Chapter 2

Phobic symptoms as Predictors of Nonresponse to Drug therapy in Panic Disorder patients (a preliminary report)

Bernhard R. Slaap, M.A.
Irene M. van Vliet, M.D.
Herman G.M. Westenberg, Ph.D.
Johan A. Den Boer, M.D., Ph.D.

J Affect Disord 1995; 33: 31-8
Abstract

Factors that predict nonresponse to drug therapy (brofaromine or fluvoxamine) were investigated in a sample of 44 panic disorder patients. We used a strict definition of nonresponse to find patients who did not respond at all after 12 weeks of treatment. Using this definition 15 patients (32.6%) were considered nonresponders. Nonresponders had a higher score on the Blood-Injury subscore of the Fear Questionnaire and more often had high scores on several Fear Questionnaire subscores, indicative of comorbid phobic symptoms. These variables were subsequently used to predict nonresponse.
Introduction

The principal management strategy for patients with panic disorder (PD) with or without agoraphobia (DSM III-R, American Psychiatric Association, 1987) is drug therapy in combination with behaviour therapy. Various drugs have been shown to be effective in the treatment of PD: tricyclic antidepressants (for review see, Modigh, 1987; Liebowitz, 1989), selective serotonin reuptake inhibitors (for review see: Den Boer and Westenberg, 1990; Westenberg and Den Boer, 1994) and monoamine oxidase inhibitors (for review see, Tyrer and Shawcross, 1988). In all these studies beneficial effects on the number of panic attacks were reported. However, not all patients respond to treatment: between 20% to 40% of the patients are nonresponders. At present it is unclear whether there are differences in psychological or biological characteristics of responders vs. nonresponders.

Predicting response or nonresponse to antidepressant drugs would be very helpful, since it takes about four weeks for these drugs to become clinically effective. There is scarce literature on predictors of response in PD. Compared with the vast amount of literature on the prediction of response in depression (see for instance Joyce and Paykel, 1989) this area still seems relatively unexplored in PD. Some predictors of response to drug therapy have been reported in the literature: (1) early improvement on the number of spontaneous panic attacks during treatment with alprazolam (Albus et al., 1990), (2) lower baseline scores on the Hamilton Anxiety Scale (HAS; Hamilton, 1959) (Liebowitz et al., 1986; Rosenberg et al., 1991; Scheibe et al., 1992; Woodman et al., 1994), (3) lower baseline scores on the Hamilton Depression Scale (HDS; Hamilton, 1967) (Rosenberg et al., 1991), (4) age over 40 (Woodman et al., 1994) and (5) lower baseline levels of phobic symptoms (Woodman et al., 1994).

In the present study we report on possible predictors for nonresponse to drug treatment in PD patients. The idea to study the nonresponders is not without precedent: there have been others who have tried to define clinical characteristics of nonresponders to e.g. behaviour therapy (Emmelkamp and Foa, 1983; Emmelkamp and van den Hout, 1983).

The aim of the present study is to look for clinical variables, measured at baseline, which may distinguish responders from nonresponders in a patient sample suffering from PD. The variables that differ significantly between the groups will be used to predict nonresponse to drug therapy.

Materials and Methods

Design

For the present study the data of two previously published studies were pooled. In these studies brofaromine, a selective and reversible monoamine oxidase inhibitor (MAOI), was compared with either fluvoxamine, a selective serotonin reuptake inhibitor (SSRI) (van Vliet et al., 1994) or placebo (van Vliet et al., 1993). Both studies had a double blind design and
lasted 12 weeks. The psychometric scales were similar in both studies. By pooling the data we obtained a data base of 60 patients. Twenty nine patients were treated with brofaromine, 15 patients were treated with fluvoxamine and 16 patients received placebo. The 44 patients who received drug treatment have been studied in this paper. The patients treated with placebo were excluded from the study because we were interested predictors of nonresponse to active drug treatment. Possible predictors of nonresponse to placebo will be the subject of another article.

The patients who received drug treatment where analysed as one group in this study. Analysis of variance with drug (brofaromine or fluvoxamine) as covariate showed no significant differences between the drug groups. Furthermore from the study of van Vliet et al. (1994) it appears that there are no significant differences between brofaromine and fluvoxamine on any of the outcome measures.

Nonresponders were defined as patients who still had panic attacks at endpoint and who had a reduction of less then 50% on the Agoraphobia subscore of the Fear Questionnaire (FQ; Marks and Mathews, 1979). Patients who were free of panic attacks at endpoint and/or showed an improvement of 50% or more on the Agoraphobia subscore were considered to be responders.

Patients

For each study thirty patients were recruited from the outpatient clinic of the department of Biological Psychiatry of the University Hospital in Utrecht. The studies were approved by the Ethics Committee of the Academic Hospital and informed consent was obtained from all patients. Included in the studies were patients suffering from PD with Agoraphobia (59 patients) or without Agoraphobia (1 patient) according to DSM-III-R criteria. Excluded were patients with other anxiety disorders, major affective disorder or psychotic disorder, alcohol abuse, severe sleep disturbance and patients suffering from other medical problems on the basis of a complete medical evaluation. Patients with a score of 15 or more on the HDS were also excluded. During treatment the use of other psychotropic drugs was not allowed except the use of oxazepam to a maximum of 20 mg daily, if required. Sixty patients, 54 females and 6 males, were enrolled and treated for 12 weeks using a double-blind placebo controlled design. Mean age (± SD) was 36.6 ± 7.1 years (ranging from 20 to 50) and the mean duration of illness was 9.7 ± 6.2 years (ranging from 0.6 to 32).

In each study patients were randomly allocated to one of the two treatment groups: brofaromine or placebo in one study (van Vliet et al., 1993) brofaromine or fluvoxamine in the other (van Vliet et al., 1994).

Symptom assessment

At baseline and at the end of treatment the HDS was completed. Efficacy of treatment was further assessed using the FQ and the HAS. The FQ and the HAS were completed on
baseline and at the end of week 1, 2, 4, 8 and at the end of week 12. The Utrecht Panic Inventory (UPI) was completed daily. This is a questionnaire, based on the DSM-III-R definition of a panic attack, measuring the frequency and intensity of panic attacks and the associated symptoms. Blood plasma levels of brofaromine or fluvoxamine were monitored to ensure compliance to treatment.

Data analysis

Data were analysed using a commercially available statistical package (SPSS Inc.). To analyse the differences between responders and nonresponders an ANOVA was performed on the baseline variables. When the assumption of normality was violated a nonparametric test (Kruskal-Wallis analysis of variance) was applied. The categorical data were tested with the Fisher exact test (two-tail).

In order to further investigate the influence of phobic symptoms on nonresponse indicator variables were computed which divided patients in high or low scorers on a FQ subscore. Patients were considered high scorers on a FQ subscore when they had a score of 20 or higher. (The maximum score on subscore is 40.) From normative data of the FQ in the article of Oei et al. (1991) it appears that approximately half of the patients with PD with agoraphobia had a score of 20 or more on the FQ Agoraphobia subscore (FQ-AG). About 30% of the patients had a score of 20 or more on the FQ Social Phobia subscore (FQ-SP) and about 25% had a score of 20 or more on the FQ Blood-Injury phobia subscore (FQ-BI).

For the prediction of nonresponse to drug therapy a logistic regression analysis was carried out for all significant baseline variables. Subsequently a best fitting model was made with all significant variables using logistic regression with backwards elimination. As criterion for variable selection the likelihood-ratio test was used.

Results

Clinical variables

Of the 44 patients receiving medication (brofaromine or fluvoxamine) there was one patient who did not complete the UPI, therefore this patient was not entered into the statistical analysis. Of the remaining 43 patients, 15 patients (32.6%) were nonresponders, 11 patients (37.9%) of the brofaromine group and 4 patients (28.6%) of the fluvoxamine group. The difference in the percentage of nonresponders is not significant.

There were no significant differences between responders and nonresponders on sex, age or age at onset. Based on the assessment of blood plasma levels of brofaromine and fluvoxamine it could be concluded that all patients were compliant to treatment.

Responders had a baseline score on the HAS of 24.93 ± 2.57 and nonresponders had a score of 25.27 ± 4.27 (Table 1). This difference was not significant. The difference of the
scores on the HDS between responders (9.68 ± 2.07) and nonresponders (10.80 ± 2.11) is not significant.

The FQ measures the amount of avoidance of a broad range of phobic stimuli on a nine-point scale ranging from 0 'would not avoid it' to 8 'always avoid it'. The questionnaire consists of 15 items. The sum of the item scores constitutes the Total Phobia score. Three phobic subscores can also be calculated, each containing 5 items. The subscores are: the Agoraphobia subscore (FQ-AG), the Blood-Injury Phobia subscore (FQ-BI) and the Social Phobia subscore (FQ-SP). Nonresponders showed significantly higher ratings on the Blood-Injury Phobia subscore (F=8.0; df=1,41; p=0.0072) (Figure 1). The Total Phobia score just failed to reach statistical significance (p=0.08).

There were no significant differences in the percentage of patients having a high score (20 or more) on the FQ-AG or the FQ-SP (Table 2). Of the nonresponders 53.3% had a high score on the FQ-BI. 14.3% of the responders had a high score on the FQ-BI. This difference is significant (Fisher Exact test; p=0.0117).

The difference in the percentage of patients with a high score on both the FQ-AG and the FQ-SP was not significant (Figure 2). Nonresponders more often had a high score on both the FQ-AG and the FQ-BI (Fisher Exact test; p=0.0040). There were no responders who had a high score on both the FQ-SP and on the FQ-BI. Of the nonresponders 33.3% did have a high score on both these subscores. This result is significant (Fisher Exact test; p=0.0031). The same 33.3% of the nonresponders had a high score on all three subscores of the FQ (Fisher Exact test; p=0.0031).

Two variables in Table 1 were not measured at baseline. These two variables from the UPI were measured in the first week of the study. Naturally they can not be used as baseline predictors of nonresponse, but they do give meaningful information on the number of panic attacks at the beginning of drug treatment. In week 1 nonresponders had almost twice as many panic attacks as responders (8.07 ± 1.39 vs. 4.86 ± 0.77). This difference is statistically significant (F=4.87; df=1,41; p=0.0329). Nonresponders also reported to experience more tingling sensations (Kruskal-Wallis; p=0.0199).

**Prediction of nonresponse**

For the prediction of nonresponse to drug therapy we carried out a logistic regression analysis on all significant baseline variables. Every single baseline variable significantly predicted nonresponse (p<0.01). A best fitting model was also calculated by carrying out a logistic regression analysis with all significant variables in the initial solution. The backwards elimination process resulted in a prediction based on one variable only. The indicator variable: 'having a high score on the FQ-AG, the FQ-SP and on the FQ-BI' was the only variable left in the equation. With this equation the overall percentage correctly classified patients was 76.7%. All the responders were correctly classified, but ten nonresponders (66.7%) were incorrectly classified as responders. The fit of the model was reasonable ($\chi^2 =4.54; df=1; p=0.0330$).
Discussion

In this study we found that nonresponders to drug therapy had a higher score on the Blood-Injury subscore of the Fear Questionnaire. A larger percentage of patients in the nonresponder group had a high score (of 20 or more) on various FQ subscores. At the end of week 1 they had almost twice as many panic attacks.

We were unable to replicate the findings of others that there are baseline differences between responders and nonresponders on the HAS (Liebowitz et al., 1986; Rosenberg et al., 1991) or the HDS (Rosenberg et al., 1991). A possible explanation for this might be that, in comparison with others, our sample was more homogeneous where HAS or HDS are concerned. The 95% confidence interval of the HAS in our sample (n=44) was 19.08 to 31.92. The sample (n=29) in the study of Liebowitz et al. (1986) had a 95% confidence interval of the HAS of 3.6 to 29.6. In the study of Rosenberg et al. (1991) the mean HAS and HDS of the whole sample (n=123) was not stated, but they did report on the mean (± SD) of the responders and the nonresponders on these scales. The standard deviation for the HAS and the HDS scores of responders and nonresponders was between 5.5 and 6.8. In our sample this value ranges from 2.2 to 4.3. The scores on the HAS and the HDS in our sample had a smaller range which may have obscured differences (if any) between responders and nonresponders to become evident.

Rosenberg et al. (1991) concluded that nonresponse was associated with more severe symptoms at baseline. Nonresponders in their study had higher scores on the HAS and the HDS and they had a lower panic frequency at baseline. In this study we did not have a baseline panic frequency, but our finding that nonresponders had a higher number of panic attacks at the end of week 1 seems to corroborate the conclusion of Rosenberg et al. (1991) that nonresponders are more severely ill.

Woodman et al. (1994) found lower baseline phobic symptom level to be a predictor of response to alprazolam. They used the Overall Phobia Rating (Ballenger et al., 1988) to measure general phobic anxiety. This 11-point phobic anxiety scale ranges from 0 'no phobia' to 10 'extremely distressing or restricting'. In our study we used the FQ and its subscores, which give more specific information on the phobic symptoms that the patients experience. The nonresponders in our sample had a higher score on the Blood-Injury subscore and a greater percentage of them had a high score on several subscores. Our results seem to corroborate their findings, since the Overall Phobia Rating measures distress caused by all phobias.

In contrast to the findings of Woodman et al. (1994) that a high level of phobic anxiety is associated with poor treatment response Maier et al. (1991) reported that patients with extensive avoidance behaviour had the most profit from the active drugs (alprazolam or imipramine). In their study the effect of the treatment was most pronounced with respect to avoidance behaviour. In our study there were no statistically significant differences, as measured by the FQ-AG, between responders and nonresponders on agoraphobic behav-
Comparison between studies is, however, hampered by the fact that Maier and co-workers and Woodman and co-workers used drugs with sedative properties whereas in our study we did not. It appears that the relationship between agoraphobic behaviour and response to psychopharmacological treatment is unclear. Further research is needed to clarify what the influence is of the severity of agoraphobic avoidance on treatment response to antidepressant drugs.

The higher scores of the nonresponders on the Blood-Injury subscore of the FQ and the larger percentage of patients with a high score on the FQ subscores might suggest that these nonresponders had comorbid phobic symptoms. It appeared that several patients had symptoms of a blood-injury phobia and/or a social phobia. Eight patients (53.3%) in the nonresponder group had a score of 20 or more on the FQ-BI, compared to 4 patients (14.3%) in the responder group. Five patients (33.3%) in the nonresponder group had a score of 20 or more on both the FQ-BI and the FQ-SP. There were no such patients in the responder group. These patients did not fulfil diagnostic criteria for another (comorbid) anxiety disorder, since this was one of the exclusion criteria. It is possible that some patients may have suffered from symptoms reminiscent of a simple phobia (like blood-injury phobia) or a social phobia.

The available literature on comorbidity among the anxiety disorders suggests that a large percentage of patients with PD has an additional diagnosis. The percentage of PD patients with an additional Axis I diagnosis ranges between 44% (Di Nardo and Barlow, 1990) and 83.3% (Starcevic et al., 1992). Differences in the reported percentages reflect differences in diagnostic criteria and differences between samples. It should be emphasised that the degree of diagnostic comorbidity is directly related to the threshold set to determine the presence or absence of various disorders (Frances et al., 1990). In the above cited studies as well as in other papers (Brown and Barlow, 1992; de Ruiter et al., 1989; Sanderson et al., 1990) it appears that simple phobia or social phobia is the most often occurring additional diagnosis in PD. The percentages for a comorbid simple phobia vary between 6.3% (Brown and Barlow, 1992) and 46.6% (de Ruiter et al., 1989). For a comorbid social phobia the percentages vary between 9.6% (de Ruiter et al., 1989) and 40.7% (Starcevic et al., 1992) (note: all percentages are summed over all PD patients).

If we compare our findings of baseline phobic symptoms with the findings in the literature on comorbidity it appears that our results are comparable. Of the 43 patients in the study, 12 patients (27.9%) had a high score on the FQ-BI. There are 14 patients (32.6%) with a high score on the FQ-SP. Both these percentages fall in the ranges cited above.

We have found that nonresponders to drug treatment more often have comorbid phobic symptoms, as compared to responders. A similar finding has been reported before: Pollack et al. (1993) found in their follow-up study that a comorbid social phobia was associated with poor treatment response.

That a blood-injury phobia can interfere with the treatment of PD has been noted before. Di Nardo and Barlow (1990) described a case of an agoraphobic patient with a distinct blood-injury phobia. This phobia interfered with their treatment program in such a way that
it needed to be treated first. Emmelkamp and Bouman (1991) discussed specific difficulties 
and complications in the treatment of PD. Among the additional anxiety disorders that 
complicate the treatment of PD, they described blood-injury phobia as well. Further 
research is needed to find out what the influence is of comorbid anxiety symptoms or 
syndromes on the treatment of PD.

The second aim of the study was the prediction of nonresponse to drug therapy. We first 
predicted nonresponse by using every significant baseline scale separately. All these variables 
significantly predicted treatment outcome. In addition we aimed to create a best fitting 
model by entering all significant baseline variables in a stepwise logistic regression analysis. 
This resulted in a prediction based on one variable only. The indicator variable 'having a 
high score on all three FQ subscores' was the only variable in the model. The other 
indicator variables were subsets of the indicator variable in the equation, so they did not add 
to prediction. The FQ-BI also did not add significantly to the prediction to be entered in the 
equation by the logistic regression routine. We had hoped to base a prediction on several 
variables, but this was impossible because not that many variables were significant at 
baseline.

In summary, in this preliminary report we have found that on baseline nonresponders to 
drug therapy differ from responders in that they have a higher FQ Blood-Injury subscore. 
They more often had a high score on FQ subscores, indicative of comorbid phobic symp-
toms. This predicted nonresponse to drug treatment. A methodological flaw of the present 
study might be the limited number of patients that was studied. In future studies we intend 
to include larger numbers of patients, possibly enabling us to further substantiate present 
findings.
References


Table 1: ANOVA/ Kruskal-Wallis of the psychometric scales.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Responder (mean ± sem)</th>
<th>Nonresponder (mean ± sem)</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton Anxiety Scale</td>
<td>24.93 ±2.57</td>
<td>25.27± 4.27</td>
<td>NS</td>
</tr>
<tr>
<td>Hamilton Depression Scale</td>
<td>9.68 ±2.07</td>
<td>10.80 ±2.11</td>
<td>NS</td>
</tr>
<tr>
<td>Fear Questionnaire Total Score</td>
<td>56.75 ±3.10</td>
<td>66.07 ±4.25</td>
<td>NS</td>
</tr>
<tr>
<td>Fear Questionnaire Agoraphobia subscore (FQ-AG)</td>
<td>30.36±1.54</td>
<td>30.67±1.90</td>
<td>NS</td>
</tr>
<tr>
<td>Fear Questionnaire Social Phobia subscore (FQ-SP)</td>
<td>14.79±1.75</td>
<td>17.53±2.21</td>
<td>NS</td>
</tr>
<tr>
<td>Fear Questionnaire Blood-Injury subscore (FQ-BI)</td>
<td>11.61 ± 1.44</td>
<td>17.87 ± 1.37</td>
<td>F=8.00; df=1,41; p=0.0072</td>
</tr>
<tr>
<td>UPI week1: Number of panic attacks</td>
<td>4.86 ± 0.77</td>
<td>8.07 ± 1.39</td>
<td>F=4.87; df=1,41; p=0.0329</td>
</tr>
<tr>
<td>UPI week1: Tingling sensations</td>
<td>0.64 ± 0.17</td>
<td>1.94 ± 0.49</td>
<td>Kruskal-Wallis; p=0.0199</td>
</tr>
</tbody>
</table>
Table 2: Fisher Exact test (two-tail) of the indicator variables of the Fear Questionnaire.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Responder (percentage)</th>
<th>Nonresponder (percentage)</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicator variable: Having a score &gt;= 20 on the FQ-AG</td>
<td>85.7%</td>
<td>93.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Indicator variable: Having a score &gt;= 20 on the FQ-SP</td>
<td>28.6%</td>
<td>40.0%</td>
<td>NS</td>
</tr>
<tr>
<td>Indicator variable: Having a score &gt;= 20 on the FQ-BI</td>
<td>14.3%</td>
<td>53.3%</td>
<td>p=0.0117</td>
</tr>
<tr>
<td>Indicator variable: Having a score &gt;= 20 on the FQ-AG and on the FQ-SP</td>
<td>25.0%</td>
<td>33.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Indicator variable: Having a score &gt;= 20 on the FQ-AG and on the FQ-BI</td>
<td>10.7%</td>
<td>53.3%</td>
<td>p=0.0040</td>
</tr>
<tr>
<td>Indicator variable: Having a score &gt;= 20 on the FQ-SP and on the FQ-BI</td>
<td>0.0%</td>
<td>33.3%</td>
<td>p=0.0031</td>
</tr>
<tr>
<td>Indicator variable: Having a score &gt;= 20 on the FQ-AG and on the FQ-SP and on the FQ-BI</td>
<td>0.0%</td>
<td>33.3%</td>
<td>p=0.0031</td>
</tr>
</tbody>
</table>
Figure 1: Baseline mean (SEM) subscores and Total Phobia score of the Fear Questionnaire.

Legend: * = statistically significant difference; FQ-AG = agoraphobia subscore; FQ-BI = blood-injury phobia subscore; FQ-SP = social phobia subscore; TOTAL = total phobia score
Figure 2: Percentage of patients having a high score on two subscores of the Fear Questionnaire simultaneously.

Legend: * statistically significant difference between responders and nonresponders; AG & SP >= 20: a score of 20 or more on both the agoraphobia subscore and the social phobia subscore of the FQ; AG & BI >= 20: a score of 20 or more on both the agoraphobia subscore and the blood-injury phobia subscore of the FQ; SP & BI >= 20: a score of 20 or more on both the social phobia subscore and the blood-injury phobia subscore of the FQ.