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REVIEW

Cumulative Clinical Experience of the Use of Paliperidone Palmitate 3-Monthly Long-Acting Injection in the Treatment of Schizophrenia: A Critical Appraisal

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Abstract: Paliperidone palmitate 3-monthly (PP3M), an approved maintenance treatment for patients with schizophrenia, was the first long-acting antipsychotic injectable (LAI) to require only four administrations per year. Here, we aimed to review the available evidence about its use in the management of schizophrenia to date and highlight key study findings in order to provide a balanced overview of current experience in clinical practice. For that purpose, an extensive search of available literature from PubMed, Embase, and Web of Science was conducted in March 2023. Emerging data from real-world studies appear to signal that the benefits of the use of PP3M may well extent beyond the obvious convenience for patients and resource efficiency for services and may be actually associated with improved effectiveness and patient satisfaction. Large naturalistic studies from Australia, Europe and the US comparing treatment continuation between newer LAIs and/or oral antipsychotics showed that patients treated with PP3M had higher compliance rates and a longer period of continuous use. The risk of relapse, re-hospitalization and number of bed days was also lower with PP3M compared to PP1M and other LAIs as demonstrated by several cohort studies. Furthermore, patients treated with PP3M were using lower doses of benzodiazepines and concomitant oral antipsychotics compared with other LAIs. What is more, PP3M appears to positively impact patients' satisfaction and quality of life, facilitating long-term goals. In fact, recent studies recorded better quality-adjusted life years and decreased stigma, with improved social acceptability and promotion of rehabilitation for patients transitioning to PP3M. The rates of general satisfaction rates with PP3M were also higher among psychiatrists and caregivers who reported overall less concerns. In conclusion, clinical exposure and a growing body of evidence thus far, reinforce the use of PP3M in an effort to enhance patient outcomes alongside individual experience and treatment persistence.

Keywords: paliperidone-palmitate 3-monthly, schizophrenia, long-acting injectable antipsychotics

Introduction

Schizophrenia is a chronic, complex and frequently misconstrued disorder which may cause severe emotional, social and occupational impairment. It was first described in the 19th century as dementia praecox or early dementia[1] and is mainly characterized by positive and negative psychotic symptoms and cognitive dysfunction. According to the last WHO report, the schizophrenia is estimated to affect approximately 24 million patients worldwide.[2] It remains one of the top-15 leading causes of disability[3] with a higher risk of premature mortality compared to the general population and is associated with substantially increased healthcare and wider societal costs.[4]

It has been demonstrated that the effective management of schizophrenia and other psychotic disorders requires early intervention and continuous, often long-term, treatment to reduce symptoms, maintain function, improve quality of life and prevent acute positive symptoms or disease decompensations.[5] In addition, it has been widely established that

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compliance to the antipsychotic treatment is one of the main factors modifying the course of the disease.[6] As such, poor adherence is a strong predictor of relapse and consequently associated with poorer functional outcomes, and higher rehospitalisation rates and mortality.[7,8]

Hence, some of the main advances in the area of antipsychotic medication development in the last decades have been in relation to improving adherence and treatment persistence. First-generation antipsychotics were initially developed as depot or long-acting antipsychotic injectables (LAIs) in the second half of the last century and included the 1–4 weekly formulations of haloperidol, fluphenazine and zuclopenthixol[9,10] which employed salts of long-chain alkanoic acid (decanoate and/or enanthate) in plant oils. In the early 2000s, the second generation of biweekly LAIs emerged, such as risperidone and olanzapine,[11,12] followed by monthly atypical LAIs, such as aripiprazole and paliperidone palmitate (PP1M).[13,14] Paliperidone has subsequently been also made available as a 3-monthly formulation since 2015[15] and more recently as a 6-monthly formulation from 2022.[16]

Incongruously, while the use of chronic injectable medication is a well-regarded treatment tool by both clinicians and patients, in other areas of medicine usage of long acting-injectables antipsychotics in psychiatry remains a topic of ongoing debate and controversy.[17–19] Be that as it may, pharmacokinetic and pharmacodynamics studies in the last decades have shown that, particularly the newer LAIs, improve drug delivery, regular plasma concentrations and dosing precision reducing the risk of overdose.[20] Moreover, a number of clinical studies and systematic reviews including a recent large meta-analysis of 137 studies (32 RCTs, 65 cohort and 40 pre-post studies) demonstrated that LAIs significantly reduce the risk of hospital admissions and relapses compared to oral antipsychotics in patients with schizophrenia[21] while beneficial effects of LAIs have also been reported in patients with other psychotic disorders, such as schizoaffective and bipolar disorders.[22–24]

Finally, emerging evidence suggests that LAIs with a longer dosing interval may confer additional clinical benefits beyond the implicit practical advantages, such as improved outcomes, treatment continuity and patient experience.[25] Paliperidone palmitate 3-monthly (PP3M), an approved maintenance treatment available to patients with schizophrenia who have been previously stabilised on PP1M, was the first LAI to require only four administrations per year.[26] Therefore, here we review and summarise the current expertise and use of the 3-monthly paliperidone palmitate formulation (PP3M) in the management of schizophrenia and discuss the latest available studies regarding its safety, efficacy, and clinical utility as a narrative and critical review. Thus, it is not intended to be an all-encompassing review article, but rather highlight key studies to provide an overview of experience and expected real-world benefits of the use of PP3M in clinical practice.

Methods

We searched available literature from PubMed, Embase, and Web of Science; the search was conducted in March 2023, using the following search terms in varying permutations: schizophrenia; long-acting injectable; paliperidone palmitate; 3-monthly injectable, real-world; cost-effectiveness. The studies were retained if they met the following criteria: a) included studies with subjects that had a diagnosis of schizophrenia or other mental disorders and were treated with PP3M, b) were conducted in real-world settings, c) were cohort or mirror-image studies. Moreover, a manual search for possible eligible articles from papers previously selected or from other reviews and/or meta-analysis on this topic was conducted. We limited our research to English-language reports.

Results & Discussion

Pharmacology and Mode of Action of Paliperidone

9-Hydroxy risperidone or paliperidone is an atypical antipsychotic and the primary metabolite of risperidone.[27] It is worth noting that paliperidone comprises about 31% of risperidone metabolites. Interestingly, slow metabolizers do not produce significant amounts of paliperidone, while rapid metabolizers produce higher levels of paliperidone. Thus, the subtle modification of the chemical structure between risperidone and paliperidone accounts for the small differences in the pharmacologic and pharmacokinetics features between the two molecules, such as in the receptor profile binding, liver metabolism, and biological half-life.[28]

Paliperidone is characterized by brain selectivity antagonism of dopamine D2 and $5HT2_A$ serotoninergic receptors. This mechanism may not only confer antipsychotic effects but also some antidepressant activity and a lower risk to cause extrapyramidal side effects compared to typical antipsychotics.[29] Moreover, paliperidone binds to a number of other receptors, which may be associated with potential adverse events. Alpha-1 and alpha-2 adrenergic receptors blockade, for example, may cause decrease in blood pressure, while histamine H1 receptor antagonism may be associated with weight gain. In contrast, paliperidone does not bind to β1/β2 or muscarinic receptors, which are related to anticholinergic side effects, such as dry mouth, constipation or urinary difficulties.[30]

Paliperidone palmitate once monthly (PP1M) was the first long-acting injectable formulation of the antipsychotic paliperidone. It is a palmitate ester of paliperidone; the hydroxyl group in the chemical structure of PP allows for it to be administered as the fatty acid ester, palmitic acid. While, risperidone LAI uses micrometer-sized biodegradable poly(d, l-lactide-co-glycolide) microspheres, which are loaded with risperidone and suspended in sterile saline, PP is administered as a water solution of nanocrystals of the ster, x10 smaller than the standard drug particles, equipped with a sustained-release mechanism.[31] These nanocrystals increase the drug-solution surface area resulting in slow dissolution in vivo and leading the drug solution to achieve a rapidly steady state and maintain it for a longer period of time. Free paliperidone is derived from the ester by tissue hydrolases breaking ester bonds. The hydrolysis of paliperidone palmitate is relatively rapid. In particular, PP1M peak plasma level is reached 13 days after deltoid and gluteal administration, half-life is 25–49 days and clinical effects are seen in about 8 days after injection.[31] Therefore, the standard dosing schedule consists of an induction therapy with 2 injections one week apart, followed by maintenance dose every 4 weeks.

Paliperidone Palmitate 3-Monthly Formulation

PP3M is the intramuscular injectable paliperidone formulation with a longer half-life than the PP1M formulation. It was approved by the FDA in 2015 for use in schizophrenia and schizoaffective disorders.[32] PP3M and PP1M are a mixture of paliperidone palmitate enantiomers and, similarly to PP1M, the formulation technology of PP3M is based on nanocrystals, characterized by a very low water solubility, dispersed in an aqueous suspension. PP3M differs from the monthly formulation of paliperidone in that it contains bigger particle size of the nanocrystals[33] which allows for an extended release period. Subsequently, these larger nanocrystals are dissolved slowly after intramuscular injection, hydrolyzed to paliperidone and adsorbed into systemic blood circulation.

Pharmacokinetic studies demonstrated that peak serum concentration of PP3M is reached between 23 and 34 days post-injection and serum half-life is 2–4 months.[33] Furthermore, despite PP3M being approved for gluteal and deltoid injections sites, its serum half-life is greater when injected in the gluteus muscles. In contrast, PP1M serum half-life is equivalent between those two routes of administration.

General Considerations for Prescribing of PP3M

PP3M can only be administered by a healthcare professional. To ensure that PP3M is properly dispersed it is important to shake the vial well prior to its administration, otherwise, the nanocrystal structure will not disperse properly leading to loss of effectiveness.

Prior to PP3M administration, patients must have been treated and stabilized with PP1M for at least 4 months, with the last 2 months at the same dose.[34] PP3M is then administered in place of the next scheduled monthly injection at a dose x3.5 higher than the dose of PP1M. The next PP3M administration may be scheduled 12 weeks later, although can be given 2 weeks earlier or later from the planned date. In case of missed dose between 3.5 and 4 months, the planned dose should be administered immediately and then continue with the 3-month injections.[32] Nonetheless, missed doses between 4 and 9 months must start a re-initiation regimen, and for missed doses >9 months, the patient will re-initiate treatment with PP1M before starting again with PP3M.[34]

Importantly, patients treated with PP3M must be closely monitored for any changes or adverse effects, such as motor impairment, metabolic dysregulation (weight gain, glucose, lipids, cholesterol), hyperprolactinaemia and possible effects on cardiovascular function including QT interval.

Pharmacokinetics and Pharmacodynamics

As mentioned above, PP3M is a non-aqueous crystalline structure, with a larger particle size than the one-month formulation, administered in a larger volume. PP3M is absorbed since the day of administration, the serum peak concentration takes place on days 30–33 and the half-life is 12 weeks.[33] Specifically, PP3M half-life is 118–139 days in the gluteal administration, while it is only 84–95 days when delivered in the deltoid. In fact, 3% (deltoid)–7% (gluteal) of a 525 mg dose will still be present in the circulation 18 months after last injection.[26] This difference in absorption rate is caused by the adipose tissue overlying the gluteal muscle, with a consequent faster uptake of PP3M following gluteal injection.

Paliperidone is mainly metabolised by renal excretion. Despite in vitro studies showing a narrow hepatic metabolism of paliperidone by CYP2D6 and CYP3A4, this has not been confirmed by in vivo studies. Therefore, paliperidone does not interact pharmacologically with drugs metabolised by the liver and does not need dose adjustment for smokers.[34]

Special Populations

Renal and Hepatic Impairment

Pharmacokinetic studies demonstrated that the renal elimination of paliperidone decreases as does the creatinine clearance (CrCl): decreases a 32% in patients with CrCl=50–80mL/min, a 64% when CrCl=30–50mL/min and 71% if CrCl<30mL/min.[26] This means that those patients are exposed to about 1.5, 2.6 and 4.8 times higher levels of paliperidone, respectively, compared to healthy controls. Therefore, PP3M should not be administered in patients with moderate/severe renal function impairment, defined as ClCr<50mL/min.[35] In those patients with ClCr 50–80mL/min the dose should be calculated as a 25% reduction of the PP1M equivalent dose and then x3.5 fold to PP3M with a maximum dose of 350mg. No dose adjustment is required in patients with mild or moderate hepatic impairment, or in elderly patients with normal renal function.[35]

Pregnancy and Lactation

The use of antipsychotics during pregnancy is a plight that clinicians often have to deal with. Preclinical studies with animals demonstrated that oral paliperidone and intramuscular administration of palmitate paliperidone produced reproductive toxicity but were not teratogenic. Despite data about paliperidone during pregnancy being not available from clinical trials, few scientific reports have been published. Likewise, due to the extended dosing interval of PP3M and its plasmatic levels up to 18 months from the injection, the likelihood of fetal exposure is increased when compared to other antipsychotics. In this regard, one case report of a woman treated with PP3M during pregnancy and two other case reports of women in treatment with PP1M reported no congenital malformation and no perinatal complications of the newborns.[36–38] A recent study in Germany reported that paliperidone exposure during 17 pregnancies resulted in 15 live-born babies and 2 spontaneous abortions. This study reported no malformations but an increased rate of prematurity and small for gestational age children which were at least partially explained by other risk factors and increased extrapyramidal or withdrawal symptoms in the newborn.[39] It has been also demonstrated that at least 1% of the given dose of paliperidone is excreted in breast milk in animal and human studies.[40] Therefore, the use of paliperidone palmitate in pregnancy and lactation should be a thoughtful decision with a favourable balance between the risks and benefits to the patient and the fetus.

Geriatric and Paediatric Patients

Clinical trials about PP3M in elderly patients have not been carried out specifically. Further, this group of patients is excluded in the clinical trials performed for the drug approval.[33] It may be difficult to predict the effect and response of PP3M in >65 years old patients.[26] Likewise, studies evaluating the use of LAIs in children and adolescents are rare. Most of them include patients treated with risperidone-LAI. Despite PP1M being included in some reports, none of them evaluated the use of PP3M. Therefore, clinicians should be cautious when prescribing to this groups of patients.

Clinical Evidence and Experience

Results from the initial pivotal Phase III RCTs indicated that PP3M was efficacious and generally well tolerated. Time to relapse was significantly longer and the PANSS total score significantly lower in the PP3M group vs the placebo group (p=0.001 and 0.01 respectively) in a relapse-prevention RCT comparing PP3M to placebo in 506 patients with schizophrenia. The most frequently reported side effects were headache (9% vs 4%), weight gain (9% vs 3%), nasopharyngitis (6% vs 1%), and akathisia (4% vs 1%) in the active drug vs placebo groups.[41]

A double-blind RCT designed to evaluate the non-inferiority of PP3M in 1016 patients with schizophrenia who were previously stabilized on PP1M revealed similar symptom reduction and relapse rates in both groups (8% vs 9%), They also had similar pharmacokinetic and tolerability profiles.[15]

What is more, subsequent real-world evidence emerging over the last few years appeared to signal that the benefits of the routine use of the less frequent three monthly paliperidone formulation may well extent beyond the obvious convenience for patients and resource efficiency for services and may be actually associated with improved effectiveness, level of compliance and patient satisfaction and acceptance, as summarised below.

Impact on Adherence and Treatment Persistence

Treatments with longer dosing intervals may indeed improve patient outcomes and clinical stability by enhancing overall adherence to treatment. In this regard, a real-world study from Australia comparing treatment continuation between newer LAIs in a cohort of over 700 patients[42] showed that patients treated with PP3M had higher compliance rates (78%) and a longer period of continuous use (36 months) compared to PP1M (46%, 11 months), risperidone-LAI (33%, 4 months), olanzapine-LAI (35%, 8 months) and aripiprazole-LAI (51%, 18 months).[42] Moreover, a recent population-based study, including 2275 patients with schizophrenia, demonstrated that time to medication switch was substantially longer for patients on PP3M, with over 90% continuing treatment at 12 months, whereas those receiving PP1M, aripiprazole 1-monthly (AM) or oral antipsychotics were three times more likely to change treatment over the same period of time.[43] Patients with schizophrenia from an US Medicaid database who transitioned to PP3M were 2.4 times more likely to be adherent and 4.6 times more likely to be persistent than patients on PP1M during the 12-month follow-up period.[44]

The observed beneficial effects of PP3M in clinical practice could be further enhanced by reducing the risk of partial compliance (as manifested by delayed or missed doses rather than full discontinuation) which has been shown to directly affect treatment outcomes even with monthly administration of LAIs.[45–47]

Effectiveness and Long-Term Treatment Outcomes

The overall risk of relapse and re-hospitalization appears to be low in patients treated with PP3M. Two randomised clinical trials recorded an 8.8% and 8.1% relapse rate, respectively, in patients with schizophrenia during their first year of treatment with PP3M.[17,41] A recent naturalistic multicentre study, however, reported a somewhat higher rate of relapse (18.5%) after 1 year of treatment with PP3M in a cohort of 178 patients from Canada,[48] although this difference, could be due to the fact that only patients with a diagnosis of schizophrenia were enrolled in the RCTs, while the naturalistic patient cohort also included patients diagnosed with other comorbid mental disorders, such as substance misuse and personality disorders. In fact, when the patients with psychiatric comorbidity were excluded from the analysis, the relapse rate dropped to 9.7%, which was similar to the one reported by the RCTs.

Interestingly, the three monthly formulation was found to perform better in a number of real-world studies when compared to its monthly counterpart as well as other newer LAIs. A recent population-based retrospective study[43] reported that 88.4% of patients receiving PP3M remained hospitalization free at 18 months compared to PP1M (72.1%), AM (71.0%) and oral antipsychotics (68.7%). All treatment groups had at least a two-fold significantly higher risk of psychiatric inpatient care than those receiving PP3M. Similarly, PP3M-treated patients had comparatively the lowest ER visit rates. Likewise, a large naturalistic cohort study including >800 patients from the UK and Spain showed that PP3M significantly reduced the rate of hospital admissions compared to A1M and bi-weekly LAIs.[49]

A 5-year mirror-image study in London, UK, evaluated the rate of hospitalizations and bed days 3 years before and 2 years after starting PP1M and switching to 3-monthly in a cohort of 76 patients with schizophrenia.[50] Their results demonstrated that PP3M treatment initiation decreased both the rate of hospital admissions (0.05 vs 0.55, $p<0.001$) and the number of bed days (23.0 vs 32.2, $p=0.004$) per year compared to PP1M. Likewise, another 2-year mirror-image study showed that switching to PP3M, decreased the number of hospital admissions in comparison with PP1M (4.8% versus 10.7%) in a cohort of 84 patients with schizophrenia.[51] In agreement with these findings, a prospective study of 305 patients treated with PP1M with clinically stable schizophrenia also demonstrated a reduction of the proportion of patients requiring hospital admission for psychiatric reasons one year after switching to PP3M from 13.5% to 4.6% compared to the year before.[52] Furthermore, this study also showed that 56.8% achieved symptomatic remission and 31.8% of patients achieved both symptomatic and functional remission, respectively, recording improvements in the Personal and Social Performance scale total scores as well as in the Positive and Negative Syndrome Scale and in Clinical Global Impression-Severity and -Change scores during treatment with PP3M.[52] A recent small observational study showed that PP3M reduced Positive and Negative Symptom Scale scores and the scores of Hamilton Rating Scale for Depression compared to PP1M.[53] Similarly, a retrospective study comparing 438 patients with a diagnosis of psychotic disorders and treated with PP3M to 1136 matched patients treated with PP1M in the US[54] found a significantly lower relapse rate for patients on the longer-acting formulation (10.5% on PP3M vs 15.7% on PP1M) after 15-months of follow-up. Likewise, recent naturalistic studies in Asia demonstrated a lower proportion of patients with at least one hospitalization following PP3M treatment (1–3%) compared to 12 months prior to switching (17%).[55,56] Overall, these results highlight the importance of continuous maintenance treatment in patients with schizophrenia.

Furthermore, a recent study evaluated the role of PP1M, PP3M versus oral paliperidone and risperidone in the first episode of psychosis.[57] Patients in the PP3M group achieved significant improvements compared to oral treatments in overall clinical symptom severity and saw a substantial improvement in the main domains of personal and social functioning after 1 year. Also this study demonstrated that patients treated with PP3M associated a lower concomitant use of benzodiazepines.[57]

In this regard, more recent evidence suggests that the use of LAIs and PP3M in particular may have a beneficial effect on the need for concomitant medication. For example, a large Spanish cohort of psychiatric patients demonstrated that benzodiazepine use was considerably lower for patients on long-acting compared to oral antipsychotics.[58] In addition, naturalistic cohort studies in Spain showed that PP1M and PP3M LAIs were associated with a lower risk of being prescribed with and using lower doses of benzodiazepines and antipsychotics compared with RLAI and AM.[59–61] These data are consistent with a large European multicentre cohort study including patients diagnosed with schizophrenia spectrum, schizoaffective, and bipolar disorders.[49] Although, the overall efficacy of paliperidone is not significantly different from that of other antipsychotics, some studies demonstrated that it may represent a more effective way in managing psychotic symptoms with aggressive behaviour compared to alternatives, which may in part explain the above findings.[62–64]

Level of Protection Following Treatment Discontinuation

The benefits of longer-acting antipsychotic treatments may well extent beyond any potential planned or planned treatment discontinuation. A randomized controlled trial[65] in patients with schizophrenia comparing oral paliperidone, PP1M and PP3M, demonstrated that 50% of patients who were withdrawn from oral paliperidone, PP1M, or PP3M remained relapse-free for 2, 6 and 13 months, respectively. Similar results have been shown in a recent post-hoc study of three clinical trials including 473 patients treated with PP3M or PP1M and a placebo group of 449 patients.[66] Along the same lines, a review highlighted that PP3M was effective in maintaining a longer symptom-free period after discontinuation[67] and concluded that administering PP3M may be an effective way to prevent relapse in patients with schizophrenia even when they do not persist with treatment.

Patient Experience and Satisfaction

Most notably, based on quality studies, the ultra-long paliperidone appeared to lead to improved patient satisfaction and acceptance compared to PP1M. A French study reported a better quality adjusted life years when using PP3M

compared to PP1M.[68] Furthermore, a multi-centre survey recently carried out in patients with schizophrenia spectrum-disorders[69] reported higher general satisfaction rates with PP3M (69%) compared to PP1M among patients but also among psychiatrists (95%). Moreover, 79% of the caregivers conveyed less concerns about non-adherence after switching to PP3M and the majority of patients, relatives, and mental health professionals reported similar or in some cases even greater effectiveness and similar or in some cases even less adverse events on PP3M compared to PP1M. Fernández-Miranda et al[51] recorded an even higher patient satisfaction rate (85%) with PP3M than PP1M in a mirror-image study of 84 patients with severe schizophrenia. Main reasons included less injections/year and feeling less sedated and less medicated.[51] Similarly, the majority of patients in a study conducted in the UK reported feeling satisfied (89.2%) and safer (93.5%) during the recent pandemic after switching to the three-monthly paliperidone formulation from PP1M. Participants highlighted several advantages such as convenience (93.5%), improved quality of life (58.7%), decreased stigma (39%) and better adherence (28.3%).[70] In contrast, a 1-year observational study showed no differences between haloperidol-LAI, PP1M and PP3M in self-perception and quality of life in a cohort of 90 patients with schizophrenia.[71]

Gopal et al[72] pooled data from two studies involving a total of 1498 caregivers of patients with a diagnosis of schizophrenia from 27 countries. They found that PP1M and PP3M decreased the need to encourage patient self-care and accept medication advice, as well as the hours spent caregiving and had a positive impact on the stress levels of caregivers. Lastly, a recent study based on qualitative personal interviews with 24 patients with schizophrenia across 3 countries concluded that participants prioritised and emphasized the value of trustful relations with healthcare professionals, therapeutic conversations, antipsychotic medication in a 3-monthly formulation, and support from relatives.[73] Overall, the positive attitudes and experience of all parties with PP3M may expand its use and potentially improve the clinical outcomes. The PP3M main advantage is reducing the number of administrations, thus allowing patients greater freedom and lower risk of stigma and dependence on services. Initial concerns that reduced clinician contact may lead to increased rates of relapse or disengagement did not materialise and patients did not raise this as an issue of concern either. Quite the reverse, less frequent treatments may be associated with improved social acceptability and inclusion and promotion of rehabilitation[74] which in turn may improve the overall patient experience and collaborative process.[75]

Safety and Tolerability

The early RCTs established a similar tolerability profile between the PP1M and PP3M which was confirmed by subsequent real-world studies. A 2-year mirror-image study of 84 patients with schizophrenia switching from PP1M and treated with PP3M showed that there were no significant changes in weight or prolactin levels (although both mean values decreased after switching) or in most other biological parameters apart from a lower incidence of parkinsonism, sedation and orthostatic hypotension with PP3M.[51] An 8-year mirror-image study in residential chronic patients with severe schizophrenia[76] demonstrated that there was a significant decrease in BMI, glucose, cholesterol and triglycerides patients under treatment with PP3M when compared with baseline values under treatment with clozapine. Hepatic cholestasis enzymes and GGT, were also significantly elevated with clozapine when compared to PP3M.[77] A study in Asia evaluating the safety of PP3M among Asiatic and non-Asiatic patients with schizophrenia demonstrated that the incidence of side effects related to PP3M was similar in the Asian subgroup (28.6%) and overall study population (30.0%).[55] Likewise, a subgroup analysis of two large clinical trials including over 1900 patients with schizophrenia showed that Latin American patients on PP3M had no new adverse effects as compared to patients from all over the world.[78] Finally, a post hoc subgroup analyses of the REMISSIO clinical trial comparing the side effects of PP3M 52 weeks after switching from PP1M found that PP3M generally exhibited a favourable safety profile and was well tolerated in both age (younger or older than 35 years old) and disease duration (< or >3 years). Nonetheless, the proportion of patients who suffered a side effect leading to treatment discontinuation was similar in all groups.[79]

Cost-Effectiveness of PP3M

The economic burden of schizophrenia and other mental disorders on both society and healthcare systems is substantial.[80,81] The annual costs of schizophrenia for each patient range between 26,000–34,000$ in the US and 500–13,000€ in Europe.[81,82] It has been estimated that hospitalization comprised 38.5% of the total costs, while treatment

accounted for 12.8%.[83] In this regard, recent evidence demonstrated that PP3M came out better in the cost-effectiveness, cost-utility and quality of life analyses compared to PP1M in the treatment of chronic relapsing schizophrenia.[84,85] Similarly, PP3M was found to be more cost-effective for treating chronic schizophrenia compared to PP1M, haloperidol-LAI, risperidone-LAI and oral olanzapine treatment in another study.[86] Finally, a study from the US showed that PP3M is more cost-effective compared to PP1M but inferior to the newest PP6M.[87]

Conclusions

The evolution of the PP3M formulation was unique in that it was the first LAI allowing for longer than monthly administration intervals and in fact remains the only quarterly dosage LAI in the market. Studies from clinical trials and in real clinical settings indicate that PP3M is a safe treatment that has been shown to have a similar and often more favourable effectiveness compared to PP1M and other LAIs in the management of schizophrenia due to enhanced adherence and decreased risk of hospitalisation and relapse even after several months of treatment discontinuation/withdrawal. It is worth noting that PP3M appears to positively impact patients' and caregivers' satisfaction and quality of life facilitating long-term goals in support of a "less is more" type of principle. The importance of enhanced access (for example, in rural areas or primary care settings) as well as safety with less frequent medication administration under pandemic conditions should be also highlighted.[80] Interestingly, although PP3M has been shown to be cost-effective compared to PP1M and other LAIs primarily in Western countries (where it has been thus far mostly used), further studies are needed in the context of different health systems or countries including in those with scarce resources or large rural areas. Finally, some real-world studies evaluated the effectiveness of PP3M in schizoaffective, bipolar and even personality disorders have also shown encouraging outcomes, although more clinical research is needed in this subgroup of patients.

Overall, clinical exposure to a growing body of evidence thus far, may reinforce the use of PP3M and other less frequent LAIs in an effort to enhance patient outcomes alongside individual experience and treatment persistence.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

JAGC received both speaker and research honoraria from Neuraxpharm and consulting honoraria from Teva. SP has received honoraria as a consultant or speaker from Janssen, Recordati, Rovi, Lundbeck, Sunovion and Otsuka and a research grant from Recordati, all outside the submitted work.

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