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Association between symptom control and functional improvement in patients with acute schizophrenia: A post hoc analysis of an open-label, single-arm, multi-center study of paliperidone-extended release formulation

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ABSTRACT

Both symptom control and functional improvement are important goals in schizophrenia treatment. A post hoc analysis of an 8-week, open-label, single-arm, multi-center study of paliperidone-extended release formulation was conducted to evaluate the correlation between personal/social functioning and symptom control in the acute phase, and to identify factors associated with psychosocial functioning, in patients with acute schizophrenia. Of 608 enrolled patients, 602 (99%) were included in the full analysis set. Correlation and regression analyses were applied to identify the association of Personal and Social Performance (PSP) total scores with Positive and Negative Syndrome Scale (PANSS) total scores and other factors. A significant negative correlation was observed between PSP and PANSS at all visits (week 1: $r = -0.55$; week 2: $r = -0.79$, $p < 0.0001$). Patients with PSP score improvement ($\geq$10 point) showed a higher possibility of symptom improvement (PANSS reduction $\geq$30%). Duration of illness, PANSS Marder factors, and satisfaction with prior treatment, sleep quality, and daytime drowsiness influenced change in PSP total score at endpoint. These results suggest symptom outcome as an important factor to predict functional improvement in acute schizophrenia.

1. Introduction

Symptom control in patients with schizophrenia is considered the mainstay approach for achieving physical and cognitive improvements, though it may not always result in better functional outcomes (Chien et al., 2013). Many antipsychotics improve symptoms in patients with schizophrenia; however, improvement in the overall quality of life (QoL) and social functioning of patients is still a challenge (Patrick et al., 2010). In the real-world setting, functional outcomes in patients with schizophrenia determine their overall treatment success (Juckel and Morosini, 2008; Nasrallah et al., 2005). Improvement in psychosocial functioning directly affects psychotic symptom reduction, relapse and treatment compliance (Chien et al., 2013; Jelastopulu et al., 2014). Furthermore, a correlation between negative symptoms and social dysfunction has commonly been observed (Corcoran et al., 2011; Smith et al., 2002; Weinberg et al., 2009). Age, employment status, and duration of illness are additional factors that influence psychosocial functioning (Brune, 2005; Rocca et al., 2014; Weinberg et al., 2009).

The Personal and Social Performance (PSP) and Positive and Negative Syndrome Scale (PANSS) scales are reliable tools for the assessment of symptoms and functional outcomes in the acute and stable stages of schizophrenia (Birchwood et al., 1990). The PSP scale evaluates an entire array of socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behavior of patients (Patrick et al., 2009). PANSS focuses on evaluation of positive and negative symptoms, i.e. excess and diminution of normal functions, respectively (Birchwood et al., 1990; Kay et al., 1987).

Although functional improvement is correlated with symptom control in the maintenance phase of schizophrenia (Jelastopulu et al., 2014; Mausbach et al., 2009), there is a paucity of evidence focusing on this correlation in the acute phase. Several studies evaluating use of paliperidone-extended release (pali-ER) in patients with acute symptoms of schizophrenia have shown that improvement in symptoms and psychosocial functioning is associated with favorable outcomes, but only a few studies have shown a direct correlation between functional improvement and symptom control (Li et al., 2018; Nakagawa et al., 2015; Patrick et al., 2009).

Perception of psychosocial functioning may vary among different cultures, and results obtained in one socio-cultural setting cannot be extrapolated to other settings (Huang et al., 2012). It was therefore of

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interest to conduct a China-specific study in order to understand the perception of psychosocial functioning in this population.

Results from an 8-week, open-label, single-arm, multi-center study showed favorable efficacy, safety and tolerability profiles of flexible doses (3 ~ 12 mg/day) of pali-ER in Chinese patients with acutely exacerbated schizophrenia (Li et al., 2010). A post hoc analysis of this study was conducted to determine the correlation between psychosocial functioning (using PANSS scores) and psychotic symptom control (using PSP scores) in the acute phase of schizophrenia. In addition, variables influencing social functioning in the acute phase of schizophrenia were evaluated.

2. Methods

The primary study was an 8-week, open-label, single-arm, multi-center study to evaluate efficacy, safety and tolerability of flexible doses of pali-ER (3–12 mg/day) tablets in patients with acutely exacerbated schizophrenia. The study was conducted at 20 sites in China.

Patients (age ≥18 years) of either sex, with a diagnosis of acute schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition [DSM-IV] criteria), and with a PANSS total score ≥70 at baseline were enrolled in the study. Patients with diagnosis of substance dependence (current or within the previous 6 months), history of tardive dyskinesia or neuroleptic malignant syndrome, or significant risk of suicide or violent behavior were excluded from the study.

Patients were hospitalized within the first 7 days after study initiation. Follow-up visits were scheduled at weeks 2, 4, and 8. Changes in PANSS subscale scores, PANSS total score, PANSS Marder factors, PSP scale, Clinical Global Impression - Severity Scale (CGI-S), treatment satisfaction, sleep quality and daytime drowsiness were assessed at every visit (baseline, week 1, week 2, week 4, and week 8).

2.1. Statistical methods

Correlation between PSP total scores and PANSS total scores at all visits was assessed with the subgroups divided by change in PSP total scores (≥10; <10) and change in PANSS total scores (≥30%; <30%). Pearson's correlation coefficient (r) was used to determine the relationships between PSP total scores and PANSS total scores at all visits. Univariate logistic regression analysis of change in PSP total scores (≥10) at endpoint was performed with change in PANSS total score (≥30%) at all visits from baseline as influencing factor.

To explore the factors associated with functioning, univariate logistic regression analysis of PSP total scores >70 and change in PSP total scores at endpoint from baseline was performed with the subgroups divided by disease duration, age, gender, baseline PANSS total score, and PANSS reduction distribution (≥30% versus <30%), satisfaction in patients from previous medication, sleep quality, weight and waist circumference at endpoint. A multivariable stepwise linear regression analysis was used to identify predictive factors (PANSS Marder factors, quality of sleep, daytime sleep and patient satisfaction at endpoint, sex, age, weight, duration of illness, and BMI) of functioning (PSP total score) at endpoint.

The Full Analysis Set (FAS) was used for post hoc analysis and included patients who received pali-ER and had at least one efficacy evaluation after baseline. Last Observation Carried Forward (LOCF) method was used to fill missing data for efficacy assessments in FAS. All statistical analyses were performed using SAS (Version 9.1.3, The SAS institute, Cary, NC). Unless stated otherwise, the hypothesis test was two-sided with 0.05 significance; $p \leq 0.05$ was considered significant.

3. Results

3.1. Patient characteristics

Of 608 enrolled patients, 602 (99%) were included in FAS used for this post hoc analysis. The mean (SD) age was 32.4 (11.31) years and 51.99% were women. The majority of patients were diagnosed with paranoid schizophrenia (57.48%) followed by undifferentiated type of schizophrenia (37.87%). Insufficient efficacy was the major reason (59.96%) among patients for switching to pali-ER treatment at baseline. The mean (SD) number of hospitalizations was 1.72 (3.05), and the mean (SD) number of antipsychotic drugs received prior to treatment was 1.25 (0.81) (Table 1).

Table 1
Demographic and baseline characteristics (full analysis set).

Parameters	FAS N = 602
Age, *n* (%)	
N	601
Mean (SD)	32.4 (11.31)
Sex, *n* (%)	
Women	313 (51.99)
BMI, kg/m^2	
N	593
Mean (SD)	22.2 (3.69)
PSP total scores	
N	601
Mean (SD)	43.49 (12.81)
PANSS total scores	
N	602
Mean (SD)	89.86 (13.57)
Duration of schizophrenia	
N	597
Mean (SD)	7.82 (8.49)
Duration of antipsychotics treatment	
N	562
Mean (SD)	6.39 (8.10)
Reasons for switching to paliperidone, *n* (%)	
N	567
Insufficient efficacy	340 (59.96)
Poor compliance	148 (26.10)
Poor tolerance or safety	43 (7.58)
Other	36 (6.36)
Number of previous hospitalizations	
N	532
Mean (SD)	1.72 (3.05)
Number of previous antipsychotic treatments[a]	
N	559
Mean (SD)	1.25 (0.81)

[a] Past 6 months before patients enrolled in the trial.

3.2. Correlation between symptom control and functional outcome

Among patients (n = 480) with PSP total score change ≥10 (baseline to endpoint), a consistent increase in the proportion of patients with PANSS reduction ≥30% was observed at all visits (week 1: 38.33%, week 2: 65.42%, week 4: 86.46%, week 8: 95.00%). A consistent decrease was observed in the proportion of patients with PSP total scores change <10 (baseline to endpoint, n = 118) with PANSS reduction <30% (week 1: 80.51%, week 2: 66.95%, week 4: 63.56%, week 8: 66.95%) (Table 2). Similarly, for the patients with PANSS reduction ≥30% at endpoint (n = 495), a gradual increase was observed in the proportion of patients with PSP score change ≥10 at all visits (week 1: 39.19%; week 2: 67.27%, week 4: 81.62%, week 8: 92.12%). However, most of the patients from the subgroup with PANSS reduction <30% at endpoint (n = 103) showed a moderate decrease in the proportion of patients with PSP score change <10 at all visits (week 1: 81.55%; week 2: 69.90%; week 4: 71.84%; week 8: 76.70%) (Table 3). The results indicated that the symptoms for majority of the patients were well-controlled when patients showed improvement in function.

Patients with PSP total score change ≥10 at all visits showed higher odds for better symptom control (PANSS score reduction ≥30%) at endpoint (week 1: OR = 2.85; week 8: OR = 38.48, Table 4). PSP and PANSS total scores were negatively correlated at all visits (p < 0.0001,

Table 2
Correlation of functions and symptoms based on PANSS reduction at all visits with change in PSP total scores at endpoint from baseline.

	Week 1 LOCF	Week 2 LOCF	Week 4 LOCF	Week 8 LOCF
PANSS reduction ≥30% with change in PSP total scores ≥10				
N (missing)	480 (0)	480 (0)	480 (0)	480 (0)
Yes, *n* (%)	184 (38.33)	314(65.42)	415 (86.46)	456 (95.00)
PANSS reduction <30% with change in PSP total scores <10				
N (missing)	118 (0)	118 (0)	118 (0)	118 (0)
Yes, *n* (%)	95 (80.51)	79 (66.95)	75 (63.56)	79 (66.95)

LOCF, Last observation carried forward; PANSS, Positive and negative syndrome scale; PSP, Personal and social performance.

Table 3
Correlation of functions and symptoms based on change in PSP total scores at all visits from baseline and PANSS reduction at endpoint.

	Week 1 LOCF	Week 2 LOCF	Week 4 LOCF	Week 8 LOCF
% Change in PSP total scores ≥10 with PANSS reduction of ≥30%; *n* (%)				
N (missing)	495 (2)	495 (2)	495 (2)	495 (2)
Yes, *n* (%)	194 (39.19)	333 (67.27)	404 (81.62)	456 (92.12)
% change in PSP total scores <10 with PANSS reduction of <30%; *n* (%)				
N (missing)	103 (2)	103 (2)	103 (2)	103 (2)
Yes, *n* (%)	84 (81.55)	72 (69.90)	74 (71.84)	79 (76.70)

LOCF, Last observation carried forward; PANSS, Positive and negative syndrome scale; PSP, Personal and social performance.

Table 4
Univariate logistic regression analysis of PSP total scores (≥10) with change in PANSS reduction (≥30%) at all visits from baseline as influencing factor.

	Week 1 LOCF	Week 2 LOCF	Week 4 LOCF	Week 8 LOCF
Change in PSP total scores ≥10 from baseline (≥10 vs <10)				
OR	2.85	4.77	11.33	38.48
95% CI	1.68–4.84	3.01–7.57	6.97–18.41	21.94–67.49
p value	0.0001	<0.0001	<0.0001	<0.0001

CI, Confidence interval; LOCF, Last observation carried forward; OR, Odds ratio; PANSS, Positive and negative syndrome scale; PSP, Personal and social performance.

Table 5
Correlation of PSP total scores and PANSS total scores at all visits.

	Week 1 LOCF	Week 2 LOCF	Week 4 LOCF	Week 8 LOCF
PSP total scores vs. PANSS total scores (*n* = 599)				
Correlation coefficient	−0.55	−0.62	−0.69	−0.79
p value	<0.0001	<0.0001	<0.0001	<0.0001

LOCF, Last observation carried forward; Positive and negative syndrome scale; PSP, Personal and social performance.

Table 6
Simple linear regression analysis to explore and model various predictor variables of PSP total score at endpoint.

Factors	*N*	*R*	*p* value
Age	549	−0.01501	0.7256
Age (section)	549	0.01056	0.8051
Disease duration	520	−0.16566	0.0001
Disease duration (section) (>3 or <=3 years)	520	−0.10798	0.0138
Sex	562	−0.02267	0.5918
BMI	548	−0.00651	0.8792
PANSS total score	562	−0.79524	<0.0001
Positive symptom factor	562	−0.70893	<0.0001
Negative symptom factor	562	−0.62485	<0.0001
Thought disorder factor	562	−0.67659	<0.0001
Uncontrolled hostility/exciting factor	562	−0.58393	<0.0001
Anxious/depressed factor	562	−0.39323	<0.0001
Weight	553	0.02061	0.6286
Waistline	541	−0.00401	0.9258
Quality of sleep	558	0.37138	<0.0001
Daytime drowsiness	558	−0.19912	<0.0001
Treatment satisfaction	560	−0.55813	<0.0001

Independent variables which have statistical correlation ($p \leq 0.05$) were included in multiple linear regression.

Table 5).

3.3. Factors associated with functioning

Significant correlation ($p \leq 0.05$) was observed between various independent factors and PSP total score at endpoint. These factors included disease duration, PANSS total scores at baseline and endpoint, all the PANSS subscale scores (including PANSS Marder factors), treatment satisfaction with previous medication, sleep quality, and daytime drowsiness at endpoint (Table 6). Also, all of these factors, excluding PANSS positive subscale scores at baseline, significantly influenced the PSP total scores >70 at endpoint ($p \leq 0.05$) (Table 7). Univariate analysis for number of previous hospitalizations ($p = 0.149$) and number of previous antipsychotic treatments ($p = 0.240$) were not significantly different between the PSP total score >70 and PSP total score ≤70 subgroups; thus, these variables were not included in the logistic regression analysis.

The multiple linear regression showed variance in PSP total score to a significant extent ($p < 0.0001$) with respect to PANSS positive symptom factors (50%), PANSS negative symptom factors (9%), and uncontrolled hostility/excitement factors (4%) (Table 8). The results showed that PANSS positive symptom factors had a greater association than the PANSS negative symptom and uncontrolled hostility/

Table 7
Univariate logistic regression analysis of PSP total scores >70 at endpoint with disease duration, age, gender and other influencing factors.

Factor	OR	95% CI	*p* value
Disease duration distribution (>5 years vs. ≤5 years)	0.5970	0.43–0.83	0.002
Disease duration distribution (>3 years V.S. ≤3 years)	0.6468	0.46–0.91	0.013
Age distribution (18 years～,25 years～,30 years～, 50 years～,65 years～)[a]	0.9650	0.82–1.13	0.66
Gender (female vs. male)	0.7651	0.55–1.06	0.11
PANSS total scores at baseline	0.9749	0.96–0.99	.0001
PANSS positive subscale scores at baseline	1.0232	0.99 −1.05	0.11
PANSS negative subscale scores at baseline	0.9034	0.88–0.93	<0.0001
PANSS total scores at endpoint	0.8603	0.83–0.88	<0.0001
PANSS reduction distribution at endpoint (≥30 V.S. <30)	103.6348	14.35–748.48	<0.0001
PANSS positive subscale scores at endpoint	0.6800	0.63–0.73	<0.0001
PANSS negative subscale scores at endpoint	0.7584	0.72–0.80	<0.0001
PANSS general psychopathological symptom subscale scores at endpoint	0.7667	0.7325–0.8025	<0.0001
PANSS positive symptoms factor scores at endpoint	0.6981	0.6577–0.741	<0.0001
PANSS negative symptoms factor scores at endpoint	0.7572	0.7223–0.7937	<0.0001
PANSS cognition impairment factor scores at endpoint	0.6717	0.6234–0.7237	<0.0001
PANSS uncontrolled excitement hostility factor scores at endpoint	0.5571	0.4786–0.6485	<0.0001
PANSS anxiety depression factor scores at endpoint	0.722	0.6492–0.8031	<0.0001
Treatment efficacy satisfaction in patients from previous medication at endpoint[b]	0.2336	0.17–0.31	<0.0001
Tolerance satisfaction in subjects from previous medication at endpoint[b]	0.3572	0.2784–0.4582	<0.0001
Daytime drowsiness scores at endpoint	0.9818	0.97–0.99	<0.0001
Sleep quality scores at endpoint	1.0345	1.02–1.05	<0.0001

CI, Confidence interval; LOCF, Last observation carried forward; OR, Odds ratio; PANSS, Positive and negative syndrome scale; PSP, Personal and social performance.
[a] Meant that the age distribution was grouped by the age calculated according to the birth date;
[b] Treatment efficacy satisfaction and tolerance satisfaction were measured on levels like, very satisfied, satisfied, in general, dissatisfied, very dissatisfied.

Table 8
Multivariate linear regression of PSP total score.

Factor	Parameter	R^2	Model R^2	*F* value	*p* value
PANSS Positive symptom	−0.962	0.4977	0.4977	509.34	<0.0001
PANSS Negative symptom	−0.9196	0.0899	0.5877	111.89	<0.0001
Uncontrolled hostility/ excitement	−1.2637	0.0403	0.6279	55.43	<0.0001
Quality of sleep	0.04506	0.0019	0.6298	2.57	0.1094
Intercept	98.7829				

Stepwise method was used for the multivariate linear regression model. PANSS, Positive and negative syndrome scale; PSP, Personal and social performance.

excitement factors with PSP total scores in this analysis.

4. Discussion

More than half of patients with schizophrenia demonstrate poor basic personal and social functional skills despite remission in their psychotic symptoms (Patrick et al., 2009). Therefore, it is important to improve patients' functional parameters, in addition to controlling their symptoms. PSP, a valid and reliable scale used to measure psychosocial functioning and QoL, has shown correlation with the PANSS scale, another tool to assess psychotic symptoms in patients with schizophrenia (Patrick et al., 2009). Results from this post hoc analysis of a study conducted in Chinses patients showed a negative correlation between PSP and PANSS scores, suggesting the role of PSP in assessing clinical manifestations in acute schizophrenia.

Pearson's correlation coefficients between PSP and PANSS (week 1: $r = -0.55$; week 8: $r = -0.79$; $p < 0.0001$) showed that psychotic symptoms and social functional skills were strongly correlated in the acute phase of schizophrenia. Also, univariate logistic regression analysis for PSP suggested improved function in the acute phase and better psychotic symptomatic amelioration at all visits. These results are in agreement with previous studies that showed a negative correlation between PSP and PANSS in ethnicities other than Chinese such as Greek, Italian, etc. (Huang et al., 2012; Jelastopulu et al., 2014; Mauri et al., 2015; Ucok et al., 2015).

Although a correlation between psychotic symptoms and psychosocial functioning has been observed (Huang et al., 2012; Mauri et al., 2015; Ucok et al., 2015), there is a lack of consensus on the relative strength of correlation of positive and negative symptoms with functional outcomes. Negative symptoms have been observed as predictors of poor verbal performance and IQ, difficulty in maintaining personal and social relationships, and independence in everyday functioning (Addington and Addington, 1993; Howanitz et al., 2000; Rocca et al., 2014). Positive symptoms were reported to have a stronger association than negative symptoms with instrumental work functioning (Racenstein et al., 2002). In Thai patients, the association of psychosocial skills was found to be stronger with negative symptoms than with positive symptoms (Suttajit et al., 2015).

In the present study, both positive ($r = -0.70$, $p < 0.0001$) and negative symptoms ($r = -0.62$, $p < 0.0001$) demonstrated a strong correlation with functional score. However, in a multivariate regression analysis, the negative symptoms accounted for 9% variance ($p < 0.0001$) in PSP total score compared with 50% variance ($p < 0.0001$) explained by positive symptoms. With PANSS positive subscale, there were greater odds of PSP total score >70 at endpoint (OR = 1.023), compared with negative symptoms (OR = 0.90). These results are consistent with the existing literature about comparative strength of correlation of positive and negative symptoms (Corcoran et al., 2011; Rocca et al., 2014; Weinberg et al., 2009).

In the study conducted among Thai patients, the PANSS Marder hostility/excitement score was determined to be an important predictor of PSP scale- disturbing and aggressive behavior score. Along with the CGI-S score, and the age of the patient at disease onset, PANSS Marder negative, hostility/excitement score, and disorganized thought scores were observed as influencing factors of PSP total score (adjusted $R^2 = 0.45$) (Suttajit et al., 2015). Similarly, in the present study, PANSS Marder hostility/excitement score accounted for 63% variance in PSP total score (adjusted $R^2 = 0.63$).

Chronic sleep disorder is common in patients with schizophrenia and includes increased sleep latency, reduced sleep efficiency and time, alterations in slow-wave sleep, and rapid-eye movement (REM) latency or density (Bromundt et al., 2011; Hofstetter et al., 2005; Miller, 2004). Sleep disorders are a risk factor for increased distress, thought disorder, and symptoms of excitement, and may be indicative of more relapses of psychotic episodes (Hofstetter et al., 2005). Daytime drowsiness is also commonly associated with many psychiatric disorders; however, the prevalence and relevance of daytime drowsiness in these patients is

largely unknown (Hawley et al., 2010). Patients with poor sleep quality and drowsiness may experience difficulties with social and interpersonal relationships and are expected to have less social and professional satisfaction (Miller, 2004).

In the present study, daytime sleepiness had a negative correlation, while quality of sleep had a positive correlation with PSP total score at endpoint. Sleep quality influenced the PSP total score <70 at endpoint (OR, 1.03) and daytime drowsiness had slightly lesser odds of PSP total score <70 at endpoint (OR 0.98). Although these findings support the hypothesis that patients with schizophrenia who have poor quality of sleep may have difficulties with adequate social and vocational functioning, further exploration is warranted.

This post hoc analysis explored the correlation of PSP scores with only one scale of symptom control (i.e. PANSS), which limited the ability to draw conclusions in relation to other scales such as CGI-S. Also, the correlates and predictors of CGI-S cannot be generalized across all four domains of the PSP score.

Overall, a strong association of psychosocial functioning was observed with psychotic symptoms and other variables influencing personal and social functionality. Psychiatrists often focus on reducing symptom severity during the acute phase of schizophrenia and consider functional recovery in maintenance phase. However, results from this study suggest that patients with longer disease duration, positive or negative symptoms, treatment dissatisfaction with previous therapies, and sleep disorders in the acute phase of schizophrenia, need more careful assessment of psychosocial functioning for better treatment outcomes. The findings of this analysis may support identification of specific treatment targets in patients with acute schizophrenia.

Conflict of interest

All authors except Tian Mei Si are employees of Xian Janssen Pharmaceuticals. Tian Mei Si is associated with Peking University Institute of Mental Health and has been a consultant and advisor to Janssen Research & Development, LLC (Beijing), Pfizer, Lundbeck and Otsuka. She received honoraria and grant support from Janssen Research & Development, LLC(Beijing), and Lundbeck (Grant no. ESCITALDEP4001), Pfizer (Grant no. CHN2007CNS001) and Otsuka (Grant no. ARI-IIT-02).

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Supplementary materials

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