Eur Arch Psychiatry Clin Neurosci (1991) 241:22–30

European Archives of Psychiatry and Clinical Neuroscience

Subtyping Panic Disorder by Major Depression and Avoidance Behaviour and the Response to Active Treatment

Wolfgang Maier[1], Raben Rosenberg[2], Nicholas Argyle[3], Raimund Buller[1], Sir Martin Roth[4], Sydney Brandon[5], and Otto Benkert[1]

[1]Department of Psychiatry, University of Mainz, Untere Zahlbacher Strasse 8, W-6500 Mainz, Federal Republic of Germany
[2]Department of Psychiatry, Rigshospitalet, 9, Blegdamsvej, 2100 Copenhagen, Denmark
[3]Anxiety and Depression Clinic, New York Hospital, Westchester Division, 21 Bloomingdale Road, White Plains, NY 10605, USA
[4]University of Cambridge Clinical School, Level 5, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK
[5]Leicester University, Leicester Royal Infirmary, P.O. Box 65, Leicester LE2 7LX, UK

Received October 10, 1990

Summary. In order to establish the clinical validity of currently used ways of subtyping panic disorder the predictive power of associated current avoidance behaviour and (secondary) major depression for the response to active treatment (alprazolam, imipramine) was tested. The analysis was based on the data from the Cross-National-Collaborative-Panic-Study. Limited support for validity evidenced by predicting drug response was found for grading panic disorder by the severity of avoidance behaviour: patients with panic attacks and agoraphobia are more responsive to imipramine (compared with alprazolam) when using the reduction of the total number of panic attacks (or of spontaneous panic attacks) as the outcome criterion; patients without any avoidance behaviour did better with alprazolam (compared with imipramine).

Key words: Panic disorder – Imipramine – Alprazolam – Agoraphobia

Introduction

The relationship between avoidance behaviour, depression and panic attacks is currently a topic for controversial discussion [11, 21, 26]. Previous concepts of anxiety disorders (neuroses) considered avoidance behaviour (phobia) in addition to generalized anxiety as core syndromes of anxiety disorders and did not pay special attention to panic attacks. Traditionally, the presence of phobias and generalized anxiety have been the guidelines for diagnosing anxiety or phobic neuroses (e.g. in ICD-9) [32]. In the case of the coexistence of anxiety and depressive symptoms, a diagnosis of depression was obtained if depressive symptoms occurred primarily during the course of illness or dominated the clinical picture [13, 18]. Panic attacks had no major impact on classification in this approach; they were considered to be facultative symptoms in anxiety as well as in depressive disorders and to be of no major importance for diagnosis or treatment outcome, probably because patients with panic attacks only rarely asked for professional help or because the majority of anxious patients also had additional diagnoses (comorbidity).

This position changed after Klein [9] found that spontaneous panic attacks could be successfully treated with imipramine. The concept of panic disorder arose, which was adapted by RDC [30] and DSM-III [1, 2]: in panic disorder, according to Klein, panic attacks are a crucial symptom defining a separate diagnostic category. Agoraphobia is considered to be mainly secondary symptoms to panic attacks. Secondary depression is thought to be a final consequence (demoralization), both avoidance behaviour and secondary depression being indicators of the severity of panic disorder [10]. Avoidance behaviour was subsequently considered a subtyping variable of panic disorder by DSM-III and DSM-III-R.

This approach to subtyping panic disorder by avoidance behaviour and major depression needs to demonstrate clinical utility and validity. Criteria for this are associated with family history and biological variables, prediction of future course assessed at follow-up and of response to treatment [8]; the last-mentioned criterion of validity is most essential for planning treatment. Up to now at least three drugs – imipramine [12], alprazolam [4] and phenelzine [15] – have been shown to be efficacious in panic disorder (compared with placebo treatment). The predictive power of subtyping by major depression was previously investigated in a series of drug trials with active treatment for panic disorder using imipramine or alprazolam as active treatment [12, 15]; the majority of studies did not find a more favourable response to either imipramine or alprazolam in patients with panic disorder and major depression. Subtyping by avoidance behaviour and the interaction of both subtyping variables was not examined for its predictive power in short-term treatment with either of the active drugs.

The impact of avoidance behaviour and major depression was investigated using the data of the second phase of the Cross National Collaborative Paric Study (CNCPS) [6, 14] the most comprehensive trial in pharmacological treatment. Two active drugs (imipramine, alprazolam) and placebo were allocated randomly to the patients for an 8-week drug trial. Phase I of the CNCPS using alprazolam as active treatment was not able to address the issue of the impact of avoidance behaviour on the classification and treatment outcome in panic disorder because of the very low frequency of patients without avoidance behaviour [4]; only the relationship between panic disorder and secondary depression was analysed by the data of phase I of the CNCPS [15]. A more heterogeneous sample has been recruited for phase II of the CNCPS, providing the opportunity to examine the impact of both avoidance behaviour and secondary major depression on the classification and treatment outcome of panic disorder.

The response to the active treatments with alprazolam and imipramine observed in CNCPS phase II has been tested with regard to the two following hypotheses:

1. Patients with avoidance behaviour and major depression are less responsive to any kind of treatment than patients without these associated features as both additional features are predicting a less favourable course (main effects for avoidance behaviour and major depression).
2. Panic disorder with major depression is especially responsive to imipramine which is an efficacious antidepressant (interaction effect of major depression and treatment).

Methods

Study Procedure

The data presented for validating diagnostic subtypes of panic disorder are derived from the CNCPS. This study was conducted to test the efficacy of alprazolam in panic disorder in a placebo and standard medication (imipramine) controlled study. The design of the CNCPS has been extensively described [14]; therefore, only those features of the studies which are of major relevance for this paper will be described.

The CNCPS was a randomized and double-blind outpatient drug study, taking place in 14 countries (Belgium, Brazil, Canada, Colombia, France, Federal Republic of Germany/Austria, Italy, Mexico, Spain, Sweden/Denmark, United Kingdom, United States) and 23 sites, mainly university outpatient clinics. The medication was allocated randomly to the patient (12 randomization blocks) and started after at least a 1-week drug-free period. The efficacy of both active drugs in the total sample is the topic of a forthcoming paper [6].

The diagnostic inclusion criterion for participating was the DSM-III diagnosis of panic disorder and, in addition, three panic attacks within the last 3 weeks (before entering the wash-out period). It was required that no history or present episode of schizophrenia, schizoaffective disorder, mania, cyclothymia, hypomania, alcohol, substance or drug abuse, obsessive-compulsive disorder or major depression (MDE) with melancholia was reported. Patients with a current or past MDE could be included, if: (1) features of anxiety were more prominent than those of depression during the present episode; and (2) panic disorder had onset before depression in the present episode.

Ratings and Reliability

A structured clinical interview (SCID-UP) [29] was administered for checking the diagnostic inclusion and exclusion criteria (especially for panic disorder) and for the assessment of associated diagnostic features (e.g. major depression and social, simple phobia). The reliability of the SCID-UP and the outcome measures was controlled during a common training of the investigators before starting the study and by the requirement for all participating centres to tape at least three SCID-UP interviews. The tapes were blindly evaluated. A test-retest reliability study and an investigation in the procedural validity of the SCID-UP were performed; the results for the diagnoses MDE, panic disorder and avoidance behaviour were highly satisfactory [19].

Ratings of the severity and of the changes of the symptomatology were carried out at baseline (before starting medication) and at the end of week 1, 2, 3, 4, 6 and 8 by the treating physician or the patient. The following rating scales were included: a global rating by the physician for the overall improvement relative to baseline (ranging from 0 to 10, with 0 worst, 10 best and 5 indicating no change); an analogue global rating for the overall improvement by the patient; a global rating for overall phobia (ranging form 0 to 10, with 0 being best and 10 being worst). In addition, the number of spontaneous and of situational panic attacks during the last week were recorded by the treating physician, using data from a standardized patient diary.

The subtyping by current avoidance behaviour and current major depressive episode (DSM-III) can be extracted from the SCID-UP. Avoidance behaviour is defined in the SCID-UP as a variable with three levels: panic disorder without avoidance behaviour (panic disorder uncomplicated), panic disorder with limited avoidance behaviour and panic disorder with excessive avoidance behaviour (panic disorder with agoraphobia). The last category is considered to be present if the patient is either staying at home or is unable to leave the house without being accompanied because of the fear of a panic attack that may happen outside. Limited avoidance behaviour includes all less severe types of objective avoidance behaviour or a marked subjective impairment if leaving the house or carrying out activities in spite of the fear of a panic attack.

Sample Size, Characteristics and Completion Rates

Patients ($n = 1168$) were randomized after meeting the selection criteria. The sample size for the baseline evaluation was $n = 1134$ as $n = 34$ data sets were incomplete.

A total of 381 patients received placebo, 379 alprazolam and 374 imipramine. The patients treated either with alprazolam or imipramine only are included in the analysis presented in this paper.

After the first 3 weeks of treatment 352 patients were still on imipramine, 310 on alprazolam, and 309 on placebo. At the scheduled end of the trial (week 8) 272 patients were still in the imipramine group, 220 in the alprazolam group and 191 in the placebo group. The substantially higher drop-out rate in the placebo group questions the comparability of the three treatment groups and recommends separate analysis of the active treatment disregarding the placebo treatment.

The two active treatment groups showed the following sociodemographic characteristics at baseline: mean age 34.3 years (alprazolam) and 33.5 years (imipramine); sex ratio (% males): 36% (alprazolam) and 36% (imipramine); maritial status (% married): 68% (alprazolam) and 64% (imipramine). Mean age at onset of panic disorder was 28.9 years in the alprazolam group and 28.8 years in the imipramine group. The distribution of subtypes across the two treatment groups analysed is reported in Table 1.

Statistical Methods

The criteria of validity were introduced as dependent variables, and the diagnostic variables to be validated as independent variables into the statistical analysis. Both the main effects for avoidance behaviour and MDE and the interaction effects between both of these variables are of interest for deciding if both factors are working in an additive, subadditive or superadditive manner. Additionally, the interaction terms subtype × treatment (alprazolam/imipramine) are of interest (e.g. for hypothesis 2) for identifying different response rates across the different subtypes.

Two other factors need ot be controlled: sex and the different participating sites. Previous studies have stated that avoidance behaviour and MDE are more frequent in female than in male patients [26]. Therefore, significant main effects for these diagnostic variables may be due to the sex differences. Furthermore, the manner of recruiting the patients was not standardized and therefore a broad variety of recruitment procedures have probably been applied in the different sites due to cross-national differences in mental health care systems. National subsamples may not only differ by sex distributions and the diagnostic variables under study, but also by other factors (e.g. chronicity of the disorder, acceptance of psychopharmacological therapy), which may have their own impact on the criteria of validity. Including sex and site as additional independent variables requires control of all two-way interactions of the sex and of the site variables with themselves and with the diagnostic variables. The main independent variables are treatment (alprazolam, imipramine) variables and all two-way interaction effects with other independent variables.

Finally, the criteria of validity describe improvement during treatment. Consequently, change scores representing improvement must be derived unless they are already defined by a direct assessment of change (as the physicians' and the patients' global score of improvement). A standard procedure for deriving an improvement score for continuous variables is to control the outcome measure of the dependent variable for the baseline measure of the same variable by using the residuals [16] as change scores for the numbers of panic attacks.

The drug trial was scheduled for 8 weeks. As there were a substantial number of patients who dropped out before completing the trial, statistical analysis cannot rely merely on the completers (completer analysis). As an alternative, patients staying at least for a minimal period of time (3 weeks) on the treatment were also evaluated by using their final measures when completing or before dropping out (so-called endpoint or carrying forward analysis). Neither of the approaches is free of disadvantages: completer analysis is preselected for favourable outcomes, as most patients drop out because of insufficient efficacy of their treatment; endpoint analysis is negatively biased, as those dropping out miss the chance to improve during the remaining time of the study. As it was decided before starting the study that a patient is evaluable when staying in the trial for at least 3 weeks, a third type of analysis was carried out in those who participated for at least 3 weeks, measuring the outcome by the end of week 3 (Week-3 analysis).

The analysis of variance (ANOVA) for ordinally scaled dependent variables provides estimates of the main and the interaction effects by F-statistics; the ANOVA loses power if the dependent variable is not normally distributed; as the frequency distribution of the total number of panic attacks was skewed to the left, the log transformation of this variable which is close to a normal distribution is preferred.

Two manners of ANOVA are applicable: type I is a stepwise procedure dependent on the order in which the independent variables are entered; in addition type I analysis is dependent on the cell counts and requires the absence of interaction effects for a valid interpretation of the main effects [7]; Type III analysis uses a simultaneous procedure and is therefore not dependent on the order of the independent variables; the other two disadvantages of type I analysis are also absent. However, type III analysis is less powerful than type I analysis [20]. Consequently, type I as well as type III analysis are reported; the type III analysis is considered to provide the most informative results.

Only significant F-values are reported in the tables. Comparisons between the three levels of avoidance behaviour are reported using Tukey's studentized range test.

Results

1. Frequencies of Subtypes Across Sites

Agoraphobia was most frequent among the patients of the U.S. site Ann Arbor (60%) and most rare in the Swedish site (19%). Panic disorder uncomplicated was most frequent in Swedish patients (33%) and most rare

in the Canadian sample (8%). Major depression was most frequent among the Mexican patients (31%) and most rare among the Italian patients (4%). The distribution of the relative frequency of MDE (current) as well as of avoidance behaviour across different sites turned out to be heterogeneous (chi-square = 108.0, $df = 22$, $P < 0.001$ for avoidance behaviour; chi-square = 64.2, $df = 11$, $P < 0.001$ for MDE current). A detailed report on the impact of the site variable and of sociodemographic variables is the topic of special papers [20].

The occurrence of major depression and of avoidance behaviour is strongly associated in both active treatment groups (chi-square = 20.76, $df = 2$, $P < 0.001$); this association remains highly significant after controlling for the variation across the different sites and sex (log linear analysis chi-square = 9.81, $df = 2$, $P = 0.01$). A detailed report of the impact of avoidance behaviour and major depression on psychosocial features and on the symptomatology on baseline is the topic of another paper [20].

Table 1. Sample sizes during the trial in diagnostic subgroups defined by avoidance behaviour and major depression in both groups (Alprazolam, Imipramine)

	Panic disorder			Panic disorder	
	Uncomplicated	Limited avoidance	Agoraphobia	Without MDE	With MDE
Alprazolam:					
Sample size on baseline	89	148	136	311	62
Sample size week 3	87	138	131	297	59
Sample size week 8	79	119	116	261	53
Imipramine:					
Sample size on baseline	82	156	140	321	57
Sample size week 3	67	131	119	267	50
Sample size week 8	51	112	102	231	34

2. *Prediction of Improvement by Treatment*

Neither the presence of a major depressive episode, nor the presence of avoidance behaviour was associated with dropping out in either of the two groups with active treatment (Table 1). Patients treated with imipramine were more likely to drop out irrespective of the diagnostic subtype (Table 1).

2.1 *Global Measures of Improvement*

Significant main effects for the "site" variable were uncovered by type I analysis for all three time points when change was directly and globally measured by the physician; the more conservative type III approach did not find this effect to be significant (Table 3). The physicians' rated change after 3 weeks was predicted by the level of

Table 2. Means of outcome measures in various subtypes by treatments and timepoints of measurements

Outcome measures by subtype	Treatments by time							
	Alprazolam				Imipramine			
	Baseline	Week 9	Week 8	Endpoint	Baseline	Week 3	Week 8	Endpoint
Physician's global Evaluation								
Panic disorder uncomplicated	5.0	7.8	8.5	8.2	5.0	6.9	8.5	7.7
Panic disorder limited avoidance	5.0	7.3	8.3	8.0	5.0	7.2	8.5	8.2
Panic disorder with agoraphobia	5.0	7.3	8.3	7.8	5.0	6.7	8.1	7.7
Panic disorder without MDE	5.0	7.4	8.4	8.1	5.0	6.9	8.4	7.9
Panic disorder with MDE	5.0	7.3	8.2	7.8	5.0	7.1	8.1	8.1
Patient's Global Evaluation								
Panic disorder uncomplicated	5.0	7.6	8.4	8.1	5.0	6.8	8.4	7.6
Panic disorder limited avoidance	5.0	7.2	8.1	8.0	5.0	6.9	8.2	8.0
Panic disorder with agoraphobia	5.0	7.0	8.1	7.6	5.0	6.5	8.0	7.6
Panic disorder without MDE	5.0	7.3	8.2	7.9	5.0	6.7	8.1	7.7
Panic disorder with MDE	5.0	7.0	8.0	7.6	5.0	6.6	8.1	7.8
Total number of panic attacks (log.)								
Panic disorder uncomplicated	1.6	−0.2	−0.7	−0.6	1.8	0.4	−0.2	0.1
Panic disorder limited avoidance	1.8	0.2	0.2	−0.2	1.9	0.3	−0.5	−0.5
Panic disorder with agoraphobia	2.1	0.3	−0.4	−0.1	2.0	0.7	−0.4	−0.1
Panic disorder without MDE	1.8	0.0	−0.6	−0.4	1.9	0.4	−0.5	−0.2
Panic disorder with MDE	2.3	0.2	−0.2	0.1	2.5	0.6	−0.1	−0.1

Table 3. Determinants of physician's global assessment of change during active treatment trial of panic disorder (alprazolam, imipramine)

	df	Week 3	Week 8	Endpoint
Main effects				
Site	11	3.19*** (1.18)	3.29*** (1.54)	2.71*** (1.29)
Sex	1	–	–	–
Avoidance behaviour	2	3.21* (0.30)	–	–
MDE	1	–	–	–
Treatment	1	17.56** (6.08*)	–	43.28*** (17.82***)
Interaction Effects				
Site × sex	11	–	–	–
Site × avoidance behaviour	22	–	–	–
Site × MDE	11	–	–	–
Sex × avoidance behaviour	22	–	–	–
Sex × MDE	1	–	–	–
Avoidance behaviour × MDE	2	–	–	–
Treatment × site	11	–	1.19* (1.88*)	2.91*** (2.61**)
Treatment × sex	1	–	–	–
Treatment × avoidance behaviour	2	–	–	–
Treatment × MDE	1	–	–	–
Treatment × avoidance behaviour × MDE	2	–	–	–

Multivariate analysis of variance (degrees of freedom, F-values); F-value for type I analysis and for type III analysis (in parentheses) if significant effects are found; –, non-significant effects in type I or III analysis

* $0.01 \leq P \leq 0.05$

** $0.001 \leq P \leq 0.01$

*** $0.0001 \leq P \leq 0.001$

avoidance behaviour on baseline when using type I analysis; this result was not stable by type III analysis. Improvement at endpoint or after 8 weeks (completers) was not predicted either by avoidance behavior or by major depression or by the interaction between the two (Table 3). A significantly more pronounced improvement was observed for alprazolam after 3 weeks of treatment; alprazolam and imipramine were of equal efficacy in the endpoint and the completer (week 8) analysis (Tables 3, 4). The only significant interaction effect became apparent for treatment × site (week 8 and endpoint analysis in Table 3); this effect is due to a less favourable outcome for the alprazolam group in Northern European countries and a more favourable outcome for alprazolam in Southern America.

The figures for the outcome measure by the patients rated global improvement were very similar to the physicians' rated global improvement (Table 4); the main and the interaction effects with significant F-values were the same for both outcome measures with the exception of the main effects for "site", which were less important when using the patients' instead of the physicians' rated scale (Table 4).

2.2 Number of Panic Attacks

The total number of panic attacks per week decreased during the trial by a mean of approximately 80% (Table 2). The site variable explained a significant amount of variance of the change in the log transformed number of total panic attacks evidenced by type I as well as type III analysis (Table 5) for all three points of measurement. Again, the analysis of the outcome after three weeks of treatment demonstrated that the reduction of the number of panic attacks occurred earlier with alprazolam (Table 5). Avoidance behaviour predicted a less favourable response described by the change in the total number of panic attacks only in the endpoint analysis (type I); this significant main effect was not stable in the type III analysis of variance (Table 5).

Major depression revealed a significant impact on the change of the number of panic attacks only in the completer analysis (type III); this result was not obtained by type I analysis or the endpoint analysis.

Treatment with alprazolam was predictive for a faster response measured by the total number of panic attacks evidenced by a significant main effect of treatment in week-3 analysis (Table 5). The average degree of improvement was similar for both active treatments at the end of the trial in the completer and the endpoint analysis.

Interaction effects were found for "treatment × site" by the endpoint analysis (type I analysis); this effect was not found by type III analysis and was never observed for completer analysis (Table 5). A more stable interaction effect was observed for "treatment × avoidance behaviour", which was obtained in the completer as well as in the endpoint analysis, and by type I as well as by type III analysis; a more favourable improvement in panic disorder uncomplicated by evoidance behaviour treated with alprazolam was responsible for this effect (Table 2).

Separate analyses of variance were performed for the improvement in log transformed number of spontaneous panic attacks and in log transformed number of situa-

Table 4. Determinants of patient's global assessment of change during the treatment trial of panic disorder (alprazolam, imipramine)

	df	Week 3	Week 8	Endpoint
Main Effects				
Site	11	2.4* (1.70)	1.8 (1.4)	1.7 (1.4)
Sex	1	–	–	–
Avoidance behaviour	2	3.1* (1.3)	–	–
MDE	1	–	–	–
Treatment	1	15.1** (5.92*)	–	–
Interaction effects				
Site × sex	11	–	–	–
Site × avoidance behaviour	22	–	–	–
Site × MDE	11	–	–	–
Sex × avoidance behaviour	22	–	–	–
Sex × MDE	1	–	–	–
Avoidance behaviour × MDE	2	–	–	–
Treatment × site	11	–	1.82* (1.86*)	1.98* (1.82*)
Treatment × sex	1	–	–	–
Treatment × avoidance behaviour	2	–	–	–
Treatment × MDE	1	–	–	–
Treatment × avoidance behaviour × MDE	2	–	–	–

Multivariate analysis of variance (degress of freedom, F-values); F-value for type I analysis and for type III analysis (in parentheses) if significant effects are found; –, non-significant effects in type I or III analysis

* $0.01 \leq P \leq 0.05$
** $0.001 \leq P \leq 0.01$
*** $0.0001 \leq P \leq 0.001$

Table 5. Determinants of the total number of panic attacks (logarithm) during active treatment of panic disorder (alprazolam, imipramine)

	df	Week 3	Week 8	Endpoint
Main Effects				
Site	11	2.79** (0.90)	3.53 (1.93*)	2.71* (2.12*)
Sex	1	–	–	–
Avoidance behaviour	2	–	–	3.52* (0.90)
MDE	1	–	3.60 (4.70*)	–
Treatment	1	7.12** (4.16*)	–	–
Interaction effects				
Site × sex	11	–	–	–
Site × avoidance behaviour	22	–	–	–
Site × MDE	10	–	–	–
Sex × avoidance behaviour	2	–	–	–
Sex × MDE	1	–	–	–
Avoidance behaviour × MDE	2	–	–	–
Treatment × site	11	–	–	–
Treatment × sex	1	–	–	–
Treatment × avoidance behaviour	2	–	3.02* (3.07*)	3.49* (3.40*)
Treatment × MDE	1	–	–	–
Treatment × avoidance behaviour × MDE	2	–	–	–

Multivariate analysis of variance (degress of freedom, F-values for significant *P* values only); F-value for type III analysis are given in parentheses if significant interaction effects are found in type I analysis; –, if the *P* values in type I or type III analysis are non-significant ($P \geq 0.05$)

* $0.01 \leq P \leq 0.05$
** $0.001 \leq P \leq 0.01$
*** $0.0001 \leq P \leq 0.001$

tional panic attacks (dependent variables); the same sequence of independent variables were used as in the previous ANOVAs. Using the reduction of the number of spontaneous panic attacks as the outcome criterion, only a single independent variable contributed significantly by type I as well as by type III analysis: "treatment × avoidance behaviour" was significant by completer as well as endpoint analysis; this significant effect is due to a more favourable response of panic disorder uncomplicated to alprazolam and a more favourable response of agoraphobia to imipramine. No independent variable consistent across both methods of statistical analysis (type I, III) contributing to the reduction of situational panic attacks was obtained either for completer or for endpoint analysis.

Discussion

Major Findings

The validity of subtyping panic disorder by avoidance behaviour only received limited support. Subtyping by avoidance behaviour was not consistently predictive for the globally rated improvement at endpoint or after 8 or 3 weeks of treatment with active drugs; consequently, hypothesis 1 is rejected as far as subtyping by avoidance behaviour is concerned. However, a significant interaction of avoidance behaviour × treatment was found when defining outcome by the change of the number of panic attacks; this significant interaction was stable across different manners of analysis (endpoint as well as completer analysis, type I as well as type III analysis). This finding is mainly due to a more favourable response of panic disorder uncomplicated to alprazolam and a more favourable response of agoraphobia to imipramine. This finding may help in planning treatment. Consequently the validity of discriminating between panic disorder without avoidance behaviour and panic disorder with agoraphobia is supported. However, P values are only between 0.01 and 0.03, raising the question as to whether the statistical significance reflects clinical significance. Furthermore, a similar effect was not observed when using global assessment of change either by the physician or the patient as outcome measure. Consequently, this positive finding can only be interpreted as preliminary, and needs confirmation in an independent sample. A reaffirmation of the observation that subtypes have impact on outcome under active treatment would help when planning treatment in panic disorder and to confirm the clinical validity of subtyping panic disorder by avoidance behaviour.

Subtyping by major depression was not consistently predictive in any of the analyses (week 3, completer, endpoint) for either the global improvement scales or the change in the total number of panic attacks or in the number of spontaneous or situational panic attacks; a significant effect was only detected for completer analysis when defining the outcome by the change of the total number of panic attacks or the number of spontaneous panic attacks in type I analysis without being replicable by type III analysis. No other main effect or interaction effect including the variable "major depression" was found to be significant. Consequently neither hypothesis 1 nor hypothesis 2 could be confirmed as far as major depression is concerned. This result must be considered in the light of the exclusion criteria for selecting patients; cases of severe major depression and cases with primary major depression were excluded from the study.

Methodological Considerations

The CNCPS was primarily designed as a study of testing the efficacy of alprazolam in comparison with imipramine and placebo in panic disorder. Therefore a methodological condition desirable for testing the validity of subtyping panic disorder has not been fulfilled: the criterion of validity should be measured independently of the measure to be validated. In the design of the CNCPS the SCID-UP, which was the basis for subtyping according to avoidance behaviour and MDE, on the one hand, and the criteria of validity (treatment related data), on the other hand, were usually rated by the same physician. The relevance of this methodological shortcoming is hard to quantify. It may be that the raters had explicit or implicit hypotheses on the relationship between the variables to be validated and the criteria of validity which may blur the ratings: as there was no major support for the validity of subtypes in this report, it is unlikely that this kind of bias was relevant.

A further problem is that patients with a past major depressive episode, but without a current one, are allocated to the patient group without depression. It might be speculated that this subgroup behaves more like the depressed patient group; therefore, the differences between the depressed and the non-depressed patient group may be reduced. Two arguments motivated us to reject this possibility: the SCID-UP did not identify patients without current but with previous avoidance behaviour; therefore no alternative way was evident to handle the previous depressive and phobic symptomatology in an equivalent manner; additionally the study by Lesser et al. [15] using data from phase I of the CNCPS did not indicate a significant influence of past episodes of major depression on the major criteria of validity.

Comparison with Other Studies

Two previous studies compared the efficacy of imipramine and alprazolam in panic disorder [25, 28]. Both of these studies found that the two treatment groups improved comparably in global ratings, panic and agoraphobia by week 6 and later and imipramine took longer to improve agoraphobia. The results obtained in the CNCPS are similar to these previous findings. The low sample size in both cited previous studies precludes the analysis of subgroups and therefore they cannot contribute to the problem of the predictive power of agoraphobia.

The previous phase I of the CNCPS tested only alprazolam as active treatment in a more homogeneous sample than phase II. Both phases were rather similar

with respect to the selection criteria for the patients. The impact of avoidance behaviour on response to alprazolam in phase II cannot be compared with phase I, as corresponding analyses were not published for phase I, probably because the number of patients without agoraphobia was too low (only 5% had panic disorder uncomplicated, similar to the American centre in phase II).

No studies are available exploring the impact of avoidance behaviour on the outcome in anxiety symptomatology during drug treatment. However, several naturalistic follow-up studies [5, 17, 23] have shown that agoraphobia predicts an unfavourable outcome and chronic course. If this observation were also true for the short-term follow-up in a sample systematically treated with active drugs, a main effect for "avoidance behaviour" should emerge from the analyses of variance reported in this paper. However, this was not the case. Hence the phase II data indicate that the conclusion drawn from long-term follow-up studies with regard to the predictive status of agoraphobia is not transferrable to the short-term follow-up during treatment with active drugs.

On the other hand, the relevance of subtyping by avoidance behaviour for predicting differential response as found in this study, recommending alprazolam for panic disorder uncomplicated and imipramine for panic disorder with avoidance behaviour, has not been reported previously. However, this might be due to the low number of cases with panic disorder uncomplicated in previous drug trials. Because of the rather weak significance of this finding the validity of subtyping panic disorder by avoidance behaviour is not conclusively confirmed and it must rely for support mainly on long-term follow-up and family studies [5, 17, 23, 24].

This study can only partly contribute to the extended issue of comorbidity between panic and depressive disorders, as patients with primary major depression were excluded. Additionally, depression was defined by the DSM-III category "major depression", placing relatively high emphasis on non-specific features of autonomic disturbances; this concept may be too broad and may therefore miss the diagnostic value of more specific concepts of depression [27]. Under these limitations the comorbidity with MDE was not predictive for treatment outcome in measures of anxiety; the same result was observed by Lesser et al. [15] when active treatment was restricted to alprazolam. These findings focus on response of anxiety symptoms to active treatment and do not mean that the presence of secondary MDE in panic disorder patients is without any validity: the analysis of the baseline data of the CNCPS evidenced the descriptive validity of the concept of comorbidity [28]. The validity of this concept has also been demonstrated by follow-up and family study data [3, 23, 24]; it may also turn out that recognition of an MDE is necessary for treating associated depressive features [3].

Acknowledgements. This is a report form the Cross National Collaborative Panic Study, Second Phase. This study consists of a Steering Committee: James H. Coleman, Chairman (Kalamazoo, Mich., USA); Gerald L. Klerman, Co-Chairman (New York, NY, USA). Project Directors: Jose Luis Ayuso (Madrid, Spain); Per Bech (Hillerod, Denmark); Otto Benkert (Mainz, FRG); Sydney Brandon (Leicester, UK); Giovanni B. Cassano (Pisa, Italy); Jorge A. Costa e Silva (Rio de Janeiro, Brazil); George C. Curtis (Ann Arbor, Mich., USA); Juan R. de la Fuente (Mexico City, Mexico); Jose Guimon (Bilbao, Spain); Hanns Hippius (Munich, FRG); Yves Lecrubier (Paris, France); Carlos A. Leon (Cali, Colombia); Juan J. Lopez-Ibor Jr (Madrid, Spain); Heinz Katschnig (Vienna, Austria); Juan Massana (Barcelona, Spain); Mogens Mellergaard (Glostrup, Denmark); Jan-Otto Ottoson (Goteborg, Sweden); Ole J. Rafaelsen (deceased); Raben Rosenberg (Copenhagen, Denmark); Martin Roth (Cambridge, UK); Javier Sepulveda (Mexico City, Mexico); Leslie Solyom (Vancouver, B.C., Canada); Marco Versiani (Rio de Janeiro, Brazil); Jean Wilmotte (Marchienne-au-Pont, Belgium).

Data processing and preparation of the tape were performed by Dennis B. Gillings, Quintiles (Chapel Hill, N.C., USA) and by Philip W. Lavori and the staff of the Biostatistical Unit, Massachusetts General Hospital (Boston, Mass., USA). Statistical analysis reported in these papers was performed mainly by Philip W. Lavori and the staff of the Biostatistical Unit, Massachusetts General Hospital (Boston, Mass., USA). Dennis B. Gillings and the staff of Quintiles (Chapel Hill, N.C., USA) and A. Marx (Mainz, FRG) also contributed statistical advice and analyses.

This study has been sponsored and supported by The Upjohn Company, Kalamazoo, Mich., USA, through its Psychopharmacology Research Unit, Division of Medical Affairs, Robert P. Purpura, director; Carl P. Lewis; Cathy A. White.

References

1. American Psychiatric Association (1987) Diagnostic Criteria from DSM-III-R. Washington, D.C.
2. American Psychiatric Association (1988) Diagnostic and Statistical Manual of Mental Disorders, 3rd edn. Washington, D.C.
3. Argyle N (1990) A comparison of various categorical and dimensional descriptions of depression as an influence on outcome in the treatment of panic disorder.
4. Ballenger JC, Burrows GD, DuPont RL, Lesser IM, Noyes R, Pecknold JC, Rifkin A, Swinson RP (1988) Alprazolam in panic disorder and agoraphobia: results from a multicenter trial. Arch Gen Psychiatry 45:413–422
5. Cloninger CR, Martin RL, Clayton P, Guze SB (1981): A blind follow-up and family study of anxiety neurosis. Preliminary analysis of the St. Louis 500. In: Klein DE, Rabkin JG (eds) Anxiety: new research and changing concepts. Raven Press, New York, pp 137–154
6. Cross-National Collaborative Panic Study, Second Phase Investigators (1991) Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine and placebo. Br J Psychiatry (in press)
7. Freund RJ, Littell RC, Spector PC (1986) SAS system for linear models. Cary, N.C.
8. Kendell RE (1989) Clinical validity. Psychol Med 19:45–55
9. Klein DF (1964) Delineation of two drug responsive syndromes. Psychopharmacologia 5:397–408
10. Klein DF (1981) Anxiety reconceptualized. In: Klein DF, Rabkin JG (eds) Anxiety, new research and changing concepts. Raven Press, New York, pp 235–265
11. Klein DF (1987) Anxiety reconceptualized. Gleaning from pharmacological dissection – early experience with imipramine and anxiety. In: Klein DF (ed) Anxiety. Karger, Basel, pp 235–263
12. Klein DF, Klein HM (1989) The utility of the panic disorder concept. Eur Arch Psychiatry Neurol Sci 238:268–279
13. Klerman GL (1988) Anxiety and depression. In: Burrows G, Davies B (eds) Handbook of studies on anxiety. Elsevier, New York, pp 145–164
14. Klerman GL (1988) Overview of the Cross-National Collaborative Panic Study. Arch Gen Psychiatry 45:407–412

15. Lesser IM, Rubin RT, Pecknold JC, Rifkin A, Swinson RP, Lydiard RB, Burrows GD, Noyes R, DuPont RL (1988) Secondary depression in panic disorder and agoraphobia. Arch Gen Psychiatry 45:437–443
16. Lord FM (1963) Elementary models for measuring change. In: Harris CW (ed) Problems in measuring change. The University of Wisconsin Press, Madison, pp 21–38
17. Maier W, Buller R (1989) One year follow-up of panic disorder. Outcome and predictions of course. Eur Arch Psychiatry Neurol Sci 238:105–109
18. Maier W, Buller R, Sonntag A, Heuser I (1986) Subtypes of panic attacks and ICD-9 classification. Eur Arch Psychiatry Neurol Sci 235:361–366
19. Maier W, Philipp M, Buller R (1988) The value structured clinical interview. Arch Gen Psychiatry 45:963–964
20. Maier W, Rosenberg R, Argyle N, Buller R, Roth M, Brandon S, Benkert O (1989) Avoidance behaviour and major depression in panic disorder: a report from the Cross National Collaborative Panic Study. Psychiatr Dev 2:123–142
21. Marks IM (1987) Fears, phobias, and rituals. Oxford University Press, New York
22. Marks IM, Matthews AM (1979) Brief standard self-rating for phobic patients. Behav Res Ther 17:263–267
23. Noyes R, Clancy J, Hoenk PR, Slymen OJ (1980) The prognosis of anxiety neurosis. Arch Gen Psychiatry 31:173–177
24. Noyes R, Crowe RR, Harris EL, Hamra BJ, McChesney CM, Chaudhry DR (1986) Relationship between panic disorder and agoraphobia. Arch Gen Psychiatry 43:227–232
25. Rizley R, Kahn RJ, McNeir DM, Frankentheler LM (1986) A comparison of alprazolam and imipramine in the treatment of agoraphobia and panic disorder. Psychopharmacol Bull 16: 61–63
26. Roth M, Argyle N (1988) Anxiety, panic and phobic disorders: an overview. J Psychiatr Res 22:33–54
27. Roth M, Mountjoy CQ, Caetano D (1987) Further investigations into the relationship between depressive disorders and anxiety state. Pharmacopsychiatry 15:135–141
28. Sheehan DV (1982) Current views on the treatment of panic and phobic disorders. Drug Ther Hosp 7:179–193
29. Spitzer RL, Williams JBW (1988) Revised diagnostic criteria and a new structured interview for diagnosing anxiety disorders. J Psychiatr Res 22:55–85
30. Spitzer RL, Endicott J, Robins E (1978) Research diagnostic criteria: rationale and reliability. Arch Gen Psychiatry 35: 773–782
31. Tyrer P, Shawcross C (1988) Monoamine oxidase inhibitors in anxiety disorders. J Psychiatr Res 22 [Suppl 1]:87–98
32. World Health Organization (1978) International classification of diseases, 9th revision. WHO, Geneva