

PSYCHIATRY

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Characteristics of the response to treatment in outpatients with the first episode of schizophrenia spectrum disorders*E. M. Chumakov*^{1, 2}, *N. N. Petrova*¹, *O. V. Limankin*^{2, 3, 4}¹ St. Petersburg State University,
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Identifying predictors of treatment response in patients with the first episode of schizophrenia spectrum disorders is an important issue in the field. The objective of the study was to assess the incidence of poor response to treatment and the factors that influence it in outpatients with the first episode of schizophrenia spectrum disorders. Medical records of the outpatients seeking treatment in 2017 in 3 day inpatient departments of the two districts in St. Petersburg, Russia, were examined. 73 patients diagnosed with schizophrenia spectrum disorders (ICD-10) met the criteria for the first episode (the duration of the disease is up to 5 years, the number of episodes is not more than three) and made up the study group. It has been established that up to 49% of outpatients with the first episode of schizophrenia spectrum disorders were characterized by poor responses to antipsychotic therapy during outpatient treatment. Factors predicting a poor response to therapy may include earlier onset of illness, concomitant brain damage, and low adherence to therapy.

Keywords: schizophrenia, schizophrenia spectrum disorders, first episode, treatment response, outpatients.

In the past decade there has been increasing interest in early stages of schizophrenia spectrum disorders (SSD) [1]. It's considered that the early stages after the onset of a first

episode of psychosis are crucial for the long-term outcome of the disease [2]. Early response to treatment is one of the main factors associated with improved long-term prognosis [3].

However there is currently no consensus on whether the response to therapy is better in patients with a first episode of psychosis than in patients with multiple episodes. On the one hand, it seems to be generally accepted that patients suffering from a first episode of SSD tend to be more responsive to antipsychotic treatment and need lower doses of antipsychotic drugs to achieve remission than patients with multiple episodes [4]. On the other hand approximately 15% of patients with the first episode of SSD do not respond to the first antipsychotic drug [5] and are more susceptible to side effects of antipsychotic therapy [6]. Approximately 30% of patients with first-episode psychosis manifest a minimal response to antipsychotics [7].

However, original data comparing first episode with multiple episode SSD with respect to the acute treatment response are rare [1]. Lieberman J. et al [8] have revealed that the antipsychotic treatment response of first-episode patients with schizophrenia is better than in multi episode patients. Another research has shown that treatment response becomes less favorable during the course of schizophrenia illness that might be associated with progressive neurobiological alterations [1].

Despite the fact that it is not possible currently to clearly determine the therapeutic prognosis in patients with schizophrenia [9], several factors associated with a poor treatment response in patients with the first episode of SSD have been identified. Psychotic symptoms may be more resistant to treatment in patients with long-term untreated psychosis [10]. And reduction in the duration of untreated psychosis may be associated with a more favourable treatment outcome [11]. Primary negative symptoms in the structure of the first episode are a risk factor for insufficient response to antipsychotic therapy [12]. Cannabis use by patients with the first episode of SSD is associated with the administration of more different antipsychotic drugs, indicating clinical assessment of antipsychotic treatment as not being effective enough [13].

According to current guidelines, the treatment of the first episode of schizophrenia includes the use of the lowest effective dose of second-generation antipsychotic where possible [14]. The amount of data that can be used to select a drug for efficacy in patients with the first episode of schizophrenia is insufficient, so the choice of antipsychotics in this case should be based on a profile of side effects [15]. Supportive treatment should be preferred even in stable patients after the first episode of schizophrenia [16]. Specialized treatment programs that integrate psychosocial interventions with optimal medication management have improved outcomes in first episode schizophrenia [17] although negative symptoms, subsyndromal depressive symptoms, and functional impairment often persist.

Poor adherence to antipsychotic treatment and lack of criticism of the disease are common in people with the first episode of SSD [18] and associated with increased relapse rates [19]. Lack of criticism contributes to a lack of adherence to medication and leads to a deterioration in disease and functioning [20]. Additionally, three-quarters of all patients who experience a remission from a first episode of psychosis will have a recurrence of psychotic symptoms within a year of treatment discontinuation [21]. Nonadherence to medication seems to represent the highest risk factor (a 4-fold risk) for relapse after the first episode of psychosis [22]. The use of second-generation prolonged antipsychotics is warranted in patients with the first episode of SSD [23].

Only one-third of patients with the first episode of SSD successfully recover to pre-morbid functioning without any significant psychotic symptoms [24]. The course and outcome of schizophrenia are characterized by mainly unexplained heterogeneity [25], showing good outcome in less than 50% of patients [26]. Using stricter functional recovery criteria reduces the recovery rate to 13.5% [27]. Longer duration of untreated psychosis and lower pre-morbid adaptation are associated with weaker recovery from the first episode of schizophrenia [28]. The longer duration of untreated psychosis is also associated with higher severity of negative symptoms [29]. An earlier onset, more pronounced initial negative symptoms and longer duration of untreated psychosis have been suggested as factors predicting an early transition to therapeutic resistance [30]. Identifying predictors of treatment response in patients with the first episode is an important issue in the field.

The objective of the study

To assess the incidence of poor response to treatment and the factors that influence it in outpatients with the first episode of schizophrenia spectrum disorders.

Materials and methods

Medical records of the outpatients seeking treatment in 2017 in 3 day inpatient departments of the two districts in St. Petersburg, Russia, were examined. It was found that among all patients who applied for treatment in day inpatient departments in 2017 ($n = 844$), 39.1% ($n = 330$) were diagnosed with SSD according to the criteria of ICD-10 (F2). 22.1% ($n = 73$) of patients diagnosed with SSD met the criteria for the first episode (the duration of the disease is up to 5 years, the number of episodes is not more than three) and made up the study group. Patients in the study group were between 18 and 46 years, as the departments where the study was conducted provide care for adult patients, mean age 24.8 ± 6.5 (67.1% male). While working with medical records, the experience of taking drugs before admission, the response to therapy during current treatment, the frequency of side effects of therapy, the reasons for the replacement of the main drug (antipsychotic), and the characteristics of social adaptation were assessed.

Statistical analysis of the obtained results was carried out in SPSS Statistics 21.0. Due to continuous variables had abnormal distribution (Shapiro-Wilk test's $p < 0,05$), Mann-Whitney test was used to compare them. The correlation between the indices was calculated by the Spearman test. Categorical variables were compared by Pearson Chi-square test with additionally calculated odds ratio (OR). In order to determine significant predictors for categorical variables' changing, binominal logistic regression was employed. Critical significance level was assumed to be $p < 0.05$.

Results

Diagnoses of mental disorders for which patients with first episode of SSD received outpatient treatment in the study departments are shown in Fig. 1.

18 patients (24.7%) were directed to the day inpatient department after inpatient treatment in the hospital, while the rest of the patients were directed by a psychiatrist from the neuropsychiatric dispensary. 9 patients (12.3%; all men) were hospitalized in the day

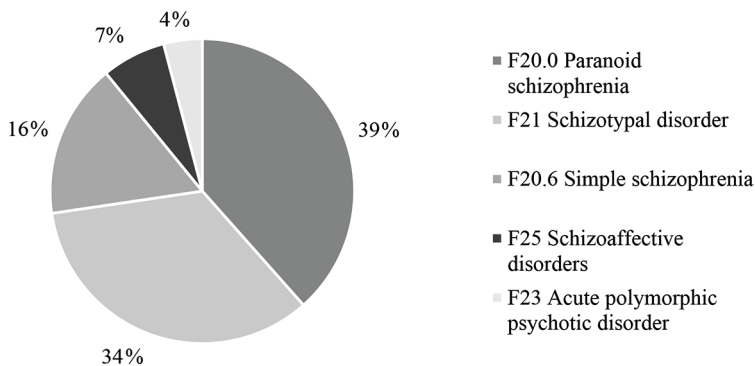


Fig. 1. Diagnoses of the first episode SSD

inpatient department for screening before being called up for military service and were diagnosed with SSD.

The patients treatment results in the sample were analyzed. The duration of treatment in all cases was not less than recommended. It was established that according to the medical records 37 patients (50.7%) had reached remission by the time of discharge. Remission was defined as the absence of psychopathological syndrome at the time of discharge from the department, both in terms of patient and physician assessment. The other patients (n=36) had clinically significant psychopathological symptoms at the time of discharge (the conclusion was based on the doctors' records), and 6 of these patients were hospitalized to inpatient services due to their deteriorating condition. In order to further assess the factors related to the response to therapy, the sample was divided into 2 groups — those who had reached remission (Group 1) and those who had not reached remission (Group 2). The age of the debut of the mental disorder was lower in Group 2 patients, but without statistical significance (23.78 ± 6.42 and 18.28 ± 7.10 years for Groups 1 and 2, respectively). At the time of the study, the patients in the Group 1 were older (26.91 ± 6.87 and 22.53 ± 5.23 years for Groups 1 and 2, respectively; $p = 0.047$).

Social characteristics of patients are presented in Table 1. Patients in Group 1 were more socially adaptable — they had a better education, worked more often, were less likely to be recognized as disabled, had more frequent relationships or were married. All these

Table 1. Social characteristics of the study groups

Social characteristics	Group 1 (n = 37)	Group 2 (n = 36)	OR	p
Employment	35.1% (n = 13)	13.9% (n = 5)	3.36 (95% CI 1.05 — 10.72)	0.035
Continued their training	27.0% (n = 10)	25.0% (n = 9)	1.11 (95% CI 0.39 — 3.17)	0.84
Didn't work or study	37.8% (n = 14)	61.1% (n = 22)	0.39 (95% CI 0.15 — 1.0)	0.047
Education is lower than secondary	5.4% (n = 2)	22.2% (n = 8)	0.2 (95% CI 0.04 — 1.02)	0.037
University education	32.4% (n = 12)	11.1% (n = 4)	3.84 (95% CI 1.1 — 13.36)	0.028
Disability	2.7% (n = 1)	19.4% (n = 7)	0.12 (95% CI 0.01 — 0.99)	0.022
Had a relationship or were married	24.3% (n = 9)	5.6% (n = 2)	5.46 (95% CI 1.09 — 27.39)	0.025

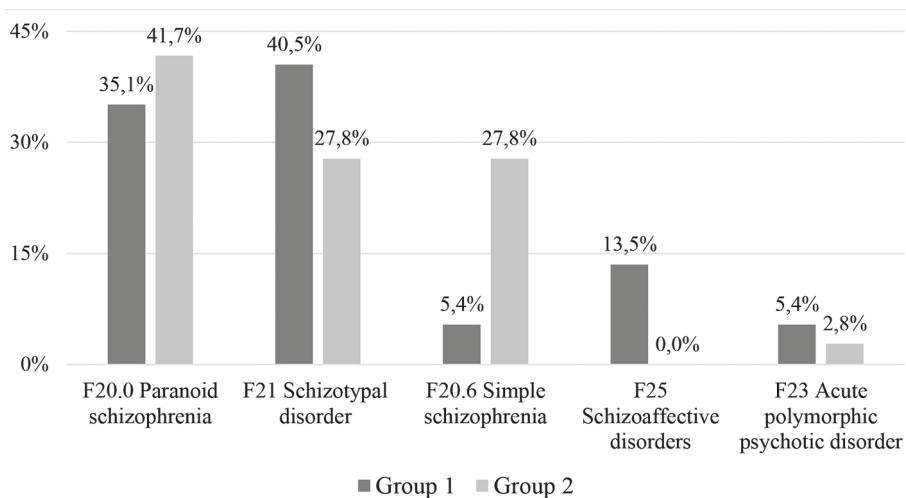


Fig. 2. Diagnoses of the first episode SSD in groups

characteristics, taking into account the age of the onset of the disorder in the Group 1, indicate that the disorder in these patients was more favorable.

The frequency of mental disorders diagnoses in the Groups is shown in Fig. 2. Group 1 patients were more frequently diagnosed with schizoaffective disorder ($p = 0.022$) and less frequently with simple schizophrenia ($p = 0.01$). The frequency of other diagnoses did not have statistically significant differences in the groups.

Clinical characteristics of patients associated with the response to therapy are shown in Table 2. All patients were consulted by a neurologist during treatment. Patients with a comorbid diagnosis of encephalopathy of various etiologies were found to have less often had a good response to antipsychotic therapy ($r = 0.36$; $p = 0.002$). In each of the groups, more than half of the patients required consecutive prescribing of more than one antipsychotic during treatment. This means that even patients who achieved remission did not respond to the first prescribed antipsychotic (67.6% of Group 1 patients). The frequency of antipsychotic replacements and their causes did not differ significantly in the groups. It is worth noting, however, that replacement of antipsychotics in Group 1 patients focuses on the side effects of treatment, while Group 2 focuses on the poor response to therapy. The largest number of consecutive antipsychotics prescribed during this treatment was 5 in Group 1 and 4 in Group 2. Patients who did not follow the treatment regimen were more likely to have a poor response to therapy ($r = 0.3$; $p = 0.011$).

Discussion

This article is focused on the response to antipsychotic therapy in outpatients with the first episode of SSD. We reviewed the medical histories of patients who met the criteria for inclusion in the study and received treatment in day inpatient departments in two districts of St. Petersburg in 2017. The study found that up to 22% of patients with SSD who received outpatient treatment in day inpatient departments met the criteria for the

Table 2. Clinical characteristics related with the response to treatment in the groups

Clinical characteristics	Group 1 (n = 37)	Group 2 (n = 36)	OR	p
Co-diagnosis of encephalopathy	5.4 % (n = 2)	33.3 % (n = 12)	0.11 (95 % CI 0.02 — 0.56)	0.002
Treatment after discharge from hospital	29.7 % (n = 11)	33.3 % (n = 12)	0.84 (95 % CI 0.32 — 2.27)	0.74
Number of antipsychotics that were prescribed before this treatment	1.89 ± 1.85	1.69 ± 2.23	–	0.38
Received more than one antipsychotic during current treatment	67.6 % (n = 25)	61.1 % (n = 22)	1.33 (95 % CI 0.51 — 3.47)	0.56
Number of antipsychotics that were prescribed during the current treatment	1.97 ± 0.98	1.94 ± 1.14	–	0.19
Frequency of antipsychotics replacement	1.21 ± 1.79	1.08 ± 1.27	–	0.28
Replacement of antipsychotics due to side effects	48.6 % (n = 18)	30.6 % (n = 11)	2.15 (95 % CI 0.83 — 5.61)	0.11
Replacement of antipsychotics due to poor response to therapy	35.1 % (n = 13)	55.6 % (n = 20)	0.43 (95 % CI 0.17 — 1.11)	0.07
Replacement of antipsychotics due to poor compliance to therapy	10.8 % (n = 4)	16.7 % (n = 6)	0.61 (95 % CI 0.16 — 2.36)	0.47
Received first-generation antipsychotic	70.3 % (n = 26)	61.1 % (n = 22)	1.5 (95 % CI 0.57 — 3.98)	0.41
Received second-generation antipsychotics	64.9 % (n = 24)	72.2 % (n = 26)	0.71 (95 % CI 0.26 — 1.92)	0.49
The treatment was completed with a second-generation antipsychotic	59.5 % (n = 22)	58.3 % (n = 21)	1.05 (95 % CI 0.41 — 2.66)	0.92
Number of patients who did not have side effects on any of the prescribed antipsychotics	40.5 % (n = 15)	47.2 % (n = 17)	0.76 (95 % CI 0.3 — 1.93)	0.57
Had treatment breakdowns	21.6 % (n = 8)	47.2 % (n = 17)	0.31 (95 % CI 0.11 — 0.86)	0.021
Been discharged for treatment irregularities	5.4 % (n = 2)	22.2 % (n = 8)	0.2 (95 % CI 0.04 — 1.02)	0.037

first episode (duration of the disorder is less than 5 years and the number of exacerbations is up to 3 inclusive).

Approximately 30 % of patients with the first-episode psychosis manifest a minimal response to antipsychotics [7]. We revealed that up to 49 % of patients with the first episode of SSD do not reach full remission during the treatment in day inpatients departments and have clinically significant psychopathological symptoms at the time of discharge. We found a very high level of poor response to the first prescribed antipsychotic (67.6 %) which is significantly higher than the previous published [5].

Although the frequency of antipsychotic replacement and its causes did not differ significantly between patients with a good and poor response to therapy, it is worth noting, however, that the replacement of antipsychotics in patients with a good response was more associated with side effects of treatment, while in patients who did not reach remission, the drug was replaced more frequently because of insufficient response to the therapy with a drug.

The statistically significant factors that affect the response to the treatment of patients with the first episode of SSD are the lack of compliance with therapy and the concomitant brain pathology — encephalopathy of various etiologies diagnosed by a neurologist. Poor adherence to antipsychotic treatment and lack of criticism of the disease are common in people with the first episode of schizophrenia spectrum disorders [18].

It is well known that an earlier onset have been suggested as factor predicting an early transition to therapeutic resistance [30] and lower pre-morbid adaptation is associated with weaker recovery from the first episode of schizophrenia [28]. Analysis of social factors in the study group showed that patients with a good response to therapy probably had a more favorable course of mental disorder, as indicated by the later age of the disease's debut, lower frequency of initial chronic forms of disorder (simple schizophrenia), as well as a higher degree of social adaptation, which was manifested in the higher frequency of employment and higher education, and being in a relationship or married at the time of admission to the department. Our findings confirm that the primary negative symptoms (an obligate sign of simple schizophrenia) in the structure of the first episode are a risk factor for insufficient response to antipsychotic therapy [12]. Another important indication that patients with a good response to therapy during this treatment had a more favorable course of disorder was that these patients were less likely to be recognized as disabled.

The use of second-generation antipsychotics for the treatment of the first psychotic episode is currently recommended [14], but our study found that patients received both first-generation and second-generation antipsychotics with approximately the same frequency. In more than half of the cases, the patients were discharged with a recommendation to continue taking second-generation antipsychotics.

The limitation of this study is that we only evaluated outpatients, while inpatients may have a different frequency of good response to therapy. Also, for a more accurate assessment of treatment response, follow-up evaluation of patients included in the study over time is required. Another limitation of the study is the relatively small sample, which may have affected the lack of statistical significance of the study results. Also, we were unable to assess the period of untreated psychosis and the frequency of illicit drug use, as this was not indicated in all medical histories. We did not describe the frequency of specific antipsychotics prescription and the specific manifestations of side effects due to the very wide range of options and the impossibility of statistical data processing.

Conclusion

It has been established that up to 49% of outpatients with the first episode of schizophrenia spectrum disorders are characterized by poor responses to antipsychotic therapy. Factors predicting a poor response to therapy may include earlier onset of illness, concomitant brain damage, and low adherence to therapy. The author confirms that the submitted data do not contain a conflict of interests.

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