

# Disorganized Symptoms Predicted Worse Functioning Outcome in Schizophrenia Patients with Established Illness

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## Abstract

Most patients with schizophrenia will have subsequent relapses of the disorder, with continuous impairments in functioning. However, evidence is lacking on how symptoms influence functioning at different phases of the disease. This study aims to investigate the relationship between symptom dimensions and functioning at different phases: acute exacerbation, nonremission and remission. **Methods:** Patients with schizophrenia were grouped into acutely ill (n=89), not remitted (n=89), and remitted (n=69). Three exploratory stepwise linear regression analyses were performed for each phase of schizophrenia, in which the five PANSS factors and demographic variables were entered as the independent variables and the total Global Assessment of Functioning Scale (GAF) score was entered as the dependent variable. An additional exploratory stepwise logistic regression analysis was performed to predict subsequent remission at discharge in the inpatient population. **Results:** The Disorganized factor was the most significant predictor for acutely ill patients ( $p < 0.001$ ), while the Hostility factor was the most significant for not-remitted patients and the Negative factor was the most significant for remitted patients ( $p = 0.001$  and  $p < 0.001$ , respectively). In the logistic regression, the Disorganized factor score presented a significant negative association with remission ( $p = 0.007$ ). **Conclusions:** Higher disorganization symptoms showed the greatest impact in functioning at acute phase, and prevented patients from achieving remission, suggesting it may be a marker of symptom severity and worse outcome in schizophrenia.

**Key Words:** Remission in Schizophrenia, Functional Remission, Symptom Dimensions, Disorganized Schizophrenia

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## Introduction

Most patients with schizophrenia will present recurrent psychotic relapses with brief asymptomatic periods between episodes (1, 2). According to the staging model for schizophrenia proposed by McGorry et al. (3), patients who do not achieve complete remission or recovery after the first episode would fall under the stage 3, while the stage 4 comprises chronic patients presenting severe, persistent, and continuous unremitting illness with functional impairments. Regardless of the stage, treatment for a patient with schizophrenia should progress from symptomatic response to functional remission, or even recovery (4). Symptomatic remission has been repeatedly reported as an increasingly attainable state (5) and, according to a recent systematic review (6), remission rates can range from 16 to 67% in multiple-episode schizophrenia and from 17 to 78% in first-episode schizophrenia. In a reanalysis of the CATIE study

### Clinical Implications

The results of our study show that the Disorganized factor had the greatest impact on functioning in the acute phase of schizophrenia and the Negative factor was also significant, although to a lesser degree. It was only during the remitted phase that the Disorganized factor was not significant in functioning. On the other hand, the Disorganized factor was the only significant PANSS factor to prevent inpatients from attaining subsequent remission. Taken together, these findings suggest that acutely ill patients presenting predominant disorganized symptoms are less likely to achieve remission. These findings are consistent with those of Metsanen et al. (16), who identified Disorganized symptoms in formal thought disorder as risk factors for a worse course of illness. Furthermore, in a review conducted by Owens et al. (17), odd behavior increased the risk of relapse and reduced the likelihood of a favorable one-year outcome by 90% when repeatedly manifested, and by 85% if present exclusively in the month preceding admission.

(7) by Levine et al. (8), approximately 44.5% of the patients achieved symptomatic remission for any period.

When the Positive and Negative Syndrome Scale (PANSS) (9) is used to assess psychopathology, it generally produces a five-factor solution (10, 11) regarded as “symptom dimensions,” which are Positive, Negative, Disorganized, Depressed/Anxiety and Excited/Hostility. As the course of illness develops, negative symptoms will prevail over positive symptoms (1) and prominence of continuous negative symptoms in chronic patients has been associated with worse functional outcome (12, 13). However, higher rates of disorganization have also been correlated with worse response to treatment, while continuous illness has been associated with worse long-term prognosis (14-18). In addition, Karow et al. (19) reported a lack of functional remission in patients that met criteria for symptomatic remission, whereas disorganized symptoms and emotional distress were present with at least moderate severity in a significant portion of remitted patients.

Much attention has been given to negative and cognitive symptoms with regards to treatment outcome in schizophrenia, while studies addressing the outcome when the disorganized symptoms are the prominent presentation are lacking. Predicting how symptom dimensions impair functioning in schizophrenia may help clinicians in determining therapeutic strategies focused in target symptoms.

The goal of this study is to investigate the role of symptom dimensions in functioning among patients in the stages 3 and 4 of schizophrenia at different illness phases: acute exacerbation, nonremission and remission.

## Methods

### Subjects

The sample comprised 247 patients with schizophrenia recruited from two different centers: the Inpatient Psychiatric Unit of Hospital das Clínicas Luzia de Pinho Melo (Mogi das Cruzes, Brazil) (n=89), and the outpatient schizophrenia program of the Federal University of São Paulo (São Paulo, Brazil) (n=158), between 2011 and 2014. The main reason for admission to the inpatient unit was severe exacerbation

of illness characterized by risk of self-injury or aggressive behavior. The outpatient program provides a full spectrum of evaluation, treatment and case management services for individuals with schizophrenia. Inclusion criteria were: an established diagnosis of schizophrenia for more than one year as defined by the *DSM-IV* (20), have experienced more than one episode of acute exacerbation, and are between 14 and 65 years of age. Exclusion criteria were: first episode of psychosis; psychosis due to medical condition; and severe premorbid intellectual disability (assessed by a family interview focused on neurodevelopment as well as social and cognitive skills in school).

### Diagnosis and Assessment of Symptoms

Assessment of the outpatient population was cross-sectional and the inpatient population was assessed at baseline, at every four weeks of antipsychotic treatment or any switch of antipsychotic, and at discharge. For diagnostic purposes, modules A, B, C, D and E of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (21) were administered. Psychopathology was assessed using the PANSS and functioning was assessed by the Global Assessment of Functioning Scale (GAF) (22). All SCID, PANSS and GAF raters trained together in periodic meetings. The study was approved by the local research ethics committees (2013/01 and 1737/06), and all subjects and their relatives provided written informed consent for participation.

### Remission Criteria

Patients were grouped in remitted and not remitted. Symptomatic remission was defined as a severity of mild (score of 3 on a scale of 1 to 7) or less for the following selected PANSS items: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), unusual thought content (G9), mannerism and posturing (G5), blunted affect (N1), passive/apathetic social withdrawal (N4), and lack of spontaneity and flow of conversation (N6). These are the specific items proposed by the remission criteria developed by the Remission in Schizophrenia Working Group (RSWG) (23). The six-month criterion was not considered in this study;

**Table 1** Clinical and Demographic Characteristics Comparison Between Each Clinical Phase of Schizophrenia (N=247)

Characteristics	Acute N=89	Non- Remitter N=89	Remitter N=9	P-Value
Gender-Male (%)	57.2	74.5	62.2	<b>0.001</b>
Age-Years (Mean±SD)	36±11	37±11	36±10	0.967
Age of Onset-Years (Mean±SD)	22±8	22±7	23±6	0.665
Duration of Illness-Years (Mean±SD)	13±8	13±8	11±6	0.062
Years of Education (Mean±SD)	8±4	8±3	8±2	0.744
Total PANSS Score (Mean±SD)	133±17	70±13	48±9	<b>&lt;0.001</b>
GAF (Mean±SD)	18±9	43±9	58±11	<b>&lt;0.001</b>

SD=standard deviation

thus, the outpatients had to be in symptomatic remission for at least one week at the moment of assessment, while the inpatients were considered in symptomatic remission if they fulfilled the above mentioned criterion for at least one week prior to discharge.

### Data Analysis

Psychopathological dimensions of each population were disclosed by previous factor analysis (11, 24). The final factors were: Positive—P1, P3, P5, P6, G9; Disorganized—P2, G5, G10, G11, G13, G15; Negative—N1, N2, N3, N4, N6, G7; Depression—G3, G6; and, Hostility—P4, P7, G8, G14. Difficulty in abstract thinking (N5) was intentionally excluded from the disorganized factor to control for cognitive functional impairment (25). Early response to antipsychotic was defined as a reduction  $\geq 40\%$  in total PANSS score at fourth week. The peak of effect of antipsychotics typically occurs within 2–4 weeks (when there is an expected reduction of at least 25% in total PANSS score), which means that satisfactory subsequent clinical response is unlikely (26).

Three exploratory stepwise linear regression analyses were performed for each phase of schizophrenia, in which the PANSS factors, age, and duration of illness were entered as the independent variables and the total GAF score was entered as the dependent variable. In addition, an exploratory stepwise logistic regression analysis was performed to predict subsequent remission in the inpatient population, in which the index PANSS factors, age, duration of illness and early response to antipsychotic were entered as the independent variables and symptomatic remission at discharge was entered as the dependent variable. One-way ANOVA was performed between the groups for clinical and demographic characteristics. Statistical significance was considered at the

level of  $<0.05$ . All statistical analyses were made with the Statistical Package for the Social Sciences (SPSS), version 20.0.

### Results

Except for gender, demographic characteristics were homogeneous between the groups while the clinical characteristics were widely heterogeneous (see Table 1). In the stepwise linear regression analyses (see Table 2), the Disorganized factor was the most significant predictor of worse functioning in acutely ill patients, while the Hostility factor and the Negative factor were the most significant for not-remitted patients and remitted patients, respectively. The variances of the final models (all  $p < 0.001$ ) were: acutely ill (adjusted  $R^2 = 0.535$ ), not remitted ( $R^2 = 0.410$ ), and remitted (adjusted  $R^2 = 0.450$ ). In the logistic regression for prediction of subsequent remission in the inpatient population, the model was statistically significant, indicating that the predictors distinguished between remitters and nonremitters with a precision of 80.0% (sensitivity=0.54, specificity=0.91,  $\chi^2 = 26.00$ ,  $df = 3$ ,  $p < 0.001$ ). The Wald criterion demonstrated that the variables Early response to treatment, Depression factor score and Disorganized factor score made a significant contribution to prediction of remission (see Table 3).

### Discussion

The results of our study show that the Disorganized factor had the greatest impact on functioning in the acute phase of schizophrenia and the Negative factor was also significant, although to a lesser degree. It was only during the remitted phase that the Disorganized factor was not significant in functioning. On the other hand, the Disorganized factor was the only significant PANSS factor to prevent inpatients from attaining subsequent remission. Taken together, these

**Table 2 Multiple Linear Regression of GAF Score for Each Clinical Phase of Schizophrenia (N=247)**

Independent Variables	B	SE	$\beta$	T	P-Value
<b>Acutely Ill</b>					
Disorganized factor	-1.02	0.13	-0.63	-7.77	<0.001
Negative factor	-0.23	0.09	-0.19	-2.38	0.019
<b>Nonremitted</b>					
Hostility factor	-1.30	0.36	-0.31	-3.63	<0.001
Negative factor	-0.71	0.23	-0.31	-3.08	0.003
Disorganized factor	-0.77	0.31	-0.25	-2.43	0.017
<b>Remitted</b>					
Negative factor	-2.53	0.39	-0.59	-6.43	<0.001
Positive factor	-0.92	0.40	-0.20	-2.25	0.028

B=standardized coefficient

**Table 3 Exploratory Logistic Regression for Subsequent Symptomatic Remission in Acutely Ill Schizophrenia Inpatients (N=89)**

Independent Variables	B	SE	Wald	P-Value	Exp (B)
Early response	1.32	0.61	4.59	0.032	3.97
Disorganized factor	-0.17	0.06	7.32	0.007	1.18
Depression factor	0.23	0.08	7.17	0.007	0.79

B=unstandardized coefficient; SE=standard error of B

findings suggest that acutely ill patients presenting predominant disorganized symptoms are less likely to achieve remission. These findings are consistent with those of Metsanen et al. (16), who identified Disorganized symptoms in formal thought disorder as risk factors for a worse course of illness. Furthermore, in a review conducted by Owens et al. (17), odd behavior increased the risk of relapse and reduced the likelihood of a favorable one-year outcome by 90% when repeatedly manifested, and by 85% if present exclusively in the month preceding admission.

Interestingly, the Hostility factor was the most significant contributor to impaired functioning in not-remitted patients along with Negative and Disorganized factors. Similarly, a previous study has associated hostility with nonadherence to antipsychotics and, by implication, with recurrent relapses (26).

In a recent study, Levine et al. (12) suggested that remission is almost an unattainable objective in the presence of predominant negative symptoms. In our results, even when remission was achieved, the remaining negative symptoms were the most important contributors to prevent the patients from attaining functional gains. Even though the introduc-

tion of clozapine led to a breakthrough in the treatment of refractory schizophrenia, it has shown only a modest impact on negative symptoms. On the other hand, both persistent hostility and disorganized symptoms may respond satisfactorily to clozapine (18, 28).

Other baseline factors related with subsequent remission in the inpatient population were to present higher rates of baseline depressive symptoms and an early response to antipsychotics. Although continuous presence of depressive symptoms in chronic schizophrenia patients is a marker of worse outcome (29), other studies have reported that higher rates of depression during the acute phase seems to be associated with good outcome and an increased likelihood of clinical remission (30). Concerning early improvement, it has been repeatedly associated with remission and good functioning in schizophrenia (31).

Finally, a number of limitations need to be considered. First, this study is limited by the lack of data on the six-month time criterion for remission. Secondly, the duration of untreated psychosis was not assessed, although it has been reported to be a good predictor of outcome in functioning (17, 32). Thirdly, our data lacked the information on stage

1 (prodromal stage) of the illness. Hence, patients at first episode, which correspond to stage 2 (3), were intentionally excluded to keep homogeneity of the sample. Though not possible in this study, identifying symptom predictors across all the different illness stages is desirable and would have provided much more information. Nevertheless, the present study contributes to the debate on symptom dimensions and the role they play in schizophrenia outcome. The dimensional approach describes better the heterogeneity of schizophrenia and has been recently added to the psychotic disorders chapter in *DSM-5* (33).

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