The course of schizophrenia: E. Kraepelins view and current studies

Norbert Müller*, Hans-Jürgen Möller

Abstract:
Kraepelins concept of dementia praecox and Bleulers concept of the group of schizophrenias differ mainly under the aspect of course of the disorder.
Follow-up studies play an important role for research regarding course, outcome and prognosis of psychiatric disorders, especially in terms of validation of psychiatric diagnoses and other psychiatric concepts, such as the concept of schizophrenic negative symptoms. Long-term studies also have their place in the description and evaluation of first treatment procedures. This paper will describe some general aspects of the long-term course and outcome of schizophrenic psychoses. The problem of relapses and relapse prevention will then be discussed. Especially data from recent studies will be considered in this overview.
Key-words: Schizophrenia; Kraeplin.

LONG-TERM COURSE AND OUTCOME OF SCHIZOPHRENIC PSYCHOSES

Only a few studies address the discrimination of the course of schizophrenia from that of other psychiatric illnesses. These studies basically come to the same conclusion, that the course and outcome of schizophrenia is less favourable than that of affective and schizoaffective disorders[1, 2, 3, 4, 5, 6].

Outcome description in terms of negative symptoms is of special interest. The presence of negative symptoms in schizophrenia was described early on by Kraepelin[7] and Bleuler[8]. In Kraepelin's dichotomic concept of schizophrenic versus affective psychoses, negative symptoms, conceptualized as the deficit syndrome, were fundamental. Affective disorders were regarded as having a remitting course and relatively favorable overall outcome. However, Kraepelin considered schizophrenia to be a nonremitting illness characterized by continuous deterioration with predominating negative symptoms.
More recent research in this area has criticised this dichotomic model. A subgroup of patients with affective disorders has recurrent episodes and does not have such favourable courses of illness as was once believed but develops an affective residual syndrome[9]. On the other side, studies have shown that schizophrenia is not necessarily associated with poor outcome. A large subgroup of patients experiences a phasic course without developing a deficit syndrome. This heterogeneity in outcome may depend on a variety of factors, such as biological predispositions, severity of symptoms at onset, comorbidity, expressed emotions of relatives, social support, working conditions, stressful life events, sociocultural factors and therapeutic strategies[10].

To give one example of outcome results of schizophrenic patients in comparison to affective patients some findings of our 15-year Munich follow-up study will be reported here. In this 15-year long-term follow-up study, a comparative approach was used to assess course and outcome in terms of psychopathological and psychosocial aspects for the

*Klinik für Psychiatrie und Psychotherapie der Ludwig-Maximilians-Universität

different main groups of functional psychoses (schizophrenic, schizoaffective and affective psychoses). As to the more general outcome characteristics, in terms of ICD-9, at follow-up schizophrenic patients had a significantly greater number of rehospitalisations, a longer duration of hospital stay during the follow-up period and a worse overall functioning and a greater severity of illness at the 15-year follow-up assessment than schizoaffective and affective patients. Poor outcome in terms of severity of symptoms and/or disturbances of social functioning, defined as a Global Assessment Scale (GAS) rating lower than 51, were seen cross-sectionally at follow-up in 34.21 % of the schizophrenic, 26.32% of the schizoaffective and only 3.12% of the affective patients (Table 1).

	Schizophrenic psychoses (N = 85)	Schizoaffective psychoses (N = 68)	Affective psychoses (N = 48)
Number of rehospitalisations	3.03 ± 2.93	2.79 ± 2.89	1.50 ± 1.39
Total duration of hospital stays (months)	8.30 ± 12.90	5.21 ± 7.22	2.56 ± 2.76
GAS at follow-up (mean)	58.59 ± 20.44	62.26 ± 16.83	73.06 ± 14.07
Percentage of patients with GAS<51 at follow-up	34.21	26.32	3.12
Percentage of patients with GAS>60 at follow-up	43.42	55.26	87.50
GAS max. in the year before follow-up (mean)	60.25 ± 20.28	66.34 ± 16.75	74.81 ± 13.64
Percentage of patients with GAS max. <51 in the year before follow-up	34.21	18.42	3.12
CGI (mean)	4.25 ± 1.79	3.84 ± 1.55	2.94 ± 1.08

Table 1 - Global outcome parameters. GAS <51 indicates severely ill patients, GAS>60 indicates patients with mild or no symptoms (clinical diagnoses according to ICD-9 [46].

As demonstrated in our earlier follow-up study[4], more rigid diagnostic criteria lead to a more pronounced differentiation between the outcome of schizophrenic and schizoaffective/affective patients. The psychopathological data, assessed with the AMDP system, from three points of assessment (Table 2) revealed that especially at the first admission all diagnostic groups were more or less characterised by a plethora of different psychopathological dimensions, including paranoid-hallucinatory, negative as well as affective symptoms. During hospitalisation, all psychopathological syndromes remitted to a substantial degree in all diagnostic groups. In schizophrenia the negative syndrome reached the lowest grade of remission of all assessed syndromes and was also the most prominent syndrome of all, both at the time of discharge and at follow-up. The special significance of negative symptoms for schizophrenia was underlined further by the

finding that of all psychopathological syndromes, the negative syndrome was the one that was significantly more pronounced in schizophrenic patients compared to schizoaffective or affective patients, at all times of assessment[11].

	Average percentages of the maximum summary score (mean ? SD)		
	Schizophrenic psychoses (N = 85)	Schizoaffective psychoses (N = 68)	Affective psychoses (N = 48)
Negative syndrome			
Admission	21.88 ± 12.35**$	15.44 ± 8.91$$	16.12 ± 10.32
Discharge	8.32 ± 8.63**$	2.42 ± 4.14$$	1.64 ± 3.30
Follow-up	15.77 ± 16.93**$	6.28 ± 8.23$$	4.96 ± 6.38
Paranoid-hallucinatory syndrome			
Admission	24.49 ± 17.17***$	25.11 ± 18.11&&	1.98 ± 5.16
Discharge	2.99 ± 8.08*&	0.72 ± 2.30$$	0.11 ± 0.74
Follow-up	7.03 ± 15.43*$	2.19 ± 8.43$$	0.16 ± 1.11
Depressive syndrome			
Admission	11.19 ± 10.03**$	18.29 ± 12.62&&	40.33 ± 19.81
Discharge	2.32 ± 4.68***&	1.89 ± 2.86&&	5.29 ± 7.65
Follow-up	8.30 ± 9.62***$	7.95 ± 13.72$$	6.94 ± 11.43
Manic syndrome			
Admission	10.25 ± 15.40**§	19.30 ± 16.16&&	9.72 ± 18.42
Discharge	1.96 ± 3.84***§	2.39 ± 6.16$$	1.04 ± 3.38
Follow-up	2.35 ± 4.38***§	1.81 ± 4.13$$	1.39 ± 3.68

* = P (schizophrenic vs. schizoaffective)<0.05; ** = P (schizophrenic vs. schizoaffective) < 0.01; *** = P (schizophrenic vs. schizoaffective) = not significant; & = P (schizophrenic vs. affective) < 0.05; $ = P (schizophrenic vs. affective) < 0.01
§ = P (schizophrenic vs. affective) = not significant; && = P (affective vs. schizoaffective) < 0.01; $$ = P (affective vs. schizoaffective) = not significant

Table 2 - Average percentages of the maximum summary score of AMDP syndromes at three points of assessment (clinical diagnoses according to ICD-9) [47].

The main results of this ongoing study presented here focus on negative symptoms under the leading hypothesis that negative symptoms are more prominent in schizophrenic than in affective or schizoaffective psychoses, and that in general schizophrenic patients have a more unfavourable outcome in terms of negative symptoms than patients with affective or schizoaffective psychoses[12]. At follow-up, negative symptoms (defined as a summary score greater than "0" when measured with different scales) could be observed in a remarkable number of patients. When assessed with the AMDP system, 75% of the schizophrenic, 68% of the schizoaffective patients and 44% of the patients with affective psychoses had negative symptoms. Findings with the SANS scale were comparable to those with the AMDP system. Seventy-eight percent of the patients with schizophrenia, 74% of those with schizoaffec-

tive and 47% of those with affective disorders had negative symptoms in the SANS scale. In contrast to these results, the percentage of patients with negative symptoms in the PANSS scale was lower: 59% for the schizophrenic group, 53% for the schizoaffective group and 34% for the affective group. In comparison to the results on positive symptoms, which cannot be described in detail here, negative symptoms discriminate schizophrenic psychoses on average better from other functional psychoses, especially at the 15-year follow-up when such a design with sequential cross-sectional measurements at fixed time points is used. This does not deny in any way the relevance of relapses. Of course, they are characterised predominantly by positive symptoms (see below).

The findings mentioned above indicate that negative symptoms, when assessed with different instruments at admission, discharge and follow-up, were more frequent and also more strongly expressed in schizophrenia than in both other diagnostic categories, but were not specific for schizophrenia. In order to test whether narrower concepts of the negative symptom spectrum lead to higher specificity for schizophrenia, the deficit syndrome concept described by Carpenter and colleagues[13] was applied. No patient with an affective psychosis fulfilled the criteria for the syndrome, based on AMDP data, at discharge or at follow-up. At follow-up, the number of patients with an AMDP deficit syndrome was only elevated in the schizophrenic and schizoaffective groups and not in the group of affective patients. These results underline the discriminatory power of negative symptoms in subdividing schizophrenic and affective patients.

Following a slightly modified version of the course typology suggested by Watt and colleagues[14], many more patients with schizophrenia in terms of ICD-10 had a course with relapses and residual symptoms than patients with schizoaffective or affective psychoses. Schizophrenia is more often associated with a course that is not only defined by relapses but also by residual symptoms. In detail, the results show that it is possible to make a good prediction of the long-term course of affective psychoses: 92% of cases have an episodic-fully remitting course, 5% a single episode and only 3% a chronic course. In contrast, 57% of schizophrenic psychoses have a chronic course, 40% a course with relapses and complete remission and only 3% a single episode. Only 15% of schizoaffective psychoses have a chronic course, 68% a course with relapses and complete remission, and as many as 17% single episodes. The characterisation of non-affective psychoses into schizophrenic on the one hand and schizoaffective on the other therefore allows a good prediction of the long-term course since both groups differ from each other. However, the prediction of course is not as clear-cut as for the affective psychoses because after all 43% of schizophrenic psychoses have a non-chronic and 15% of schizoaffective psychoses a chronic course.

Various characteristics were found to be predictors of outcome. In a multiple logistic regression model the „duration of untreated psychoses" (DUP) demonstrated the highest prognostic value (Table 3): a long duration of untreated psychosis is associated with a poorer outcome with respect to several outcome criteria[15, 16, 17]. Earlier studies showed that prognosis scales, which were not applied in this study, have greater prognostic value than individual predictors, particularly the Strauss-Carpenter Scale[12]. However, in comparison to other individual predictors the DUP seems to have a particularly strong predictive value, as demonstrated here. This finding, and similar findings from other studies[18], can be seen as a justification for the necessity of early diagnosis/early intervention. Under biological aspects the prognostic relevance of DUP leads to the interpretation that at least in a subgroup of patients a neurodegenerative/neurotoxic process might superimpose the earlier neurodevelopmental process in the aetiopathogenesis of schizophrenia[19, 20, 21, 22, 23].

The outcome of the study supports at least partly Emil Kraepelin's view, because in the long term outcome a high percentage of the schizophrenic patients show an unfavourable course of the disease. This result from modern studies show at the other hand that the therapeutic possibilities in schizophrenia are limited until now, especially regarding the long-term course and the negative symptoms.

Early intervention seems to have advantages for the long term course. On the other hand, research should focus on the pathophysiogy of schizophrenia in order to develop better therapeutic facilities.

	Outcome Domains									
	GAS		**SANS**		**PANSS (Negative scale)**		**PANSS (Positive scale)**		**PANSS (General psychopathology scale)**	
FACTOR	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**
Gender	2.56 **(4.97*)**	0.83-9.87 (1.21-20.34)	0.36 (0.28)	1.10-1.39 (0.07-1.12)	0.56 (0.46)	0.18-1.77 (0.13-1.53)	**0.22*** **(0.18*)**	0.06-0.81 (0.05-0.73)	0.50 (0.57)	0.15-1.66 (0.16-2.01)
Age	1.01 (1.0)	0.96-1.07 (0.94-1.06)	0.91 (0.969)	0.91-1.02 (0.91-1.02)	0.98 (0.98)	0.94-1.03 (0.93-1.03)	0.98 (0.98)	0.93-1.04 (0.93-1.04)	0.99 (1.0)	0.95-1.04 (0.94-1.05)
Mode of onset	1.20 (3.84)	0.27-5.42 (0.55-26.95)	0.85 (0.55)	0.18-4.07 (0.09-3.35)	1.27 (1.0)	0.30-5.33 (0.02-4.95)	1.61 (1.11)	0.34-7.57 (0.19-6.34)	1.07 (0.99)	0.25-4.55 (0.20-4.86)
Duration of psychosis	**0.26*** **(0.17*)**	0.9-0.78 (0.04-0.58)	**4.1*** **(4.8*)**	1.37-12.19 (1.41-16.38)	1.55 (1.82)	0.65-3.66 (0.69-4.82)	**3.11*** **(3.48*)**	1.08-8.99 (1.08-11.21)	**2.89*** **(2.91)**	1.06-7.89 (0.99-8.51)

Table 3 - Impact of prognostic factors on different outcome domains 15 years after first hospitalization. Values in parentheses represent the findings for the subgroup of patients (N=52) who were not treated with neuroleptics, or at the most for 4 weeks, prior to first hospitalization) (Based on unpublished data, Ludwig-Maximilians-University, Munich).

References

1. Grossman LS, Harrow M, Goldberg JF, Fichtner CG. Outcome of schizoaffective disorder at two long-term follow-ups: comparisons with outcome of schizophrenia and affective disorders. Am J Psychiatry 1991; 148: 1359-1365.

2. Marneros A, Deister A, Rohde A. Affektive, schizoaffektive und schizophrene Psychosen. Eine vergleichende Langzeitstudie. [Affective, schizoaffective and schizophrenic psychoses. A comparative long-term study]. Monogr Gesamtgeb Psychiatr Psychiatry Ser 1991; 65: 1-454.

3. McGlashan TH. A selective review of recent North American long-term followup studies of schizophrenia. Schizophr Bull 1988; 14: 515-542.

4. Möller HJ, Schmid Bode W, Cording-Tömmel C, Wittchen HU, Zaudig M, von Zerssen D. Psychopathological and social outcome in schizophrenia versus affective/schizoaffective psychoses and prediction of poor outcome in schizophrenia. Results from a 5-8 year follow-up. Acta Psychiatr Scand 1988; 77: 379-389.

5. Sheperd M. A Study of the Major Psychoses in an English Country. London: Chapman and Hall, 1957.

6. Tsuang MT, Woolson RF, Fleming JA. Long-term outcome of major psychoses. I. Schizophrenia and affective disorders compared with psychiatrically symptom-free surgical conditions. Arch Gen Psychiatry 1979; 36: 1295-1301.

7. Kraepelin E. Dementia Praecox. Edinburgh: E.S. Liningstone, 1919.

8. Bleuler M. Dementia Praecox or the group of schizophrenias. New York: International University Press, 1950.

9. Goldberg JF, Harrow M, Grossman LS. Course and outcome in bipolar affective disorder: a longitudinal follow-up study. Am J Psychiatry 1995; 152: 379-384.

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

11. Möller HJ, Bottlender R, Wegner U, Wittmann J, Strauß A. Long-term course of schizophrenic, affective and schizoaffective psychosis: focus on negative symptoms and their impact on global indicators of outcome. Acta Psychiatr Scand 2000; 102 (Suppl. 407): 54-57.

12. Möller HJ. Zur Vorhersage des mittelfristigen Verlaufs schizophrener Psychosen. In: Heinrich K, Klieser E, Lehmann E, (eds). Prädiktoren des Therapieverlaufs endogener Psychosen. Stuttgart New York: Schattauer, 1993: 85-105.

13. Carpenter Jr WT, Heinrichs DW, Wagman AM. Deficit and nondeficit forms of schizophrenia: the concept. Am J Psychiatry 1988; 145: 578-583.

14. Watt DC, Katz K, Shepherd M. The natural history of schizophrenia: a 5-year prospective follow-up of a representative sample of schizophrenics by means of a standardized clinical and social assessment. Psychol Med 1983; 13: 663-670.

15. Bottlender R, Sato T, Jager M, Wegener U, Wittmann J, Strauss A, et al. The impact of the duration of untreated psychosis prior to first psychiatric admission on the 15-year outcome in schizophrenia. Schizophr Res 2003; 62: 37-44.

16. Jäger M, Bottlender R, Wegner U, Wittmann J, Strauss A, Möller HJ. 15-Jahres-Katamnese schizophrener Psychosen im Vergleich zu affektiven und schizoaffektiven .

17. Möller HJ, Bottlender R, Groß A, Hoff P, Wittmann J, Wegner U, et al. The Kraepelinian dichotomy: preliminary results of a 15-year follow-up study on functional psychoses: focus on negative symptoms. Schizophr Res 2002; 56: 87-94.

18. Bottlender R, Strauß A, Möller HJ. Impact of duration of symptoms prior to first hospitalization on acute outcome in 998 schizophrenic patients. Schizophrenia Research 2000; 44: 145-150.

19. Hirsch SR, Gaind R, Rohde PD, Stevens BC, Wing JK. Outpatient maintenance of chronic schizophrenic patients with long-acting fluphenazine: double-blind placebo trial. Report to the Medical Research Council Committee on Clinical Trials in Psychiatry. Br Med J 1973; 1: 633-637.

20. Hogarty GE, Goldberg S, Schooler N, Ulrich R. Drug and sociotherapy in the aftercare of schizophrenic patients. II. Two-years relapse rates. Arch Gen Psychiatry 1974; 31: 603-608.

21. Hogarty GE, Goldberg SC. Drug and sociotherapy in the aftercare of schizophrenic patients. One-year relapse rates. Arch Gen Psychiatry 1973; 28: 54-64.

22. Müller P. Die Patienten und das Ergebnis der Rezidivprophylaxe. In: Müller P, (ed). Zur Rezidivprophylaxe schizophrener Psychosen. Stuttgart: Enke, 1982: 15-23.

23. Rifkin A, Quitkin F, Rabiner CJ, Klein DF. Fluphenazine decanoate, fluphenazine hydrochloride given orally, and placebo in remitted schizophrenics. I. Relapse rates after one year. Arch Gen Psychiatry 1977; 34: 43-47.

Chua SE, Lam IW, Tai KS, et al: Brain morphological abnormality in schizophrenia is independent of country of origin. Acta Psychiatr Scand 2003 ; 108: 269-275.

Psychosen. In: Möller HJ, Müller N, (eds). Schizophrenie: Langzeitverlauf und Langzeittherapie. Wien: Springer, 2004: 23-30.

Lieberman J, Chakos M, Wu H, et al: Longitudinal study of brain morphology in first episode schizophrenia. Biol Psychiatry 2001; 49: 487-499.