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REVIEW ARTICLE

Long-Acting Injectable Second-Generation Antipsychotics: An Update and Comparison Between Agents

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Abstract Schizophrenia is a chronic medical condition with periods of remission and relapses over a patient's lifetime. Antipsychotic medications represent the mainstay of treatment for this disease. Long-acting injectable (LAI) formulations of antipsychotics are an attractive alternative to their oral counterparts, as they enhance patient adherence. A number of second-generation antipsychotics (SGAs) are available in LAI formulations. These include paliperidone, aripiprazole, olanzapine, and risperidone. This article reviews the most recently developed and approved of these formulations—aripiprazole monohydrate, aripiprazole lauroxil, and paliperidone palmitate. While all were initially available as once-monthly formulations, a paliperidone palmitate 3-monthly injection formulation has been approved and is the first LAI agent to extend the dosing administration beyond the typical monthly time period. In addition, aripiprazole lauroxil every 6-week and 8-week administration preparations have been developed. LAI preparations of the SGAs have all demonstrated superiority over placebo and are comparable to their oral counterparts in terms of safety and tolerability, if injection site reactions are not taken into account. First-generation antipsychotic LAI preparations (e.g., haloperidol decanoate) have recently been compared with SGA LAI agents, and both formulations demonstrated comparable efficacy with the expected adverse events seen with each drug. Despite their availability, barriers to the use of LAIs remain. Education of both patients and clinicians on the use of LAI formulations and the continued development of these agents are important steps in ensuring these medications are available to the patients they would be most likely to benefit.

Key Points

The pharmacokinetic and pharmacodynamic properties of long-acting injectable (LAI) antipsychotics are well known and can be modeled with computer simulations.

LAI formulations of second-generation antipsychotics (SGAs) have been developed that allow dosing administration intervals of greater than 1 month or expanded therapeutic indications.

Comparison and switching studies between LAI antipsychotic agents have reported comparable efficacy with the expected adverse events.

1 Introduction

Antipsychotic medications are the foundational therapeutic treatment for patients with schizophrenia, bipolar, and schizoaffective disorders, and other medical conditions that include psychotic symptoms. Schizophrenia, like many other psychiatric diseases, is a chronic medical condition with periods of remission and relapses over a patient's lifetime. Patient adherence to antipsychotic

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pharmacotherapy can minimize acute relapse episodes but remains a major challenge over prolonged time periods. The development of depot or long-acting injectable (LAI) antipsychotics in the early 1960s represented a major shift in therapeutics that enhanced patient adherence compared with that observed with oral daily drug regimens [1–3]. However, despite their availability, barriers to the use of long-acting antipsychotics remain for a variety of reasons. Approaches to overcoming these barriers have been developed for LAI agents, but their routine and consistent implementation continues to be challenging for everyone [4].

The LAI formulations of the first-generation antipsychotics (FGAs) developed in the 1960s incorporated the esterified drug molecule into a vehicle consisting of either sesame oil or viscoleo (cooking oil) as the preparation [2]. Only depot fluspirilene differed from the other FGAs; it was formulated in a microcrystalline microsphere preparation in an aqueous suspension [2]. Aqueous-based LAI preparations are preferred since they are associated with reduced incidence and severity of pain upon intramuscular administration [5]. The arrival of the second-generation antipsychotics (SGAs) offered significant improvements in reducing the risk of extrapyramidal symptoms (EPS) but had other adverse consequences such as the long-term risks of weight gain and development of the metabolic syndrome [6]. The long-acting SGAs shown in Table 1 are primarily indicated for the treatment of patients with schizophrenia. Risperidone microspheres, aripiprazole monohydrate, and paliperidone palmitate 1-month are approved for bipolar I and schizoaffective disorders, respectively. Each LAI antipsychotic preparation is unique, which leads to differences in whether their corresponding oral agent is required during the initial dosing time period.

This article focuses on the latest information from randomized controlled trials, secondary publications, observational studies, post hoc analyses, and pharmacokinetic approaches to the clinical application of LAI SGAs. The article's primary focus is to examine the most recent developments in LAI studies for efficacy and safety. Clinical trials with the earlier risperidone and olanzapine LAIs can be reviewed with other references [6]. Also, the phase III paliperidone palmitate 1-month (1MPP) studies were not reviewed in this article, but the latest studies with haloperidol decanoate and switch studies were included. A comprehensive PubMed search with the keywords depot, long-acting injectable, SGA, paliperidone palmitate, aripiprazole, iloperidone, pharmacokinetic, deltoid, gluteal, and switching was conducted. LAI SGA studies only in English and within the last decade were included for review. Finally, an update with the latest published information on the post-delirium sedation syndrome (PDSS) primarily noted with olanzapine pamoate is provided. PDSS is a serious medical condition that typically requires hospitalization with treatment and careful patient monitoring.

2 Formulation

The technology for the development of SGA LAIs poses unique challenges for the pharmaceutical industry and cannot be overemphasized as the approved and marketed formulation dictates the product's storage conditions, pharmacokinetic profile, oral dosing requirements during the initial treatment phase, and long-term usage. A brief description of the SGA LAI formulations is presented here. For an in-depth review of LAI antipsychotic formulation

Table 1 Summary of second-generation long-acting injectable antipsychotics

Agent	US FDA approval date	Indication	Formulation design technology	Oral dosing initiation	References
Risperidone	October 2003	Schizophrenia	Microspheres	Yes, 21 days	[8]
	May 2009	Bipolar I			
Olanzapine	December 2009	Schizophrenia	Pamoic acid crystal	Not needed	[9]
Paliperidone					
1-month	August 2009	Schizophrenia	Nanocrystals	Not needed	[10]
	November 2014	Schizoaffective			
3-month	May 2015	Schizophrenia	Nanocrystals	Not needed[a]	[11]
Aripiprazole					
Monohydrate	February 2015	Schizophrenia	Polymorphic	Yes, 14 days	[14]
	July 2017	Bipolar I			
Lauroxil	October 2015	Schizophrenia	Pro-drug; 2-step hydrolysis	Yes, 21 days	[15]
Iloperidone	?	Schizophrenia	Crystalline	Yes, 21 days	[17]

[a]Must be previously treated with the 1-month formulation

properties that details the complex process of developing a depot antipsychotic, the reader is referred elsewhere [7]. As shown from Table 1, risperidone is formulated with a polylactic glycolic acid (PLGA) microsphere as hydrolysis of the polymer occurs gradually, resulting in a slow, steady release of drug that is designed for administration every 2 weeks [7, 8]. Because risperidone LAI is slowly released from the injection site, use of this preparation requires simultaneous administration of oral risperidone for the first 21 days. The oral regimen is necessary to achieve or maintain adequate risperidone serum concentrations during the transition from oral to LAI therapy.

Olanzapine pamoate is a micronized crystalline salt formulation in monohydrate form. The olanzapine preparation slowly dissolves into an active drug and pamoic acid where the medication enters the systemic circulation. Olanzapine can be given every 2 or 4 weeks without an initial oral dosing scheme depending upon the dose and the patient's clinical condition. Olanzapine pamoate upon injection into the vasculature results in the drug rapidly solubilizing, leading to prompt elevations in plasma drug concentrations causing the PDSS clinical manifestations (see Sect. 6) [7, 9].

Paliperidone palmitate employs Nanocrystal® technology for both the 1MPP and the 3-month (3MPP) administration formulations [7, 10]. The solid particle size must fit through the supplied needles (e.g., 22 gauge) without clogging. Particle size is inversely related to the rate of drug release, as the dissolution rate of smaller particles is more rapid than that of larger particles because of the larger surface area of the former. Unlike the other LAIs, the first two doses of 1MPP are given over a 1-week period that achieves therapeutic serum drug concentrations without the need for concurrent oral dosing. The 3MPP preparation has larger nanocrystals than the 1MPP formulation, resulting in prolonged and sustained serum drug concentrations. Of note, patients must be stabilized on the 1MPP preparation prior to receiving the 3MPP formulation [11].

Two different aripiprazole LAI formulations have been developed. The once-monthly polymorphic monohydrate–water preparation has a lower molecular weight (m.w. = 466.4 g/mol), and the aqueous suspension can be lyophilized [7, 12]. The second aripiprazole depot injection preparation uses a prodrug approach, where the lauroxil formulation (*N*-acyloxymethyl) results in a higher molecular weight compound (m.w. = 660.7 g/mol). Lauric acid (also known as dodecanoic acid) is a fatty acid found in cow, coconut, and human breast milk. After intramuscular injection, aripiprazole lauroxil undergoes cleavage by the body's natural enzyme esterase to *N*-hydroxymethyl aripiprazole (plus lauric acid) and then to aripiprazole (plus formaldehyde). Formaldehyde is found in living organisms and is created by amino acid metabolism; as such, in small amounts, it is not toxic [7, 12, 13]. Aripiprazole lauroxil is available in formulations that can be administered every 4, 6, and 8 weeks. Their different LAI formulations mean the corresponding oral dosing regimens differ between the two aripiprazole depots. The monohydrate and lauroxil preparations require 14 and 21 days of oral dosing, respectively, to achieve adequate serum drug concentrations [14, 15].

Iloperidone LAI continues to be under development by the sponsor. Presently, the only information available on this preparation is from a single poster presentation. Iloperidone LAI is a crystalline salt structure similar to paliperidone and olanzapine LAI formulations. The LAI preparation has a 28-day dosing interval and requires initiation with a 21-day oral dosing regimen [16, 17].

3 Clinical Pharmacokinetics and Pharmacodynamics

The pharmacokinetic principle for any sustained-release product (including LAI antipsychotic agents) where a drug's absorption rate constant is longer than its elimination rate constant is "flip-flop" kinetics. For drug formulations that display flip-flop kinetics, the time needed to achieve steady-state conditions depends on the absorption rate. Once steady-state is achieved, serum drug concentrations become dependent on the drug's elimination rate [18, 19]. An important advantage of LAI agents over oral antipsychotic medications is that LAI formulations are not subject to drug loss during gastrointestinal absorption and presystemic metabolism. Orally administered medications may display unpredictable absorption profiles (e.g., a double peak drug concentration) that cannot be described by a simple first-order model. Therefore, multiple models (e.g., mixed zero-order) may be required to accurately characterize the disposition of these agents [20].

3.1 General Pharmacokinetic Principles

The generalized flip-flop model, which can be applied to all LAI antipsychotic agents, is described by a simple first-order one-compartment model with first-order elimination. As such, achieving steady-state conditions with LAI antipsychotics takes longer than with oral drug administration [20]. After injection, the drug is gradually released in a relatively predictable manner, as absorption is the key factor affecting the antipsychotic's pharmacokinetic properties. Of note, paliperidone and olanzapine depot formulations are exceptions in that they do not undergo a lag period prior to achieving steady-state conditions; therefore, they do not require concurrent oral dosing during initiation of their depot formulations. Paliperidone palmitate utilizes

a higher dose of 234 mg followed in 1 week by a second dose of 156 mg to reach therapeutic plasma concentrations within a few days [21]. Olanzapine pamoate provides peak plasma concentrations 2–4 days post-intramuscular injection and has an elimination half-life of 2–4 weeks [22].

The 3MPP preparation pharmacokinetic profile differs from that of the 1MPP formulation. Population pharmacokinetics of the previously mentioned 1MPP regimen are described by a one-compartment model with first order absorption and elimination [23]. The 3MPP population pharmacokinetic model had two saturable absorption compartments and the following variables had a significant influence on absorption rate (K_a): sex, age, injection volume (IVOL) and injection site. The fraction of the dose entering the systemic circulation from the injection site (f_2) was influenced by sex, body mass index (BMI), needle length, injection site, and IVOL. Paliperidone clearance (CL) was associated with creatinine clearance and volume of distribution (Vd) and was related to BMI and sex [24]. However, as patients were stabilized on the 1MPP formulation for 4 monthly doses prior to implementation of the 3MPP, a different population pharmacokinetic model emerged. The 3MPP formulation is expected to provide a lower peak plasma concentration (C_{max}) than the 1MPP formulation, but achieve the same dose-proportional area under the curve (AUC). A conversion factor of 3.5 was identified when converting from 1MPP to 3MPP. Upon analysis, 3MPP displayed a one-compartment model with first-order elimination. However, the absorption rate was best fitted to a model with two saturable absorption compartments, including "rapid" and "slow" absorption phases that follow a more atypical absorption profile [25]. The saturable 3MPP absorption model is similar to the 1MPP model except that the 3MPP model is described by a zero-order process until saturation occurs, at which point it becomes a first-order process. Based on the final population pharmacokinetic model, only renal status was shown to affect drug CL. Sex, BMI, and injection site did not influence paliperidone exposure [24].

3.2 Deltoid versus Gluteal Administration

The administration site for LAI antipsychotics has been directed towards the deltoid or gluteal muscles. Drug entrance from the injection site into the systemic circulation is dependent upon blood flow to and from those muscles. Blood flow was evaluated in three pairs of muscles (gluteus maximus, vastus lateralis, and deltoid) in 20 healthy adult volunteers using 133Xenon [26]. Deltoid muscle blood flow (MBF) was 19% greater ($p < 0.05$) than gluteal MBF, with vastus MBF in between.

According to the manufacturer's instructions, LAI risperidone administration can occur in either the deltoid or gluteal muscles, as these two sites were interchangeable [27]. Olanzapine pamoate is given via deep intramuscular administration in the gluteal muscle to minimize possible exposure to blood [22]. Aripiprazole monohydrate and lauroxil preparations can be administered in either the deltoid or the gluteal muscles [28, 29]. 1MPP is unique in that it must be injected into the deltoid muscle for the first two doses; additional doses may be injected into either the deltoid or gluteal muscle [30]. 3MPP can be given in either the deltoid or gluteal muscle [11].

Various safety and tolerability studies have examined the differences between deltoid versus gluteal LAI antipsychotic administration. A pharmacokinetic and bioequivalence study was conducted with depot risperidone [27]. Patients with schizophrenia ($n = 170$) were given doses of 25, 37.5, or 50 mg every 2 weeks in single- and multiple-dose formats in either the deltoid or the gluteal muscle, then crossed over to the other injection site. The results showed a dose-dependent, linear pharmacokinetic pattern with C_{max} and AUC. Significant differences in C_{max} and AUC were found between some but not all drug doses when compared between the deltoid and gluteal injection sites. For example, the group receiving 50 mg had a C_{max} mean (± standard deviation [SD]) for the deltoid site of 37.8 ng/ml ± 17.2 compared with the gluteal site, which was 41.1 ng/ml ± 18.9, indicating that the two sites are interchangeable for risperidone LAI administration.

Aripiprazole lauroxil 441 mg single-dose intramuscular injection was given to patients with schizophrenia ($N = 44$) and randomly assigned to either the deltoid or the gluteal site [28]. Plasma drug concentrations for C_{max} and AUC were 23–34% greater from the deltoid injection site than from the gluteal injection site. The dehydro-aripiprazole AUC was also estimated to be 24–48% higher for the deltoid injection site. No differences in the safety profile between the two injection sites were observed except that the deltoid injection site had a greater incidence of pain than did the gluteal site (67.3 vs. 27.3%). Based on the pharmacokinetic profiles, the study concluded that the two injection sites were interchangeable. Aripiprazole monohydrate 400 mg was administered to patients with schizophrenia ($N = 35$) as an injection followed by 4 monthly doses randomly assigned to either deltoid or gluteal intramuscular administration [29]. The median time to achieve C_{max} (T_{max}) was shorter for deltoid versus gluteal administration (7.1 vs. 24.1 days, respectively) and the mean C_{max} was 31% higher for deltoid versus gluteal administration (170 ± 58.6 vs. 136 ± 70.3 ng/ml, respectively). The mean elimination half-life was shorter from the deltoid site than from the gluteal site (17.8 ± 7.45 vs. 24.0 ± 7.36 days, respectively). The deltoid:gluteal geometric mean ratio (GMR) for the aripiprazole AUC was 1.24 (range 0.91–1.68). Dehydro-aripiprazole plasma

concentrations were not assayed in this study. This investigation with the monohydrate product slightly differs from the lauroxil study [28] in that the gluteal site was preferred for the monohydrate preparation, with the deltoid site used as an alternative site. However, the incidence of injection site pain reactions between the two injection sites did not differ in the monohydrate study.

The 1MPP formulation was evaluated in 170 patients with schizophrenia. Study subjects were randomly assigned to receive either deltoid or gluteal injections and then crossed over to the other injection site [31]. Each group then received three different doses: 50 (78 mg), 75 (117 mg), and 100 mg (156 mg), with determination of serum drug concentrations. Patients reported slightly more intense pain upon deltoid injection with the lower two doses. A slightly higher incidence of adverse events, which did not include EPS, was also observed among the cohorts receiving the lower two doses. During the first week of treatment, median plasma paliperidone concentrations were higher in the deltoid muscle group (days 8 and 36), with minimal differences seen thereafter once steady-state conditions were reached. A single-dose pharmacokinetic study to assess dose proportionality of 1MPP was conducted in 201 patients with schizophrenia [30]. Subjects were randomly assigned to one of the following dosing cohorts: 25 mg (39 mg), 50 mg, 100 mg or 150 mg (234 mg). Each subject received intramuscular injections in the deltoid and gluteal muscles in crossover fashion. Doses were separated by 126 days. The geometric mean C_{max} was 28% higher (range 109–165) for the deltoid injection site versus the gluteal site. The deltoid site geometric mean AUC was also higher than the gluteal site but not as pronounced (range 103–118%). The T_{max} was 13–14 days and 13–17 days for the deltoid and gluteal sites, respectively. These findings led to the initial approved dosing scheme for 1MPP in which higher plasma drug concentrations occurred with slightly more painful deltoid administration.

The pharmacokinetics of the 3MPP formulation were evaluated between the deltoid and gluteal injection sites in patients with schizophrenia ($N = 228$). Doses ranged from 175 to 525 mg (819 mg) [32]. Both C_{max} and AUC were dose proportional. When concentrations were dose normalized (DN), the C_{max} for the deltoid site was higher than for the gluteal site (38.5 vs. 30.3 ng/ml) with a least squares (LS) ratio of 1.27 (90% confidence interval [CI] 107.9–149.6). Interestingly, AUC_{∞} did not significantly differ with an LS ratio of 102.2 (90% CI 94.3–110.8). Similarly, there was no difference in safety between the two injection sites. The median elimination half-life for the deltoid site was shorter than for the gluteal site (56.9 vs. 68.5 days). This study recommends that 3MPP can be administered to either site because only four injections per year are needed.

Estimations of LAI antipsychotic pharmacokinetics and bioequivalence can be challenging because of their extended dosing intervals as determined by technological advances in drug delivery. The 3MPP, aripiprazole lauroxil 6-week and 8-week formulations are excellent examples. It is likely other pharmaceutical sponsors will be investigating other LAI antipsychotic formulations with dosing intervals that extend beyond 28 days. The partial AUC (pAUC) calculation was reported to be a method of analysis in addition to the standardized method of determining a drug's LAI AUC [33]. The pAUC can be measured around the time of absorption and is supplemented by existing information. It does have some limitations, such as the need for appropriate sampling to accurately characterize early drug exposure. Further research with LAI drug-delivery technology will aim to optimize the pharmacokinetics of these drugs, resulting in improved dosing regimens.

However, pharmacokinetic and bioequivalence studies that compare drug administration in the deltoid versus the gluteal sites may not reflect what happens in the clinical environment. A case report described a significant drop in plasma risperidone concentration when a patient was switched from deltoid to gluteal injection. The concentration declined from 16 to 5 ng/ml, and the patient ultimately had to be switched to another antipsychotic [34]. Another case report described a patient who was stabilized on 1MPP 150 mg every 28 days for 14 months, with each injection given in the gluteal muscle [35]. After breakthrough symptoms occurred, the patient was switched to 150 mg every 3 weeks in the deltoid muscle for the next 9 months without any problems. Unfortunately, plasma paliperidone concentrations were not obtained before the next injection, so whether any shifts in drug exposure occurred was unclear. Both cases illustrate the potential impact that injection site may have on patient response to LAI antipsychotic agents. Indeed, differences in the MBF between the deltoid and gluteal muscles can lead to potential altered therapeutic responses and patient outcomes. The injection sites for LAI antipsychotics may be bioequivalent from a regulatory perspective but may not be therapeutically equivalent. As such, clinicians should be aware of any changes in the drug's administration site and diligently document such changes in the patient's chart [36].

3.3 General Pharmacodynamic Principles

The pharmacodynamic actions of LAI antipsychotics are similar to those produced by their corresponding oral preparations once the medication enters the systemic

circulation from the injection site. The reader is referred elsewhere for an in-depth discussion on this topic [20]. Only updated information applying to LAI agents is presented in this section. The clinical relationship between pharmacokinetics and pharmacodynamics can be traced to a drug's dose, systemic exposure, and binding properties to receptors located in the central nervous system (CNS) and peripheral nervous system (PNS). Using clinical trial data, open-label studies, and case reports, various therapeutic plasma concentration ranges have been recommended by the Arbeitsgemeinschaft für Neuropsychopharmakologie and Pharmakopsychiatris (AGNP) in their 2011 consensus guidelines [37]. The 'therapeutic' reference range for the antipsychotic agents are as follows: aripiprazole 150–500 ng/ml, iloperidone 5–10 ng/ml, olanzapine 20–80 ng/ml, paliperidone 20–60 ng/ml, and risperidone (plus 9-hydroxyrisperidone) 20–60 ng/ml. These ranges are also mentioned by the American Society of Clinical Psychopharmacology [38]. Although these recommended ranges are used by various investigators and clinicians, these guidelines are not accepted universally and are not included in various antipsychotic policy statements by professional organizations. Serum drug concentration detection generally reflect at least partial or full compliance with medications. Regarding the LAI antipsychotics, it was interesting to note that about 10% of patients ($N = 41$) treated with risperidone microspheres had no detectable serum drug concentrations after injections. Some explanations for this finding could be the sampling time and other factors that could affect drug clearance [39].

Like their oral antipsychotic formulations, the pharmacokinetic/pharmacodynamic (PK/PD) effects of LAI antipsychotics are primarily linked to their interaction with dopamine type 2 (D_2) receptors, which results in the drug's antipsychotic drug efficacy and EPS. Evidence for the role of D_2 receptors in antipsychotic drug activity are supported by data from positron emission tomography (PET), and preclinical animal and human studies [40, 41]. Improvement in psychotic symptoms occurs when striatal D_2 receptor blockade is at least 65% [20]. A meta-analysis of eight different atypical antipsychotics showed that the drugs followed a sigmoidal maximum possible effect (E_{max}) curve with regard to receptor blockade, and all displayed a similar relationship that matched their recommended daily doses. Collectively, D_2 receptor blockade was between 65 and 80% [42]. Clinical improvement with aripiprazole as indicated by decreasing Positive and Negative Syndrome Scale (PANSS) scale scores, was associated with serum drug concentrations of at least 150 ng/ml. Aripiprazole doses in this study were 10–30 mg/day and produced receptor occupancy between 65 and 80%. Two patients with plasma concentrations of 442 and 663 ng/ml, respectively, with D_2 receptor occupancy > 90%, experienced EPS [43].

PET studies can be further expanded to examine clinical response beyond improvement in psychotic symptoms. A single-dose aripiprazole study, using PET scans for striatal D_2 receptor occupancy, was conducted in 15 healthy volunteers, each of whom received doses of between 2 and 30 mg [44]. Working memory was evaluated with a variety of cognitive assessments. Results indicated that memory impairment occurred with D_2 receptor blockade of about 73%, suggesting that clinicians need to balance the benefits of psychotic symptom relief with possible cognitive impairment. As LAI agents are used for long-term therapy, stabilization of the positive symptoms along with improvement in the negative symptoms, and minimal cognitive symptoms represent the key goals of antipsychotic pharmacotherapy.

4 Paliperidone Palmitate

Paliperidone palmitate is available as 1MPPand 3MPP preparations, with the 3MPP formulation employing a NanoCrystal® technology that uses an increased particle size [11]. Patients placed on 3MPP must be stabilized for at least 4 months on the 1MPP formulation beforehand. The efficacy and safety of 1MPP has been established in patients with schizophrenia who experience acute exacerbations and in patients requiring maintenance treatment [45, 46]. The pharmacokinetics of 3MPP were characterized in a single-dose study in which patients received doses ranging from 75 to 525 mg (819 mg) [30]. The 3MPP T_{max} ranged from 24 to 34 days and from 23 to 31 days when given in the deltoid and gluteal muscles, respectively. Dose proportionality was observed with AUC_{∞}. For example, the median AUC_{∞} for the 75- and 150-mg doses were 22,214 ng × h/ml (range 10,671–34,683) and 42,963 ng × h/ml (range 26,283–49,399), respectively. The elimination half-life for both injection sites ranged from 45 to 82 days. As previously described in Sect. 3.1, the pharmacokinetic model for the conversion factor of 3.5 when switching from 1MPP to 3MPP was determined from simulation studies, as the 3MPP model was described by a one-compartment model with first-order elimination and two saturable absorption compartments [47].

In a randomized multicenter clinical trial, 506 patients with schizophrenia received 3MPP in four phases: (1) screening, (2) 1MPP treatment for 17 weeks, (3) 3MPP single-dose administration, and (4) double-blind randomization of drug-versus-placebo (1:1) [48]. A dosing conversion factor of 3.5 was used when switching patients from 1MPP to 3MPP based on 1MPP and 3MPP pharmacokinetic profiles (Table 2). The primary efficacy outcome

Table 2 Summary of long-acting injectable aripiprazole clinical trials[a]

Agent	Comparator	N	Study duration	Time to relapse	Comments	Reference
AOM	Placebo	340	12 weeks	NA	Efficacy in acute exacerbation with ↓ total PANSS score	[52]
AL	Placebo	623	12 weeks	NA	Efficacy in acute exacerbation with ↓ total PANSS score; severely ill patients (PANSS > 92) analyzed	[62]
AOM	Placebo	403	52 weeks	Longer for LAI HR 4.72	↑ total mean PANSS for placebo ($p < 0.001$)	[54]
AOM	AOM 50 mg Oral ARI 10–30 mg/day	662	26 weeks	AOM = oral > AOM 50 mg; HR 0.64	All ARI had similar AEs	[55]
AOM	Oral ARI 6–24 mg/day	445	52 weeks	Non-relapse rate difference was 0.3%	Asian patients with AEs not different between groups	[56]
AOM	Placebo	266	52 weeks	Recurrence of any mood episode longer with AOM, HR 0.45	Bipolar I patients stabilized on AOM then randomized 1:1	[59]

[a]Only aripiprazole LAI studies were included in Table 2 due to their recent publications in drug development

AE adverse events, *AL* aripiprazole lauroxil, *AOM* aripiprazole monohydrate 400 mg, *ARI* aripiprazole, *HR* hazard ratio, *LAI* long-acting injection, *NA* not applicable, *PANSS* Positive and Negative Syndrome Scale

was time from randomization to first relapse. Secondary endpoints included changes in total PANSS scores, 5-factor scores, and subscale, Clinical Global Impression Scale (CGIS), and Personal and Social Performance (PSP) scores. The interim analysis revealed a significant difference in efficacy in favor of the 3MPP treatment group (hazard ratio [HR] 3.45 [95% CI 1.73–6.88]; $p < 0.001$). The median time to relapse for the placebo group was 274 days, whereas the time to relapse for the 3MPP group could not be determined as the actual number of patients that relapsed was 31 (23%) for the placebo group and 11 (7%) with the 3MPP group. As a secondary measure, the mean (± SD) PANSS score from randomization to study endpoint was significantly different between the placebo and 3MPP groups: 6.7 ± 14.40 versus -0.5 ± 8.36 ($p < 0.001$), respectively. Significant differences were also found in the CGIS and PSP scores between the two groups ($p < 0.001$). Safety data revealed that headache, weight gain, and nasopharyngitis occurred more commonly in the 3MPP group than in the placebo group; however, the incidence of these side effects was similar between 3MPP and 1MPP [21]. The incidence of EPS-related adverse effects (AEs) and akathisia was slightly greater for the 3MPP group than for the placebo group (8 vs. 3 and 4 vs. 1%, respectively) and was comparable to the incidence of these side effects in the 1MPP study [21]. The median plasma paliperidone concentrations from the pharmacokinetic assessment from all plasma drug concentrations were within the AGNP's recommended therapeutic range of 20–60 ng/ml except for concentrations in the lowest dose group ($N = 6$; 10–20 ng/ml) [37]. Therefore, the paliperidone 3MPP dose of 273 mg may be reserved for those few patients who respond to this low amount of drug.

A non-inferiority clinical trial was conducted with 3MPP versus 1MPP for a 48-week double-blind study in patients with schizophrenia [49]. Patients ($N = 1106$) were randomized to receive either MPP formulation. Those assigned to the 3MPP group also received a placebo injection of 20% Intralipid at monthly intervals between active drug administration. The primary efficacy endpoint was the percentage of patients who remained relapse free. Secondary endpoints included change in PANSS score from baseline to endpoint, PANSS subscales, CGIS scores, Marder factor scores, and PSP scores. Significant differences in relapse rates between the 3MPP and the 1MPP groups were not found (8 vs. 9%, respectively; $p > 0.05$). Further, there were no significant differences in secondary endpoints between the two products (e.g. PANSS score ≥30% improvement: – 36.4% 3MPP vs. 36.1% 1MPP). No new safety signals were discovered. Only the lowest doses for each group (50 mg for 1MPP [$N = 16$] and 175 mg for 3MPP [$N = 13$]) had median plasma drug concentrations < 20 ng/ml. These results confirm that 3MPP is non-inferior to 1MPP.

A "real-world" setting study was conducted in patients with schizophrenia ($N = 1545$) to examine the adherence rate upon conversion from 1MPP to the 3MPP formulation [50]. The study reported that 88% of the patients kept their clinic outpatient appointment for their second 3MPP injection and 90% received their third 3MPP administration. The two most common 3MPP dosages used were 546 mg (33%) and 819 mg (53%). A decreased frequency

of emergency room and inpatient visits with 3MPP usage was noted compared with the 1MPP dose, suggesting that patient adherence to the longer administration interval provided acceptable clinical outcomes.

5 Aripiprazole

Oral aripiprazole, which was approved for the treatment of schizophrenia in 2002, has a target dose of 10–15 mg/day with an overall effective dose up to 30 mg/day [20]. The LAI aripiprazole monohydrate was approved by the US FDA for the treatment of bipolar I disorder. The aripiprazole median minimum plasma concentration at steady state was reported to be 94 ng/ml with an oral dose of 10 mg/day [12]. A database search of aripiprazole studies that included plasma concentrations and therapeutic drug monitoring suggested a target plasma concentration range of 150–210 ng/ml [43]. The latest 2011 AGNP guidelines recommend target aripiprazole plasma concentrations of 150–500 ng/ml [37]. Currently, two LAI aripiprazole formulations are available to treat patients with schizophrenia; they are dosed to achieve a minimally effective concentration and target a concentration range [12].

5.1 Aripiprazole Monohydrate (AOM)

The pharmacokinetics and tolerability of aripiprazole monohydrate (AOM) was reported in an open-label, parallel-arm, multiple-dose study in patients with schizophrenia ($N = 41$) who were randomly assigned to receive 200, 300, or 400 mg each month [51]. After the 5th monthly injection, the mean (± SD) plasma aripiprazole concentrations ($C_{ss,min}$) for the 200-, 300-, and 400-mg doses were 95 ng/ml (86.2), 156 ng/ml (67.7), and 212 ng/ml (113), respectively. The C_{max} typically occurred 1 week post-injection with mean (± SD) plasma aripiprazole concentrations for the 200, 300, and 400 mg doses reported as 100 ng/ml (68.4), 269 ng/ml (128), and 316 ng/ml (160), respectively. The most common AEs for the 400 mg aripiprazole dose were vomiting (14.3%), injection site pain (28.6%), and tremors (21.4%), none of which were deemed to be clinically significant. The incidence of AEs for the two lower doses observed only vomiting (13.3%) without any reports of injection site pain and tremors. Laboratory results were within normal limits except for one patient who experienced elevated prolactin concentrations, which were not felt to be related to the study drug. Based upon these findings, the AOM 300 and 400 mg monthly doses were selected for use in clinical trials. Of note, simulations with the AOM 400-mg dose suggested that this formulation would yield mean plasma aripiprazole concentrations comparable to those achieved with oral aripiprazole doses between 10 and 30 mg/day [12].

A summary of LAI ARI clinical trials is presented in Table 2. A 12-week phase III clinical trial of AOM 400 mg was conducted in patients with schizophrenia ($N = 340$) experiencing acute exacerbations [52]. After screening, each patient received oral aripiprazole 10 mg/day for 3 days (tolerability test) before a 7-day washout period. Patients were then randomized 1:1 to receive AOM 400 mg or placebo. For the group receiving AOM 400 mg, patients received oral aripiprazole 10–20 mg/day for the first 14 days after the initial injection. The placebo-treated patients received oral placebo for 14 days along with the first placebo injection. The study design allowed for the AOM 400-mg dose to be reduced to 300 mg one time for tolerability. A single-dose increase back to 400 mg was allowed if needed for symptomatic treatment. The primary efficacy outcome was change in total PANSS score from baseline to week 10. The secondary outcomes were $\geq 30\%$ reduction in total PANSS scores and changes in CGIS and PSP scores. Safety assessments included laboratory and treatment-emergent AEs (including EPS). The LS mean (LSM) change in total PANSS scores and CGIS scores from baseline to week 10 was significantly greater in the AOM 400-mg group than in the placebo group: PANSS -15.1; 95% CI -19.4 to -10.8 ($p < 0.0001$) and CGIS -0.8; 95% CI -1.1 to -0.6 ($p < 0.0001$), respectively. Secondary outcomes also showed a greater improvement in the AOM 400-mg group versus the placebo group, with $\geq 30\%$ reduction in total PANSS scores (37 vs. 14.4%; $p < 0.0001$) and PSP LSM (± standard error [SE]) scores (12.3 ± 1.2 vs. 5.2 ± 1.2; $p < 0.0001$). The most commonly reported AEs for AOM 400 mg were weight gain (16.8%), headache (14.4%), and akathisia (11.4%); however, no patients were discontinued from the study due to AEs. The main AE in the placebo group was headache (16.3%). The mean (± SD) weight increases in the AOM and placebo groups were 3.5 (5.8) kg and 0.8 (4.3) kg ($p < 0.0018$), respectively. No laboratory differences were found between the two groups. Mean (± SD) prolactin concentrations were significantly lower in the AOM 400-mg group than in the placebo group (-6.4 ± 13.5 vs. -1.1 ± 14.5; $p < 0.0176$, respectively).

A post hoc analysis was conducted from the previous study by Ismail et al. [53] study, which focused on the heterogeneous nature of schizophrenia as captured by the spectrum of the PANSS scale grouped into five areas: positive and negative symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety and depression (5-factor model known as Marder factors). The PANSS Excited Component subscale (PEC) was also developed and validated. Analysis of the 5-factor Marder factors and PEC scores from baseline to 12 weeks showed

significant improvement for AOM 400 mg. The mean percentage improvements noted for the AOM 400-mg group with the Marder factors were 25.5% (positive symptoms), 13.8% (negative symptoms), 9.3% (uncontrolled hostility/excitement), and 23.3% (anxiety/depression). PEC score improvement was 14.1%. The placebo group experienced no improvement in hostility/excitement (10.5% worsening) and PEC (2.3% worsening), with slight improvements in positive (13.2%) and negative (5.3%) symptoms. The subanalysis showed that AOM 400 mg was effective in treating the symptoms of acute exacerbation of schizophrenia and that placebo produced only minimal improvement.

Patients with schizophrenia (N = 403) stabilized on oral aripiprazole 10–30 mg/day were enrolled into a 52-week study [54]. After enrollment, study subjects received an initial AOM dose of 400 mg then continued on oral aripiprazole 10–20 mg/day for 2 weeks. Patients were then randomized to continue AOM or placebo (2:1 ratio). Patients were allowed to undergo a single reduction in dose from 400 to 300 mg based upon tolerability; the dose could then be increased back to 400 mg if needed for symptomatic control. The primary outcome was time to exacerbation of psychotic symptoms or impending relapse. Relapse rates were significantly lower in the AOM group (HR 5.03; 95% CI 3.15–8.02) versus placebo. The reasons for relapses in patients receiving AOM (N = 27/269 [10%]) were PANSS/CGIS scores that increased (20/27), hospitalization (7/27), and suicide risk and violent behavior (each 1/27). The number of relapses reported for the placebo group was 53/134 (39.6%), but reasons for these relapses were not reported. The most commonly reported AOM-related AEs were insomnia (10%), tremor (5.9%), and headache (5.9%). Results from this study showed that AOM significantly delayed the time to impending relapse compared with placebo and was well-tolerated.

A non-inferiority clinical trial with AOM (400 mg) compared it with oral aripiprazole 10–30 mg/day and a low dose of AOM 50 mg (dose below the therapeutic threshold for assay sensitivity) with a randomization ratio of 2:2:1 [55]. Kaplan–Meier curves were used to characterize the primary outcome (impending relapse rate) at week 26 of treatment. Secondary outcomes included analysis of PANSS and CGIS scores from baseline to week 26. Relapse was defined as CGIS score $\geq$ 5, increase of any specific four PANSS items $\geq$ 4 (e.g., hallucination), CGI-SS score of 4 or 5, hospital admission, or violent behavior. The study design allowed for the aripiprazole dose to be reduced one time in the following manner if necessary to improve tolerability: AOM 400 mg to 300 mg, AOM 50 mg to 25 mg, and oral aripiprazole 10–30 mg/day but not below 10 mg/day. Doses could be increased once for symptom control and could not exceed 30 mg/day for the oral aripiprazole group. Oral aripiprazole was continued for 14 days after the initial dose of AOM 400 or 50 mg. At week 26, the following relapse rates were reported for these groups: AOM 400 mg (7.12%), oral aripiprazole (7.76%), and AOM 50 mg (21.80%). The relapse rate in the AOM 50-mg group was significantly higher than in the AOM 400-mg group and oral aripiprazole groups ($P < 0.005$ for both comparisons). Conversely, there was no difference in the relapse rate between ARI 400 mg and the oral aripiprazole groups ($p = 0.79$). Mean ($\pm$ SE) total PANSS score changes from baseline to week 26 for the AOM 400 mg and oral aripiprazole groups were -1.66 (0.72) and 0.58 (0.71), indicating a slight improvement with AOM 400 mg and minimal change with oral aripiprazole. However, the AOM 50-mg group reported an increase of 3.08 (1.01) in mean total PANSS scores. A similar finding occurred with the CGIS scores for the AOM 400-mg and oral aripiprazole groups. A significant increase in mean ($\pm$ SD) CGIS scores was reported for the AOM 50-mg group (3.08 $\pm$ 1.02 vs. 4.02 $\pm$ 1.32; $p < 0.001$). The most commonly reported AEs and their frequencies were similar for all three groups. Injection site pain was higher for AOM 400 mg (7.5%) than for placebo injection with oral aripiprazole (2.3%) and AOM 50-mg injection (0.8%). The study concluded that AOM 400 mg was non-inferior to oral aripiprazole and both regimens were significantly superior to AOM 50 mg in terms of relapse rate.

Another non-inferiority clinical trial in four Asian countries evaluated AOM 400 mg versus oral aripiprazole 6–24 mg/day in stabilized patients with schizophrenia [56]. Although the study duration was set at 52 weeks, primary efficacy and safety endpoints were reported at week 26. The study design and definition for stabilized patients were similar to the two previous clinical trials discussed above [54, 55]. The oral aripiprazole dose was slightly lower in this study than in the study by Fleischhacker et al. [55], but only 12% of the study patients were receiving 6 mg/day as their final dose during the oral stabilization phase. The AOM 400-mg dosing scheme was also similar in that patients were able to undergo a single decrease to 300 mg with an increase back to 400 mg if needed. The dosing scheme for the oral aripiprazole group allowed patients to have their dose lowered by 6 mg one time (but not $<$ 6 mg/day) and increased back by 6 mg if needed. Placebo injections and oral placebo tablets were also employed during the study. The primary efficacy endpoint was the non-exacerbation of psychotic symptoms/non-relapse rate at week 26 using these four criteria: (1) CGIS score $\geq$ 5, (2) hospitalization, (3) Clinical Global Impression-Severity of Suicidality (CGIS-SS) score of 4 or 5, or (4) violent behavior. Secondary endpoints included total PANSS scores and CGIS scores with safety and tolerability assessments. At week 26, the mean ($\pm$ SE) non-

exacerbation/non-relapse rate was nearly identical between the two study groups (95.0 ± 1.5 vs. 94.7 ± 1.6%). The proportion of patients who relapsed at week 52 was identical (6.6%) for both treatment groups. The difference in PANSS and CGIS scores was the same (0.4 points) between both treatment groups from baseline to week 26. Similarly, there were no significant differences in AEs between the AOM 400-mg and oral aripiprazole groups (e.g., insomnia rate 7.5 vs. 8.8%, respectively). The incidence of injection-site pain was higher with AOM 400 mg than with oral aripiprazole (28.1 vs. 18.9%). This study also confirmed the non-inferiority of AOM 400 mg to oral aripiprazole with regard to efficacy and tolerability.

A meta-analysis of the clinical trials comparing AOM 400 mg and oral aripiprazole was recently conducted [57]. The analysis concluded that AOM was superior to placebo in decreasing total PANSS scores (standardized mean difference [SMD]) by −0.65 (95% CI −0.90 to −0.41; $n = 1126$) but did not significantly differ from oral aripiprazole (SMD −0.08; 95% CI −0.31–0.14). The AOM group had a lower incidence of all-cause discontinuation than oral aripiprazole, with a risk ratio (RR) of 0.78 (95% CI 0.64–0.95; $n = 986$). However, significant differences were not found in lack of efficacy, adverse events, death, or EPS. To this end, the meta-analysis showed that AOM was equally effective to oral aripiprazole with a low risk of discontinuation due to AEs.

An extension study with AOM 400 mg was available for patients ($N = 88$) who completed the initial study [58]. Patients were given the opportunity to enroll for six additional once-monthly injections with additional safety assessments, and health-related quality-of-life scale (QLS) and CGIS evaluations. QLS scores showed sustained improvement during the study and CGIS scores were maintained. Safety assessments did not reveal any additional AEs beyond those detected in the primary clinical trial. There was a reported incidence of increased weight (7/88 patients) and headache (3/88 patients). AOM 400 mg showed continued benefit in QLS assessments, as symptoms of schizophrenia stabilized.

AOM 400 mg was evaluated in a clinical trial in patients with bipolar I (BPI) in a 52-week maintenance treatment study [59]. Patients with BPI (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision [DSM-IV-TR]) were treated with oral aripiprazole 15–30 mg/day for 2–8 weeks then given AOM 400 mg for 12–28 weeks. Subjects were then randomized 1:1 to AOM 400 mg or placebo for the next 52 weeks. The primary endpoint was time for recurrence of any mood episode using the following criteria: (1) hospitalization, (2) Young Mania Rating Scale (YMRS) score ≥ 15, (3) Montgomery–Asberg Depression Scale (MDRS) score ≥ 15, (4) CGIS-BP > 4, or (5) addition of mood stabilizer, antidepressant, or antipsychotic drugs. The secondary endpoint was the proportion of patients meeting criteria for recurrence of any mood episode. Compared with placebo, subjects receiving AOM 400 mg experienced a significantly longer time before recurrence of any mood episode (HR 0.45; 95% CI 0.30–0.68). Further, the proportion of patients with recurrence of any mood episode was significantly lower with AOM than with placebo (35/132 [26.5%] vs. 68/133 [51.1%]; $p < 0.001$). When assessing the recurrence by mood type, AOM was significantly better at preventing recurrence of manic episodes than placebo (12/132 vs. 40/133; $p < 0.001$) but not for the depressive or mixed episodes. The AE profiles were similar between treatments except for the incidence of akathisia, which was higher with AOM (21.2 vs. 12.8%). However, the mean (± SD) scores for the Barnes Akathisia Rating Scale (BARS) were not significantly different between the groups (AOM 0.05 ± 0.91 vs. placebo −0.05 ± 0.58), indicating that akathisia in the AOM group was mild. Incidence of pain at the injection site was not reported but was noted as being generally low, and it diminished with continued injections. The FDA granted approval of AOM 400 mg for use in patients with BPI in 2017.

5.2 Aripiprazole Lauroxil

The aripiprazole lauroxil (AL) and AOM formulations differ, as AL utilizes a pro-drug method for drug delivery into systemic circulation. A population pharmacokinetic study was conducted using data from oral and AL LAI clinical studies in 616 patients with schizophrenia. In all, 21,620 plasma concentrations from phase I and II studies were included [60]. AL doses of 441, 662, and 882 mg given every 4 weeks corresponded to oral daily aripiprazole doses of 10, 20, and 30 mg, respectively. An additional dosing scheme of 882 mg every 6 weeks was explored to assess the impact of a dosing delay, as might be expected in a "real-world" scenario. Median $C_{min,ss}$ values for aripiprazole when the drug was administered every 4 weeks were 112, 166, and 219 ng/ml for doses of 441, 662, and 882 mg, respectively. The median $C_{min,ss}$ for the 882-mg dose given every 6 weeks was 128 ng/ml. These findings show that the AL doses of 662 and 882 mg achieve the minimal therapeutic aripiprazole plasma concentration of 150 ng/ml. Although the 441-mg dose can be used, clinicians should carefully monitor patients because of the wide interpatient aripiprazole variability in plasma concentrations. Whereas some patients had plasma aripiprazole concentrations > 150 ng/ml, most patients had plasma aripiprazole concentrations below the minimal recommended threshold [37, 43]. Pharmacokinetic simulations predicted that plasma concentrations will return to therapeutic levels when the time between doses does not

exceed 8 weeks for the doses of 662 or 882 mg, or 6 weeks for the 441-mg dose.

A new AL 2-month formulation was recently investigated in a phase I study in patients with schizophrenia ($N = 104$) using AL 1064 mg given every 8 weeks over the course of 24 weeks [61]. A population pharmacokinetic analysis was conducted using previous AL pharmacokinetic data and the data collected from this study. After screening, patients were randomly assigned to 441 mg every 4 weeks ($N = 35$), 882 mg every 6 weeks ($N = 34$), or 1064 mg every 8 weeks ($N = 35$) without oral aripiprazole. Plasma samples were collected (maximum 48 samples per patient) over the next 309 days. Pharmacokinetic parameter values were calculated using non-compartmental analysis. The mean (% CV) $C_{avg,ss}$ for 441, 882, and 1064 mg were 126 ng/ml (63.3), 131 ng/ml (47.4), and 141 ng/ml (40.7), respectively. The aripiprazole T_{max} ranged from 24.4 to 35.2 days and the elimination half-life ($t_{½}$) ranged from 53.9 to 57.2 days. The population pharmacokinetic model simulated median aripiprazole concentrations with the 21-day oral aripiprazole dosing with the three dose groups that showed the 1064 mg group was comparable to the other approved AL dosing schemes. The population pharmacokinetic model characterized the aripiprazole uptake from the AL 2-month preparation as having a 3.2-day lag time with a 43-day absorption duration, and a total duration of drug input into the systemic circulation of 46 days. The 2-month formulation adequately maintained the recommended therapeutic plasma aripiprazole concentration range [37].

A phase III clinical trial with AL was conducted in patients with schizophrenia ($N = 623$) who had an acute exacerbation of symptoms at baseline and exhibited a mean (± S) total PANSS score > 92 and a CGIS score > 4.0 [62]. Patients were randomized 1:1:1 into three groups: AL 441 mg (aripiprazole 300 mg equivalent), AL 882 mg (aripiprazole 600 mg equivalent), and placebo (Intralipid®, fat emulsion). Each dose was injected into the gluteal muscle every 4 weeks for the duration of the 12-week study. Oral aripiprazole 15 mg was given for 21 days to the AL groups, and matching oral placebo tablets were given to the placebo group. Patients receiving both AL doses (441 and 882 mg) experienced a significant and clinically meaningful improvement from baseline to the end of the study. Mean total PANSS score decrease by − 10.9 (1.8; $p < 0.001$) and − 11.9 (1.8; $p < 0.001$), respectively. Patients in both AL dosing groups also reported CGIS ratings that were "very much" or "much improved" compared with placebo group ratings ($p < 0.05$). Significant improvement was noted in subjects receiving AL by day 8 after the first injection, with patients continuing to improve throughout the study. Safety assessments reported that only akathisia occurred in > 5% of all subjects receiving AL. This was approximately twice the rate of akathisia observed in the placebo group. Most reports of akathisia occurred within 3 weeks following the first dose of study drug and none were reported after 1 month. The other most commonly reported AEs were insomnia, headache, and anxiety. AL injection site pain was slightly greater with 882 mg than with 441 mg (4.8 vs. 3.4%, respectively) and higher than with placebo (1.9%). Otherwise, AL was shown to be efficacious in patients with schizophrenia with acute episodes of symptoms.

A subanalysis of the patients with schizophrenia ($N = 309$) who were considered severely ill (total PANSS score > 92) was conducted to determine AL efficacy and safety [63]. Again, clinical and statistical improvement ($p < 0.001$) was found when comparing AL 441 mg and 882 mg versus placebo, noted by decreases in mean total PANSS scores of − 14.7 and − 16.6, respectively. The overall responder rates with the total PANSS score (defined as ≥ 30% decrease) for the 441-mg and 882-mg dosing groups were 49% and 61%, respectively ($p < 0.001$ for both comparisons). Response in the placebo group was non-significant at 18% ($p > 0.05$). The safety profile was similar except that the injection site pain did not differ between groups. Another subanalysis of the endocrine and metabolic profiles of AL 441 and 882 mg was conducted [64]. Mean prolactin concentrations decreased during AL use, whereas no changes occurred in the placebo group. Lipid, glucose, and glycated hemoglobin assessments for the AL groups were comparable to those for the placebo group. A body weight increase (≥ 7%) was considered an AE and was reported in 2.9% of AL 441 mg recipients, 2.4% of AL 882 recipients, and 0.5% of placebo recipients. Overall, AL was associated with a low risk of changes in metabolic parameters, which were similar to placebo over the 12-week study. The conversion from oral aripiprazole 10 mg, 15 mg, and ≥ 20 mg/day to monthly AL was recommended to be 441, 662 and 882 mg, respectively, following an overlap of 21 days of oral administration [65].

6 Post-Injection Delirium/Sedation Syndrome with Olanzapine Pamoate Update

Olanzapine pamoate (OLZP) was approved by the EU in 2008 and the FDA in 2009 for the treatment of schizophrenia [66]. PDSS was observed in patients in 2008 during the clinical development of the product. Since its regulatory approvals, PDSS was noted in about 0.07% of injections or in approximately 1.4% of patients treated with OLZP [66]. As a result, the regulatory agencies imposed a 3-h supervision period for patients to remain at the treatment facility. New Zealand and Australia request a 2-h period [66]. Symptoms of PDSS include heavy sedation

(possibly including coma), delirium, ataxia, confusion, or other alterations in consciousness. As previously documented, olanzapine monohydrate is an insoluble salt but, when exposed to blood, the change in pH causes rapid dissolution of olanzapine monohydrate to yield olanzapine and pamoic acid; this results in a sharp elevation in plasma olanzapine concentrations [7]. A case report noted a plasma olanzapine concentration > 160 ng/ml (therapeutic range 20–80 ng/ml) 6 h after an injection of LAI OLZP 300 mg [67]. An analysis of PDSS cases (N = 388) revealed that, in 91% of the cases, symptoms occurred ≤ 1 h, 7% at 1–2 h, and only two cases at 2–3 h post-injection [68]. The analysis was broken down further to assess the incidence of symptoms during the first h after injection: 52% of symptoms occurred within 0–15 min, 27% within 16–30 min, and 20% within 31–60 min. Most PDSS occurrences took place in patients who had received one to nine injections (73%). PDSS occurred less frequently in patients who received 10–20 injections (13%), and ≥ 21 injections (13%). Some patients required medications (31%), intravenous fluids (25%), and intensive care unit admission (18%) to treat PDSS. Only a small number of patients (19%) did not require treatment.

A post hoc analysis was conducted by the EU to assess patient satisfaction with the 3-h post-injection observation period, and the OLZP dosing regimen. The analysis was performed before and after implementation of the post-injection monitoring requirement. The study was conducted in open-label fashion over a 6-year period [69]. Patient preference for either oral or LAI therapy was assessed. Patients (N = 966) remained clinically stable as total PANSS scores remained unchanged (2–3 points) during the study. Also, Investigator's Assessment Questionnaire (IAQ) scores and other quality-of-life measures remained stable. This study concluded that the 3-h observance time did not significantly impact patient satisfaction with continued long-term treatment. Subsequently, an additional post hoc analysis (N = 669) was conducted that showed CGIS scores remained stable for patients up to 6 years on OLZP [70]. Safety assessments revealed that weight gain ≥ 7% occurred in 41% of subjects, with a mean increase of 2.19 kg. Other AEs were unremarkable. PDSS occurred in 24 patients (3.6%), but no fatalities were observed, and patients recovered within 72 h. Interestingly, 19 of 24 patients (82.6%) continued with OLZP treatment. Clinicians should carefully examine and document the balance between benefits and risks associated PDSS and OLZP usage for each individual patient.

7 Comparison Between LAI Agents

7.1 Comparison Between First- and Second-Generation Agents

The ACCLAIMS study was a multi-site, parallel-group, double-blind, randomized clinical trial (National Institute of Mental Health [NIMH] sponsored) that evaluated haloperidol decanoate (HLD) versus paliperidone palmitate 1MPP [71]. Patients with schizophrenia or schizoaffective disorders (N = 311) were randomly assigned to monthly HLD 25–200 mg or 1MPP 39–234 mg. Dosages were adjusted to the clinical situation, allowing for oral antipsychotic supplementation as needed for 24 months. The primary outcome was efficacy failure as determined by an outcome panel committee of three research psychiatrists who were blinded to the treatment groups. The criteria for efficacy failure included psychiatric hospitalization, crisis stabilization, increased frequency of outpatient visits, repeated need for oral supplementation, and HLD or 1MPP discontinuation due to inadequate benefit as determined by the patients' clinician. Secondary outcomes included safety and laboratory assessments. The study results showed that HLD and 1MPP were not statistically different in their rates of efficacy failure (HR 0.98; 95% CI 0.65–1.47) with the actual percentages of failures reported as 32.4% for HLD and 33.8% for 1MPP. The most common reason for efficacy failure (as judged by the panel) was hospitalization, which was 90% for 1MPP and 72% for HLD. The mean monthly doses for HLD and 1MPP ranged from 67 to 83 mg and from 129 to 169 mg, respectively. With regard to secondary outcomes, overall mean weight change for 1MPP and HLD was 2.17 kg (95% CI 1.25–3.09) and -0.96 (95% CI −1.88 to −0.04), respectively. Only seven 1MPP-treated patients and one HLD-treated patient discontinued treatment due to weight gain. Significant differences in laboratory and Abnormal Involuntary Movement Scale (AIMS) assessments between HLD and 1MPP were not found. However, the incidence of akathisia was significantly higher with HLD than with 1MPP (10.6 vs. 2.8%; p = 0.006). Conversely, serum prolactin concentrations were significantly higher with 1MPP than with HLD in both men and women ($p < 0.001$); however, there were no significant differences in sexual dysfunction or galactorrhea. In conclusion, clinical efficacy between 1MPP and HLD did not differ, and AEs observed with both agents were not unexpected.

7.2 Comparison Between Second-Generation Agents

Monthly AOM 400 mg and 1MPP were compared in an industry-sponsored non-inferiority, open-label, rater-blinded, head-to-head study conducted in patients with schizophrenia ($N = 295$) for 28 weeks [72]. Subjects in the AOM group received AOM 400 mg, allowing for a dose reduction to 300 mg as an option for tolerability issues. The 1MPP dose ranged from 78 to 234 mg. Patients were placed on oral conversion, LAI initiation for 5 weeks, and then once-monthly LAI continuation for five subsequent injections. The primary efficacy instruments utilized were the Heinrichs-Carpenter Quality of Life (QLS), CGIS, and the IAQ. Both the QLS and the IAQ are validated assessment tools. Patient data were further analyzed by age (≤ 35 and > 35 years). The mean ($\pm$ SE) dose at week 24 for AOM 400 mg was 387 ± 3.4 mg and for 1MPP was 110 ± 3.6, which was equivalent to the US dose of 172 mg. Significant differences were found for AOM 400 mg in QLS, CGIS, and IAQ scores at week 24 ($p < 0.05$). For patients aged ≤ 35 years, a significant difference in the IAQ was found between AOM 400 mg and 1MPP, favoring AOM 400 mg (LSM -2.65; 95% CI -5.28 to -0.02; $p = 0.048$). However, this difference was not observed for patients aged > 35 years (LSM -1.02; 95% CI -2.77–0.73; $p = 0.25$). A similar effect was observed for the QLS and CGIS assessments in patients aged ≤ 35 years. In the QLS domains, the one symptom cluster that was found to be significantly different was the intrapsychic foundations, which favored AOM 400 mg (LSM 1.75; 95% CI 0.09–3.41; $p < 0.039$). No new safety signals were detected in either treatment group. For example, weight gain ≥ 7 was 11.1% for AOM 400 mg and 14.6% for 1MPP with psychotic disorder and insomnia AEs slightly greater with 1MPP than with AOM ($N = 3$/119 and $N = 6$/109, respectively).

8 Switching Studies

A switch from oral antipsychotic therapy to LAI 1MPP was conducted in a post hoc single-arm, multicenter, open-label, 6-month clinical trial in patients with schizophrenia [73]. Patients were required to be "stable" but symptomatic on oral antipsychotic therapy with a total PANSS score ≥ 70 or ≥ 2 items with a score ≥ 4 in the PANSS positive or negative symptoms or ≥ 3 items ≥ 4 in the PANSS general psychopathology. Patients ($N = 472$) were directly switched to 1MPP without oral supplementation based on the approved dosing scheme, which was 150 mg (or 234 mg equivalent USA) on day 1, 100 mg (or 156 mg equivalent USA) on day 8 ($\pm$ 2 days) and then monthly doses ($\pm$ 7 days) between 50 and 150 mg (78–234 mg equivalent USA) based on clinical judgment (PALMFlexS [Paliperidone Palmitate Flexible Dosing in Schizophrenia]). The primary efficacy outcome for non-acute symptomatic patients was defined as $\geq 20\%$ improvement in total PANSS score from baseline to 6 months. Other secondary outcomes included changes in CGIS and PSP scores and safety assessments. Prior to switching, patients were on five different atypical agents (aripiprazole $N = 46$, olanzapine $N = 87$, paliperidone ER [PALI] $N = 104$, quetiapine $N = 44$, and risperidone $N = 191$). The three main reasons for switching were the patient's desire to switch (45%), lack of efficacy (22%), and lack of compliance (25%). A total PANSS score improvement of $\geq 20\%$ was noted for each agent (aripiprazole 52.2%, olanzapine 60.9%, PALI 57.7%, quetiapine 65.9%, and risperidone 73.8%). Interestingly, some patients had $\geq 50\%$ improvement in total PANSS scores (aripiprazole 21.1%, olanzapine 29.9%, PALI 29.8%, quetiapine 27.3%, and risperidone 37.2%), indicating that about 30–50% of the treated patients had substantial benefit from 1MPP. Total PANSS, CGIS, and PSP scores were significantly improved with 1MPP ($p < 0.05$). The 1MPP formulation was well-tolerated without the occurrence of any new AE signals. The reasons for the improvement observed in patients who switched to 1MPP may be related to enhanced compliance, consistent medication treatment, and perceived benefits from an LAI agent. An important limitation to this study is that it was not designed to detect differential effects of each oral antipsychotic. As such, head-to-head comparisons between treatments could not be determined. Therefore, the findings of this post hoc study should be viewed as an exploratory analysis. However, this study does support the concept that patients receiving oral antipsychotic therapy who do not have an adequate therapeutic response may be candidates for LAI agents.

A subanalysis of the post hoc study was conducted in patients treated with aripiprazole ($N = 46$) in the PALM-FlexS trial [74]. The primary efficacy outcome was the change in the PANSS scale, which included the negative symptom subscales, PANSS Marder factor scores, quality-of-life scales, and the PSP scale. Safety assessments were also completed. Aripiprazole-treated patients were switched to 1MPP due to lack of efficacy ($N = 13$/46) and other reasons that were not specified in the paper ($N = 33$/46). The mean ($\pm$ SD) total PANSS score significantly decreased from baseline to endpoint (74.7 ± 14.9 vs. 62.6 ± 16.5; $p < 0.0001$). As previously noted, ≥ 20 and $\geq 50\%$ in total PANSS scores were found (52.2 and 21.7%, respectively). Significant improvements were noted with the negative PANSS subscale and Marder factor scores ($p < 0.0001$ for both comparisons) and the PSP scale ($p < 0.05$). No new AE signals were noted. Study

limitations included the lack of an active comparator group, non-randomized design, and the post hoc study design. Interestingly, the improvements found in the negative symptoms and Marder factor scales tend to support the notion that switching from an oral agent to an atypical LAI drug could assist patients in achieving their long-term therapeutic goals.

9 Summary and Conclusion

Patient adherence will continue to be a major issue in the treatment of schizophrenia because of the inherent nature of the disease. The lack of patient insight into their illness often leads to long-term medication adherence challenges. FGA and SGA LAI preparations were developed to address the unmet needs of patients with antipsychotic adherence problems. The pharmacokinetic principles for LAI agents are well known where the flip-flop properties are incorporated into model development, which is used for examining various dosing parameters, including missed doses. These models can accurately predict plasma drug concentration patterns and are accepted by regulatory agencies for their dosing, dosing administration schedules, drug injection sites, and other administration parameters to improve patient adherence. Additionally, these models are used for examining various dosing parameters that include missed doses.

LAI antipsychotic formulations were initially designed for administration every 2 or 4 weeks. However, the technology for LAI formulations is very complex, and rapidly evolving, as evidenced by there being currently 306 patents associated with paliperidone palmitate, 538 patents with AOM and AL, 993 patents for risperidone, and 1022 patents with OLZP [7]. The 3MPP and AL 2-month formulations break new ground in extending the LAI dosing administration schedule. Other LAI antipsychotic agents with 2- to 3-month (or possibly longer) administration schedules could be developed. Potential problems affecting the development of LAI agents with longer dosing intervals include (1) the need for larger doses, (2) the volume size of the injection, and (3) the extent of the drug delivery technology (e.g., implantable biodegradable polymers [75]).

Studies have reported that LAI antipsychotics enhance patient compliance to continued treatment and reduce the risk of rehospitalization by 20–30% compared with oral agents [76, 77]. Clinical trial methodologies and studies have been established for LAI antipsychotic agents where either a placebo-control group (FDA) or an active comparator agent (EU and Asia non-inferiority) are incorporated into the study design. These studies can include different phases with oral testing, stabilization with oral and LAI medications, and then the study phase. The typical study duration is 26 or 52 weeks, with the primary efficacy outcome measure being time to relapse. These agents are initially available as oral medications then subsequently as LAI formulations. The safety information from the oral antipsychotics serves as a basis for their LAI products. PDSS has been uniquely associated with LAI OLZP. Currently, iloperidone decanoate remains under clinical development. Once a new LAI agent is approved after regulatory agency review, studies are conducted to address additional questions that include switching between oral and LAI agents or comparing efficacy and safety between LAIs. The use of LAI eliminates any concern regarding patient compliance. The switch study from oral to an injectable antipsychotic noted that patients' desire for an injectable product was greater than problems with compliance [73]. Conversions from oral or other LAI antipsychotics to SGAs LAIs have been established [78]. The major focus for LAI antipsychotic development and treatment are expanded disease indications beyond schizophrenia and longer dosing administration intervals [79]. Barriers persist with LAI antipsychotics as patients and clinicians alike have limited knowledge of their use. Education of both parties will be necessary to ensure that LAIs are offered as a treatment option for patients in need of antipsychotic therapy. Patients who have had an inadequate response to oral antipsychotics may benefit from an LAI trial. Antipsychotic LAI agents have had an interesting history of usage, technology development, and misconceptions. However, clinical trial development of LAI antipsychotics has been established and accepted by the regulatory agencies. The incorporation of all LAI agents should be integrated into treatment guidelines for the care of patients with schizophrenia and other mental illnesses. This is an important recognition for LAI agents that will assist policy makers and healthcare managers to maximize all available therapeutic options for patients.

Compliance with Ethical Standards

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