

Patient perspectives in the development and use of long-acting antipsychotics in schizophrenia: focus on olanzapine long-acting injection

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Abstract: Schizophrenia is a chronic mental disorder generally treated with antipsychotic medication. However, non-adherence and partial adherence to antipsychotic medication treatment is common and long-acting injectable “depot” preparations of antipsychotic medications have been used as an alternative to oral medication therapy for patients for whom adherence is a clinically significant problem, as well as for the sake of convenience and in response to patient preference. Olanzapine long-acting injection (OLAI) is a new treatment option and has been approved by several regulatory agencies for the treatment of schizophrenia. OLAI is a crystalline salt formulation of olanzapine and pamoic acid. Efficacy was established in 2 double-blind randomized clinical trials of OLAI for the treatment of acute schizophrenia and for the maintenance of response. The therapeutic OLAI dosages are 150 mg q2 weeks, 210 mg q2 weeks, 300 mg q2 weeks or q4 weeks, and 405 mg q4 weeks, administered by deep intramuscular gluteal injection with a 19-gauge needle. Injection volume ranges from 1 to 2.7 mL. OLAI has essentially the same general tolerability as that of oral olanzapine; however with the depot there is the additional risk of a post-injection delirium sedation syndrome occurring at a rate of 0.07% of injections, requiring a risk management plan that includes observing the patient for 3 hours post injection.

Keywords: adherence, antipsychotic, depot, long-acting, olanzapine pamoate, schizophrenia

Introduction

Schizophrenia is a chronic mental disorder generally treated with antipsychotic medication. However, non-adherence and partial adherence to antipsychotic medication treatment is common and has been observed in about half or more of all patients with schizophrenia.¹⁻³ It is estimated that about 75% of patients with schizophrenia become nonadherent within 2 years of hospital discharge.⁴ Non-adherence elevates the risk for relapse and re-hospitalization,⁵⁻⁷ inadequate treatment response,⁸ aggressive behavior,⁹ suicide,¹⁰ and substance use.¹¹ One approach to the problem of non-adherence is the use of long-acting injectable “depot” formulations of antipsychotic medication instead of, or in addition to, oral preparations. In addition, depot injections can be considerably more convenient for the patient and caregiver, and may be preferred over oral options by all the parties concerned.

The purpose of this review is to summarize key issues related to non-adherence and its management and to introduce information on a new medication option – olanzapine long-acting injection (OLAI) – together with data on patient-focused perspectives and OLAI’s potential place in the treatment of schizophrenia. Information on OLAI was

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obtained primarily from a prior review¹² and information provided to the US Food and Drug Administration (FDA).¹³

Factors related to non-adherence

Non-adherence can be due to many different reasons. These include illness-related factors such as substance use comorbidity,^{1,14,15} symptom severity,¹ poor insight into mental illness at discharge,¹⁶ impaired memory, and possibly hostility.⁸ In addition, patient-related factors can include a history of medication non-adherence for other disorders. There may also be extant several system factors such as medication availability on a formulary, access to a “depot clinic,” or treatment cost. Important to consider are also treatment-related factors such as regimen complexity,¹⁷ side-effects or tolerability,¹⁸ or inefficacy of treatment.^{18,19} Weight gain, extrapyramidal symptoms such as stiffness, tremor, and akathisia, and associated dysphoria, as well as sexual dysfunction are the common side-effects of antipsychotics that patients may not tolerate and that thus result in non-adherence. The availability of second-generation antipsychotics, although better tolerated in terms of extrapyramidal symptoms, has led to only a small improvement in adherence rates.²⁰

Unrecognized nonadherence can lead to the faulty impression that a medication regimen is ineffective. This can lead to unnecessary changes in medication,²¹ increases in drug dose,^{21,22} concomitant medications,²¹ and the inaccurate categorization of patients as being treatment resistant rather than non-adherent.²¹

Addressing and managing non-adherence: non-pharmacological techniques

Treatment adherence can be improved by taking a psychosocial and psychoeducational approach and exploring with the patients and their families their beliefs about the illness and its treatment, their expectations, explaining the treatment and its effects, asking about the patients’ preferences, and making treatment decisions and recommendations in collaboration with the patients and families.^{23,24} Interview style is important in fostering a therapeutic alliance.^{25–27} The strength of a therapeutic alliance is predictive of adherence and better outcomes.²⁸ Cognitive behavioral therapy may also be beneficial in improving adherence to antipsychotic medication among patients with schizophrenia.^{29,30} Cognitive adaptation training, a psychosocial treatment that uses environmental supports, can also improve adherence and functional outcomes.³¹ The individual patient’s circumstances

and preferences should be considered when determining the appropriate general clinical approach and intervention strategy, with the proviso that “when considering adherence attitudes, patient belief is always reality”.²⁷

Addressing and managing non-adherence: depot antipsychotics

Depot antipsychotics do offer guaranteed delivery of a medication over an extended period of time. Covert non-adherence, as seen with “cheeking” of oral medication, is not possible with an injection, and for many years has been thought to lead to greater effectiveness³² and reduced risk of relapse.³³ An “early-warning” system is in place when a patient fails to show up for his or her scheduled injection, allowing case management staff to intervene expeditiously before further problems ensue. In the inpatient setting, using a q2 week or monthly medication administration schedule can save staff time and avoid daily medication administration struggles. Although the acquisition cost of newer depot medication products can be relatively high, these costs may be small when compared with the time saved by staff (when administering medication biweekly or monthly rather than up to 4 times per day) and by shortening hospital stays and improving patient outcomes. During the important inpatient to outpatient transition period, long-acting injectable antipsychotics may be advantageous in getting patients to attend outpatient clinic programs.⁴

In the US, depot neuroleptics have been in use since 1963, when fluphenazine enanthate was approved for marketing. Fluphenazine decanoate became available soon afterward, followed by haloperidol decanoate in 1986 (1982 in the UK). Several other first-generation antipsychotic depot formulations are available outside the United States. Up to very recently there has been only one second-generation antipsychotic available in a depot formulation – risperidone microspheres, available since 2003.^{34,35} In August 2009 paliperidone palmitate, whose active moiety is the 9-OH metabolite of risperidone, received FDA approval in 2009.³⁶

Olanzapine long-acting injection

OLAI is a crystalline salt formulation of olanzapine and pamoic acid that can be administered every 2 or 4 weeks.^{12,13} The FDA is currently evaluating OLAI which was given a positive opinion by the European Medicines Agency³⁷ and has been commercialized in Australia and New Zealand.³⁸ Oral olanzapine, available since 1996, is an efficacious^{39–42} and effective^{18,43} antipsychotic. Olanzapine is also available

in a rapid-acting (non-depot) intramuscular formulation specifically for the treatment of agitation.⁴⁴ Similar to most other second-generation antipsychotics, olanzapine has a favorable profile in terms of extra-pyramidal side-effects but olanzapine can be associated with substantial weight gain and the development of hyperlipidemia, as well as hyperglycemia.⁴⁵ Other potential adverse effects include orthostatic hypotension, syncope, sedation, and somnolence.⁴⁶

Formulation, pharmacology, and pharmacokinetics

OLAI is composed of micron-sized crystals suspended in water. Upon intramuscular injection, OLAI slowly dissociates over a period of several weeks into the separate molecular entities of olanzapine (base) and pamoic acid, with both components entering the bloodstream. Plasma concentrations remain quantifiable for several months after the last OLAI injection.³⁸ The half-life of OLAI is 30 days compared to 30 hours for oral olanzapine,³⁸ thus achieving steady state takes several months. The elimination phase is complete approximately 6 to 8 months after the last injection.³⁸

Efficacy

Two randomized controlled pivotal studies are extant. One study tested OLAI for the acute treatment of schizophrenia,^{13,47} and the second focused on the maintenance of antipsychotic response.¹³ Six open-label studies were also conducted.¹³

The acute study enrolled 404 acutely ill patients with schizophrenia^{13,47} who were randomized to receive double-blind OLAI 210 mg q2 weeks, 300 mg q2 weeks, or 405 mg q4 weeks, or placebo, without any oral antipsychotic supplementation, for up to 8 weeks. The primary outcome measure was change in the Positive and Negative Syndrome Scale (PANSS) total score and this change was significantly greater for all olanzapine doses tested relative to placebo. Acute efficacy was established by demonstrating separation from placebo as early as 3 days (the first time point where the PANSS was measured after starting double-blinded treatment) for the 300 mg q2 weeks and 405 mg q4 weeks treatment arms, and as early as 7 days for the subjects receiving 210 mg q2 weeks. Table 1 summarizes several of the clinically relevant categorical outcomes, together with the effect size measure of number needed to treat (NNT).⁴⁸

A 24-week maintenance study enrolled 1205 outpatients and although the study was randomized and double-blind, it was not placebo-controlled.¹³ Patients were eligible to be randomized to OLAI or oral olanzapine provided they had

maintained stability on open-label oral olanzapine (10, 15, or 20 mg/day) for 4 to 8 weeks. There were 5 treatment groups: OLAI 405 mg q4 weeks, 300 mg q2 weeks, 150 mg q2 weeks, 45 mg q4 weeks, or 10, 15, or 20 mg/day oral olanzapine (whichever oral dose they had been stabilized on prior to randomization). The low-dose treatment arm of OLAI (45 mg q4 weeks) was included to serve as a comparator for the superiority analysis to therapeutic doses of OLAI, and can be considered as a placebo-equivalent. No supplementation with oral antipsychotic therapy was permitted after randomization. At randomization, the mean PANSS total score was 56, indicating a low level of psychopathology. The primary outcome studied was time to exacerbation of illness, defined by worsening of positive symptoms (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) since randomization, or hospitalization due to worsening of positive psychotic symptoms. Each of the therapeutic OLAI doses was statistically superior to the 45 mg q4 weeks dose with respect to time to exacerbation of symptoms. In a non-inferiority analysis, subjects receiving OLAI 150 or 300 mg q2 week had a similar non-exacerbation rate compared to the oral olanzapine group (90% versus 93% for depot and oral respectively) and was thus non-inferior to the oral olanzapine treatment group. In addition, OLAI 405 mg q4 weeks was non-inferior to the oral olanzapine and the pooled q2 weeks depot dosing groups. Categorical outcomes are described in Table 2.

Safety

The general safety and tolerability profile for OLAI is similar to that for oral olanzapine.⁴⁵ However, during the OLAI clinical trial program a small number of adverse events termed post-injection delirium/sedation syndrome (PDSS) was observed in a small proportion of patients.¹³ PDSS appears to be related to potential intravascular injection of a portion of the OLAI dose.¹³ As of May 30, 2008, a total of 29 PDSS events have been identified in 28 patients during OLAI clinical trials. Based on more than 40,000 OLAI injections given to 2054 patients in clinical trials through May 30, 2008, PDSS events have occurred in approximately 0.07% of injections, or 1.4% of patients.⁴⁹ Signs and symptoms in PDSS events appear consistent with olanzapine overdose and include dizziness, confusion, disorientation, slurred speech, altered gait, weakness, and a reduced level of consciousness ranging from mild sedation to coma.⁴⁹ When plasma levels for olanzapine were available immediately after a PDSS event, a much higher olanzapine plasma concentration was observed than would have been expected.¹³ Onset of signs

Table I OLAI acute schizophrenia study

N (randomized)	404
Length	8 weeks
Arms, completion rate, NNT for completion vs placebo and 95% confidence interval	Placebo (N = 98), 57% OLAI 210 mg q2 weeks (N = 106), 68%, NNT 10 (ns) OLAI 300 mg q2 weeks (N = 100), 67%, NNT 11 (ns) OLAI 405 mg q4 weeks (N = 100), 72%, NNT 7 (4, 60)
Timing of improvement over placebo	OLAI 210 mg q2 weeks – Day 7 Olanzapine 300 mg q2 weeks – Day 3 Olanzapine 405 mg q4 weeks – Day 3
Response by at least 40% improvement in the PANSS total score from baseline to endpoint, NNT vs placebo and 95% confidence interval	Placebo, 20.4% OLAI 210 mg q2 weeks, 47.2%, NNT 4 (3, 7) OLAI 300 mg q2 weeks, 48.0%, NNT 4 (3, 7) OLAI 405 mg q4 weeks, 40.0%, NNT 6 (4, 15)
Treatment-related adverse events leading to discontinuation, NNT vs placebo and 95% confidence interval	Placebo, 5.1% OLAI 210 mg q2 weeks, 2.8%, NNT 44 (ns) OLAI 300 mg q2 weeks, 6.0%, NNT –112 (ns) OLAI 405 mg q4 weeks, 4.0%, NNT 91 (ns)
Weight gain of at least 7% of baseline, NNT vs placebo and 95% confidence interval	Placebo, 12.4% OLAI 210 mg q2 weeks, 23.6%, NNT 9 (5, 102) OLAI 300 mg q2 weeks, 35.4%, NNT 5 (3, 9) OLAI 405 mg q4 weeks, 27.0%, NNT 7 (4, 26)
Changes in plasma cholesterol	Significant group differences were observed for mean baseline-to-end point changes in fasting total cholesterol (210 mg q2 weeks, 8.2 mg/dL; 300 mg q2 weeks, 5.5 mg/dL; 405 mg q4 weeks, 10.4 mg/dL vs placebo, –7.0 mg/dL)
Changes in plasma triglycerides	Significant group differences were observed for mean baseline-to-end point changes in fasting triglycerides (OLAI 210 mg q2 weeks, 26.3 mg/dL; 405 mg q4 weeks, 30.3 mg/dL groups vs placebo, –9.4 mg/dL); a significantly greater percentage of patients in the OLAI 210 mg q2 weeks (12.8%) and 300 mg q2 weeks (14.3%) groups experienced changes in triglyceride levels from <150 mg/dL to 200–500 mg/dL vs placebo (3.4%), with a NNT of 11 and 10, respectively
Changes in plasma glucose	Mean baseline-to-end point changes in fasting glucose did not differ significantly between treatment groups
Extra-pyramidal adverse events	Extrapyramidal symptoms were low at baseline for all treatment groups, and none of the group differences in baseline-to-end point changes on the Simpson-Angus, Barnes Akathisia or Abnormal Involuntary Movement scales were clinically meaningful
Changes in plasma prolactin	Not reported

Notes: ns – NNT not significant (95% confidence interval includes ∞).

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Abbreviations: OLAI, olanzapine long-acting injection; PANSS, Positive and Negative Syndrome Scale; NNT, number needed to treat.

and symptoms may be between 5 minutes and <5 hours (1 case occurred 3 to 5 hours after injection; median time to onset is 20 minutes; approximately 80% of patients had onset <60 minutes). None of the PDSS events involved sudden onset of profound sedation or incapacitation; instead, all began with milder symptoms, which progressed to more severe symptoms in some events. In general, the later the onset of symptoms, the slower their progression. All patients fully recovered from the events within 24 to 72 hours after injection, and the majority continued to receive further injections of OLAI.⁴⁹ One patient experienced two PDSS events.

He is the only patient to have experienced the event more than once, and these events occurred approximately 6 months apart.¹³ On average, PDSS events occurred after the patient had received several months of injections (median number of injections was 17) and ranged in occurrence from 1 event at the first injection to 1 event at the 40th injection. The mean number of days (from starting treatment with OLAI) to an event was 278 days.¹³ The cumulative risk of a PDSS event occurring in an individual is estimated to be 0.7% to 1.2% after 1 year, 2.1% to 2.9% after 5 years, and 3.8% to 4.8% after 20 years of treatment.¹³ Potential risk factors include a

Table 2 OLAI maintenance of antipsychotic response in schizophrenia study

N (randomized)	1065
Length	24 weeks
Arms, completion rate, NNT for completion vs OLAI 45 mg q4 weeks and 95% confidence interval	OLAI 45 mg q4 weeks ^a (N = 144), 52.8% OLAI 150 mg q2 weeks (N = 140), 64.3%, NNT 9 (5, 825) OLAI 300 mg q2 weeks (N = 141), 75.9%, NNT 5 (3, 9) OLAI 405 mg q4 weeks (N = 318), 70.0%, NNT 6 (4, 14) Olanzapine oral 10, 15, or 20 mg/day (N = 322), 80.1%, NNT 4 (3, 6)
Free of exacerbation at 24-weeks, NNT vs OLAI 45 mg q4 weeks and 95% confidence interval	OLAI 45 mg q4 weeks, 69% OLAI 150 mg q2 weeks, 84%, NNT 7 (4, 18) OLAI 300 mg q2 weeks, 95%, NNT 4 (3, 6) OLAI 405 mg q4 weeks, 90%, NNT 5 (4, 8) Olanzapine oral 10, 15, or 20 mg/day, 93%, NNT 5 (4, 7)
Treatment-related adverse events leading to discontinuation, NNT vs OLAI 45 mg q4 weeks and 95% confidence interval	OLAI 45 mg q4 weeks, 4.2% OLAI 150 mg q2 weeks, 5.0%, NNT -125 (ns) OLAI 300 mg q2 weeks, 2.8%, NNT 76 (ns) OLAI 405 mg q4 weeks, 3.1%, NNT 98 (ns) Olanzapine oral 10, 15, or 20 mg/day, 2.5%, NNT 60 (ns)
Weight gain of at least 7% of baseline, NNT vs OLAI 45 mg q4 weeks and 95% confidence interval	OLAI 45 mg q4 weeks, 8.3% OLAI 150 mg q2 weeks, 16.4%, NNT 13 (7, 205) OLAI 300 mg q2 weeks, 20.7%, NNT 9 (5, 24) OLAI 405 mg q4 weeks, 15.2%, NNT 15 (8, 130) Olanzapine oral 10, 15, or 20 mg/day, 21.4%, NNT 8 (6, 15)
Changes in plasma cholesterol	Increases in fasting total cholesterol and fasting LDL cholesterol were significantly greater for the therapeutic OLAI doses relative to the 45 mg q4 weeks dose; No significant between group differences were observed for baseline-to-endpoint changes in HDL cholesterol levels; Analyses of categorical changes in cholesterol at any time revealed no significant group differences
Changes in plasma triglycerides	No significant between group differences were observed for baseline-to-endpoint changes in fasting triglyceride levels; analyses of categorical changes in fasting triglycerides evidenced a greater proportion of patients shifting from <150 mg/dL to high in the OLAI 300 mg q2 weeks group (26%) relative to the 405 mg q4 weeks (9%), 150 mg q2 weeks (5%) and 45 mg q4 weeks (4%) groups (NNT of 6, 5, and 5, respectively)
Changes in plasma glucose	No significant between-group differences were observed for baseline-to-endpoint changes in fasting glucose; analyses of categorical changes in fasting glucose at any time revealed no significant group differences
Extra-pyramidal adverse events	Extrapyramidal symptoms were low at baseline and throughout the study for all treatment groups; no statistically significant differences were observed between treatment groups with respect to changes on the Simpson-Angus, Barnes Akathisia or Abnormal Involuntary Movement scales; no statistically significant differences in treatment-emergent extrapyramidal symptoms
Changes in plasma prolactin	Increases in prolactin were significantly greater for the therapeutic OLAI doses relative to the 45 mg q4 weeks dose; as dose increased, mean changes in prolactin were greater

Notes: ns – NNT not significant (95% confidence interval includes ∞); ^aOLAI 45 mg q4 weeks can be considered as a placebo-equivalent.

Adapted with permission from Table 2 in Citrome L. Olanzapine pamoate: a stick in time? A review of the efficacy and safety profile of a new depot formulation of a second-generation antipsychotic. *Int J Clin Pract.* 2009;63(1):140–150.¹² Copyright © 2009.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; OLAI, olanzapine long-acting injection; NNT, number needed to treat.

higher dose (related to an increased injection volume), greater age, and low body mass index (BMI), however risk remains low even for patients with these specific risk factors.¹³ For example, a logistic regression model predicted that a 50-year-old patient with a BMI of 22 kg/m² who received a 405 mg injection would have a probability of 0.0032 for experiencing a PDSS event.¹³

One possible explanation for why PDSS can occur is that OLAI is more soluble in blood or plasma than in muscle.¹³

Partial injection into vasculature, vessel injury associated with the intramuscular injection such as with a nick or puncture of the blood vessel, or substantial bleeding at the injection site may result in a rapid release of a portion of the OLAI dose.

Because of PDSS, risk management plans have been put into place.^{49,50} Elements of the plan adopted by the European Medicines Agency are outlined in Table 3. The central feature is that after each injection, patients should be observed in a healthcare facility by appropriately qualified personnel for

Table 3 Risk minimization plan**Appropriate labeling**

Provide adequate labeling to prescribers and patients about clinically relevant safety observations, including those related to post-injection syndrome.

Specific information and instructions to be included in the label will provide:

- Description of post-injection syndrome proposed as a warning in the summary of product characteristics (SPC)
- Description of reconstitution and proper administration technique
- Recommendation for a 3-hour on-site observation period post injection
- Recommendation that prior to giving the injection, the health care professional should determine that the patient will not travel alone to their destination
- Recommendation for informing patients that for the remainder of the day of the injection, they should not drive or operate machinery, should be vigilant for signs and symptoms of a post-injection syndrome event, and should be able to obtain assistance if needed
- Description of the most common symptoms reported with olanzapine overdose that represent the clinical manifestation in post-injection syndrome events
- Recommendation for appropriate monitoring until the event resolves if an event should occur

Risk-minimization training and communication

- Product Introduction Letter sent to all psychiatrists and other targeted prescribers of depots
- Provide targeted health care professional education about proper administration techniques, the risk of accidental intravascular injection with intramuscularly injected drugs, as well as the clinical presentation and management of patients reporting post-injection syndrome events
- Provide patients with a card containing a description of the most common symptoms associated with the post-injection syndrome together with appropriate contact details and advice
- Assess effectiveness of risk minimization measures (that is, annual assessment of risk minimization training program [duration will be based on the assessment of these data and in agreement with the Committee for Medicinal Products for Human Use], an evaluation of adherence to SPC/ guidelines by prescribers, and implementation of an observational study)

Education program for doctors, nurses, and pharmacists – specifics

- Description of post-injection syndrome
 - Education about the two intramuscular formulations of olanzapine, including packaging differences
 - Description of reconstitution and proper administration technique
 - Recommendation for a 3-hour on-site observation period post injection
 - Recommendation that prior to giving the injection, the health care professional should determine that the patient will not travel alone to their destination
 - Recommendation for informing patients that for the remainder of the day of the injection, they should not drive or operate machinery, should be vigilant for signs and symptoms of a post-injection syndrome event, and should be able to obtain assistance if needed
 - Description of the most common symptoms reported with olanzapine overdose that represent the clinical manifestation in post-injection syndrome events
 - Recommendation for appropriate monitoring until the event resolves if an event should occur
- Recommendations for monitoring of patients for glucose, lipids, and weight
 - Promote awareness of appropriate metabolic monitoring by distributing utilized published antipsychotic guidelines

Contents of patient card distributed to all patients

- Description of post-injection syndrome
- Recommendation for a 3-hour on-site observation period post injection
- Recommendation that prior to giving the injection, the health care professional should determine that the patient will not travel alone to their destination
- Recommendation for informing patients that for the remainder of the day of the injection, they should not drive or operate machinery, should be vigilant for signs and symptoms of a post-injection syndrome event, and should be able to obtain assistance if needed
- Description of the most common symptoms reported with olanzapine overdose that represent the clinical manifestation in post-injection syndrome events
- Recommendation for appropriate monitoring until the event resolves if an event should occur

⁴⁸**Sources:** European Medicines Agency. Assessment Report for Zypadhera, 2008. <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Zypadhera/H-890-en6.pdf>. Accessed September 2009;⁴⁹ European Medicines Agency. Annex: Conditions or Restrictions with Regard to the Safe and Effective Use of Medicinal Product to be Implemented by the Member States, 2008. http://ec.europa.eu/enterprise/pharmaceuticals/register/2008/2008111950550/anx_50550_en.pdf. Accessed September 2009.⁵⁰

at least 3 hours and that they should not drive or operate machinery for the remainder of the day of the injection. In New Zealand, product labeling further specifies that OLAI be administered in a healthcare facility with access to emergency services for management of olanzapine overdose and that active monitoring for alertness take place every 30 minutes during the 3 hour post-injection observation period.³⁸

In addition to routine post-marketing surveillance, OLAI's manufacturer plans to undertake a multinational Phase IV, non-interventional, prospective cohort study, focusing on PDSS risk in approximately 5000 patients. The study will estimate the crude incidence of PDSS events over a 2-year period in patients treated with OLAI in clinical practice and identify potential risk factors associated with the occurrence of PDSS events and further characterize the clinical presentation of these events in a naturalistic setting. It will also provide the opportunity to compare the incidence, severity, and outcomes of PDSS events in clinical trials with normal clinical practice to determine if there are any clinically meaningful differences.¹³

Dosing and administration

New information is available on the optimal dose for oral olanzapine that may have implications on what dose of OLAI would be best. The optimal dose of oral olanzapine for most patients is likely 10 to 20 mg/day, as evidenced by a fixed-dose randomized clinical trial comparing olanzapine 10 mg/day, 20 mg/day, and 40 mg/day.⁵¹ Over the 8 weeks of the study, non-treatment-resistant patients with schizophrenia or schizoaffective disorder responded to all 3 doses of olanzapine, without a statistically significant dose-response relationship, suggesting that for many patients with schizophrenia or schizoaffective disorder, particularly those who are mildly or moderately ill, 10 mg/day should be the initial dose of choice. In terms of tolerability, the 40 mg/day group demonstrated greater weight gain and change in plasma prolactin than the 10 mg/day group.⁵¹ See Citrome and Kantrowitz⁵² for a review of dose response for olanzapine.

The therapeutic OLAI dosages are 150 mg q2 weeks, 210 mg q2 weeks, 300 mg q2 weeks or q4 weeks, and 405 mg q4 weeks. Three vial strengths are available (210 mg, 300 mg, 405 mg) and are reconstituted to a fixed concentration of 150 mg/mL, for a volume of injection of 1 to 2.7 mL, for deep intramuscular gluteal injection with a 19-gauge needle.³⁸ Systemic olanzapine exposures with OLAI at these doses are at levels that are comparable to those associated with once-daily oral administration of olanzapine

within the range of 10 to 20 mg/day. Table 4 provides the dose correspondence between OLAI and oral olanzapine at steady state.¹³ Based on analyses of the pivotal 24-week maintenance study at 2 months, in order to minimize the risk for exacerbation at the start of treatment, the recommended start dose of OLAI for the first 2 months of treatment (in effect a "loading dose") differs from the maintenance dose, as shown in Table 5. Although OLAI has not been systematically studied in patients 65 years and over, product labeling in New Zealand suggests a low starting dose of 150 mg q4 weeks if used in this population.³⁸ As noted in a commentary, a further complicating factor is that each OLAI vial strength requires a different volume of the supplied diluent.⁵³ There is more diluent in the vial than is needed to reconstitute. Thus, staff administering OLAI will need to be vigilant to ensure correct dosing.

Patient-focused perspectives

Patient-focused perspectives such as quality of life, patient satisfaction, and acceptability are important. Patient perception of medication benefit has been shown to be a strong predictor of treatment duration.⁵⁴

The need for outcome measures other than those for psychopathology has been appreciated for many years. Patients with schizophrenia do not necessarily see their condition the same way as their treating clinician.⁵⁵ Among 53 chronic out-patients with schizophrenia on maintenance treatment with depot neuroleptics, 60% of the patients viewed depot medication positively. Insight was limited: only 49% of patients thought they had a psychotic illness, and there was no correlation between the patients' own evaluation of the severity of their illness and their score on the PANSS or the treating physician's evaluation. Mental side-effects such as subjective akathisia, dysphoria, and emotional indifference

Table 4 Dose correspondence between OLAI and oral olanzapine at steady state

Dose of oral olanzapine	Corresponding dose of OLAI administered q2 weeks	Corresponding dose of OLAI administered q4 weeks
10 mg/day	150 mg	300 mg
15 mg/day	210 mg	405 mg
20 mg/day	300 mg	NA

Source: Table 3.1 in Eli Lilly and Company. Zyprexa Olanzapine Pamoate (OP) Depot, Psychopharmacological Drugs Advisory Committee Briefing Document, 3 January 2008. <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4338b1-03-Lilly.pdf>. Accessed September 2009.¹³

Abbreviation: OLAI, olanzapine long-acting injection.

Table 5 Recommended dose schedule for OLAI relative to oral olanzapine: start dose (2 months) and maintenance dose^a

Target oral olanzapine dose	Recommended starting dose of OLAI	Maintenance dose after 2 months of OLAI
10 mg/day	210 mg q2 weeks or 405 mg q4 weeks	150 mg q2 weeks or 300 mg q4 weeks
15 mg/day	300 mg q2 weeks	210 mg q2 weeks or 405 mg q4 weeks
20 mg/day	300 mg q2 weeks	300 mg q2 weeks

Source: Table 3.1 in Eli Lilly and Company. Zyprexa Olanzapine Pamoate (OP) Depot, Psychopharmacological Drugs Advisory Committee Briefing Document, 3 January 2008. <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4338b1-03-Lilly.pdf>. Accessed September 2009.¹³

Abbreviation: OLAI, olanzapine long-acting injection.

were most often observed by the patients, while hypokinesia and hyperkinesia were least noticed by them, but most often observed by the physician. Quality of life did not correlate with either side-effect score or PANSS score.⁵⁵

Limited information is available about satisfaction and attitudes towards OLAI. In one of the open-label clinical trials (HGKB),¹³ the Patient Satisfaction with Medication Questionnaire–Modified (PSMQ) was administered. The PSMQ-Modified as such is unpublished but the original scale has been described⁵⁶ and consists of 10 questions, including a likert-type question on satisfaction with current medication and another on perception of frequency of side-effects with the current medication. There are also narrative questions such as “Overall do you prefer your current medication or your previous medication?” and “Has any caretaker made any comments on any differences between you being on your current medication and previous medications?” The majority of patients (70.6%) reported satisfaction with OLAI; 69% reported that they preferred OLAI over previous oral medications; and 71.6% reported experiencing less impact from side-effects on OLAI compared with previous oral medications.¹³ Of interest, 16 of the 24 patients experiencing a PDSS event weighed the benefits against the risks of OLAI treatment and continued to receive OLAI.¹³

Place in therapy

Long-acting injectable depot preparations of antipsychotics offer a guaranteed delivery system that eliminates the possibility of covert non-adherence. By not coming to the clinic for the next injection, non-adherence becomes readily identifiable and further outreach can be done expeditiously. By providing a steady amount of a therapeutic dose of an antipsychotic, maintenance of response is enhanced and

relapse can be prevented or delayed. However, despite these advantages, the use of depot antipsychotics faces several obstacles among psychiatrists, nurses, and patients. These will be required to be addressed in order for OLAI to be used successfully.

There is a belief among psychiatrists that their patients are sufficiently compliant with oral antipsychotic medication.⁵⁷ Moreover there are concerns that first-generation depots ought to be avoided because of the risk for extrapyramidal side-effects, and that second-generation long-acting injectable drugs are expensive.⁵⁷ In a survey of psychiatrists in the UK,⁵⁸ 40% believed that depots are old fashioned and 48% thought they were stigmatizing. Although almost all (91%) thought that depots are as efficacious as oral medication, there was a belief among 69% that depots would be less acceptable to patients. However, respondents did endorse advantages: 81% considered depots being able to enhance patient compliance; 94% endorsed the belief that depots prevent relapse. The authors note that psychiatrists would be persuaded to prescribe depots if they were associated with fewer side-effects, in patients where compliance is an issue, and if second-generation antipsychotics were available, presumably because they would have a lower incidence of side-effects.

Nursing obstacles have also been identified.^{59,60} Negative views include the thought that depots are old fashioned, stigmatizing, and the perception that most patients always prefer to have oral medication and that force is sometimes required when administering a depot. However, familiarity with depots and knowledge of side-effects were positively associated with favorable attitudes.⁶⁰

Although depot antipsychotics can be perceived as more coercive than oral medications by some patients⁶¹ it appears that many patients would be willing to take depot antipsychotics if they were made available.⁶² Patient preferences for a depot formulation versus on oral tablet are likely related to current and past experiences with depot.^{62,63} Thus, when a new depot formulation becomes available, differences from past injectables needs to be emphasized when offering the new choice.

OLAI was demonstrated to be efficacious in acutely ill patients,⁴⁷ and in the maintenance of response.¹³ OLAI shares the same general safety profile as oral olanzapine. This includes both favorable aspects (low potential for extrapyramidal effects) and an unfavorable metabolic profile (high potential for weight gain, lipid abnormalities, and insulin resistance).⁴⁵ A risk unique to the depot formulation of olanzapine is that of PDSS, requiring the implementation

of a risk management plan. This requirement may limit access to OLAI.

When assessing potential benefit and risk, OLAI may be best suited for patients who have a clear history of response to olanzapine and for whom a depot may enhance their ability to remain adherent. Alternatives include first-generation depot antipsychotics, risperidone microspheres, and paliperidone palmitate. Studies directly comparing these options would be desirable to discern whether or not there are any differences in terms of prevention of exacerbation, relapse and/or hospitalizations among the different choices.

Practical considerations for the three commercially available second-generation antipsychotics are summarized in Table 6.^{38,64,65} Needle gauge is largest for OLAI and smallest for paliperidone palmitate. The latter agent is unique in that it comes in prefilled syringes. In contrast to risperidone microspheres, OLAI and paliperidone palmitate

do not require refrigeration, can be given monthly, and do not require oral supplementation when initiating therapy. Both OLAI and paliperidone palmitate require different doses for initiation and for maintenance. OLAI must be administered in the gluteal muscle but risperidone microspheres and paliperidone palmitate may also be administered in the deltoid muscle. OLAI is unique in requiring a 3-hour post-injection monitoring period.

Conclusions

Depot antipsychotics are an important treatment option for patients with schizophrenia who are nonadherent or partially adherent to their medication treatment. They also represent a convenient option for patients who prefer a monthly injection over a more complicated regimen. Up to now, choices for a second-generation depot antipsychotic have been limited. Newly available is OLAI. Treatment with OLAI

Table 6 Characteristics of the three commercially available depot second-generation antipsychotics

Characteristic	OLAI ^a	Risperidone microspheres ^b	Paliperidone palmitate ^c
Year commercialized	2009	2003	2009
Active moiety	Olanzapine	Risperidone and 9-OH-risperidone	9-OH-risperidone
Approved indications	Acute and maintenance treatment of schizophrenia in adults	Schizophrenia; bipolar I disorder maintenance treatment (as monotherapy or as adjunctive therapy to lithium or valproate)	Acute and maintenance treatment of schizophrenia in adults
Dosage forms/strengths	Vial kits of 210, 300, and 405 mg	Vial kits of 12.5, 25, 37.5, and 50 mg	Prefilled syringes of 39, 78, 117, 156, and 234 mg
Approved injection sites	Gluteal muscle	Deltoid or gluteal muscle	Deltoid or gluteal muscle
Needle gauge	19 G	21 G (deltoid) or 20 G (gluteal)	22 G (deltoid, patient weight ≥ 90 kg) or 23 G (deltoid, patient weight < 90 kg) or 22 G (gluteal)
Injection frequency	q2 weeks or q4 weeks	q2 weeks	q4 weeks
Starting dose	Can vary (see Table 5)	25 mg	234 mg on treatment day 1 and 156 mg 1 week later; both administered in the deltoid muscle
Maintenance dose	Can vary (see Table 5)	25 mg (maximum recommended dose 50 mg)	117 mg (recommended range 39–234 mg)
Requirement for oral supplementation	No	Yes (21 days)	No
Requirement for refrigeration	No	Yes	No
Requirement for observation post injection	Yes (3 hours)	No	No

^aEli Lilly and Company (NZ) Limited. Zyprexa Relprev, Olanzapine (as pamoate monohydrate) depot injection. Data Sheet. July 2009.³⁸

^bJanssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. Risperdal Consta (risperidone) Long-Acting Injection. Product Information. July 2009. <http://www.risperdalconsta.com/risperdalconsta/shared/pi/risperdalconsta.pdf>. Accessed September 2009.⁶⁴

^cJanssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. Invega Sustenna (paliperidone palmitate) Extended-Release Injectable Suspension. Product Information. July 2009. <http://www.invegasustenna.com/invegasustenna/shared/pi/invegasustenna.pdf>. Accessed September 2009.⁶⁵

Adapted with permission from Table 5 in Citrome L. Paliperidone palmitate – review of the efficacy, safety, and cost of a new second-generation depot antipsychotic medication. *Int J Clin Pract*. In press. 2009.³⁶ Copyright © 2009.

Abbreviation: OLAI, olanzapine long-acting injection.

210 mg q2 weeks, 405 mg q4 weeks, and 300 mg q2 weeks appears efficacious in acutely ill patients with schizophrenia. OLAI was also demonstrated to be efficacious in the maintenance of response with either the q2 weeks or q4 weeks dosing options. The general safety profile for OLAI is similar to that for oral olanzapine however there is a small additional risk of PDSS, occurring at a rate of 0.07% of injections or 1.4% of patients. This risk requires that patients be supervised by health care personnel for 3 hours post injection. OLAI appears to be best suited for the patient who responds well to olanzapine but who is having difficulties remaining adherent to oral antipsychotic medication.

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References

- Valenstein M, Ganoczy D, McCarthy JF, Myra Kim H, Lee TA, Blow FC. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. *J Clin Psychiatry*. 2006;67(10):1542–1550.
- Byerly MJ, Nakonezny PA, Lescouffair E. Antipsychotic medication adherence in schizophrenia. *Psychiatr Clin North Am*. 2007;30(3):437–452.
- Perkins DO. Predictors of noncompliance in patients with schizophrenia. *J Clin Psychiatry*. 2002;63(12):1121–1128.
- Weiden P, Rapkin B, Zygmunt A, Mott T, Goldman D, Frances A. Postdischarge medication compliance of inpatients converted from an oral to a depot neuroleptic regimen. *Psychiatr Serv*. 1995;46(10):1049–1054.
- Law MR, Soumerai SB, Ross-Degnan D, Adams AS. A longitudinal study of medication nonadherence and hospitalization risk in schizophrenia. *J Clin Psychiatry*. 2008;69(1):47–53.
- Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr Serv*. 2004;55(8):886–891.
- Morken G, Widen JH, Grawe RW. Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. *BMC Psychiatry*. 2008;8:32. DOI:10.1186/1471-244X-8-32.
- Lindenmayer JP, Liu-Seifert H, Kulkarni PM, et al. Medication non-adherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. *J Clin Psychiatry*. 2009;70(7):990–996.
- Alia-Klein N, O'Rourke TM, Goldstein RZ, Malaspina D. Insight into illness and adherence to psychotropic medications are separately associated with violence severity in a forensic sample. *Aggress Behav*. 2007;33(1):86–96.
- Herings RM, Erkens JA. Increased suicide attempt rate among patients interrupting use of atypical antipsychotics. *Pharmacoepidemiol Drug Saf*. 2003;12(5):423–424.
- Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. *J Clin Psychiatry*. 2006;67(3):453–460.
- Citrome L. Olanzapine pamoate: a stick in time? A review of the efficacy and safety profile of a new depot formulation of a second-generation antipsychotic. *Int J Clin Pract*. 2009;63(1):140–150.
- Eli Lilly and Company. Zyprexa Olanzapine Pamoate (OP) Depot, Psychopharmacological Drugs Advisory Committee Briefing Document, 3 January 2008. <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4338b1-03-Lilly.pdf>. Accessed September 2009.
- Olfson M, Mechanic D, Hansell S, Boyer CA, Walkup J, Weiden PJ. Predicting medication noncompliance after hospital discharge among patients with schizophrenia. *Psychiatr Serv*. 2000;51(2):216–222.
- Hunt GE, Bergen J, Bashir M. Medication compliance and comorbid substance abuse in schizophrenia: impact on community survival 4 years after a relapse. *Schizophr Res*. 2002;54(3):253–264.
- Novak-Grubic V, Tavcar R. Predictors of noncompliance in males with first-episode schizophrenia, schizophreniform and schizoaffective disorder. *Eur Psychiatry*. 2002;17(3):148–154.
- Grunebaum MF, Weiden PJ, Olfson M. Medication supervision and adherence of persons with psychotic disorders in residential treatment settings: a pilot study. *J Clin Psychiatry*. 2001;62(5):394–399.
- Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–1223.
- Shajahan P, Macrae A, Bashir M, Taylor M. Who responds to aripiprazole in clinical practice? An observational study of combination versus monotherapy. *J Psychopharmacol*. 2008;22(7):778–783.
- Dolder CR, Lacro JP, Dunn LB, Jeste DV. Antipsychotic medication adherence: is there a difference between typical and atypical agents? *Am J Psychiatry*. 2002;159(1):103–108.
- Velligan DI, Wang M, Diamond P, et al. Relationships among subjective and objective measures of adherence to oral antipsychotic medications. *Psychiatr Serv*. 2007;58(9):1187–1192.
- Velligan DI, Lam YW, Glahn DC, et al. Defining and assessing adherence to oral antipsychotics: a review of the literature. *Schizophr Bull*. 2006;32(4):724–742.
- Fenton WS, Schooler NR. Editors' introduction: evidence-based psychosocial treatment for schizophrenia. *Schizophr Bull*. 2000;26(1):1–3.
- Dolder CR, Lacro JP, Leckband S, Jeste DV. Interventions to improve antipsychotic medication adherence: review of recent literature. *J Clin Psychopharmacol*. 2003;23(4):389–399.
- Weiden, PJ. Why did John Nash stop his medication? *J Psychiatr Pract*. 2002;8(6):386–392.
- McCabe R, Heath C, Burns T, Priebe S. Engagement of patients with psychosis in the consultation: conversation analytic study. *BMJ*. 2002;325(7373):1148–1151.
- Weiden P. Understanding and addressing adherence issues in schizophrenia: from theory to practice. *J Clin Psychiatry*. 2007;68(Suppl 14):14–19.
- Frank AF, Gunderson JG. The role of the therapeutic alliance in the treatment of schizophrenia. *Arch Gen Psychiatry*. 1990;47(3):228–235.
- Rathod S, Kingdon D, Smith P, Turkington D. Insight into schizophrenia: the effects of cognitive behavioural therapy on the components of insight and association with sociodemographics – data on a previously published randomised controlled study. *Schizophr Res*. 2005;74(2–3):211–219.
- Turkington D, Kingdon D, Weiden PJ. Cognitive behavior therapy for schizophrenia. *Am J Psychiatry*. 2006;163(3):365–373.
- Velligan DI, Diamond PM, Mintz J, et al. The use of individually tailored environmental supports to improve medication adherence and outcomes in schizophrenia. *Schizophr Bull*. 2008;34(3):483–493.

32. Levine J, Schooler NR, Cassano GB. The role of depot neuroleptics in the treatment of schizophrenic patients. *Psychol Med.* 1979;9(2): 383–386.
33. Hogarty GE, Schooler NR, Ulrich R, Mussare F, Ferro P, Herron E. Fluphenazine and social therapy in the aftercare of schizophrenic patients. Relapse analyses of a two-year controlled study of fluphenazine decanoate and fluphenazine hydrochloride. *Arch Gen Psychiatry.* 1979;36(12):1283–1294.
34. Möller HJ. Long-acting injectable risperidone for the treatment of schizophrenia: clinical perspectives. *Drugs.* 2007;67(11):1541–1566.
35. Harrison TS, Goa KL. Long-acting risperidone: a review of its use in schizophrenia. *CNS Drugs.* 2004;18 (2):113–132.
36. Citrome L. Paliperidone palmitate – review of the efficacy, safety, and cost of a new second-generation depot antipsychotic medication. *Int J Clin Pract.* In press 2009.
37. European Medicines Agency. Committee for Medicinal Products for Human Use Summary of Positive Opinion for Zypadhera. Press release, 25 Sept 2008. http://www.emea.europa.eu/pdfs/human/opinion/Zypadhera_34254208en.pdf. Accessed September 2009.
38. Eli Lilly and Company (NZ) Limited. Zyprexa Relprevv, Olanzapine (as pamoate monohydrate) depot injection. *Data Sheet.* 2009 July.
39. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry.* 2003;60(6): 553–564.
40. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet.* 2009;373(9657):31–41.
41. Leucht S, Komossa K, Rummel-Kluge C, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry.* 2009;166(2):152–163.
42. Leucht S, Arbter D, Engel RR, Kissling W, Davis JM. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Mol Psychiatry.* 2009;14(4):429–447.
43. Kahn RS, Fleischhacker WW, Boter H, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet.* 2008;371(9618): 1085–1097.
44. Wagstaff AJ, Easton J, Scott LJ. Intramuscular olanzapine: a review of its use in the management of acute agitation. *CNS Drugs.* 2005;19(2): 147–164.
45. Kantrowitz J, Citrome L. Olanzapine: review of safety 2008. *Expert Opin Drug Saf.* 2008;7(6):761–769.
46. Eli Lilly and Company. Zyprexa Prescribing Information, 19 March 2009. <http://pi.lilly.com/us/zyprexa-pi.pdf>. Accessed September 2009.
47. Lauriello J, Lambert T, Andersen S, Lin D, Taylor CC, McDonnell D. An 8-week, double-blind, randomized, placebo-controlled study of olanzapine long-acting injection in acutely ill patients with schizophrenia. *J Clin Psychiatry.* 2008;69(5):790–799.
48. Citrome L. Compelling or irrelevant? Using number needed to treat can help decide. *Acta Psychiatr Scand.* 2008;117(6):412–419.
49. European Medicines Agency. Assessment Report for Zypadhera, 2008. <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Zypadhera/H-890-en6.pdf>. Accessed September 2009.
50. European Medicines Agency. Annex: Conditions or Restrictions with Regard to the Safe and Effective Use of Medicinal Product to be Implemented by the Member States, 2008. http://ec.europa.eu/enterprise/pharmaceuticals/register/2008/2008111950550/anx_50550_en.pdf. Accessed September 2009.
51. Kinon BJ, Volavka J, Stauffer V, et al. Standard and higher dose of olanzapine in patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, fixed-dose study. *J Clin Psychopharmacol.* 2008;28(4):392–400.
52. Citrome L, Kantrowitz JT. Olanzapine dosing above the licensed range is more efficacious than lower doses: fact or fiction? *Expert Rev Neurother.* 2009;9(7):1045–1058.
53. Taylor DM. Olanzapine pamoate – blockbuster or damp squib? *Int J Clin Pract.* 2009;63(4):540–541.
54. Liu-Seifert H, Houston JP, Adams DH, Kinon BJ. Association of acute symptoms and compliance attitude in noncompliant patients with schizophrenia. *J Clin Psychopharmacol.* 2007;27(4):392–394.
55. Larsen EB, Gerlach J. Subjective experience of treatment, side-effects, mental state and quality of life in chronic schizophrenic out-patients treated with depot neuroleptics. *Acta Psychiatr Scand.* 1996;93(5): 381–388.
56. Kalali A. Patient satisfaction with, and acceptability of, atypical antipsychotics. *Curr Med Res Opin.* 1999;15(2):135–137.
57. Heres S, Hamann J, Kissling W, Leucht S. Attitudes of psychiatrists toward antipsychotic depot medication. *J Clin Psychiatry.* 2006; 67(12):1948–1953.
58. Patel MX, Nikolaou V, David AS. Psychiatrists' attitudes to maintenance medication for patients with schizophrenia. *Psychol Med.* 2003;33(1):83–89.
59. Patel MX, Yeung FK, Haddad PM, David AS. Psychiatric nurses' attitudes to antipsychotic depots in Hong Kong and comparison with London. *J Psychiatr Ment Health Nurs.* 2008;15(9):758–766.
60. Patel MX, DE Zoysa N, Baker D, David AS. Antipsychotic depot medication and attitudes of community psychiatric nurses. *J Psychiatr Ment Health Nurs.* 2005;12(2):237–244.
61. Patel M, de Zoysa N, Bernadt M, Bindman J, David A. Are depot antipsychotics more coercive than tablets? *J Psychopharmacol.* 2009 Mar 20. [Epub ahead of print].
62. Heres S, Schmitz FS, Leucht S, Pajonk FG. The attitude of patients towards antipsychotic depot treatment. *Int Clin Psychopharmacol.* 2007;22(5):275–282.
63. Patel M, De Zoysa N, Bernadt M, David A. Depot and oral antipsychotics: patient preferences and attitudes are not the same thing. *J Psychopharmacol.* 2009;23(7):789–796.
64. Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. Risperdal Consta (risperidone) Long-Acting Injection. Product Information. July 2009. <http://www.risperdalconsta.com/risperdalconsta/shared/pi/risperdalconsta.pdf>. Accessed September 2009.
65. Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. Invega Sustenna (paliperidone palmitate) Extended-Release Injectable Suspension. Product Information. July 2009. <http://www.invegasustenna.com/invegasustenna/shared/pi/invegasustenna.pdf>. Accessed September 2009.

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