One-Year Outcome and Its Prediction in First-Episode Schizophrenia – A Naturalistic Study

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\textbf{Abstract}

\textbf{Background:} The literature suggests that the early course of schizophrenia is a strong predictor of long-term outcome. We sought to test this notion in a sample of first-episode patients. \textbf{Sampling and Methods:} Forty patients with a first episode of DSM-IV diagnoses of schizophrenia, schizo-affective, or schizophreniform disorder were assessed with well-established instruments such as the Positive and Negative Syndrome Scale and the Strauss–Carpenter Scale. Reassessment was performed 14 months later and included the Global Assessment of Functioning Scale in addition to the aforementioned instruments and a psychiatric interview. Regression analyses for the Global Assessment of Functioning Scale and symptomatology were used to identify outcome predictors. \textbf{Results:} At follow-up, 27 patients (67.5\%) were in remission. Women's outcome was significantly better with respect to intimate relationships and domiciliary independence. Although symptomatology of the whole group remained stable during the follow-up period, a subgroup of patients experienced a significant decrease in symptom levels whereas symptoms increased in another subgroup. The most important predictor of outcome was compliance with atypical antipsychotic medication during the follow-up period. \textbf{Conclusions:} These results suggest that there is a prognostic divide early in the course of the disease, that compliance with medication is of overriding importance towards 1-year outcome, and that for the individual patient the question of chronicity may be answered very early in the course of the disease.


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come as long-term outcome was consistent with early outcome and was related to the percentage of time patients experienced psychotic symptoms during the first 2 years [29].

Besides the early course, a variety of clinical and biological variables consistently emerged to be associated with outcome including among others gender, age and mode of onset of illness, duration of untreated psychosis (DUP) and response to medication [26, 30–34]. The latter constitutes one of the most reproducible findings in clinical psychiatry [2, 35–37] and is interwoven with early and late course and outcome. Atypical compounds cause less extrapyramidal side-effects than typical neuroleptics and thus lead to better quality of life as well as to less stigmatisation [38]. Although recently much attention has been paid to the treatment of first-episode patients, studies on their course and outcome have – to our knowledge – not been restricted to the use of atypical antipsychotics.

This study aimed to examine the early course in first-episode schizophrenic patients in a naturalistic study. We hypothesised that predictors of outcome are identifiable early during the course of the disease, and that they include compliance with antipsychotic medication.

**Methods**

**Patients**

Initially, 62 patients in the acute phase of their first psychotic episode, necessitating hospital admission, were consecutively included into the study after proceedings had been fully explained and consent had been obtained. All patients were Caucasians from a homogenous middle-class population. They had no lifetime history of any therapy with neuroleptic medication of more than 2 weeks. Patients with a past history of or a concomitant neurological or severe medical disorder or persistent or severe substance abuse were excluded. Subjects met diagnostic criteria for schizophrenia, schizoaffective disorder or other psychotic disorder according to DSM-IV. Neuroleptic treatment was initiated with benperidol to achieve fast remission of symptoms and changed to atypical compounds after 1–2 weeks on average. At the time of the study, the atypicals clozapine, risperidone, and olanzapine were available in Germany. For patients who had developed extrapyramidal side-effects during initial treatment, the second-choice medication was clozapine (n = 29) because there is no risk at all of such side-effects. However, medication was not a controlled variable in this study, but the best possible treatment was considered to be the drug regimen that optimised reduction of symptoms and side-effects and was determined empirically by the treatment team.

During hospital stay, in addition to pharmacological therapy, patients took part in a psychosocial treatment programme including individual and group therapies, and psycho-education for patients and family members.

One year after discharge, all subjects were invited by mail to take part in a follow-up study. Fifteen declined to participate in the follow-up assessment and 7 were lost to follow-up. Forty subjects (22 women, 18 men; age 29 years, SD 8.3) responded, gave informed consent and received reimbursement of their transportation costs to the hospital. The exact catamnestic interval amounted to 14.1 months (SD 1.6). The study was performed on an acute admission ward at the Department of Psychiatry, University of Heidelberg, Germany, and was approved by the ethics committee of the Medical Faculty of the University of Heidelberg.

**Instruments**

At remission (t1), diagnoses were assessed with the Structured Clinical Interview for DSM-IV [39]. Psychopathological symptoms were rated on the Positive and Negative Syndrome Scale (PANSS) [40] on three occasions, namely admission to the hospital, seventh day of treatment and on remission of the acute symptoms. Predictors of outcome were assessed by using the Strauss-Carpenter Scale (SCS) [41]. In addition, information on the DUP and on premorbid adjustment was obtained from the SCS items on work, relationships, and duration of symptoms prior to admission (<1 month, 1–6 months, 6–12 months, 1–2 years, >2 years). Side-effects of medication were documented after remission of the acute symptoms on the scales by Simpson and Angus [42], Barnes [43], and on the Abnormal Involuntary Movement Scale [44].

On follow-up (t2), all patients underwent a psychiatric interview which was partially structured and partially semi-structured. The former section was directed at the determination of present symptoms on the PANSS and side-effects of medication on the above-indicated scales. It also included the reassessment of diagnoses by the Structured Clinical Interview for DSM-IV, the rating of the Global Assessment of Functioning (GAF) [45] taking into account the worst week during the month before the interview, as well as measures of outcome on the SCS. From the semi-structured part of the interview, information was obtained on the following issues and rated on a three-dimensional scale: subjective well-being, compliance with outpatient treatment and medication, side-effects of medication, possible relapse, employment, sources of income, household duties, intimate relationships, and relationships with family and friends. Ratings were performed by the same trained raters on both occasions. To maintain intra- and interrater reliability and avoid rater drift, we implemented an ongoing programme of regular reliability checks.

**Data Analysis**

Consistent with the literature, symptomatic and functional remission was defined according to a GAF score of ≥61 [5, 28, 46] during the month prior to assessment. This indicates absent or mild symptoms and/or impairment in the psychosocial dimensions work and relationships. Also following the literature [47], DUP was defined as short or long according to a cut-off of 1 year. For statistical analyses, data from the semi-structured interview were expressed dichotomously summarising the two lower functional levels, because the respective cells contained only a few observations each.

Psychometric data of patients who agreed to a follow-up examination and those who did not were compared using t tests. Analyses of variance and χ² tests, extended by Fisher's exact test
if warranted, served to compare clinical variables between the sexes. All variables which had been rated twice were analysed with repeated-measures analyses of variance. Additionally, the whole patient group was split into two subgroups according to their median PANSS follow-up scores to further analyse PANSS scores with respect to suspected differential changes; subgroups were compared with respect to the other clinical parameters. In order to determine predictors of outcome, multiple regression analyses were calculated for follow-up symptoms according to the PANSS total score and for the GAF. Variables were entered as possible predictors if they depicted information which preceded the follow-up interview and were hypothesised to be relevant to outcome in accordance with the literature [26–28, 30–34, 44], namely family history of serious psychiatric disease, age, gender, behavioural abnormalities since the age of 12, level of education, DUP, response to initial treatment, level of symptoms on discharge from initial treatment, compliance with medication as well as use of alcohol and drugs during the follow-up period.

All analyses were performed with the SPSS.

**Results**

*Diagnoses and Treatment*

Patients who agreed to a follow-up examination did not differ from those who did not regarding psychopathological symptoms on remission. Thus, representativeness is closely approximated.

The initial assessment of 40 patients with a first psychotic episode had revealed the following diagnosis: schizophrenia (n = 20), schizoaffective disorder (n = 3), schizophreniform disorder (n = 16) and psychosis not otherwise specified (n = 1). On follow-up, diagnoses were schizophrenia (n = 34), schizoaffective disorder (n = 4) and schizophreniform disorder (n = 2). A diagnostic shift was present in 16 cases, namely from schizophreniform disorder to schizophrenia in 14 subjects, from psychosis not otherwise specified to schizophrenia, and from schizophrenia to schizoaffective disorder in 1 subject each. The initial in-patient treatment had lasted for 42.8 days (SD 24.0), and medication on discharge was either clozapine, olanzapine or risperidone with a mean of 579.5 mg (SD 267.3) of chlorpromazine equivalents.

Thirty-four individuals (85%) were compliant with psychiatric outpatient treatment during the follow-up period, 32 (80%) of whom received continuous antipsychotic treatment as indicated above. One individual received a mood stabiliser and 3 patients antidepressants in addition to the antipsychotic medication, the individuals with schizoaffective disorder received antidepressants only. The dose of antipsychotic medication amounted to a mean of 297.7 mg (SD 235.5) of chlorpromazine equivalents. Side-effects of medication were low at both assessments, namely scores of 0 (range 13 at t1; range 5 at t2) on the Abnormal Involuntary Movement Scale, 0 (range 4 at t1; range 3 at t2) on the scale by Barnes [43], and 12 (range 7) at t1 and 11 (range 4) at t2 on the scale by Simpson and Angus [42]. This was to be expected in a patient sample treated with atypical antipsychotic medication.

*Symptomatology on Follow-Up and Outcome*

Patients’ total mean PANSS score amounted to 52.8 (SD 25.2) which does not represent a statistically significant difference from the mean remission score of 52.0 (SD 12.2). The mean SCS score amounted to 58.5 (SD 11.4), this not being a significant difference from the mean initial score of 57.5 (SD 11.4).

A median split of the patient group according to their follow-up PANSS scores revealed two subgroups: 21 patients had decreasing and 19 increasing symptom scores. The circles indicate outliers.

**Fig. 1.** Psychopathological symptoms as rated on the PANSS of 40 first-episode patients at remission (PANSS t1) and 14-month follow-up (PANSS t2). A median split of PANSS t2 scores revealed two subgroups: 21 patients had decreasing and 19 increasing symptom scores. The circles indicate outliers.
During the follow-up period, 2 patients had been continuously ill. Relapses had occurred in 14 individuals, 6 of whom had been in symptomatic and functional remission for at least 1 month at the time of the second interview. The remaining 8 subjects still suffered from symptoms of psychosis (n = 5) or were readmitted to the hospital due to an exacerbation (n = 3). During the month before the follow-up interview, patients reached a mean GAF score of 69.4 (SD 15.9). The above-indicated criteria for remission yielded rates of 67.5% (n = 27) good outcome with none or mild impairment and 32.5% (n = 13) poor outcome with patients being markedly or severely ill and impaired.

Five individuals (20%) used cannabis regularly, another 2 irregularly; 4 of the cannabis users were also regular alcohol users. Psychosocial parameters at follow-up are given in table 1. A larger proportion of the patients were not married or living with a partner, nor were they living independently. Nineteen individuals were still living with parents, 4 had a guardian. There was no homeless person. Fifty percent were in paid employment or in vocational or educational training, 10 of whom also had educational achievements. The rate of part-time employment amounted to 27.5%, only 22.5% were unemployed. There was a lack of close contact with friends in 17.5% of patients, 22.5% had some contact and 60% frequent contact with friends.

Eight patients had a family history of serious psychiatric disease, however this was not related to any of the outcome measure. Age correlated with intimate relationship, domiciliary and financial independence as was to be expected. It also correlated with social relationships and ability to enjoy recreational activities, and was inversely correlated with educational achievement, family relations and overall life satisfaction.
Gender differences emerged with respect to intimate relationships (women: yes:no = 12:10; men: yes:no = 1:17; \( p < 0.005 \)) and independent living arrangements (women: yes:no = 14:8; men: yes:no = 3:15; \( p < 0.005 \)). Women were functioning better in these domains, which is in accordance with a tendency towards better predictors of outcome on the initial SCS (women: 60.5, SD 11.0; men: 53.8, SD 11.2; \( p = 0.069 \)). Although women were older than men, a statistical significance level was not reached.

**Prediction of Outcome**

Variables which possibly influence outcome were entered in a multiple linear regression analysis for levels of psychopathological symptoms and GAF on follow-up. The total PANSS score on follow-up (\( R = 0.91; R^2 = 0.83 \); adjusted \( R^2 = 0.80; F = 33.42; d.f. = 5, 35; p < 0.001 \)) was best explained by the following predictors (in the given order): medication compliance during the catamnestic period (\( \beta \) weight = –0.67; \( t = –8.24, p < 0.001 \)), alcohol use during this time (\( \beta \) weight = –0.33; \( t = –4.40, p < 0.001 \)), DUP prior to initial treatment (\( \beta \) weight = –0.22; \( t = –2.83, p < 0.001 \)), symptom levels at remission (\( \beta \) weight = 0.22; \( t = 2.82, p < 0.001 \)) and family history of major psychiatric disease (\( \beta \) weight = 0.21; \( t = 2.68, p < 0.001 \)). Analysis for GAF scores on follow-up (\( R = 0.54; R^2 = 0.30 \); adjusted \( R^2 = 0.28; F = 16.39; d.f. = 1, 39; p < 0.001 \)) revealed medication compliance only (\( \beta \) weight = 0.54, \( t = 4.05, p < 0.001 \)).

Thus, medication compliance during the follow-up period emerged as the most important predictor of outcome symptomatology and functioning in this patient sample.

**Discussion**

**Symptomatology on Follow-Up and Outcome**

Our results on low and unchanging psychopathological symptoms during the follow-up period of 1 year are in line with the literature. Stability of symptomatology has been reported in first-episode and chronic patients by several authors [9, 23, 48]. Also, the level of symptoms according to the PANSS in our study compares to results on early and long-term course from another first-episode sample in an industrialised society [49].

Two patient subgroups were revealed by the median split of symptom levels at follow-up. The subgroup with decreasing psychopathological symptoms reached levels of absent or questionable symptoms on the PANSS total and subscales whereas the second subgroup exhibited moderate and slightly increasing symptoms. Not only did the subgroups differ regarding symptom remission, persisting psychopathology was also related to worse compliance with medication as well as worse functioning on important domains of outcome, i.e. educational achievement, vocational training and social functioning. Moreover, the rate of patients reporting subjective well-being was much higher in the well-functioning group. There are two possible causes for symptom deterioration in our study: firstly, this subgroup encompassed patients with no compliance with medication, and secondly, the natural course of the disease was unfavourable in some patients. The second hypothesis is supported by the fact that – although patients with a favourable course were more likely to be compliant with antipsychotic medication than those with a poor course – a large number of the latter reported regular intake of medication. Therefore, compliance with medication might only be one among several factors which prevent chronicity.

Only two other groups have noted a similar effect of early differentiation within a patient group with respect to negative symptoms after 1 year [50] and regarding GAF scores after 6 months [49]; in both studies, patients fell into a low-symptom group and a high-symptom group. These findings suggest that there is a prognostic divide very early in the course of the disease as does our recent study on the Negative Syndrome Scale [51]. This again is supported by the notion of several authors on the predictive value of symptom severity at discharge for 1-year outcome [23, 48, 52, 53] and the findings of others [53, 54] that improvement occurs within the first months of treatment as opposed to years 1 and 2. In concert with the fact that results from short-term follow-up studies are in line with those arising from long-term follow-up, we hypothesise that for the individual patient the question of chronicity is answered very early in the course of the disease.

Outcome was operationalised according to GAF scores and thus encompasses functional as well as symptomatologic outcome. According to internationally renowned criteria based on GAF, 67.5% of patients in this study reached good outcome, i.e. were rated as remitted in terms of symptoms and function. This remission rate compares to several prospective first-episode studies [32, 48, 53, 55–57] and depicts at least a 15% higher rate of remission than is reported in the few first-episode studies with longer catamnestic intervals [16, 26, 28].

Comparing occupational functioning between this and other follow-up studies which reported on these domains, both in first-episode and chronic patients, the rates in our
study are in the range of several investigations [9, 28, 58] and higher than reported in others [10, 16, 53, 59]. These relatively high rates with one half of patients being employed or a full-time housewife or student and another 27.5% in part-time employment are surprising at first sight because unemployment rates were high in the general population and patients’ employment rates partly reflect the availability of work in a region. However, students accounted for a considerable amount of those employed, which is also reflected by the low rate of financial and domiciliary independence as paid work is a prerequisite for this as is overall functioning. Social functioning in the presented patients seems to be better than in a WHO study [16] and compares to Shepherd et al. [58] although the latter group did not differentiate first-episode and chronic patients. However, although in our study up to two thirds of patients had social relationships and were on good terms with their families, only one third had an intimate relationship at follow-up – the majority of them being women.

Overall, despite the different concepts and changing definitions with respect to outcome, relatively unambiguous results emerge regarding early outcome following a first psychotic episode in schizophrenia.

**Predictors of Outcome**

Compliance with medication emerged as the most important predictor of outcome in the presented study. Further influences were exerted by alcohol use during follow-up, symptom levels at remission, DUP, and family history of serious psychiatric disease.

Each of these predictors has been identified to exert an important influence on outcome. The introduction of neuroleptic treatment has changed the outcome of schizophrenia towards increased remission rates [2, 35, 60]. First-episode studies reported an up to fivefold increase of relapse rate after medication discontinuation [55, 61] and resistance to biological treatment ranges among the dimensions of chronicity [20]. Comorbidity including drug and alcohol abuse has recently been identified as a negative predictor of outcome [20, 61–63], which supports our results. Surprisingly, alcohol rather than cannabis use appeared to be influential in our study although cannabis usually enhances symptoms of psychosis rather than does alcohol. However, there may be a confounding effect as most of the alcohol users also consumed cannabis. Regarding symptom levels at remission, a review on first-episode studies [64] concludes that the illness severity at initial assessment influences treatment response and outcome. Another review [23] emphasises that symptoms at admission are not predictive of outcome but those on discharge are. The latter was confirmed by a study on first-episode patients [65] and by Breier et al. [9] who stress the relation of symptoms ‘during optimal medication’ to follow-up symptomatology. Along these lines [52, 63], some authors did not find any influence of the index illness and its treatment on outcome. Concerning DUP, an increasing body of literature has unanimously identified a longer duration of psychosis, mostly of more than 1 year, prior to first treatment as being detrimental to outcome [32, 55, 57, 62, 66–73]. The negative influence of family history of severe psychiatric disease was addressed by several researchers [20, 74–76] and less family history is consistently related to better outcome.

In the literature, several other factors have been identified to influence outcome, for example age, gender, cognitive functioning, affective symptoms, childhood behavioural abnormalities, and side-effects of medication [26–28, 30–34, 44]. Although these factors did not emerge as contributors in the regression analysis of the presented study, a gender effect was found with respect to domiciliary independence and intimate relationship at follow-up. This may be confounded with age because women were slightly older than men. However, the finding is in line with the literature [63, 77] and has already been described by Bleuler [78]. Cognitive functioning was not assessed in this study, and side-effects of medication were negligible throughout. As opposed to the literature, age was significantly higher in the group with more psychopathology; however, this is most likely due to a confusion with long DUP.

**Strengths and Limitations**

The study used a naturalistic, prospective design as well as standardised instruments. Outcome was assessed with different instruments to take into account its different dimensions [23, 38]. Patients were initially consecutively included in the study as they necessitated hospital treatment, and patients who were not accessible for follow-up did not differ from those who underwent catamnestic assessments, which renders recruitment bias unlikely. Follow-up rates in our study were not high but within the range reported in an international study [29], which is due to the very nature of the disease. The diagnostic shift from schizophreniform disorder and psychosis not otherwise specified to schizophrenia in 15 cases over time is in keeping with a study on the long-term course of schizophrenia and schizophreniform disorder [79]. Antipsychotic medication was not standardised but restricted to atypical compounds after a maximum of a 2-week treatment with typical antipsychotics and chosen according to the patients’
individual needs – pharmacotherapy was aimed at symptom reduction with minimal side-effects, and indeed side-effects were rare. As treatment with atypical antipsychotics is the gold standard, no comparison group receiving typicals was available. Relapse rates were not analysed in detail because it has been shown that symptoms and functioning may return to baseline levels [3].

A critical point is the lack of differentiation between remission and recovery in this study as has been called for in the literature [80]. However, the discussion only came to a preliminary conclusion in terms of defining remission after collection of our data was terminated and therefore could not be taken into account. Also, international consensus has not been reached to date regarding the definition of recovery.

Finally, we did not control for multiple statistical testing, however the total number of tests was rather limited.

Conclusions

Our results support the notion that there is a prognostic divide early in the course of schizophrenia and that compliance with medication is an important predictor of early outcome. This provides a strong argument for addressing the question of compliance as early as possible in the course of the disease.

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References


41 Strauss JS, Carpenter WT Jr: The prediction of outcome in schizophrenia. II. Relationships between predictor and outcome variables: a report from the WHO international pilot study of schizophrenia. Arch Gen Psychiatry 1974;31:37–42.


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Fenton WS: Course and outcome in schizophrenia. Curr Opin Psychiatry 1997;10:40–44.


