The prediction of nonresponse to pharmacotherapy in panic disorder
Slaap, Bernhard Reinier

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2001

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Chapter 4

Responders and Nonresponders to Drug Treatment in Social Phobia: Differences at baseline and prediction of response

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

Summary

Differences between responders and nonresponders to drug therapy were investigated in social phobia. Two previously published studies were pooled to obtain data of 30 patients who were treated for 12 weeks with brofaromine or fluvoxamine. Four criterion variables were used to divide patients in responders and nonresponders. Depending on the criterion variable up to 72% of the patients were regarded as responders. Nonresponders differed from responders in that they had a higher heart rate and a higher blood pressure. They were also characterised by higher scores on several psychometric scales, indicative of illness severity.
Introduction

In panic disorder (PD) there is a growing interest in the prediction of response, or non-response to treatment, as witnessed by the increasing number of studies concerning this topic. Factors which have been identified as being predictive of nonresponse to treatment in PD are: severity of illness (Noyes, Jr. et al 1984; Rosenberg et al 1991; Scheibe et al 1992; Basoglu et al 1994; Woodman et al 1994), intensity of phobic avoidance (Rosenberg et al 1991; Basoglu et al 1994; Woodman et al 1994), duration of illness (Noyes, Jr. et al 1984; Basoglu et al 1994), presence and severity of depressive symptoms (Rosenberg et al 1991; Basoglu et al 1994; Woodman et al 1994) and comorbidity (Mavissakalian and Hamann 1987; Reich 1988; Black et al 1994).

In contrast, publications on the prediction of response in social phobia (SP) are still very scarce. Gelernter et al. (1991) acknowledged that ‘it will be important to examine the clinical and biological characteristics of partial and complete responders and nonresponders to delineate predictors of treatment response’, but our search of the literature came up with only very few studies on this subject. Recently Reich and co-workers (1994) reported on a follow-along study of the course of SP. No significant differences between responders and nonresponders were found in this study with a duration of 65 weeks. Alcohol abuse has been reported as being associated with poor outcome in an open trial with tranylcypromine (Versiani et al 1988). In this study patients with a comorbid diagnosis of alcohol abuse or alcohol dependence were included. Five out of eight patients with comorbid alcohol abuse or dependence did not respond, whereas only one out of 21 patients with only SP appeared to be a nonresponder. In a pilot study Turner (1987) reported that in SP the existence of a DSM-III (1980) personality disorder was associated with poor treatment response to short-term cognitive behaviour therapy. Seven patients with a concomitant personality disorder all showed significantly less improvement after 16 weeks of treatment than the six patients without an Axis II diagnosis.

In this study we investigated differences on baseline between responders and nonresponders to drug treatment with brofaromine, a selective and reversible monoamine oxidase-A inhibitor (MAO-A-I), or fluvoxamine, a selective serotonin reuptake inhibitor (SSRI). The purpose of this study was to identify possible differences, like demographic variables, psychological characteristics, as derived from psychometric scales, and illness characteristics which might predict response to treatment.

Materials and Methods

Design

For the present study the data of two previously published studies were pooled. In these placebo controlled studies the effect of brofaromine, a MAOI (van Vliet et al 1992), or fluvoxamine, an SSRI (van Vliet et al 1994), was evaluated. Both studies had a double blind
design and lasted 12 weeks. In both studies patients could enter the second part of the study (the follow-up study), in which they were treated for another 12 weeks under double blind conditions, if they considered themselves improved. The psychometric scales were similar in both studies. By pooling the data we obtained a data base of 60 patients. Fifteen patients were treated with brofaromine, 15 patients were treated with fluvoxamine and 30 patients received placebo. The 30 patients who received active drug treatment are presented in this paper.

The patients treated with placebo were excluded from the study because we were interested in predictors of nonresponse to active drug treatment. No separate analysis was performed for the placebo group because hardly any patients on placebo could be considered as responders. The response rates of the patients treated with placebo varied between 4% and 11%, which forbade any comparison.

For the analysis of nonresponse to drug treatment we defined four criterion variables, which divide the patients in responders and nonresponders. The criteria were:

- A reduction of 50% or more on the score of the Hamilton Anxiety Scale (HAS; (Hamilton 1959))
- A reduction of 50% or more on the score of the Social Phobia Scale-Fear subscale (SPS-fear; (Liebowitz 1987))
- A reduction of 50% or more on the score of the Social Phobia Scale-Avoidance subscale (SPS-avoid)
- Patient entered the follow-up study

Three criteria correspond to a significant and clinically relevant improvement. The fourth criterion is an operationalisation of improvement according to the patient. Only those patients who thought themselves improved or much improved decided to enter the follow-up study, in which they were treated for another 12 weeks under double blind conditions.

Patients

For each study thirty patients were recruited from the outpatient clinic of the department of 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 social phobia according to DSM-III-R criteria. Excluded were patients with another anxiety disorder, major affective disorder or psychotic disorder, alcohol or drug abuse 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. Not many patients used oxazepam: About half of the patients did not use any oxazepam at the beginning of the study, nor at the end. About 40% of the patients used 5 to 10 mg oxazepam incidentally, only when necessary, at the beginning of the study. About 10% of
the patients used 10 mg daily and one patient used 20 mg daily. None of the patients used more oxazepam at the end of the study than at the beginning.

Sixty patients, 37 females and 23 males, were enrolled and treated for 12 weeks using a double-blind placebo controlled design. Mean age (± SD) was 34.0 ± 8.6 years (ranging from 21 to 54) and the mean duration of illness was 13.0 ± 9.1 years.

In each study patients were randomly allocated to one of the two treatment groups: brofaromine or placebo in one study (van Vliet et al 1992) fluvoxamine or placebo in the other (van Vliet et al 1994).

**Symptom assessment**

Efficacy of treatment was assessed using the Social Phobia Scale (SPS; (Liebowitz 1987)) and the Hamilton Anxiety Scale (HAS; (Hamilton 1959)). The SPS is a 22-item self-rating scale that contains a broad range of items social phobics have difficulty with. This scale contains items of social and performance difficulties that are rated separately on four-point scales for anxiety and avoidance. At baseline and at the end of the treatment period the Hamilton Depression Scale (HDS; (Hamilton 1967)) was completed. At these same timepoints patients completed the 90-item Symptom Checklist (SCL-90; (Derogatis et al 1973)). The SPS and the HAS were completed on baseline and at the end of week 1, 2, 4, 8 and at the end of week 12. Blood plasma levels of brofaromine or fluvoxamine were monitored to ensure compliance to treatment. At every timepoint heart rate and blood pressure (both measured with the patient in a supine position) were recorded.

Illness characteristics that were included in the analysis were: type of social phobia (generalised vs. specific), a family history of social phobia (yes/no), use of alcohol as self-medication (yes/no), previous treatment with antidepressants (yes/no), previous treatment with benzodiazepines (yes/no) and previous behavioural therapy (yes/no).

**Data analysis**

Data were analysed using a commercially available statistical package (SPSS Inc.). Patients who received drug treatment where analysed as one group in this study. Analysis of variance with drug (brofaromine or fluvoxamine) as factor showed no significant differences between the drug groups for most of the variables.

To analyse the differences between responders and nonresponders an ANOVA was performed on the baseline variables. For the variables with a significant difference between treatment groups an ANOVA with drug as covariate was used. When the assumption of normality was violated a nonparametric test (Kruskal-Wallis analysis of variance) was applied. The categorical data were tested with the Chi Square or Fisher exact test (two-tail), as appropriate.

To analyse the relation between the different criterion variables two-tailed Pearson correlation coefficients were calculated.
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**

**Differences at baseline**

Of the 30 patients who received active medication (brofaromine or fluvoxamine) there was one patient in the fluvoxamine group who dropped out in the second week due to severe side effects. This patient was not included in the analysis. The response rates did not significantly differ between the drug groups on any of the criterion variables (Table 1).

Three variables were different between the drug groups: the mean score (± SD) on the HAS was higher in the fluvoxamine group (20.9 ± 3.4) compared to the brofaromine group (17.9 ± 3.9) (F=4.78; df=1,27; p=0.038), less patients in the fluvoxamine group had been treated previously with benzodiazepines (7.1% vs. 46.7%; Fisher exact test; p=0.035) and more patients in the fluvoxamine group had been treated previously with behavioural therapy (57.1% vs. 13.3%; Fisher exact test; p=0.021).

The criterion variable ‘50% reduction of the SPS-fear’ did not differentiate responders from nonresponders (Table 2). Most of the differences between responders and nonresponders were evident with ‘entered the follow up’ as criterion variable.

There were no significant differences between responders and nonresponders to drug therapy on demographic variables like sex, age or duration of illness. Nonresponders had a significantly higher heart rate at baseline. The systolic blood pressure of nonresponders was also higher, and this difference was significant on three criterion variables. The diastolic blood pressure was also elevated in nonresponders, but this difference was only evident with ‘entered the follow-up’ as criterion variable. Nonresponders also had a higher baseline score on the HAS, the HDS and the anxiety and interpersonal sensitivity subscores of the SCL-90. Most of the illness characteristics did not significantly differentiate between responders and nonresponders. Only one variable was found to significant. Of the patients with less than 50% improvement on the SPS-avoid 47.6% had a family history of SP, while none of the responders had such a history.

The response rates of the patients on the criterion variables differed considerably. With ‘entered the follow-up’ as criterion variable 72.4% of the patients were considered responders, while with ‘50% reduction of the SPS-avoid’ as criterion variable only 27.6% were considered responders.

There was a significant correlation between 50% improvement on the SPS-fear and the SPS-avoid (Table 3). The correlation between 50% improvement on the HAS and the SPS-fear just failed to reach statistical significance (p=0.061). ‘Entered the follow-up’ as criterion variable was uncorrelated with the other criterion variables.
Prediction of nonresponse

For the prediction of nonresponse to drug therapy we carried out a logistic regression analysis on all significant baseline variables. The purpose was to see if any of the variables could predict nonresponse. All significant baseline variables were predictors of nonresponse (p<0.05).

A best fitting model was also calculated for the criterion variable ‘entered the follow-up study’, because there were several significant variables associated with this criterion. A logistic regression analysis with backward elimination was performed on the significant baseline variables. These variables were: heart rate, systolic and diastolic blood pressure, the HAS, the HDS and the SCL-90 subscores of anxiety and interpersonal sensitivity. The backwards elimination process resulted a model with a perfect fit, which was not unique. It was therefore decided to split up the variables into two groups: heart rate and blood pressure in one group and the psychometric variables in the other. The groups were entered one after the other in the logistic regression analysis. The backwards elimination process resulted in a prediction based on two variables. With heart rate and the SCL-90 interpersonal sensitivity subscore left in the equation, 92.0% of the patients were correctly classified. Of both the responders and the nonresponders only one patient was misclassified.

Discussion

To the best of our knowledge this is the first study in which a systematic search was undertaken to find differences on baseline between responders and nonresponders to short-term drug therapy in social phobia. Apart from the recent follow-along study of Reich and co-workers (1994) no systematic studies have been reported concerning this issue.

In this study we report on baseline differences between responders and nonresponders to short-term drug therapy. Nonresponders differed from responders in that they had a higher heart rate and a higher blood pressure. They were also characterised by higher scores on several psychometric scales, indicative of illness severity. Nonresponders had a higher score on the HAS, the HDS and the anxiety and interpersonal sensitivity subscores of the SCL-90. Nonresponders more often seemed to have a family history of social phobia.

Most of the differences that were found were not evident on all criterion variables. A possible explanation might be that the criterion variables were very different from one another. The low correlations between the criterion variables (see Table 3) and the difference in response rates (see Table 1) may illustrate this.

With the criterion variable ‘entered the follow-up study’, which is an indicator of improvement according to the patient, it appeared that nonresponders where more severely ill. They had a higher baseline score on the HAS, the HDS and the anxiety and interpersonal sensitivity subscales of the SCL-90. These variables, indicative of illness severity, only differed significantly with this criterion variable. Again the low correlations between the criterion variables might be an explanation for this finding. Apparently the rating by the
patients differed from that of the clinician where treatment outcome was concerned. This
difference is also reflected in the response rates (see Figure 1): more than 70% of the
patients thought themselves improved, whereas the other criterion variables reflected an
improvement between 21% and 50%. It seems that patients who are more severely ill at
baseline, according to objective measures of illness severity, are less likely to find themselves
improved at the end of the treatment period.

One of the remarkable differences was that nonresponders had a higher heart rate at
baseline and a higher blood pressure. This finding seems comparable with the findings of
Slaap et al. (1996), who reported on differences between responders and nonresponders in
panic disorder. They also found that nonresponders to drug therapy had a higher heart rate
at baseline. A possible explanation might be that nonresponders had a disturbed functioning
of the autonomic system. There is some evidence that disturbances in the autonomic system
are a part of social phobia. Stein et al. (1994) found that social phobia patients (generalised
type) exhibited an increased blood pressure responsivity to Valsalva and an exaggerated
vagal withdrawal in response to isometric exercise as compared to healthy controls. They
did not investigate whether there was a relation between the severity of the illness and
abnormalities in autonomic system functioning. Another method to establish the
functioning of the autonomic system is the analysis of heart rate variability (Akselrod et al
1981; Akselrod et al 1985). In panic disorder Klein et al. (1995) found a correlation between
illness severity and a measure of heart rate variability. Illness severity was found to be a
predictor of nonresponse in panic disorder (Noyes, Jr. et al 1984; Rosenberg et al 1991;
Scheibe et al 1992; Basoglu et al 1994; Woodman et al 1994). Further research is needed to
analyse whether autonomic system functioning, as measured by the analysis of heart rate
variability, is associated with nonresponse to treatment in panic disorder and in social
phobia.

From two studies it known that there is a familial contribution to the development of
social phobia (Reich and Yates 1988; Fyer et al 1990). Reich and Yates (1988) found that
social phobics had significantly more relatives with social phobia. Fyer et al. (1990) found a
threefold increased relative risk for social phobia among relatives of social phobia patients.
In this study nonresponders with less than 50% improvement on the SPS-avoid more often
had a family history of social phobia. The relation between nonresponse and a family history
of SP is not clear and should be investigated further in future research.

In this study we did not find the use of alcohol as selfmedication to be a predictor of
nonresponse, as suggested by the study of Versiani et al. (1988). A possible explanation
might be that patients with a comorbid diagnosis of alcohol abuse or alcohol dependence
were excluded from our study, whereas in the study of Versiani et al. (1988) these patients
were included. Patients in our study were asked if they sometimes used alcohol as self-
medication to reduce social phobic symptoms. This episodic use of alcohol did not predict
nonresponse.

All the variables that showed a significant difference on baseline also predicted non-
response.
With ‘entered the follow-up study’ as criterion variable several variables predicted non-response. Heart rate, blood pressure and several indicators of illness severity were found to be predictors of nonresponse. With these variables a best fitting model was constructed. The backward elimination process resulted in a prediction based on heart rate and the SCL-90 subscore of interpersonal sensitivity. These two variables predicted nonresponse better than the other variables, and the prediction did not dramatically improve when more variables were used for the prediction. The combination of a higher heart rate and a higher score on the interpersonal sensitivity subscore of the SCL-90 was found to be a very effective predictor of non-response. Of the 29 patients only 2 patients were misclassified. Replication in another, larger sample of social phobic patients is needed to reveal if heart rate and interpersonal sensitivity are key factors in nonresponse to treatment.

During the treatment period patients were allowed to use oxazepam up to 20 mg daily. Not many patients used oxazepam, and most patients who did use oxazepam only used it incidentally and in a lower dose at the beginning of the study (see the ‘patients’ section of the methods). It therefore appears that the possibility of an effect of oxazepam on the treatment outcome is remote. Plasma levels of oxazepam were not monitored however, in the studies of van Vliet et al. (1992, 1994). These might have given more accurate information on the use of oxazepam.

Certain methodological weaknesses make this a preliminary study. The small sample size and the fact that three variables were different between the treatment groups make it difficult to generalise our findings. This study should be replicated to gain more certainty about differences between responders and nonresponders to drug treatment in social phobia. Two factors that should be investigated in further research are the influence of a comorbid Axis II diagnosis and the influence of altered heart rate variability.
References


**Table 1:** Response rates in each treatment group after 12 weeks of treatment.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Criterion variables</th>
<th>HAS reduction ≥50%</th>
<th>SPS-fear reduction ≥50%</th>
<th>SPS-avoid reduction ≥50%</th>
<th>In Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>brofaromine</td>
<td></td>
<td>50%</td>
<td>47%</td>
<td>33%</td>
<td>73%</td>
</tr>
<tr>
<td>fluvoxamine</td>
<td></td>
<td>50%</td>
<td>43%</td>
<td>21%</td>
<td>71%</td>
</tr>
</tbody>
</table>

**Legend:** HAS = Hamilton Anxiety Scale; SPS-fear = fear subscale of the Social Phobia Scale; SPS avoid = avoidance subscale of the Social Phobia Scale.
Table 2: Significant differences at baseline between responders and nonresponders; tabulated for each response criterion.

<table>
<thead>
<tr>
<th>baseline variables</th>
<th>Responders (mean ± sd)</th>
<th>nonresponders (mean ± sd)</th>
<th>significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAS reduction ≥ 50%</td>
<td>Systolic BP 126.1 ± 9.2</td>
<td>136.8 ± 16.0</td>
<td>F=4.71; df=1,26; p=0.039</td>
</tr>
<tr>
<td>SPS fear reduction ≥ 50%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SPS-avoid reduction ≥ 50%</td>
<td>Systolic BP 127.5 ± 22.4</td>
<td>133.3 ± 8.9</td>
<td>Kruskal-Wallis; p=0.027</td>
</tr>
<tr>
<td>Family history of SP</td>
<td>0%</td>
<td>47.6%</td>
<td>Fischer exact test; p=0.027</td>
</tr>
<tr>
<td>Entered follow-up</td>
<td>Pulse 65.9 ± 6.0</td>
<td>78.5 ± 9.5</td>
<td>F=16.36; df=1,23; p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Systolic BP 128.6 ± 9.8</td>
<td>140.0 ± 19.5</td>
<td>F=4.48; df=1,27; p=0.044</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP 80.5 ± 7.6</td>
<td>89.4 ± 15.2</td>
<td>F=4.48 df=1,27; p=0.044</td>
</tr>
<tr>
<td></td>
<td>HAS* 18.4 ± 3.7</td>
<td>21.6 ± 3.7</td>
<td>F=4.77; df=1,26; p=0.038</td>
</tr>
<tr>
<td></td>
<td>HDS 8.9 ± 1.9</td>
<td>10.6 ± 1.8</td>
<td>F=4.84; df=1,27; p=0.037</td>
</tr>
<tr>
<td></td>
<td>SCL-90 anx 2.6 ± 0.9</td>
<td>3.6 ± 0.8</td>
<td>F=7.28; df=1,27; p=0.012</td>
</tr>
<tr>
<td></td>
<td>SCL-90 is 2.6 ± 0.9</td>
<td>3.4 ± 0.6</td>
<td>F=6.75; df=1,27; p=0.015</td>
</tr>
</tbody>
</table>

Legend: * = ANOVA with drug (brofaromine or fluvoxamine) as covariate; HAS = Hamilton Anxiety Scale; SPS-fear = fear subscale of the Social Phobia Scale; SPS avoid = avoidance subscale of the Social Phobia Scale; BP = blood pressure; SCL-90 anx = anxiety subscale of the SCL-90; SCL-90 is = interpersonal sensitivity subscale of the SCL-90.
Table 3. Pearson correlation coefficients of the criterion variables.

<table>
<thead>
<tr>
<th>Criterion variables</th>
<th>HAS reduction ≥50%</th>
<th>SPS-fear reduction ≥50%</th>
<th>SPS-avoid reduction ≥50%</th>
<th>In Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAS reduction ≥50%</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPS-fear reduction ≥50%</td>
<td>0.358</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPS-avoid reduction ≥50%</td>
<td>0.316</td>
<td>.685 *</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>In Follow Up</td>
<td>0.316</td>
<td>.091</td>
<td>.036</td>
<td>1.000</td>
</tr>
</tbody>
</table>

**Legend:** * = p < 0.001; HAS = Hamilton Anxiety Scale; SPS-fear = fear subscale of the Social Phobia Scale; SPS avoid = avoidance subscale of the Social Phobia Scale.