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Stefan Klingberg · Gerhard Buchkremer · Rolf Holle
Heinrich Schulze Mönking · W. Peter Hornung

Differential therapy effects of psychoeducational psychotherapy for schizophrenic patients – results of a 2-year follow-up*

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Abstract There is increasing evidence of the efficacy and effectiveness of psychosocial interventions in schizophrenic patients. However, little research has been done on differential therapy effects. In a prospective, randomized clinical trial we carried out psychoeducational medication management training, cognitive psychotherapy, and key-person counseling. The patients of the control group participated in structured free-time activities for control of therapeutic commitment. Data from a total of 156 schizophrenic patients (DSM-III-R, no first-admissions) were available at 2-year follow-up. We analyzed in this study whether there are differential therapy effects of these interventions, depending on patient characteristics at baseline. There was a significant statistical interaction between treatment condition (specific/non-specific) and prognosis with respect to treatment outcome. Patients with a favorable prognosis and better social functioning had a better course under the specific treatment but a less favorable outcome in the non-specifically treated control group. These results suggest that more vulnerable patients are not sufficiently capable of learning and using coping strate-

gies for relapse prevention. We need to learn more about differential indications for psychosocial treatment.

Key words Schizophrenia · Psychoeducation · Cognitive psychotherapy · Differential effects

Introduction

Psychoeducational and psychotherapeutic interventions based on cognitive-behavioral therapy are becoming increasingly widespread in the treatment of schizophrenic patients. Literature reviews and meta-analyses have meanwhile shown that these measures are effective overall and may contribute to an improvement in symptoms (Penn and Mueser 1996; Roth and Fonagy 1996; De Jesus Mari and Streiner 1994).

Yet there is a broad range of methods: social skills training (Lieberman and Corrigan 1993; Marder et al. 1996), cognitive-behavioral family management (Hogarty et al. 1991; Falloon and Coverdale 1994; Leff 1994; Tarrier et al. 1994; Schooler et al. 1997), cognitive-behavioral psychotherapy (Tarrier et al. 1993a; Tarrier et al. 1993b; Kingdon and Turkington 1994; Hogarty et al. 1995; Drury et al. 1996a; Drury et al. 1996b; Kuipers et al. 1997; Garety et al. 1997), and psychoeducational training (Eckman et al. 1992; Hornung et al. 1996). These interventions are targeted at various stages of illness, from acute treatment to long-term rehabilitation. While relatives are integrated as a rule, this concept is not always observed. The therapeutic contents cover a broad spectrum: from provision of information, medication management, coping with stressful everyday problems, and coping with persistent psychopathologic symptoms, to complex rehabilitation programs aimed at therapeutic change processes at different levels among patients and relatives. The duration of the interventions ranges from a few months to several years.

This differentiation of therapeutic procedures gives rise increasingly to the question of criteria for differential indication. From the very outset, it cannot be expected that all treatments will help all patients in the same way.

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S. Klingberg · G. Buchkremer
Department of Psychiatry, University of Tübingen,
D-72076 Tübingen

R. Holle
Institute of Medical Biometry and Informatics,
University of Heidelberg, D-69120 Heidelberg
and GSF – National Research Center for Environment and Health,
D-85764 Neuherberg

H. Schulze Mönking
St. Rochus Hospital, D-48291 Telgte

W. P. Hornung
Department of Psychiatry, University of Münster,
D-48129 Münster

S. Klingberg (✉)
Universitätsklinik für Psychiatrie und Psychotherapie,
Osianderstr. 24, D-72076 Tübingen, Germany
e-mail: stefan.klingberg@med.uni-tuebingen.de

Studies which might provide clear-cut information on better or poorer suitability of specific interventions in dependence on patient characteristics have yet to be published (Penn and Mueser 1996). Mueser et al. (1991; 1992) found that impairment of verbal memory and a higher level of symptoms at pre- and posttreatment assessments were predictors for improvement of social skills after a short inpatient-oriented social skills training. On the other hand, clinical and demographic characteristics as well as pre-treatment symptomatology did not contribute to prediction of differential treatment effects. Schaub et al. (1998) also found no predictive utility of clinical and demographic variables. Since both studies had no untreated control condition the question of treatment-specific predictors is still unanswered.

The aim of this study is to investigate which patients benefit in a special way from psychoeducational and cognitive-behavioral interventions. For this purpose the results of a controlled, prospective intervention study are analyzed to determine whether patients achieving significantly better success in the therapy group compared with the control group can be identified on the basis of pre-treatment data.

The following treatment components were used and investigated:

- psychoeducational medication management training: this group method serves to provide information on the illness and its treatment as well as to provide emotional relief of patients. It is designed to support the setting up of a functional disorder concept.
- cognitive-behavioral psychotherapy, based on the problem-solving approach, aimed at improving the ability to cope with everyday problems and persistent positive or negative symptoms.
- relatives' groups, which initially serves to take some of the strain off relatives and care-givers and is furthermore aimed at providing adequate ability to cope with problems in routine contact with patients and a better understanding of the illness and the therapeutic measures.

A detailed description of the intervention study is given in Buchkremer et al. (1997). The study design provided for an 8-month therapeutic phase and a two-year follow-up period. The intervention used in the study comprised 10 hours of psychoeducational medication management training (PMT), combined partly with 15 hours of cognitive psychotherapy (CP) in accordance with the problem-solving approach and partly with 15 hours of key person counseling (KC). Therapy fidelity was ensured by previously prepared treatment manuals, by protocols of therapy sessions and by holding supervision sessions at regular intervals. Using balanced randomization, the patients were assigned to the following conditions: PMT, PMT+CP, PMT+KC, PMT+CP+KC, control with an allocation ratio of 1:1:1:1:2. The effect of these interventions was compared with the effect of a non-specific control intervention. Within the same time frame, structured leisure-time groups were implemented with the control patients. At

2-year follow-up there was a rehospitalization rate of 38% in the total treatment group as compared to 50% in the control group. This difference was not significant. In the treatment group receiving all three therapy components (PMT+CP+KC) the lowest rehospitalization rate of 24% was found. The difference of rehospitalization rates between this group and the control group is clinically relevant. These results gave evidence to the presumption that psychoeducation alone is not sufficient and that the combination of psychoeducation, cognitive behavioral psychotherapy, and engagement of the families is necessary.

The present study focuses on interindividual differences of patients with respect to treatment outcome. The main issue of this study is the examination of the hypothesis that patients displaying more severe symptoms or poorer psychosocial adaptation benefit to a lesser degree from these specific interventions. This hypothesis reflects the experience gained in implementing the therapy.

Method

Study design

The investigation reported here is part of a randomized, controlled intervention study of relapse-prone schizophrenic patients diagnosed according to DSM-III-R, who had been stable for at least 4 weeks in an outpatient setting immediately before baseline. Patients with first-onset schizophrenia, schizoaffective psychoses, and with the comorbidity substance abuse were excluded.

The present study focuses on interactive effects which can be analyzed by virtue of the control-group design. It investigates whether the effect of the treatment differs in comparison with the control group, depending on predictor variables. To obtain a sufficiently large number of cases for this analysis, the four treatment conditions were combined. The difference between the therapy approach of all four treatment conditions and the approach of the control group seemed sufficient to justify this combination for this kind of analysis.

Patients

A total of 191 patients (80 female, 111 male) from the outpatient departments of nine psychiatric hospitals and a number of psychiatric practices were recruited between May 1989 and February 1990. The mean age of the patients was 31.3 years (SD 7.0), the mean age at onset of illness was 22.9 (SD 5.8) years, the mean number of hospitalizations was 4.7 (SD 3.6), and the total duration of hospitalization was 56.4 weeks (SD 52.5). The mean dose of CPZ equivalents was 463.9 (SD 680). 40% of the patients received depot only, 49% oral, and 11% combined oral and depot medication. Compliance was rated as good in 72% of patients. The mean GAS score was 55.1 (SD 10.4), the mean total BPRS 29.4 (SD 7.4), the mean total SANS 6.6 (SD 4.0), and the mean Strauss-Carpenter Prognosis Score 47.8 (SD 7.4). Responsibility for medication and for the decision for readmission was left with those psychiatrists who had been treating the patients prior to baseline. These psychiatrists were not members of the research team.

Measurement instruments

Case history and follow-up data were recorded with reference to the Past History and Sociodemographic Description Schedule (WHO). The prognosis was rated with the Strauss-Carpenter Prognosis Index (Strauss and Carpenter 1977) and with the Münster Prognosis Scale (MPS), a brief, readily applied, dichotomous scale

with the following items: number of hospitalizations (≤ 2 ; > 2), course of illness during the past year (favorable/unfavorable), pre-morbid social adaptation (favorable/unfavorable), and stability of the social environment (favorable/unfavorable). A favorable prognosis was assumed, if a maximum of one item was negative. (Schulze Mönking et al. 1986; Schulze Mönking and Klingberg 1997). This scale was the best course predictor in a previous, independent study (Buchkremer et al. 1991). Psychopathologic symptoms were rated according to the BPRS (Overall and Gorham 1962) and SANS (Andreasen 1989). The inter-rater reliability of the project staff was ensured by holding rater training sessions before each measurement. Other instruments used were GAS (Endicott et al. 1976), medication questionnaire with therapist rating and medication compliance, determination of total chlorpromazine equivalents, and subjective attitudes to the illness (Linden et al. 1988). Medication compliance was defined as the therapist's dichotomous rating (based on all available information) of the extent to which the patient takes his neuroleptic medication consistently, regularly without interruption, and as prescribed. These data were recorded by trained project staff who were not "blind" with respect to the group to which the patients were assigned. Readmission was defined as a stay at a psychiatric hospital for more than 36 hours or at a day-hospital for more than 7 days. In this way, only truly relevant events were to be recorded. The main endpoint of the study was readmission in follow-up time after completion of therapy. The underlying consideration was that crisis-coping strategies first have to be learned and can take effect only in the medium term. Secondary endpoints were time to first readmission and level of psychopathologic symptoms.

Measurement intervals

Data were recorded at baseline and immediately on completion of the 8-month treatment phase. Follow-up data were recorded 12 and 24 months after completion of treatment. The predictors used for this study were registered prior to the start of therapy. Data on the course of illness refer in this study to the 24-month-follow-up. At this measuring time, the data required for this study were available from 153 patients, with 38 patients having withdrawn their consent.

Statistical methods

The Institute of Medical Biometry and Informatics at the University of Heidelberg served as an independent Statistics and Data Center responsible for randomization, data entry, plausibility checks, and statistical analysis. For the outcome variables "readmission" and "psychopathologic symptoms" (improvement in BPRS score), we performed logistic regression analyses, and for the independent variable "time to first readmission" we used Cox's proportional hazard regression model. In order to control the probability of an error of the first kind, i.e., of claiming false interactions that have occurred only by chance, we selected only four predictor variables before inspection of the data. These variables were the Münster Prognosis Scale, the Global Assessment Scale, the Brief Psychiatric Rating Scale, and the Compliance Rating. These variables were taken up as forced-entry variables, with the respective interactions with treatment condition being taken additionally into account by forward stepwise selection. For verification of the proportionality assumption in Cox regression analyses, the method proposed among others by Christensen (1987) was selected, which is based on the graphical inspection of the logarithm of the cumulative hazard functions in different strata.

Results

Readmission

In the first step, a logistic regression model was calculated for the main endpoint of the study, readmission within the

Table 1 Readmission in 2-year follow-up time: logistic regression

Variable	Exp(B)	95% CI for Exp(B)		P
		Lower	Upper	
Prognosis	0.97	0.65	1.46	0.899
GAS	1.32	0.90	1.92	0.150
BPRS	0.96	0.66	1.39	0.835
Compliance	0.70	0.48	1.01	0.059
Treatment	0.71	0.48	1.05	0.087
Prognosis X Treatment	0.66	0.44	0.98	0.038

Table 2 Time from baseline to first readmission: proportional hazards regression

Variable	Exp(B)	95% CI for Exp(B)		P
		Lower	Upper	
Prognosis	0.84	0.64	1.11	0.22
GAS	1.11	0.86	1.44	0.411
BPRS	1.02	0.80	1.29	0.890
Compliance	0.72	0.57	0.91	0.006
Treatment	1.35	1.03	1.77	0.028
Prognosis X Treatment	1.54	1.18	2.02	0.002
GAS X Treatment	1.28	1.00	1.64	0.048

2-year follow-up period. As detailed above, the predictors were taken up as forced-entry variables, while the inclusion of interactions with the therapy condition was guided by step-by-step variables selection. Table 1 shows the odds ratios Exp(B), the pertinent 95% confidential intervals, and the p-values after the last step of regression analysis. The odds ratio for an event (e.g., readmission) is the ratio of the odds of the event in one group to those of another group. The odds is the probability that an event will occur divided by the probability that it will not occur. The only significant term in the regression model is the interaction of prognosis (MPS) and therapy condition ($p = .38$). The inclusion of this term contributes to a higher explanation of variance compared to a model without this term (improvement: $\chi^2 = 4.431$; $df = 1$; $p = .0353$).

In a further step, a proportional hazard regression model according to Cox was performed in the same way. The endpoint here is the time between enrollment in the study and first rehospitalization (Table 2). In the first step of regression analysis, it was only compliance that displayed a significant primary effect. In the second and third steps, significant partial correlations of the interaction variables "prognosis X treatment" and "GAS X treatment" were revealed. In the final model, the treatment variable gains a significant effect, as is shown in Table 2. The analysis of the proportionality of hazards by the method detailed above showed no violation of the proportional hazards assumption.

These results are illustrated by univariate analyses of treatment effects in subgroups defined by each predictor

Table 3 Readmission rates at two-year follow-up in treatment group and control group depending on predictors

Predictors	Percentage and number of patients readmitted at 2-year follow-up		p χ^2 test (two-tailed)
	Total treatment group	Control group	
<i>Prognosis (MPS)</i>			
Favorable	26% (10/39)	60% (9/15)	0.027
Unfavorable	51% (36/71)	45% (14/31)	0.670
<i>Global Assessment Scale</i>			
> 55	23% (11/47)	52% (12/23)	0.029
≤ 55	51% (36/70)	50% (12/24)	0.99
<i>Compliance</i>			
Favorable	35% (30/85)	49% (16/33)	0.211
Unfavorable	53% (17/32)	57% (8/14)	0.99
<i>Psychopathology (BPRS)</i>			
≤ 28	37% (22/60)	50% (13/26)	0.339
> 28	46% (25/55)	55% (11/20)	0.602
<i>Strauss-Carpenter prognosis</i>			
≥ 48 favorable	32% (19/59)	55% (17/31)	0.044
< 48 unfavorable	48% (28/58)	44% (7/16)	0.785

(Table 3). These analyses are based on all available data. Differences in sample sizes are due to missing data. For patients with an initially favorable prognostic score or social adaptation, univariate analysis reveals a significant superiority of the therapy condition. To investigate whether the results of the MPS could be reproduced by using the well-known Strauss-Carpenter Prognosis Scale, we included this in Table 3 as well. The result was comparable with that of the MPS.

The Figs. 1 and 2 show survival curves for the time to first rehospitalization. Figure 1 focuses on patients having

a favorable prognosis regarding MPS, Fig. 2 shows a comparable curve for patients having an unfavorable prognosis. The strata are the therapy condition combining psychoeducational medication management training, cognitive psychotherapy, and key-person counseling (PMT+CP+KC), on the one hand, and the control group, which had a structured leisure-time program, on the other hand. Only in patients with favorable prognosis can a relevant difference in the time to first relapse be observed (Fig. 1, Log-Rank Test, $p = .003$). No rehospitalization occurs in this therapy condition for 29 months. With an unfavorable prognosis, the course of rehospitalization is comparable in both the therapy and the control condition (Figure 2, Log-Rank Test, $p = .41$).

Psychopathology

The pretreatment median score of BPRS was 28 (Mean 29.4; SD 7.4). The median BPRS score at 2-year follow-up was 27 (Mean 28.9; SD 8.1). To analyze the interaction of predictors and treatment condition with respect to symptomatology, a dichotomous variable reflecting change in symptomatology had to be created. An improvement was defined as a reduction in total BPRS score by half a standard deviation of the baseline values (4 points). This cut-off score was chosen because the pretreatment median score was relatively low and the change to 2-year follow-up was small in the total sample. Applying a higher criterion (e.g., 8 points/one SD) would result in a very unequal number of patients in each group and, therefore, reduce the statistical power. In addition, it is important to realize that this analysis does not serve to investigate treatment response in the sense of a confirmative analysis. For this endpoint, a logistic regression model was calculated with the same strategy of variables input (Table 4). In the first

Fig. 1 Time to first rehospitalization in patients having a *favorable prognosis* that were treated in the treatment-group combining psychoeducational medication management training, cognitive psychotherapy, and key-person counseling (-----) or the control group (—)

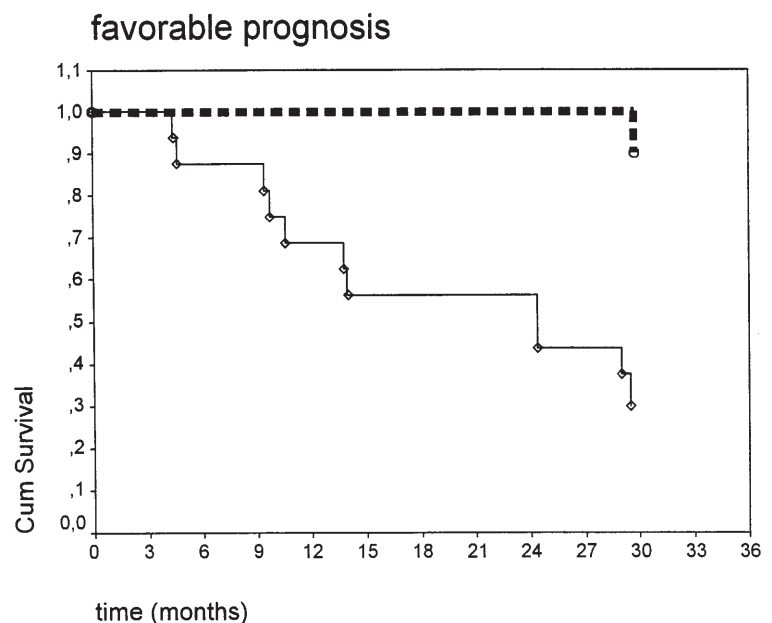


Fig. 2 Time to first rehospitalization in patients having an *unfavorable prognosis* that were treated in the treatment-group combining psychoeducational medication management training, cognitive psychotherapy, and key-person counseling (-----) or the control group (—)

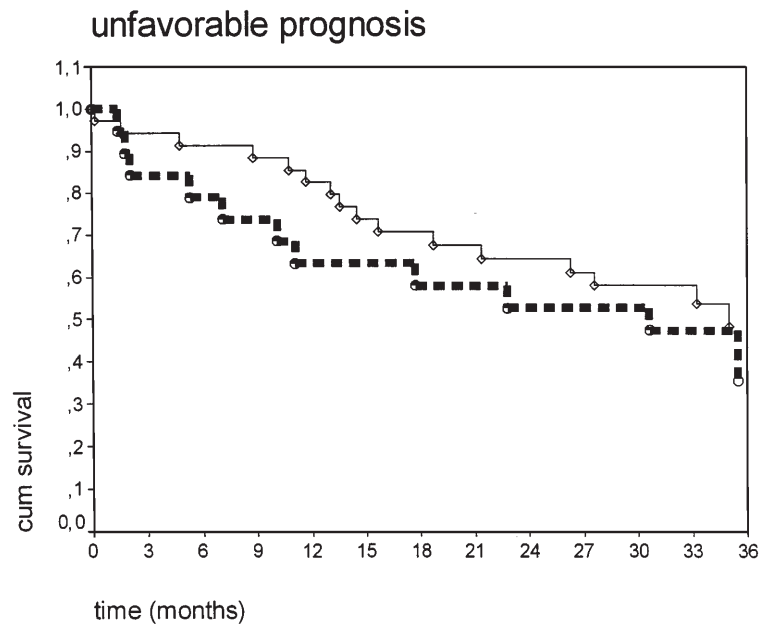


Table 4 Psychopathology (improvement in BPRS score): logistic regression

Variable	Exp(B)	95% CI for Exp(B)		P
		Lower	Upper	
Prognosis	1.36	0.72	2.58	0.347
GAS	3.29	1.71	6.36	< 0.001
BPRS	0.41	0.22	0.76	0.005
Compliance	1.77	0.86	3.61	0.119
Treatment	0.73	0.36	1.50	0.397
Compliance X Treatment	2.30	1.10	4.83	0.027

step, GAS and BPRS displayed significant partial correlations. However, since the probability of an improvement is naturally higher with initially high BPRS scores, an artificial correlation may well occur here. It must also be borne in mind that BPRS and GAS are substantially correlated. Neither for patients with favorable compliance nor for those with unfavorable compliance does the univariate analysis show a significant treatment effect with respect to psychopathological findings. However, the interaction is expressed in the fact that the improvement rate in the therapy group is markedly lower with unfavorable compliance (10%) than with favorable compliance (40%), while the improvement rates in the control group are the same with both compliance types (25%).

Discussion

Various methodologic aspects have to be taken into account before the results of this study can be interpreted. To obtain a sufficiently large number of cases for this analysis, the different therapy conditions, including those with and without relatives being integrated, had to be

combined. It must be borne in mind that relatives' groups were carried out here and that both Vaughan et al. (1992) and Buchkremer et al. (1995) reported that such groups alone had no significant impact on the course of illness, although they had positive effects on the key-persons themselves. This combining also seems justified when the therapy contents are compared with the leisure-time condition of the control group. Because psychoeducational and psychotherapeutic interventions appeal to patients as active and responsible individuals, they make high demands on patients. All therapy conditions were aimed at evolving active coping strategies with different focuses on medication, relatives, or psychological coping skills. In the control condition, in contrast, no coping skills were practised but only leisure-time structuring improved.

Selection of rehospitalization as a criterion involves numerous problems; in particular it is not a psychopathologic criterion (Falloon 1984). The monthly interviews required with a psychopathologic definition of relapse could not be carried out in this study. On the other hand, this criterion was registered under "blind" conditions, as the decision for readmission was not made by members of the study team, and the doctors making the referral were unaware of the treatment condition. Because survival-analytic methods were used, moreover, the temporal course of readmissions could be taken into account with this criterion. Psychopathologic parameters were nevertheless recorded as cross-sectional parameters and could be taken into account at least in repeated follow-ups.

The analyses described in this paper are not the primary confirmatory analysis of the study. In order to avoid a purely retrospective data-derived search for correlations, a limited number of four predictors was selected based on clinical experience gained during the study, but before inspection of the data.

Analysis of the sample characteristics reveals a sample of relapse-prone chronic schizophrenic patients with relatively good psychosocial adaptation and comparatively

few psychopathologic symptoms. Comparable samples are reported, for example, by Hogarty et al. (1986), Eckman et al. (1990), and Tarrier et al. (1993 a). This sample is well suited to the issue dealt with in this study, as all the psychosocial treatments are claimed to achieve positive effects in this group. Based on the sample characteristics, it is quite conceivable that the patients comprising this sample could also have been treated with social skills training or family therapy (provided the patient has a family). As with Linszen et al. (1996), patients from low-EE families were included.

Despite the stated methodologic problems, there seems to be some justification in drawing the following conclusions: first, it is to be recorded that the described intervention has differential effects in different patient groups. Using a very limited number of predictors, we found it is possible to register statistically significant interaction of patient characteristics and treatment outcome. This statement lends weight to the demand for intensified investigation of differential effects (Penn and Mueser 1996).

The psychopathologic symptoms showed no difference in improvement between both treatment groups, with high pretreatment BPRS scores and favorable pretreatment GAS scores correlating with the improvement. Although the interactive effect of treatment and compliance in the multiple regression analysis produces no relevant effects in univariate analysis, patients with unfavorable compliance have lower improvement rates in the therapy condition, and patients with favorable compliance have higher improvement rates than those in the control group. In this context it is important that no specific symptom reduction training was carried out, as presented among others by Kuipers et al. (1997). In the therapy groups, training was primarily in stress coping. This may have led to a longer stay in the community without having a differential effect in reducing psychopathologic symptoms.

One clear-cut differential effect with respect to readmission is reflected in the prognosis rating (MPS as well as Strauss-Carpenter Prognosis) and – to a slightly lesser extent – in the Global Assessment Scale. Patients with favorable prognosis and social adaptation had a significant better treatment outcome in the therapy condition, but not in the control condition. Various studies have shown that anamnestic data, and in particular the number of previous hospitalizations, are general predictors of the further course of illness (Mortensen and Eaton 1994; Haro et al. 1994; Hoffmann 1994). On the other hand, Mueser et al. (1991; 1992) and Schaub et al. (1998) found no predictive utility of clinical and demographic data with respect to prediction of skill acquisition. The main point here is that prognosis and social adaptation differentiate in the treatment group, but not in the control group. The given data offer some justification for the assumption that patients with a favorable prognosis have a greater potential for improving their coping strategies and benefit in a specific way. In particular, there were no readmissions during a 29-month period among patients with a favorable prognosis in the treatment group receiving the most intensive treatment offer in this respect. More precise clarification of this issue,

however, demands a more process-oriented study design in which the change of therapy-specific measurements is recorded and related to the course of illnesses. Studies of this kind are planned for the future. The content-based interpretation of prognostic measurements is problematic, however, as anamnestic data, psychopathologic ratings, and social variables are integrated here (Möller et al. 1986; Strauss and Carpenter 1977). A post hoc analysis showed that none of the four items comprising our brief prognosis scale can account on its own for the predictive significance of the total score. This emphasizes once again that prognosis scales are superior in their predictive capacity to individual variables (Möller et al. 1986). In a very broad sense, these measurements can be understood as an expression of individual vulnerability. Despite these difficulties in giving an exact description of the content of the construct in question, these variables differentiate significantly here between successful and less successful patients in the treatment group.

On the other hand, there is no significant difference in outcome with respect to prognosis in the control group. The survival curve of patients with favorable prognosis in the control group indicates a worse course compared to patients with unfavorable prognosis in the control group. However, the difference in outcome between the prognostic groups is not significant in the control group and should, therefore, not be overinterpreted.

If these results were found to be replicable, they would have clear-cut implications for decisions on indication. The recording of prognostic measurements in the psychiatric practice is unproblematic and easily performed. A more targeted indication can be expected to provide a further improvement in treatment outcome. In this respect it is relevant that the described intervention strategies prove to be superior to the control condition when account is taken of prognosis and social adaptation. As reported by Buchkremer et al. (1997), a more favorable but not significantly superior course in the collective treatment group is revealed with no further differentiation. More targeted diagnosis would entail for the patients an improvement in the treatment prognosis, as failures resulting from excessive stress or insufficient challenge could be avoided.

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