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SPECIAL ISSUE

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Depression in the long-term course of schizophrenia

Abstract Depressive symptoms are quantitatively and qualitatively among the most important characteristics of schizophrenia. The following contribution reports on the prevalence of depression in 107 patients of the ABC schizophrenia study over 12 years after first hospital admission, looks into a preponderance of depression at certain stages of the illness and the predictive value of depressive symptoms for course and outcome. All but one of the 107 patients experienced one to 10 episodes of depressed mood between index assessment and long-term follow-up. In any month of the observation period about 30–35 % of the patients presented at least one symptom of the depressive core syndrome (depressive mood, loss of pleasure, loss of interests, loss of self-confidence, feelings of guilt, suicidal thoughts/suicide attempt). Depressive symptoms are particularly frequent during a psychotic episode at a rate of approximately 50 %. There were moderate but statistically significant correlations between the amount of depressive symptoms during a psychotic episode and the frequency of relapses, defined by hospital admissions as well as the total length of inpatient treatment. Depression occurring in the interval was not associated with an increased need for inpatient treatment.

Key words schizophrenia · depressive syndrome · long-term course · stage-specific depression · prediction of outcome

Introduction

The analyses of the ABC Schizophrenia Study showing that depressive symptoms are quantitatively and qualitatively among the most important characteristics of incipient schizophrenia (Häfner et al., this volume) prompted us to study depression, its frequency, type of course and association with other psychopathological features in the early and medium-term course of schizophrenia (see Häfner et al. 1999a, 2002). The present contribution reports on first analyses from the ABC Study into depression in the long-term course of schizophrenia.

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Depressive symptoms preceding a psychotic episode

Depressive symptoms are among the earliest and most frequent signs of schizophrenia onset (Häfner et al. 2002; Yung and McGorry 1996). The lifetime prevalence rate for 'depressed mood' at first admission to inpatient treatment was over 80 % in the ABC Schizophrenia Study. The main types of occurrence were continuous and episodic (Häfner et al. 1995, 1999a). Compared with age- and sex-matched healthy controls patients with schizophrenia showed 2 to 3 times higher cumulative prevalence rates for depression.

In the further course of schizophrenia depressive symptoms are among the most frequent signs of an imminent relapse (e. g., Gaebel et al. 2000; Herz and Melville 1980; Hirsch and Jolley 1989; Subotnik and Nuechterlein 1988; Tarrier et al. 1991). In a first systematic retrospective study of prodromal symptoms based on 145 patients with schizophrenia and 81 family members Herz and Melville (1980) found that depressive symptoms are the most prevalent prodromal signs, reported by over 60 % of the probands and over 75 % of the family members. Comparably high rates have been reported by Birchwood et al. (1989, and this volume), who interviewed key informants of 42 patients. Tarrier and colleagues (1991) concluded from their analysis of prodromal symptoms in 56 patients suffering from schizophrenia that psychotic relapses can be predicted in 75 % of cases on the basis of increasing scores for hallucina-

tions and depressive symptoms in the last two months preceding a relapse.

Depressive symptoms in a psychotic episode

Bleuler (1911) already observed the occurrence of depressive symptoms in schizophrenia in such a frequency that he came to regard depression as a genuine part of the illness process. Meanwhile, several studies have confirmed the close association between depressive symptoms and acute psychotic episodes reflected for example in the finding that the amount of depressive symptoms correlates negatively with remitting psychotic symptoms (Donlon et al. 1976; Knights and Hirsch 1981). The high prevalence rates of depressive symptoms in psychotic episodes seem to be particularly pronounced at the early course of the disorder (Addington et al. 1998; Koreen et al. 1993). In the study of Addington et al. (1998) depression scores were significantly elevated in first episodes of schizophrenia compared with relapses. But in chronic schizophrenia, a moderate association has also been found between depressive symptoms and symptoms such as hallucinations and poverty of speech (Barnes et al. 1989).

Depressive symptoms following a psychotic episode

Postpsychotic depression (PPD) is defined as a corollary of psychotic exacerbation that manifests itself when psychotic symptoms remit (McGlashan and Carpenter 1976; Steinberg et al. 1967; Stern et al. 1972). PPD is presumed to persist over a defined period of time, in some cases even for months. The clinical picture may include all characteristics of the depressive syndrome. PPD has also been included in the ICD-10 as post-schizophrenic depression. The diagnosis (F20.4) is limited to cases presenting a prolonged depressive episode in the aftermath of a psychotic episode irrespective of whether depression is regarded as a new development, part of the disease process or as a reaction to the illness.

Depressive symptoms without a direct, temporal association with a psychotic episode

The main causes of depressive symptoms in this category are

- Responses to psychological stress or deficits: especially patients experiencing psychotic deterioration or suffering from chronic schizophrenia are often well aware of their deficits in various domains (Birchwood et al. 1993; Birchwood, this volume; Liddle et al. 1993);
- Side-effects of neuroleptic medications: especially 1st-generation neuroleptics have been observed to produce extrapyramidal side-effects and depressive symptoms (Siris 1987; van Putten and Marder 1987);
- Alcohol and drug abuse, a frequent comorbidity disorder of schizophrenia (Bühler et al. 2002; Schuckit 1983; Weissman and Myers 1980), is associated with an increased rate for depression;
- Other (organic) diseases (Hall et al. 1981): according to Bartels and Drake (1988) physical diseases associated with depression – some go unrecognised – frequently occur in the course of schizophrenia.

Besides the aetiological heterogeneity of depression a further difficulty in studying depressive symptoms in schizophrenia is the overlap between the depressive and the negative syndrome (Carpenter et al. 1985; Siris et al. 1988). McGlashan (1982) suggested diagnosing depression by psychological characteristics only, such as sadness, feelings of guilt, hopelessness and lack of self-confidence; in contrast, negative symptoms could be identified by affective symptoms such as reduced or flat affect. Although Kay and colleagues (1987) were able to show on the basis of the Positive and Negative Syndrome Scale (PANSS) that negative symptoms do not correlate with depressive symptoms, there are recent findings indicating that distinguishing the two syndromes is not that easy (Collins et al. 1996; Fitzgerald et al. 2002).

In sum, the picture is a complex one. It is hardly possible to decide on the basis of a cross-sectional assessment whether depressive symptoms indicate an imminent relapse, represent a side-effect of neuroleptic medication or a postpsychotic syndrome produced by a preceding psychotic exacerbation or is attributable to an independent cause.

Our knowledge of the prognostic power of depressive symptoms for course and outcome in schizophrenia is incomplete. Depressive symptoms in the early course prior to first admission predict a greater severity of the first psychotic episode and a significantly higher number of positive and depressive symptoms and less affective flattening in the medium-term course (five years; Häfner et al. 1999a). While depressive symptoms appearing in the psychotic episode are seen as indicating a favourable course of schizophrenia (Emsley et al. 1999; Kay and Lindenmayer 1987; Vaillant 1964), depressive symptoms occurring in the psychosis-free interval seem to be associated with an unfavourable course (Bartels and Drake 1988; Becker 1988; Johnson 1981).

To study the role of depressive symptoms in the course of schizophrenia in an appropriate way and to assess their prognostic power, Koreen and colleagues (1993) were among the first to address these questions in a prospective study. The authors collected information on psychotic and depressive symptoms in 70 first-episode patients of schizophrenia at first every two weeks, later monthly over a total period of five years. Depending on the operational definition used they found, at the beginning of the study, prevalence rates for depressive symptoms ranging from 52 % (Hamilton Crite-

ria; Endicott et al. 1981) to 22 % (Hamilton criteria plus RDC criteria; Spitzer et al. 1975). The authors observed a highly significant correlation between psychosis and depression. In most cases depressive symptoms disappeared with remitting psychosis.

Questions studied

In the following we will present results on the prevalence and course of depressive symptoms in schizophrenia. These data are based on 107 patients from the ABC Schizophrenia Study who participated in the long-term follow-up at a mean of 12 years after first admission to inpatient treatment. Following our previous results on depression in the early and medium-term course of schizophrenia and with reference to the study conducted by Koreen et al. (1993) we analysed the following questions:

1. How prevalent are depressive symptoms in first-episode patients of schizophrenia followed up over a period of 12 years after first admission?
2. At which stages of illness – from the first psychotic episode on – do depressive symptoms mostly occur during the long-term course?
3. Are depressive symptoms associated with course and outcome criteria?

Samples

In the ABC Study initial assessments were done in the years 1987 to 1989. The original sample comprised consecutive first admissions to any of ten adult and child- and adolescent psychiatric hospitals and units serving a semi-urban, semi-rural population of 1.5 million in Mannheim, Ludwigshafen, Heidelberg, Rhine-Neckar District and Eastern Palatinate. The inclusion criteria were a broad clinical diagnosis of schizophrenia (ICD-9: 295, 297, 298.3, 298.4) and age between 12 and 59 years. Exclusion criteria were diagnosed or suspected organic psychosis or severe mental retardation. The study population has been described in detail elsewhere (Häfner et al. 1994; Häfner, this volume).

276 patients were included in the study (*first-admission sample*); 232 patients (= 84 % of the first-admission sample) were in their first psychotic episodes (*first-episode sample;* Fig. 1). 130 patients of the first-admission sample – of these 115 were first episodes – were followed up at 6 months, 1, 2, 3 and 5 years.

Long-term follow-up assessments started in the spring of 1999. Despite great efforts on the part of the interviewers only 107 probands – 46 % of the first-episode sample – could be interviewed. Since the first wave of assessment 24 probands had died, 11 persons could not be reached and 90 persons refused to participate. Based on these 107 probands a mean period of 12.3 years (range: 11.2 to 14.6 years) had elapsed from first admission.

To obtain data for judging the level of social development and the social status of patients with schizophrenia at 12-year follow-up population controls from the study area matched by age and sex to the 107 probands with schizophrenia were interviewed on phone using a shortened version of the IRAOS (see below).

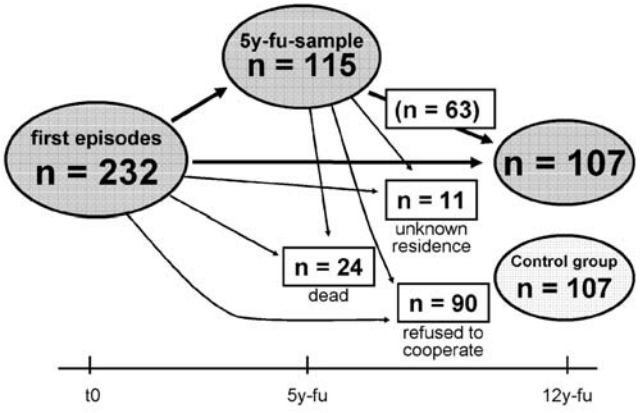

Fig. 1 ABC study: Participants over 12 years after first hospital admission

Assessment instruments

The instruments used at the long-term follow-up had to include those used at the initial assessment and at five-year follow-up. For instance the following instrument were applied: IRAOS (see below), SANS – Scale for the Assessment of Negative Symptoms (Andreasen 1989); PSE – Present State Examination (Wing et al. 1974) for measuring psychopathology; PIRS – Psychological Impairment Rating Scale (Biehl et al. 1989); DAS-M – Disability Assessment Schedule (Jung et al. 1989). With the exception of the IRAOS all these instruments were used at all the cross sections.

The main instrument of the ABC study is the "*Interview for the Retrospective Assessment of the Onset of Schizophrenia*" (IRAOS). Originally developed for studying incipient schizophrenia (Häfner et al. 1990), the instrument has been expanded in scope now permitting the assessment of the course of any type of psychotic illness (Häfner et al. 1999b, 2003). The following domains are included:

- Symptoms – also comprising unspecific and prodromal symptoms as well as deviant behaviour.
- Psychological/social and functional impairment.
- Objective social indicators.
- Help-seeking behaviour (contacts with counselling and health services) and therapeutic interventions.

All this information is collected retrospectively for the period in question (illness onset – last assessment) and entered in a time matrix. The reliability of the retrospectively gathered information on symptoms and signs of illness was tested and found to be satisfactory (Häfner et al. 1990).

The IRAOS is based on modules. The section on

symptoms encompasses a total of 128 symptoms and signs of illness allowing their beginning, end and type of course being documented even in case of multiple occurrence. Of these 128 symptoms 18 can be subsumed under the depressive syndrome (Table 1). To avoid overlap with the negative syndrome and to ensure compatibility with analyses based on the first IRAOS version the subsequent analyses of the depressive core syndrome will be limited to the following symptoms[1]: 1) depressive mood (including loss of pleasure and loss of interests), 2) loss of self-confidence, 3) feelings of guilt, 4) suicidal thoughts/suicide attempt.

All these indicators except one (loss of pleasure) are also included in the PSE. Hence, we were able to calculate prevalence rates at any cross section in the five-year period and at the long-term follow-up also on the PSE data: (a) proportions of patients presenting at least one of the core symptoms in a moderate or severe form (rated 1 or 2 in the PSE; suicidal thoughts/attempted suicide: rated 1 to 3), (b) proportion of patients presenting at least one of the three core symptoms in a severe form (rated 2 in the PSE; suicidal thoughts/attempted suicide: rated 2 to 3). Comparing the prevalence rates based on the IRAOS and the PSE at the seven cross sections in those 63 patients who participated in both 5- and 12-year follow-up (Fig. 1), we found that the prevalence figures showed parallel courses and, apart from two exceptions (first admission[2] 3 years later), the IRAOS figures lay between those based on the two operational PSE definitions (Fig. 2).

Table 1 IRAOS: 18 indicators of psychiatric illness from the depressive syndrome

Depressive mood
Loss of pleasure
Increased tiredness, love of drive
Loss of self-confidence
Loss of self-esteem
Feelings of guilt
Pessimism, hopelessness
Thoughts of death, suicidal thoughts
Suicide attempt
Feeling worst early in the morning
Lack of concentration
Loss of interests
Difficulties getting off to sleep
Early morning wakening
Sleeplessness
Increased appetite
Loss of appetite
Loss of weight

A further section of the IRAOS ("Episodes and intervals of mental disorder") focuses on the documentation of episodes. In the ABC Study a psychotic episode was defined as "a period of psychiatric symptoms, which is preceded and followed by 30 days during which the patient is symptom-free" or as a clear-cut exacerbation of symptoms,"... whereas a state not entirely symptom free but of relative stability ... could be observed during the 30 days before and after this period" (Häfner et al. 2003, p. 21). Documented are the onset and end of an episode, psychotic or non-psychotic, main symptoms and treatment modalities.

Results

Representativity and description of the long-term follow-up sample

One of the major difficulties in prospective long-term follow-up studies of schizophrenia covering more than 10 years is attrition between first assessment and follow-up. In the *NIMH Longitudinal Study of Chronic Schizophrenia* Carpenter and Strauss (1991) were able to assess only 40 % of the initial sample 11 years after first admission. In the *Vermont Longitudinal Study* (Harding et al. 1987) 62 % were interviewed on average 32 years later, in the *Chestnut Lodge Study* (McGlashan 1984) 65 % on average 15 years later.

As shown in Fig. 1, just under half (46 %) of the ABC Study first-episode sample could be re-assessed an average of 12 years after initial assessment. For this reason it had to be tested whether the 107 probands assessed at 12-year follow-up were representative of the sample interviewed at first assessment.

For this purpose we compared the age and gender distributions and various characteristics of the early illness course (Table 2). We tested whether the proportion of females at follow-up had changed and whether the proband's age in the follow-up sample when they first fulfilled various criteria for illness onset was comparable with that age in the original sample. Since all the age distributions differed highly significantly from a normal distribution (Shapiro-Wilk test for normality), the analyses were based on medians.

None of the characteristics tested differed significantly between the first-episode and the follow-up sample. At follow-up 12 years after first admission to inpatient treatment under a diagnosis of schizophrenia the

[1] Our previous analyses of the depressive core syndrome (e. g. Häfner et al., 1999a) were based on the following four symptoms: depressive mood, loss of self-confidence, feelings of guilt, attempted suicide. When the IRAOS section on symptoms and signs was expanded from 66 symptoms in the first version to 128 symptoms in the current version, the symptom *depressive mood* was split into *depressive mood*, *loss of pleasure* and *loss of interests* in accordance with the operational definition of that symptom; *attempted suicide*, a rare event, has been supplemented by more frequent *suicidal thoughts* in the current version.

[2] A weakness of the comparisons based on the first assessment is that the four weeks covered by the PSE interview fall primarily in the pre-treatment period preceding first admission, in which the probands were not yet on medication, while the first assessment done with the IRAOS covers the first month following first admission and thus a period under therapy.

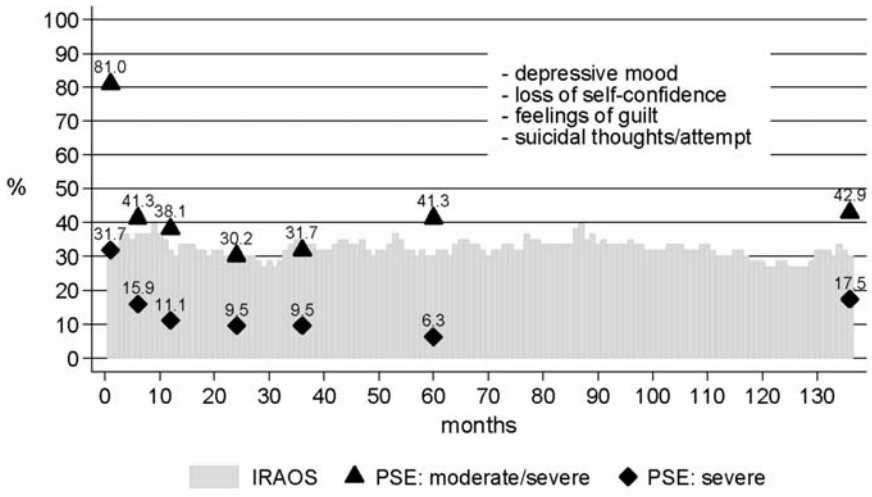

Fig. 2 Course of depressive core syndrome: IRAOS vs. PSE (prevalence per month over the period of 136 months (n = 63))

Table 2 ABC sample at baseline and at 12y-fu: testing for differences

	ABC sample		p	test
	t0 (n = 232)	12y-fu (n = 107)		
Proportion of women	53.5 %	55.1 %	n. s.	Chi^2 goodness of fit
Age at	21.5	21.3	n. s.	Wilcoxon signed-rank test
…. first sign (median)				
…. first negative symptom (median)	23.3	22.8	n. s.	Wilcoxon signed-rank test
…. first positive symptom (median)	25.8	25.4	n. s.	Wilcoxon signed-rank test
…. maximum of positive symptoms (median)	27.5	26.4	n. s.	Wilcoxon signed-rank test
…. first hospital admission (median)	27.5	26.5	n. s.	Wilcoxon signed-rank test

sample comprised 48 men and 59 women (44.9 % vs. 55.1 %); at first assessment the respective figures had been 46.5 % vs. 53.5 %. Women at follow-up had a mean age of 44.1 years (median = 41.7), and men 38.7 years (median = 36.4).

Just under one third (32.7 %) of the follow-up sample had a regular job at follow-up, 11.2 % were unemployed. Since the initial assessment the unemployment rate in the sample had come down almost by half, but this result was almost entirely accounted for by the fact that at the final assessment 25.2 % of the patients were eligible for disability pensions. For 10.2 % sheltered work played a minor role. In this domain the differences to population controls/PC were highly significant: regular job 70.1 %; unemployment 1.9 %; disability pension 2.8 %.

Almost half of the patients (46.7 %; PC: 21.5 %) were single and about one third (34.5 %; PC: 69.2 %) were married. The proportion of divorced was twice as high in the sample (13.1 %) as among controls (6.5 %).

In the ABC cohort a total of 501 admissions to inpatient treatment were counted in the follow-up period. Of this period with a mean duration of 12.3 years from first admission to final assessment each proband spent 11.3 months or 7.7 % of the time on average in the hospital. Most readmissions occurred in the first year following first admission. Over the years a trend towards a decreasing need for inpatient treatment emerged. However, the number of inpatient treatments showed a very uneven distribution in the cohort: in about one fourth of the probands first admission was the only instance of inpatient treatment in the period studied. Twenty-four patients, and thus fewer than one-third of the sample, accounted for about half of the total inpatient episodes.

Prevalence of depressive symptoms in the long-term course

As stated above, the mean follow-up period as based on the 107 probands was 12.3 years with a range from 134 to 174 months. Consequently, at 11 years and two months the first patient was excluded from the analysis. To obtain a uniform basis for the subsequent analyses, the follow-up period for each patient was limited to 136 months following first admission.

Table 3 shows the frequencies at which the core

Table 3 Number and mean duration of depressive symptoms in the long-term course of schizophrenia

Number	Depressive mood*	Loss of self-confidence	Feelings of guilt	Suicidal thoughts/ attempt
0	1	28	60	47
1	45	57	39	31
2	25	15	5	9
3	14	3	3	6
4	5	2	–	4
5	6	2	–	2
6–10	4	–	–	1
Total number	215	114	58	99
Mean duration/pb	39.9 months	28.1 months	8.3 months	5.4 months

* including loss of pleasure and loss of interests

symptoms of the depressive syndrome occurred in the follow-up sample after first admission. Depressed mood (including loss of pleasure and loss of interests) was the core symptom showing the highest frequency. A total of 215 spells were recorded for this symptom. Of the 107 patients, 106 experienced one to 10 episodes of depressed mood.

To calculate symptom prevalence the percentages of patients presenting at least one of the core depressive symptoms were determined for each month of the observation period (Fig. 2). At first admission the prevalence of moderate or severe depressive episodes – as based on PSE-9 – was 81.0%. In the first months following the first hospital admission the figure shows a short-term increase to about 40% and fairly stable values around 30–35% in the remaining period. These figures are somewhat higher than the modal value (about 25%) reported by Siris and Bench (2003) from their meta-analysis of various empirical studies. It is remarkable that no essential increase or decrease in the proportion of patients affected occurs in the long term.

The association between a psychotic relapse and depression

Depressive symptoms representing an integral part of the psychotic episode should be manifest particularly *during* the episode, and decrease to a lower level in the interval between episodes.

The analysis depicted in Fig. 2 did not permit us to draw any such conclusions about the role of the depressive syndrome in the course of schizophrenia, because – apart from the first months following first admission – probands' individual stage of illness in the follow-up period was not considered in this context. The approach needed is to link these data with information about psychotic episodes, gathered by the IRAOS section "Episodes and intervals of mental disorder" on the documentation of psychotic episodes and the IRAOS section "Indicators of psychiatric illness" on symptoms and signs.

In the following analyses of the association between depressive symptoms and psychotic episodes (as defined in the paragraph preceding the 'Results' section) all those episodes defined exclusively by one or more of the depression characteristics listed in Table 1 will be excluded.

In a first step all the episodes recorded for the 107 patients as occurring after discharge from first inpatient treatment were arranged chronologically. Next we determined for each patient individually how the occurrence of depressive spells indicated by the IRAOS section on symptoms and signs temporarily relates to the onset of psychotic episodes. Finally, we calculated the proportion of patients presenting at least one of the depressive core symptoms in each of the 10 months preceding and following the onset of a psychotic episode. The result as based on a total of 333 episodes is depicted in Fig. 3a.

The result seems clear. While in the ten months preceding a psychotic episode the prevalence rates vary fairly uniformly around 30%, they rise to just under 50% in the first two months following the onset of the psychotic episode, steadily falling in the subsequent period. Hence, depressive symptoms seem first and foremost to be an integral part of the schizophrenic episode in psychotic relapses.

As stated before, the onset of an episode was identified by the interviewer on the basis of all information available and according to the definition (cf. section "Assessment instruments"). This procedure does not allow putting the symptoms in a chronological order. Therefore we cannot distinguish whether the increase of a depressive symptom in a given month was preceded, accompanied or followed by other psychotic symptoms constituting the episode, a prerequisite to define prodromal symptoms. We also cannot decide on the basis of this preliminary analysis whether the depressive syndrome occurs as a direct reaction to the ongoing psychotic episode or just as part of the symptoms of the episode – like delusions and hallucinations. Analyses of how schizophrenia develops (see Häfner et al., this volume) have shown that depressive symptoms start frequently in the prodromal stage to accumulate long before positive symptoms appear in the first psychotic episode. This suggests that it is the underlying neurodegenerative or dysfunctional process that brings fourth both symptom categories in a clear-cut order in incipient schizophrenia (Häfner et al., this volume).

One might presume that a depressive syndrome occurring as a reaction to the stressful experience of a psychotic episode is more pronounced at first occurrence than at repeated manifestations. A possible habituation should be reflected in smaller increases in the prevalence of the depressive syndrome in later episodes. Besides a higher prevalence of depressive symptoms in the first episode (see Häfner et al., this volume) the separate analysis of the first, second, third and later psychotic

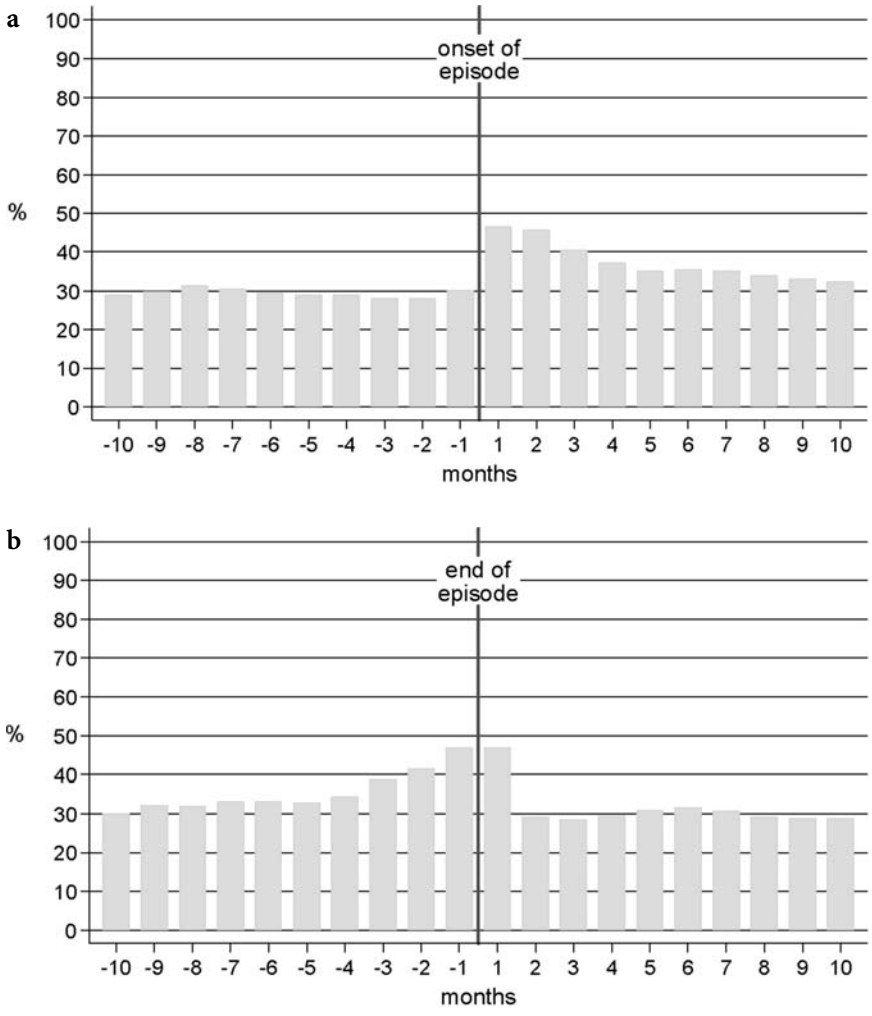

Fig. 3 Depression before (**a**) and after (**b**) the onset of a psychotic episode (prevalence per month (n = 333 psychotic episodes))

episodes after first hospital admission did not yield any substantial differences in the depression rates.

To analyse prevalence rates and trends of depressive symptoms after remission of the psychotic episode an analogous approach was adopted, the only difference being that the occurrence of depressive symptoms was now related to the end of the psychotic episode. Fig. 3b shows the result for the total of 333 psychotic episodes.

This result, too, is fairly clear-cut: depressive symptoms are particularly frequent before the end of the psychotic episode at a rate approximating 50 %. This high rate continues to persist in the first month following the end of the episode, thereafter markedly falling to values just over 30 %. The short-term persistence at a fairly high level after the end of the psychotic episode does not qualify the depressive syndrome as postpsychotic depression, because per definition the rates should have started to increase only after the remission of the episode. However, this does not rule out short-term depressive reactions to the stressful experience of the psychosis.

Basically these results do not exclude the plausibility of hypotheses postulating other causes for the occurrence of depressive symptoms in the course of schizophrenia. However, these possible alternative effects are probably not strong enough to mask the associations detected to any substantial degree, overall indicating their weaker impact.

Depressive symptoms as predictors of course and outcome

The follow-up data collected in the ABC Study permitted us to examine hypotheses about associations between depressive symptoms occurring in the psychotic episode and in the interval between episodes and to test how they influence the illness course. For this purpose, again, information from the IRAOS sections on the documentation of episodes (onset and end of psychotic episodes) and symptoms and signs (onset and end of spells with depressive symptoms) was linked (cf. appendix).

Included in the analysis were a total of 417 psychotic episodes, a mean of 3.9 episodes per patient (median: 3; range: 1 to 27)[3].

[3] The higher number of episodes compared to Fig. 3 is accounted for by the fact that in the following analysis we also included psychotic episodes coinciding with the first inpatient treatment.

Table 4 Statistics on episodes and intervals with/without depressive symptoms

	mean	median	range
(a) months 'in episode'	13.7	11	0–52
(b) months with depressive core symptoms	47.1	14	0–136
(c) months 'in episode' with depressive core symptoms	7.0	3	0–52
(d) months 'in interval' with depressive core symptoms	40.1	6	0–136
(e) share of (c) on time 'in episode'	42.4%	33.3%	0–100%
(f) share of (d) on time 'in interval'	33,3%	5,3%	0–100%

The probands spent an average of 13.7 months (median: 11) in a psychotic episode (Table 4). This makes up 10.1 % of the follow-up period of 136 months. Each patient spent an average of about 47 months with manifest depressive symptoms. Seven of the months spent with depressive symptoms fell in a psychotic episode. A comparison of means and medians shows that all these distributions are strongly skewed to the right.

For analysing the association between depressive symptoms and schizophrenia outcome we used the following course and outcome criteria: number of readmissions to hospital in the follow-up period and total length of inpatient treatment. Proceeding from the literature (e. g. Becker 1988; Emsley et al. 1999, see above) the following hypotheses were tested:

1. The higher the proportion of time spent with manifest depressive symptoms during psychotic episodes, the lower the number of readmissions and the shorter the total length of inpatient treatment.
2. The higher the proportion of time spent with depressive symptoms in the interval between psychotic episodes, the higher the number of readmissions and the longer the total length of inpatient treatment.

We presumed the effects to be particularly pronounced in probands showing a reciprocal relation of these proportions (high proportion of time spent with depression in the interval and low proportion in the episode and vice versa). Computing the association between the proportions of time with depression in the episode and in the interval we found, however, that both are fairly highly correlated (Spearman's rank correlation rho: 0.79; $p < 0.001$): patients who spend a high proportion of time with depression in episodes also spend a higher proportion of time with depression in the intervals and vice versa.

To study how these two features are associated with the course/outcome criteria, again, Spearman's rank correlations were computed because of the skewed distributions of the variables included. This procedure allowed us to determine monotonous associations between two variables.

The results were moderate, but statistically significant correlations between the amount of depressive symptoms in the episode and the frequency of readmissions (Spearman's rho: 0.21; $p < 0.05$) and the total length of inpatient treatment (Spearman's rho: 0.27; $p < 0.01$). In contrast, there was no substantial association between depressive symptoms in the interval and frequency of hospital stays (Spearman's rho: 0.10; p = n. s.) or total length of inpatient treatment (Spearman's rho:.17; p = n. s.). Fig. 4 illustrates the association on the basis of the study population divided into two groups by the median of depressive symptoms.

Patients showing fewer depressive symptoms in the episode (< median) had an average of four readmissions in the follow-up period, whereas those with a greater frequency of depressive symptoms (> median) had 5.2 readmissions. On the criterion *total length of inpatient treatment* the difference between these two groups was about 100 days. A frequency of depressive symptoms above or below the average in the interval had no such impact on the need for inpatient treatment.

Hence, our results failed to support the hypotheses derived from the literature that a higher frequency of depressive symptoms in psychosis is a predictor of fewer relapses (Emsley et al. 1999; Kay and Lindenmayer 1987). In our prospective analyses of the 5-year illness course at five cross sections following first admission we had shown that depression in the early course is a significant predictor of a higher frequency of depressive and psychotic symptoms, but of less affective flattening in the further course. Depression occurring in the psychotic episode is also associated with a greater need for inpatient treatment in the long-term course.

Discussion

Our main result on the prevalence of depressive symptoms in the long-term course of schizophrenia was that in any month over a follow-up period of about 12 years about 30–35 % of the patients with schizophrenia present at least one of the core symptoms of the depressive syndrome[4]. This does not mean that in individual cases the prevalence of depressive symptoms remains stable and is not subject to considerable variation with episodes and intervals. The frequency of depressive symptoms – and this is another major finding – seems to be independent of the duration of illness. The fact that the rates calculated on the basis of IRAOS data coincide with the cross-sectionally collected PSE data is an indication of the validity of the finding.

Regarding the association between depression and psychotic relapses, the data for the ABC sample showed that depressive symptoms increase along with the onset

[4] The considerable difference to the prevalence rates before first admission (cf. Häfner et al., this volume) is probably attributable to lack of pharmacological treatment at the prodromal stage. The analyses of the medium-term course (Häfner et al., 2002), too, showed falling prevalence rates for depressive episodes (according to ICD-10) from 73.9 % at first admission to 27 % six months later.

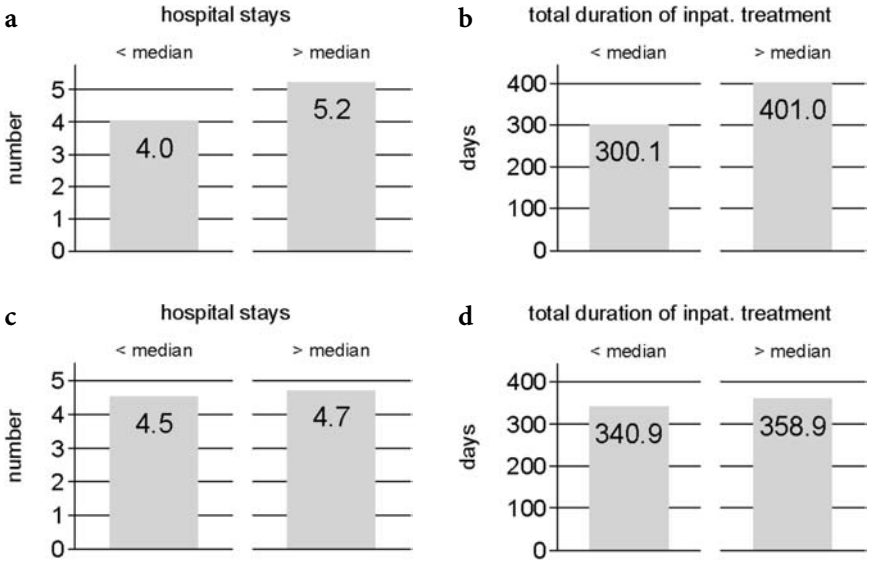

Fig. 4 The impact of depressive symptoms in episode on hospital stays (**a**) and total duration of inpatient treatment (**b**). The impact of depressive symptoms in interval on hospital stays (**c**) and total duration of inpatient treatment (**d**)

of the psychotic episode and decline shortly after the remission of psychotic symptoms. In that respect our results are basically in line with those reported by Koreen and colleagues (1993) from their study of new cases of schizophrenia. These authors found a significant association between psychotic episodes and depressive symptoms: Depressive symptoms declined with the remitting episode. Similar findings have also been reported by Green and colleagues (1990) from their study of 27 patients with an RDC diagnosis of schizophrenia or schizoaffective disorder. Their data, collected using an extended version of the BPRS (Lukoff et al. 1986) on a two-week basis over a mean period of 153 weeks, showed that depressive symptoms correlated only with psychotic exacerbation.

Depression occurring in a psychotic episode seems to be associated with an increased need for inpatient treatment, whereas depression occurring in an interval is not. This association is not very strong. But marked differences were not expected to emerge anyway because of the strong correlation we found between the proportions of time spent with depression in episodes versus intervals. Patients who suffer from depression for longer than average do so fairly independently of the illness stage.

Depressive symptoms are a heterogeneous category regarding their causes. The only regularity their occurrence showed in our analyses was their coincidence with psychotic symptoms. This result could be interpreted as indicating that in a core group of patients depressive symptoms are part of the process of schizophrenia (cf. Häfner et al., this volume). A finding pointing to this direction was that the proportion of depressed patients did not decline even long after schizophrenia onset or in relapse episodes. This might also explain why a higher prevalence of depressive symptoms is associated with a greater need for inpatient treatment.

Our results do not rule out the effects of other causes. Depression occurring as a psychological reaction to experienced disability and its consequences is not tied to certain phases of illness, but might offer an explanation for the high baseline rate of depression of about 30 % in the interval.

Appendix

Depression and outcome: an analytic strategy

Formally, linking information from the IRAOS section on the documentation of episodes and the section on symptoms and signs provides a picture shown as Fig. 5.

Over the course of schizophrenia we can distinguish: 1) episodes and stages of psychotic episodes with versus without manifest depressive symptoms, and 2) intervals (= periods between two episodes) and stages of intervals with versus without depressive symptoms[5].

On the basis of this information we can determine for each patient for how long that patient presented depressive symptoms in a schizophrenic episode or in an interval. In practice the observation period was divided into months. As stated, the period analysed was limited to 136 months following first admission. For each patient information was available on the onset and end of psychotic episodes and the onset and end of spells with depressive symptoms[5].

Complementary, periods were defined as time spent 'in interval' and 'without depressive symptoms'. In sum, the following statistics were computed for each patient: (a) months 'in psychotic episode', (b) months with depressive core symptoms, (c) months 'in psychotic episode' with depressive core symptoms, (d) months 'in interval' with depressive core symptoms.

The indices (c) and (d) were related to the total time spent 'in psychotic episode' or 'in interval' and correlated with the outcome measures.

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[5] at least one of the following: depressive mood, loss of pleasure, loss of interests, loss of self-confidence, feelings of guilt, suicidal thoughts, attempted suicide

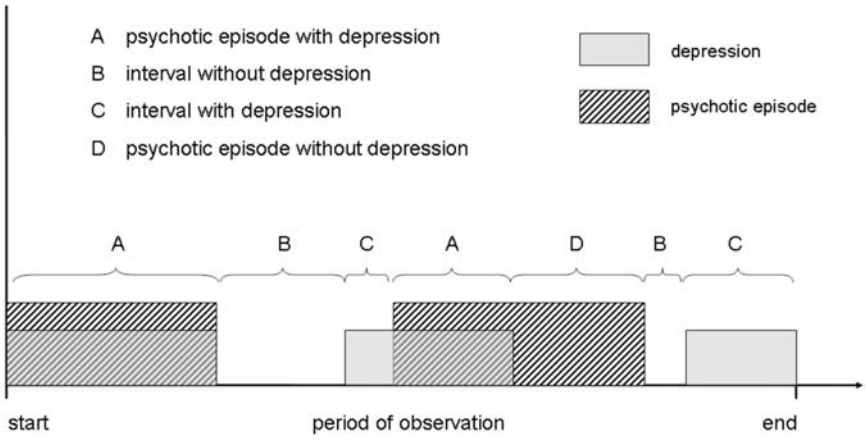

Fig. 5 Schizophrenic episodes and depressive core syndrome: variables for analysis

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