Asociación Colombiana de Psiquiatría ACP

Revista Colombiana de Psiquiatría

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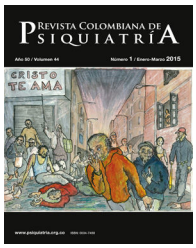

Artículo original

Effectiveness of Paliperidone Palmitate on Treatment Adherence and Relapse in the Adult Schizophrenia Population: A One-Year Mirror-Image Study in a Colombian Mental Health Care Facility

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ARTICLE INFO

Article history:
Received 12 April 2022
Accepted 9 June 2022
Available online 2 August 2022

Keywords:
Antipsychotics
Paliperidone palmitate
Schizophrenia
Adherence
Relapse

ABSTRACT

Introduction: The benefits of long-acting injectable antipsychotics have been documented in several observational studies, but data remain scarce in Latin America. This study aimed at evaluating the effectiveness of paliperidone palmitate once monthly (PP1M) on treatment adherence and relapse in the schizophrenia population followed in a government-funded mental health care facility in Colombia.

Methods: A mirror-image study was conducted. Adult schizophrenia patients treated with oral antipsychotics who subsequently received ≥2 PP1M injections between Jan. 1st, 2015 and Oct. 31st, 2018 were included. The study consisted of two retrospective phases: 12 months before and after the first PP1M injection. Outcomes were treatment adherence (proportion of days covered ≥80%), hospitalized relapse, hospital length of stay, and non-hospitalised relapse. Effect of PP1M on outcomes was assessed through multivariable conditional Poisson regression.

Results: 123 patients were eligible (mean age, 30.3 years; 79.7% males). Adherence was 23.6% in the pre-phase and 89.4% in the post-phase (RR = 3.77; 95%CI, 2.75-5.17). The proportion of patients with hospitalised relapse decreased from 46.3% to 35.0% (RR = 0.76; 95%CI, 0.59-0.99). In the 75 (61.0%) patients who continued PP1M throughout post-phase, beneficial effect on hospitalised relapse was stronger (RR = 0.64; 95%CI, 0.42-0.98). The proportion of patients with non-hospitalised relapse symptoms increased from 6.5% to 18.7% (RR = 2.27; 95%CI, 1.11-4.64).

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https://doi.org/10.1016/j.rcp.2022.06.001

Conclusions: PP1M initiation led to a dramatic improvement in treatment adherence and a decrease in hospitalised relapse. Observed increase in non-hospitalised relapse may be explained by a decrease in severity. Limitations are absence of a parallel comparison group and a generalisability limited to the population treated at this facility. Study provides data for the Latin America region and strength is the assessment of non-hospitalised relapse symptoms.

Efectividad Del Palmitato de Paliperidona en la Adherencia al Tratamiento y Las Recaídas en la Población Adulta Con Esquizofrenia: Un estudio en Imagen Especular de un Año en un Centro de salud Mental en Colombia

Palabras clave:
Antipsicóticos
Palmitato de paliperidona
Esquizofrenia
Adherencia
Recaída

RESUMEN

Introducción: Los beneficios de los antipsicóticos inyectables de acción prolongada se han documentado en varios estudios observacionales, pero los datos de América Latina siguen siendo escasos. El estudio se dirige a evaluar la efectividad del palmitato de paliperidona 1 vez al mes (PP1M) en la adherencia al tratamiento y las recaídas en la población con esquizofrenia seguida en un centro público de salud mental en Colombia.

Métodos: Se realizó un estudio en imagen especular. Se incluyó a pacientes adultos con esquizofrenia tratados con antipsicóticos orales que posteriormente recibieron > 2 PP1M entre el 1 de enero de 2015 y el 31 de octubre de 2018. El estudio consistió en 2 fases retrospectivas: 12 meses antes y después de la primera inyección de PP1M. Se evaluó la adherencia al tratamiento (proporción de días cubiertos ≥ 80%), la recaída hospitalizada, la duración de la estancia hospitalaria y la recaída no hospitalizada. El efecto del PP1M se evaluó mediante la regresión de Poisson.

Resultados: Fueron elegibles 123 pacientes (media de edad, 30,3 años; el 79,7% varones). La adherencia fue del 23,6% en la fase previa y del 89,4% en la segunda (RR = 3,77; IC95%, 2,75-5,17). La proporción de pacientes con recaída hospitalizada disminuyó del 46,3 al 35,0% (RR = 0,76; IC95%, 0,59-0,99). De los 75 pacientes (61,0%) que continuaron PP1M en la segunda fase, el efecto beneficioso en la recaída hospitalizada fue más fuerte (RR = 0,64; IC95%, 0,42-0,98). La proporción de pacientes con síntomas de recaída no hospitalizados aumentó del 6,5 al 18,7% (RR = 2,27; IC95%, 1,11-4,64).

Conclusiones: La iniciación de PP1M llevó a una drástica mejora en la adherencia al tratamiento y a una disminución de la recaída hospitalizada. El aumento observado en la recaída no hospitalizada puede explicarse por una disminución de la gravedad. Las limitaciones son la ausencia de un grupo de comparación paralelo y que la generalizabilidad se limita a la población tratada en este centro. La fortaleza del estudio es la presentación de datos de la región de América Latina y la evaluación de síntomas de recaída no hospitalizada.

Introduction

In 2013, the Ministry of Health of Colombia reported a prevalence of schizophrenia of 1%, corresponding to about 471,052 people affected by the disease in this country.[1] Like elsewhere, prevalence is low but the disease results in a tremendous health, social, and economic burden linked to the early onset of the disease, its incurable nature as well as persisting symptoms.[2]

Antipsychotics are the cornerstone treatment of schizophrenia with the aims of functional rehabilitation, prevention of symptom worsening, enhancement of psychosocial functioning, and improvement of quality of life.[3] However, non-adherence to oral antipsychotics (OAPs) ranges between 34% and 81%, which greatly affects their effectiveness in the real-world setting.[4] Despite a good response to initial treatment, schizophrenia symptoms often return, which are especially frequent after treatment discontinuation.[5] Consequently, the prevention of relapse is a primary treatment goal for the successful long-term management of schizophrenia.[6]

Long-acting injectable (LAI) formulations have become available to enhance adherence and thereby improve outcomes. According to a meta-analysis of 10 randomized controlled trials (RCTs) published in 2011, LAIs are associated with a lower risk of relapse compared to OAPs (relative risk

[RR] = 0.70; 95% confidence interval [95%CI], 0.57-0.87).[7] Since then, the benefits of LAIs compared to OAPs have also been shown through observational studies, mainly those that use a mirror-image study design.[8] Paliperidone palmitate administered once monthly (PP1M) is one of the LAIs approved for the treatment of schizophrenia,[9,10] and real-world studies have shown that PP1M is associated with significantly fewer inpatient admissions compared to OAPs, mainly due to improved treatment adherence.[11–14] Because these previous studies have used hospitalization as a measure of relapse, effectiveness of PP1M on a broader manifestation of relapse, such as symptoms not leading to hospitalization, remains poorly examined. Furthermore, there is a paucity of data in the Latin American region on the characteristics of schizophrenia patients treated with PP1M and on its effectiveness on real-world outcomes in this setting.

Our study aimed at evaluating the effectiveness of PP1M on treatment adherence and relapse in the adult schizophrenia population followed in a government-funded mental health care facility with a broad geographical coverage in Bello, Antioquia (Colombia).

Materials and methods

Study design

We conducted a single-arm, non-interventional pre-post comparison ("mirror-image") study to describe the characteristics of adult patients with schizophrenia who initiated PP1M, and to compare treatment adherence and relapse before and after the PP1M initiation. Study was conducted in the inpatient and outpatient settings of E.S.E. Hospital Mental de Antioquia, a 250-bed facility situated in Bello (vicinity of Medellin), Colombia. There were two retrospective treatment phases: 12 months prior to the first injection of PP1M (pre-phase) and 12 months after the first injection (post-phase). The date of first injection was referred to as the index date. The study was approved by the research ethics committee at the E.S.E. Hospital Mental de Antioquia.

Data sources

The main data source consisted of secondary use of existing electronic medical records (EMRs) at E.S.E. Hospital Mental de Antioquia. There are approximately 65,000 psychiatric consultations per year at this hospital, and it is estimated that medical records are available for approximately 25,000 psychiatric care patients of all ages.[15] Dispensed medications, including PP1M, OAPs, and concomitant drugs, were obtained through linkage with the hospital pharmacy database, which dispenses the totality of in- and out-patient psychiatric drugs to patients followed at the facility. We ascertained non-hospitalized relapse through the examination of physicians' notes (narratives) found in the EMRs.

Study population

We identified the study population over the period January 1st, 2015 to October 31st, 2018 in order to have a 12-month pre- and a 12-month post-phase for all study patients (first pre-phase started January 1st, 2014 and last post-phase ended October 31st, 2019).

We included patients who met the following inclusion criteria: *a)* a confirmed diagnosis of schizophrenia (ICD-10 codes: F20.0 [Paranoid schizophrenia], F20.1 [Disorganized schizophrenia], F20.2 [Catatonic schizophrenia], F20.3 [Undifferentiated schizophrenia], F20.5 [Residual schizophrenia], F20.6 [Simple schizophrenia], F20.8 [Other schizophrenia], and F20.9 [Schizophrenia, unspecified]) identified at least one year prior to index date; *b)* to have been prescribed an OAP treatment, regardless of treatment duration and number of products, in pre-phase; *c)* age ≥18 years (adult patients) at first injection of PP1M (index date); *d)* to have received an initial dose of ≥2 injections of PP1M in a period of one week, regardless of concomitant use of OAPs, treatment duration, and subsequent switches to other LAIs or switch back to OAPs only, and *e)* to have been followed at the E.S.E. Hospital Mental de Antioquia for at least 12 months prior to, and 12 months after the index date in order to ensure completeness of the EMR. We excluded patients who: *a)* were diagnosed with refractory schizophrenia; *b)* used LAIs in pre-phase; *c)* initiated PP1M in hospital and were never discharged during the following 12 months, and *d)* died or were lost to follow-up in the post-phase.

Outcomes

Treatment adherence

We measured treatment adherence using the proportion of days covered (PDC), defined as the proportion of days with an active antipsychotic drug (total number of days supply) over the entire pre- and post-phase, with the removal of overlapping prescriptions.[16] This means that the number of days supply of a drug that is left at the time of switch to a new product is not counted in the PDC calculation. Furthermore, because schizophrenia requires continuous treatment, PDC was calculated in each phase using the entire 365 days as denominator. For OAPs, the total number of days supply was calculated using the dispensing dates and the number of days dispensed. Patient was considered adherent to treatment if PDC was ≥80%.[16] Because the risk of hospitalization increases with every missed day of OAP use,[17] no allowance (i.e., no grace period) was given to assess the number of days with active prescription for OAPs. In accordance with previous published studies, each injection of PP1M was associated with 45 days of active prescription.[18,19] Because of the inclusion criterion of at least two injections in a period of one week, the PDC in the post-phase was calculated starting at 45 days following the second injection. We also conducted a sensitivity analysis, where PP1M was associated with 30 days of active prescription.

Although hospital-supplied medication during inpatient stay is recorded in the hospital database, adherence is a measure of patient's behavior. Adherence to OAPs during hospitalization is expected to be 100% and would thus lead to an overestimation of the overall PDC during the 12-month period. Hence, for patients who were hospitalized, the number of days of inpatient stay was not considered for the PDC calculation (neither in the PDC's numerator or denominator).

Relapse

Clinically, relapse is defined by the presence of at least one of the following criteria: *a)* involuntary or voluntary admission to a psychiatric hospital for decompensation of the patient's schizophrenic symptoms (psychiatric hospitalization or emergency department [ED] visit); *b)* suicidal/homicidal ideation judged clinically significant; c) deliberate self-injury; *d)* clinically meaningful worsening of symptoms as determined by the treating physician's judgment, and *e)* violent behavior resulting in clinically significant injury to the patient or another person, or property damage.[20–24] Hence, we assessed relapse using objective measures of the composite variable of hospitalization or ED visit during the study period (pre- and post-phase) as well as hospital length of stay (LoS). In addition, we identified relapse symptoms (also referred to as "relapse signatures") through a manual review of clinical notes. Those relapse symptoms not leading to hospitalization or ED visits were then categorized into four categories: suicidal/homicidal ideation; deliberate self-injury; clinically meaningful worsening of symptoms; violent behavior.

We therefore derived five measures of relapse for each patient and for each phase: *a)* at least one hospitalized relapse (binary variable); *b)* number of hospitalized relapses (count); *c)* total hospital LoS; *d)* at least one occurrence of relapse symptoms not leading to hospitalization or ED visit (binary variable), and *e)* number of relapse symptoms not leading to hospitalization or ED visit (count).

Potential confounders

Since patients served as their own reference, confounders that remain unchanged over time were controlled for by design. However, we considered as potential confounders variables that vary over time and that may influence the study outcomes —i.e., comorbidities, concomitant psychiatric illnesses, alcohol use, tobacco use, illicit drug use, psychosocial interventions, electroconvulsive therapy— and, for the outcomes of relapse symptoms not leading to hospitalization or ED visit, number of psychiatric outpatient visits (since there would be more opportunity for the detection of relapse symptoms).

Statistical analyses

Comparison of treatment adherence and relapse between pre- and post-phase

We conducted descriptive analyses on patient sociodemographic and clinical characteristics, schizophrenia subtype and number of years since diagnosis, pattern of OAP use in the pre-phase (number and name of OAP products), status of patient at PP1M initiation (inpatient or outpatient), reason for PP1M initiation, and discontinuation of PP1M during follow-up (switch to OAP only, or to another LAI with or without OAP). As these were descriptive analyses, there was no hypothesis-testing.

We compared frequencies of treatment adherence, hospitalized relapse (dichotomous and count), total hospital LoS, and non-hospitalized relapse symptoms (dichotomous and count) between the pre- and post-phase. A McNemar test on discordant pairs between pre- and post-phase was used to assess the consistency in adherence, hospitalized relapse, and non-hospitalized relapse. Crude and multivariable conditional Poisson regression models were developed for these outcomes. Confounders that varied over time (described in subsection Potential confounders) were included in the multivariable analyses. We conducted subgroup analyses for patients who continued PP1M and for patients who discontinued (dropped out) during post-phase.

To account for immortal time bias, we conducted a sensitivity analysis for the outcomes of hospitalized relapse and number of hospitalized relapses, whereby the index hospitalization was excluded from the pre-phase for patients who initiated PP1M in hospital.

Results

Patient identification flow chart

Figure 1 in the supplementary material presents the patient selection flow chart for the study. A total of 372 adult patients initiated PP1M at E.S.E. Hospital Mental de Antioquia between January 1st, 2015 and October 31st, 2018, out of whom 123 (33.1%) were included in the study. Main reason for exclusion was LAI use in the pre-phase (n = 180, 48.4%). There were 54 patients who were lost to follow-up, all for administrative issues such as change of contact information or moving to a different geographical area. There were no death and loss to follow-up was not attributable to treatment failure.

Patient characteristics

As shown in Table 1, most patients were young (mean age, 30.3 years) and males (n = 98, 79.7%). The majority was diagnosed with paranoid schizophrenia (n = 74, 60.2%), followed by other schizophrenia (i.e., ICD-10 code F20.8). Most patients initiated PP1M as outpatient (n = 86, 69.9%) and poor adherence with OAPs was the primary reason for PP1M initiation for half the patients, followed by a lack of efficacy.

Treatment characteristics

Number and types of OAP used during pre- and post-phase are shown in Table 2. As expected, mean number of OAP products use was higher in the pre-phase than in the post-phase, since it was an inclusion criterion for the study. The most common prescribed OAPs in pre-phase were risperidone and olanzapine while in the post-phase, it was clozapine and olanzapine.

Discontinuation of PP1M occurred in 48 patients (39.0%), on average 6 months after initiation. A minority switched to another LAI (pipotiazine palmitate [n = 6] and risperidone [n = 4]), with or without use of OAPs, while 29 (60.4%) switched to OAPs only. Details are shown in Table 3. The number of patients who discontinued PP1M did not increase in the sensitivity analysis when considering 30 days of active treatment instead of 45.

Outcomes

Table 4 presents the number of patients with outcomes in pre- and post-phase. More patients were adherent in the

Table 1 – Patient socio-demographic and clinical characteristics, patient status at index date, and primary reason for PP1M initiation.

Characteristic	N = 123
Age (years)	
Mean (SD)	30.3 (10.1)
Median	28
Min-Max	18-60
Sex, n (%)	
Female	25 (20.3)
Male	98 (79.7)
Schizophrenia ICD-10 subtype, n (%)	
Paranoid schizophrenia	74 (60.2)
Other schizophrenia	48 (39.0)
Residual schizophrenia	1 (0.8)
Patient status at PP1M initiation, n (%)	
Outpatient	86 (69.9)
Inpatient	37 (30.1)
Primary reason for PP1M initiation, n (%)	
Adherence issue with OAPs	62 (50.4)
Lack of efficacy of OAPs	44 (35.8)
Patient preference	7 (5.7)
Tolerance issue	6 (4.9)
Other	4 (3.3)

ICD-10: International Classification of Diseases 10th Revision; OAP: oral antipsychotic; PP1M: paliperidone palmitate once monthly; SD: standard deviation.

Table 2 – OAP treatment during pre- and post-phase.

	N = 123	
Characteristic	Pre-phase	Post-phase
Number of OAP products use, n (%)		
Mean (SD)	1.8 (0.90)	1.5 (0.83)
Median	2	1
Min-Max	1-7	0-4
Type of OAP use, n (%)		
Risperidone	68 (55.3)	43 (35.0)
Olanzapine	57 (46.3)	50 (40.7)
Clozapine	40 (32.5)	51 (41.5)
Paliperidone	24 (19.5)	11 (8.9)
Other	34 (27.6)	32 (26.0)

OAP: oral antipsychotic; SD: standard deviation.

Table 3 – LAI treatment during post-phase (N = 123).

PP1M discontinuation, n (%)	
Yes	48 (39.0)
No	75 (61.0)
Time to PP1M discontinuation (days)	
n	48
Mean (SD)	186.9 (113.7)
Median	147
Min-Max	53-360
Switch back to OAP only, n (%)	
Yes	29 (60.4)
No	19 (39.6)
Switch to another LAI, n (%)	
Yes	10 (20.8)
No	38 (79.2)

LAI: long-acting injectable; OAP: oral antipsychotic; PP1M: paliperidone palmitate once monthly; SD: standard deviation.

post-phase than in the pre-phase, 110 (89.4%) vs 29 (23.6%). Results remained the same, whether the number of days of active prescription assigned to each PP1M injection was 45 or 30 in the sensitivity analysis. McNemar test, which tests difference in discordant pre-post pairs, was statistically significant ($P < 0.0001$). The number of patients with at least one hospitalized relapse decreased from 57 (46.3%) in pre-phase to 43 (35.0%) in post-phase. McNemar test was statistically significant ($P = 0.0433$). The only relapse symptom not leading to hospitalization or ED visit reported for this study was "clinically meaningful worsening of symptoms". The number of patients reported as having had this symptom increased in post-phase. McNemar test was statistically significant ($P = 0.0039$).

Table 4 – Treatment adherence and patient relapse during pre- and post-phase.

Outcome in pre-phase, n (%)	Outcome in post-phase, n (%)			McNemar *P*-value
Adherence (PDC ≥80%)	Yes	No	Total	
Yes	28 (22.8)	1 (0.8)	29 (23.6)	< 0.0001
No	82 (66.7)	12 (9.8)	94 (76.4)	
Total	110 (89.4)	13 (10.6)	123	
	Hospitalized relapse			
Hospitalized relapse	Yes	No	Total	
Yes	26 (21.1)	31 (25.2)	57 (46.3)	0.0433
No	17 (13.8)	49 (39.8)	66 (53.7)	
Total	43 (35.0)	80 (65.0)	123	
	Non-hospitalized relapse			
Non-hospitalized relapse	Yes	No	Total	
Yes	2 (1.6)	6 (4.9)	8 (6.5)	0.0039
No	21 (17.1)	94 (76.4)	115 (93.5)	
Total	23 (18.7)	100 (81.3)	123	

PDC: proportion of days covered.

Table 5 – Number of hospitalized relapses, total LoS, and non-hospitalized relapses (N = 123).

	Pre-phase n (%)	Post-phase n (%)	P-value
Number of hospitalized relapses			
Mean (SD)	0.89 (1.21)	0.54 (0.93)	0.0012[a]
Median	0	0	
Min-Max	0-5	0-5	
Overall total hospital LoS (days)[b]			
Mean (SD)	12.2 (21.9)	11.4 (21.4)	0.7713[a]
Number of relapse symptoms not leading to hospitalization or ED visit			
Mean (SD)	0.07 (0.29)	0.25 (0.61)	0.0013[a]
Median	0	0	
Min-Max	0-2	0-3	

ED: emergency department; LoS: length of stay; SD: standard deviation.

[a] Wilcoxon signed rank test.

[b] The number of days for the index hospitalization is divided between the pre-phase (prior to index date) and the post-phase (on or after index date).

As shown in Table 5, the mean number of hospitalized relapses decreased from 0.89 ± 1.21 in pre-phase to 0.54 ± 0.93 in post-phase ($P = 0.0012$), while total hospital LoS decreased from 12.2 to 11.4 days ($P = 0.7713$). Conversely, the mean number of non-hospitalized relapse increased from 0.07 ± 0.29 to 0.25 ± 0.61 ($P = 0.0013$).

Adjusted relative risks based on conditional Poisson regression, along with 95%CIs, are presented in Table 6 for each outcome. Only potential confounders that changed between pre- and post-phase (i.e., illicit substance use and number of psychosocial interventions) were included in the multivariable model and interaction was tested between all variables of the model. In addition, for the outcome of relapse symptoms not leading to hospitalization or ED visit, the number of outpatient medical visits was added to the multivariable model. The sensitivity analysis, whereby the index hospitalization was excluded from the pre-phase for those who started PP1M as inpatients, is also presented for the outcomes of hospitalized relapse, number of hospitalized relapses and hospital total LoS.

Probability of being adherent to any antipsychotic treatment in post-phase was 3.77 times higher than in pre-phase (95% CI, 2.75-5.17). This probability was similar for patients who continued and for patients who discontinued PP1M in post-phase, as adherence was determined for all treatments combined (PP1M and/or OAPs). The risk of hospitalized relapse (RR = 0.76; 95% CI, 0.59-0.99) and the number of hospitalized relapses (RR = 0.61; 95% CI, 0.45-0.83) decreased in post-phase. These decreases were greater in patients who continued PP1M (RR = 0.64; 95% CI, 0.42-0.98; and RR = 0.52; 95% CI, 0.33-0.83 respectively) and not significant for patients who discontinued PP1M (RR = 0.91; 95% CI, 0.65-1.25; and RR = 0.67; 95% CI, 0.44-1.03 respectively). In contrast, the risk of relapse symptoms and the number of relapse symptoms increased in post-phase (RR = 2.27; 95% CI, 1.11-4.64; and RR = 2.51; 95% CI, 1.16-5.40 respectively), and these increases were more important for patients who discontinued PP1M (RR = 3.33; 95% CI, 0.95-11.70; and RR = 3.95; 95% CI, 1.25-12.48, respectively for relapse symptoms and number of relapse symptoms) than for patients who continued PP1M (RR = 2.15; 95%CI, 0.79-5.81; and RR = 2.18; 95% CI, 0.77-6.20, respectively for relapse symptoms and number of relapse symptoms).

In the sensitivity analyses, when removing the index hospitalization for patients who started PP1M as inpatients, the risk of hospitalized relapse and the number of hospitalized relapses became statistically nonsignificant between pre- and post-phase (RR = 1.05; 95% CI, 0.79-1.38; and RR = 0.93; 95% CI, 0.67-1.29 respectively). The results were also statistically nonsignificant for patients who continued PP1M and for those who dropped out. Conversely, the mean hospital LoS in the pre-phase was 9.5 days decreasing to 6.0 days in the post phase ($P = 0.017$).

Discussion

In this single center study, adherence to OAP prior to the initiation of PP1M was 23.6% using the threshold of 80% of the PDC, which is lower than estimates reported in the literature (34% to 81%).[4] However, this was to be expected due to the selection of the study population. As this was a mirror-image study, by design all patients initiated PP1M and it was shown that half of these patients initiated PP1M because of poor adherence to OAP. Similar to previous mirror-image studies, PP1M initiation significantly improved treatment adherence. It can therefore be concluded that in patients who are not adherent to OAPs, PP1M initiation greatly improves adherence over a period of one year, even if some patients discontinue the product.

Initiation of PP1M was associated with a RR of 0.76 for hospitalized relapse. Such protective effect is lower than that found in a meta-analysis of six observational studies that included the LAI dropouts (RR = 0.44; 95%CI, 0.28-0.67).[8] However, in this meta-analysis, estimates were pooled even in the presence of very high statistical heterogeneity between studies (I^2 >90%). The magnitude of the reduction in hospitalized relapse found in the current study is nearly the same as that found in a meta-analysis of RCTs (RR = 0.7).[7] Several studies found in the literature were based on administrative claims data (where symptoms are not documented) while in the hospital EMRs, reasons for hospitalizations are very well

Table 6 – Conditional Poisson regression for the effect of PP1M initiation on adherence and relapse for all patients, patients who continued and patients who discontinued PP1M during follow-up.

Outcome	All patients N = 123 RR (95%CI)	Continued PP1M N = 75 RR (95%CI)	Discontinued PP1M N = 48 RR (95%CI)
Adherence (PDC ≥80%)[a]	3.77 (2.75-5.17)	3.77 (2.59-5.48)	3.88 (2.16-6.96)
Relapse[a]	0.76 (0.59-0.99)	0.64 (0.42-0.98)	0.91 (0.65-1.25)
Number of relapses[a]	0.61 (0.45-0.83)	0.52 (0.33-0.83)	0.67 (0.44-1.03)
Relapse symptoms[b]	2.27 (1.11-4.64)	2.15 (0.79-5.81)	3.33 (0.95-11.70)
Number of relapse symptoms[b]	2.51 (1.16-5.40)	2.18 (0.77-6.20)	3.95 (1.25-12.48)

CI: confidence interval; PDC: proportion days covered; PP1M: paliperidone palmitate once monthly; RR: relative risk.

[a] Adjustment variables were illicit substance use (yes/no) and number of psychosocial interventions.

[b] Adjustment variables were illicit substance use (yes/no), number of psychosocial interventions, and number of outpatient psychiatric visits.

documented. Quality of outcome ascertainment may partly explain some of the discrepancies between the effect size found in the current study with those of previous observational studies.

Initiation of PP1M also led to a decrease in the number of hospitalized relapse episodes with a RR of 0.61 (95% CI, 0.45-0.83). This protective effect is lower than the one previously reported in the meta-analysis of five observational studies that included the LAI dropouts, although it is within the 95% CI of the published estimate (RR = 0.42; 95% CI, 0.29-0.63).[8] In this meta-analysis, estimates were also pooled even in the presence of very important statistical heterogeneity ($I^2 = 93.5\%$). The beneficial effect of PP1M on the rate of hospitalization disappeared when removing the index hospitalization in the sensitivity analysis. Conversely, decrease in mean LoS became statistically significant. Previous studies have also shown that the removal of the index hospitalization not only affected hospitalization rate but also accentuated the beneficial effect of PP1M on total LoS. It was therefore suggested that PP1M would be more cost-effective when started in an outpatient setting.[12] To further elucidate this hypothesis, the effect of PP1M on hospitalization rate and LoS, stratification of findings according to initiation setting (inpatient or outpatient) would need to be conducted.

Although it is known that treatment discontinuation is highly associated with the worsening of schizophrenia symptoms, there were no studies found in the literature that examined the effect of PP1M initiation on non-hospitalized relapse. Such data gap is mainly due to the absence of qualitative information on clinical symptoms in administrative claims databases. In contrast, symptoms worsening is well documented in the hospital EMRs. Study showed that PP1M initiation resulted in an increase in the proportion of patients with non-hospitalized relapse. This may partly be attributable to the fact that patients who are treated with PP1M must attend the clinic monthly to receive their injection at this hospital, which is accompanied by a medical follow-up visit. Such increase in regular follow-up visits, compared to prephase, increases the opportunity for the assessment of relapse symptoms and thus, introduce a detection bias (which is a form of information bias). It is also common that in time periods between changes in medication, especially antipsychotics, some patients could experience an exacerbation of symptoms of schizophrenia that are not severe enough to initiate hospitalized care.

Comparing the effect of initiating PP1M on hospitalized and non-hospitalized relapse, one may thus conclude that avoided hospitalizations due to relapse may have contributed to the increase in relapses that were managed in the outpatient setting. Such impact is thus clinically meaningful.

Generalizability of study results is limited to the population who receives mental health services at the E.S.E. Hospital Mental de Antioquia. The eligibility requirement of at least two PP1M injections may introduce selection bias because the start of follow-up predates eligibility. This is a period often labeled as “immortal time”. This period, however, was not included in the calculation of adherence. Because it was necessary to allow for a 12-month post-phase period, patients who died or were lost to follow-up during post-phase were not included, and hence, may have overestimated the benefits of PP1M. Nevertheless, loss to follow-up of 54 patients who initiated PP1M was due to administrative issues (e.g., change of contact information or, moved to a different geographical area). There were no deaths among these 54 patients. The removal of the index hospitalization in the sensitivity analysis removed the benefits of PP1M on hospitalization rates but accentuated the effect on LoS, which may suggest that the greatest benefits are observed in patients who started PP1M as outpatients. This hypothesis would, however, need further investigation using a larger sample size stratifying by inpatient and outpatient status at PP1M initiation. Due to the absence of a comparison group (i.e., non-PP1M initiators), it was not possible to differentiate relapses attributable to the initiation of PP1M from those attributable to the natural history of the disease.

Conclusions

PP1M initiation led to a dramatic improvement in treatment adherence as well as to a decrease in the occurrence and number of hospitalized relapse episodes. Conversely, there was an increase in the management of relapse symptoms in the outpatient setting, even after taking into account detection bias. This increase could be explained by an improvement in the psychiatric follow-up after PP1M initiation. It is also common that in time periods between changes in medication,

especially antipsychotics, some patients could experience an exacerbation of symptoms of schizophrenia that are not severe enough to initiate hospitalized care.

Funding

This study was funded by McNeill Panama. The funding source was involved in the study design and in the decision to submit the article for publication. The funder had no role in the conduct of the study, i.e., patient selection, data collection, management, analyses, and interpretation of findings.

Conflicts of interests

OR is a member of an advisory board and a speaker for Janssen on diseases unrelated to this study. AMC, GC, and YM are employees of YolaRX Consultants, which designed this study, conducted the statistical analyses, interpreted the results, and wrote the manuscript under contractual agreement. LMA has nothing to disclose. GM and VM were employees of Janssen at the time the research was conducted.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.rcp.2022.06.001.

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