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The long-term course of panic disorder—an 11 year follow-up

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Abstract

Background: The purpose of this study was to assess the naturalistic long-term course of panic disorder over a period of 11 years. **Method:** Thirty DSM-III-R panic disorder patients, who had suffered from panic disorder for 6 years on average and who had taken part in an 8-week multicenter drug trial, were included in the intent-to-follow-up group to be reinterviewed 11 years after the end of the trial. At baseline and at follow-up the same instruments were used to assess frequency of panic attacks, level of phobic avoidance, and disabilities. Treatments received during the follow-up period and attempted suicides were assessed with a structured interview. Periods of well-being during the follow-up period were elicited retrospectively with a specifically designed longitudinal chart. **Results:** Twenty-four patients could actually be reinterviewed after 11.3 years. While at baseline all patients had suffered from panic attacks and had been severely disabled on a number of measures, 66.7% had no panic attack during the year before follow-up. During the month before follow-up 87.5% had no panic attack, and 54% showed no or only mild phobic avoidance. In the areas of work and family life 90% showed no or only mild disabilities, whereas in the area of social life this percentage was lower (67%). Thirty-three percent of the patients were completely remitted according to a composite remission criterion. **Conclusions:** Panic disorder is not a uniformly chronic and progressing disorder. Over a period of 11 years there is a good chance of recovery from panic attacks and disabilities, and full remission is also possible.

Keywords: Panic disorder; Disabilities; Phobic avoidance; Long-term course; Follow-up

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1. Introduction

Panic disorder is a frequent disorder with lifetime prevalence rates ranging between 1.5 and 3.5% (American Psychiatric Association, 1994). While clinical, biological, and treatment issues have been extensively studied, scientifically based knowledge about the long-term course of panic disorder and the predictors of outcome are still scanty. This is deplorable since it has been shown that panic disorder generates considerable suffering and disabilities (Leon, Shear, Portera, & Klerman, 1992), as well as enormous costs in the general health care system (Klerman, Weissman, Ouellette, Johnson, & Greenwald, 1991).

No follow-up studies of persons diagnosed in population surveys as suffering from panic disorder have been carried out so far, but some data are available on the long-term course of the disorder in clinical samples. The widely held assumption that panic disorder is a progressing and unremitting condition seems to be only partly supported by such long-term empirical studies of clinical populations. Pre-DSM-III studies show that, after many years, a majority of patients experience symptomatic improvement despite absence of complete remission (Marks & Lader, 1973; Noyes, Clancy, Hoen, & Slymen, 1980). In a review of 16 follow-up studies carried out in the DSM-III era, covering a minimum period of 1 year and using multiple outcome criteria at follow-up, an average of 54% of patients were panic-free, 31% showed a remission of phobic avoidance, and 50% had no functional impairment. In other words, however, between 46 and 69% were still symptomatic or impaired (Roy-Burne & Cowley, 1995).

Katschnig et al. (1995) have reported about the largest and longest (2–6 years, median 4 years) follow-up study published so far, in which 423 patients were included, who had originally participated in one of two large international multicenter drug trials (Ballenger et al., 1988; Cross-National Collaborative Panic Study Second Phase Investigators, 1992). The main finding was that 61% of all patients were still experiencing at least occasional panic attacks at follow-up (i.e., 39% were panic-free), while far fewer suffered from phobic avoidance or disabilities in various life domains—a remarkable dissociation between panic attack frequency and other outcomes. A few potential predictors of outcome have been identified so far, including subtypes of panic disorder (uncomplicated, limited phobic avoidance, extensive phobic avoidance) and Axis I and II comorbidity (depression and personality disorders) (Katschnig & Amering, 1998; Roy-Burne & Cowley, 1995).

While these findings are of interest, they relate to rather short follow-up periods of a few years at the most. Shear (1996) has consequently pointed out that long-term outcome studies covering *extensive* periods are ‘‘desperately needed.’’ The present study covers such an extensive follow-up period. We report on a naturalistic follow-up study of panic disorder patients, with the advantage, that it covers an 11-year period, and the relative disadvantage of a rather small sample size of 30 patients.

2. Method

2.1. Subjects and procedures

The follow-up sample consisted of the 30 panic disorder patients defined according to a modified version of DSM-III, closely resembling DSM-III-R (see further), who had initially taken part at the Austrian site of the Cross-National Collaborative Panic Study Phase II, in an 8-week clinical drug trial comparing imipramine, alprazolam and placebo (Cross-National Collaborative Panic Study Second Phase Investigators, 1992). The main exclusion criteria had been neurological or somatic illnesses, such as epilepsy, renal, hepatic or cardiac disease, as well as psychiatric disorders (psychosis, bipolar disorder, dementia and substance abuse). Patients were to be interviewed 11 years after they had left the clinical trial. Patients were contacted by telephone and those who were willing to be reinterviewed were asked to choose a date and place for the follow-up appointment. The interviews were carried out face to face by trained clinicians, and lasted on average 50–60 min. All patients had already had the experience of being interviewed for a 4-year follow-up study including also other sites (Katschnig et al., 1995).

2.2. Methods of assessment

For baseline assessment, when entering the clinical trial, patients had been diagnosed with the help of a structured clinical interview modified from the SCID (SCID-UP = Structured Clinical Interview for DSM-III, Upjohn Version, Spitzer & William, 1983).

The following scales had been used at baseline (Cross-National Collaborative Panic Study Second Phase Investigators, 1992): the Panic Attack Scale (Sheehan & Sheehan, 1982), which measures the frequency of panic attacks during the week and the month preceding the assessment; the Marks-Sheehan-Scale (Marks & Matthews, 1979), an 11-point scale for rating global phobia (0 none, 1–3 mildly, 4–6 moderately, 7–9 markedly, and 10 very severely phobic); and the similarly constructed 11-point Sheehan Disability Scales for the assessment of three areas of disability (work, family life/home, and social life/leisure) (Sheehan, 1983). The Marks-Sheehan-Scale and the Sheehan Disability Scales had been applied to the 4 weeks preceding baseline.

For the follow-up assessment the same instruments were used. For the month before the follow-up assessment panic attack frequency was, as it was at baseline, measured with the Panic Attack Scale; for eliciting phobic avoidance and disabilities the same 11-point rating scales were administered as had been used at baseline. Panic attack frequency was also assessed for the whole year before the follow-up interview.

In addition, a specifically designed interview was used, containing the same version of the SCID as used at baseline, and a follow-up chart for the retrospective

assessment of periods of well-being as well as suicide attempts during the whole follow-up period (Katschnig et al., 1995). Treatments received during the follow-up period were also recorded.

2.3. Statistical analysis

For statistical analysis chi-square tests, Wilcoxon Signed Ranks tests, and Student's *t*-tests were applied.

3. Results

3.1. Reinterview rate and duration of follow-up

Twenty-four patients could be reinterviewed for the 11-year follow-up. Of the remaining six patients (one male, five female), four (13.4%) could not be located, and two (6.7%) refused to be interviewed.

The actual mean duration of follow-up between the end of the clinical trial and the follow-up interview was 11.3 years (135.3 months (S.D.: 4.3); median 134 months; range 129–143 months).

3.2. Demographic and clinical characteristics

The sex and age distributions at baseline were not significantly different between the 30 patients of the original sample (63.3% female; mean age 37.7 (S.D.: 10.5), median 37.0 years) and those 24 patients who could be reinterviewed for the 11-year follow-up (58.3% female; mean age 38.8 (S.D.: 11.2), median 37.0 years). The same applies to diagnostic criteria and illness duration. Uncomplicated panic disorder at baseline was present in 4 patients of the original sample (13.3%) and in 3 of the 24 patients actually reinterviewed (12.5%), panic disorder with limited phobic avoidance was present in 16 patients of the original sample (53.3%) and in 11 patients of the sample reinterviewed (45.8%), panic disorder with extensive phobic avoidance was present in 10 patients of the original sample (33.3%) and in 10 patients actually reinterviewed (41.7%). The average illness duration before the clinical trial was 5.8 years (S.D.: 6.8) in the original sample; the 24 patients actually followed up had been suffering from panic disorder for an average of 6.3 years (S.D.: 7.3) at baseline.

3.3. Outcomes 1

Comparison of cross-sectional evaluation at baseline and at follow-up (Table 1, Fig. 1).

Table 1
Mean values of phobic avoidance, work disability, family life/home disability, and social life/leisure disability at baseline and at follow-up ($N = 24$ and 18 for work disability)

	Baseline	Follow-up	*P*-values*
Phobic avoidance	8.20 ± 1.79	3.34 ± 3.31	<.0001
Work disability	3.66 ± 1.23	1.18 ± 2.68	<.04
Family life/home disability	3.04 ± 1.54	1.04 ± 2.44	<.04
Social life/leisure disability	3.79 ± 1.17	2.41 ± 2.91	<.029

* *P*-values are based on Student's *t*-tests.

3.3.1. Diagnosis

While at baseline all patients had fulfilled diagnostic criteria for panic disorder, at the 11-year follow-up 21 patients (87.5%) did not fulfill criteria for panic disorder. The remaining three patients (12.5%) fulfilled criteria for panic disorder with limited phobic avoidance. At follow-up no patient suffered from uncomplicated panic disorder or panic disorder with extensive phobic avoidance.

3.3.2. Remission

There is no general consensus on operationalized remission criteria for panic disorder, and different studies have used different outcome criteria (Roy-Burne & Cowley, 1995). In our study remission was defined by a combination of several outcome measures, namely the absence of panic attacks during the year before follow-up assessment *plus* a score of 3 or less on the global phobia rating scale, and on each of the disability scales during the month preceding follow-up. This remission criterion was fulfilled by eight patients (33%) at the time of the follow-up interview.

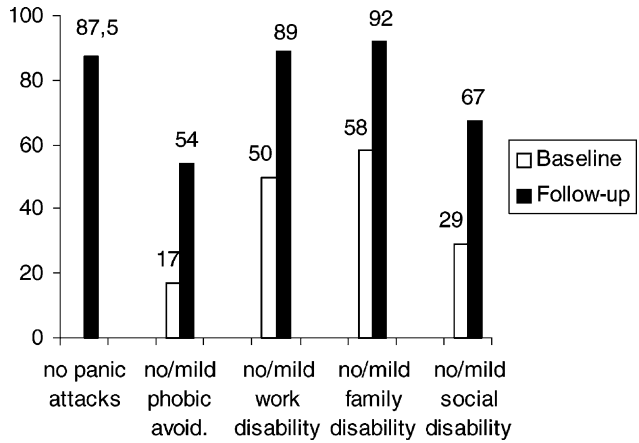

Fig. 1. Percentage of patients with no panic attacks, no or mild phobic avoidance, and no or mild disabilities at baseline and at follow-up ($N = 24$ and 18 for work disability; month before the interview).

3.3.3. Panic attacks

While at baseline by definition all patients had suffered from panic attacks, 21 patients (87.5%) did not experience any panic attack during the month before the follow-up interview, and 16 patients (66.7%) had been free of panic attacks during the year before the follow-up assessment.

3.3.4. Phobic avoidance

At baseline 17% of the patients had shown no or only mild phobic avoidance during the preceding month; at follow-up this percentage had risen to 54%. In terms of mean values there was a significant decrease between baseline and follow-up (Table 1).

3.3.5. Disabilities

For all three areas of disability (work, family life/home, social life/leisure) substantial improvements occurred between baseline and the follow-up interview. Of those patients who were in the labor force 50% had shown no or only mild disability at baseline. This percentage had risen to 89% at follow-up. Concerning disability in home and family life an essentially similar picture emerged. Fifty-eight percent had shown no or only mild disability at baseline, but 92% were not or only mildly disabled at follow-up assessment. In the areas of social life and leisure improvement was less pronounced. Twenty-nine percent had been not or only mildly disabled at baseline, and 67% belonged to this category at follow-up. In terms of mean values there was as significant decrease in all three areas (Table 1).

3.4. Outcomes 2: longitudinal course

3.4.1. Well-being

The longitudinal pattern of subjective well-being was assessed retrospectively with the help of the follow-up chart described in Section 2. During the whole follow-up period of 11.3 years (135 months) the total group of patients had experienced on average 52.4 months of complete well being (S.D.: 3.1) (median 62 months, range 0–120 months), which is equivalent to a percentage of 38.7% of the total time-period. Three patients had felt well more than 75% of the whole follow-up period, 6 patients had felt well between 50 and 74%, 4 patients between 25 and 49%, and 11 patients had felt well less than 25% of the whole follow-up period. Twelve patients (50%) had felt well during the last 3 years before the follow-up interview.

3.4.2. Suicide attempts

For the whole follow-up period of 11.3 years no suicide attempts were reported.

3.4.3. Treatment during follow-up

Since this was a naturalistic study, the meaning of any treatment received during the follow-up period is unclear as far as the results of this study are

concerned. Also the validity of the reports over such a long period as 11 years is doubtful. Nevertheless, an attempt was made to single out those patients who credibly reported having not sought or received any treatment during the follow-up period. Ten of the 24 patients belonged to this group. Of the 14 remaining patients 8 reported use of psychotropic medication (serotonin reuptake inhibitors, tricyclic antidepressants, and benzodiazepines) either over the whole time-period (4 patients) or over significant periods during follow-up (4 patients). One of these patients had undergone psychotherapeutic treatment in addition to drug treatment. Seven further patients reported having received various forms of psychotherapeutic treatments over prolonged time spans without having been treated with psychotropic medication. This group of 14 patients was compared with the 10 patients who had not received any form of treatment during the follow-up period. No significant difference was found between the two groups with respect to the outcome variables "no panic attacks" ($\chi^2 = 0$, $P = 1.00$), to "no or mild phobic avoidance" ($\chi^2 = 5.50$, $P = .59$), "no or mild work disability" ($\chi^2 = 3.51$, $P = .47$), "no or mild social life disability" ($\chi^2 = 4.86$, $P = .56$), and "no or mild family life disability" ($\chi^2 = 6.22$, $P = .28$).

4. Discussion

This study represents the longest follow-up of patients suffering from panic disorder published so far. We have studied a group of panic disorder patients who were reinterviewed 11 years after the end of an 8-week placebo-controlled clinical drug trial. Twenty-four of 30 patients could be reinterviewed.

The problem concerning definition of adequate outcome criteria in follow-up studies of panic disorder has been repeatedly discussed in the literature (Shear & Maser, 1994), but until now there is no general consensus as to which are the best criteria to choose. To confine outcome measurement to presence or absence of specific symptoms or the fulfillment of operational diagnostic criteria for panic disorder is certainly an oversimplification (Katschnig & Amering, 1998). This approach does not reflect the complex and varied structure of the disorder in individual patients with possible improvement in one but not another dimension of psychopathology, and does not take into account the persistence of subthreshold symptoms or functional impairments. We have therefore used several approaches to assess outcome. First we reassessed the presence of diagnostic criteria for panic disorder, secondly we used a composite outcome measure, and finally, we also looked into specific symptoms and disabilities.

On the diagnostic level the result was quite surprising, since at follow-up 21 patients (87.5%) no longer fulfilled DSM-III-R criteria for panic disorder. However, only one-third of all patients were considered as completely remitted on a combination of outcome measures, including the absence of panic attacks, plus no or a very low degree of phobic avoidance and of disabilities. Concerning specific symptoms and disabilities, at the follow-up interview, 11 years after the

end of the clinical trial, 66.7% had been panic-free during the year before the interview. During the month preceding the follow-up assessment 87.5% of all patients had been panic-free, 54% were not or only mildly phobic, and 90% were not or only mildly disabled in the domains of family and work functioning. Social functioning was less improved, with 67% being not or only mildly disabled. Thus, residual symptoms and disabilities at follow-up consisted mainly of phobic avoidance and social life disability.

These results are in accordance with the findings of most previous studies which used shorter follow-up periods, where the outcome of ''zero panic attacks'' at follow-up has been shown to be more frequent than that of remission of other symptoms (Roy-Burne & Cowley, 1995). In contrast, Katschnig et al. (1995) found that phobic avoidance had improved to a larger extent than panic attacks in a 4-year follow-up. Such discrepancies underline the necessity to use multiple outcome criteria as was proposed by Shear and Maser (1994), since improvement can obviously be better in one and worse in another criterion, i.e., some degree of dissociation may occur. For instance, continuous avoidance of situations, which usually trigger panic attacks, could lead to the disappearance of panic attacks in the long run. On the other hand, certain patients might have learned to live without being disabled despite experiencing occasional panic attacks.

How can the finding of a rather favorable outcome for a large proportion of patients, who had suffered from panic disorder 6 years on average before entering the study, be explained? First, since patients were rather ill at baseline, a regression to the mean effect may explain our finding (Davis, 1976). One other obvious possibility is—and this is not improbable also for other psychiatric disorders—that panic disorder is not a uniform condition and that several ''natural'' subgroups exist, with one subgroup attaining complete remission and other subgroups experiencing an episodic or a persistent course of the disorder (Katschnig & Amering, 1998). A third possibility is that unsystematic treatments received during the follow-up period could be an explanation. Yet, the 14 patients who had received treatment during the follow-up period did not achieve a more favorable outcome. The definite meaning of this finding is unclear, since self-selection mechanisms probably have played a role. In order to clarify this point, more long-term clinical trials with uniform methodology and standardized treatments are needed.To what extent nonpharmacological factors could be responsible for the favorable course of panic disorder in quite a few patients is difficult to answer. First, psychological factors, operating during the original drug trial, could have played a role, since, before the clinical trial most patients knew very little about panic disorder and were educated during the course of the trial. Also, they learned to monitor their symptoms with the help of a diary, which is usually used in clinical trials of panic disorder. Katschnig et al. (1995) have suggested that this increased self-monitoring, which has been shown to be therapeutic in itself (Nelson, 1977), could be responsible for improvement. Finally, in cases of agoraphobia, inadvertent exposure in vivo might have been a psychological mechanism which has led to improvement. Agras, Sylvester, and

Oliveau (1969) have suggested that spontaneous remission observed in many cases of childhood phobia could be due to such naturally occurring exposure.

While the extremely long follow-up period is unmatched by any other study to date, our study has some limitations. First, it suffers from a small sample size. Second, while use of the same instruments for assessing the cross-sectional status at baseline and follow-up can be considered as a strength, the validity of data collected retrospectively for the whole follow-up period, such as well-being, attempted suicide and treatments received, is probably limited, though all patients had already had the experience of being reinterviewed 7 years earlier (Katschnig et al., 1995). Third, patients, who have taken part in a clinical drug trial, clearly represent a selected group: on the one hand, they have been recruited into a clinical trial because their disorder had reached a certain degree of severity. On the other hand, due to exclusion of comorbid conditions, they may in fact have been less ill than many other patients. This third limitation is shared, though, with most other naturalistic long-term follow-up studies in panic disorder. It could only by avoided by studying epidemiologically derived samples of persons suffering from panic disorder.

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