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Preliminary data from a 4-year mirror-image and multicentre study of patients initiating paliperidone palmitate 6-monthly long-acting injectable antipsychotic: the Paliperidone 2 per Year study

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Abstract

Background: Paliperidone palmitate 6-monthly (PP6M) is the first long-acting antipsychotic injectable (LAI) to allow for only two medication administrations per year, though there is presently limited insight into its effectiveness and potential added value in real clinical practice conditions.

Objectives: To present our ongoing study and draw its preliminary data on patient characteristics initiating PP6M and adherence during the first year of treatment.

Methods: The paliperidone 2 per year (P2Y) study is a 4-year, multicentre, prospective mirror-image pragmatic study taking place at over 20 different sites in Europe. The mirror period covers 2 years either side of the PP6M LAI initiation. Retrospective data for the previous 2 years are collected for each patient from the electronic health records. Prospective data are recorded at baseline, 6, 12, 18 and 24 months of drug administration and also cover information on concomitant psychiatric medication, relapses, hospital admissions, side effects, discontinuation and its reasons. Meanwhile, here we present preliminary data from the P2Y study at basal and 6-month period (first and second PP6M administration).

Results: At the point of PP6M initiation, the most frequent diagnosis was schizophrenia (69%), the clinical global impression scale mean score was 3.5 (moderately markedly ill) and the rate of previous hospital admissions per patient and year was 0.21. PP6M was initiated after a median of 3–4 years on previous treatment: 146 (73%) from paliperidone palmitate 3-monthly, 37 (19%) from paliperidone palmitate 1-monthly and 17 (9%) from other antipsychotics. The mean dose of the first PP6M was 1098.9 mg. The retention rate at 6 months and 1 year of treatment on PP6M in our cohort was 94%.

Conclusion: Patient and clinician preference for LAIs with longer dosing intervals was the main reason for PP6M initiation/switching resulting in high treatment persistence. Future data are needed to evaluate the full impact of PP6M in clinical practice.

Keywords: long-acting injectable antipsychotics, paliperidone palmitate 6-monthly, schizophrenia

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Introduction

Schizophrenia is a severe mental disorder characterized by positive and negative symptoms, disorganization and cognitive deterioration impairing self-care and interpersonal relationships.[1] The prevalence of schizophrenia is ~24 M of patients worldwide and is one of the top 15 leading causes of disability worldwide.[2] For its management and treatment, several approaches are important such as social support, psychological therapies and psychoeducation. Nonetheless, it is well established that schizophrenia is produced by altered dopamine and glutamate neurotransmitter levels in the brain[3] and pharmacotherapy, mainly antipsychotics, remains one of the most important cornerstones in the management of schizophrenia in reducing symptoms, maintaining function and improving quality of life.

However, patients with schizophrenia characteristically suffer from anosognosia or a lack of insight into the nature of the symptoms and difficulties associated with the illness.[4] Therefore, effective treatment is often jeopardized by lack of adherence and compliance. Long-acting injectable antipsychotics (LAIs) have been shown to improve adherence by reducing the risk of full and partial compliance and may therefore enhance the collaborative process.[5,6] However, LAIs are frequently underused in current practice, with a highly heterogeneous pattern of use among countries and many other barriers to their adoption exist, such as the overestimation of patient adherence, patient refusal or perceived coercion, underfunded or administrative barriers of health providers services.[7]

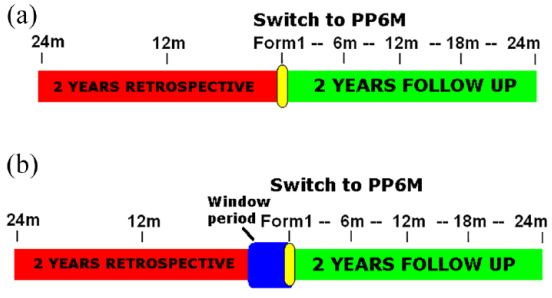

Figure 1. Study timeline desing. (a) for patients previously treated >6 months with paliperidone palmitate 1-monthly (PP1) or paliperidone palmitate 3-monthly (PP3M) prior the switch to paliperidone palmitate 6-monthly (PP6M) and (b) for patients previously treated with other oral or LAI antipsychotics before the switch to PP6M. The window period covers the needed treatment with PP1M (4 months) or PP3M (3 months) before switching to PP6M.

Paliperidone palmitate is a LAI, first made available as a 1-month administration formulation (PP1M) in 2009 and subsequently as 3-month formulation (PP3M) in 2015. Recently, the new 6-month formulation (PP6M) has been marketed and is available in Europe and other Western countries since May 2022. As demonstrated in a clinical trial, the efficacy of PP6M was noninferior to that of PP3M in preventing relapse at 52 weeks in patients with schizophrenia adequately treated with PP1M or PP3M.[8] This study found that 92.5% of patients treated with PP6M and 95% of those treated with PP3M were relapse-free at 12 months. Furthermore, a number of studies showed additional benefits in terms of patient treatment outcomes and satisfaction with less frequent LAIs and particularly with PP3M, the first long-acting treatment allowing for quarterly administrations.[9,10] Nonetheless, there is as yet a lack of studies evaluating the effectiveness and potential added value of PP6M in real-world clinical practice. Hence, we aim to present our ongoing study protocol and draw its preliminary data on patients initiating PP6M, including baseline sociodemographic, clinical and treatment characteristics and adherence at 6 months.

Methods

Study design

The paliperidone 2 per year (P2Y) study is a 4-year, multicentre, prospective mirror-image pragmatic study. Enrolment takes place from January 2023 to December 2024, at 20 different sites in Spain, Italy and the UK. The present study does not interfere with patient treatment in any way, and PP6M is prescribed according to clinical need. The mirror period covers 2 years either side of the PP6M LAI initiation. Retrospective data for the previous 2 years are collected for each patient from the electronic health records. PP1M or PP3M was considered as the 'previous treatment' only if patients were treated with either for more than 6 months [Figure 1(a) and (b)].

The study is conducted in accordance with International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki and approved by the corresponding Ethics Committee (ref. CEI.23-11_PY2_2022). Before study initiation, written informed consent covering

retrospective, screening and prospective collecting data was obtained from participants (or their legal representatives, if appropriate). The protocol and consent forms were approved by the respective institutional ethics committee at each site.

Inclusion and exclusion criteria. Participants were eligible for inclusion if they were (1) adults (>18 years), (2) under the care of a mental health service, (3) had a diagnosis of schizophrenia, or other psychiatric disorder such as schizophrenia spectrum disorders (schizoaffective, psychotic and delusional disorders) bipolar or personality disorders, intellectual disability and autism spectrum disorders according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria and (4) initiating PP6M treatment. Patients <18, pregnant women and those without medical records in the past 2 years were excluded. The present study was drawn up following the 'STrengthening the Reporting of OBservational studies in Epidemiology' Statement items.[11]

Study measures

Study data were collected and managed using REDCap electronic data capture tools hosted at Murcia Health Service.[12] Patients' baseline characteristics and 2-year retrospective data were extracted from patients' medical records by the study team at the time of first PP6M injection. Data collected included demographic information such as age, sex, marital status, employment, tobacco and substance use (i.e. alcohol, cannabis, cocaine, heroin or amphetamines), and clinical data such as primary psychiatric and other diagnosis, comorbid substance use disorder, body mass index, cholesterol levels, cardiac QTc interval interval, number of hospital admissions as well as concomitant psychiatric medications, including the use of benzodiazepines, oral antipsychotics, antidepressants, mood stabilizers and anticholinergics.

At each subsequent PP6M injection, the following information was collected: date of injection, PP6M dose received, reason for dose or interval change if applicable, any addition of oral antipsychotics (including treatment indication).

Prospective data are recorded at 6, 12, 18 and 24 months of drug administration and also cover information on concomitant psychiatric medication, relapses, hospital admissions, side effects, discontinuation and its reasons. For the final PP6M administration at 24 months, additional information regarding clinical severity [clinical global impression (CGI) scale endocrine levels and QTc interval] interval as well as patient satisfaction with PP6M will be captured. Meanwhile, here we present preliminary data from the P2Y study at basal and 6-month period (first and second PP6M administration).

Diazepam and haloperidol equivalents. In order to compare the concomitant use of benzodiazepines and oral antipsychotics, we calculate the corresponding daily dose equivalents of diazepam or haloperidol (mg/day) as standards as previously described.[13]

All cause treatment discontinuation and side effects. As recommended per manufacturer, the corresponding dose of PP6M can be given 2 weeks before or 3 weeks later than the scheduled date. After this date, it is advised to administer one equivalent dose of PP1M and resume PP6M in 30 days. Nonetheless, we consider treatment discontinuation if the dose of PP6M is not administered within 3 weeks after the expected date for the next dose. The reasons for treatment discontinuation are also collected as follows: no adherence, tolerability, ineffectiveness, all-cause mortality or patient, clinician or family preference of other treatment. The type and prevalence of side effects of PP6M have been reported similar to those of PP3M in a previous clinical trial.[8] Nonetheless, we record the specific side effects if they lead to treatment discontinuation, including weight gain, extrapyramidal effects, insomnia, raised prolactin, QTc prolongation, high blood pressure, sedation, digestive effects, haematological disorders, neuroleptic malignant syndrome or other side effects.

Patient, relatives and psychiatrists satisfaction assessment. We evaluate the satisfaction levels for PP6M antipsychotic formulation on a visual scale from 1 (extremely dissatisfied) to 5 (extremely satisfied) as expressed by the patient, their relatives and their psychiatrist 1 and 2 years after initiating PP6M. Similarly, we also evaluate the experienced effectiveness by the patient, the relatives and the psychiatrists 1 and 2 years after first PP6M administration compared with the previous treatment using a similar visual scale.

Statistical analysis and confounding factors

All analyses were performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY,

Table 1. Cohort demographic data.

	n **= 200**
Sex (%)	
Women	68 (34)
Men	132 (66)
Age (year ± SEM)	50.9 ± 0.9
Race (%)	
Caucasian	188 (94)
Latin American	5 (3)
Black	7 (3)
Living at	
Home	113 (57)
Chronic hospital	87 (43)
Employed	
No	184 (92)
Yes	16 (8)
Tobacco and drugs (%)	120 (60)
Tobacco	115 (58)
Alcohol	22 (11)
Cannabis	24 (12)
Cocaine	20 (10)
Heroin/opiates	3 (1)
Amphetamines	3 (1)
SUD diagnosis	28 (15)
Mental disorder (%)	
Psychosis	6 (3)
Schizoaffective Dis.	28 (14)
Schizophrenia	137 (69)
Delusional Dis.	4 (2)
Bipolar Dis.	6 (3)
Personality Dis.	8 (4)
Autism spectrum Dis.	1 (1)
Intellectual disability	10 (5)

Dis., disorder; SEM, standard error media; SUD, substance use disorder.

USA). We expressed quantitative variables as means [standard error media] and categorical variables as numbers (percentage). We assessed normality of distributions using histograms and the Shapiro–Wilk test. Sample basal characteristics were analyzed by Student's *t*-test, chi-square and univariate analysis. Variables associated in the univariate analysis and variables with statistical trend ($p < 0.1$) were entered as factors in a multivariate logistic regression model to identify the risk factors or patients characteristics associated with being initiated with PP6M treatment. Differences with a p value <0.05 were considered significant.

Results

Here, we present preliminary data on patients characteristics and predictors of treatment initiation with PP6M as well as adherence at 6 months.

A total of 200 patients were recruited and included in this preliminary analysis from the P2Y study; their basic sociodemographic characteristics are presented in Table 1. Of this initial cohort, 66% were male and 94% Caucasian with a mean age of 50.9 years. At the point of PP6M initiation, the most frequent diagnosis was schizophrenia (69%), 57% lived at home and 43% in a chronic residential care or mental health facility and 92% were unemployed. A majority of patients smoked tobacco (58%), whereas 11–12% of patients consumed alcohol, cannabis or cocaine. In this regard, 15% of patients carried of formal diagnosis of comorbid substance use disorder. Furthermore, the CGI-S mean score was 3.5 (moderately markedly ill) at PP6M initiation (Table 2) while 13% (26) and 17% (34) of patients had at least one psychiatric admission in the first- and second-year, respectively, prior to PP6M initiation with a rate of 0.21 hospital admissions per patient and year. At the time of PP6M initiation, BMI was 28.35 ± 0.82 (kg/m^2), total cholesterol 184.95 ± 6.34 (mg/dL), LDL cholesterol 115.94 ± 5.43 (mg/dL), HDL cholesterol 42.67 ± 3.81 (mg/dL) and the QTc interval 391.22 ± 64.53 (ms).

Treatment characteristics are detailed in Table 2. PP6M was initiated after a median of 3–4 years on previous treatment. In total, 146 (73%) patients were switched from PP3M, 37 (19%) directly from PP1M and 17 (9%) were changed over from other LAIs [aripiprazole-LAI, risperidone-LAI (R-LAI) and zuclopenthixol-LAI (Z-LAI)] and

Table 2. Cohort clinical data.

		***n* = 200**
CGI-S score		3.5 = Moderately markedly
Previous LAI/OAP-Dose		
OAP	8 (4)	*
PP1M	37 (19)	171.6 ± 13.8
PP3M	146 (73)	539.6 ± 22.9
A1M	7 (4)	400
R-LAI	1 (1)	300
Z-LAI	1 (1)	285
Duration previous treat		3–4 years
Antipsychotic monotherapy (%)		78 (39)
Reason for switching to PP6M		
Side effects		2 (1)
No adherence		7 (4)
Ineffective		4 (2)
Patient prefer PP6M		85 (43)
Family prefer PP6M		2 (1)
Psychiatrist prefer PP6M		100 (50)
N benzodiazepines (%)		
1		128 (64)
2		10 (5)
3		5 (3)
N antipsychotics (%)		
1		94 (47)
2		18 (9)
3		10 (5)
Anticholinergics (%)		32 (16)
Antidepressants (%)		
1		30 (15)
2		6 (3)
Mood stabilizers (%)		
1		34 (17)
2		4 (2)
PP6M initiated at:		
Acute Hospital		9 (4)
Outpatient		191 (96)
PP6M initial dose		1098.9 ± 34.1

A1M, aripiprazole-1-month; LAI, long-acting injectable; CGI, clinical global impression scale; OAP, oral antipsychotic; PP1M, paliperidone palmitate 1-month; PP3M, paliperidone palmitate 3-month; PP6M, paliperidone palmitate 6-month; R-LAI, risperidone-LAI; Z-LAI, zuclopentixol-LAI.

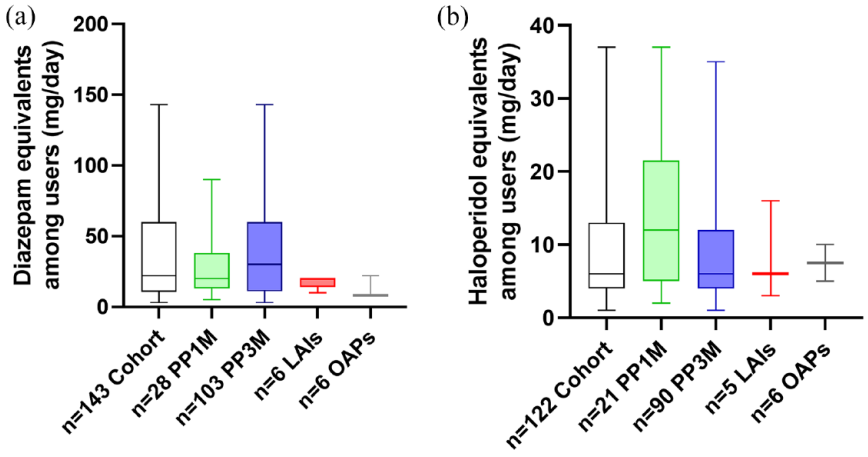

Figure 2. Psychiatric concomitant treatments. Dose of benzodiazepines and antipsychotics showed as (a) diazepam and (b) haloperidol equivalents (mg/ day) among users by long acting injectable (LAIs) or oral antipsychotics (OAPs) groups before switching to paliperidone palmitate 6-monthly (PP6M). Data are expressed as the mean SEM. PP1M = paliperidone palmitate-1-month; PP3M=paliperidone palmitate-3-month, LAIs including aripirazole 1-montlhy, risperidone-LAI and zuclopentixol-LAI; OAPs = oral antipsychotics.

oral antipsychotics. Only 78 patients (39%) were previously treated with antipsychotic monotherapy. In this regard, at baseline (before switching to PP6M), 122 (61%) patients were receiving concomitant oral antipsychotics, 143 (72%) of them received benzodiazepines, 32 (16%) of them received anticholinergics, 36 (18%) of them received antidepressants and 38 (19%) patients received mood stabilizers. Moreover, the mean daily doses of benzodiazepines and concomitant oral antipsychotics are shown in Figure 2 as (a) diazepam and (b) haloperidol equivalents. Mean daily dose of diazepam and haloperidol equivalents among users were 36.12 mg (±2.81) and 9.55 mg (±0.69), respectively. No statistical differences were found between groups according to previous treatments (PP1M, PP3M, other LAIs and oral antipsychotics). The reasons for discontinuing the previous treatment and initiating PP6M were mainly patient and clinician preference for a less frequent administration of LAI ($n=85$, 43% and $n=100$, 50%, respectively). At the time of the first PP6M injection, 182 patients (96%) were treated in a general outpatient psychiatric service, 9 (4%) of them in an acute hospital unit (six of them in an early intervention program) and 9 (7%) of them in an assertive community treatment team. The mean dose of the first PP6M was 1098.9 mg.

As shown in Tables 2 and 3, patients had been treated with PP1M with a mean dose of 171.6 mg/month with an interval dose between 100 and 300 mg/month. PP6M was initiated at doses of 700 ($n=3$ and $n=1$ from oral quetiapine), 1000 ($n=9$ and $n=3$ from other oral and LAIs antipsychotics), 1400 ($n=4$ and $n=1$ from Z-LAI) and 2000 mg/6-month ($n=5$). Similarly, the group of patients treated with PP3M was administered with a mean dose of 539.6 mg/3month interval dose between 263 and 1575 mg/3-month interval. PP6M was initiated at doses of 700 ($n=48$), 1000 ($n=65$ and $n=1$ from R-LAI), 1400 ($n=9$), 1700 ($n=18$), 2000 ($n=5$) and 3000 mg/6-month ($n=1$). The dosage switch from PP1M or PP3M to PP6M was made in agreement with the x6.7–7 or x1.9–2 ratios, respectively, recommended by the product monograph for 85% of the patients in both PP1M and PP3M.

Among the 158 patients (94 outpatients and 64 inpatients) who already had an appointment for the next scheduled PP6M administration, 149 of them received the second injection. Therefore, the retention rate and 1 year treatment adherence to PP6M in our cohort was 94%. Among the nine patients who refused the second PP6M injection, all of them were outpatients: one reported side effects, one died for other medical causes, one was lost the follow-up and the other six preferred other treatments (four oral antipsychotics and two the previous PP3M LAI).

Discussion

The P2Y observational, 4-year mirror-image study is being conducted at multiple sites in Europe in order to capture the wider clinical use and

Table 3. Switch to PP6M and dosage.

***n* = 200**		***n* (PP6M administered dose mg)**
Previous LAI/OAP-Dose mg		
OAP	**n = 8**	
Olanzapine 15	3 ▶ PP1M 150	3 (1000)
Quetiapine 300	1 ▶ PP1M 100	1 (700)
Aripiprazole 15	4 ▶ PP1M 150	4 (1000)
PP1M	**n = 37**	
100	12	10 (700), 2 (1000)
150	10	10 (1000)
200	7	3 (1000), 4 (1400)
225	2	1 (1700) 1 (2000)
300	6	1 (1000), 5 (2000)
PP3M	**n = 146**	
263	8	8 (700)
350	43	40 (700), 3 (1000)
525	69	61 (1000), 6 (1400), 2 (1700)
740	5	1 (1000), 3 (1400), 1 (1700)
875	5	5 (1700)
1050	15	10 (1700), 5 (2000)
1575	1	1 (3000)
A1M	**n = 7 ▶ PP1M 150**	7 (1000)
R-LAI	**n = 1 ▶ PP3M 525**	1 (1000)
Z-LAI	**n = 1 ▶ PP1M 200**	1 (1400)
Retention rate dose 2 PP6M		149/158 = 94%

A1M, aripiprazole-1-month; LAI, long-acting injectable; OAP, oral antipsychotic; PP1M, paliperidone palmitate 1-month; PP3M, paliperidone palmitate 3-month; PP6M, paliperidone palmitate 6-month; R-LAI, risperidone-LAI; Z-LAI, zuclopentixol-LAI.

application of PP6M. The study aims to describe patient characteristics, reasons for prescribing PP6M, use and changes in concomitant treatments, hospital admissions, as well as level of adherence, discontinuation rates and patient satisfaction up to 24 months after PP6M initiation in real-world clinical practice. Here, we present the baseline patient characteristics and treatment patterns for the first 200 patients initiated on PP6M across multiple European settings for the first time.

Our preliminary findings suggest that PP6M is mostly prescribed in middle-aged male patients diagnosed with schizophrenia or schizophrenia spectrum disorders. Nonetheless, some patients were carrying a primary diagnosis of personality, bipolar or autism spectrum disorders and intellectual disability. In fact, previous studies have shown that paliperidone LAIs formulations is sometimes used for the maintenance treatment of bipolar disorder[14,15] as well as for the treatment

of personality, autistic disorders or mental retardation to help manage aggression, self-harm or impulsivity.[16–19]

Furthermore, although the majority of patients are treated with doses that fall within the recommended range, a few were prescribed with higher doses of PP6M and previous treatments of PP1M and PP3M. This is akin to previous reports detailing the occasional use of higher than recommended doses of PP1M and PP3 in clinical practice.[20–22] Interestingly, although the cohort of patients presented a moderate severity illness, measured by CGI-score, they required an oral antipsychotic therapy supplementation in most cases. Although high-dose prescribing of antipsychotic medication may often lead to worsening tolerability without necessarily any efficacy gains, recent evidence from meta-analysis advices caution in reducing the dose of antipsychotic during the maintenance treatment phase in schizophrenia below the optimal level used for acute stabilization because it may be associated with an increased risk of both relapse and treatment discontinuation.[23,24] Future data from the P2Y study are needed to assess whether patients treated with PP6M need lower doses of concomitant treatments such as antipsychotics or benzodiazepines.

Many patients with schizophrenia and other psychotic disorders often display varying degrees of anosognosia which may impact treatment adherence and the shared decision-making process. Interestingly, in this naturalistic cohort, most patients were previously treated with PP1M and PP3M for long periods of time and 43% indicated their preference for a less frequent injection treatment as the main reason for switching to PP6M. Indeed, evidence shows that patients' participation in their own treatment could encourage better adherence and improve outcomes.[5,25]

In this regard, previous data from real-world studies demonstrated retention rates as high as 78% and 87% at 1 year for PP1M and PP3M, respectively.[26–28] A 1-year continuation rate of 87% has also been shown for PP6M in a recent clinical trial.[8] In our naturalistic cohort, the retention rate for the second dose of PP6M was even higher (94%) and also for the outpatient subgroup (90%), confirming the experience thus far that LAIs with longer dosing intervals may have favourable treatment persistence. In this regard, a recent systematic review showed the benefits of PP3M in the management of schizophrenia due to improved adherence, decreased risk of relapse (even after several months of treatment discontinuation) and its positive impact on patients' and caregivers' satisfaction/quality of life facilitating long-term goals.[29] Therefore, long-term LAI as PP6M could favour the recovery of schizophrenia and improve ill course with a reduced risk of relapse and hospitalizations as well as the risk of isolation and social drift induced by schizophrenia spectrum disorders. Future data and studies are needed to assess the impact of PP6M in clinical practice compared with other LAIs.

Having said that, the extended dose interval administration does not necessarily have to translate to less frequent clinical contact. Importantly, the time saved for administration and the time spent discussing the need of the treatment can be utilized for other therapeutic rehabilitation, psychotherapy or to improve the patient–clinician therapeutic alliance. To this end, there is a growing body of evidence supporting patient satisfaction and acceptance with the use of PP3M and longer-acting treatments in general, leading to improved quality of life and less stigma.[30,31]

Finally, the mean number of hospitalizations 2 years before PP6M was overall low as most patients had been on either PP1M or PP3M, which has been repeatedly associated with a significant reduction in bed usage.[32–34] Moreover, a recent model study in the US concluded that for each 5% of patients with relapsing schizophrenia who switch to PP1M, and subsequently to PP3M/PP6M, the cumulative 3-year cost savings were estimated at $2.0 M with 223 relapses avoided.[35] Nonetheless, further data from this and future studies are needed to establish the potential overall and cost-effectiveness of PP6M in clinical practice.

Conclusion

To the best of our knowledge, the P2Y is the first ongoing mirror-image naturalistic study evaluating the clinical impact of PP6M. We showed that despite PP6M being mainly initiated in patients with schizophrenia, it can on occasions also be used for other indications and/or higher than recommended doses. Patient and clinician preference for LAIs with longer dosing intervals was the main reason for PP6M initiation/switching. The retention rate at 6 months (at the point of the second injection) was 94%. Future data from the

P2Y and other studies in clinical practice are needed to evaluate the full impact of PP6M in the long-term management of patients in clinical practice.

Limitations

Given that our inclusion/exclusion criteria were not restrictive, our cohort could provide high external validity and allow for some degree of generalizability across other Western countries. Nonetheless, due to the naturalistic study design, the present report does not allow any causal inference. Moreover, the estimates of concomitant oral medication intake may be inaccurate as it was quantified by using the electronic prescription registry, and it could be over or underestimated due to different prescription trends among the different countries and regions of centres included in the study. Additional factors that could affect the prescription of a LAI are the psychiatrists' choice and the cost, which were not included and may confound our study results. Also, in the present report, we present very preliminary data at baseline and 6 months after PP6M initiation. Other aspects concerning changes in BMI, cholesterol levels and QTc interval as well as patient, relatives and psychiatrists experience and satisfaction with PP6M will be underscored in the following reports concerning the P2Y study.

Declarations

Ethics approval and consent to participate

The study was conducted according to the World Medical Association Declaration of Helsinki, and it was approved by the Ethics Research Committee from the coordinating centre, the Santa Lucía University Hospital (ref. CEI.23-11_PY2_2022) in February 2023. Authorization to access patients' medical records was granted by each site's Professional Services Directorate. Oral and written information about the study was given, and written informed consent from the patient or their legal guard was obtained to participate in the P2Y study.

Consent for publication

Not applicable.

Author contributions

Juan Antonio García-Carmona: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

Alba García-Pérez: Data curation; Investigation; Writing – review & editing.

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