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ORIGINAL PAPER

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One year outcome in first episode schizophrenia

Predictors of relapse

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Abstract The aim of this study was to identify the predictors of outcome at one year follow-up after the first psychotic episode of schizophrenia. Seventy-nine first-episode schizophrenia patients were assessed monthly with the Brief Psychiatric Rating Scale (BPRS), Scale for Assessment of Positive Symptoms (SAPS), and Scale for Assessment of Negative Symptoms (SANS) after discharge from their first hospitalization. Outcome measures were presence of relapse and rehospitalization, level of global functioning, employment status and severity of symptoms at one year. A total of 33% of the patients had a relapse, and 12.1% were rehospitalized during one year follow-up. Premorbid childhood functionality was worse in patients who had relapse, but there was no correlation between premorbid adjustment scores and BPRS, SANS and SAPS scores at one year. There was no difference in duration of untreated psychosis (DUP) between patients who had relapse and not; however, the patients who had double relapse, had longer DUP than those without relapse. The time period between discharge and rehospitalization was shorter in patients with longer DUP. Functionality in childhood and noncompliance to the treatment independently contributed to the relapse rate. Functionality in late adolescence independently contributed to the Global Assessment of Functioning (GAF) scale score at one year and the GAF score at discharge appeared as a predictor of employment. The results of the present study suggest that treatment compliance and early premorbid adjustment level seem to be important predictors of relapse rate in first episode schizophrenia.

Key words schizophrenia · first episode · predictors · relapse · outcome

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Introduction

Outcome in schizophrenia is multidimensional and, thus, consists of clinical, humanitarian rehabilitative and cost domains (Gaebel and Frommann 2000). Patients with first episode schizophrenia usually respond well to treatment, but the relapse rate is high during the first years of the illness, and may be associated with clinical deterioration. Relapse rate at the end of one year follow-up has been reported to be 3.5% to 41% (Gaebel et al. 2004; Robinson et al. 1999; Kane et al. 1982; Rabiner et al. 1986; Linszen et al. 1994; Novak-Grubic and Tavcar 2002). Recent studies reported that duration of untreated psychosis (DUP) has an independent contribution to outcome throughout first year of the illness (Larsen et al. 2000; Malla et al. 2002; Harrigan et al. 2003). Longer DUP was found to be associated with more severe negative and/or positive symptoms at 12 months (Harrigan et al. 2000).

Noncompliance to the medication is one of the most common causes of psychotic relapse and rehospitalization in patients with schizophrenia. Mojtabai et al. (2002) reported that 63% of the patients with first episode schizophrenia had one or more gaps in use of antipsychotics during the one year period after discharge. Fenton et al. (1997) found that relapse rates were an average of 3.7 times higher in patients who were rated as noncompliant. Recent studies reported that noncompliance is also important for relapse in first-episode psychosis (Robinson et al. 1999; Novak-Grubic and Tavcar 2002).

Male gender appears to be another possible predictor

of poor outcome. In most of the studies men have much higher hospitalization numbers and stay longer than women (Usall et al. 2003; Doering et al. 1998; Angermayer et al. 1990; Test et al. 1990). In a recent study, Harrigan et al. (2003) found a relationship between female gender and good outcome during the one year period. While Geddes et al. (1994) reported longer hospitalization periods after first episodes in males, Vasquez-Barquero et al. (1999) found outcomes to be better in males. Yet, two recent studies could not find any relation between one year remission rates and gender (Malla et al. 2002; Larsen et al. 2000).

Clinical attributes during first episode were also studied as potential predictors for relapse. The presence of subjective depressive feelings during the first admission was associated with earlier relapse while the presence of depressive delusions and higher educational attainment protected against early relapse (Geddes et al. 1994). Altamura et al. (2001) stated that patients having multiple episodes after the first episode had a lower starting Brief Psychiatric Rating Scale (BPRS) score and more negative indications.

In recent studies, poor premorbid adjustment was significantly related to earlier first relapse following response from a first episode of schizophrenia or schizoaffective disorder (Robinson et al. 1999), lower levels of remission (Malla et al. 2002) and higher the Positive and Negative Syndrome Scale (PANSS) negative and general symptoms as well as a lower the Global Assessment of Functioning (GAF) score (Larsen et al. 2000) at one year follow-up.

In contrast to chronic patients, for whom certain individual risk variables of relapse may be detected over time, conclusions concerning the individual course of first episode patients can hardly be drawn a priori. Therefore it is important to detect the variables that predict outcome in the early course of the illness. Although research about outcome of first episode schizophrenia is increasing, inclusion of mixed diagnostic groups (i. e. the inclusion of non-affective groups out of schizophrenia), retrospective quality of analysis, mostly including only male gender, and using different definitions for relapse or outcome still make it difficult to interpret the results of these studies.

Thus the aim of this study was to identify the predictors of outcome at one year follow-up after first psychotic episode in a homogenous group of patients with schizophrenia according to DSM-IV criteria. Outcome measures were presence of relapse and rehospitalization, level of global functioning, employment status and severity of symptoms at one year. We hypothesized that DUP, premorbid social functioning, severity of symptoms at first episode and compliance to treatment would be important predictors of outcome at one year.

Materials and methods

Subjects

Subjects in this study were recruited from a still ongoing prospective study, namely First-episode Schizophrenia Follow-up Project, since 1996. Inclusion and exclusion criteria for this Project have been described in detail in a previous report (Ucok et al. 2004). All patients with schizophrenia who were treated for their first psychotic episode in the inpatient clinic, and met criteria for remission at discharge were invited to the follow-up phase of the study. Eighty-three patients were eligible. Nine of them refused to participate in the follow-up study. The remaining seventy-four (38 men, 36 women) patients formed the study group. Eleven patients dropped out before they completed one year follow-up (mean 6.3 months). Five of them had experienced a relapse before they dropped out.

Patients diagnosed as schizophrenic by means of the Structured Clinical Interview for DSM-IV (SCID) were then reevaluated at a consensus meeting to incorporate the clinical and SCID data (First et al. 1997). Patients with first psychotic episode were included if all of the following conditions were fulfilled: no past diagnosis of non-affective possible psychosis; no previous antipsychotic treatment and inpatient care. The date of onset of the first identifiable positive symptoms was timed by the senior psychiatrist (principal investigator) on the basis of a best-estimate approach using data gathered from multiple sources including medical records, the patient, and a family interview. We defined DUP from the time of onset of the first positive symptoms to the first hospitalization.

The majority of the patients were of paranoid subtype (n = 45). There were 6 disorganized, 4 catatonic and 19 undifferentiated patients. Since this is an observational follow-up study patients received adequate antipsychotic treatment as scheduled by the treating physician, following the baseline procedures. Compliance to prescribed medication was inquired at each visit with the patient and his/her relatives. If a patient had used less medication than prescribed or completely skipped his/her medication for 10 consecutive days that patient was regarded as "noncompliant".

Sixty-eight percent of the patients were receiving atypical, and the rest, conventional antipsychotics. Most frequently used antipsychotics were olanzapine (n = 17, mean dose = 13.4 ± 2.9 mg/day), zuclopentixol (n = 14, mean dose = 17.8 ± 5.5/day), risperidone (n = 12, mean dose = 3.7 ± 1.2 mg/day), and quetiapine (n = 4, mean dose = 587 ± 34.5 mg/day). Mean equivalent dose of typical antipsychotic (n = 24) treatment was 11.4 ± 8.1 mg/day of haloperidol. Fifteen percent of the patients were in the lower socioeconomic status (SES), 76 % of them were in the middle and 9 % in the higher SES.

Measures

We evaluated the psychopathology by monthly visits using BPRS (Lukoff et al. 1986), Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984), and Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1983). All measures were collected by two trained raters. Inter-rater reliabilities for the BPRS, SANS and SAPS total scores were acceptable ($\kappa = 0.78$, $\kappa = 0.76$, and $\kappa = 0.83$ respectively).

The Premorbid Adjustment Scale (PAS) was used to assess premorbid functioning (Cannon-Spoor et al. 1982). PAS describes levels of functioning on social accessibility-isolation, peer relationships, ability to function outside the nuclear family (school performance and adaptation to school), and the capacity to establish social-sexual relationships. These abilities are described in childhood (up to 11 years), early adolescence (12–15 years), late adolescence (15–18 years), and adulthood. Since we assumed that the illness itself would influence the premorbid scores in adulthood we only considered the first three periods (up to 18 years). The ratings were carried out by the principal investigator during admission based on interviews with at least one first degree relative of the patient who was knowledgeable about the patient's childhood and adolescence. Since 24 of the patients were 15–18 years old on admission, we did not apply the related

part of the PAS to these patients. PAS was scored by converting raw scores into the proportion of a potential total score, so that the worst possible adjustment score would be 1. The mean PAS score was the mean of the three subscale scores.

Relapse and remission as two measures of outcome were defined based on the scores of BPRS Positive subscale which consists of hallucinations, unusual thought content and conceptual disorganization. Remission was described as being rated 3 or below on all items of the BPRS positive subscale for at least one month. We defined relapse using the same criteria as those described by Nuechterlein et al. (1992): i) a rating of 6 or 7 on any items of the BPRS positive subscale for at least two weeks or ii) a rating of 5 plus a 2 point increase on one of the other two items. Three patients who showed persistent psychotic symptoms after initial remission, but did not meet the criteria for relapse, were excluded during the analysis of relapse predictors. The mean GAF score of these three patients at one year was 68.3.

Occupational status during the one year was rated according to direct interviews with the patient and relatives in combination with social worker reports. Besides the patients in paid/volunteer work; full time students, housewives and retired subjects performing expected activities were rated as employed.

Statistics

The Mann-Whitney U-test was used for not normally distributed continuous variables, and the chi-square test for categorical variables. As DUP, and PAS scores were not normally distributed, Spearman's correlation analyses were used to examine the relationship between DUP, PAS, clinical measures and GAF scores at one year. Cox regression analysis was used to analyze the predictors of relapse. Multiple regression analysis was applied with the GAF score at one year as the dependent variable to investigate the independent contribution of DUP, age at onset, mean PAS score, and education status. We used logistic regression analysis to search the variable that independently contributed to employment status at one year. All tests of significance were two-tailed. The statistical software used was SPSS for Windows, version 9.0.

Results

Clinical characteristics of the patients are presented in Table 1. There were not any differences between the patients in the study group and those 20 who refused to participate or dropped out before completing the one year follow-up in terms of age, sex, education, DUP, clinical measures like SANS, SAPS, BPRS, and GAF scores at admission and discharge.

Twenty-five patients (33.7 %) had relapse, and 9 patients (12.1 %) were rehospitalized during one year follow-up. The cumulative number of the patients who had relapse, and the number of available patients each month are presented in Fig. 1. First relapse was at 5.8 ± 3.1 months, and first rehospitalization was at 4.8 ± 2.4 months after discharge from the hospital. The male patients experienced more relapse than female pa-

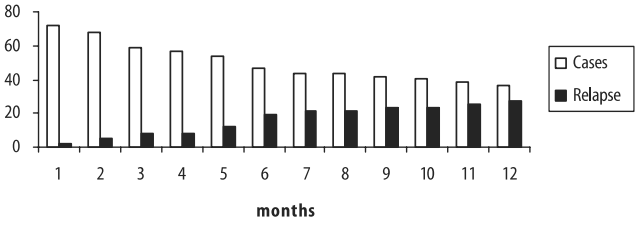

Fig. 1 Black bars show cumulative number of relapses, and white bars show the number of available patients after the patients who have relapse or dropped out were excluded

Table 1 Sociodemographic and clinical characteristics of first-episode schizophrenia group

	Total (n = 74)	Patients relapsed (n = 25)	Patients without relapse (n = 42)	
	Median (SD)	Median (SD)	Median (SD)	Z
Age	21.2 (4.9)	20.3 (5.8)	21.4 (3.5)	1.91
Age at onset	19.9 (5.6)	21.1 (5.6)	18.8 (34)	–1.54
DUP (median, months)	7 (9.7)	5 (6.5)	7 (11.4)	–0.6
GAF score at discharge	35.5 (12.1)	35 (8.9)	36.9 (12.4)	–0.81
GAF score at one year	71.1 (11.1)	74.5 (11)	61.7 (11.7)	–3.59*
SANS score at admission	43.1 (18.9)	48.5 (21.7)	32.1 (18.4)	–2.64*
SANS score at discharge	29.9 (13.3)	32 (21.1)	16.6 (11.6)	–2.78*
PAS-childhood	0.15 (0.19)	0.22 (0.22)	0.11 (0.16)	–2.01**
PAS-early adolescence	0.22 (0.23)	0.23 (0.11)	0.19 (0.17)	–0.76
PAS-late adolescence	0.40 (0.29)	0.43 (0.31)	0.41 (0.18)	–0.97
Full-time education, years	10.9 (3.1)	9.8 (3.3)	11.1 (2.9)	–0.15
	%	%	%	χ^2
Gender				
Men	51.3	69.2	30.8	4.1**
Women	48.7	30.8	69.2	
Employment status at one year				
Employed	47.5	35.3	61.1	3.63**
Unemployed	52.5	64.7	38.9	

* $p < 0.01$; ** $p < 0.05$

DUP Duration of untreated psychosis; *GAF* Global Assessment of Functionality; *PAS* Premorbid Assessment Scale

tients ($\chi^2 = 4.1$, df = 1, p = 0.04, Table 1). Patients who had a relapse had higher scores of SANS both on admission (Z = –2.64, p = 0.008) and discharge (Z = –2.78, p = 0.005). The patients who were taking typical antipsychotics had more relapses than those who were taking atypical antipsychotics (51.5 % vs. 27.3 %, $\chi^2 = 4.06$, df = 1, p = 0.04).

The PAS scores were presented in Table 1. The mean PAS score was 0.25 ± 0.24. We found a negative correlation between both the mean PAS score (r = –0.348, p = 0.01) and the PAS score for late adolescence (r = –0.328, p = 0.02) and education. The PAS score for childhood was higher in patients who had relapse (Z = –2.1, p = 0.04). There was no correlation between PAS scores and BPRS, SANS and SAPS scores during the one year period.

Of patients followed for one year, 24 fit the noncompliance definition. The only predictor for noncompliance during the follow-up was higher BPRS-suspiciousness item score at discharge (2.7 vs. 2.1, t = 1.96, df = 61, p = 0.05). Noncompliance was more frequent in patients with relapse than those with no relapse (70 % vs. 25 %, $\chi^2 = 11.2$, p = 0.001). The GAF score at one year follow-up was higher in patients without relapse (Z = 6.31, p = 0.001). There was no difference in terms of DUP between the patients who had relapse and not (8 ± 9.5 and 8.6 ± 9.7 months respectively, p = 0.8). However, the patients who had double relapses (n = 7) had longer DUP than those without relapse (12.4 ± 7.1 vs. 7.6 ± 9.1 months, Z = 2.08, p = 0.03).

The median DUP was 7 months. We divided the patients into two groups with a long (> 7 months) and a short (≤7 months) DUP. The time period between discharge and rehospitalization was shorter in patients with long DUP (n = 3) than those with short DUP (n = 6) (2 ± 1 months vs. 6.3 ± 1.2 months, Z = –2.34, p = 0.01). No difference was detected in terms of relapse and hospitalization rates, GAF, BPRS, SANS, and SAPS scores at one year follow-up between short and long DUP groups.

DUP was not correlated with the GAF, BPRS, SANS and SAPS scores at one year follow-up. No significant correlations were seen between the clinical measures (including the GAF score) at discharge from first hospitalization, and degree of clinical improvement during acute treatment at first admission and the GAF score at one year. On the other hand, the GAF score was higher (73.6 ± 11 vs. 67.4 ± 13.1, t = 2.11, df = 60, p = 0.05), and the BPRS score was lower (32.5 ± 9.6 vs. 38.4 ± 10.1, t = 2.23, df = 60, p = 0.03) in women at one year follow-up. GAF score at one year was also higher in patients who were taking atypical antipsychotics (72.5 ± 11.3 vs. 66.1 ± 12.3, Z = 2.26, p = 0.02)

In order to explore the predictors of relapse, Cox regression analyses were used. Psychotic relapse was a dependent variable, and PAS-1 score, gender, and compliance to antipsychotic treatment, were independent variables. Functionality in childhood and noncompliance to the treatment independently contributed to relapse (Table 2).

Bivariate correlations showed that GAF score was significantly related to the PAS score for late adolescence (r = –0.329, p = 0.02), but not in childhood, early adolescence and the mean PAS score.

The GAF score at one year was taken as a dependent variable, DUP, decrease on the BPRS score during the hospitalization, PAS-3, and SANS scores at discharge were taken as predictor variables in multiple linear regression analysis. Only PAS-3 independently contributed to overall outcome in regression analysis (B = –6.77, Beta = –0.347, t = –2.16, p = 0.03).

Thirty-four patients (54 %) were employed at one year. These patients were more educated (t = 2.62, df = 62, p = 0.01), had higher GAF score at discharge (t = 3.38, df = 62, p = 0.002), and lower PAS-1 scores (t = –3.35, df = 64, p = 0.001) and total PAS scores (t = –2.9, df = 64, p = 0.006). Only the GAF score at discharge (B = –0.08, wald = 3.51, df = 1, p = 0.05) appeared as a predictor for the employment in logistic regression analysis.

Discussion

In this study we investigated the predictors of relapse and one year outcome in a homogenous group of patients with first episode schizophrenia. Considering the multi-dimensionality of the outcome concept presence of relapse and rehospitalization, level of global functioning, employment status and severity of symptoms at one year were analyzed. Premorbid social functioning in early childhood and compliance to the treatment were independently contributed to occurrence of relapse as hypothesized. Contrary to our expectations, the results of this study did not support the importance of DUP and severity of symptoms as predictors of one year outcome in first episode schizophrenia.

Twenty-five patients had relapse at least once, three patients had persistent psychotic symptoms, and 62.9 % of the patients were in remission at one year follow-up. The 33.7 % relapse rate of our study is very similar to the 37.5 % reported by Novak-Grubic and Tavcar (2002).

Table 2 Predictors of relapse after first episode at one year follow-up (Cox regression analysis)

	B	S.E.	wald	d.f.	p	Exp (B)
Compliance to medication	1.606	0.547	8.61	1	0.003	4.98
PAS-1	2.653	1.182	5.03	1	0.02	14.19
Gender	–0.960	0.541	3.14	1	0.07	0.38

Lowest relapse rate (3.8 %) at one year was recently reported by German Research Network on Schizophrenia (Gaebel 2004). Randomized double blind antipsychotic treatment (haloperidol or risperidone) combined with psychosocial treatment in this study represent an almost optimal treatment approach. Our relapse rates are also higher than the 16 % of Robinson et al. (1999); the difference can be explained by the inclusion of only hospitalized patients in our study. Similarly, 17 % of one year relapse rate reported by Linszen et al. (1994) might well be a result of the ideal therapy which combines psychosocial therapy and family intervention aiming to increase the compliance following the three-month inpatient period. Our results should be interpreted as representing a naturalistic follow-up of first episode patients who were treated in an inpatient clinic. We found that childhood functionality measured by PAS-1 is independently related to early relapse. This finding is similar to Robinson et al. (1999) where early adolescent premorbid adjustment had a relation with early relapse. The influence of impaired functionality in childhood can support the importance of neurodevelopmental factors in the etiology of schizophrenia in early relapsing patients. In this case longer exposure of pathologic conditions may contribute to the worse outcome. We did not find an association between PAS scores and severity of symptoms at the end of the first year contrary to some previous studies (Malla et al. 2002; Larsen et al. 2000). As we defined high relapse rate with positive symptoms, we can conclude that there is insufficient control of positive symptoms with antipsychotic treatment in patients with impaired premorbid functioning. Likewise, patients with poor premorbid adjustment show low general functionality and low employment level at one year. This shows that premorbid functionality as well as positive symptoms at one year affect the patients' general functionality.

Compliance to antipsychotic medication seems to be another predictor of better outcome at one year. Our findings are similar to the results of two previous first episode follow-up studies (Robinson et al. 1999; Novak-Grubic and Tavcar 2002) with regard to noncompliance rates. We determined a high amount of incompatibility (38.7 %) with medication among the patients who completed one year follow-up. It would be higher if the dropouts are also taken into consideration. The fact that higher suspiciousness score of noncompliant patients upon discharge is consistent with the findings of Marder et al. (1983). In addition to this, Novak-Grubic and Tavcar (2002) reported that insight is lower in noncompliant first-episode patients upon leaving the hospital. Although we did not measure insight, a high suspiciousness score may also have negative effect on insight and thus on compliance.

We determined that patients with higher negative symptoms at admission and/or discharge developed earlier relapses. Altamura et al. (2001) also reported that patients with severe negative symptoms appear to be more likely to present worse course of illness. It has been reported that negative symptoms start before psychotic symptoms and over a longer period of time (Häfner et al. 1993). Negative symptoms are not affected by the delay in treatment (Ucok et al. 2004) and less affected by antipsychotic treatment when compared to positive symptoms. Although relapse is defined on the basis of positive symptoms, negative symptoms which start before the illness and not affected by treatment seem to be predictors of the relapse and can determine the early course of schizophrenia.

Our results on relapses, GAF and BPRS scores at one year indicate a better course for schizophrenic women than for men. Similar results were reported for chronic patients (Usall et al. 2003; Harigan et al. 2003) as well as first episode schizophrenia (Geddes et al. 1994; Vasquez-Barquero et al. 1999). Szymanowski et al. (1995) reported that a better pharmacological response rate of the first-episode female patients is consistent with the gender differences in degree of symptom improvement with medication. The tendency for female patients to make more use of treatment may also be a factor in a better course of illness.

There were no differences between patients who had a relapse and who had not in terms of DUP. However, we found that patients with longer DUP were rehospitalized earlier and had more relapses during one year follow-up. These findings may indicate that DUP is partially related with a more severe course at one year. In a previous study we also reported that DUP is related with better improvement on both positive symptoms and general clinical severity at first hospitalization (Ucok et al. 2004). Similarly, Drake et al. (2000) concluded that DUP's relationship to outcome is strongest in the initial months of psychosis. Our findings also suggest that the relationship between DUP and the clinical course is more clear in the earlier phase of the illness and this effect may vanish with time.

Since this is a naturalistic follow-up, and investigators were free in their choice of treatment, to investigate its effect is beyond the scope of this study. However, our findings suggest that the patients taking atypical antipsychotics had fewer relapses and had a higher level of functioning at one year.

While interpreting our results, it should be kept in mind that this is an observational follow-up study where only first episode patients who were treated in an inpatient clinic are included. Although this has no effect on the validity, the generalization of our results to the entire patient population may be limited. It can also be argued that the necessity of informed consent systematically excludes the most uncooperative patients. Because of the naturalistic design, we did not control the differences for medication. Nonetheless all patients received antipsychotic drugs, and patterns of prescription tend to be homogeneous among the clinicians who participated in the study. However, in a research area where prior data are very limited, the sample of this study consisting of an homogenous group of patients with schizophrenia according to DSM-IV criteria and a relatively balanced

gender distribution can be considered as important strength.

Recently much research was performed to understand the etiology of schizophrenia (Kitamura et al. 2005; Kampman et al. 2004). Despite our study not focussing on biological markers, the results indicated that early childhood period and neurodevelopmental factors may affect the outcome during the first year of schizophrenia. Further prospective studies especially focussing on early childhood indications in risk groups and long-term follow-ups with the biological markers can be explanatory for a neurodevelopmental hypothesis of schizophrenia. We are still recruiting new patients to this project and are planning to follow-up these patients for at least five years. We believe that the results of longer follow-up of this study will be more helpful to understand the impact of premorbid features on early course of the illness.

In conclusion, the results of the present study suggest that treatment compliance and early premorbid adjustment are among the important predictors of relapse in first episode schizophrenia. Thus, psychosocial interventions targeting to increase compliance may have a positive effect on relapse during the first year of follow-up. Since the relationship between clinical and social factors, and outcome in first-episode schizophrenia is complicated, the importance of neurodevelopmental factors in the etiology of schizophrenia in early relapsing patients deserves more attention.

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