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Patient and Health Care Provider Perspectives on Long Acting Injectable Antipsychotics in Schizophrenia and the Introduction of Olanzapine Long-Acting Injection

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Abstract: Olanzapine long acting injection has joined risperidone and paliperidone as the second generation long acting antipsychotic injection options for treatment of patients with schizophrenia. Long acting injections are important alternatives to oral medications for patients who have difficulty adhering to daily or multiple daily medication administrations, yet may be underutilized or not well understood. Patient perceptions, adherence, and preferences are important issues for health care providers to address when discussing treatment options with their patients. Reviewed here are overall patient and health care provider attitudes and perceptions regarding long acting injections and the details of olanzapine long acting injectable, the newest agent, and how it will fit in the marketplace. In addition, efficacy, safety, dosing and use data regarding this newest long acting agent are reviewed and compared to other available long acting agents.

Keywords: long acting injectable, olanzapine, schizophrenia, patient perspective, antipsychotic

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Introduction

The availability of second generation antipsychotics (SGA) as long-acting formulations has been eagerly anticipated, as data regarding the adherence rates of oral SGA do not appear strikingly different from adherence rates of oral first generation antipsychotics (FGA).¹ Lack of illness insight, challenges to adherence and the risk of relapse may lead to significantly decreased functioning and quality of life in schizophrenia, thus, the use of long-acting antipsychotics are emerging options to ensure stable levels of medication dosing.

Although these new formulations appear to be viable treatment options for symptom control in patients with schizophrenia, the use of these agents is not as prevalent as may be expected or as seen in other countries.² There are various reasons for this, including attitudes and preferences of patients as well as health care providers. The considerations of patient and provider views on long acting agents may be as important as pharmacological efficacy and side effects in the consideration of treatment selection.

Olanzapine pamoate joins risperidone microspheres and paliperidone palmitate as second-generation antipsychotics available for use as alternative dosing forms to oral medications. Olanzapine pamoate's pharmacologic activity includes antagonism of dopamine (D) and serotonin (5HT). Antipsychotic activity is thought to be achieved through the D and 5HT₂ antagonism. Olanzapine binds with high affinity to 5HT_{2A/2C}, 5HT₆, D₁₋₄, and adrenergic α ₁ receptors, and with moderate affinity to 5HT₃ and muscarinic M₁₋₅.³

This article begins with a review of the importance of the availability of long-acting injectables (LAI), including the effects on adherence and relapse, and also discusses patient and health care providers' attitudes and perspectives regarding the use of LAI. This article concludes by reviewing the efficacy and safety data of olanzapine pamoate, prescribing data in comparison to other second-generation antipsychotics, and a discussion of long-acting antipsychotics taking into consideration patient and health care professionals preferences and attitudes.

Adherence and Relapse with Oral Medications: Important Challenges in Medication Delivery

Studies suggest that 25% to 60% of people with schizophrenia may not take their antipsychotic medication

as prescribed.⁴⁻⁶ Nonadherence in schizophrenia is driven by several factors, one of the most commonly reported being forgetfulness, along with comorbid substance use, little family involvement, medication side effects and poor therapeutic alliance.^{5,7,8} Several studies also report that poor insight is a strong predictor of medication nonadherence.⁹⁻¹¹ In a review of 39 studies, insight is a factor most consistently associated with nonadherence to treatment in schizophrenia.⁵ Since up to 80% of people with schizophrenia may lack insight,¹² patient acceptance of and cooperation with treatment planning may be challenging.

Antipsychotic nonadherence is a well-documented risk factor for relapse in schizophrenia. Rittmannsberger and colleagues (2004) reported that of 95 consecutive patients hospitalized for a psychotic disorder, 57% reported being partially or fully nonadherent in the month prior to admission.¹³ In fact the risk of relapse has been found to be 3.7 times greater for nonadherent schizophrenia patients as compared to those who adhered to their pharmacologic treatment.¹⁴ Long acting injections (LAI), as discussed below, are means of dose delivery that ensure adherence, and therefore may be potentially advantageous agents in improving relapse risk for certain patients.

Impact of Long Acting Injectable (LAI) Antipsychotics on Relapse and Adherence

Long acting injection medications are dosing formulations that alleviate the potential for patients to stop taking or even moderate their prescription antipsychotic usage without the knowledge of the prescriber. These formulations were first developed in the 1960s, and offer the advantages of constant antipsychotic delivery.¹⁵ Many studies have shown that LAI may reduce rehospitalization rate and relapse in people with schizophrenia.^{16,17} A meta analysis of LAI antipsychotic use found a statistically significant advantage for LAI in global improvement compared to oral agents.¹⁸ In addition, a subsequent meta-analysis calculated a one-year relapse rate of 27% for LAI antipsychotics compared to 42% for oral medications.¹⁷ A recently published systematic review and meta analysis of oral and LAI antipsychotics and their effects on relapse in long term trials is now published.¹⁹ This paper utilized data from 10 studies and found significantly fewer relapses among people taking



depot as compared to oral antipsychotics (21.6% vs. 33.3%). While not all data support the advantages of LAI in relapse as compared to oral, this recent review suggests that this method of delivery is likely to improve long term relapse rates in schizophrenia.²⁰ Despite improving relapse, few published studies are available to support the advantage of LAI vs. oral agents on medication adherence.^{5,21} The prescription of a LAI may not ensure adherence, as patients may still miss clinic appointments, however, surveillance of nonadherence becomes simplified, as covert nonadherence (skipping doses, or cheeking medications) may be prevented. Nonadherence is estimated to occur in about one quarter of patients with schizophrenia treated with LAI agents (range 0%–54%),^{22,23} which is likely lower than oral medication nonadherence rates.

It is important to note that many variables influence adherence to treatment and follow-up care and little work is published on the outcomes and attitudes on medication adherence in patients with schizophrenia who have been treated with LAI antipsychotics. Also of note clinician ratings of adherence and patient ratings of adherence may not be measuring the same dimensions.²⁴ Furthermore physicians and patients may not even measure the antipsychotic adverse effects similarly.²⁵ More research is needed to better understand patient perspectives and opinions on strategies and treatments that may better improve adherence to pharmacologic treatments. The following sections explore the issues surrounding prescribing and acceptance of LAI, both from prescriber and patient perspectives.

Prescribing of Long Acting Injectable Antipsychotics

Prescribing of LAI medications tends to occur in challenging and more chronic patients despite the potential advantages of using earlier in the illness phase. Few treatment naïve patients are given long acting injections as efficacy and tolerability to oral medications may be more safely and easily established. In a study examining LAI preferences and attitudes, Heres and colleagues (2007) found that patients currently prescribed LAI medications were older than patients never prescribed LAI, but had been younger at first hospitalization and had been more frequently hospitalized in the past.²⁶ Nonadherence is not always

a factor leading to the use of LAI. Only 18% of patients were prescribed LAI in a recent study, although up to 49% of this sample had significant adherence issues in a past one year.²⁷ One three—year study²⁸ found only 12% of patients recently nonadherent on oral antipsychotics were initiated on LAI. This study also reported that patients initiated on LAI agents were more likely to be hospitalized at initiation or the previous 30 days, to have recent involvement with the criminal justice system, recent illicit drug use, recent switching or augmentation of oral antipsychotics, and recent treatment with oral typical antipsychotics as compared to those initiated on oral treatment.²⁸ The fact that more challenging, longer duration of illness, and nonadherent patients are prescribed LAI may introduce challenge in accurate study of this population and the effectiveness of these agents.

Stigma has also surrounded injectable antipsychotics particularly in the US as other countries utilize LAI more widely.²⁹ In addition, the difficulty with specific, reliable dose conversions between oral and injections, and the complicated pharmacokinetic patterns of injections, have led to the potential of prescribing too much or too little medication. Inconsistent dosing may put patients at risk of either efficacy shortfalls or increased side effect burden. With the advent of second-generation antipsychotics, the use of FGA long acting injections decreased. More recently however it is being recognized that SGA effectiveness with treatment and adherence may not be strikingly better than the FGA use and emerging literature with the introduction of new SGA LAI suggests a resurgence in interest in these dosage formulations.³⁰ Some clinicians report that LAI are underutilized.^{2,31,32} The use of long acting agents, however, should take into account the perspectives, attitudes, preferences and beliefs of the patients we treat and the associated health care providers to ensure the optimal use of these agents.³³

Health Care Professional Perspectives on LAI Antipsychotics

There is little data published to date on the perspectives and attitudes of health care professionals on newer LAI antipsychotics. However, since various health care professionals often play a role in antipsychotic selection, the attitudes and perspectives of health care professionals are important in the prescription and success of use of LAI.



A wide international and regional variation in both utilization of and attitudes/perspectives regarding LAI among health care professionals has been reported.^{34,35} Patel and colleagues³⁵ reported that the majority of community mental health nurses in a UK study note that their patients played a role in antipsychotic selection (79%), and they reported favorably of their role on administration of LAI.³⁵ However in this study about one third of the nurses believed that LAI were old fashioned, about 40% felt they were stigmatizing and coercive, and about one quarter of those surveyed felt that LAI compromised patient autonomy. Another study in Hong Kong also reported that health care professionals generally had positive perceptions of their role in administration, however, they reported perceptions of less favorable patient opinions regarding LAI.³³ Negative views expressed on LAI use included the perception that most patients preferred oral medications and that force may be required for administration.³³

Other reports suggest that health care professionals believe that LAI are not acceptable to patients.³⁶ LAI agents are only offered to about one third of all eligible patients with schizophrenia.³⁷ However, a survey of schizophrenia patients prior to hospital discharge reported that only 30% of the sample would have refused LAI.²⁶ Therefore, acceptance rate may be higher than the perceptions of patient acceptance by the health care team and higher than actual prescription rates.

Different health care disciplines may have different attitudes and perceptions due to their differing medical training and differing relationships with patients and their symptoms (prescribers, nurses, social workers, psychologists, etc.). Lambert and colleagues³⁸ reported that nursing and allied health professionals were more likely than medical staff to consider variables such as weight gain, injection site reactions, and patient preferences when prescribing LAI. In a systematic review of eight relevant studies, the attitudes of psychiatrists, psychiatric nurses, community mental health nurses, and other mental health professionals (nurses, psychologists, social workers, etc.) were assessed.³⁹ Factors that led to opposing the use of LAI included side effects, cost, the inability to abruptly discontinue, presumed adherence to oral medications in patients, and the professionals' perception of patient preference. In addition, a positive

correlation has been found between attitudes toward LAI and extent of knowledge about the medication formulations.³³ A recent study examined psychiatrists' attitude of using LAI in first episode schizophrenia and concluded that there is little specific reasons noted for not prescribing in this population.⁴⁰ It should be noted that most studies examining health care professional perceptions were published prior to the availability of second-generation injectable medications. In fact, data indicate psychiatrists noted their willingness to prescribe more LAI if there were fewer side effects, or if SGA were available in long acting form.³⁶

Therefore it appears that health care providers should be well informed as to the risks and benefits of long acting injectables and knowledge of these agents is critical for improving success. More work is needed to better understand how the new LAI entering the marketplace are accepted and if perspectives and attitudes are now changing. In order to help improve knowledge on the second generation agents entering the marketplace we review the newest agent below and compare to the other newer long acting agents. We also consider and review what is known about patient perspectives as ultimately the patient needs to be aware of the benefits and risks, have a choice in the prescription and have the support of the team and others such as the family to help make informed and good choices.

Patient Perspectives on Prescribing of Long-Acting Injectable Antipsychotics

Involving patients with schizophrenia in the decision making process with the health care team may be challenging due to the inherent nature of psychosis and potential lack of insight. Many patients feel they are not involved sufficiently in treatment decisions.⁴¹ Fortunately in recent years there has been an increase in shared decision making in severe mental illness as joint education and choices may lead to a process that enhances recovery.⁴² Recent data suggests that shared decision making may have positive outcomes on relapse prevention.⁴³ For example, data suggest a trend for fewer hospitalizations in a chronic inpatient population that participated in shared decision making.⁴⁴ It is felt that incorporating shared decision making into antipsychotic prescribing will improve outcomes⁴⁵



and it is important to have an understanding of what motivates choice-making in patients.⁴¹

Heres and colleagues²⁶ explored the subjective rationale for LAI treatment in schizophrenia patients with past or current experience with LAI. Of the 300 patients included, 95 (32%) had been treated with LAI in the past and 20% were currently on LAI. Approximately 46% of these patients with current or past experience indicated that they were prescribed long acting medication for its reliable efficacy, 45% reported taking for convenience, 26% were taking because they often forgot to take their oral medication, and 24% were taking because the medications has better side effect profiles and improved their quality of life. In this study, including those currently, previously, and never treated with LAI, the majority of patients (54%) agreed it was more convenient to receive an injection every two to four weeks compared to taking tablets on a daily or multiple-daily dose regimen. Approximately 43% thought the injection was preferred for preventing relapse, 40% saw injections as away of putting more distance between themselves and their illness, and 35% saw benefit of potential lower antipsychotic dose. Schizophrenia patients currently treated with LAI formulations recognized the benefits most often, followed by those previously treated with LAI and then those never treated with LAI.²⁶

It is important to note that published reports suggest that some patients do view LAI as coercive. Nineteen percent of patients in the Heres et al study noted their experience with LAI agents as compulsory measures.²⁶ Patel and colleagues⁴⁶ examined patient's perspectives (N = 72) of coercion (defined as perceived by the patient, not legal detention status) regarding oral and long acting antipsychotic medication. Total coercion scores, perceived coercion and negative pressure subscales, were significantly higher for LAI antipsychotics compared to oral medications.⁴⁶ It should be noted, however, that the population currently more likely prescribed LAI are often more chronic and have existing adherence issues. In a recent study, 46% of outpatients with current or previous LAI experience felt they were forced to start treatment with long acting agents³³ despite literature suggesting favorable attitudes toward LAI.³⁶ The following section will address patient preferences and attitudes of LAI and oral antipsychotic agents.

Patient Preferences and Attitudes Regarding Long Acting Injectables Compared to Oral Agents

Many times, prescribers assume that patients will not want to accept a LAI if they are stabilized on an oral medication. Not all data, however, support this view. Wistedt⁴⁷ reported that roughly 60% of patients switched from oral antipsychotics to LAI formulations stated they felt better, and preferred the LAI formulation to the oral. In addition, a review of the published literature of patient and nurse attitudes toward LAI showed that five of six studies reviewed demonstrated patient preference and high acceptance to the LAI agents.⁴⁷ Endorsement of LAI in patients currently taking these formulations has ranged from 23 to 93% (median 61%). However, these data were focused among schizophrenia patients who attended regular injection clinics.

Not all reports show patients favoring LAI. For example, Castle and colleagues⁴⁸ reported that the long acting injection group (FGA) had the highest rate of persons rating medications as unhelpful, with those lacking insight to their illness rated medications lower. Bradstreet and Norris⁴⁹ found that 43% of persons who had used LAI rated them as unhelpful while 38% rated them as helpful. About half of the patients rated LAI helpful for specific issues such as symptom relief.

Preference of antipsychotic formulation has been found to be related to prescribed formulation that patients were taking at the time of asking about preferences. Patel and colleagues⁵⁰ reported that LAI antipsychotics were preferred by 43% of those currently prescribed them, while LAI preference was only demonstrated by 6% of those currently taking oral medications. Those patients currently taking oral medications preferred their current formulation, but those taking current LAI formulations were indifferent. This outpatient study found that current prescribed formulation (LAI or oral) predicted preference to treatment but did not predict the attitude of the patient to treatment. Attitudes were more influenced by illness duration, extrapyramidal side effects and insight. Twenty-four percent of the patient sample felt embarrassed or ashamed to attend the clinic for medications regardless of being on LAI or oral, and 21% of those surveyed stated there was more reason to feel embarrassed or



ashamed if someone was taking a LAI as compared to oral medication.⁵⁰

There have been a few recent studies reporting on attitudes and perceptions of second generation LAI. A recent study reported the results of switching stable patients with schizophrenia from LAI and oral antipsychotics to risperidone LAI.⁵¹ In this nonrandomized study patients with schizophrenia or other psychotic disorders reported statistically significant improvement in both patient satisfaction and quality of life at endpoint. The proportion of patients who rated risperidone LAI treatment as 'very good' increased from 10% to 40%.⁵¹ Likewise, high patient satisfaction was reported in a 12 week double blind clinical trial of risperidone LAI.⁵² However, not all data have been positive. No differences in Drug Attitude Inventory scores, subjective well being, or health related quality of life were found in a 48 week study with LAI risperidone in Korean patients with schizophrenia after switching from oral medications.⁵³

One open label clinical trial with olanzapine LAI reported that over 70% of patients were satisfied with olanzapine LAI and 69% reported that they preferred LAI over previous oral medications. Seventy-two percent report having less impact from side effects compared to previous oral agents.^{54,55} A recently completed, yet unpublished two-year study found no difference in patient satisfaction with medication or patient attitude toward treatment in Drug Attitude Inventory scores among patients treated with olanzapine pamoate compared with oral olanzapine.⁵⁵ It is worth noting that while comparative studies of patient attitudes and perspectives of LAI agents are not yet available, a recent paper examined patient perspectives among oral antipsychotics in a sample of 1062 subjects treated with haloperidol, risperidone, ziprasidone or olanzapine. This paper found that the olanzapine treated patients had significantly higher percentage of patients reporting positive attitude on Drug Attitude Inventory (DAI-10) items compared to the other medications, including haloperidol (6 items), risperidone (2 items), and ziprasidone (1 item).⁵⁶ In this study, patients with positive attitude toward medications had a greater likelihood of treatment completion, and on items of the DAI-10, patients reporting positive attitude toward treatment had significantly higher completion rates than did those reporting negative attitudes. In addition, patient

favorable attitudes toward current treatment were also associated with improvements in symptom severity. Although this study utilized oral rather than depot formulations, it is of note that olanzapine performed better than other antipsychotics in at least one item of DAI in comparison with each comparator.

Thus, in summary, patient perspectives and attitudes are critical and need to be evaluated by the health care team in order to address potential issues, and to help patients understand what LAI medications can offer. Many patients once satisfactorily treated with LAI prefer being on this treatment for the long term. Unfortunately, to date there is no research guiding clinical teams on the preferences and attitudes of the newest class of LAI antipsychotics (olanzapine pamoate, risperidone microspheres and paliperidone palmitate) and decisions remain largely based on health care team input. Yet, the largest paper to date on oral medication reported the highest treatment satisfaction scores with olanzapine compared to a host of other agents. This is despite some of its pitfalls such as weight gain and metabolic complications. While this may not be translated into the same findings in long acting it is important to review this new medication in the long acting form to know its risks and benefits for both the health care team and the patients themselves.

Olanzapine Pamoate Long Acting Injection: A New Choice in LAI Preparations

Olanzapine pamoate is a long acting injection formulation of olanzapine, and is the newest LAI available for use in patients with schizophrenia. Olanzapine pamoate has been marketed as Zyprexa Relprevv and is indicated for the treatment of schizophrenia in adults.³ For a full review of risperidone long acting (Risperdal Consta) or paliperidone long acting (Invega Sustenna) we suggest the following references: Citrome 2010 and Fleischhaker 2010.^{57,58} Nonetheless at the paper conclusion we briefly review comparison data among long acting agents.

Olanzapine LAI is available as olanzapine pamoate powder for suspension in vials of 210 mg, 300 mg, and 405 mg. These agents must be suspended in a diluent prior to administration; the approved diluent is provided in the kit accompanying the active medication. Olanzapine pamoate should be given



as deep intramuscular gluteal injection only with a 19-gauge, 1.5 inch needle, or larger if patient is obese. In order to receive the olanzapine pamoate LAI in the US, the prescriber, patient, facility, and pharmacy must all be enrolled in the Zyprexa Relprevv Patient Care Program. The Patient Care Program has been developed in order to increase monitoring of patients after administration of OLAI. In addition to the boxed warning regarding death in elderly patients that accompanies the oral formulation, a boxed warning regarding Post-Injection Delirium Sedation Syndrome (PDSS) has been added. This warning indicates the possibility that patients are at risk for severe drowsiness, unconsciousness, coma, confusion, and disorientation after each injection and must stay at the doctor's office or clinic for at least 3 hours after the injection is given.³

Dosing Recommendations for Olanzapine LAI

Dosing recommendations for Olanzapine LAI have been developed both from occupancy studies and from relapse data from clinical trials. Positron-emission tomography (PET) was used to explore the occupancy of D2 receptors in 14 patients with schizophrenia or schizoaffective disorder taking olanzapine long acting injection 300 mg every 4 weeks for six months.⁵⁹ Supplemental oral olanzapine was used for half of the patients during the first 4 injection cycles; no patients were prescribed supplemental oral olanzapine during periods of PET scan. The need for oral supplementation subsided as D2 occupancy reached 60% or greater, which is consistent with D2 occupancy with most antipsychotics. By the fifth injection cycle the D2 occupancy resembled baseline oral olanzapine (84%).⁶⁰

The dosing recommendations may be found on Table 1. After initial use of olanzapine oral formulation to establish tolerability, olanzapine pamoate may be initiated. A two-step dose prescribing system is recommended in the olanzapine long acting injectable labeling due to the delay in reaching steady state. This involves using a higher dose or increased duration of injection for the first 8 weeks, followed by either a decrease in dose or duration once steady state is established. Dose regimens range from 150 mg every 2 weeks, to 300 mg every 4 weeks, to 210 mg every 2 weeks, to 405 mg every 4 weeks,

to 400 mg every 2 weeks. Doses in excess of 405 mg every 4 weeks or 300 mg every 2 weeks have not been evaluated. For a goal of reaching 10 mg oral equivalent, for example, it is recommended to give 210 mg every two weeks or 405 mg every four weeks for the initial 8 weeks of treatment. After the eighth week, dosing may progress to a maintenance dose of 150 mg every 2 weeks or 300 mg every 4 weeks. For a goal of 15 mg/day equivalents, initiate with 300 mg every two weeks for the first 8 weeks. After the first 8 weeks of treatment, the dose may be adjusted to 210 mg every 2 weeks or 405 mg every 4 weeks. For a goal of 20 mg olanzapine day equivalents, there is only one dose recommended, and no adjustment at week 8. Patients should be given 300 mg every 2 weeks for the duration of therapy.³ Data supporting the dose recommendations for differing doses of oral olanzapine to long acting injection have been published or presented.⁶⁰⁻⁶³ After 2 months of treatment the patient should be evaluated for maintenance dosing.

Efficacy of Olanzapine LAI

Oral formulations of olanzapine are efficacious in short term acute and maintenance treatment of patients with schizophrenia.⁶⁴⁻⁶⁶ In addition, olanzapine oral treatment has shown effectiveness in recent comparison studies and meta analyses as other FGA and SGA agents.^{67,68} Likewise, olanzapine pamoate LAI has shown efficacy for acute⁶⁹ and maintenance⁷⁰ treatment of adults with schizophrenia. In addition, a recently completed two-year study has released preliminary data (clinicaltrials.gov ID: NCT00320489), although it has not yet been published in the literature.⁵⁵ Poster reports of 160 and 190-month data of a four year study have been presented.^{71,72} Zhao and colleagues⁷³ compared the results of clinical trials of olanzapine LAI, oral olanzapine, and haloperidol to analyze the comparable efficacy of LAI. Using data derived from marketing trials of olanzapine oral,^{64,65} olanzapine LAI had a similar magnitude of symptom reduction as those treated with oral olanzapine or oral haloperidol.⁷³ Clinical trial information for olanzapine pamoate injection may be found in Table 2.

Lauriello and colleagues⁶⁹ reported an 8 week study of acutely ill patients randomized to double blind olanzapine pamoate LAI 210 mg every 2 weeks, 300 mg every 2 weeks, 405 mg every four weeks,

Table 1. Second generation long acting injection agents.

Medication	Dose forms	Dosing recommendations for schizophrenia	Half life	Comments	Common adverse reactions (at least 5% in schizophrenia studies)
Paliperidone palmitate ⁸⁵	39, 78, 117, 156, or 234 mg paliperidone palmitate prefilled syringes	Initiation (deltoid IM injection): 234 mg day 1 156 mg 1 wk later Recommended monthly maintenance (deltoid/gluteal IM injection): one month after 2nd dose; 117 mg recommended; some pts may benefit from lower/higher doses (39 mg to 234 mg) Deltoid or gluteal IM injection: 25 mg IM Q2 weeks Maximum dose should not exceed 50 mg Q2 weeks Oral supplementation of antipsychotic for 3 weeks after 1st injection Upward dose adjustment not more frequently than Q4 weeks Gluteal IM injection: 150 mg/2 wk, 300 mg/4 wk, 210 mg/2 wk, 405 mg/4 wk, 300 mg/2 wk To target oral 10 mg/day dose: either 210 mg/2 weeks or 405 mg/4 weeks during first 8 weeks; maintenance after 8 weeks: 150 mg/2 weeks or 300 mg/4 weeks To target oral 15 mg/day dose: 300 mg/2weeks for first 8 weeks, then maintenance dose after 8 weeks to 210 mg/2 weeks or 405 mg/4 weeks To target 20 mg/day oral dose: 300 mg/2 weeks during first 8 weeks, continue with 300 mg/2 weeks for maintenance	25–49 days	No refrigeration needed. 22 G needle for deltoid and ≥90 kg or 23 G deltoid for <90 kg or 22 G gluteal	Injection site reactions, somnolence/sedation, dizziness, akathisia, EPS
Risperidone long acting injection ⁸⁴	12.5, 25, 37.5, 50 mg/vial powder for suspension		3–6 days	Refrigeration needed. 21 G deltoid, 20 G gluteal; alternate injection sites; reconstitute with special diluent, and administer only with provided needle	Headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increased, extremity pain, dry mouth
Olanzapine pamoate long acting injection ³	210, 300, 405 mg/vial powder for suspension		30 days	Do not confuse with rapid acting IM injection; must reconstitute with included diluent; measure amount to inject from vial (there will be remaining suspension in vial); 3 hour observation period and pt must be accompanied to destination. No refrigeration needed. 19 G needle	Headache, weight gain, sedation, cough, diarrhea, back pain, nausea, somnolence, dry mouth, nasopharyngitis, increased appetite, vomiting



or placebo in a 1:1:1:1 ratio. No oral supplementation of antipsychotic was permitted. All patients were hospitalized during study entry, washout, and first 2 weeks following randomization. Significant separation from placebo was shown for all doses of olanzapine pamoate; separation from placebo occurred for the 300 mg every 2 weeks and 405 mg every 4 week regimens at the first PANSS measurement, three days after first dose. At 7 days, the 210 mg every 2 weeks dose group separated from placebo. At endpoint, all doses of olanzapine pamoate injection were significantly superior to placebo in reduction of PANSS total score. All olanzapine doses had improved clinical global impression-improvement scale scores compared to placebo.^{69,74}

Kane and colleagues⁷⁰ investigated the efficacy of olanzapine pamoate (at three therapeutic doses and one reference dose) for maintenance of stability over 24 weeks in a double-blind, randomized trial in patients with schizophrenia stabilized on oral olanzapine. This study, involving 1065 randomized (1205 enrolled) outpatients evaluated olanzapine pamoate compared with oral olanzapine with 5 dosing groups (450 mg every 4 weeks, 300 every 2 weeks, 150 mg every 2 weeks, 45 mg every 4 weeks as a reference dose, or 10, 15, or 20 mg/day oral olanzapine). Overall efficacy of these doses was comparable to oral olanzapine with no apparent differences between the use of 2 and 4 week dosing intervals. Each therapeutic dose group of olanzapine pamoate was superior to the reference dose (45 mg every 4 weeks) of olanzapine pamoate in time to exacerbation. This study found the high dose (300 mg every 2 weeks) was superior to the low dose (150 mg every 2 weeks). Ninety-five percent of the high-dose group remained exacerbation free, as well as 90% of the medium-dose (405 mg every 4 weeks) group, and 84% of the low-dose group. Only 69% of the very low reference dose group remained exacerbation-free. There was a statistically significantly shorter time to exacerbation for the low-dose injection group relative to the high-dose ($P = 0.005$) and the oral olanzapine ($P = 0.004$) groups. In addition, the every 2 week pooled group (150 mg and 300 mg every 2 weeks) was shown to be non-inferior to oral olanzapine in non-exacerbation rate.^{3,70,75,76}

A long-term two-year study was completed in September 2009 but has not yet been published.

Long-acting injection (405 mg at initial injection, then four weeks later flexible dosing of 150 mg to 405 mg every four weeks) was compared to oral olanzapine (10 mg daily for four weeks then 5–20 mg flexible daily dosing once daily). No difference in all cause time to discontinuation was found between long acting injectable pamoate (644.5 days, range 162–740 days) and oral (677.5 days, range 169.5–740 days) in this outpatient study of those at risk for relapse.⁵⁵

In addition, a four-year trial is ongoing⁷⁷ but has not yet been completed. Interim results from this long-term, open-label safety extension study of from one of three double blind trials of olanzapine long acting injection (maximum duration = 190 weeks) for treatment of schizophrenia patients ($n = 931$). During the open-label extension, all patients received flexibly-dosed olanzapine LAI at injection intervals of approximately 2 to 4 weeks. At the time of the report, the rate of study discontinuation from the open label extension of long acting olanzapine injectable was 46.3%, while the discontinuation rate at 18 months was 34.3%. The most common reasons for discontinuation were: subject decision (23.4%), adverse event (6.7%), and lost to follow-up (5.7%). Mean CGI-S scores remained stable throughout the open label follow-up of the three studies (2.9 at baseline to 2.8 at endpoint).^{71,77}

Side Effects of Olanzapine LAI

Adverse effects of olanzapine LAI are reported to be similar to those of oral olanzapine, with higher doses predictably associated with increase in side effect risk.^{76,78} Short term safety data has been collected from two double-blind studies and 6 open-label studies have also been analyzed for adverse effects. No differences in discontinuation due to adverse reactions were found between LAI and placebo (4% vs. 5%, respectively). The most common treatment emergent adverse events occurring in at least 5% of participants and greater than the placebo group were: headache, sedation, weight gain, cough, diarrhea, back pain, nausea, somnolence, dry mouth, nasopharyngitis, increase in appetite, and vomiting. Long term (190 week) data from an ongoing study shows discontinuation of 46.3%, a discontinuation rate due to adverse event of 6.7%.⁷¹ Similarly to the shorter-term studies, the adverse effects observed in at least 5% of patients included increased weight, insomnia, somnolence, anxiety, headache, and nasopharyngitis.^{3,71}

**Table 2.** Clinical trials with olanzapine pamoate injectable antipsychotic.

Ref.	Design	Endpoints	Population
Eli Lilly and Company, data from clinical trials.gov) ⁵⁵ NCT00320489	Randomized open label trial	Time to discontinuation	n = 264 pamoate, 260 oral; schizophrenia
Kane et al, ⁷⁰ NCT00088491	Open label olanzapine oral lead in to double-blind pamoate vs. oral	Efficacy and tolerability for maintenance treatment of schizophrenia	n = 1065 enrolled stable outpatients with schizophrenia;
Lauriello et al, ⁶⁹ NCT00088478	Double blind, placebo controlled	Fixed-dose kinetic, efficacy, superiority, Safety; primary outcome measure = PANSS positive and negative syndrome scale total score	n = 404 randomized; schizophrenia
Eli Lilly and Company, McDonnell D et al, ⁷¹ NCT00088465	Open label	Safety, effectiveness, pharmacokinetics	n = 931 enrolled schizophrenia or schizoaffective disorder previously completed olanzapine pamoate clinical trial
Kurtz et al, ⁸⁸ Detke et al, abstract; Eli Lilly and Company	Open label	Safety and tolerance after single and multiple doses	n = 282 enrolled; symptom stabilized patients with schizophrenia
Eli Lilly and Company (not published) ^{89,90}	Open label	Safety, pharmacokinetics, olanzapine pamoate metabolites	n = 9 enrolled patients with schizophrenia or schizoaffective disorder
Eli Lilly and Company (not published) ^{89,90}	Fixed sequence parallel design, open label study	Safety, particle size distribution, product quality bioavailability performance of olanzapine pamoate	n = 134 randomized stable patients with schizophrenia or schizoaffective disorder
Mamo et al ⁵⁹	Open label, one arm	PET study of receptor occupancy, safety, efficacy	n = 14 schizophrenia
Eli Lilly and Company (not published) ^{89,90}	Healthy volunteers; one dose of olanzapine pamoate	Safety, tolerance, pharmacokinetics and pharmacodynamics	n = 18 healthy male volunteers

Weight gain is a significant concern with olanzapine treatment. In a 24 week study comparing 3 doses of olanzapine pamoate, weight gain was significantly higher in the 300 mg every 2 week group (11%) compared to the medium dose (405 mg every 4 weeks) group (5%), but similar to the oral olanzapine (8%) or the 150 mg every two weeks (low dose injection) groups (9%). Patients gaining at least 7% of body weight did not differ significantly between either

two week group and oral nor did it differ between the four week group and oral (19%, 15%, and 21% for two week, four week, and oral groups).^{3,70}

Changes in laboratory parameters are seen with olanzapine LAI. Mean change in prolactin was higher in the 300 mg every two weeks (high dose) group (3.57 ng/ml) compared to both medium dose (405 mg every 4 weeks) (-2.76 ng/ml) and low dose (150 mg every 2 weeks) (-5.61 ng/ml). Change in



Duration	Dosing	Comments	Outcome
104 weeks	405 mg IM, then 4 weeks later flexible dose 150–405 q4 weeks for 96 weeks; oral: 10 mg daily for 4 weeks followed by flexible dosing 5–20 mg for 100 weeks	Not yet published	No difference in all cause time to discontinuation; 644.5 days vs. 677.5 oral $P = 0.1612$; adverse events were similar among the 2 groups
24 weeks	150 mg every 2 weeks; 405 mg every 4 weeks; 300 mg every 2 weeks; 45 mg every 4 weeks reference dose; or stabilized dose of oral olanzapine.	July 2004 to September 2006	93% of oral, 95% high, 90% medium, 84% low doses of injection remained exacerbation free; statistically significantly shorter time to exacerbation for the low-dose injection group vs. high-dose ($P = 0.005$) and oral ($P = 0.004$) groups; every 2 week pooled group (150 mg and 300 mg every 2 weeks) non-inferior to oral olanzapine
8 weeks	Fixed dose: 210 mg Q2 weeks, 300 mg Q2 weeks, 405 mg Q4 weeks vs. placebo	June 2004-April 2005	PANSS base to end point change was greater for all regimens vs. placebo; improvement as CGI-Improvement scale higher for all olanzapine pamoate groups vs. placebo
4 years (190 week data abstracted in 2009)	Flexible doses: 45 to 405 mg at 2, 3, or 4 week intervals	Proposed completion date Dec 2010	Discontinuation rates at 190 week analysis were 46.3%; at 18 months was 34.3%
24 weeks	Single dose 50–450 mg; multi dose 100–405 mg Q2 to Q4 weeks	Concluded	
8 weeks	Four 300 mg injections Q2 weeks	Concluded	
7 weeks	Single dose 405 mg; olanzapine pamoate vs. rapid IM olanzapine vs. oral olanzapine	Concluded	
24 weeks	300 mg olanzapine pamoate Q4 weeks	Concluded	
Single dose	10–40 mg olanzapine pamoate	Concluded	

fasting triglycerides from normal to elevated levels was 24.5%, 9.8% and 6.5% in the high, medium and low dose groups, respectively. About 30% had elevations in random total cholesterol above 200 ng/ml and about 5% were above 240 ng/ml during long acting olanzapine injectable treatment. Approximately 5% of patients increased from <100 mg/dL to at least 126 mg/dL at any point in the study and elevations in LDL and decreases in HDL were also observed.^{3,70}

A post-hoc analysis was performed on data from patients enrolled in the 24-week maintenance study⁷⁹ that provided further information supporting these adverse effect reports. Safety and tolerability measures, including unsolicited treatment emergent adverse effects, mean changes in weight, fasting glucose, lipids, and prolactin, and treatment emergent categorical changes in these laboratory levels were examined. Number needed to harm (NNH) values



were calculated for categorical safety measures. Of the treatment emergent adverse events occurring in at least 5% of patients in the dose groups or with between groups $P < 0.10$, only increased appetite showed significant dose association. Increased dose, defined as calculated oral equivalent daily dose, was related to increased incidence of increased appetite ($P = 0.031$). Significant dose-associated changes were identified for weight and prolactin, both showing increases with increasing doses. Significant dose associations were found for incidence of categorical changes in laboratory measures at endpoint, with significant associations identified for HDL cholesterol normal at baseline to low at endpoint and fasting triglycerides normal at baseline to high at endpoint, and the incidence of these increased with increasing dose. Number needed to harm for changes in HDL cholesterol normal at baseline to low at endpoint was calculated to 6 (95% CI: 4–43) compared to high and low dosage groups. Change in triglycerides from normal at baseline to high at endpoint NNH was 8 (95% CI: 5–64) comparing high dose with medium dose and 7 (95% CI: 4–24) comparing the high dose with the low dose group.⁷⁹

Interim data from a long-term (4 year) open label extension study of patients treated with olanzapine pamoate LAI have recently been reported.⁷¹ In this 190-week interim data presentation, adverse events occurring in at least 5% of patients were: increased weight, insomnia, anxiety, somnolence, headache, and nasopharyngitis. After treatment for 190 weeks, and consistent with other studies of olanzapine, weight gain occurred at an average of + 1.88 kg, with 32.1% of patients experiencing clinically significant weight gain. About 5% of patients increased from normal to high values on fasting glucose and total cholesterol while over 14% increased on triglyceride levels.

In contrast to olanzapine oral formulations, patients may be at risk for injection site reactions during the administration of olanzapine pamoate. Injection site reactions of any kind were reported in 3% to 8% of patients in placebo-controlled trials.^{3,80} In addition, a post-injection delirium sedation syndrome (PDSS) was reported in approximately one percent of patients during clinical trials.

This PDSS is described as unexpected sedation, confusion, and/or delirium within the first several

hours following injection. Reported occurrences resolve within 1.5 to 72 hours; however, due to this potential adverse effect, a monitoring plan was developed. As a result, the prescribing of olanzapine pamoate injection requires registration of the patient, prescriber, healthcare facility and pharmacy with the Patient Care Program designed to provide for the safe administration of the injection to patients in the US. Each injection must be administered in a health care facility with access to emergency response. Patients must be observed for three hours prior to leaving the facility in a facility with resuscitation capabilities and must be accompanied to their destination upon leaving. Patients should refrain from driving or operating machinery for the remainder of injection day.³

Based on approximately 45,000 injections given to 2054 patients in clinical trials (through October 2008), PDSS occurred in approximately 0.07% of injections or 1.4% of patients (30 cases occurred in 29 patients).⁸¹ PDSS occurred at varying dose cycles, anywhere from the first to the 66th injection. Symptoms that occurred were consistent with olanzapine overdose (sedation, confusion, slurred speech, altered gait, or unconsciousness). No significant changes in vital signs were observed. Median time to onset post-injection was 25 minutes. The onset of symptoms ranged from immediately post injection to 3–5 hours post injection. All patients recovered within 1.5 to 72 hours. The majority of the patients in the trials continued to receive subsequent injections without incident after the event. No consistent risk factors have been identified.

While the cause of PDSS is unknown, it may be due to accidental intravascular administration of the dose. McDonnell and colleagues⁸² collected and investigated data related to all PDSS reports and found that no unusual occurrences were listed during the injections and no anomalies were found within product batches of medication used. His group also reported that in the studies that lacked PDSS, olanzapine concentrations did not abruptly increase. Generally blood levels increase slowly after injection reaching plasma concentrations between 5–73 ng/ml. Available samples for PDSS cases (12/30) were associated with concentrations of olanzapine that exceeded 100 ng/ml and in some cases >600 ng/ml during first hours after injection. These concentrations followed a pattern of



substantial increase in concentration to high levels in the immediate hours after injection. Levels then returned to expected ranges within 24 to 72 hours after the injection. Symptom resolution also followed this pattern.⁸² PDSS has only been recognized as a side effect specific to long acting olanzapine and not the other new long acting formulations. Importantly these agents all have differences and selecting among them often depends on the patient characteristics and the experience of the patient and health care team.

Comparisons of Olanzapine LAI with Other Long Acting Injectable Antipsychotics

The mechanisms by which antipsychotics have been reformulated in long acting injection form vary. FGAs such as haloperidol and fluphenazine are esterified and dissolved in an oil-based solvent and have been available for a few decades. After injection into muscle tissue, the medication slowly diffuses into the blood stream and is hydrolyzed to active parent compound.⁸³ Risperidone is encapsulated in a biodegradable polymer to permit its formulation as a long acting agent.⁸⁴ Paliperidone, the active metabolite of risperidone, is available as paliperidone palmitate, an aqueous extended release suspension dispensed in pre-filled syringes.⁸⁵ Olanzapine is combined to form a salt form, olanzapine pamoate, then suspended in solvent for injection. Slow dissolution from intramuscular injection leads to introduction in to the blood stream and transformation into active olanzapine.³ A comparison of the second generation long acting injection agents may be found in Table 1.

Risperidone LAI (as microspheres for suspension) was the first second generation long acting agent approved for use in the US. Studies have shown efficacy for treatment of schizophrenia and bipolar disorder.⁸⁴ This agent is available as a powder for reconstitution. Doses must be given every two weeks, and concomitant oral supplementation is recommended for the first three weeks after initial injection.

Paliperidone palmitate LAI has recently been approved for use in patients with schizophrenia in the US. This agent is available as prefilled syringes for injection and is approved for adults with schizophrenia.

No oral supplementation is required; patients will have the first two initial injections one week apart, and be dosed monthly thereafter. Efficacy and safety data support its use in this patient population.^{57,58,85}

Olanzapine pamoate LAI does not require oral supplementation after the first dose, and does not require an additional injection one week later, in comparison to risperidone and paliperidone, respectfully. However, the two-step dosing recommendations that advise the reduction in dose after 8 weeks of therapy for most doses may introduce confusion, and the possibility of prescribing in excess of the lowest possible dose. In addition, the restriction of use of olanzapine pamoate to a patient care registry system which requires all parties (patient, prescriber, facility, and pharmacy) to be registered, and that the patient not only be observed for three hours after injection but also must be accompanied to final destination, may decrease the likelihood of appropriateness for some potential patients (See Table 1).³

Few data exist that compare the second generation LAI in head to head comparisons. One head to head comparison of paliperidone palmitate and risperidone LAI has been published.⁸⁶ This 13-week, noninferiority, double-blind study of paliperidone palmitate and risperidone LAI in adults with schizophrenia demonstrated noninferiority of paliperidone palmitate to risperidone long acting injection, and PANSS total score decreased similarly in both groups. Safety and tolerability of both agents were similar.⁸⁶

To date, there have been no head to head comparisons of olanzapine pamoate LAI and the other long acting antipsychotics. A recent presentation reported a comparison of completion rates of olanzapine pamoate and risperidone microspheres from open label single arm completed studies. Twelve-month completion rates for olanzapine and risperidone were 72.9%–81.5% for olanzapine and 47%–59.1% for risperidone.⁸⁷ However, differences in study designs and populations make these results difficult to generalize or to use for drawing definitive conclusions. Head to head efficacy studies are needed to determine whether significant differences exist between the long acting agents.

Despite little comparison data, side effects in addition to the preparation and initial dosing differences of these medications often play a role in health care



provider selection. Olanzapine pamoate is associated with similar side effects to oral such as weight gain and some elevations in lipid parameters. Risperidone and paliperidone are associated with weight gain but lesser than olanzapine. These agents do have elevations in prolactin and may cause hormonal dysregulation and sexual dysfunction to a greater degree. Risperidone may be associated with more extrapyramidal side effects (EPS) than olanzapine at the higher doses. Thus, in conclusion among the agents, important differences to help guide selection would be the following:

- Oral antipsychotic coverage (Needed for risperidone not olanzapine and paliperidone)
- Reconstitution (Needed for risperidone and olanzapine not paliperidone)
- Refrigeration (Needed for risperidone not olanzapine and paliperidone)
- Patient care registry (Needed for olanzapine not risperidone and paliperidone)
- Two dose initiation (Needed for paliperidone not olanzapine or risperidone)
- Less than monthly injection (Needed for risperidone not paliperidone or certain dose schedules of olanzapine)
- Side effects (more weight gain with olanzapine, more EPS (higher doses) and prolactin elevations with risperidone).

Conclusions

In summary, adherence and relapse are frequent problems in people with schizophrenia. Long acting injectable antipsychotics may offer benefits over oral agents particularly in the prevention of relapse. Perspectives and attitudes of health care providers and patients are mixed but generally favorable but these agents remain underutilized. It appears that better understanding and education may lead to wider use. It may be that the newer class of second generation antipsychotics that are available in long acting formulation may be perceived by health care providers and patients as a more desirable treatment option however this remains unknown. Olanzapine pamoate LAI is the newest addition to the available long acting options to treat patients with schizophrenia. Both acute and maintenance efficacy in patients with schizophrenia stabilized on oral medications

prior to switching to injection has been demonstrated in published and unpublished clinical trials. Although no head to head comparisons to other long acting injections exist, olanzapine long acting is similar in efficacy to oral olanzapine. Despite its efficacy, the perceived cost of the injection, as well as the restriction of use to patients enrolled in the Patient Care program, may limit the use of this medication. However as adherence continues to be a significant problem in schizophrenia, LAI may offer an important treatment option and a more convenient way to ensure ongoing antipsychotic treatment. More research is needed to best understand the benefits of LAI, the hurdles and barriers that prevent more widespread use, cost effectiveness analyses and personalized treatment strategies as to which patients may be best candidates for treatment. Nonetheless, this next generation of people treated with LAI will hopefully benefit more integrated and knowledgeable health care teams regarding long acting agents and from increased shared decision making and patient input to avoid the downfalls and pitfalls of past long acting injection treatment.

Disclosures

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