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One-year Follow-up of Panic Disorder

Outcome and Prognostic Factors

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Summary. A 1-year follow-up study was carried out in 77 patients with panic attacks (panic disorder). Of these patients 43% were remitted; avoidance behaviour and chronic anxiety were more persistent than panic attacks within the 1-year period. The main predictor for features of anxiety in the follow-up was avoidance behaviour. The most prominent prognostic factor for features of depression was the history of previous depressive episodes. Female patients had a poorer outcome than male patients.

Key words: Panic attacks – Follow-up study – Prognosis – Classification – DSM-III-R

Introduction

Panic disorders have been validated by phenomenological, treatment-response and family studies (Klein 1981; Noyes et al. 1986; Leckman et al. 1983; Zitrin et al. 1983). Another aspect contributing to the diagnostic validity – the course of the disorder – has not so far been investigated adequately. The validity of panic disorders has been supported in comparison with primary unipolar depression by a retrospective follow-up study (Coryell et al. 1983). However, apart from this retrospective study, there has been little published about the course of panic disorder; also, predictors of the course of panic disorder are unknown.

Previously, the diagnosis of anxiety neurosis (e.g. in ICD-9) was made in patients with spontaneous panic attacks. Several retrospective studies have investigated the course of anxiety neurosis (Shapira et al. 1972; Marks and Lader 1973; Kerr et al. 1974; Greer 1976; Clancy et al. 1978; Noyes et al. 1980); unfortunately the subgroup of patients with panic disorder cannot be identified in these follow-up studies. The common result of these studies on anxiety neurosis was a relatively poor outcome and a high degree of chronicity. Secondary depression (i.e. major depression developing after the manifestation of panic disorders) has been found to be the best predictor of poor outcome in some studies (Clancy et al. 1978; Noyes et al. 1980); the prognostic relevance of sexual status is controversial (Kerr et al. 1974; Noyes et al. 1980). It remains unclear whether these results are also valid for patients with panic disorders. Special follow-up studies in panic disorders are therefore needed in order to predict the clinical course of this disorder and to test its diagnostic validity.

We therefore carried out a prospective 1-year follow-up study in order to assess the course of panic attacks and of panic disorder. We tested psychopathological and socio-demographic baseline variables for their predictive power with regard to outcome and course. A special hypothesis to be tested in this study was the predictive power of secondary depression as an indicator of an unfavourable course.

Diagnostic schedules for anxiety disorders usually adhere to the hierarchical principle that the diagnosis of anxiety disorder is ruled out by affective disorders which are primary to the anxiety syndrome. This principle is not supported by empirical data (Leckman et al. 1983). Therefore we used the approach of DSM-III-R in changing the hierarchical structure, including all patients with panic attacks occurring with minimum frequency. Hence we decided to include all patients with this particular anxiety syndrome and without psychotic disorders; in this way we were able

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to test the predictive value of the hierarchical diagnostic approach.

Patients and Methods

With the intention of studying the complete spectrum of panic anxiety – taking no aetiology into account – 122 subjects acutely suffering from panic attacks and symptoms of anxiety were drawn from a variety of clinical settings during a 3-month period. For evaluation, all patients complaining of at least one panic attack in the previous 3 weeks were referred from the practices of two general practitioners, two internists and three psychiatrists. Likewise, patients were recruited from the university outpatient departments of cardiology, psychosomatic medicine and psychiatry as well as from the psychiatric inpatient clinic. Only patients first contacting one of these agencies in order to receive treatment for panic attacks and other symptoms of anxiety were included. All patients were free of organic disease.

Sample. From the 122 recruited subjects, all patients with schizophrenia (DSM-III or RDC) or schizoaffective disorder (RDC) or schizophreniform disorder (DSM-III) were excluded ($n = 18$). Likewise, all patients without at least one 3-weeks period with three panic attacks were excluded ($n = 7$). The index assessment was thus carried out in 97 patients; in addition all patients fulfilled the criteria for panic disorder according to DSM-III-R (APA 1987) with four attacks in 4 weeks and with the maximum intensity of symptoms in some attacks within 10 min after the beginning of the first symptom noticed.

One year after index evaluation, patients were invited to a follow-up-interview. Of the original 97 patients, 8 could not be located, 8 refused to cooperate and 4 patients had died (3 natural deaths, 1 suicide). The remaining 77 patients (making up 80% of the original sample) were interviewed.

As in previous follow-up studies in anxiety neurosis no attempt was made to standardize medication. In this way treatment could be regarded as representative of practice at the time of the study. However, since only patients who had sought treatment were entered into the study no statement can be made about the course of the disorder without any treatment.

The diagnoses of the sample under study are shown in Table 1. A high degree of commorbidity associated with other disorders can be recognized. Of the patients investigated, 62% were either hospitalized during the index episode (psychiatric/psychosomatic/medical department) or had been hospitalized previously.

Initially, during the month previous to the index episode assessments, 68% of the patients received benzodiazepines for anxiolytic treatment; 30% of the patients received antidepressants mainly for antidepressant treatment; three patients received beta-blockers. No patients received psychotherapeutic treatment initially.

During the follow-up period treatment was not standardized. Most patients (76%) received benzodiazepines during the 1-year follow-up period from their treating physicians; the mean duration of benzodiazepine treatment was 5.3 months. Antidepressants were intermittently given only when a prominent depressive syndrome was present; 25% of the patients received antidepressant pharmacotherapeutic treatment at some time during the 1-year follow-up period; the mean duration of the antidepressant treatment was 2.3 months. Three patients received psychotherapeutic treatment.

Changes in treatment during the follow-up period (starting or cessation or change of drugs) were reported in 74% ($n = 57$) of the patients: 66% ($n = 51$) stopped the benzodiazepine or the antidepressant treatment mainly because of significant improvement; 9% ($n = 7$) started benzodiazepine or antidepressant treatment during the follow-up period because of worsening of the symptoms of anxiety or depression. At the follow-up assessment 49% ($n = 38$) of the patients were receiving benzodiazepines and 11% ($n = 9$) antidepressants.

Table 1. Sociodemographic variables and diagnoses of the sample ($n = 77$)

Sex (male : female)	20 : 57
Age (mean)	41.0 years
Age of onset of panic attacks (mean)	34.0 years
Mean duration of illness	8.6 years
Marital status	
married	57 %
divorced or widowed	21 %
never married	22 %
Hospitalization	
(ever hospitalized in a psychiatric hospital)	62 %
DSM-III classification	
Panic disorder	62 %
Agoraphobia with panic attacks	32 %
Major depressive episode	6 %
Avoidance behaviour	
ICD-9 classification	
Anxiety state	29 %
Neurotic depression	12 %
Affective psychosis – depressed	21 %

Assessments. The index evaluation was carried out about 1 month after anxiolytic and antidepressant treatment had been started. The data reported were collected by one of three experienced psychiatrists at the index evaluation and 1 year later using an extended version of the structured clinical interview SCID (Spitzer and Williams 1987) and the Global Assessment Scale (GAS) (Spitzer et al. 1978). The reliability of the assessment was confirmed by ten previous training sessions; all diagnostic and outcome variables had kappa-coefficients higher then 0.80.

The 1-year follow-up period was monitored by the SCID, focusing on this 1-year period only and establishing the symptomatology for each of the 12 months separately.

Statistical Evaluation. The prognostic ability of features assessed at the index evaluation (predictor variables assessed on baseline – independent variables) for features assessed at the follow-up evaluation (outcome variables assessed 1 year later, dependent variables) was estimated by the stepwise logistic regression, which is applicable not only to normal distributions but also to a broad range of other distributions; this is the best procedure available for categorical variables (Andersen and Phillips 1983). Continuous variables have been dichotomized at their median prior to the application of the statistical evaluation. The stepwise logistic regression uses a t-statistic as an indicator of the significance of a predictor.

The set of predictor variables (independent variables) was identical in all regression analyses; the following variables

were included: age, sex, marital status; social impairment assessed by the GAS, age at onset of panic attacks, duration of illness, hospitalization in a psychiatric hospital; frequency of panic attacks in the worst week and in the last week prior to assessment, frequency of symptoms during the most severe panic attack, degree of anticipatory anxiety, avoidance behaviour, social phobia, chronic anxiety (symptoms of generalized anxiety disorder acording to DSM-III during at least 10 months within the last year); history of a major depressive episode (DSM-III), present major depressive episode, history of a major depressive episode primary to panic attacks, chronic depression (symptoms of dysthymic disorder according to DSM-III for at least 10 months within the last year).

Because of the high degree of overlap between different variables investigated for their predictability, it is possible that the set of predicting variables for a particular outcome measure is highly misleading. To overcome this problem, the method proposed by Day et al. (1982) has been used: a variable only has predictive value if the loss of predictive power after removal of this variable cannot be compensated for by the set of remaining variables.

Results

Rates of Improvement

The most improvement during the 1-year follow-up period was prominent for the frequency of panic attacks in the last week prior to assessment ($P < 0.01$). Avoidance behaviour also improved (62% of the patients affected initially and 39% affected 1 year later), but the improvement was not significant. Chronic anxiety showed a higher degree of persistence (52% suffering from this syndrome initially and 45% 1 year later). The number of patients with major depressive episodes decreased significantly during the 1-year follow-up period. A significant degree of improvement could also be observed for the associated syndrome of chronic depression (45% initially and 21% 1 year later).

Out of 77 patients, 33 (43%) were free of any snydrome during the month before the follow-up assessment; 19 out of 77 patients (25%) were free of any syndrome during the 6 months prior to the follow-up assessment (Table 2).

The occurrence of a major depressive episode during the 1-year follow-up period (chronic depression, new depressive episode, maximal duration of depressive symptomatology) was related to the prescription of antidepressant drug treatment ($P < 0.01$); the duration of depression was associated with the duration of antidepressant treatment ($P = 0.04$). Avoidance behaviour and chronic anxiety during the 1-year follow-up were associated with the duration of treatment with benzodiazepines ($P = 0.05$). No further variable listed in Table 2 showed significant associations ($P < 0.05$) with the duration of antidepressant or benzodiazepine treatment.

Table 2. Change in psychopathological features within the 1-year follow-up period ($n = 77$)

	Index assessment	Assessment after 1 year
Feature of anxiety		
Frequency of panic attacks		
last week	4.49	1.81**
worst week during the preceding year	8.50	4.30**
last month	20.6	7.29**
Maximal duration of panic-free episode (weeks) (mean)	./.	22.9
Number of patients with panic attacks		
last month	100 %[a]	30 %**
last 6 months	100 %[a]	55 %**
Number of patients with avoidance behaviour (limited or extended)	62 %	39 %**
Number of patients with chronic anxiety (1 year)	52 %	45 %
Features of depression:		
Depressive episode present at time of assessment	48 %	14 %**
Maximal duration of depression-free episodes (weeks) (mean)	./.	41.36 %
Number of patients with a new depressive episode	./.	30 %
Number of patients with chronic depression (1 year)	45 %	21 %*
History of depression	64 %	65 %
depression primary to panic attacks	49 %	49 %
depression secondary to panic attacks	25 %	26 %

[a] By selection criteria
*, **: $P < 0.05$, < 0.01 by t-test or McNemar-test respectively

Predictors of Outcome and Course of Psychopathological Features

Performing stepwise logistic regression in order to predict the outcome and the course of psychopathological variables gave the following relevant results (Table 3). Avoidance behaviour at index assessment is the best predictor of the severity of anxiety features at the time-point of the follow-up assessment (dichotomized number of panic attacks during the last week, avoidance behaviour) and for anxiety features during the 1-year follow-up period (dichotomized maximal duration of panic-free time, absence of panic attacks in the month prior to follow-up assessment); after controlling for the duration of benzodiazepine and of antidepressant medication, avoidance behaviour remained predictive. Furthermore, the sexual status (female) predicted avoidance behaviour, a higher number of panic attacks in the week prior to follow-up assessment and the presence of panic attacks with-

Table 3. Prognostic factors for psychopathological features of the follow-up period [stepwise logistic regression]

Variable to be predicted (follow-up assessment)	Predicting variable (index assessment) – significant predictors only ($P \leq 0.05$) – [a]	Level of significance for prediction (t-variable degree of freedom)
Number of panic attacks during week prior to follow–up assessment	*Avoidance behaviour* (*present*/absent)	2,5 ($df = 76$)*
	Sex male/*female*)	2,0 ($df = 76$)*
Avoidance behaviour at follow-up assessment	*Avoidance behaviour* (*present*/absent)	2,5 ($df = 75$)**
	Sex (male/*female*)	2,0 ($df = 75$)*
	Major depressive episode	2,6 ($df = 75$)*
Chronic anxiety	*Avoidence behaviour* (*present*/absent)	1,9 ($df = 77$)
Maximal duration of the depression free episodes	*History of depression* (*present*/absent)	2,3 ($df = 77$)*
New depressive episode	*History of depression* (*present*/absent)	2,5 ($df = 77$)*

* Predictive of $0.01 \leq P \leq 0.05$ (two-sided test)
** Predictive of $P \leq 0.01$
[a] Predictors of unfavourable outcome are set in italics

in the month prior to the follow-up assessment; after controlling for the duration of drug treatment, the sex was still predictive. The occurrence of a depressive episode or of chronic depression had no predictive value for features of anxiety after controlling for the overlap between predictive variables by using the method of Day et al. (1982) (Table 3).

Depressive features (dichotomized maximal duration of depression-free interval, new depressive episode) were predicted by a history of depression at index assessment; after controlling for the duration of benzodiazepine and of antidepressant medication, the variable remained predictive for depressive features. Primary versus secondary status of the previous episode of depression had no predictive value. The coefficients calculated in regression analyses can be used to reclassify the patients. All regression analyses listed in Table 3 brought about a rate of correct reclassification higher than 75%; thus, the results of the regression analyses are meaningful.

Discussion

The outcome and course of panic disorders, even without systematic treatment, are not as unfavourable as may be expected on the basis of previous follow-up studies of anxiety neurosis: 43% of the patients in this study totally remitted (i.e. had no syndrome according to DSM-III-R) during the month before the follow-up evaluation and 25% totally remitted during the 6 months before follow-up evaluation. These remission rates as well as the improvement observed for particular psychopathological syndromes are partly due to a phenomenon called "regression to the mean"; patients were recruited when they were severely impaired (first contacting one of the treatment sites); a priori it may be expected that the degree of impairment is less at all other fixed future points in time, which are not defined by the behaviour or the complaints of the patients. However, the figures observed for remission and improvement can be compared with those reported in other follow-up studies which are equally affected with a bias due to the regression to the mean.

The remission rate observed is at variance with the retrospective follow-up study of Coryell et al. (1983), who reported that only 12.5% of inpatients retrospectively diagnosed as having panic disorders remitted within 1 year. The reason for this discrepancy may be that in contrast to the majority of other follow-up studies, our patients were also recruited in non-psychiatric (general practitioners, cardiologist) as well as psychiatric outpatient clinics. Patients in non-psychiatric services show a lower prevalence of associated syndromes at the index assessment (Noyes et al. 1980), which may contribute to a more favourable outcome in this study.

The main predictor of a higher prevalence of anxiety features during the 1-year course is the presence of avoidance behaviour. Cross-sectionally, avoidance behaviour is also an indicator of the severity of panic attacks and is associated with secondary depressive episodes in the sample under study (Buller et al. 1986) as well as in other samples (Breier et al. 1984;

Thyrer et al. 1985). The prediction of the features of anxiety by the avoidance behaviour in the follow-up period additionally emphasizes the distinct status of agoraphobia in patients with panic attacks. It is remarkable that avoidance behaviour is a better predictor of the frequency of panic attacks than the frequency or the severity of panic attacks at index assessment. The predictive value together with the cross-sectional discriminative ability (Buller et al. 1986) can be considered as a validation of subtyping of panic disorder according to the associated avoidance behaviour, as is proposed in DSM-III-R (APA 1987).

Depressive features in the follow-up period are mainly predicted by a history of a depressive episode at the index assessment; depression present at or previous to baseline was not predictive of features of anxiety during the follow-up period. The distinction between depressive episodes primary to panic attacks vs. depressive episodes secondary to panic attacks does not enhance the predictive power significantly. This result lends only limited support to the hypothesis derived from previous studies that depression secondary to anxiety neurosis is an indicator (Clancy et al. 1978; Noyes et al. 1980) or a predictor (Kerr et al. 1974) of globally assessed poor outcome; secondary depression was not predictive of anxiety; primary depression and secondary depression were equally predictive of depression during the follow-up period.

An uncontrolled factor in this study may contribute to the low predictive value of depressive symptomatology for the features of anxiety observed: additional antidepressant treatment mainly given to patients with depressive syndromes during the 1-year follow-up may also suppress panic attacks and avoidance behaviour (Zitrin et al. 1983); the association between previous depression and depression during the follow-up period may thus indirectly contribute to an underestimation of the predictive value of depressive symptomatology for features of anxiety. However, after controlling for the duration of treatment retrospectively, the predictive status of avoidance behaviour, previous depressive episodes, and sex remained unchanged. Perfect control of confounding factors is, however, only possible by prospective studies.

The relevance of the sex for the prognosis of anxiety states is controversial. Kerr et al. (1974) found that female patients have a more unfavourable course than male patients; Noyes et al. (1980) found that male patients have a more unfavourable prognosis. In this study, female sex was predictive of some aspects of a more unfavourable course. Cultural factors may be responsible for the differences in the predictive value of sex between different follow-up studies.

The limited number of patients in the sample under study precluded the possibility of a cross-validation of our results by splitting the sample; further support for the results reported is therefore necessary. Also, the relevance of different treatment strategies and of culturla factors needs to be studied in further follow-up studies of panic disorder.

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