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Avoidance Behaviour: a Predictor of the Efficacy of Pharmacotherapy in Panic Disorder?

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Summary. The impact of the avoidance behaviour on the psychopharmacological treatment of panic disorder was explored in the Cross National Collaborative Panic Study ($n = 1134$ patients); in this double blind randomized trial alprazolam, imipramine and placebo were compared during an 8-week treatment period. Patients with extensive avoidance behaviour (agoraphobia) had the most profit from the active drugs. Counter expectancy these specific drug effects were most pronounced in avoidance behaviour. Active drugs (in particular imipramine) were especially more effective than placebo if the patients presented with associated avoidance behaviour. The results suggest that agoraphobia defines more a particular type of anxiety disorder overlapping with panic disorder than merely a severe state of panic disorder.

Introduction

The relationship of agoraphobia and panic disorder is currently a matter of debate. It is still questioned whether agoraphobia without current panic attacks or a history of panic attacks can really be found in treatment settings or in the community (Klein and Klein 1989). But even if panic attacks and agoraphobia are co-occurring it is unclear whether agoraphobia is just the consequence of preceding panic attacks or a particular new condition being aetiologically and by response to treatment different from the associated panic attacks. This unresolved issue is reflected by a discrepancy between two recently published major classification schedules: DSM-III-R (APA 1987) and ICD-10 (WHO 1989). Following DSM-III the DSM-III-R considers agoraphobia in patients with panic attacks as an indicator of enhanced severity of the basic panic disorder. This view is justified by the theory and the findings of Klein claiming that agoraphobia usually occurs as a sequela of recurrent spontaneous panic attacks (Klein and Klein, 1989). On the other hand, ICD-10 keeps agoraphobia and panic disorder separate; if both conditions occur together, agoraphobia takes priority. This position is indebted to the hypothesis that panic attacks, as other symptoms of dysphoria, are unspecific concommittants of more distinct conditions such as agoraphobia (Marks 1983). Roth and Argyle (1988) explored all alternative views on the relationship between panic and agoraphobia on the basis of the empirical studies available without coming to a clear decision and they recommended that this issue should be submitted to further empirical inquiry.

Both views might be tested by psychopharmacological treatment studies including patients with panic disorder with and without agoraphobia. Treatment studies may help to delineate a core psychopathological feature particularly responsive to this particular treatment among the variety of overlapping syndromes. The core psychopathological pattern identified may serve (1) as a target syndrome for treatment and (2) as a diagnostic entity likely to be linked to the pathophysiology of the disorder (Klein and Klein 1989). Keeping to this rationale panic attacks (in particular spontaneous panic attacks) and panic disorder (DSM-III/DSM-III-R) were isolated among the various symptoms of anxiety by their response to imipramine (Klein and Klein 1989). The priority taken by panic attacks with regard to associated phobic symptoms (DSM-III-R) is furthermore in line with the notion that imipramine and other effective antipanic drugs have no direct but only a later, secondary effect on avoidance behaviour (Klein and Klein 1989). The particular status of panic disorder in relation to depression is justified by the observation that the antipanic drug effects are not generally due to antidepressant drug effects (Klein and Klein 1989).

The following hypotheses are therefore implicit in the diagnostic entity of panic disorder as defined by DSM-III-R:

1) Imipramine blocks panic attacks (especially spontaneous panic attacks) more effectively than placebo.

2) Imipramine may also reduce avoidance behaviour and other features of anxiety.
3) The beneficial effect of imipramine on panic attacks and avoidance behaviour is not due to the association with depression.
4) The beneficial effect on avoidance behaviour is due to the benefit on panic attacks; the effect on avoidance behaviour is secondary and slower than the effect on panic attacks.

Other compounds (mainly alprazolam – Ballenger et al. 1988) have been found to affect panic attacks and avoidance behaviour in a similar manner. Therefore the hypotheses may be extended to these compounds too.

Hypothesis 4 is crucial for deciding between the DSM-III-R and the ICD-10 approach; the DSM-III-R approach is supported (1) if active compounds are efficacious by reducing panic attacks in absence as well as in presence of avoidance behaviour and (2) if they are efficacious by reducing phobic avoidance only if the number of panic attacks is also reduced significantly be these drugs. The ICD-10 approach is to be preferred if the efficacy of imipramine on the number of panic attacks requires the presence of agoraphobia.

Up to now this comparison has not been performed, as the comprehensive drug trials in panic disorder were mainly conducted in patients with associated marked avoidance behaviour, (e.g. the Cross National Collaborative Panic Study Phase I – a placebo-controlled 8-week trial using alprazolam as active treatment; Ballenger et al. 1988). The sample of the Cross National Collaborative Panic Study Phase II (1991) – a placebo-controlled 8-week trial using imipramine and alprazolam as active treatments in more than 1000 panic disorder patients recruited in 14 countries –, is more heterogeneous, with a variety of features including diagnostic subgroups (Klerman 1988); therefore, this sample allows one to compare patients with agoraphobia and avoidance behaviour with patients with panic disorder uncomplicated by avoidance behaviour with respect to the forementioned hypotheses.

Methods

Study Procedure

The CNCPS was a randomized and double-blind out-patient drug study, taking place in 14 countries (Belgium, Brazil, Canada, Colombia, France, Germany/Austria, Italy, Mexico, Spain, Sweden/Denmark, U.K., USA) and 23 sites, mainly University hospitals (outpatient clinics). Alprazolam or imipramine or placebo was assigned randomly to the patients (12 randomization blocks with 30 patients each) and started after at least a one-week drug-free period; in each randomization block, 10 patients received alprazolam, 10 received imipramine, and 10 received placebo. The overall efficacy of the treatments is reported in a forthcoming paper (CNCPS, Principal Investigators 1991).

The diagnostic inclusion criterion 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 or compulsive disorder or major depression (MDE) with melancholia was reported. Patients with a current or past MDE could be included, if the following conditions were fulfilled: (a) features of anxiety should be more prominent than those of depression during the present episode and (b) panic disorder had an onset before depression in the present episode. Patients receiving psychotherapy (including behaviour therapy) were excluded; exposure instructions should not be given.

Ratings and Reliability

A structured clinical interview (SCID-UP) (Spitzer and Williams 1988) was administered for checking the diagnostic inclusion and exclusion cirteria (especially for panic disorder) and for the assessment of associated diagnostic features (e.g. major depression, social, and simple phobia).

Ratings of the severity and of the changes in 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 being worst, 10 being best and 5 indicating no change; a global rating for severity of overall phobia (ranging from 0 to 10, with 0 being best and 10 being worst); the Hamilton-Anxiety-Scale (HAMA) (Hamilton 1959). 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. These five measures rated at week 8 or at endpoint were used as outcome measures in this report.

The reliability of the SCID-UP and the outcome measures were checked 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 and revealed sufficient reliability (Kappa/intraclass coefficient higher than 0.80). In addition, 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 (Maier et al. 1988).

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 with limited avoidance behaviour and panic disorder with extensive avoidance behaviour (panic disorder with agoraphobia). The last category is considered to be present if the patient is either staying at home or unable to leave the house without being accompanied because of the fear of a panic attack that may occur 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

One thousand one hundred and sixty-eight patients were randomized after meeting the selection criteria. The sample size for the baseline evaluation was $n = 1134$, as $n = 34$ data sets were incomplete. Three hundred and eighty-one patients received placebo, 379 alprazolam and 374 imipramine. After the first 3 weeks of treatment, 309 patients were still on placebo, 310 on alprazolam, and 352 on imipramine. At the scheduled end of the trial (end of week 8) 191 patients were still in the placebo group, 220 in the alprazolam group and 272 in the imipramine group.

The treatment groups are comparable in the following sociodemographic characteristics at baseline: mean age 34.6 years (placebo), mean age 34.3 years (alprazolam) and 33.5 years (imipramine); sex-ratio (% males): 39% (placebo), 36% (alprazolam) and 36% (imipramine); maritial status (% married): 64% (placebo), 68% (alprazolam) and 64% (imipramine). Mean age at onset of panic disorder was 29.2 years in the placebo group, 28.9 years in the alprazolam group, and 28.8 years in the imipramine group. Table 1 gives the distribution of subtypes across the treatment groups.

Table 1. Sample sizes during the trial in diagnostic subgroups defined by avoidance behaviour and major depression in the three treatment groups (alprazolam, imipramine, placebo)

	Panic disorders			Panic disorder	
	uncomplicated	limited avoidance	agoraphobia	without MDE	with MDE
Alprazolam					
Sample size on baseline	89	148	136	311	62
week 3[a]	87	138	131	297	59
week 8	79	119	116	261	53
Imipramine					
Sample size on baseline	82	156	140	321	57
week 3[a]	67	131	119	267	50
week 8	51	112	102	231	34
Placebo					
Sample size on baseline	85	156	140	320	61
week 3[a]	68	130	111	258	51
week 8	44	80	67	160	31

[a] Sample size for endpoint analysis

Data Analysis

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, also patients staying at least for a minimal period of time (3 weeks) on the treatment were evaluated by using their final measures when completing or before dropping out (so called endpoint or carrying forward analysis). Both approaches are not free of disadvantages: completer analysis was preselected for favourable outcomes, as most patients drop out because of insufficient efficacy of their treatment; endpoint analysis is biased, as those dropping out missed the chance to improve during the remaining time of the study.

Analyses of variance (ANOVA) within the framework of the general linear model (GLM) was used to test the efficacy of active treatment broken down by diagnostic subgroups (e.g. three subtypes defined by the various levels of avoidance behaviour). Five outcome measures were defined as the dependent variables: the global change measured by the physician, the number of spontaneous and situational panic attacks, the degree of phobic avoidance and global score of the HAMA. The variation across sites was controlled for by the first independent variable (categorical variable identifying the 12 centres). The second independent variable is also nominally scaled and defined by identifying all diagnostic subgroup × treatment combinations (e.g. three subtypes and three treatments define nine classes and therefore this independent variable has nine categories).

The first step of analysis is testing whether or not a significant proportion of variance of the outcome measure is explained by the subgroup × treatment variable (after extracting the variance due to variation across the centres). If a significant proportion of variance can be explained by this interaction term, the impact of diagnostic subgroups on treatment outcome is investigated with regard to the hypotheses to be examined: means of outcome measures between subgroups of patients (defined by diagnostic subtype and treatment) are tested for equality by Tukey's test (Kendall and Stuart, 1983, p 46); this method renders *simultaneous* confidence intervals for differences between group means (contrasts). Tukey's test takes the problem of multiple testing into account by considering *all* differences among subgroups referring to the same outcome measure simultaneously.

The general linear model loses power in estimating main effects, interaction effects and contrasts if the dependent variable does not fit to a normal distribution; as the frequency distributions of the number of panic attacks were skewed to the left, log transformation of these variables which are close to a normal distribution were preferred (for statistical analysis).

Table 2. Means of outcome measures by subtype, medication and time of measurement during the 8-week treatment phase

Subtype	Treatment	Global change (Physician)		Number of spontaneous panic attacks per week		Phobia score		HAMA global score	
		week 8	endp.	week 8	endp.	week 8	endp.	week 8	endp.
Uncomplicated	Placebo	7.6	6.9	1.2	2.1	1.7	2.1	7.6	9.5
	Alprazolam	8.5	8.3	0.2	0.6	1.5	1.5	6.6	7.0
	Imipramine	8.3	7.6	1.3	1.4	1.3	1.9	5.8	8.0
Limited avoidance behaviour	Placebo	7.8	7.1	0.8	1.8	2.8	3.6	7.7	10.2
	Alprazolam	8.2	8.0	1.3	1.1	2.6	2.9	8.0	8.6
	Imipramine	8.6	8.2	0.4	0.8	2.5	2.8	7.2	8.0
Extensive avoidance behaviour	Placebo	7.2	6.2	1.2	3.0	4.9	5.7	9.1	12.6
	Alprazolam	8.2	7.8	0.5	1.7	3.3	3.8	8.0	9.3
	Imipramine	8.1	7.7	0.4	0.7	3.4	3.9	7.6	9.1
With MDE	Placebo	7.6	6.7	1.1	2.4	3.2	4.0	7.9	10.7
	Alprazolam	8.3	8.0	0.7	0.9	2.4	2.7	7.4	8.1
	Imipramine	8.4	7.8	0.6	0.9	2.4	2.9	6.7	8.2
Without MDE	Placebo	7.7	6.9	0.6	1.8	3.8	4.5	10.0	12.0
	Alprazolam	8.2	7.8	0.8	2.9	3.4	3.7	9.2	10.4
	Imipramine	8.2	8.2	0.8	0.7	3.7	3.6	9.4	9.8

Results

1. Improvement During Treatment by Subtype

Direct measurements (global assessment of change by the physician) demonstrate a substantial improvement for all three subtypes in all treatment groups, as is revealed by Table 2. But the final scores of the outcome measures in any treatment group under any treatment indicate only imperfect remission in the mean (Table 2); therefore, a "ceiling effect" is unlikely for any subgroup or any treatment.

Table 2 shows the improvement during treatment described by selected outcome measures. The three treatments were randomly assigned and consequently baseline scores are balanced between the treatments for any subtype; the score at week 8 and endpoint might therefore serve as the criterion of efficacy of the active treatments.

2. Subtyping by Avoidance Behaviour

The subtype × treatment variable contributed significantly to the variation of all five outcome measures in the endpoint-analysis after allowing for the variation across sites (Table 3). The completer analysis, however, revealed a significant impact of the subtype × treatment interaction on only the two outcome measures "global change" and "severity of phobia avoidance". Focussing on each of the three particular diagnostic subgroups, both active drugs were significantly superior to placebo on the majority of outcome measures only in the agoraphobia subgroup. All five outcome measures indicated these specific beneficial drug effects in this diagnostic subgroup; the significant differences between active drugs and placebo with regard to the number of panic attacks and the global score of the HAMA, however, were only relatively small and were only found in the endpoint but not in the completer analysis.

In the two other diagnostic subgroups there were significant effects (compared with placebo) only on the global improvement score, on which imipramine but not alprazolam exerted beneficial effects (compared with placebo) in the subgroup defined by limited avoidance behaviour. Alprazolam (but not imipramine) exerted beneficial effects in the subgroup uncomplicated by phobic avoidance (Table 3); this effect was restricted to endpoint analysis.

3. Controlling for Association with Depression

Subtyping by avoidance behaviour is associated with the occurrence of current major depression (Maier et al. 1989). There have been reports on a more favourable response of panic disorder to psychopharmacological treatment if major depression is present at baseline; it has to be ruled out that a more favourable response in the "extensive avoidance behaviour" group is due to the increased rate of major depression. Therefore, such analogue analyses as in the previous section using the identical dependent variables (outcome measures) and subtyping by current major depression (yes/no) instead of by

Table 3. Response to treatment by various outcome measures: medication by avoidance behaviour-interactions (Results of completer analysis without brackets; results of endpoint analysis in brackets)

Outcome measures:	Global change (Physician)	Number of spontaneous panic attacks[a]	Number of situational panic attacks[a]	Phobis score	HAMA global score
Sources of variance (f-values)					
Sites ($df = 11$)	4.65 *** (3.88 ***)	2.05 * (1.99 *)	1.65 (1.31)	2.26 * (2.17 *)	3.67 *** (5.13 ***)
Medication × Avoidance behaviour (uncomplicated/limited/extensive) ($df = 8$)	6.61 *** (13.58 ***)	1.64 (5.01 ***)	1.15 (4.82 ***)	3.57 *** (8.44 ***)	1.53 (5.10 ***)
Contrasts of interest (p-values)					
Extensive × AL − Extensive × PL	** (**)	−(*)	−(*)	** (***)	−(*)
Extensive × IMI − Extensive × PL	* (**)	−(*)	−(*)	** (***)	−(*)
Limited × AL − Limited × PL	−(*)	−(−)	−(−)	−(−)	−(−)
Limited × IMI − Limited × PL	* (*)	−(−)	−(−)	−(−)	−(−)
Uncompleted × AL − Uncompleted × PL	* (**)	−(−)	−(−)	−(−)	−(−)
Uncompleted × IMI − Uncompleted × PL	−(−)	−(−)	−(−)	−(−)	−(−)

AL Alprazolam; IMI Imipramine; PL Placebo; − = $P > 0.05$; * = $0.01 < P < 0.05$; ** = $0.001 < P < 0.01$; *** = $P < 0.001$

[a] Transformation by log 10

Table 4. Response to treatment by various outcome measures: medication by depression-interactions (Results of completer analysis without brackets; results of endpoint analysis in brackets)

Outcome measures:	Global change (Physician)	Number of spontaneous panic attacks[a]	Number of situational panic attacks[a]	Phobis score	HAMA global score
Sources of variance (f-values)					
Sites ($df = 11$)	4.19 *** (3.56 ***)	1.88 * (2.04 *)	1.65 (1.31)	2.14 * (2.31 **)	3.57 *** (5.06 ***)
Medication × Major depression (yes/no) ($df = 5$)	8.25 (18.62 ***)	0.93 (5.43 ***)	1.04 (3.68 **)	3.96 ** (9.07 ***)	2.20 (7.32 ***)
Contrasts of interest (p-values)					
MDE yes × AL − MDE yes × PL	−(−)	−(−)	−(−)	−(−)	−(−)
MDE yes × IMI − MDE yes × PL	−(*)	−(−)	−(−)	−(−)	−(−)
MDE no × AL − MDE no × PL	** (**)	−(*)	−(*)	* (**)	−(**)
MDE no × IMI − MDE no × PL	** (**)	−(*)	−(*)	* (**)	−(**)

AL Alprazolam; IMI Imipramine; PL Placebo; − = Not significant; * = $0.01 < P < 0.05$; ** = $0.001 < P < 0.01$; *** = $P < 0.001$

[a] Transformation by log 10

avoidance behaviour were performed. Overall The differences between placebo and active treatments in the group of patients with major depression were not significantly higher than zero for any of the outcome measures ($P \leq 0.05$) (Table 4); these was only one single exception: imipramine was superior to placebo by endpoint analysis measured by the global improvement score but not for measures of anxiety: this significant result does not hold in the completer analysis. It is apparent from these results that the major depression subgroup is not more responsive to active treamtent than to placebo if the treatment outcome is measured by anxiety symptoms. On the other hand, the active treatments were significantly more effective ($P \leq 0.05$) than placebo only among inpatients without major depression (Table 4). Therefore, the higher rate of current major depression in the agoraphobia subgroup cannot account for the more favourable response to active treatment compared with placebo in this subgroup.

The impact of major depression on the outcome in the agoraphobia group might, however, be more complex; major depression might, for example, predict a more favourable response to active treatment only in the presence of avoidance behaviour; or, to put it in statistical terms, a three-way interaction treatment × avoidance behaviour × depression might affect the treatment outcome. In order to rule out this possibility, a further multivariate analysis testing the impact of the three-way interaction controlled for the variation across sites, the treatment × depression − and the treatment × avoidance behaviour − interaction was conducted; these analyses of variance were specified by a sequence of four independent variables: the site-variable, the two-way interactions avoidance behaviour × treatment and depression × treatment and finally the three-way interaction avoidance behaviour × major depression × treatment (defined as a variable with $3 \times 2 \times 3 = 18$ categories). Five analyses were conducted, one for each of the five outcome measure (dependent variables). The proportion of variance explained by this fourth independent variable (3-way interaction) was not significant ($P \leq 0.05$) for any of the outcome measures used. Consequently, an additional impact of the interaction between avoidance behaviour and major depression on any outcome measure was ruled out.

Discussion

Effects of Active Treatment on Panic Attacks and Avoidance Behaviour (Hypothesis 1 and 2)

The main report on the Phase II of the Cross National Collaborative Panic Study (CNCPS Phase II Principal Investigators, 1990) found imipramine and alprazolam to be efficacious in the whole sample; the number of spontaneous and situational panic attacks and the degree of phobic avoidance are significantly more improved by the active drugs than by placebo in the endpoint analysis, but not consistently so in the completer analysis; hypothesis 1 and hypothesis 2 presented in the introduction are supported by this result.

However, the present report reveals that the efficacies of both active drugs are not stable across different subtypes of panic disorder: the efficacy of active compounds compared to placebo, with regard to global measures, panic attacks and phobic avoidance was mainly due to agoraphobic patients, who did significantly better under imipramine and alprazolam. Panic disorder uncomplicated, however, responded nearly equally well to placebo, imipramine and alprazolam with regard to global measures of improvement, the number of panic attacks and the degree of phobic avoidance. The global measure of improvement indicated that alprazolam, but not imip-

ramine is efficacious also in the absence of avoidance behaviour.

In the subgroup of patients with limited phobic avoidance, imipramine but not alprazolam was effective, as measured by the global improvement score, but so not by the reduction of the number of panic attacks and of the degree of phobic avoidance. Compared with placebo, alprazolam was even less effective than imipramine in this subgroup.

This result cannot be accounted for by baseline differences between treatments in the agoraphobia group, as they were allocated randomly to the patients. Furthermore, these results cannot be accounted for by a ceiling effect in the less impaired group (panic disorder uncomplicated), as substantial improvements were indicated by all outcome measures in all comparison groups and the final scores are still far from being zero.

Endpoint analyses indicated significant improvements by the active drugs (compared with placebo) more often than completer analyses. The different drop-out rates in the placebo and the active treatment groups contribute to this discrepancy: patients on placebo are less likely to improve and may therefore drop out earlier. The completers of the 8-week trial are therefore preselected by a favourable drug response; given that the drop-outs under placebo are mainly due to insufficient improvement (CNCPS Phase II Principal Investigators, 1990), the discriminative power between placebo and active treatments is lower in the completer compared with the endpoint analysis.

Comorbidity with Depression and Therapeutic Effects (Hypothesis 3)

The therapeutic effects of the active compounds were not due to the presence of major depression. On the contrary, their beneficial effects were only found in absence of major depression. Hypothesis 3 presented in the introduction is therefore supported. Simultaneously, the thesis of Marks (1983) that imipramine is only superior to placebo by reducing the number of panic attacks if a substantial level of depression is present at baseline is clearly rejected. With regard to alprazolam, we were able to confirm the result of the Phase I study (Lesser et al. 1988) that specific therapeutic effects of alprazolam are not mediated by the presence of major depression at baseline.

Response of Panic Attacks Related to Presence and Improvement of Phobic Avoidance (Hypothesis 4)

The relationship among the specific pharmacological effects on the number of panic attacks and on the avoidance behaviour may be regulated by one of the following three patterns of dependence and independence among both dimensions:

a) the improvement of avoidance behaviour is mediated by the reduction of the number of panic attacks; this condition is identical to hypothesis 4 in the introduction.
b) the reduction of the number of panic attacks is mediated by the improvement of avoidance behaviour.
c) the beneficial effects of particular drugs on both syndromes are independent.

The first mentioned hypothesis predicts (1) that improvement in avoidance behaviour, as far as it due to the specific effect of the active compound, can only be observed if the number of panic attacks respond to these agents, too, and (2) that the specific effect on the number of panic attacks is more pronounced than the specific effects on avoidance behaviour within the first 3 months of treatment (Zitrin et al. 1983)

The results of this analysis did not support this view: on the contrary, significant effects of active compounds on the number of panic attacks were only found if avoidance behaviour was treated efficaciously by these compounds; the specific effects on avoidance behaviour are more pronounced than those on the number of panic attacks. Completer analysis did not reveal any significant difference measured by the number of panic attacks between the active compounds and placebo in any subgroup defined by avoidance behaviour or major depession; on the other hand, phobic avoidance was significantly improved by both active compounds in the presence of agoraphobia and in the absence of major depression by completer as well as by endpoint analysis. It is also difficult to conclude that the beneficial effects of imipramine and of alprazolam are due to the reduction of spontaneous panic attacks, as has previously been postulated (Zitrin et al. 1983). Our results are in agreement with Mavissakalian (1982), who also reported the difference between imipramine and placebo to the higher when measured by the degree of phobic avoidance than when measured by the number of panic attacks. As far as alprazolam is concerned, there is also agreement with the Cross National Collaborative Panic Study Phase I, where alprazolam was reported to be superior to placebo in reducing the number of spontaneous as well as the number of situational panic attacks only for the endpoint but not for the completer analysis; in contrast, the severity of avoidance behaviour was significantly improved by alprazolam compared with placebo in both types of analyses in the Phase I Study (Ballenger et al. 1988).

On the other hand, the study by Klein et al. (1987) in patients with agoraphobia found, by analysing intraindividual temporal patterns of improvement in panic and avoidance after 3 months treatment with imipramine, strong beneficial effects on the number of panic attacks but only milder effects on avoidance behaviour; the study by Zitrin et al. (1983) points in a similar direction. A comparison with both of these studies is limited by the different temporal length of the period of treatment; Klein et al. (1987) and Zitrin et al. (1983) reported data only for a scheduled treatment priod of 3 months. It is evident that a discussion of the mediation of anxiolytic drug effects should primarily rely on shorter periods of treatment; consequently the results of both studies do not invalidate our conclusions with regard to the medication of anxiolytic drug effects. Apart from these discrepancies with respect to the relative size of improvement

in both dimensions, there is agreement that in agoraphobic patients both the number of panic attacks and the degree of phobic avoidance are more responsive to imipramine compared with placebo (Klein et al. 1987, Zitrin et al. 1983).

Following the rationale proposed by Zitrin et al. (1983), we infer that the anxiolytic drug effects are due to the clinical features common to those patient groups responding to the specific effects of active drugs (especially imipramine) and absent in those patient groups not profiting from the specific effects of active drugs. As a beneficial effect of imipramine can only be found if a certain degree of avoidance behaviour is present at baseline, we infer that avoidance behaviour mediates the specific anxiolytic effects of imipramine in patients with panic disorder (DSM-III-R). Furthermore, a convincing beneficial effect of imipamine as well as of alprazolam can only be observed for the agoraphobia group; therefore the specific anxiolytic effects of both active drugs might be mediated by avoidance behaviour. This argument is not at variance with the findings of Klein et al. (1987) and Zitrin et al. (1983), as they did not include panic disorder patients without agoraphobia. Therefore, it is suggested that in the treatment settings the presence of avoidance behaviour and the improvement in avoidance behaviour is a pre-condition for a reduction of the number of panic attacks. However, the support of this hypothesis is only derived by comparing subgroups of patients and outcome measures within subgroups; the hypothesis needs to be further investigated by examining the intraindividual temporal pattern of the improvement in panic attacks and avoidance behaviour.

Limitations

Conclusions drawn from Table 3 are limited by different sample sizes in the three comparison groups. The subgroups defined by extensive and by limited avoidance behaviour are comparable by sample size, but the subgroup defined by uncomplicated avoidance behaviour is substantially smaller, although its size is sufficient to detect valid differences between the three treatments. Consequently, the "true" differences between the subgroup defined by agoraphobia and the subgroup defined by absense of avoidance behaviour might be less strong, as is apparent from Table 2.

The consideration of the raw values of the contrasts between active and placebo treatment for each subtype show that the differences between subgroups with regard to sample sizes cannot fully explain the observed relationship between presence of avoidance behaviour at baselines and the efficacy of active treatment (in particular of imipramine). Furthermore, active treatments are more efficacious in the subgroup defined by extensive avoidance behaviour compared to the subgroup defined by limited phobic avoidance; the comparison between both subgroups is not hampered by substantially different sample sizes.

This paper reports a retrospective analysis of potentially predictive variables in a drug trial which was designed to test the overall efficacy of alprazolam. This approach to predictor analysis does not take into account intervening confounding factors (e.g. variation of sample size among subgroups). Therefore, the predictive factors found by means of this type of retrospective analysis must be considered as preliminary and require replication.

Impact on Classification

DSM-III-R keeps to the principle that different degrees of phobic avoidance define different levels of severity of panic disorder. This view is supported by cross-sectional and family study data (Maier et al. 1989, Noyes et al. 1986). This notion leads to the hypothesis that all three subtypes of panic disorder defined by grades of severity of avoidance behaviour should respond similarly in a qualitative sense to the specific and non-specific treatment effects. Indeed, the three subtypes of panic disorder defined by different levels of avoidance behaviour were very similar in the substantial improvement due to the non-specific factors of psychopharmacological treatment indicated by substantial improvements on placebo. However, the subtype with agoraphobia and the subtype without avoidance behaviour were qualitatively different, as shown by the differences between placebo and active treatment (primarily imipramine) with regard to the number of panic attacks and the degree of phobic avoidance. This observation is compatible with the idea that panic disorder with agoraphobia as defined in DSM-III-R should be kept diagnostically separate from the other subtypes, as is, for example, proposed by ICD-10. This distinction might be relevant for planning treatment: agoraphobic patients are in need of specific treatment, whereas other panic disorder patients do equally well under a variety of conditions providing strong non-specific treatment factors.

A further argument is in favour of a diagnostic distinction between agoraphobic and other panic disorder patients; mainly the response of phobic avoidance but not the reduction of the number of panic attacks contributed most to the overall improvement, owing to specific treatment factors in patients with extensive phobic avoidance. Consequently, phobic avoidance in patients with panic disorder and extensive avoidance behaviour (DSM-III-R) presents as the major target syndrome for pharmacological treatment; phobic avoidance therefore should also be the main variable to identify the diagnostic class.

Impact on Treatment

The results reported provide useful guides to planning treatment in panic disorder and agoraphobia. Patients on placebo improved substantially on all outcome measures recorded; as a consequence, the difference between placebo and active treatments became rather small. Unspecific treatment factors are probably responsible for the high response rate on placebo; as the concept of panic disorder was not used in most of the participating centres outside the US before starting this ambitious study, patients received a lot of attention by the treating physician with regard to diagnosis and to monitoring the response to treatment; the physician explained exten-

sively the new concept of disease patients were suffering from; the patients received a diary and self-rating scales in order to observe and to monitor their complaints daily. These conditions share a number of features with behaviour therapy and may therefore partly share its therapeutic effects. A couple of treatment studies using psychopharmacological as well as psychotherapeutic strategies have demonstrated that specific pharmeco therapeutic effects become small or are even abolished if patients are simultaneously receiving behaviour therapy (Marks and O'Sullivan 1989). The substantial degree of improvement and the relatively small specific effects of alprazolam and imipramine show that extensive attention and instruction to patients are major tools in treating panic disorder. Drugs such as imipramine and alprazolam may be useful as supplements, and they are clearly indicated if the patient presents with agorapobia.

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