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ORIGINAL RESEARCH

Early Improvement of Psychiatric Symptoms with Long-Acting Injectable Antipsychotic Predicts Subsequent Social Functional Remission in Patients with Schizophrenia

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Purpose: The aim of this study was to clarify whether early symptomatic improvement in response to a long-acting injectable antipsychotic (LAI) contributes to subsequent social functional remission in patients with schizophrenia using the previous clinical trial data (EudraCT registration number: 2011-004889-15). Associations between other factors and social functional remission were also explored.

Patients and Methods: We analyzed 428 patients with schizophrenia in which the personal and social performance scale (PSP) and the involvement evaluation questionnaire (IEQ) at the time of the base line were recorded. Social functional remission was defined as participants who scored PSP >70 at the end of 65 weeks. Logistic regression analyses were done to examine associations between social functional remission and clinical and demographic characteristics including early symptomatic response evaluated by Positive and Negative Syndrome Scale (PANSS) at week one.

Results: One hundred out of 428 patients showed social functional remission at the end of the observation period. Shorter duration of illness, higher baseline score of supervision evaluated by IEQ and higher baseline PSP were significantly associated with the social functional remission. Improvement of positive subscale of PANSS at one week was significantly associated with later social functional remission when baseline PSP scores were excluded from predictive variables.

Conclusion: Shorter duration of illness, residual type of schizophrenia, higher baseline score of supervision and higher baseline social functioning were predictors of subsequent social functional remission. Although its effect seems to be limited, early symptomatic improvement could be also was a predictor of social functional remission.

Keywords: schizophrenia, social function, functional outcome, long-acting injectable antipsychotics; LAI

Introduction

The improvement of social function and consequent functional remission are important outcomes for patients with schizophrenia.[1–4] Impaired interpersonal relationships and daily living skills, as well as diminished occupational, social, and community interactions are common features that diminish the quality of life of schizophrenic patients. Patients with schizophrenia being confronted not only with the effects of an erroneous social perception of labeling and avoidance, but also with self-stigmatization, such as loss of self-esteem, difficulties in maintaining

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social relationships, or serious problems on both educational and professional levels, leading to a low socioeconomic status. These could influence not only the severity of the symptoms, but also the response to pharmacological treatment strategies.[5]

Several factors such as upbringing, premorbid personality and adjustment, social context, and short duration of untreated psychosis have been considered to be contributed to functional outcome in schizophrenia patients.[6–10] Antipsychotics are used primarily to control symptoms, especially positive symptoms, and have no direct therapeutic effect on cognition, social functioning, or quality of life related to functional outcomes, however, improvements in functional outcomes, including social functioning, should be mediated by symptomatic control.[11] Indeed, several studies have also suggested associations between symptomatic response to antipsychotics and favorable functional outcome, remission, and recovery.[1–4,11–18] Some studies suggested association between symptomatic response to antipsychotics and favorable functional outcome, even in patients with chronic schizophrenia.[16,17,19] In line with previous studies suggesting association between functional outcomes and early symptomatic responses to treatment, our previous study demonstrated associations between early improvement of positive symptoms and social functional remission.[18] However, our previous study on an oral antipsychotic did not evaluate several important factors possibly associated with functional remission,[19] therefore, whether early improvement of positive symptoms contribute to functional remission remains to be clarified. Furthermore, type of antipsychotic treatment and the route of administration are also important aspects that can be related to both clinical and functional remission.[20] To evaluate factors related to social functional remission, we analyzed data from a previously conducted clinical trial with long-acting injections (EudraCT registration number: 2011-004889-15)[21] data evaluating paliperidone palmitate. To clarify the relationship between symptomatic improvement and the social functional remission: the relationship between early symptom responses to treatment with a long-acting injection of paliperidone palmitate and social functional remission and which domain of symptomatic improvements, such as positive and negative symptoms, contributes to social functional outcome.

Patients and Methods

Subjects

This study is an explanatory post hoc analysis of the previously reported clinical trial.[21] Therefore, the subjects of this study are essentially the same as in the previous study.[21] Adult schizophrenia patients (men and women, aged 18–70 years) based on the Diagnostic and Statistical Manual of Mental Disorders (4th Edition, DSM-IV), with a total Positive and Negative Syndrome Scale (PANSS) score[22] between 70 and 120 at baseline screening and worsening of symptoms were enrolled.[21] The following are major exclusion criteria: 1) active DSM-IV diagnosis other than schizophrenia; 2) significant risk of suicidal behavior; 3) history of substance dependence within six months before screening; 4) involuntary status in a psychiatric hospital at screening; or history of neuroleptic malignant syndrome, tardive dyskinesia, any unstable or significant medical or neurological illness; 5) morbid obesity (BMI >40 kg/m2), or other systemic disease; 6) mental retardation; and 7) risk factors for prolonged QT interval, torsade de pointes, or sudden death. Patients with a history of intolerability, hypersensitivity, or lack of response to risperidone or paliperidone were also excluded from the study.[21] More details can be found in previous papers.[21] An independent ethics committee or institutional review board at each study site approved the study protocol (listed in Supplement File). The study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki and International Conference on Harmonization. All patients or representatives provided written informed consent.

Study Design

The study design is also the same as in the previous study.[21] The study consists of four phases: screening (up to three weeks), open-label (OL) stabilization study (17 weeks, flexible dosing), double-blind (DB) study (48 weeks, fixed dosing), and follow-up study.[21] During screening, patients underwent a washout of disallowed psychotropic medications and oral tolerability test. In the OL phase, all patients were treated with PP1M for 17 weeks. Patients who were clinically stable at weeks 14 and 17 (defined as a total PANSS score of ≤70 and a PANSS, Clinical Global Impression-Severity [CGI-S] score decrease of ≥1 point from OL baseline) were randomized to receive a fixed dose of PP3M or PP1M and entered a DB phase.[21] More details can be found in the previous papers.[21]

Definition of Social Functional Remission

Personal and social performance scale (PSP) was applied to evaluate social function,[23] and social functional remission was defined as participants who scored PSP >70[24] at the end of 65 weeks.

Statistical Analyses

Differences of demographic data between participants with social functional remission and participants without remission were tested by Chi-squared test for categorical data or two sample *t*-test for continues variables. To identify variables that explain social functional remission, logistic regression analysis was performed. Variance inflation factor (VIF) was used to check for multicollinearity. The factors associated with social functional remission were regressed on patient's demographic characteristics such as gender, duration of illness, and type of schizophrenia (Catatonic, Disorganize, Paranoid, Residual, and Undifferentiated), caregiver involvement at baseline assessed by involvement evaluation questionnaire (IEQ)[25] and early response to antipsychotic treatment. Since there was a significant correlation between duration of illness and age, we chose duration of illness rather than age as the variable for logistic regression analysis to avoid multicollinearity. Early response to antipsychotic treatment was defined as percentage-change between baseline and one week after treatment and percentage-change between baseline and one week after treatment in sub-sores of PANSS: PANSS general, PANSS positive, and PANSS negative. Since social function at baseline (baseline PSP scores) was expected to be highly associated with the future social functional remission, the above-mentioned logistic regression models including baseline PSP score were performed separately to evaluate sensitivity and independency of other factors.

Results

Baseline Demographics and Clinical Characteristics

We analyzed 428 patients in which the PSP and the IEQ at the time of the OL base line and the final evaluation of PSP at 65 weeks were recorded. Patient characteristics of each analytical group are summarized in Table 1. One hundred out of 428 patients showed social functional remission at the end of the observation period. Age, duration of illness, baseline PSP scores, and baseline PANSS negative scores were significantly different patients with remission from those without remission. The remission group was younger than the no remission group (mean ± SD age of the remission group was 36.08 ± 11.11, meanwhile the no remission group was 38.91 ± 11.97, p=0.03, two sample *t* test), had a shorter duration of illness (mean ± SD duration of illness of the remission group was 8.53 ± 7.85, meanwhile the no remission group was 11.06 ± 9.33, p=0.03, two sample *t* test), and had a higher baseline PSP score than the no remission group (mean ± SD baseline PSP score; the remission group was 54.25 ± 11.30 and the no remission group was 48.48 ± 10.38. p<0.0001 tested by two sample *t*-test). Regarding schizophrenic symptoms evaluated by PANSS, the remission group had significantly lower PANSS negative scores at baseline than the no remission group. There was no significant difference in total and subscale of PANSS score at one week and percentage changes of those at one week, however, the percentage change of PANSS positive scores at one week showed a trend level of difference (p=0.079) (Table 1). At the end of 65 weeks, the remission group had a significantly lower total and subscales of PANSS score than the no remission group (Table 1). Other baseline characteristics and treatment assignment during the randomized phase (PP1M or PP3M) appeared similar in both analytical groups.

Factors Associated with Social Functional Remission

The baseline PSP score of patients with subsequent social functional remission was 47.75 points in the first quartile, 55.00 points in the median, and 63.00 points in the third quartile, respectively (Table 2). On the other hand, the baseline PSP score of patients without subsequent social functional remission was 42.00 points in the first quartile, 48.00 points in the median, and 55 points in the third quartile, respectively (Table 2). This suggests that patients with higher baseline PSP scores are more likely to achieve social and functional remission than those with lower baseline PSP scores. To evaluate sensitivity and independency of other factors, we separately performed two logistic regression models including baseline PSP score and without baseline PSP.

The results of the logistic regression analysis excluding baseline PSP scores are shown in Table 3. None of the VIF values were up to 7, indicating that multicollinearity in the following logistic regression model is not evident. A logistic regression analysis by using percentage changes

Table 1 Demographic Data of Analyzed Subjects

	Total	Social Functional Remission	No Social Functional Remission	P value
No. of cases	428	100	328	(*t*-test or Fisher's exact test)
Age (y.o.)	38.25 ± 11.82	36.08 ± 11.11	38.91 ± 11.97	0.0301*
Duration of illness	10.47 ± 9.06	8.53 ± 7.85	11.06 ± 9.33	0.0077*
Gender				
Male/Female	228/200	53/47	175/153	1.0000
Treatment during random phase				
PP1M/PP3M	213/215	52/48	161/167	0.6485
Race				
White	288(67.29)	67(67.00)	221(67.38)	1.0000
Asian	116(27.10)	27(27.00)	89(27.13)	1.0000
Black	22(5.14)	4(4.00)	18(5.49)	0.7959
Others	2(0.47)	2(2.00)	0(0.0)	0.0542
Type of schizophrenia				
Catatonic	0(0.0)	0(0.0)	0(0.0)	NA
Disorganized	9(2.10)	1(1.00)	8(2.44)	0.6918
Paranoid	351(82.01)	79(79.00)	272(82.93)	0.3747
Residual	16(3.74)	7(7.00)	9(2.74)	0.0673
Undifferentiated	52(12.15)	13(13.00)	39(11.89)	0.7298
Baseline PSP score				
Total	49.82 ± 10.87	54.25 ± 11.30	48.48 ± 10.38	<0.0001*
21 ~ 45	166(38.79)	21(21.00)	145(44.21)	<0.0001*
46 ~ 52	97(22.66)	24(24.00)	73(22.26)	0.7850
53 ~ 70	164(38.32)	54(54.00)	110(33.54)	0.0004*
71 ~	1(0.23)	1(1.00)	0(0.0)	0.2336
Social useful	3.83 ± 0.80	3.52 ± 0.82	3.92 ± 0.76	<0.0001*
Social relationship	3.61 ± 0.68	3.34 ± 0.77	3.69 ± 0.63	<0.0001*
Self care	2.23 ± 0.93	2.11 ± 0.91	2.27 ^ 0.93	0.1313
Aggressive	1.58 ± 0.76	1.69 ± 0.77	1.55 ± 0.76	0.1183
Baseline PANSS score				
Total	85.64 ± 9.66	85.15 ± 9.56	85.79 ± 9.70	0.5621
Positive	20.13 ± 4.37	20.57 ± 3.94	19.99 ± 4.49	0.2150
Negative	23.53 ± 4.25	22.34 ± 3.73	23.90 ± 4.33	0.0006*
General	41.98 ± 5.58	42.24 ± 5.46	41.90 ± 5.62	0.5885
PANSS score at one week				
Total	81.24 ±9.93	80.41±9.78	81.49 ±9.98	0.336
Positive	18.69 ±4.26	18.82 ±3.82	18.66±4.39	0.717
Negative	22.80 ±4.22	21.61 ±3.82	23.17 ±4.28	0.001*
General	39.74 ±5.55	39.98 ±5.44	39.67 ±5.59	0.621
Percentage change PANSS score at one week (v/s) baseline				
Total	−5.03 ±6.38	−5.45±-5.45	−4.91 ±6.39	0.456
Positive	−6.72 ± 10.50	−8.23±9.42	−6.26±10.77	0.079
Negative	−2.94±7.06	−3.11 ±7.81	−2.89 ± 6.83	0.797

(*Continued*)

Table 1 (Continued).

	Total	Social Functional Remission	No Social Functional Remission	P value
General	−5.08 ±7.87	−5.17 ± 6.98	−5.06 ± 8.13	0.888
PANSS scores at end of 65 weeks				
Total	52.57 ±9.86	46.53 ±8.20	54.41±9.60	<0.001*
Positive	10.53 ±3.12	9.58±2.52	10.82 ±3.23	<0.001*
Negative	16.34 ±4.61	13.57±3.66	17.19 ±4.54	<0.001*
General	25.70 ±4.98	23.38 ±4.52	26.4 ±4.91	<0.001*
Baseline IEQ score				
Supervision	2.99 ± 3.26	3.46 ± 3.78	2.84 ± 3.08	0.1401
Tension	6.88 ± 4.58	6.99 ± 4.77	6.84 ± 4.53	0.7875
Urging	10.19 ± 5.98	9.83 ± 5.95	10.30 ± 5.99	0.4951
Worrying	10.57 ± 5.07	10.67 ± 5.56	10.54 ± 4.92	0.8334

Abbreviations: PSP, personal and social performance scale; PANSS, positive and negative syndrome scale; IEQ, involvement evaluation questionnaire.

of PANSS score at one week as early treatment response showed that the duration of illness (p=0.005), baseline score of supervision evaluated by IEQ (p=0.006), type of schizophrenia (residual type, p=0.018), and an improvement positive score of PANSS at one week (p=0.047) were significantly associated with the socially functional remission (Table 3).

Results of logistic regression analyses including baseline PSP scores show Table 4. Logistic regression analysis by using percentage changes of PANSS score at one week as early treatment response showed that duration of illness (p=0.010), baseline score of supervision evaluated by IEQ (p=0.006), and baseline PSP score (p<0.001) were significantly associated with the socially functional remission (Table 4). Regarding type of schizophrenia, residual type showed trend level of association with social functional remission (p=0.059). Whereas percentage change of PANSS score at one week were not associated with social functional remission.

Discussion

The current post hoc analyses were aimed at determining the factors associated with subsequent remission of social function (PSP >70 at 65w) in patients with schizophrenia treated with long-acting injection of Paliperidone palmitate. The PSP scale evaluates an entire array of socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behavior of patients.[23] We identified that shorter duration of illness, higher baseline score of supervision evaluated by IEQ and higher baseline PSP were significantly associated with the social functional remission. Although early improvement of schizophrenia symptoms evaluated with PANSS was not associated with subsequent social functional remission when baseline PSP scores were treated as a predictive variable, improvement of positive subscale of PANSS at one week was significantly associated with subsequent social functional remission when baseline PSP scores were excluded from predictive variables. Regardless of predictive models, shorter duration of illness was

Table 2 Distribution of Baseline PSP Scores

	No. of Subjects	Minimum Value	1st Q	Median	Mean	3rd Q	Maximum Value
Total	428	21.00	42.00	49.00	49.82	59.00	80.00
Patients with later social functional remission	100	21.00	47.75	55.00	54.25	63.00	80.00
Patients without later social functional remission	328	21.00	42.00	48.00	48.48	55.00	70.00

Abbreviation: PSP, personal and social performance scale.

Table 3 Results of Logistic Regression Analysis without Baseline PSP Scores

Factor	Odds Ratio	Confidence Interval	p value
AUC	0.66		
Male	0.95	0.59 ~ 1.52	0.830
Race			
White	1.00		
Asian	0.75	0.42 ~ 1.34	0.323
Others	1.36	0.49 ~ 3.81	0.558
Type of schizophrenia			
Paranoid	1.00		
Disorganized	0.31	0.03 ~ 2.77	0.293
Residual	3.68	1.25 ~ 10.87	0.018
Undifferentiated	1.08	0.51 ~ 2.29	0.849
Duration of illness	0.96	0.93 ~ 0.99	0.005
Early improvement (one week) of PANSS score (%)			
General	1.02	0.98 ~ 1.06	0.336
Positive	0.97	0.95 ~ 1.00	0.047
Negative	1.00	0.97 ~ 1.04	0.944
Open label baseline IEQ score			
Supervision	1.14	1.04 ~ 1.24	0.006
Tension	1.00	0.94 ~ 1.06	0.996
Urging	0.96	0.91 ~ 1.01	0.130
Worrying	0.98	0.92 ~ 1.04	0.498

Abbreviations: PSP, personal and social performance scale; PANSS, positive and negative syndrome scale; IEQ, involvement evaluation questionnaire.

Table 4 Results of Logistic Regression Analysis with Baseline PSP Scores

Factor	Odds Ratio	Confidence Interval	p value
AUC	0.71		
Male	0.89	0.55 ~ 1.44	0.633
Race			
White	1.00		
Asian	0.79	0.44 ~ 1.44	0.446
Others	1.97	0.67 ~ 5.81	0.221
Type of schizophrenia			
Paranoid	1.00		
Disorganized	0.22	0.02 ~ 2.49	0.222
Residual	3.03	0.96 ~ 9.55	0.059
Undifferentiated	1.26	0.57 ~ 2.75	0.567
Duration of illness	0.96	0.93 ~ 0.99	0.010
Early improvement (one week) of PANSS score (%)			
General	1.02	0.98 ~ 1.06	0.433
Positive	0.98	0.95 ~ 1.01	0.128
Negative	1.00	0.97 ~ 1.04	0.941
Open label baseline IEQ score			
Supervision	1.14	1.04 ~ 1.25	0.006
Tension	1.00	0.94 ~ 1.06	0.982
Urging	0.98	0.93 ~ 1.03	0.400
Worrying	0.99	0.93 ~ 1.06	0.805
Baseline PSP score	1.06	1.03 ~ 1.08	< 0.001

Abbreviations: PSP, personal and social performance scale; PANSS, positive and negative syndrome scale; IEQ, involvement evaluation questionnaire.

significantly associated with social functional remission. Type of schizophrenia also showed relatively robust association with social functional remission. Residual type of schizophrenia showed trend level of association with social functional remission (p=0.059) when baseline PSP scores were included as predictive variables. When baseline PSP scores were excluded from predictive variables, residual type schizophrenia was significantly associated with social functional remission. Regardless of the predictive model, gender and race were not associated with social functional remission.

In our analyses, the most important predictive factor for social functional remission were baseline social function. It should be plausible that patients with better social function at the beginning of treatment showed subsequent social functional remission. Indeed, our previous study also showed baseline PSP score was associated with functional outcome.[26] Except the social function at the beginning of the treatment, duration of illness was a robust factor related to social functional remission. A previous review documented that duration of illness influences treatment response, suicide risk and loss of social functioning in schizophrenic patients.[27] Regarding social functioning, a three-year follow–up study reported that having a shorter duration of illness is significantly associated with remission[28,29] and functional outcomes in schizophrenia.[30–32] Another study of PP1M also showed an association between shorter duration of illness and better outcomes.[26] A meta-analysis of social cognition found that greater deficits in emotion processing were associated with longer duration of illness.[33] In line with those previous studies, our analysis also demonstrated an

association between duration of illness and social functional outcome. Several magnetic resonance imaging studies demonstrated brain morphological changes, especially reduced grey matter volume in the prefrontal cortex, associated with a long duration of illness.[34] A recent meta-analysis reported that that individuals with schizophrenia who had greater whole brain and front-limbic volumes had better functional outcomes.[35] These data would explain underlining neurobiological mechanisms of association with duration of illness and social functional outcomes. Another robust factor association with social functional remission was type of schizophrenia. In this study, residual type of schizophrenia was associated with social functional remission. A previous study exploring predictors of relapse and rehospitalization in schizophrenia and schizoaffective disorders revealed that the diagnosis of residual type related to a lower relapse rate.[36] However, number of residual type patients was small in the present study, we have no clear explanation for this association at present.

It is not as robust as duration of illness and type of schizophrenia; however early symptomatic improvement was also partially associated with social functional remission. In our analyses, early improvement of positive symptoms (one week after start of the treatment) was associated with subsequent social functional remission. Univariate analysis showed no significance between remission group and no remission group, however, early improvement in PANSS positive scale showed trend level of difference between two groups. Identification of factors related to treatment response influencing subsequent functional outcomes should be important, because it might facilitate informed decision–making for future therapy, especially in ineffective cases. Although antipsychotics have been considered to have no direct effects on social functioning, several studies have demonstrated associations between symptomatic improvement caused by antipsychotic treatment and functional outcomes including social function.[1–4,11–19,26] Indeed, the present study showed a social remission group had significantly lower PANSS score than a no remission group at the end of 65 weeks. This suggests that symptomatic improvement and maintenance should be important for functional outcome. A previous study of PP1M showed PANSS reduction at five weeks was a strong factor associated with favorable response in clinical outcomes of symptoms and function.[26] In addition to the previous PP1M study, our study demonstrated association between reduced PANSS positive at one week and social functional remission. These results suggested that early symptomatic improvement should contribute to social functional outcomes. Similar to the previous study, our real-world study with oral antipsychotics also showed an association between early improvement of positive symptoms and better social functional outcomes.[19] An analysis of 12 studies also identified early symptomatic improvement as one of the predictors of symptomatic remission.[37] Although negative symptoms and cognitive function have been considered to be related to social function, a 10-year longitudinal study demonstrated a significant relationship between psychosis and increased impairment of work functioning.[38] The author of the 10-year study considered that one of the primary reasons for association between work difficulties and psychosis included "distrust of other people". Such a feature of psychosis (positive symptoms) should deteriorate social functioning.[38] Some studies exploring the association between early improvement and later outcomes have used atypical antipsychotics, such as risperidone, olanzapine, and paliperidone[17,19,37] On the other hand, studies using both typical and atypical antipsychotics have reported associations between early symptomatic improvement, regardless of whether the patients were treated by typical or atypical antipsychotics.[7,8,10,37] Taken together, we think that early symptomatic improvement including improvement of positive symptoms could be a predictor of symptomatic remission but also be a predictor of functional remission. The American Psychiatric Association suggested that patients receive treatment with a LAI antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence.[39] However, some studies suggest that long-acting injectable antipsychotics (LAI) should be considered earlier in therapy.[20,40] In such a situation, not only maintenance of symptomatic improvement but also early symptomatic improvement should be required for LAI. A previous study of PP1M demonstrated early symptomatic improvement (within a few days).[41] Pharmacokinetic studies demonstrated that PP1M achieves therapeutic, steady-state plasma levels rapidly on initiation without oral antipsychotics supplementation.[42,43] Such pharmacokinetics may explain early symptomatic improvement observed with PP1M therapy. These data suggested a relevance of earlier use of LAI in therapy. However, our results suggested that predetermined factors such as baseline social functioning, duration illness and type of schizophrenia should contribute more to social functional remission rather than effects of pharmacological

intervention. Although current antipsychotics are highly effective against positive symptoms, they are considered to have limited direct effects on functional outcomes including social function. Development of new drugs that are more effective for social functions should be warrant. In this analysis, we also identified that a higher baseline score of supervision evaluated by IEQ was significantly associated with social functional remission. The role of the caregiver is important in chronic diseases; however, of the many studies in patients with schizophrenia, relatively few focus on the influence of caregiver burden on therapy. At present, we have no clear explanation for the association between higher baseline scores of supervision and social functional remission. One possible explanation is that patients having higher scores of supervision could be protected from excessive alcohol consumption and taking illegal drugs (these items are included items for scoring of supervision). A previous study demonstrated that comorbid substance use disorder had negative impacts on both symptomatic and functional remission.[7] However, patients with a history of drug dependence within six months prior to screening were excluded in this study, the relationship between high-scoring supervision and protection from drug use does not seem plausible to draw from the present study.

Finally, we should mention some limitations of the analysis. The study consisted of four phases: screening (up to three weeks), OL stabilization (17 weeks, flexible doses), DB (48 weeks, fixed doses), and a follow-up phase. Only clinically stable patients at weeks 14 and17 then entered the DB phase. For analyses exploring relationship between symptomatic improvement and subsequent functional outcomes, such a study design could be a source of selection bias. Because unstable subjects were excluded from analyses. We consider that such a selection bias could be related relatively lesser robust association with small effect size between symptomatic improvement and subsequent social functional remission. In addition, such a selection bias should be interpreted with caution when applying the present results to schizophrenia in general population. For example, the social functional remission rate in the present study may be overestimated due to the survival bias.

Conclusion

We found that shorter duration of illness, residual type of schizophrenia, higher baseline score of supervision, and higher baseline social functioning were predictive variables of subsequent social functional remission. Although its effect seems to be limited, early symptomatic improvement could could be a predictor of social functional remission.

Data Sharing Statement

The data set used is owned by Janssen pharmaceutical company and data sharing is restricted. The authors may not make their study data available at the time of publication, but in accordance with the Neuropsychiatric disease and Treatment Availability Policy, they promise to provide all authors with access to the data they request that form the basis of the findings described in this study. However, in accordance with the Neuropsychiatric Disease and Treatment Availability Policy For further information, please contact https://yoda.yale.edu/.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors have disclosed that they are full-time employees of Janssen Pharmaceutical K.K. of Johnson & Johnson in Japan. The authors report no other conflicts of interest in this work.

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