olanzapine long-acting injection; oral Olz, oral olanzapine. Concentration data are shown for the subsets of patients entering the point of randomization taking a comparable oral Olz dose to which they were assigned during OLAI treatment versus those staying on the same oral dose.

Fig. 8



Distribution of olanzapine plasma concentrations for (a) oral olanzapine and (b) OLAI dosing regimen in smokers and nonsmokers. *N*, number of patients; OLAI, olanzapine long-acting injection. The boxes show the median and the 25th–75th percentiles. The bars show the 10th–90th percentiles. Circles show the 5th–95th percentiles. Horizontal reference lines show the 10th (5 ng/ml, 5 mg dose) to 90th (69 ng/ml, 20mg dose) percentiles of the concentrations after oral olanzapine doses from a large phase 3 trial historical database.

concentrations may be useful to clinicians as a 'reference range'. Clinicians can multiply these values by any specific mg/day dosage for OLAI to provide a reasonable approximation of the anticipated steady-state olanzapine plasma concentration range that is associated with prolonged OLAI treatment.

Neither clinical nor pharmacokinetic data after the discontinuation of OLAI are available from trials. Because the absorption half-life of OLAI is ~30 days, the amount of olanzapine to be absorbed from intramuscular tissues is predicted to decrease by ~50% every 30 days (Fig. 4). Thus, after the last injection, systemic olanzapine plasma concentrations decrease slowly over a period of months. The concentration may be measureable or detectable, especially by a sensitive assay, for a long period (6–8 months) after discontinuation (Eli Lilly and Company Limited, 2013).

How does olanzapine long-acting injection compare with rapid-acting intramuscular olanzapine?

To fully appreciate the pharmacokinetic properties of olanzapine pamoate and differentiate it from olanzapine (free base), it is important to know that a RAIM olanzapine formulation is available (olanzapine injection, powder, for solution) (Eli Lilly and Company, 2013). Olanzapine RAIM is indicated for the treatment of acute agitation associated with schizophrenia and bipolar I mania, and it is not intended, specifically, for chronic use. The RAIM olanzapine formulation is injected intramuscularly after reconstitution into a solution of olanzapine (free base). Pharmacokinetic studies with RAIM olanzapine show that olanzapine is rapidly absorbed from the intramuscular site of injection; peak olanzapine concentrations are obtained within 15–45 min, and the peak concentrations are two-fold to five-fold higher than those for a corresponding oral dose (Altamura *et al.*, 2003). Therefore, the maximum recommended dose for RAIM olanzapine is 10 mg. Olanzapine after an injection of the RAIM formulation is absorbed quickly within minutes from muscle tissue in contrast to the prolonged depot absorption following OLAI. The intramuscular formulations of olanzapine (OLAI and RAIM) are not interchangeable and should not be confused.

What is postinjection delirium/sedation syndrome or postinjection syndrome and is it related to the pharmacokinetics of olanzapine long-acting injection?

The formulation of OLAI established the slow in-situ dissolution of the olanzapine pamoate salt in muscle tissue as the means to achieve a desirable depot release profile. It was subsequently found that the olanzapine pamoate salt dissolves more rapidly when in contact with a considerable volume of blood or plasma, which can result in the dissolution and systemic availability of a considerable amount of the OLAI dose over a short period, resulting in supratherapeutic olanzapine plasma concentrations (McDonnell *et al.*, 2010). This event, known as PDSS or postinjection syndrome, has been reported to occur within minutes to hours after the injection and is characterized by symptoms consistent with olanzapine overdose (such as sedation, confusion, slurred speech, altered gait, or unconsciousness) (Detke *et al.*, 2010). Although the exact mechanism is unknown, this occurrence most likely is the result of unintended direct or partial intravascular injection or blood vessel injury during the injection process (even with a proper injection technique), with subsequent seepage of the medication into the vasculature (Detke *et al.*, 2010; McDonnell *et al.*, 2010). Such events occurred in less than one in 1000 depot injections in the premarketing clinical trials (Detke *et al.*, 2010), but the risk of possible PDSS is present each time the injection is administered. When this clinical event occurs, it can be mild but may also develop into considerable and acute morbidity (including coma). Although most PDSS patients were hospitalized and a small number required intubation, symptoms typically resolved within 24–72 h, and the resolution was associated with the decrease in the olanzapine concentration.

Plasma samples collected from patients before, during, and after a PDSS event (McDonnell *et al.*, 2010) have shown excessively high olanzapine concentrations during a PDSS event when compared with the olanzapine plasma concentrations of the same or other patients when not experiencing a PDSS event. Olanzapine plasma concentrations during the time that the patients were symptomatic with PDSS were observed in the range of 87–665 ng/ml, with most above 200 ng/ml (McDonnell *et al.*, 2010), representing higher concentrations that would typically be expected if the medication had been deposited into muscle tissue as intended. Not only was the finding atypical compared with other OLAI patients but it also appeared atypical for the affected patients themselves, who had not previously shown any abnormal tendencies with respect to olanzapine plasma concentrations. Moreover, with the exception of one patient who went on to have a second PDSS event at a later date, patients who continued receiving OLAI injections after their PDSS event showed a 'typical' pharmacokinetic profile at subsequent injections in the clinical trials (McDonnell *et al.*, 2010). This observation of excessive or elevated olanzapine concentrations during PDSS is believed to be mechanistically related to the finding of an enhanced rate of dissolution of OLAI in blood as compared with the intentional slow rate of dissolution of OLAI in muscle tissue. It should also be noted that some patients in the clinical trials, including control patients receiving oral olanzapine, had measured olanzapine plasma concentrations above 87 ng/ml or in some cases even above 100 ng/ml during routine evaluation (see Figs 7 and 8) and yet were not symptomatic for PDSS. Thus, a higher than typical olanzapine concentration is

not necessarily indicative of PDSS. Instead, the syndrome must be defined by the onset of specific clinical symptoms in close proximity to the injection (see Detke *et al.*, 2010 for the case definition of PDSS).

Discussion

Pharmacokinetic results from simulations as well as observed data from five clinical trials are presented to address clinical questions on the pharmacokinetic profile of OLAI. Basic pharmacokinetic differences between the long-acting and oral olanzapine formulations are presented, including time to peak olanzapine concentration per dose (occurring within a few days for OLAI and within several hours for oral olanzapine) and length of half-life (30 days for OLAI and 30 h for oral olanzapine). Also, although oral dosing reaches steady-state conditions within days, the slow-release properties of the depot result in a much longer time to reach a steady state. Olanzapine concentrations from OLAI increase gradually, taking $\sim$3 months to reach steady-state conditions as the total olanzapine concentration at any given time is not only the result of the most recent injection but also arises from portions of the concentrations from OLAI injections of the last several months. Despite this slower time to reach steady-state conditions, data indicated that therapeutic concentrations were available within hours of the first OLAI injection, irrespective of the presence of previous oral olanzapine. For patients being switched from oral olanzapine, there is a decrease in concentrations for a period of some weeks while olanzapine from the OLAI is ramping up to a steady state. Again, however, concentrations during this initial period are still in a therapeutic range, but are not yet at the target dose level. These findings hold true irrespective of the dose or the injection interval of OLAI being administered. Thus, the pharmacokinetic behavior of the 2-week injection dosing is similar to that of the 4-week dosing, as the same principles apply.

Selection of dosing interval

As OLAI can be injected every 2 or 4 weeks, two important factors have to be taken into account. The first factor is whether differences in the peak-to-trough fluctuation as a result of longer or shorter dosing intervals are clinically relevant. The observed, overall peak-to-trough fluctuation in plasma concentration was greater in patients receiving an injection every 4 weeks compared with patients receiving an injection every 2 weeks. Although the peak-to-trough olanzapine fluctuation for OLAI was found to be no greater than the fluctuation for a daily oral dose, the convenience of a once-monthly injection needs to be balanced against a possible decrease in efficacy at the end of a 4-week injection interval during the trough concentrations or the potential risk for a higher incidence or greater severity of adverse events early in the injection interval near the peak concentrations. Clinical observations for safety and efficacy coupled with an appropriate expectation of depot pharmacokinetic performance are needed to decide whether more frequent injections are appropriate for a particular patient. For example, for the antipsychotic risperidone, the fluctuation in concentration was perhaps a factor affecting which patients were more likely to develop extrapyramidal symptoms. Bai *et al.* (2007), in comparing the tolerability of oral risperidone versus risperidone long-acting injection, found that extrapyramidal symptoms were reported less often in patients treated with risperidone long-acting injection than oral risperidone. However, such clinical differences were not observed when comparing patients treated with OLAI administered every 2 or 4 weeks (Kane *et al.*, 2010).

Previous oral olanzapine dosing

Another consideration is the dosing of oral olanzapine before the switch to OLAI. Both the LOBE and the HGKA studies included long-term data from patients who were stabilized on oral olanzapine before switching to OLAI. Treatment with oral olanzapine before the first OLAI injection adds to the systemic concentrations of olanzapine for almost a week even when the dosing for oral olanzapine is discontinued upon starting OLAI therapy. This brief initial period during the first OLAI injection may alter the olanzapine peak concentration, and drug persisting from the preceding oral regimen should be a part of the clinical considerations and evaluations during this brief interval.

An additional benefit of previous olanzapine dosing is the establishment of a planned 'target dose' for the OLAI. If the previous dose was satisfactory from the perspective of both efficacy and safety when taken compliantly, clinicians may use the mg/day dose of oral olanzapine to determine a target initiation dose and target maintenance dose for OLAI therapy by using the dosing guidance table provided in the product labeling information. The target OLAI maintenance dose can also be directly translated from the oral dose by dividing the OLAI dose per injection by the number of days planned between consecutive injections (i.e. the dosing interval). For example, a 210 mg OLAI dose divided by 14 days is approximately equivalent to a dose of 15 mg/day for oral olanzapine at steady state.

Clinical management before steady state

Clinically relevant olanzapine plasma concentrations are available within hours of the OLAI injection, and this immediate onset of olanzapine absorption is predicted to provide the desired pharmacological and clinical effects. Therefore, even though OLAI is a depot intramuscular formulation, the drug's action will not be delayed in contrast to other depot drug formulations. Thus, at initiation of OLAI treatment at approved dosages, a therapeutic dose is provided immediately.

If the clinician wishes to avoid the gradual ramp-up to a steady state, however, and to instead have a transition as direct as possible to approximate the concentrations from the previous oral olanzapine dose, additional clinical measures may be considered. Administration of a supplementary oral antipsychotic or a loading dose of the long-acting injection may be helpful to alleviate the potential for any reduction in effectiveness in the period of transition between oral and OLAI treatments. Detke *et al.* (2011) and the product labeling (Eli Lilly and Company, 2011; Eli Lilly and Company Limited, 2013) recommend the use of a higher OLAI dose during the first 8 weeks of treatment for patients whose target oral-equivalent dose would be 10 or 15 mg/day olanzapine (i.e. any OLAI dose <300 mg/2 weeks or ≤ 405 mg/4 weeks). Specifically, for patients whose target OLAI dose is 210 mg/2 weeks or 405 mg/4 weeks, an initial 8-week loading dose of 300 mg/2 weeks is recommended. For patients whose target OLAI dose is 150 mg/2 weeks or 300 mg/4 weeks, an initial 8-week loading dose of 210 mg/2 weeks or 405 mg/4 weeks is recommended. These loading-dose recommendations are principally based on theoretical considerations on the risk of relapse (Detke *et al.*, 2011). After the initial 8 weeks of the loading dose, the intent is to reduce the OLAI dose to the target 'maintenance dose' if this change in the OLAI dosage is considered by the patient's response and physician's clinical observation as appropriate and clinically feasible (Eli Lilly and Company, 2011; Eli Lilly and Company Limited, 2013). As no clinically relevant differences in observed relapses occurred when switching from 20 mg oral olanzapine to 300 mg/2 weeks OLAI, no loading dose is recommended for this OLAI dose regimen.

Individual patient factors

The effect of smoking and sex on olanzapine plasma concentrations following OLAI dosing in the HGKA study showed a trend consistent with historical oral olanzapine data in which the range of olanzapine concentrations is known to be shifted toward a higher but overlapping distribution of values in nonsmokers than in smokers and in women than in men. The magnitude of the shift in the distribution of concentrations appears slightly larger after oral olanzapine dosing than after OLAI dosing, possibly because of these factors having a greater impact on the extent of first-pass metabolism for the oral treatment. Nevertheless, dosage modifications on the basis of sex should not be required with either formulation, and dosage modifications are not routinely recommended on the basis of smoking status.

Although routine monitoring of a patient's antipsychotic concentrations is not always possible or practical, a number of clinicians (e.g. Hiemke *et al.*, 2011) value the use of plasma concentrations measured in an individual patient to facilitate optimization of the therapeutic outcome of antipsychotic drugs. Known more broadly as therapeutic drug monitoring, measurement of antipsychotic drug concentration has become an accepted clinical practice for a number of psychopharmacological agents. Clinicians using therapeutic drug monitoring rely on reference parameters to establish optimal clinical treatment (Hiemke *et al.*, 2011; Patteet *et al.*, 2012). Among other findings, therapeutic drug monitoring investigations have shown that antipsychotic plasma concentrations measured are highly predictive of dopamine receptor occupancy and that drug concentrations provide a high degree of correlation with antipsychotic treatment response (Uchida *et al.*, 2011). However, on the basis of the prolonged concentration–time course of OLAI and the inherent changes in concentration during the initial ramping-up period, it is our opinion that the application of therapeutic drug monitoring will likely have more limited utility for OLAI, and the use of such monitoring is not recommended in labeling for either oral olanzapine or OLAI.

Long-term dosing and discontinuation of olanzapine long-acting injection

As ongoing systemic olanzapine accumulation does not occur upon prolonged OLAI treatment, the target dose of OLAI can provide a stable olanzapine plasma concentration suitable for a maintenance regimen over the course of long-term treatment. Nonetheless, periodic clinical assessment of the adequacy of a maintenance regimen with OLAI is appropriate. Clinicians should remain aware that when OLAI treatment is discontinued, the olanzapine plasma concentrations will decrease only slowly, and the contribution of the previous OLAI treatment toward a patient's pharmacotherapy should be considered when initiating a subsequent antipsychotic treatment and deciding its dosing.

Similar to the gradual accumulation toward a steady state during initiation, olanzapine concentrations will slowly decrease after discontinuation, and clinically relevant amounts of olanzapine may still be present even beyond a 2–3-month period. With very sensitive assay methods, a detectable amount of olanzapine in plasma may persist for more than 6 months after the last OLAI injection. Although the clinical impact of low residual amounts of olanzapine in a patient is unknown, this aspect is important to consider when initiating another regimen of antipsychotic treatment after the discontinuation of any long-acting injection.

Postinjection syndrome

Postinjection syndrome, called PDSS in some geographies, has been observed following $\sim 0.07\%$ of OLAI injections (Detke *et al.*, 2010) in clinical trials as well as in general clinical use. These events are believed to be associated with accidental intravascular entry of a portion of the dose, most likely following vessel injury during the injection process (Detke *et al.*, 2010; McDonnell *et al.*,

2010), leading to olanzapine concentrations well above the therapeutic range. The pharmacokinetic behavior of OLAI during a postinjection syndrome or PDSS event is to be seen as an adverse event, is atypical, and does not reflect the normal behavior of the OLAI formulation when successfully deposited in muscle tissue. In case of a postinjection syndrome event, physicians have to act upon the emerging symptomatology and may consider blood withdrawals for pharmacokinetic measures. Given this risk of potentially serious adverse event, it is imperative that physicians and patients closely follow the precautions outlined in the respective product information, including adherence to a postinjection observation period and caution for the rest of the day of injections. Because more frequent injections present more opportunities for a postinjection syndrome event, use of the 4-week injection interval may decrease the cumulative risk of an event. However, any advantage of a less frequent injection needs to be balanced against the clinical necessity of a higher dose that may require a more frequent injection.

Limitations

A number of limitations of our analysis must be considered. In some of the studies, pharmacokinetic data were not assessed in the entire patient population, but only in a subgroup of patients. Therefore, we cannot rule out the possibility that results for other participants in these trials may have differed from the data described here. Nonetheless, the overall sample size of patients whose pharmacokinetic data are shown in our overview is considerable; therefore, the risk of a potential selection bias is limited.

Furthermore, clinical trials have specific inclusion (e.g. stabilization on oral olanzapine before randomization) and exclusion criteria (e.g. comorbid substance dependence disorders, an acute suicide risk, or a history of poor response to antipsychotic drug treatment) that may limit the generalizability of study outcomes for applicability to an actual clinical setting. Factors such as selected patient characteristics, dosage regimens, and/or concurrent use of a variety of drugs may affect olanzapine pharmacokinetics and the OLAI pharmacokinetic outcome found in these clinical trials. In the case of study LOAZ, the use of healthy individuals necessitated that only very low (subtherapeutic), single OLAI doses could be studied because healthy individuals usually cannot tolerate therapeutic doses of antipsychotics (Cutler, 2001). Therefore, as the very first pharmacokinetic and tolerability study of OLAI, the doses administered were not representative of a typical clinical course of OLAI treatment.

Simulation models present an idealized pharmacokinetic profile that is useful to illustrate and understand complex principles. In contrast, the actual plasma concentration profiles from patients in these clinical trials or observed in actual clinical usage of OLAI will be influenced by many different, additional, variable factors for which a simulation model cannot account.

Because clinical outcomes such as antipsychotic efficacy or tolerability were not within the scope of this article, the interested reader should refer to recommendations from respective publications on the underlying clinical trials and approved product information.

Conclusion

Pharmacokinetic assessment of OLAI indicates that olanzapine plasma concentrations are observed immediately upon injection and are sustained owing to a prolonged intramuscular absorption (half-life $\sim$30 days); this is differentiated from the oral formulation's more rapid absorption and elimination half-life of $\sim$30 h, which necessitates daily dosing. Simulations and clinical pharmacokinetic data show that a switch from oral to OLAI requires $\sim$3 months for the transition but can be accomplished without oral supplementation. When using lower OLAI doses (such as 150 or 210 mg/2 weeks or 405 mg/4 weeks), a loading-dose regimen is recommended to minimize the impact of the initially lower olanzapine plasma concentrations after the first few injections. Once steady-state conditions are attained, clinical trial data show that consistent olanzapine concentrations are maintained long term (6 years) and that additional accumulation during maintenance treatment is not observed; thus, a patient can remain on the same dose long term if needed and if appropriate from an efficacy and tolerability perspective (although no controlled trials have been conducted to evaluate how long patients should be treated with OLAI). Also, olanzapine steady-state concentrations are similar for comparable doses of OLAI versus oral olanzapine, for example 300 mg OLAI every 2 weeks versus 20 mg orally once daily, making OLAI a clinically useful alternative to daily oral dosing.

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Conflicts of interest

Dr Heres has received honoraria from Janssen-Cilag, Sanofi-Aventis, Bristol-Myers-Squibb, Eli Lilly, and Johnson & Johnson. Dr Heres has accepted travel or hospitality payment from Janssen-Cilag, Sanofi-Aventis, Johnson & Johnson, Pfizer, Bristol-Myers-Squibb,

AstraZeneca, Lundbeck, Novartis, and Eli Lilly. Dr Heres participated in clinical trials sponsored or supported by Eli Lilly, Janssen-Cilag, Johnson & Johnson, Bristol-Myers-Squibb, AstraZeneca, Lundbeck, Novartis, Servier, Laboratoires Pierre Fabre, Pfizer, and Merck. Dr Bergstrom is a retiree from and stockholder of Eli Lilly and Company. Dr Kraemer and Dr Detke are employees and stockholders of Eli Lilly and Company.

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