

One-year follow-up of patients with first-episode schizophrenia (comparison between remitters and non-remitters)

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Abstract: Patients admitted to hospital after being diagnosed with first-episode schizophrenia were comprehensively assessed prior to acute treatment (on admission), at the end of the acute treatment (at discharge), and at follow-up after 1 year. The psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS). 93 patients were reassessed after 1 year. 73/93 (78%) of the patients fulfilled the criteria for remission. No statistically significant differences in the total PANSS or subscales scores were found between remitters and non-remitters before or after the first episode treatment. However, non-remitters had a significantly higher total PANSS score after 1 year than remitters. There was no significant difference in mean psychopathology on admission or at discharge, with the exception of items conceptual disorganization, difficulty in abstract thinking, and lack of judgment and insight between remitters and non-remitters. However, significantly higher mean values were found for all items after 1 year in non-remitters than remitters. On admission the occurrence of positive, negative and general symptoms was balanced; at discharge and after 1 year negative and general symptoms were the most frequently observed. At the 1-year follow-up the impairment of insight and judgment is one of the most frequent symptoms in both remitters (10%) and non-remitters (70%).

Keywords: first-episode schizophrenia, remission, negative symptoms, general psychopathology

Introduction

The diagnosis of schizophrenia is associated with substantial variability between patients with regard to symptoms, treatment response, course, and etiologic risk factor dimension (Arango et al 2004; Keshavan et al 2004). The early course of schizophrenia, in particular, is highly variable across patients and is not generally well characterized in the literature. It seems that the occurrence of individual symptoms and their dynamics are very important for the outcome, but such a detailed analysis has not, to our knowledge, been published. Some symptoms may be state dependent and vary also in patients with a different outcome.

Our department has been specializing, on a long-term basis, in the problems of first episodes and investigation of individual biological markers of this disease. Since 1996 we have recorded in our databases more than 160 male patients who have been observed longitudinally from the first index hospitalization. The patients are reassessed at 1-, 3-, 5-, and 10-year follow-ups. We evaluate psychopathology, neuropsychological profile, neuroendocrinology parameters, neurological soft signs, and data from structural and functional neuroimaging methods (Češková et al 2003, 2005; Přikryl et al 2006). The aim of this study was a comparison of temporal changes in psychopathology between remitters and non-remitters at the 1-year follow-up.

Methods

The study was designed as an open, naturalistic, follow-up study. Included in the study were males hospitalized for the first time with the diagnosis first-episode

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schizophrenia (according to ICD-10 diagnostic criteria for research), who provided written informed consent, and were reassessed at the 1-year follow-up. ICD-10 diagnoses were made on the basis of a comprehensive assessment of symptoms and history, and all other available information about the patients. The diagnosis was confirmed by consensus of two psychiatrists during separate interviews.

Clinical assessment

The psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS, Kay et al 1987) before the acute treatment (on admission), at the end of the acute treatment (at discharge), and at follow-up after 1 year. The patients were divided into remitters and non-remitters when they were reassessed after one year. For remission achievement a score of 3 (mild) or less was required in all eight of the following PANSS items: P1 delusions, P2 conceptual disorganization, P3 hallucinatory behaviour, G5 mannerisms and posturing, G9 unusual thought content, N1 blunted affect, N4 passive/apathetic social withdrawal, N6 lack of spontaneity, and flow of conversation for a minimum of 6 months (Kane et al 2003; Andreasen et al 2005).

Treatment

Most patients were drug-naïve on admission. After a baseline assessment all patients were treated openly by monotherapy with an antipsychotic chosen by the patient's treating clinician and individually dosed. Risperidone was the drug of

first choice; other options were selected according to clinical judgment and drug availability. The only concomitant treatments allowed were benzodiazepines for tension, anxiety, and insomnia, and biperidene for extrapyramidal symptoms. After discharge from the index hospitalization the patients were treated as outpatients.

Statistical analysis

The statistical analysis was based on descriptive statistics and nonparametric methods (the Mann-Whitney U test, Wilcoxon matched paired test, chi square test) and performed using STATISTICA software, version 6.

Results

Sample characteristics

93 patients (mean age 23 years, mean duration of illness 0.77 years) were reassessed after 1 year. 73/93 (78%) of the patients fulfilled the criteria for remission. The average daily dose of antipsychotics during the index hospitalization and at the 1-year follow-up was 228 mg and 127 mg, respectively. 17/93 (18.3%) of the patients had discontinued their medication, the rate of discontinuation was higher in non-remitters 7/20 (35%) than in remitters 10/73 (13.7%) (NS).

Psychopathology—the total PANSS score

No statistically significant differences in the total PANSS or subscales scores were found between remitters and non-remitters before or after the first episode treatment. However,

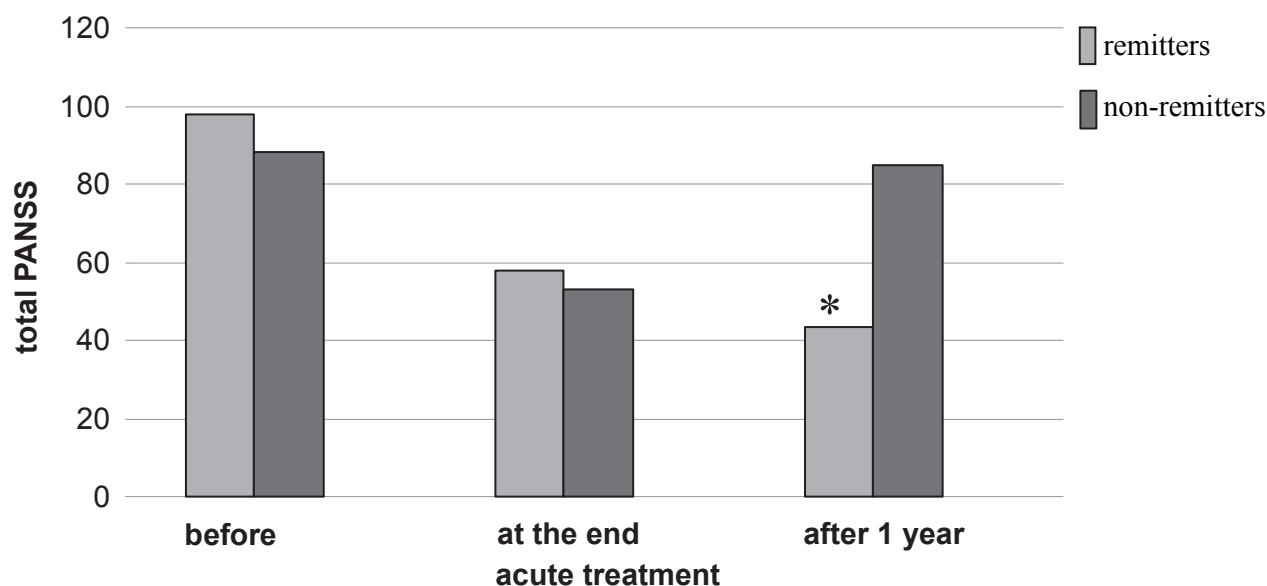


Figure 1 Psychopathology: comparison between remitters and non-remitters.

Note: *significant difference between remitters and non-remitters ($p < 0.001$).

non-remitters had a significantly higher total PANSS score after 1 year than remitters ($p < 0.001$) (Figure 1, Table 1).

The relative decrease of psychopathology was evaluated using delta PANSS 1 ($100 \times (\text{PANSS on admission} - \text{PANSS at discharge}) / \text{PANSS at discharge}$). The relative decrease of total psychopathology during the index hospitalization was similar in both remitters (38.6%) and non-remitters (36.8%). Similar values for delta positive, negative and general PANSS 1 were found for both remitters (50.6%, 27.8%, 35.4%) and non-remitters (52.4%, 25.7%, 32.4%).

After 1 year, there was further relative decrease found in remitters (20.7%) and a significant increase in non-remitters (−71.0%, $p < 0.001$ in relation to the end of acute treatment) using delta PANSS 2 ($100 \times (\text{PANSS at discharge} - \text{PANSS after 1 year}) / \text{PANSS after 1 year}$). Again, similar values were found for

delta positive, negative, and general PANSS 2 in both remitters (17.6%, 20.3%, 19.4%) and non-remitters (−97.1%, −86.4%, −61.2%, $p < 0.001$ in relation to the end of acute treatment).

Psychopathology—individual PANSS items (mean values)

When the remitters and non-remitters were compared, there was no significant difference in mean psychopathology on admission or at discharge, with the exception of items conceptual disorganization, difficulty in abstract thinking and lack of judgment and insight. The mean values of these three items were actually lower in non-remitters at discharge. However, significantly higher mean values were found for all items after 1 year in non-remitters than remitters (see Table 2)

Table 1 Comparison of individual PANSS items in remitters and non-remitters—mean values (SD)

Measure	Admission Remitters	Admission Non-remitt.	Discharge Remitters	Discharge Non-remitt	After 1 year Remitters	After 1 year Non-remitt
P1 delusions	4.7 (1.6)	4.9 (1.9)	1.6 (0.9)	1.6 (1.0)	1.1 (0.5)	3.1 (2.1) *
P2 conceptual disorganization	4.0 (1.5)	3.2 (1.8)	1.8 (1.0)	1.3 (0.6) *	1.3 (0.6)	2.9 (1.8) *
P3 hallucinatory behavior	3.7 (1.8)	3.6 (2.0)	1.2 (0.6)	1.1 (0.7)	1.1 (0.4)	2.3 (1.9) *
P4 excitement	2.7 (1.6)	2.0 (1.1)	1.3 (0.7)	1.0 (0.2)	1.1 (0.5)	1.9 (1.3) *
P5 grandiosity	1.9 (1.4)	1.7 (1.3)	1.3 (0.7)	1.2 (0.7)	1.0 (0.3)	1.7 (1.1) *
P6 suspiciousness/persecutions	4.5 (1.1)	4.5 (1.3)	2.2 (0.9)	2.0 (0.9)	1.4 (0.6)	3.1 (1.7) *
P7 hostility	1.8 (1.3)	1.7 (1.5)	1.1 (0.3)	1.0 (0.3)	1.0 (0.2)	1.7 (1.1) *
Positive subscale PANSS	23.3 (6.1)	21.8 (5.3)	10.6 (3.3)	9.4 (3.3)	8.2 (2.0)	17.0 (6.2) *
N1 blunted affect	3.2 (1.6)	3.2 (1.7)	2.6 (1.1)	2.5 (1.4)	1.9 (0.9)	3.6 (1.5) *
N2 emotional withdrawal	3.9 (1.5)	3.4 (1.4)	2.7 (1.0)	2.4 (1.1)	1.9 (0.9)	3.8 (1.6) *
N3 poor rapport	3.6 (1.7)	2.9 (1.5)	2.4 (1.1)	2.2 (0.9)	1.7 (0.8)	3.5 (1.5) *
N4 passive/apathetic social withdrawal	3.8 (1.7)	3.6 (1.4)	2.5 (1.0)	2.4 (1.2)	1.7 (0.8)	3.8 (1.8) *
N5 difficulty in abstract thinking	4.2 (1.9)	3.3 (2.0)	2.3 (1.2)	1.5 (0.8) *	1.7 (1.1)	3.2 (1.5) *
N6 lack of spontaneity	3.5 (1.7)	3.1 (1.9)	2.2 (1.1)	2.2 (0.9)	1.8 (0.9)	3.3 (1.6) *
N7 stereotyped thinking	4.0 (1.4)	3.7 (1.5)	2.5 (1.0)	2.2 (0.9)	1.8 (0.8)	3.5 (1.3) *
Negative subscale PANSS	26.2 (8.9)	23.4 (8.7)	17.3 (5.9)	15.5 (6.3)	12.6 (5.0)	24.8 (8.5) *
G1 somatic concern	2.4 (1.8)	2.8 (1.9)	1.7 (0.9)	1.7 (1.0)	1.3 (0.7)	2.3 (1.5) *
G2 anxiety	2.8 (1.6)	2.7 (1.1)	1.4 (0.8)	1.4 (0.7)	1.2 (0.6)	1.9 (1.1) *
G3 guilt feelings	2.1 (1.4)	1.4 (1.0)	1.4 (0.9)	1.1 (0.5)	1.0 (0.3)	1.6 (1.0) *
G4 tension	2.7 (1.5)	2.3 (1.0)	1.5 (0.8)	1.3 (0.6)	1.3 (0.5)	2.5 (1.2) *
G5 mannerisms and posturing	2.4 (1.4)	2.0 (1.4)	1.7 (1.0)	1.5 (0.8)	1.2 (0.6)	2.9 (1.1) *
G6 depression	2.2 (1.4)	2.4 (1.3)	1.7 (1.0)	1.6 (0.9)	1.3 (0.8)	2.3 (1.5) *
G7 motor retardation	2.5 (1.5)	2.5 (1.3)	2.1 (1.0)	2.2 (1.0)	1.6 (0.8)	2.9 (1.3) *
G8 uncooperativeness	2.7 (1.8)	1.9 (1.6)	1.3 (0.5)	1.1 (0.5)	1.1 (0.4)	2.2 (1.6) *
G9 unusual thought content	3.6 (1.3)	3.4 (1.5)	1.7 (0.8)	1.7 (0.9)	1.3 (0.6)	2.8 (1.3) *
G10 disorientation	1.9 (1.5)	1.5 (1.0)	1.0 (0.3)	1.0 (0.0)	1.0 (0.0)	1.1 (0.5) *
G11 poor attention	4.3 (1.1)	4.0 (1.0)	2.7 (0.8)	2.5 (1.0)	2.0 (0.9)	3.7 (1.0) *
G12 lack of judgment and insight	4.7 (1.4)	4.8 (1.4)	3.3 (1.1)	2.7 (1.0) *	2.1 (1.2)	4.2 (1.8) *
G13 disturbance of volition	3.9 (1.2)	3.1 (1.4)	2.6 (1.0)	2.3 (1.0)	1.8 (0.9)	3.3 (1.3) *
G14 poor impulse control	1.9 (1.3)	1.5 (1.3)	1.1 (0.5)	1.0 (0.0)	1.0 (0.3)	1.7 (1.2) *
G15 preoccupation	3.9 (1.4)	3.3 (1.2)	2.3 (1.0)	2.2 (1.0)	1.6 (0.8)	3.6 (1.3) *
G16 active social avoidance	3.9 (1.4)	3.2 (1.5)	2.3 (0.9)	2.3 (1.0)	1.70.9	3.3 (1.2) *
General subscale PANSS	48.1 (11.9)	43.1 (9.6)	29.9 (7.4)	27.5 (7.3)	22.9 (5.8)	42.8 (10.6) *
Total score PANSS	97.6 (22.3)	88.3 (19.9)	57.7 (14.4)	52.9 (14.9)	43.6 (11.0)	84.6 (21.6) *

Note: *significant difference between remitters and non-remitters ($p < 0.001$).

Abbreviations: PANSS, Positive and Negative Syndrome Scale.

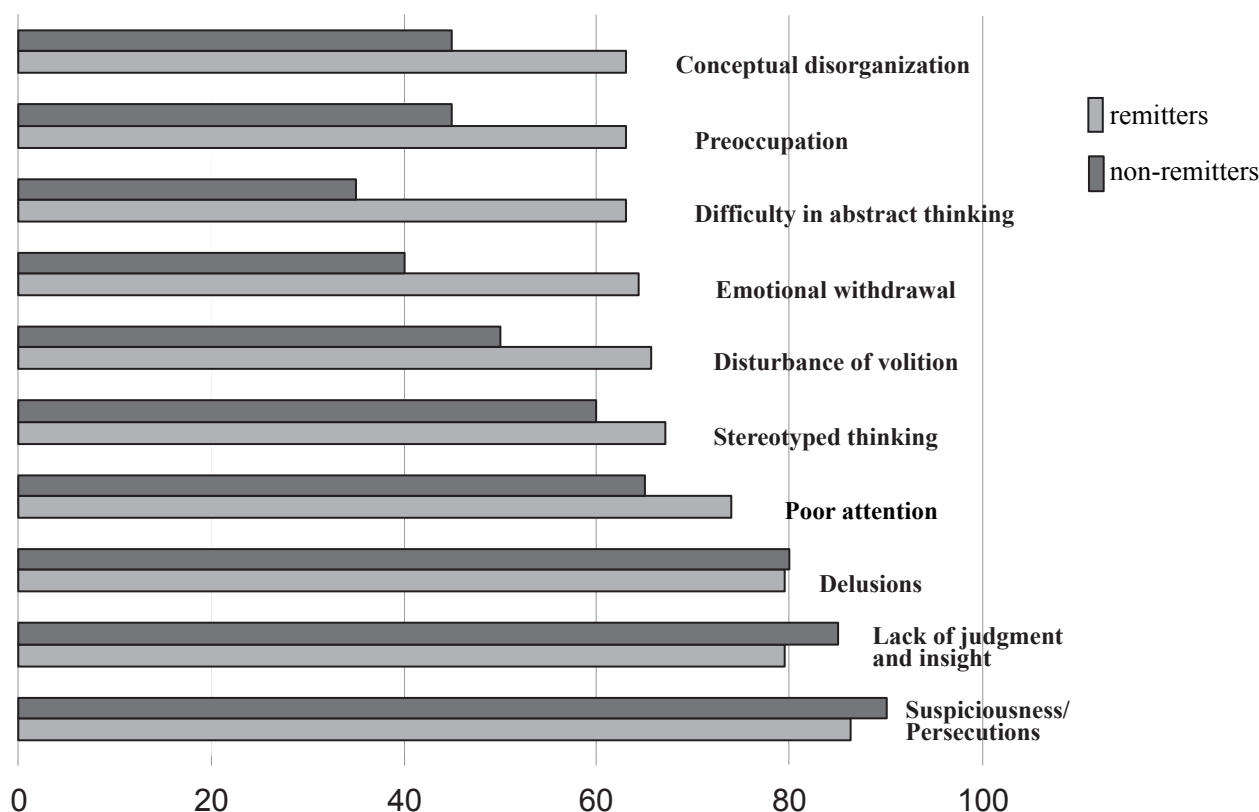


Figure 2 The most frequent items on admission in remitters and non-remitters (%).

Note: symptom presence—score minimally 4 for individual items.

Psychopathology—occurrence of individual symptoms (relative values)

A categorical evaluation of individual symptoms was performed during the index hospitalization on admission and at discharge and after 1 year. A minimum score of 4 in the individual items was required for symptom presence.

On admission

Suspiciousness (86%), delusions and lack of judgment and insight (79 %), poor attention (74%), stereotyped thinking (67%), disturbance of volition (65%), conceptual disorganization and active social avoidance (64%) were the most frequently observed symptoms on admission during the acute phase in remitters. Individual negative symptoms were present in about half of the patients. The occurrence of symptoms on admission was similar in non-remitters (Table 2, Figure 2).

At discharge

At discharge, the most frequently found symptom in remitters was lack of judgment and insight (46.6%); in non-remitters,

blunted affect (25%). Other most frequently observed symptoms were negative and non-specific symptoms in both the remitters and non-remitters (Table 2, Figure 3).

One-year follow-up

The lack of judgment and insight was the most frequent symptom in both remitters (10%) and non-remitters (70%) at the 1-year follow-up. In contrast to admission, the other most frequently observed symptoms were negative ones (with the exception of delusions) in non-remitters and non-specific general symptoms in remitters (Table 2, Figure 4).

Discussion

Our data on the occurrence of remission are in accordance with previously published studies. Remission of psychotic symptoms occurred in up to 80% at 1 year (Addington et al 2003; Lieberman et al 2003). Malla et al (2000) also observed a complete remission rate of 70% in patients with first episode schizophrenia at 1-year follow-up; however, remission was not defined according to Andreasen's criteria.

In our sample 78% of the patients were remitters and we have found that 18% of the patients discontinued their

Table 2 Comparison of individual PANSS items between remitters and non-remitters—relative values

Measure	Admission Remitters	Admission Nonremit.	Discharge Remitters	Discharge Nonremit	After 1 year Remitters	After 1 year Non-remit.
P1 delusions	79.4%	80.0%	2.7%	5.0%	0	50.0%
P2 conceptual disorganization	63.0%	45.0%	5.4%	0	0	40.0%
P3 hallucinatory behavior	60.3%	65%	1.4%	5.0%	0	35.0%
P4 excitement	28.8%	10%	0	0%	0	15.0%
P5 grandiosity	19.1%	20%	1.4%	5%	0	10.0%
P6 suspiciousness/persecutions	86.3%	85%	2.7%	5%	0	35.0%
P7 hostility	11.0%	10.0%	0	0	0	5.0%
N1 blunted affect	37.0%	45.0%	15.1%	25.0%	0	50.0%
N2 emotional withdrawal	64.4%	40.0%	16.4%	15.0%	0	50.0%
N3 poor rapport	42.5%	25.0%	10.9%	0	0	30%
N4 passive/apathetic social withdrawal	56.2%	45.0%	15.1%	15.0%	0	60.0%
N5 difficulty in abstract thinking	63.0%	35.0%	10.9%	0	5.5%	30.0%
N6 lack of spontaneity	50.7%	45.0%	6.8%	0	0	45.0%
N7 stereotyped thinking	67.1%	60.0%	12.3%	0	0	55.0%
G1 somatic concern	22.0%	35.0%	4.1%	5.0%	0	15.0%
G2 anxiety	31.5%	25.0%	0	0	0	10.0%
G3 guilt feelings	20.6%	10.0%	4.1%	0	0	5.0%
G4 tension	22.0%	10.0%	0	0	0	20.0%
G5 mannerisms and posturing	19.2%	15.0%	5.5%	0	0	35.0%
G6 depression	22%	20.%	5.5%	0	2.7%	25.0%
G7 motor retardation	31.5%	20.%	10.90	5.0%	1.4%	40.0%
G8 uncooperativeness	27.4%	15%	0	0	0	25.0%
G9 unusual thought content	50.7%	55.0%	0	0	0	35.0%
G10 disorientation	19.2%	10.%	0	0	0	0
G11 poor attention	74.0%	60.0%	9.6%	15.0%	1.4%	55.0%
G12 lack of judgment and insight	79.4%	90.0%	46.6%	20%	10.9%	70.0%
G13 disturbance of volition	65.7%	50.0%	15.1%	10.%	2.7%	45.0%
G14 poor impulse control	12.3%	10.0%	0	0	0	10.0%
G15 preoccupation	63.0%	45.0%	9.6%	5.0%	1.4%	50.0%
G16 active social avoidance	54.8%	40.0%	4.1%	5.0%	0	45.0%

Abbreviations: Positive and Negative Syndrome Scale.

medication. However, there are some limitations in the interpretation of our results because 25% of the patients invited to participate could not be reached or declined to attend the reassessment after 1 year. Remission achievement and compliance of non-participants is unknown. Patients in the early course of schizophrenia frequently request a decrease or discontinuance of their antipsychotic medica-

tions, and many have poor adherence to treatment (Scottish schizophrenia research group 1987). Non-adherence is particularly prominent in first episode patients (Novak-Grubic and Tavcar 1999). In Verdoux's (2000) study the first-admitted subjects with psychosis were assessed at 6-month intervals over a 2-year follow-up period. The proportion of subjects with poor medication adherence ranged from

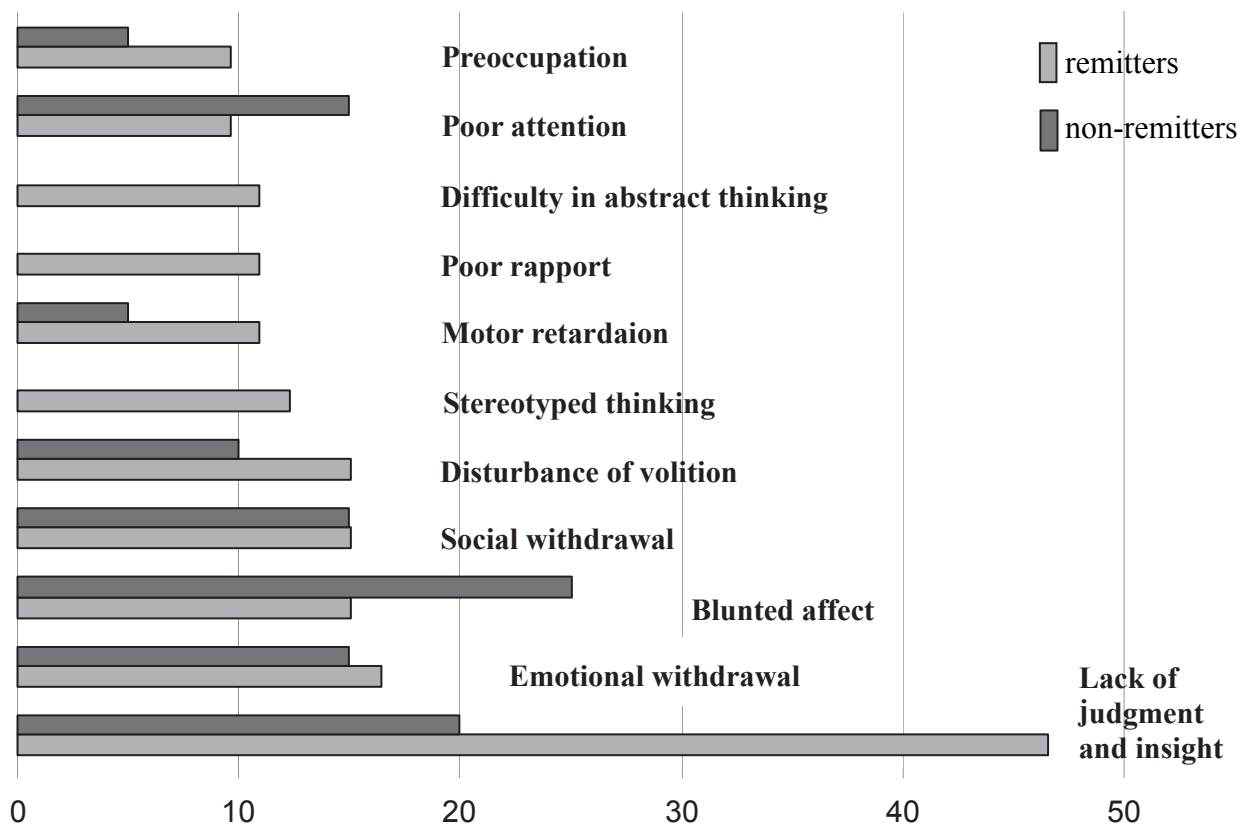


Figure 3 The most frequent items at discharge in remitters and non-remitters (%).

Note: symptom presence—score minimally 4 for individual items.

33% to 44% at each follow-up assessment. After successful antipsychotic treatment, many patients believe that they will no longer need medication. Given that the early course of the disorder is highly variable across patients and is generally not well characterized in literature, clinicians are hard put to insist on indefinite antipsychotic treatment. The role of antipsychotics after the first psychotic manifestation is not fully elucidated. However, medication discontinuation was strongly associated with the worse outcome defined in terms of the number of relapses in subjects suffering from first-episode schizophrenia (Robinson et al 1999). There are also some hints about the neuroprotective role of atypical antipsychotics (Lieberman et al 2003).

No statistically significant differences in PANSS scores were found between remitters and non-remitters in the acute phase. Given the responsiveness of first-episode patients to treatment, the further course from the first psychotic episode is highly variable and some first-episode patients become more treatment resistant over time. After one year we found that non-remitters had a significantly higher total PANSS score than remitters. This means that the period after a first psychotic manifestation is critical.

Our previous findings concerning acute treatment responsiveness showed that in the first psychotic manifestation the most frequently observed symptom was lack of judgment and insight, which persisted at discharge from the index hospitalization. The negative symptoms improved less compared to the positive ones. On admission the responders had higher scores for most symptoms, both positive and negative, than nonresponders (Češková et al 2005). Similar results were found in this study. Both on admission and at discharge a trend towards a higher score for most symptoms was observed in remitters. The difference in the case of difficulty in abstract thinking and lack of judgment and insight has reached statistical significance. Thus, there was no significant difference between remitters and non-remitters in the acute phase. However, after 1 year non-remitters had significantly higher mean scores for all PANSS items.

On admission the occurrence of positive, negative, and general symptoms was balanced; at discharge and after 1 year negative and general symptoms were the most frequently observed; at the 1-year follow-up only general, non-specific symptoms were observed in remitters. In a methodologically sound study, Peralta (2000) concluded that negative

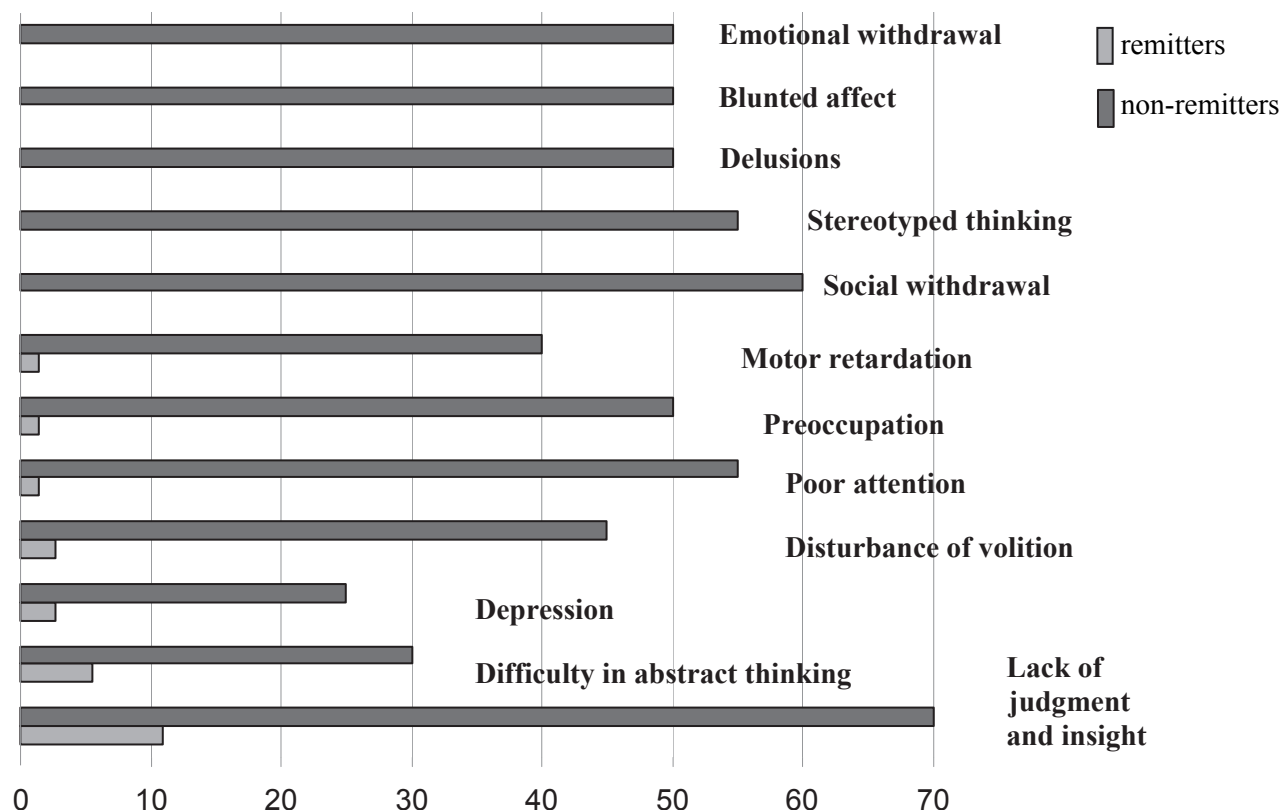


Figure 4 The most frequent items after 1 year in remitters and non-remitters.

Note: symptom presence—score minimally 4 for individual items.

symptoms rated during a first psychotic episode before and after starting antipsychotic treatment are mainly primary in character, and should be considered a direct manifestation of the basic dysfunctions of schizophrenia. Our results are also in agreement with the observation that negative symptoms decrease more slowly than positive ones and may persist in some of the patients.

The impairment of insight and judgment was one of the most frequently observed items in both remitters and non-remitters at all three time points. Insight in schizophrenia is important because of its implications for treatment adherence.

The strengths of this study are sample size and homogeneity (males with first-episode schizophrenia, mostly drug-naïve on admission). The findings are limited by the fact that the study was open, performed under routine clinical conditions and 25% of the patients could not be reached or declined to attend the reassessment.

Conclusion

The first episode of schizophrenia is characterized by pronounced treatment response which may not be the case in a

portion of patients during the further course of the disease from the first psychotic break-down. After the acute treatment and at 1-year follow-up the most frequent symptoms were negative and non-specific general symptoms. At the 1-year follow-up the impairment of insight and judgment is one of the most frequent symptoms in both remitters and non-remitters. This confirms the suggestion that the period after the first psychotic manifestation constitutes a critical period. Longitudinal follow-up of first-episode patients is of great interest in addressing this question.

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