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Paliperidone Palmitate Once-Monthly Treatment in Recent Onset and Chronic Illness Patients With Schizoaffective Disorder

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Abstract: Data from a multiphase schizoaffective disorder study (NCT01193153) were used to examine the effects of paliperidone palmitate once-monthly (PP1M) by subjects' illness duration, defined as recent onset (≤5 years since first psychiatric diagnosis; $n = 206$) and chronic illness (>5 years; $n = 461$). Symptom and functioning scores, as measured during open-label PP1M acute and stabilization treatment phases, improved in both subpopulations, with greater improvements in recent onset than chronic illness subjects ($p \leq 0.022$). Relapse rates, examined during the double-blind, placebo-controlled phase, were higher with placebo than PP1M: 30.0% *vs.* 10.2% ($p = 0.014$; hazard ratio [HR]: 2.8; 95% confidence interval [CI]: 1.11–7.12; $p = 0.029$) in the recent onset subpopulation and 35.5% *vs.* 18.1% ($p = 0.001$; HR: 2.38; 95% CI: 1.37–4.12; $p = 0.002$) in the chronic illness subpopulation. Growing evidence in the treatment of schizophrenia and schizoaffective disorder supports early intervention with long-acting antipsychotics.

Key Words: Schizoaffective disorder, recent onset, early illness, paliperidone palmitate, long-acting antipsychotic, relapse

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Early disease identification and intervention are basic tenets in medicine. For psychotic disorders, treatment during the first few years is critical in shaping patients' long-term outcomes (Birchwood et al., 1998; Heres et al., 2014). In first-episode psychosis patients, three or more months of remission during the first 2 years is predictive of good functional recovery (Cassidy et al., 2010). In schizophrenia, relapses are associated with progressively longer times to remission, worse subsequent treatment responses, and psychosocial deterioration (Lieberman et al., 2001). Antipsychotic maintenance treatment is associated with reduced relapse and better health-related quality of life (Leucht et al., 2012).

Schizoaffective disorder patients experience significant symptoms of both psychosis (*e.g.*, hallucinations, delusions, disorganized thought) and mood (*e.g.*, depression or mania) (American Psychiatric Association, 2013). Onset is typically in early adulthood, although the diagnosis may occur years following initial psychiatric symptoms (Canuso et al., 2010; Nasrallah et al., 2010). Poor treatment adherence, a well-documented problem in the management of schizoaffective disorder and schizophrenia, is a strong predictor of relapse (Alvarez-Jimenez et al., 2012; Bodén et al., 2011; Heres et al., 2014; Lindenmayer et al., 2009; Robinson et al., 1999). Long-acting injectable antipsychotic therapies provide therapeutic plasma concentrations over weeks to months and eliminate the need for daily oral treatment administration. In real-world settings, long-acting antipsychotic treatment is often reserved for chronically ill patients who are poorly compliant or experience frequent relapses. However, evidence suggests that their early initiation is associated with greater responsiveness, reduced risk for relapse, and improved long-term functioning (Heres et al., 2014; Kane et al., 2015; Llorca et al., 2013; Subotnik et al., 2015). Paliperidone palmitate once-monthly (PP1M) is an efficacious treatment for schizophrenia and schizoaffective disorder (Invega Sustenna Prescribing Information; Janssen Pharmaceuticals, Inc., 2016). This analysis builds on findings from a PP1M schizoaffective disorder study (Fu et al., 2015) by examining effects by duration of illness.

METHODS

Primary Trial Study Design

This analysis examined data from a study of adults with schizoaffective disorder experiencing a recent exacerbation of psychosis with depressive and/or manic mood symptoms (Fu et al., 2015). Study phases included 13-week open-label (OL) acute treatment with PP1M (monotherapy or with prestudy stable doses of mood stabilizers or antidepressants), 12-week OL stabilization with PP1M, and 15-month double-blind (DB) relapse prevention, where subjects were randomized to continue PP1M or withdrawal to placebo (Supplemental Figure 1, http://links.lww.com/JNMD/A28). OL stabilization, required to enter the DB phase, was defined as Positive and Negative Syndrome Scale (PANSS) total score of 70 or lower and Young Mania Rating Scale (YMRS) and Hamilton Rating Scale for Depression 21-item (HAM-D-21) scores of 12 or lower.

Analysis Sets and Statistical Evaluations

Subpopulations were defined by time since first psychiatric diagnosis as recent onset (*i.e.*, ≤5 years) and chronic illness (*i.e.*, >5 years). The patients' psychiatric history was obtained from medical records, patient recall, and the study intake interview (including the Structured Clinical Interview for *DSM-IV* diagnosis). Study measures included PANSS, HAM-D-21, YMRS, Clinical Global Impression of Severity for Schizoaffective Disorder (CGI-S-SCA), and Personal and Social Performance Scale (PSP). Mean changes were compared between subpopulations by *t*-tests and within subpopulations by paired *t*-tests. Percentages of subjects meeting OL stabilization criteria were compared using chi-square tests. Treatment differences in relapse were evaluated by a log-rank test. Time to relapse was estimated by the Kaplan-Meier method. Risk-of-relapse estimates (hazard ratio [HR] and 95% confidence interval [CI]) were determined by Cox proportional hazards models. Patients reported adverse events (AEs) and rated the Medication Satisfaction Questionnaire (MSQ; satisfied [scores 1–4] and dissatisfied [scores 5–7]). Between treatment differences for proportions were assessed using the Cochran-Mantel-Haenszel chi-Square test with modified ridit scores. No adjustments were made for multiplicity. AE rates were summarized.

RESULTS

OL Acute Treatment and Stabilization Phases

Of 667 subjects enrolled, 206 (30.9%) met the definition for recent onset and 461 (69.1%) for chronic illness (Supplemental Figure 1,

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http://links.lww.com/JNMD/A28). The mean (SD) time since first psychiatric diagnosis was 2.9 (1.4) years in the recent onset group and 18.1 (9.78) years in the chronic illness group ($p < 0.001$). Subpopulations differed in age, race, body mass index, and some disease characteristics, with no significant differences in symptom or function scores (Table 1). All subjects received PP1M, with a similar dose distribution at endpoint (2.9% at 78 mg, 7.3% at 117 mg, 50.5% at 156 mg, and 39.3% at 234 mg in recent onset; 2.6%, 7.4%, 53.8%, and 36.2%, respectively, in chronic illness). Both subpopulations had significant improvements in mean psychotic, mood, and function scores at endpoint (all $p < 0.001$; Fig. 1), with greater improvements in the recent onset versus chronic illness subpopulations (all $p \leq 0.022$). A greater percentage of recent onset subjects had a PSP total score higher than 70 (46.6% [90/143] *vs.* 29.4% [126/429]; $p = 0.026$), and met stabilization criteria (70.4% [143/203] *vs.* 60.0% [270/450], respectively; $p = 0.010$) at endpoint. Proportions of subjects satisfied (MSQ) with PP1M increased from 32.5% and 40.7% in the recent onset and chronic illness groups at baseline to 74.4% and 75.9%, respectively, at endpoint. Rates of AEs or discontinuations were not higher in the recent onset than the chronic illness subpopulation. Discontinuation rates were 42.2% and 53.4% of subjects, respectively (Table 2, Supplemental Figure 1, http://links.lww.com/JNMD/A28).

DB Relapse Prevention Phase

In the recent onset subpopulation, time to relapse was longer with PP1M than placebo (log-rank test, $p = 0.014$; Supplemental Figure 2, http://links.lww.com/JNMD/A29). Relapse rates were 30.0% (18/60) with placebo and 10.2% (6/59) with PP1M (HR: 2.81; 95% CI: 1.11–7.12; $p = 0.029$). In the chronic illness subpopulation, time to relapse was also longer with PP1M than placebo (log-rank test $p = 0.001$; Supplemental Figure 3, http://links.lww.com/JNMD/A30). Relapse rates were 35.5% (39/110) with placebo and 18.1% (19/105) with PP1M (HR: 2.38; 95% CI: 1.37–4.12; $p = 0.002$). Rates of AEs or discontinuations were not higher in the recent onset than the chronic illness subpopulation (Supplemental Table 1, http://links.lww.com/JNMD/A31; Supplemental Figure 1, http://links.lww.com/JNMD/A28).

DISCUSSION

Findings demonstrated the beneficial effects of PP1M for subjects with a recent onset of psychiatric illness and those with more chronic illness. During the OL acute and stabilization phases, effects were more robust in the recent onset patients. Results in the subsequent relapse prevention phase were similar to those observed in the total study population (Fu et al., 2015); PP1M was associated with significantly lower relapse than placebo was, with numerically lower rates in the recent onset versus the chronic illness subpopulation. Taken together, these results support the potential value of early intervention with PP1M and are consistent with previous reports (Heres et al., 2014; Kane et al., 2015; Llorca et al., 2013; Subotnik et al., 2015) that patients early in their psychiatric illness are often more responsive to treatment. Furthermore, they add to the growing body of evidence on the effects of PP1M in recently diagnosed schizophrenia patients (Bossie et al., 2011; Fu et al., 2014; Sliwa et al., 2012; Stevens et al., 2016; Zhang et al., 2015), including prospective parallel-group comparisons showing benefits with PP1M compared with daily oral antipsychotic treatment (Alphs et al., 2015; Schreiner et al., 2015). In these patients, the tolerability of PP1M's initiation dosing was similar to oral risperidone (Gopal et al., 2011). During longer-term exposure, tolerability was similar to risperidone long-acting injection (Fu et al., 2014), with no unexpected findings compared with placebo or no treatment (Bossie et al., 2011; Sliwa et al., 2012). The current analysis did not show recent onset subjects were less tolerant of treatment, as reported by others (Alvarez-Jiménez et al., 2008; Francey et al., 2010; McEvoy et al., 2007).

Recent work identifies a potential underlying pathophysiological mechanism that supports these findings. This evidence suggests that

TABLE 1. Subject Characteristics at OL Baseline

	Recent Onset ($n = 206$)	Chronic Illness ($n = 461$)	p
Age, mean (SD), range, years	33.8 (10.23), 19–60	42.1 (9.89), 20–66	<0.001[a]
Male, *n* (%)	103 (50.0)	254 (55.1)	0.223[a]
Race, *n* (%)			<0.001[a]
White	114 (55.3)	240 (52.1)	
Black/African American	33 (16.0)	162 (35.1)	
Asian	56 (27.2)	52 (11.3)	
Other	3 (1.5)	7 (1.5)	
BMI, mean (SD; range), kg/m^2	26.25 (5.309; 17.6–39.5)	28.61 (5.553; 17.3–42.3)	<0.001[b]
Age, mean (SD; range), years			
First psychiatric diagnosis	30.8 (10.29; 15–55)	24.0 (8.81; 3–53)	<0.001[b]
First schizoaffective disorder diagnosis	31.7 (10.17; 15–55)	31.4 (10.42; 7–61)	0.696[b]
Number of total known psychiatric hospitalizations, mean (SD; range)	2.2 (2.62; 0–13)	5.9 (9.55; 0–150)[c]	<0.001[b]
Number (%) of with history of attempted suicide	12 (5.8)	150 (32.5)	<0.001[a]
Number (%) with history of substance use including alcohol	45 (21.8)	202 (43.8)	<0.001[a]
PANSS total, mean (SD; range)	86.9 (11.94; 56–126)	85.3 (13.08; 42–128)	0.129[b]
HAM-D-21 total, mean (SD; range)	20.2 (8.52; 3–40)	20.4 (7.48; 3–43)	0.733[b]
YMRS total, mean (SD; range)	19.1 (9.95; 0–49)	18.3 (9.26; 0–50)	0.317[b]
CGI-S-SCA overall, mean (SD; range)	4.4 (0.57; 3–6)	4.4 (0.59; 2–6)	0.625[b]
PSP total, mean (SD; range)	50.7 (11.87; 22–88)	51.7 (10.61; 21–85)	0.287[b]

BMI indicates body mass index.

[a] p Value based on chi-square (early versus chronic illness).

[b] p Value based on *t*-test (early versus chronic illness).

[c] $n = 455$.

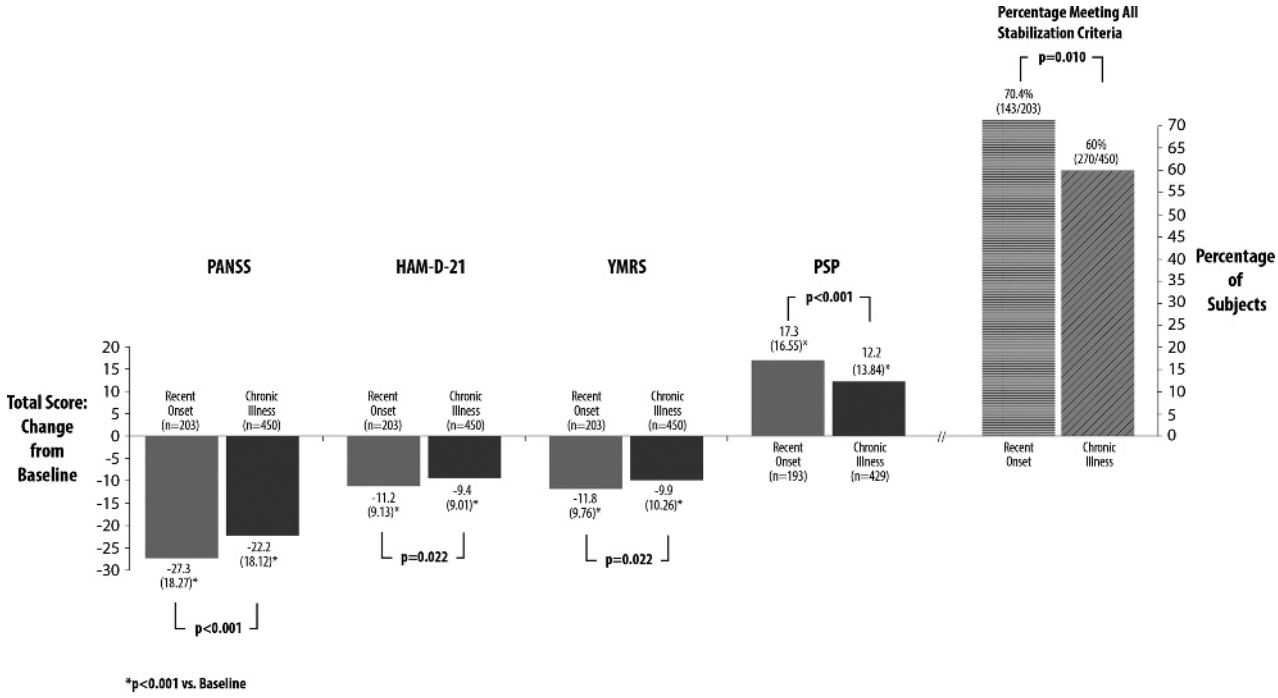

FIGURE 1. Changes in PANSS, HAM-D-21, YMRS, PSP, and percentage of subjects meeting stabilization criteria with PP1M treatment in the OL acute and stabilization phases. Subjects in both subpopulations exhibited significant improvements from baseline in PANSS total score, HAM-D-21 total score, YMRS total score, and PSP (paired *t*-test). In comparisons between the recent onset and chronic illness patients, significantly greater improvements were observed among the recent onset (*t*-test). A significantly higher percentage of subjects with recent onset illness entered the DB phase (chi-square test). Implications of instrument score changes: PANSS, HAM-D-21, and YMRS—negative changes indicate improvement; PSP—positive change indicates improvement.

TABLE 2. OL Paliperidone Monthly Treatment Phases: TEAEs and AEs of Interest

	Recent Onset (*n* = 206)	Chronic Illness (*n* = 461)
Any TEAE	117 (56.8%)	300 (65.1%)
Discontinuation due to TEAE	12 (5.8%)	38 (8.2%)
TEAEs in ≥5% of subjects in any group		
Administration site conditions	37 (18.0%)	91 (19.7%)
Headache	10 (4.9%)	26 (5.6%)
Injection site pain	15 (7.3%)	56 (12.1%)
Insomnia	16 (7.8%)	51 (11.1%)
Suicidal ideation	6 (2.9%)	25 (5.4%)
Weight increased	20 (9.7%)	37 (8.0%)
Weight change, mean (SD), kg	+1.4 (3.51)	+1.7 (4.13)
Common extrapyramidal symptom (EPS) TEAEs in >2% of subjects in any group		
Akathisia	12 (5.8%)	62 (13.4%)
Parkinsonism	15 (7.3%)	28 (6.1%)
Tremor	9 (4.4%)	14 (3.0%)
Symptomatic prolactin-related TEAEs in >2% of subjects in any group		
Libido decreased (men and women)	2 (1.0%)	10 (2.2%)
Amenorrhea (women)	9 (4.4%)	9 (2.0%)
Mean (SD) plasma prolactin level change at endpoint, μg/L		
Women	+31.5 (53.6)	+32.4 (53.5)
Men	+15.3 (19.2)	+18.8 (20.9)

TEAE indicates treatment emergent AE.

brain abnormalities are particularly progressive early in the course of schizophrenia with associated reductions in frontal lobe intracortical myelination (Bartzokis et al., 2011; Zhang et al., 2014). Treatment of first-episode patients with long-acting risperidone was associated with a significantly increased intracortical myelination volume compared with daily oral risperidone (Bartzokis et al., 2011). Similar mechanisms may exist in schizoaffective disorder.

The original study was not powered for this subgroup analysis and some baseline differences existed between subpopulations (Table 1); most were likely driven by the different duration of illness. Also, the survival curves crossed in the recent onset subpopulation (Supplemental Figure 2, http://links.lww.com/JNMD/A29). Although this is often found in underpowered studies, a significant effect of PP1M was still observed. Notably, subjects' age at first schizoaffective disorder diagnosis was approximately 31 years in both subpopulations. This reflects the longitudinal nature of establishing a diagnosis of schizoaffective disorder (*i.e.*, the diagnosis is established years after psychiatric illness is first recognized) (Canuso et al., 2010; Nasrallah et al., 2010). The mean age at first psychiatric diagnosis was approximately 24 years in the chronic illness and 31 years in the recent onset subjects. This difference may reflect an artifact of taking a database of adults (aged 18–65 years) and then identifying the subgroup of 5 years or less from their first diagnosis. In addition, the lower dropout rate in recent onset patients and the longer period of time in treatment may have contributed to better outcome in this subpopulation. Finally, the differential stabilization rate (eligibility for entry into the DB phase) in the OL phase between the recent onset and chronic illness patients represents an ascertainment bias for the DB phase. This limits the validity of any direct comparisons between the subpopulations in the DB phase.

In conclusion, PP1M significantly improved symptoms and reduced relapse in subjects with schizoaffective disorder. This was evident in both the recent onset and chronic illness subpopulations, with a more pronounced effect in patients earlier in their illness. Assuring antipsychotic intervention in the first years after a diagnosis of psychosis is increasingly accepted as a basic and critical tenet for improving the disease course and outcomes. This is supported by emerging biomarker evidence. Growing evidence may challenge the status quo supporting the use of long-acting antipsychotics earlier in the course of illness.

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DISCLOSURE

Drs Bossie, Alphs, and Fu and Ms Mahalchick are employees of Janssen Scientific Affairs, LLC, Titusville, NJ, and Dr Turkoz is an employee of Janssen Research & Development, LLC, Titusville, NJ.

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