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ORIGINAL PAPER

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The impact of duration of untreated psychosis and premorbid functioning on outcome of first inpatient treatment in schizophrenic and schizoaffective patients

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Abstract *Objective* The aim of the study was to investigate the association between the duration of untreated psychosis, premorbid functioning and outcome from first inpatient treatment in schizophrenic or schizoaffective patients. *Method* The data of 196 first-hospitalized patients with a schizophrenic or schizoaffective disorder according to the ICD-10 criteria were analyzed using univariate and multivariate methods. Patients' characteristics were prospectively assessed using standardized instruments at the time of first admission and discharge. *Results* The analyses revealed that a duration of untreated psychosis longer than 12 months was independently and significantly associated with a poorer outcome from first inpatient treatment. Premorbid functioning might have an additional influence on outcome, but this influence seems to be dependent on the diagnostic category. *Conclusions* The findings suggest that the duration of untreated psychosis is an independent prognostic factor for the outcome in schizophrenic and schizoaffective disorders.

Key words schizophrenia · duration of untreated psychosis · premorbid functioning · outcome · first admission

Introduction

During the last decade a number of studies on first-episode schizophrenic patients revealed that schizophrenic patients can exist in the community for extended periods with substantial levels of psychopathology, and that the duration of active psychosis prior to first treatment and hospitalization is often months or years. Despite some negative findings, there is overwhelming evidence, derived from retrospective and prospective studies, that the longer the duration of psychotic illness before treatment, the poorer the response to treatment and the outcome of patients (Altamura et al. 2001; Bottlender et al. 1999, 2000, 2002; Carbone et al. 1999; Larsen et al. 2000; Loebel et al. 1992; Malla and Norman 2001; McEvoy et al. 1991; Scully et al. 1997; Wyatt et al. 1991). The convergence of this evidence is striking, considering the fact that there are large methodological differences between the studies. However, the nature of the link between duration of untreated psychosis and prognosis remains unclear (McGlashan 1999). Considering that previous studies have consistently shown an association between poor premorbid functioning and poorer outcome (Addington et al. 1993; Bailer et al. 1996; Beiser et al. 1994; Childers et al. 1990), it is hypothesized that a longer duration of psychosis prior to treatment may only be an epiphenomenon of poor premorbid functioning, and that the association between duration of untreated psychosis and poor outcome is highly confounded by poor premorbid functioning.

Although some previous studies have attempted to address this important topic (Loebel et al. 1992; Edwards et al. 1998; Verdoux et al. 2001; Larsen et al. 2000; Drake et al. 2000), the results obtained by these studies are conflicting and indicate the need for further research. Given the potential clinical importance of the impact of the duration of untreated psychosis on outcome, we wanted to determine whether a relationship between duration of untreated psychosis and clinical outcome is present in a naturalistic clinical setting after controlling for premorbid functioning and other potential confounding variables.

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Methods

The patients included in the study stem from a clearly defined catchment area (Munich and surrounding areas) and were consecutively hospitalized inpatients at the Psychiatric Hospital of the Ludwig Maximilians University, Munich, from 1995 to 1998 inclusively. All patients had been admitted for the first time to a psychiatric department. Study patients had a diagnosis of schizophrenia or a schizoaffective disorder according to the ICD-10 criteria (F20.xx or F25.xx) and were treated with neuroleptics during their hospital stay. Global functioning was recorded by the Global Assessment of Functioning Scale (GAF) at admission and discharge. This is a single-dimension rating scale for the evaluation of the overall functioning of a subject on a continuum from severe psychiatric sickness (rated 0) to health (rated 100). Premorbid functioning was assessed with the Phillips Scale in the abbreviated form by Harris (1975). This scale consists of two parts: an abbreviated scale of premorbid sexual adjustment and an abbreviated scale of premorbid personal-social adjustment. The scale was developed utilizing a 7-point scale (0–6) for each part. Interrater reliability and validity of the scale have previously been demonstrated. The DUP, defined as the period between the onset of psychotic symptoms and the first psychiatric admission, was assessed during the index hospitalization through clinical interviews with the patients and their relatives. A similar method (i. e., the use of a clinical interview with patients and their relatives) to assess the duration of untreated psychosis was used previously, and was shown to be sufficiently reliable (Craig et al. 2000; Loebel et al. 1992). In accordance with earlier studies (Carbone et al. 1999; Craig et al. 2000) the DUP was categorized as follows: 1 = duration ≤ 6 months; 2 = duration > 6 months and ≤ 1 year; 3 = duration > 1 year. This categorization of the DUP into longer periods of time seems to be reasonable since there is no evidence that rather short differences in the DUP (days or weeks) have a marked impact on the outcome (e. g., Johnstone et al. 1999). Furthermore, the use of comparable categories of the DUP allows a comparison of the results from different studies.

The mode of onset of the illness was categorized into acute and non-acute forms. Acute onset was defined as follows: 1) a rapid (shorter than 1 month) deterioration of initial schizophrenic symptoms; and 2) maintenance of premorbid social functioning including interpersonal relationships until the beginning of the deterioration. If the deterioration was more gradual (longer than 1 month), the mode of onset was judged as non-acute. All assessments mentioned above were performed by well-experienced resident psychiatrists. Psychopathological rater-training sessions were regularly performed to establish and maintain a high interrater reliability.

Statistical analyses were performed using the SPSS 10.0 Software for Windows. Group differences for continuous variables were evaluated using the t-test. Group differences for all categorical variables were evaluated using the chi-square statistics. A multiple logistic regression model was used to analyze the impact of predictor variables on outcome. The odds ratio (OR) and its 95 % confidence interval (CI) were calculated for each factor. A p-value of < 0.05 (2-tailed) was considered statistically significant.

Results

Demographic and clinical characteristics of patients

In total, 196 first hospitalized patients from the years 1995 to 1998 were included in the study (152 with schizophrenia and 44 with schizoaffective disorders). The total sample consisted of 95 females (48.5 %) and 101 males (51.5 %).

The mean age at first hospitalization was 34.26 ± 12.63 years. The mode of onset of the illness was acute in 65 patients (33.2 %) and non-acute in 131 patients (66.8 %).

One hundred patients (51 %) had a duration of untreated psychosis of less than 6 months. The duration of untreated psychosis was between 6 and 12 months in 29 patients (14.8 %) and longer than 12 months in 67 patients (34.2 %).

The mean score of premorbid functioning assessed with the abbreviated form of the Phillips scale was 4.64 ± 2.79 (Score range: 0–12; remark: higher scores reflect lower premorbid functioning).

Global functioning was assessed with the GAF rating scale at admission and at discharge. The corresponding means were 38.02 ± 13.44 at admission and 62.04 ± 14.87 at discharge (median (admission) = 36; median (discharge) = 62). The mean duration of inpatient treatment was 67.71 ± 50.42 days.

Differences between patients with better and poorer outcome with respect to the duration of untreated psychosis, premorbid functioning and other variables

The outcome of patients after their first hospitalization was assessed with the GAF scale. GAF rating has been used as a clinical outcome measure in many studies (Black et al. 2001; Craig et al. 2000; Haas et al. 1998; Larsen et al. 2000). On the basis of the GAF ratings at the time of discharge, patients were categorized into a group with a better (GAF-rating ≥ 62) and one with a poorer outcome (GAF-rating < 62). This dichotomized outcome measure was also used in many previous studies (e. g., Harding et al.1987; Harrison et al. 2001). The following variables were considered to have an impact on the outcome after first hospitalization: duration of untreated psychosis, level of premorbid functioning, mode of onset, age at first admission, gender, diagnosis, GAF rating at admission and duration of inpatient treatment. In the first analysis, the variables mentioned above were compared in the better and poorer outcome groups. The corresponding findings are shown in Table 1 and indicate that the patients with poorer outcome were more likely to have a diagnosis of schizophrenia and less likely to have a schizoaffective disorder. Furthermore, it was found that the patients with a poorer outcome had significantly lower levels in premorbid functioning and a longer duration of untreated psychosis. Differences in all other variables (mode of onset, GAF rating at admission, age at first admission, gender and duration of inpatient treatment) did not reach statistical significance.

Evaluation of the impact of duration of untreated psychosis, premorbid functioning, diagnostic group and other predictor variables on outcome by logistic regression analyses

Because confounding effects between the different variables mentioned above cannot be excluded by univariate analyses, the variables that were shown to differ sig-

Table 1 Differences between patients with better and poorer outcome from first inpatient treatment

	GAF ≥ 62 (= better outcome)	GAF < 62 (= poorer outcome)	Significance[1]
Number of patients	99	97	
Age (years)	34.23 ± 11.18	34.28 ± 14.01	n. s.
Percentage of males (%)	47.5	52.5	n. s.*
Diagnosis			
Schizophrenic patients n (%), N = 152	65 (42.8)	87 (57.2)	< 0.001*
Schizoaffective patients n (%), N = 44	34 (77.3)	10 (22.7)	
GAF at admission (mean summary score)	39.09 ± 14.64	36.94 ± 12.07	n. s.
Duration of inpatient treatment (days)	68.05 ± 49.93	67.36 ± 51.16	n. s.
Percentage of patients with acute onset (%), N = 65	55.4	44.6	n. s.*
Percentage of patients with non-acute onset (%), N = 131	48.1	51.9	n. s.*
Premorbid functioning (mean summary score of the Phillips Scale)	4.04 ± 2.50	5.26 ± 2.96	0.002
DUP			
patients with a DUP < 6 months n (%), N = 100	59 (59.0)	41 (41.0)	0.005* (chi-square)
patients with a DUP > 6 and < 12 months n (%), N = 29	17 (58.6)	12 (41.4)	
patients with a DUP > 12 months n (%), N = 67	23 (34.3)	44 (65.7)	

[1] statistical analyses were performed using the two-tailed t-test for independent samples or the chi-square statistics; the latter is indicated by *.
DUP Duration of untreated psychosis

nificantly between both outcome groups were simultaneously entered into a multiple logistic regression model. The dichotomized GAF rating at discharge served as the outcome variable (GAF rating ≥ 62 = better outcome, GAF rating < 62 = poorer outcome; Table 2). This second analysis revealed that only the diagnostic group and the duration of untreated psychosis prior to first hospitalization were significantly associated with the GAF rating at discharge. Both the diagnosis of a schizophrenia and a duration of untreated psychosis longer than 12 months were predictive for a poorer outcome. The impact of the level of premorbid functioning on outcome did not reach statistical significance.

As some of the previous studies that found a significant impact of premorbid functioning on outcome did not control for diagnosis in their analyses, we further analyzed whether the inclusion of diagnosis in our analyses affected our results concerning the impact of premorbid functioning on outcome. In order to do this the variable "diagnostic group" was removed from the logistic regression model at the first step. The other predictor variables (duration of untreated psychosis and the level premorbid functioning) remained in the logistic regression model. Premorbid adjustment consequently reached statistical significance, demonstrating that higher ratings on the premorbid adjustment scale (remark: higher ratings reflect lower premorbid adjustment) were predictive of a poorer outcome (coefficient: 0.14; standard error: 0.06; two-tailed p value: 0.01; odds ratio: 1.15; 95 % confidence interval: 1.03–1.29). The impact of the duration of untreated psychosis on outcome was comparable to that obtained by the first logistic regression analysis (DP (1): not significant; DP (2): coefficient: 0.91; standard error: 0.34; two-tailed p value: 0.01; odds ratio: 2.48; 95 % confidence interval: 1.27–4.84).

The effect of premorbid functioning on outcome may differ between schizophrenic and schizoaffective patients. Therefore, we analyzed whether there was an in-

Table 2 Impact of different predictor variables on the global functioning at discharge (assessed with the GAF scale; outcome variable was split at the median GAF rating 1 = GAF ≥ 62 (= better outcome), 2 = GAF < 62 (= poorer outcome)

Factor[1]	Coefficient	SE	P	OR	95 % CI
Diagnosis[1] (0 = schizoaffective disorder, 1 = schizophrenia)	1.23	0.41	0.00	3.42	1.53–7.66
Premorbid functioning (summary score)	0.11	0.06	0.06	1.12	0.99–1.26
Duration of untreated psychosis (DUP)[2]					
DUP > 6 and < 12 months	–0.13	0.45	0.77	0.88	0.37–2.13
DUP > 12 months	0.78	0.35	0.02	2.18	1.10–4.33

[1] Diagnosis and DUP were entered as indicator variables into the logistic regression model. *SE* Standard Error, *P* Two-tailed P values, *OR* Odds Ratio, *CI* Confidence Interval
[2] The DUP was treated as a category variable. A DUP < 6 months was used as the reference category

Table 3 Impact of duration of untreated psychosis on the global functioning controlling for premorbid functioning and interaction between premorbid functioning and diagnosis

Factor[1]	Coefficient	SE	P	OR	95% CI
Premorbid functioning (summary score)	–0.13	0.11	0.26	0.88	0.70–1.10
Diagnosis X Premorbid functioning[1]	–0.28	0.10	0.004	1.33	1.09–1.61
Duration of untreated psychosis (DUP)[2]					
DUP > 6 and < 12 months	–0.12	0.45	0.79	0.89	0.37–2.15
DUP > 12 months	0.84	0.35	0.02	2.31	1.16–4.60

SE Standard Error, *P* Two-tailed P values, *OR* Odds Ratio, *CI* Confidence Interval

[1] Interaction between diagnosis and premorbid functioning was considered in the logistic regression model

[2] The DUP was treated as a category variable. A DUP < 6 months was used as the reference category

teraction between the diagnostic group and the level of premorbid functioning in our logistic regression model. Results are shown in Table 3. The interaction term between the diagnostic group and premorbid functioning was significantly predictive of outcome in this model. The computed coefficient computed for this term indicated that premorbid functioning had a greater effect on outcome in schizoaffective patients than in schizophrenic patients. Premorbid functioning alone showed no significant impact on outcome in this model, suggesting that the majority of effects of premorbid functioning on outcome (detected by results shown in the preceding analysis) were mediated by interaction between the diagnostic group and premorbid functioning. On the other hand, results concerning the duration of untreated psychosis were comparable to those obtained by our preceding analyses.

Discussion

The present study aimed to further evaluate the impact of the duration of untreated psychosis and premorbid functioning on the outcome of first inpatient treatment. All patients included in the study had their first hospitalization, stemmed from a clearly defined catchment area and were diagnosed according to the ICD-10 criteria. From a total of 196 patients, 152 had a diagnosis of schizophrenia and 44 a diagnosis of schizoaffective disorder.

A major finding of the present analyses was that a duration of untreated psychosis longer than 12 months was significantly predictive of a worse outcome from first inpatient treatment. Considering that this finding is in line with most of the previous retrospective and prospective studies (e. g., Bottlender et al. 2000, 2001; Carbone et al. 1999; Edwards et al. 1998; Haas et al. 1998; Loebel et al. 1992; McEvoy 1991; Wyatt et al. 1997), and that only a few authors reported conflicting results concerning this topic (e. g., Craig et al. 2000; Ho et al. 2000), one can say that the association between duration of untreated psychosis and poor outcome seems to be a relatively robust finding. Nevertheless, it still remains unclear whether the findings concerning this association are confounded by other factors that are known to have an impact on outcome. This question is crucial because most previous findings concerning the association between the duration of untreated psychosis and outcome did control not at all, or at the most only indirectly, for potential confounders. The present study attempted to address this question. Our findings indicate that the impact of the duration of untreated psychosis on outcome is independent of factors such as the diagnosis, the mode of onset, the age at first admission, and gender. The level of premorbid functioning was found to have different effects on outcome in schizophrenic and schizoaffective patients. The results concerning the interaction between the diagnostic group and premorbid functioning suggest that the impact of premorbid functioning is greater in schizoaffective patients than in schizophrenic patients, and that the potential impact of premorbid functioning in our sample was largely mediated by such interaction effects.

Controlling for premorbid functioning was also taken into account in some previous studies. For example, neither Loebel et al. (1992) nor Edwards et al. (1998) found any statistical association between duration of untreated psychosis and premorbid functioning. They concluded that the association between duration of untreated psychosis and poor outcome was not explained by premorbid functioning. However, they only used univariate analyses and not multivariate to explore this issue. In a recent study by Larsen et al. (2000), the 1-year outcome in 43 patients suffering from their first-episode of non-affective psychosis was investigated. Comparable to our findings, they found that both poor premorbid functioning and long duration of untreated psychosis were significantly correlated with more negative symptoms and poorer global functioning at the 1-year follow-up. Long duration of untreated psychosis remained a strong predictor of outcome, even after other factors such as premorbid functioning and gender were controlled for.

Verdoux et al. (2001) investigated a population-based sample of 65 first-admitted subjects with psychosis (n = 65). The patients were assessed at six-month intervals over a two-year follow-up. A major result of this study was that subjects with a long duration of untreated psychosis before first admission were more likely to present with psychotic symptoms and with a continuous course of illness. However, it was also shown that the effect size of the association between duration of untreated psychosis and chronicity of psychotic symptoms over the follow-up period was strongly reduced after ad-

justment for premorbid functioning. The latter finding cannot be supported by our data or by other previous studies that addressed the same outcome measure as the study by Verdoux et al. (2001). Concerning the study by Verdoux et al., it could be criticized that they investigated a sample of patients that was rather heterogeneous with regard to diagnosis (the sample included subjects with schizophrenia, schizoaffective disorder or schizophreniform disorder, psychotic affective disorders, delusional disorder, brief psychotic disorder, psychotic disorder not otherwise specified and substance-induced psychotic disorder). Since the number of subjects within each diagnostic category was small, they did not perform separate analyses by diagnostic category. However, as shown in our present analyses, controlling for the diagnostic category as well as interaction between diagnosis and premorbid functioning may affect the results.

A limitation of the present study may be that patients were treated with neuroleptics under naturalistic conditions and did not receive controlled treatments. However, this situation may also be seen as a strength of the study, because the finding of a significant impact of the duration of untreated psychosis on the outcome under naturalistic treatment conditions could hint at the relative independence of this prognostic factor from the type of treatment. This interpretation is in line with the notion by Crow et al. (1986) who studied 120 schizophrenic patients who entered a randomized placebo-controlled trial of maintenance neuroleptic medication and were followed to relapse or loss to follow-up, for two years or to the end of the study. They found that the most important determinant of relapse was duration of illness prior to starting neuroleptic medication. More recently, Verdoux et al. (2001) reported that the association between duration of untreated psychosis and continuous course of psychotic symptoms over the two-year follow-up was not reduced after adjustment for previous psychotropic treatment, previous antipsychotic treatment or previous duration of antipsychotic treatment. In addition, Carbone et al. (1999) investigated the impact of the treatment approach and the duration of untreated psychosis on 12-month outcome in first-episode psychosis. They found that patients with a short duration of untreated psychosis were more likely to have a good outcome, independent of the type of treatment they received, as long as it was of a minimum standard, and that the relationship between the duration of untreated psychosis and 12-month outcome was relatively difficult to influence through clinical intervention.

In conclusion, the present findings further support the suggestion that a longer duration of untreated psychosis is an independent predictor of poorer outcome in schizophrenia. The findings give no support to the notion that the duration of untreated psychosis is just a mediator between premorbid functioning and outcome.

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