Effects on Satisfaction and Service Engagement of Paliperidone Palmitate Compared with Oral Paliperidone in Patients with Schizophrenia: An Open Label Randomized Controlled Trial

Effects on satisfaction and service engagement of paliperidone palmitate compared with oral paliperidone in patients with schizophrenia: an open label randomized controlled trial

Running title: paliperidone palmitate compared with oral paliperidone in schizophrenia

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Abstract

Objective

Clinical practice guidelines recommend antipsychotic monotherapy, including oral and long-acting formulations, in treatment of schizophrenia**.** This open-label, randomized, controlled trial is aimed to evaluate the efficacy and tolerability in patients with schizophrenia of once-monthly long-acting paliperidone palmitate (PP1M) compared with oral paliperidone extended release (ER), with a particular focus on satisfaction, subjective well-being, and service engagement.

Method

Seventy-two consecutive outpatients with schizophrenia (DSM-5) were randomly assigned for six months to: (1) PP1M (50-150 mg equivalent) or (2) paliperidone ER (6-12 mg/day). Participants were assessed at baseline and after 6 months with the Treatment Satisfaction Questionnaire for Medication (TSQM); the Subjective Well-being under Neuroleptics Scale (SWN-K); the Service Engagement Scale (SES); the Clinical Global Impression–Schizophrenia (CGI–SCH); and the Personal and Social Performance (PSP) score. ANOVA repeated measures was performed. Intention to treat analysis with last observation carried forward was conducted.

Results

We found a significant within-subjects effect (trial duration) for all rating scales, except for cognitive symptoms and the TSQM domain “side effects”. A significant effect between subjects (treatment modality) was found for the CGI negative symptoms, the TSQM domains “overall satisfaction” and “convenience”, and the SES. Drop-outs were 7 (9.7%): 2 due to hyperprolactinemia and 5 for the lack of compliance.

Conclusions

Significant differences between the two formulations were found. PP1M was superior to paliperidone ER on global treatment satisfaction and convenience, on service engagement, and in reducing negative symptoms.

The trial was registered in the Australian New Zealand Clinical Trials Registry (ANZCTR) with the code: ACTRN12618001113246.

Key points

1) Paliperidone palmitate was found superior to paliperidone ER in improving negative symptoms, global treatment satisfaction and convenience, and service engagement.

2) Effect of long-acting paliperidone on service engagement is a new finding and can contribute to decrease of stigma associated with schizophrenia.

1. Introduction

Many people affected by schizophrenia have the potential to achieve long-term remission and functional recovery (1), but only a small proportion obtain this goal (2,3).

The recovery model refers to subjective experiences of optimism, empowerment, and interpersonal support, and is focused on a collaborative treatment approach **(**4).

In particular, during long-term therapy, subjective perception of general wellness and quality of life clearly influences and maintains adherence to treatment (5). For this reason, an important role has been recently assigned to the concepts of satisfaction, subjective well-being, and quality of life in patients undergoing antipsychotic maintenance treatment (5-8)

Subjective satisfaction is now considered a clinical index of treatment adherence and quality of life in schizophrenia (7,9-12). It is also associated with the efficacy of treatment and can be considered an indicator of the treatment success. In particular, patients who are satisfied of antipsychotic medications show a significant improvement of symptoms assessed by the Positive and Negative Symptoms Scale (PANSS), community functioning (11), quality of life (11,13), and adherence. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study found that an antipsychotic medication was most frequently discontinued because of the patients' own choice (29.9%) (14). Some authors stated that high degree of patient satisfaction with current oral atypical antipsychotics was associated with a lower rate of treatment discontinuation (9,15).

Several studies stated that the main factors that influenced patient satisfaction during an antipsychotic treatment were treatment efficacy, side effects, patient's psychological state, lack of involvement in treatment planning, and convenience (12). In particular, in terms of medication convenience, the long-acting antipsychotics are expected to improve medication convenience with lower administration frequency as opposed to daily administered oral drugs. Although favourable evidence indicated the advantages in terms of efficacy and adherence of long-acting

injectable (LAI) administration, particularly in the early phase of illness, some barriers still exist to the wider use of these formulations, both related to the patients (i.e. prejudices and stigma) and the clinicians (i.e. limited knowledge and experience) (15).

To date, patient satisfaction has not been extensively studied. The first well-designed study to measure change in patient satisfaction associated with switching from atypical oral antipsychotics to LAI atypical antipsychotics reported that switching from unsatisfactory oral atypical medication to paliperidone palmitate (PP) significantly increased patient satisfaction, mostly by improvement in medication convenience (16). In another recent study, Schreiner and colleagues (17) found that non-acute patients (considered clinically stable) with schizophrenia reached a meaningful improvement of psychotic symptoms, functioning, and treatment satisfaction when they switched from previously unsuccessful monotherapy with oral atypical antipsychotics to long-acting treatment with PP.

Another factor that plays a central role in defining the optimal framework for effectiveness of treatments is patient subjective well-being (18). Unfortunately, although the concept of subjective recovery from schizophrenia has received a growing interest in the scientific community, only few studies were aimed to compare LAI treatment and oral antipsychotics maintenance treatment in terms of patient's subjective experience of treatment. A recent observational, case-control study showed a possible advantages of LAI over oral antipsychotic administration in subjective experience of maintenance treatment, including well-being, attitudes towards drug, and quality of life in a sample of remitted patients with schizophrenia (5).

The impact of antipsychotic treatment on service engagement of patient is a relatively understudied topic. Engagement is a multi-dimensional concept including not only the compliance to predefined plans, but also the development of trust and the active involvement of patients in their care processes (19,20). In a treatment project oriented to recovery, engagement in

treatment interventions is of fundamental importance to achieve this goal (21). In fact, patients who experienced difficulties in engaging with services showed poorer outcomes. In particular, they showed higher severity of symptoms and poorer psychosocial functioning (22). To our knowledge, there are no available studies that specifically compared level of service engagement between patients with schizophrenia treated with long-acting injectable antipsychotics and controls receiving maintenance therapy with oral antipsychotics.

Efficacy of paliperidone extended release (ER) and paliperidone palmitate (PP1M) on clinical symptoms was investigated in several previous studies (12,23-28). The present open-label, randomized, controlled trial is aimed to evaluate the impact of treatment with once-monthly long-acting paliperidone palmitate (PP1M) compared with oral paliperidone extended release (ER) on satisfaction, subjective well-being and service engagement in patients with non-acute symptomatic schizophrenia.

2. Methods

Study design and participants

The study was conducted at the Department of Neuroscience of the University of Turin, at the Struttura Semplice di Coordinamento a Valenza Dipartimentale (SSCVD), Department of Neuroscience and Mental Health of the University Hospital Città della Salute e della Scienza di Torino, Italy, during the period between February 2017 and July 2017.

A sample of 66 consecutive outpatients aged between 18 and 65 years with a diagnosis of schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders, Edition 5 (DSM-5) criteria (29) was recruited. The psychiatric diagnosis was made by an expert clinician and confirmed with the Structured Clinical Interview for DSM-5 Clinical Version (SCID-5-CV) and Personalitiy Disorders (SCID-5-PD).

Each patient participated voluntarily in the study after providing written informed consent. The study was conducted in compliance with the Declaration of Helsinki guidelines. Approval was obtained from the ethics committee of the University Hospital ‘‘Citta` della Salute e della Scienza – Ospedale dell’Ordine Mauriziano’’ of Turin. The trial was registered in the Australian New Zealand Clinical Trials Registry (ANZCTR) with the code: ACTRN12618001113246.

Patients were randomly assigned to two arms of treatment for 6 months: long-acting paliperidone palmitate and oral paliperidone extended release (ER). Research Randomizer (Urbaniak and Plous, Social Psychology Net-222 work Wesleyan University, Middletown, CT), a free, web-based service for randomization, was used.

Patients were eligible for study enrollment if they had a diagnosis of stable, but symptomatic schizophrenia and were previously unsuccessfully treated with an oral antipsychotic at an adequate therapeutic dose and with a change in Clinical Global Impression–Severity [CGI-S] score ≤1 in the 4 weeks before enrollment. The exclusion criteria were: a diagnosis of dementia or other cognitive disorders, bipolar disorders, major depressive disorder, or personality disorders; a known hypersensitivity to paliperidone ER; treatments with clozapine or a long-acting injectable antipsychotic during the preceding 3 months; significant medical illness; tardive dyskinesia; neuroleptic malignant syndrome; high risk for adverse events (AEs) or self-harm; or substance dependence over the past 6 months (however, occasional substance use was allowed).

After screening, patients were randomized (1:1) to either PP1M or paliperidone ER treatment. In the present study, the patients were switched from previous unsuccessful oral antipsychotic to PP1M, in line with the indication and posology of PP1M European summary of product characteristics (SmPC) (Janssen Cilag 2015), or to oral paliperidone. PP1M was administered at a recommended dose of 150 mg equivalent (mg eq) on day 1 and 100 mg eq on day 8, both administered in the deltoid muscle. Subsequently, PP1M was administered once-monthly (±7

days) using flexible maintenance dosages within the range of 50 to 150 mg eq based on the clinical judgment of the physician. Paliperidone ER was administered at dose of 6-12 mg/day. Patients without documentation of previous treatment with paliperidone were tested for tolerability with paliperidone ER (3 mg/day) for at least 2 days prior to receiving PP1M.

In the group receiving oral medication compliance to treatment was checked with the cohabiting caregiver who administered the drug, during the monitoring visit. In both groups, receiving oral and injective formulations, patients were provided the same number and type of monitoring visits to control for any confounding factors on outcome measures.

Serum prolactin level was measured at baseline, after one and six months of treatment. Blood samples were collected in fasting patients two hours after they woke up. Hyperprolactinemia was defined as a level of serum prolactin ≥ 20 ng/mL in males and ≥ 25 ng/mL in females (30). Body weight was measured at baseline and endpoint. Weight gain at least 7% of baseline was considered significant (30).

Assessment

Primary outcome measures

The primary outcome was the change from baseline to endpoint of recovery-oriented mental health measures collected from all participants in the two treatment groups.

All participants were assessed at baseline and after 6 months with the Treatment Satisfaction Questionnaire for Medication (TSQM); the Subjective Well-being under Neuroleptics scale (SWN-K); and the Service Engagement Scale (SES).

The TSQM (31) is a 14-item psychometrically robust and validated instrument comprising four domains: effectiveness (questions 1–3), side effects (questions 4–8), convenience (questions 9–11), and global satisfaction (questions 12–14). The TSQM domain scores range from 0 to 100. Higher scores represent higher satisfaction for medication.

The SWN-K (32) is a 20-item self-rating scale, developed to measure the subjective experience of psychotic patients associated with the use of antipsychotics. The SWN short form (SWN-K) (33) consists of 20 statements (10 positive and 10 negative). It contains five subscales consisting of four items each: mental functioning, self-control, emotional regulation, social integration, and physical functioning. The total score ranges from a minimum of 20 (poor subjective experience) to a maximum of 120 (excellent subjective experience).

The SES (34) is an evaluation instrument including 14 items, rated on a 4-point Likert scale that was used to explore patients' relationship with mental health services. Items are grouped into four subscales: availability, cooperation, help seeking, and adherence to treatment. The total score ranges between 0 to 42. Higher scores reflect greater levels of difficulty engaging with services.

Secondary outcome measures

Secondary outcome was the change from baseline to endpoint of global symptomatology and functioning.

Participants were tested with the Clinical Global Impression–Schizophrenia (CGI–SCH) and the Personal and Social Performance (PSP) total score.

The CGI (35) is a clinician-rated instrument to make global assessment of illness and consists of three different measures: severity of illness, global improvement, and efficacy index (comparison between patient's baseline condition and a ratio of current therapeutic benefit and severity of side effects). The CGI-Schizophrenia (CGI-SCH) scale was developed for use in the Schizophrenia Outpatient Health Outcomes (SOHO) Study (36). Each category contains five different ratings (positive, negative, depressive, cognitive and global) that are evaluated using a seven-point ordinal scale ((1) normal, (2) borderline mentally ill, (3) mildly ill, (4) moderately ill, (5) markedly ill, (6) severely ill, and (7) extremely ill). In this study we considered the severity of illness for the five ratings. Patients were assessed with the CGI-SCH at the beginning of

treatment and after 6 months. In accordance with previous studies (36,37), we used the CGI-SCH to evaluate separately positive symptoms, negative symptoms, depressive symptoms, and cognitive symptoms of our patients.

Psychosocial functioning was measured using the (PSP) scale (38). Ratings are based on the assessment of four indicators: (1) socially useful activities, including work and study; (2) personal and social relationships; (3) self-care; and (4) disturbing and aggressive behaviors, rated on a six-point scale. The interviewer assigned a global score based upon information obtained during the interview regarding the four main areas of functioning and upon any additionally available source of information. The total score is usually divided into three levels: 71–100 (mild or no functioning difficulties); 31–70 (varying degrees of difficulties); and 0–30 (functioning so poor that the patient needs intensive support and supervision).

Statistical analysis

Statistical analysis was performed both in the group of patients who completed the trial and in the whole group of patients who were randomized, including drop-outs. In the second group, intention-to-treat (ITT) analysis was performed with the last observation carried forward (LOCF). Baseline mean scores of rating scales were compared between the two treatment groups with one-way analysis of variance (ANOVA). Comparison of score change at the end of the trial between the two groups was calculated for each rating scale with ANOVA repeated measures. Bonferroni correction was applied to correct for multiple comparisons. Effect size was calculated as eta squared ($\eta 2$).

The software system SPSS 25.0 (IBM Corporation, 2017) was used for calculations. P values were considered significant at <0.05.

3. Results

Seventy-two patients were randomly assigned to (1) PP1M (N=36) or to (2) paliperidone ER (N=36). Sixty-five out of the 72 patients (90.3%) completed the 6 months of the trial: 33 patients (50.7% of the completers) received PP1M, while 32 patients (49.3%) received paliperidone ER. Seven patients (9.7%) discontinued the treatment: three treated with PP1M and four receiving paliperidone ER. The reasons of drop-out were lack of compliance (5 patients) and hyperprolactinemia (2 patients). The final sample resulted of 65 patients with the mean age of 46.4 ± 12.9 years; they were 28 males (43.1%) and 37 females (56.9%).

Results of the ANOVA calculated for baseline mean scores of rating scales are reported in Table 1. No significant differences between groups were found at baseline between the two treatment arms.

Results of the ANOVA repeated measures of the effects of trial duration (within-subjects effect) and the treatment modality (between-subjects effect) on the score changes after 6 months in the sample of 65 completers are reported in Table 2.

We found a significant within-subjects effect (trial duration) for all rating scales ($\eta 2$ ranged from 0.07 to 0.73; P ranged from 0.001 to 0.058), except for cognitive symptoms rated with the CGI-S ($\eta 2 = 0.04$; $P = 0.122$) and the domain "side effects" of the TSQM ($\eta 2 = 0.06$; $P = 0.068$). A significant effect between subjects (treatment modality) was found for negative symptoms rated with the CGI-S ($\eta 2 = 0.1$; $P = 0.012$), the two domains "overall satisfaction" ($\eta 2 = 0.35$; $P = 0.001$) and "convenience" ($\eta 2 = 0.07$; $P = 0.037$) of the TSQM, and the SES ($\eta 2 = 0.17$; $P = 0.001$). In particular, effects of PP1M were found superior to paliperidone ER on negative symptoms, global treatment satisfaction and convenience, and service engagement.

Results of the ITT-LOCF analysis are reported in Table 3. The significant effects found in the whole sample of 72 patients recruited at baseline were not different from those found in the group

of 65 completers. In particular, a significant effect within subjects (trial duration) was confirmed for all rating scales (ηp2 ranged from 0.09 to 0.77; P ranged from 0.001. to 0.03) except for cognitive symptoms rated with the CGI-S (ηp2 = 0.05; P = 0.120) and the domain "side effects" of the TSQM (ηp2 = 0.07; P = 0.064). The significant effect between subjects (treatment modality) was confirmed with the ITT-LOCF for negative symptoms rated with the CGI-S (ηp2 = 0.14; P = 0.010), the two domains "overall satisfaction" (ηp2 = 0.39; P = 0.001) and "convenience" (ηp2 = 0.08; P = 0.032) of the TSQM, and the SES (ηp2 = 0.18; P = 0.001).

Adverse effects recorded in the sample of sixty-five completers were mild to moderate and included agitation (n =7, 10.7%), extrapyramidal symptoms (n = 7, 10.7%), gastrointestinal symptoms (n = 6, 9.2 %), sedation (n = 6, 9.2%) and insomnia (n = 5, 7.7%). Two cases of hyperprolactinemia were registered and caused drop-out. No cases of significant weight gain (≥7% of baseline) were recorded. Mean weight gain ± SD was 0.7 ± 0.8 kg. No significant difference of frequency of any adverse effect was found between the two subgroups.

4. Discussion

The present open-label randomized controlled study tested the efficacy and tolerability of PP1M in comparison with oral paliperidone ER in patients with schizophrenia. A specific focus of this trial was comparison between the two formulations of patients' satisfaction for medications, subjective wellbeing and service engagement.

In our trial we found that PP1M had an overall efficacy overlapping with paliperidone ER on clinical symptoms assessed with the CGI-SCH score, psychosocial functioning, measured with the PSP score, and on subjective wellbeing under neuroleptic, assessed with the SWN-K score. This result is in accordance with previous studies on oral paliperidone (12,25-27) and long-acting paliperidone (23,24,28,39,40). In our study we did not observe a significant decrease of cognitive

symptoms neither with PP1M, nor with paliperidone ER. Unfortunately, few studies specifically investigated the effect of paliperidone on cognitive domain. Available data showed that paliperidone, both ER and LAI, may improve this psychopathological domain in patients with schizophrenia (41-47). In contrast with this previous findings, our investigation failed to detect any effect of paliperidone on cognitive functions. A possible explanation of this inconsistency is that we did not assess cognitive symptoms with specific evaluation instruments differently from preceding investigations.

When taking into account the role of PP1M and paliperidone ER on primary outcome measures, we found that the two formulations showed significant differences in favor of long-acting paliperidone on global treatment satisfaction and convenience assessed with the TSQM, and on service engagement, measured with the SES.

Subjective satisfaction for medications plays a key role in treatment's adherence of patients. It could be influenced by efficacy on core symptoms and tolerability, but also by the route of administration (31,48,49). Some authors found that long-acting paliperidone was favored with respect to oral antipsychotics (16,50). In line with this finding, results of our study indicated that PP1M was superior to oral paliperidone in terms of global treatment satisfaction and convenience. As long-acting injection provides a lower administration frequency as opposed to daily administered oral medications and a more stable blood concentration with a better tolerability profile, it may be preferred by patients who are affected by a chronic disease that requires a long-lasting pharmacological treatment. Kwon and colleagues (16) concluded that PP1M may increase satisfaction of patients with schizophrenia by enhancing the convenience of treatment. In a study performed by Schreiner and colleagues (50), PP1M compared with oral antipsychotics showed a significant improvement across domains of the TSQM. The degree of improvement was higher in the TSQM 'convenience' subscale.

Another innovative finding of our study concerns the superior effect of PP1M on service engagement. To date, service engagement of patients in treatment with antipsychotics is understudied and no data are available on specific comparison of PP1M and oral paliperidone. Engagement of patients with schizophrenia with mental health services must be considered of the upmost importance, as effects of medications have a limited clinical meaning if there are not perceived and appreciated by patients. Antipsychotic medications, in particular long-acting injectable formulations, may improve patients' benefits also in terms of rehabilitation and re-entry into society. In addition, they make easier the ongoing relationship and therapeutic alliance between patient and caregivers that is essential for a reliable monitoring of the patient's progress and compliance (51). In patients receiving a treatment with LAIs, the low risk of adverse effects related to stable plasma concentration and the opportunity to avoid taking pills every day may increase social adaptation, autonomy, and sense of self-efficacy (20,52). A relevant consequence is the decrease of stigma associated with schizophrenia. Patients who are more engaged in mental health services also showed a lower risk of relapse and hospitalization in favor of a swifter reintegration in the community (53-57).

As we focused on the effects of medications on patients satisfaction, subjective wellbeing and service engagement, we did not systematically assess the change of symptoms with specific evaluation scales (see limitations). So, the result concerning different effects on symptoms between groups should be interpreted with caution. In our study, we observed that PP1M was superior to paliperidone ER in reducing negative symptoms, a domain that is generally hard to evaluate and treat in schizophrenia. Prominent negative symptoms, including affective flattening, poverty of speech, lack of social engagement, withdrawal, avolition, and anhedonia affect approximately 40% of patients with schizophrenia (58). Previous investigations reported the

superior efficacy of LAIs on negative symptoms, also in samples where they are a predominant component of psychopathology (39,59-62).

Some studies also confirmed our finding of superior PP1M effects on negative symptoms in non-acute patients who did not respond to oral antipsychotic (50,63). A possible explanation of this result is that patients who suffer from negative symptoms become apathetic and lose willingness and ability to adhere to prescriptions. They are likely to minimize the benefit of taking oral drugs (64). This issue may be successfully addressed by long-acting formulation.

With regard to tolerability, both treatment modalities (ER and long-acting formulations) were rather well tolerated, with only mild to moderate adverse effects reported in the majority of our cases. Adverse effects were monitored throughout the study and no significant differences in tolerability were found between the two formulations. More common side effects were insomnia, gastrointestinal disturbances, agitation, sedation and extrapyramidal symptoms. Only two cases (1 in treatment with PP1M and 1 with paliperidone ER) of hyperprolactinemia induced treatment discontinuation. The pattern of side effects in our sample was overally concordant with main investigations of paliperidone in the treatment of schizophrenia (26,47,65). Weight did not increase significantly ($\geq$ 7%) in any of our patients.

The main limitations of the present study were the lack of double-blind design, the lack of a placebo group (that is not allowed by European regulations on clinical trials), and a rather small sample size.

In addition, we used only the items of CGI-SCH and not more specific rating scales to measure severity of symptoms. A further possible limitation was the exclusion of subjects with co-occurring substance use disorder in order to avoid the influence of psychotropic substances on trial medications. Due to this choice clinical characteristics of our sample can be partially different from those observed in common clinical practice.

5. Conclusions

In conclusion, our findings indicated that PP1M was not different from paliperidone ER with regard to overall measures of efficacy and general level of tolerability. Nevertheless, some significant differences between the two formulations were found. In particular, PP1M was superior to paliperidone ER on global treatment satisfaction and convenience, on service engagement, and in reducing negative symptoms.

These results suggested that paliperidone palmitate could provide a valuable treatment option to promote patients involvement in their treatment project and to deal with the core issue of the inadequate adherence to treatment. The efficacy on negative symptoms can contribute to improve patients' participation in rehabilitation programs.

Compliance with Ethical Standards

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Conflict of interest

The Authors declares that there is no conflict of interest.

Informed Consent and Ethics approval

Each patient participated voluntarily in the study after providing written informed consent. Declaration of Helsinki guidelines (1964) were followed. Ethical approval was obtained from the

ethic committee of A.O.U. “Città della Salute e della Scienza - A.O. Ordine Mauriziano – A.S.L.” of Turin.

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Table 1. Comparison of the baseline values of symptoms and functioning rating scales between the PP1M (N=36) and paliperidone ER (N=36) treated groups.

Scale	PP1M Mean ± SD	Paliperidone ER Mean ± SD	ANOVA *P*
CGI-S total score	4.90 ± 0.82	4.53 ± 1.01	0.163
CGI-S positive	4.51 ± 1.01	4.71 ± 1.02	0.408
CGI-S negative	4.08 ± 0.90	4.42 ± 1.18	0.177
CGI-S depressive	2.99 ± 1.31	3.44 ± 1.91	0.246
CGI-S cognitive	3.24 ± 0.99	3.15 ± 1.29	0.724
PSP	52.81 ± 6.82	47.06 ± 18.31	0.103
SWN-K	67.42 ± 11.84	62.15 ± 11.78	0.065
SES	24.97 ± 7.85	25.34 ± 4.73	0.808
TSQM overall	41.68 ± 8.46	43.32 ± 14.38	0.580
TSQM convenience	48.71 ± 16.86	52.45 ± 21.13	0.434
TSQM effectiveness	44.78 ± 18.35	39.86 ± 17.98	0.259
TSQM side effects	50.36 ± 24.03	58.41 ± 36.12	0.284

Table 2. Results of ANOVA for repeated measures applied to compare score changes of the symptoms and functioning rating scales (PP1M, N=33; paliperidone ER, N=32).

Scale	Treatment	Baseline Mean ± SD	After 6 months Mean ± SD	Within-subjects effect (duration)	Between-subjects effect (treatment)
CGI-S	PP1M Paliperidone ER	4.91±0.87 4.58±1.03	4.18±1.24 3.71±1.32	P=0.001 η^2=0.55	P=0.136 η^2=0.03
CGI-S positive	PP1M Paliperidone ER	4.53±1.02 4.74±1.03	3.47±1.02 3.32±1.33	P=0.001 η^2=0.73	P=0.901 η^2=0.01
CGI-S negative	PP1M Paliperidone ER	4.09±0.93 4.45±1.21	2.91±1.06 3.87±1.48	P=0.001 η^2=0.37	P=0.012 η^2=0.1
CGI-S depressive	PP1M Paliperidone ER	2.97±1.34 3.45±1.95	2.59±1.08 3.16±1.49	P=0.031 η^2=0.07	P=0.121 η^2=0.04
CGI-S cognitive	PP1M Paliperidone ER	3.26±1.02 3.16±1.32	2.85±1.05 3.23±1.18	P=0.122 η2=0.04	P=0.608 η2=0.01
PSP	PP1M Paliperidone ER	53.12±6.91 47.48±18.50	65.41±9.91 62.39±13.33	P=0.001 η2=0.51	P=0.112 η2=0.04
SWN-K	PP1M Paliperidone ER	67.91±12.23 62.26±11.96	75.59±15.04 79.48±11.75	P=0.001 η^2=0.54	P=0.759 η^2=0.01
SES	PP1M Paliperidone ER	25.24±8.15 25.65±4.83	17.26±8.11 24.29±8.66	P=0.004 η^2=0.12	P=0.001 η^2=0.168
TSQM overall	PP1M Paliperidone ER	41.59±8.68 43.23±14.55	66.71±10.40 36.71±16.56	P=0.001 η^2=0.247	P=0.001 η^2=0.351
TSQM convenience	PP1M Paliperidone ER	48.56±17.18 52.35±21.63	52.76±17.39 64.68±15.31	P=0.002 η2=0.15	P=0.037 η2=0.07
TSQM effectiveness	PP1M Paliperidone ER	44.65±18.46 39.45±18.30	54.59±18.24 59.70±20.91	P=0.001 η2=0.38	P=0.993 η2=0.01
TSQM side effects	PP1M Paliperidone ER	50.59±24.26 58.84±36.55	57.94±26.29 69.10±32.86	P=0.068 η2=0.06	P=0.108 η2=0.04

Table 3. Results of ITT-LOCF analysis applied to compare score changes of the symptoms and functioning rating scales (PP1M, N=33; paliperidone ER, N=32).

Scale	Treatment	Baseline Mean ± SD	After 6 months Mean ± SD	Within-subjects effect (duration)	Between-subjects effect (treatment)
CGI-S	PP1M	4.90±0.82	4.16±1.21	P=0.001	P=0.141
	Paliperidone ER	4.53±1.01	3.70±1.29	η^2=0.54	η^2=0.04
CGI-S positive	PP1M	4.51±1.01	3.45±1.01	P=0.001	P=0.898
	Paliperidone ER	4.71±1.02	3.30±1.29	η^2=0.77	η^2=0.02
CGI-S negative	PP1M	4.08±0.90	2.89±1.04	P=0.001	P=0.010
	Paliperidone ER	4.42±1.18	3.86±1.45	η^2=0.39	η^2=0.14
CGI-S depressive	PP1M	2.99±1.31	2.62±1.05	P=0.030	P=0.116
	Paliperidone ER	3.44±1.91	3.13±1.46	η^2=0.09	η^2=0.06
CGI-S cognitive	PP1M	3.24±0.99	2.83±1.03	P=0.120	P=0.595
	Paliperidone ER	3.15±1.29	3.24±1.17	η2=0.05	η2=0.02
PSP	PP1M	52.81±6.82	65.22±9.64	P=0.001	P=0.119
	Paliperidone ER	47.06±18.31	62.05±12.92	η^2=0.58	η^2=0.03
SWN-K	PP1M	67.42±11.84	75.27±14.79	P=0.001	P=0.734
	Paliperidone ER	62.15±11.78	79.22±11.23	η^2=0.58	η^2=0.01
SES	PP1M	24.97±7.85	17.12±7.90	P=0.005	P=0.001
	Paliperidone ER	25.34±4.73	24.18±8.24	η^2=0.21	η^2=0.189
TSQM overall	PP1M	41.68±8.46	66.82±9.87	P=0.001	P=0.001
	Paliperidone ER	43.32±14.38	36.90±16.29	η^2=0.259	η^2=0.392
TSQM convenience	PP1M	48.71±16.86	52.92±17.08	P=0.002	P=0.032
	Paliperidone ER	52.45±21.13	64.81±14.95	η2=0.18	η2=0.08
TSQM effectiveness	PP1M	44.78±18.35	54.71±18.08	P=0.001	P=0.943
	Paliperidone ER	39.86±17.98	59.87±20.33	η2=0.46	η2=0.02
TSQM side effects	PP1M	50.36±24.03	57.54±26.07	P=0.064	P=0.154
	Paliperidone ER	58.41±36.12	68.89±32.48	η2=0.07	η2=0.05

ANOVA=analysis of variance; SD=standard deviation; ITT-LOCF = intention-to-treat last observation carried forward; PP1M=paliperidone palmitate 1 month; ER=extended release; η^2=Eta square; CGI-S=Clinical Global Impression scale – Severity item; PSP=Personal and Social Performance; SWN-K=Subjective Well-being under Neuroleptics scale; SES= Service Engagement Scale; TSQM=Treatment Satisfaction Questionnaire for Medication