EVIDENCE BASED MEDICINE

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Paliperidone Palmitate Treatment in Outpatient Care Setting: A Naturalistic Study

By Rosaria Di Lorenzo, Michela Cameli, Marisa Bolondi, Giulia Landi, Valentina Moretti, Chiara Piemonte, Gabriella Pollutri

ABSTRACT *~* ***Objective****: To evaluate paliperidone palmitate (PP) effectiveness, safety and adherence to treatment.* ***Methods****: We collected data of all patients (n = 50) affected by Schizophrenia Disorders, treated with PP for a 3 month minimum period in the outpatient setting of Mental Health Department in Modena, from 01/01/2014 to 31/01/2015. We evaluated reasons and modality for PP implementation, improvement in symptom and functioning scales, adverse effects, discontinuations and relapses. We statistically correlated socio-demographic and clinical variables of our sample with PP therapeutic variables.* ***Results****: We registered an improvement in all scales, with a superior percentage in PANSS positive subscale. The mean PP dose in some patients was lower than official indications, although our sample was clinically severe. Illness relapses affected 60% and dropout 18% of patients. PP was well tolerated and in just a few cases adverse events required treatment interruption. The risk factors for discontinuation were represented by "lack of therapeutic compliance" (HR = 4.11, p < 0.0001) and "inefficacy" (HR = 1.67, p < 0.0001).* ***Conclusions****: With limitations of observational design, this research highlights that PP was well tolerated and effective in improving both psychotic symptoms and functioning, but moderately effective in preventing relapse, probably due to clinical severity of our patients associated with extremely cautious and flexible PP prescriptions.*
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Introduction

Clinical management of schizophrenia remains a major challenge due to frequent relapses, persistence of psychotic symptoms, non-adherence to antipsychotic

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medications, recurrent hospitalizations, and increased burden on healthcare resources.[1,2] Typical neuroleptics, have permitted a great improvement of schizophrenia prognosis,[3,4] but one third of schizophrenic patients are treatment-resistant and about 50% of patients are non-compliant with typical antipsychotic treatment.[5] Although the atypical antipsychotic drugs have ameliorated the treatment compliance, due to the more tolerable adverse effect profile, about 20–50% of treated schizophrenic patients suffer frequent relapses after an initial symptom improvement with this therapy.[6] An absent or no constant adherence to treatment may represent the major risk of relapse[7,8] which could be improved by a long-acting antipsychotic therapy, as literature data show.[9–11] Typical long-acting injectable (LAI) preparations, synthesized by forming an ester with a fatty acid, allow slow release of the active ingredient by hydrolysis, providing a more stable steady-state concentration of medication in the blood compared with daily oral dosing, with absent "first-pass metabolism" and reduced blood peaks so to permit the prescription of the lowest effective doses.[12] LAI showed strong superiority to oral antipsychotics in preventing hospitalization and improving therapeutic adherence in patients with schizophrenia.[9,10,12] Recently, after the introduction in 2003 of long-acting injectable risperidone, realized thanks to an innovative technology,[13] the LAI of risperidone's active metabolite, paliperidone palmitate (PP), has become available and approved in the European Medicines Agency,[14] the US and in more than 50 countries worldwide.[15] In the EU, PP is a LAI antipsychotic drug indicated for the maintenance treatment of schizophrenia in adults whose disease has already been stabilized on treatment with paliperidone or risperidone.[14]

Paliperidone (9-OH-risperidone) is a metabolite of risperidone and differs from risperidone by only a single hydroxyl group, which has permitted the synthesis of palmitate ester. Binding studies have shown a fast dissociation on D2 receptors and a relative greater effectiveness in the processes of intracellular signal transmission by the paliperidone than its metabolic precursor.[16] Paliperidone displays high affinity for 5-HT2A and D2 receptors, and is also active as an antagonist at the α1 -and α2-adrenergic receptors and the H1-receptor.[17] This pharmacologic profile could explain some of its clinical effects, such as weight gain, orthostatic hypotension and sedation.[17] Paliperidone, like risperidone, presents low risk for anticholinergic side effects, including cognitive deficits and gastrointestinal disorders, since both do not have antimuscarinic properties.[18] Following an injection of PP, active paliperidone plasma levels have been detected from day 1, therefore co-administration with oral paliperidone on initiation of therapy is not required.[19] The two initial deltoid muscle injections of 150 mg

eq (234 mg) and 100 mg eq (156 mg) respectively, on days 1 and 8, as indicated by official protocol for the patients who switch from oral antipsychotic therapy, help to maintain therapeutic drug concentrations rapidly.[20] This allows a rapid control of symptoms, with the reduction of severity, observed within 4–8 days of dosing,[21–23] unlike risperidone RP, whose therapeutic concentrations in plasma are reached no earlier than the 3rd week after the initial administration.[13] Differently from its precursor, paliperidone is largely excreted unchanged in the urine. In fact, while cytochrome P450 2D6 and CYP3A4 have been implicated in the metabolism of paliperidone in *in vitro* studies, these isoenzymes play a limited role in the metabolism of paliperidone *in vivo*.[24]

Most short-term (9–13 weeks) placebo-controlled trials have observed a statistically significantly greater reduction of schizophrenia symptoms with 25–150 mg intramuscular PP in comparison to placebo. The onset of clinical response was 8 days in patients who received the recommended initial 150 mg dose of intramuscular PP into the deltoid muscle on day 1.[22,25,26] In randomized placebo-controlled long-term, PP studies a dose range of 25 to 100 mg was associated with a free time to relapse significantly longer than placebo in patients with schizophrenia.[27–29] PP was also shown to be non-inferior to risperidone long-acting injection (plus oral risperidone supplementation as needed) in other studies.[30,31] In contrast, these results were not confirmed by another longer study of the two drugs compared (most likely due to inadequate dosing of PP palmitate at initiation of therapy).[32] McEvoy et al. in a large prospective comparative effectiveness double-blind RCT (ACLAIMS) did not find any significant difference in efficacy failure between PP and haloperidol decanoate, but evidenced more prevalent side effects in the haloperidol decanoate treated group.[33] The Paliperidone Palmitate Flexible Dosing in Schizophrenia (PALMFlexS), a pragmatic 6-month, interventional study, evidenced an improvement in all 3 groups (acute, non-acute patients previously treated with oral antipsychotics and non-acute patients switched from other LAIs) of the sample treated with PP at the endpoint, supporting the use of flexibly dosed PP in non-acute patients considered clinically stable by their physician.[34–36] An observational study evidenced that 65% of 200 patients consecutively prescribed PP in normal practice were still receiving PP after 1 year with a statistically significant reduction of their admissions to hospital in the year following PP initiation.[37,38] Other open label studies confirmed the effectiveness and tolerability of PP in short,[39] and long-term treatments.[40–44] PP was reasonably well tolerated in most studies, with low rates of extrapyramidal symptoms or body weight gain, which, however, were more common at higher doses.[19,20,22,25,27,30,34–36]

Aims

- To evaluate effectiveness, safety of PP and adherence to treatment in outpatient psychiatric setting of a Mental Health Service.
- To highlight both variables favoring treatment maintenance and risk factors for discontinuation of PP treatment.

Methods

This study was conducted in accordance with the principles of the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 1964) and good clinical practice and was not sponsored by any pharmaceutical company.

This naturalistic study was conducted in the 8 outpatient services of Mental Health Department (MHD) in Modena (Az-USL of Modena), which collected patients from a catchment area of 690,000 inhabitants.

The Sample

From the electronic database of Mental Health Services and patients' clinical records we retrospectively selected the sample, which included all patients who started PP therapy from 01/01/2014 to 31/10/2014, according to the following inclusion and exclusion criteria. All patients gave their informed consent before beginning long-acting therapy, signing the Mental Health Service form.

Inclusion criteria: All the patients affected by Schizophrenia Spectrum Disorders, according to International Classification of Diseases-9th revision-Clinical Modification (ICD-9-CM)[45] criteria, treated with PP for a minimum period of 3 months.

Exclusion criteria: Patients affected by psychiatric disorders which do not belong to Schizophrenia Spectrum, patients treated by clozapine due to therapy-resistance, patients treated with PP for less than 3 months.

The Observation Period

The observation period ranged from 01/01/2014 to 31/01/2015.

The Selected Variables

For each patients we collected the following variables patients' clinical records.

- Socio-Demographic variables: gender, age, nationality, school degree, marital status, family and living environment, work activity and social and economic conditions.
- Clinical variables: psychiatric diagnosis (ICD-9 CM),[45] other psychiatric disorders in comorbidity, substance abuse and organic comorbidity, psychiatric history (period of illness from schizophrenia onset, number of previous psychiatric hospitalizations).
- Therapeutic variables of PP treatment: motivation and modalities of PP treatment implementation, oral therapy associated (kind of drugs and period of oral treatment), number of PP injections, mean dose and time interval between each PP injection, mean period of therapy, discontinuation of treatment (reasons, number of injections and days before discontinuation), adverse effects (kind and period of occurrence in comparison to PP treatment), relapses (urgent psychiatric consultations and/or hospitalizations and period of occurrence in comparison to PP treatment).
- Symptom and functioning rating scales: Brief Psychiatric Rating Scales (BPRS),[46] Positive and Negative Syndrome Scale (PANSS),[47] Clinical and Global Impression-Severity (CGI-S) and Clinical and Global Impression- Improvement Scale (CGI-I),[48] Global Assessment of Functioning (GAF),[49] Personal and Social Performance Scale (PSP),[50] Simpson-Angus Extrapiramidal Side Effect Scale (SAS),[51] administered at the beginning of PP treatment and after 3 (T3), 6 (T6), 9 (T9) and 12 months (T12).

Statistical Data Analysis

We calculated absolute frequency and percentages for categorical variables, mean and standard deviation (SD) for continuous variables. We evaluated the association between each variable and gender by using the Chi^2 test for categorical data and t-test for continuous data. We correlated "period of PP treatment" and "the dose treatment" with the variables collected (demographics, clinical, pharmacological and symptom and functioning rating scale scores) by using single and multiple linear regression. We applied the Cox proportional hazards model[52] to identify the potential risk factors of discontinuation of PP treatment. Hazard ratio (HR) and the respective 95% Confidence Interval (95% CI) were calculated for each variable's category. A HR > 1 means higher risk for recurrent admissions in comparison with the referent category. A p-value < 0.05 was considered as statistical significance. Data have been analyzed by using the statistical software STATA version 12.[53]

Results

Our sample was homogeneous for gender distribution and other demographic variables (Table 1): most of our patients were Italian, had completed junior high school (62%); more than half of them (64%) was single and lived with nuclear family (54%); 44% of them were unemployed, even if only 14% had registered serious economic problems.

Regarding gender differences, we founded that females statistically significantly differed from males both for age and length of psychiatric history: women's median age was 47 years, 8 years greater than men's age (t-test, $p < 0.05$) and, similarly, women's period of illness from schizophrenia onset was 9 years longer than males (t-test, $p < 0.05$) (Table 2).

62% of the sample suffered from paranoid type Schizophrenia and most of them did not presented any psychiatric or substance use comorbidity (Table 2); even medical comorbidity was rarely represented, since only 15 patients suffered from chronic organic diseases, like diabetes, hypertension, hypothyroidism. 60% of our patients accounted at least one psychiatric hospitalization in their clinical history, without any statistically significant difference between the two genders (Table 2). The two main reasons for PP prescription were the inefficacy of previous antipsychotic medications (42%) and the lack of therapeutic compliance (38%) (Table 3). The reasons for PP implementation were statistically significantly different between patients previously treated with oral antipsychotics and those treated before with other long-acting drugs: for the first group the lack of therapeutic compliance and for the second the inefficacy of previous drugs were the main reasons for PP implementation (Pearson test $Chi^2 = 9.32$, $p < 0.0001$). We evidenced that 83% of women had switched from a previous depot medication, whereas men had more frequently switched from previous oral antipsychotics, with a statistically significant difference (Pearson Test $Chi^2 = 4.98$, $p = 0.026$) (Table 3). In order to verify the adherence to the guidelines of PP prescription, we have carefully studied the first therapeutic dose of PP, with particular attention to the switch from the previous therapy. Only for 6 patients of all those who had started PP after switching from an oral therapy ($n = 16$), the first two injections were correctly prescribed on days 1 and 8, as suggested by the official protocol (first dose: 110.94 mg eq ± 35.32SD; second dose: 100 mg eq ± 18.26 SD). Those who had been switched from LAIR ($n = 22$) received the first dose of paliperidone palmitate as prescribed by the technical file, whereas the patients switched from haloperidol decanoate ($n = 10$) or from other depot medications ($n = 1$ with fluphenazine decanoate 25 mg/21 days, $n = 1$ with zuclopenthixol decanoate 200 mg/14 days) received variable doses of PP at first injection (first dose: 116.66 mg eq ± 30.77

TABLE 1

Socio-Demographic Variables of Our Patients, Divided by Gender (n = 50)

Variables	Sample: Females 24 (48%)	Sample: Males 26 (52%)	Total	Statistical test
Nationality, N(%)				
Italian	21 (87.5%)	21 (80.7%)	42 (84%)	
European	2 (8.33%)	1 (3.84%)	3 (6%)	NS
non-European	1 (4.16%)	4 (15.3%)	5 (10 %)	
Age, M ± SD				
Years	47.5 (± 13.1)	39 (± 15.34)	43.1 (± 14.8)	t-test $p < 0.05$
School degree, N(%)				
Primary school	4 (16.66%)	1 (3.84%)	5 (10%)	
Junior high school	14 (58.33%)	17 (65.38%)	31 (62%)	
High school	5 (20.83%)	6 (23.07%)	11 (22%)	NS
University	1 (4.16%)	2 (7.69%)	3 (6%)	
Marital status, N(%)				
Married/cohabiting	5 (20.8%)	1 (3.8%)	6 (12%)	
Divorced/ separated	6 (25%)	4 (15.3%)	10 (20%)	Pearson $Chi^2 = p < 0.05$
Single	11 (45.8%)	21 (80.76%)	32 (64%)	
Widowed	2 (8.3%)	0 (0%)	2 (4%)	
Family and living environment, N(%)				
With parents	9 (37.50%)	18 (69.23%)	27 (54%)	
With spouse/partner	10 (41.66%)	3 (6.38%)	13 (26%)	
Single	3 (12.5%)	3 (6.38%)	6 (12%)	NS
In community or protected facility	1 (4.16%)	2 (5.32%)	3 (6%)	
Homeless	1 (4.16%)	0 (0%)	1 (2%)	
Occupation, N(%)				
Unemployed	10 (41.66%)	12 (46.15%)	22 (44%)	
Employed	4 (16.66%)	10 (38.46%)	14 (28%)	NS
Retired	6 (25%)	2 (7.69%)	8 (16%)	
Invalidity pension	4 (16.66%)	2 (7.69%)	6 (12%)	
Economic conditions, N(%)				
Insufficient, with the need for social service support	2 (8.33%)	5 (19.2%)	7 (14%)	NS
Sufficient or good	22 (91.66%)	21 (80.76%)	43 (86%)	

SD). During the observation period, each patient in our sample was treated with 92 mg of PP on average, administered at a mean interval of 23 days between each injections, whose average number was 6 during a period of 155 days, without any statistically significant difference between males and females (Table 3). The rate of dropout in our sample

TABLE 2

Clinical Variables of Our Patients, Divided by Gender

VARIABLES	SAMPLE FEMALES 24 (48%)	SAMPLE MALES 26 (52%)	TOTAL	STATISTICAL TEST
PSYCHIATRIC DIAGNOSIS (ICD-9-CM), N(%)				
Disorganized Type of Schizophrenia (295.10–295.15)	0 (0%)	2 (7.69%)	2 (4%)	NS
Catatonic Type of Schizophrenia (295.20–295.25)	1 (4.16%)	0 (0%)	1 (2%)	
Paranoid Type of Schizophrenia (295.30–295.35)	13 (54.16%)	18 (69.23%)	31 (62%)	
Residual Type of Schizophrenia (295.50–295.55)	0 (0%)	0 (0%)	0 (0%)	
Schizoaffective Disorder (295.70–295.75)	4 (16.66%)	0 (0%)	4 (8%)	
Undifferentiated Type of Schizophrenia (295.80–295.85)	6 (25%)	6 (23.07%)	12 (24%)	
Unspecified Type of Schizophrenia (295.90–295.95)	0 (0%)	0 (0%)	0 (0%)	
OTHER PSYCHIATRIC DISORDERS IN COMORBIDITY, N(%)				
Absent	21 (87.5%)	24 (92.30%)	45 (90%)	NS
Present	3 (12.5%)	2 (7.69%)	5 (10%)	
SUBSTANCE ABUSE IN COMORBIDITY, N(%)				
Absent	23 (95.83%)	22 (84.61%)	45 (90%)	NS
Present	1 (4.16%)	4 (15.38%)	5 (10%)	
ORGANIC COMORBIDITY, N(%)				
Absent	14 (58.33%)	21 (80.76%)	35 (70%)	NS
Present	10 (41.66%)	5 (19.23%)	15 (30%)	
PSYCHIATRIC HOSPITALIZATIONS BEFORE PP TREATMENT, N(%)				
No hospitalizations	2 (8.3%)	5 (19.2%)	7 (14%)	NS
1–3 hospitalizations	14 (58.3%)	16 (61.5%)	30 (60%)	
4–10 hospitalizations	5 (20.8%)	3 (11.5%)	8 (16%)	
More than 10 hospitalizations	3 (0.25%)	2 (7.6%)	5 (10%)	
ILLNESS PERIOD FROM SCHIZOPHRENIA ONSET, M ± SD				
Years	16.45 ± 9.85	9.30 ± 8.30	12.74 ± 9.68	t-test $p < 0.05$

was 18% (9 patients). The remaining 41 patients (82%) maintained the treatment up to the end of the observation period although for different durations based on the start of PP therapy: 6 (15%) more than 270 days, 14 (34%) from 270 days, 14 (34%), from 179 days and 7 patients (17%)

TABLE 3

Therapeutic Variables of PP Treatment in Our Sample, Divided by Gender

VARIABLES	SAMPLE FEMALES	SAMPLE MALES	SAMPLE TOTAL	STATISTICAL TEST
REASONS FOR PP IMPLEMENTATION, N(%)				
Inefficacy of previous medication	11 (45.83%)	10 (38.46%)	21 (42%)	
Intolerance to other drugs	2 (8.33%)	3 (11.53%)	5 (10%)	NS
Lack of therapeutic compliance	7 (29.16%)	12 (46.15%)	19 (38%)	
Patient's choice	4 (16.66%)	1 (3.84%)	5 (10%)	
MODALITY OF SWITCH TO PP THERAPHY, N(%)				
From other long acting antipsychotics	20 (83.33%)	14 (53.84%)	34 (68%)	Pearson Chi^2
From oral antipsychotic treatment	4 (16.66%)	12 (46.15%)	16 (32%)	$p < 0.05$
PERIOD OF ORAL DRUGS ASSOCIATED, M ± SD				
Days	95.86 ± 86.69	88.88 ± 76.77	92.14 ± 80.74	NS
INJECTIONS, M ± SD				
Number	6.04 ± 2.66	7.34 ± 3.49	6.72 ± 3.16	NS
TIME INTERVAL BETWEEN PP INJECTIONS, M ± SD				
Days	23.47 ± 4.23	22.83 ± 6.85	23.19 ± 5.69	NS
DOSE (MG EQ), M ± SD				
All patients (n = 50)	87.90 ± 17.59	96.46 ± 28.47	92.71 ± 24	
Dropout patients (n = 9)	87.91 ± 17.59	96.47 ± 28.25	92.36 ± 23.89	NS
Patients in treatment (n = 41)	97.4 ± 5.81	104 ± 38	100.33 ± 24.04	
ADVERSE EFFECTS, N(%)				
Presents	7 (29.16%)	10 (38.46%)	17 (34%)	
Absents	17 (70.83%)	16 (61.53%)	33 (66%)	
ADVERSE EFFECT OCCURRENCE DURING PP THERAPY, M ± DS				
Days of PP treatment	37.86 ± 52.92	30.77 ± 49.3	33.33 ± 49.30	
Number of PP administration	2.57 ± 2.30	4 ± 2.55	3.37 ± 2.47	
Mean dose (mg) of PP treatment	83.90 ± 16.50	89.11 ± 32.5	88.34 ± 26	NS
RELAPSES, N(%)				
No relapses	13 (54.1%)	17 (65.3%)	30 (60%)	
Urgent psychiatric consultations	10 (41.6%)	6 (23%)	16 (32%)	
Psychiatric hospitalizations	1 (4.1%)	3 (11.5%)	4 (8%)	NS
RELAPSE OCCURRENCE DURING PP THERAPY, M ± DS				
Days of PP treatment	72.72 ± 96.3	106 ± 99.66	87.7 ± 96.72	NS

(*Continued*)

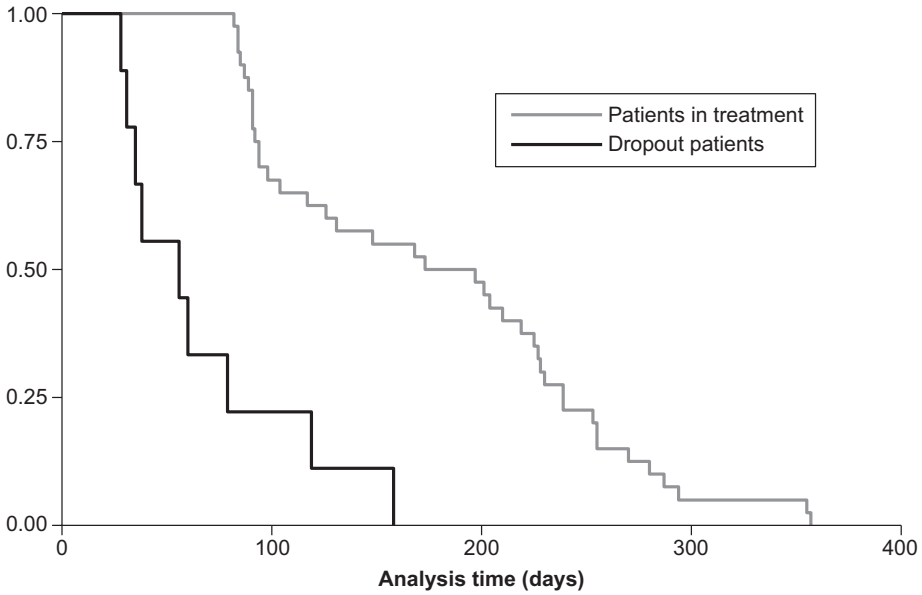
TABLE 3 (*Continued*)

VARIABLES	FEMALES	SAMPLE MALES	TOTAL	STATISTICAL TEST
Number of PP administration	3.27 ± 1.62	4.33 ± 3.74	6.2 ± 3.14	
Mean dose (mg) of PP treatment	143.66 ± 18.8	113 ± 32.51	118.47 ± 28.8	t-test $p < 0.05$
DAYS OF PP TREATMENT, M ± DS				
All patients (n = 50)	142.95 ± 76.41	166.4 ± 101.02	155.16 ± 89.93	
Dropout patients (n = 9)	68 ± 51.98	66 ± 41.49	67.11 ± 44.69	NS
Patients in treatment (n = 41)	134.32 ± 67.53	207.68 ± 86.13	174.49 ± 85.91	
PATIENTS IN TREATMENT AND DROP OUT, N(%)				
Patients in treatment	19 (79.16%)	22 (84.16%)	41 (82%)	
Dropout due to lack of therapeutic compliance	1 (4.16%)	2 (7.69%)	3 (6%)	NS
Dropout due to inefficacy	3 (12.5%)	2 (7.69%)	5 (10%)	
Dropout due to adverse effects	1 (4.16%)	0 (0%)	1 (2%)	

from 90 days before the end point. Analyzing the duration of treatment, we evidenced that most dropouts occurred after a short period of PP treatment, as showed by the Kaplan Maier curve (Figure 1). The interruption of PP therapy more frequently occurred within the first 90 days of therapy, and the main cause for dropping out was represented by treatment inefficacy, followed by lack of compliance, in a statistically significant way (Pearson's test $Chi^2 = 16.81$, $p = 0.05$). At T0, 71% of our sample assumed an oral psychiatric medication associated to PP, percentage that progressively but slightly decreased: 65% at T3, 69% at T6 and 64% at T9. At T12 only 2 patients were in treatment with PP, and one of them assumed another oral psychiatric medication. Associated oral medications were assumed for 92 days on average during the observation period and changed during the period of depot treatment. After the third month of PP injections either oral risperidone, paliperidone or mood stabilizers were interrupted, whereas many other medications, such as anticholinergic agents, were maintained until T12. Illness relapses, including both urgent psychiatric consultations and hospitalizations, affected 60% of our sample, more frequently after 3 months of treatment, at the sixth depot injection and at the mean dose of 118 mg (Table 3). Side effects affected 30% of our sample, more frequently after the first month of therapy, at the time of the third injection

FIGURE 1

Period of Paliperidone Palmitate Treatment: Patients in Treatment and Dropout (Kaplan–Meier Curve)



at the mean dose of 88 mg (Table 3). Adverse effects mostly consisted of endocrine problems such as sexual dysfunction in men and amenorrhea in women, probably due to increased prolactin levels (9%). Other side effects were represented by EPS (9%), agitation and insomnia (4%) and orthostatic hypotension (2%). In 6% of cases more than one of the above described adverse effects were observed. In both relapses and side effects, we found no statistically significant difference between men and women. In Table 4, the scores of symptom and functioning rating scales at the baseline (T0) and the percentage of improvement registered during the following months in the patients in treatment ($n = 44$ at T3, $n = 27$ at T6, $n = 11$ at T9) are shown. Because of the small dimension of the sample at T12, the rating scale evaluation at this time was not performed. In PANSS, a statistically significant improvement was registered at T3 ($t = 4.63$, $p < 0.001$, t-test), T6 ($t = 3.82$, $p < 0.001$, t-test) and T9 ($t = 5.43$, $p < 0.001$, t-test) in comparison with the baseline (T0). The BPRS scale scores showed a statistically significant improvement at T3 ($t = 4.77$, $p < 0.001$, t-test) and T6 ($t = 2.80$, $p < 0.01$, t-test) compared to T0. The CGI-S and CGI-I scores showed a statistically significant improvement at T3 ($t = 4.73$, $p < 0.001$, t-test), T6 ($t = 4.07$, $p < 0.005$, t-test) and T9 ($t = 3.32$, $p < 0.005$, t-test). The improvement in personal and social functioning, assessed by GAF scale, was progressively evidenced during the months of treatment: T3

TABLE 4

Symptom and Functioning Rating Scale Scores at T0 and Percentage of Improvement at T3, T6 and T9 in Comparison to T0

SCALES	T0: SCORES (M ± SD) (N = 50)	T3: IMPROVEMENT IN COMPARISON TO T0 (%) (N = 44)	T6: IMPROVEMENT IN COMPARISON TO T0 (%) (N = 27)	T9: IMPROVEMENT IN COMPARISON TO T0 (%) (N = 11)
PANSS Global	84.26 ± 22.29	15.84%	17.17%	29.27%
Positive Subscale	21.12 ± 10.15	23.7%	28.60%	43.67%
Negative Subscale	26.12 ± 9.31	17.77%	13.84%	15.52%
BPRS	25.16 ± 9.86	21.92%	18.55%	42.89%
CGI-S/CGI-I	4.38 ± 0.94	19.2%	19.28%	31.8%
GAF	46.9 ± 13.49	20.3%	19.46%	31.11%
PSP	45.36 ± 13.95	16.13%	12.08%	20.74%
SAS	1.13 ± 2.15	20.08%	18.93%	0%

vs T0 ($t = -4.06$, $p < 0.001$, t-test); T6 vs T0 ($t = -3.38$, $p < 0.005$, t-test); T9 vs T0 ($t = -2.65$, $p < 0.05$, t-test). A similar improvement was highlighted by PSP scale at third and sixth months compared to T0 (T3 vs T0: $t = -2.67$, $p < 0.05$; T6 vs T0, $T = -2.07$, $p < 0.05$; t-test). SAS scale scores did not statistically significantly differ from T0 to T9. By using the statistical model of multiple linear regression, we observed that, among the therapeutic variables positively related to "days of PP treatment" in a statistically significant way, "number of PP administrations" was the variables more strongly correlated (Coeff. = 24.09; SE = 1.31; 95% IC: 21.40–26.78; $p < 0.001$), followed by "time interval between PP injections" (Coeff. = 3.11; SE = 0.65; 95% IC: 1.78–4.44; $p < 0.001$) and "period of oral drugs associated with PP treatment" (Coeff. = 0.09; SE = 0.039; 95% IC: 0.01–0.17; $p < 0.005$). Among socio-demographic variables, being "widowed" (Coeff. = −213.27; SE = 80.89; 95% IC: −377.86–−48.68; $p < 0.05$) and "high school" (Coeff. = 121.55; SE = 57.05; 95% IC: 5.47–237.62; $p < 0.05$) were negatively and positively related to "days of PP treatment", respectively. By using multiple linear regression, we observed that "dose of PP", considered as a dependent variable, was positively related, in a statistically significantly way, only to the number of previous psychiatric hospitalizations (Coeff. = 37.10; SE = 15.51; CI 95%: 5.78–68.43; $p < 0.05$). The risk factors for treatment interruption, according to the Cox model, were represented by both "lack of therapeutic compliance" (HR = 4.11, $p < 0.0001$) and "inefficacy" of PP treatment (HR = 1.67, $p < 0.0001$).

Discussion

In line with other studies, PP treatment was well tolerated by our patients and, in just a few cases, it induced such adverse events as

to require discontinuation.[20,28,34,35,36] The improvement registered in symptoms and function rating scales was consistent with those in literature.[22,30,34–36] In particular, the percentage of improvement in PANSS positive subscale was superior to the negative one during the whole time of PP treatment. These results are in line with those of the PALMFlexS study,[34–36] although we obtained a lower improvement of negative symptoms, which could be explained either by the limited duration of treatment and/or by the chronicity of our patients' disease, particularly relevant on female gender.

We have to underline that our patients were affected by severe and chronic disease, as evidenced by the scale scores at baseline as well as by their clinical characteristics, long psychiatric history and high number of previous psychiatric hospitalizations (60% of our patients had been admitted at least once). Even the main reasons for PP prescription, represented by inefficacy of previous medications and lack of therapeutic compliance, indirectly delineate the clinical severity of our sample. In particular, the switch to PP treatment was more often conditioned by lack of compliance in patients previously treated orally, whereas inefficacy of previous medications was the main reason for switching from other long-acting therapy. These data lead us to hypothesize that implementation of PP treatment was conditioned by difficult clinical management in chronic and severe cases.

Analyzing the strategies of PP prescription, it should be noted that psychiatrists were extremely cautious about using high doses in switching to PP both from oral and long acting antipsychotic therapy. The average dose used was lower than that one recommended by official guidelines, in contrast to clinically severity of patients' disease. Also the intervals between PP injections did not comply with official protocols, in some cases not guaranteeing an effective blood concentration. This result is consistent with another study which highlighted that a PP dose inferior to guideline indications could be responsible for the reduced response.[32] These data could explain the high percentage of associated concomitant oral pharmacotherapy during duration of PP treatment. In our sample, adherence to treatment was relatively high and in line with the findings of most studies,[2,34–36] probably due to the good tolerance of PP. According to our statistical model, we highlight that the two main risk factors for therapy discontinuation were represented by lack of compliance and therapeutic inefficacy. Since treatment discontinuation more frequently occurred within the first 90 days because of therapeutic inefficacy, we suggest that dropout patients were resistant to this treatment, in accordance with other authors,[17] who reported that different clinical responses to second-generation antipsychotics can be explained by individual variability, probably genetically conditioned,

in receptor affinity profile.[54] In support of this hypothesis, we found that, in line with another study,[41] those patients who had continued the treatment for a longer period obtained significant improvement at the end of observation, as highlighted by scale scores at the end point. Concerning the conditioning factors on PP therapy duration, we have to put in evidence that, if the statistically significant positive correlation between "days of PP treatment" and "number of PP injections" are logically expected, the negative correlation of being "widowed" and, on the contrary, the positive correlation of "high school" degree with "days of PP treatment" could suggest that some environment and cultural factors can affect the modality of care, as most authors have already underlined.[55,56] Regarding gender differences, the different marital status between males and females could be explained by the older ager of women and their more preserved social function. Moreover, our female patients had a longer history of schizophrenia, more often switched to PP from long acting therapy and assumed higher PP doses. These data suggest a more chronic clinical state and indirectly support the epidemiological observation concerning the more frequent worsening of psychotic symptoms during later life in female gender.[57]

Strengths and Limitations

The main limit of this study consists of its observational design without any control group which did not allow a "head to head" comparison. Moreover, the sample was small, the observation period was not sufficiently long and the PP therapy period was not homogeneous for all patients due to the different start of PP treatment. Nevertheless, our study has the advantage of having collected data from a representative outpatient sample in naturalistic conditions, avoiding the risk of creating an artificial setting, as often occurred in RCTs, where adherence to medications and other behavior may have been influenced by patients' awareness of being observed (the Hawthorne effect).[58]

Conclusion

PP treatment was effective in improving both psychotic symptoms, especially positive, and functioning, as reported by our final scale scores, but it was moderately effective in preventing relapse. The clinical severity of our patients associated with cautious and flexible PP prescriptions may have influenced the response in term of effectiveness. PP therapy was well tolerated with good adherence and a small percentage of discontinuation, which occurred mainly during the first period of treatment due to inefficacy and lack of compliance.

We observed that patients who stopped PP early were more often non-responders, whereas those who continued therapy for longer period showed a high percentage of improvement at symptom and functioning rating scales, suggesting an individual variability in the PP treatment responsivity.

With the limitations of an observational study, this research has added empirical data on the use of a new atypical antipsychotic long-acting therapy in a group of patients affected by severe and chronic schizophrenia. Other prospective studies, with higher number of patients and longer observation period, taking into account the interindividual variability, are necessary in order to further investigate this new long-acting therapy.

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All authors contributed in a significant way to the manuscript: RD formulated the study design, analyzed data collected and wrote the article; MC collected data and controlled the appropriateness of collection, searched literature information on this topic, significantly contributed in statistically analyzing data and writing the manuscript; MB, GL, VM, CP, GP significantly contributed in collecting data, writing the manuscript and preparing tables and figures. All authors have read and approved the final manuscript.

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