Chapter 1

The prediction of nonresponse to pharmacotherapy in panic disorder: A review

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Depression and Anxiety: in press
Abstract

Background: Several effective pharmacotherapeutic treatments exist for panic disorder, however, not all patients respond to treatment: between 20% to 40% are nonresponders. Recent studies have reported several predictors of nonresponse to pharmacotherapy. In this review two questions are addressed: is there consensus with respect to predictors of nonresponse, and are there any differences between short-term and long-term predictors?

Methods: In this review both short-term and long-term outcome studies are discussed. Studies were included if at least DSM-III criteria were used and baseline variables were investigated as possible predictor of response, or nonresponse, to pharmacotherapy. Of each clinical predictor, tallies were made of the particular predictors employed and of those predictors that predicted nonresponse.

Results: It appears that a long duration of illness and severe agoraphobic avoidance are robust predictors of nonresponse, particularly in long-term studies. Personality disorders, or even personality traits, are possibly the most robust predictors of nonresponse.

Conclusions: several factors appear to be robust predictors of nonresponse: factors that are present before treatment and exert their influence on short-term and long-term treatment outcome. Prospective studies are needed to further investigate these factors and to test whether it is viable to intervene in an attempt to increase treatment response.
Introduction

In Panic Disorder (PD), with or without agoraphobia, it has been well established that pharmacotherapy is highly effective in reducing anxiety and the frequency of panic attacks (Feighner, 1999). Treatment with different compounds like tricyclic antidepressants (TCAs) (Modigh, 1987; Liebowitz, 1989), selective serotonin reuptake inhibitors (SSRIs) (den Boer and Westenberg, 1990; Westenberg and den Boer, 1994), high-potency benzodiazepines (Jonas and Cohon, 1993) and monoamine oxidase inhibitors (MAOIs) (Tyrer and Shawcross, 1988; van Vliet et al., 1993; van Vliet et al., 1996) have been proven effective. However, not all patients respond to treatment: between 20% to 40% are nonresponders.

Predicting nonresponse to pharmacotherapy would be very helpful for both patients and clinicians, since it takes several weeks before a clinical effect can be expected for most of these drugs. Only the high-potency benzodiazepine alprazolam (Andersch et al., 1991; Rickels and Schweizer, 1998) is characterized by a rapid onset of therapeutic action. In view of the delayed onset and side effects associated with pharmacotherapy (e.g. anticholinergic effects, sedation or nausea, depending on the compound), it is an important clinical task to identify factors which may hamper effective pharmacotherapy.

In this review we will survey the available data on predictors of nonresponse to pharmacotherapy in PD, both in short-term and in long-term studies. Two questions will be addressed: is there consensus in respect to predictors of nonresponse, and are there any differences between short-term and long-term predictors.

Method

In this review short-term studies, with a duration between 6 and 16 weeks (Table 1), and long-term studies, with a duration of 1 to 7 years (Table 2), will be discussed.

A Medline and EMBASE search was conducted on the following key words: “panic”, “agoraphobia”, “predict”, “depression”, “personality” and “follow-up”. The timeframe of this literature search was 1986 through 2000. To further insure completeness, the search results were cross-checked with cited references in these studies.

For inclusion, studies had to investigate baseline variables as possible predictors of response, or nonresponse, to pharmacotherapy. Studies were included in this review if patients were treated with an adequate dose of adequate medication for an adequate duration and if at least DSM-III criteria were used. Cowley and co-workers (1997) have demonstrated that it is essential to ensure adequacy of treatment, duration and dose before attempting any prediction of response. In their sample of 106 PD patients, previously treated by their community practitioners, only 59 (23%) of 252 documented medication trials were adequate in medication, dosage and treatment duration. Other researchers have reported similar findings (Taylor et al., 1989; Bandelow et al., 1995b). In determining the adequacy of medication, dose and treatment duration the “Practice Guideline for the Treatment of Patients with Panic Disorder”, issued by the American Psychiatric Association
(Work Group on Panic Disorder. American Psychiatric Association, 1998), were followed. For inclusion in this review, the duration of treatment had to be at least 6 weeks.

In order to predict nonresponse to treatment, it is essential to define criterion variables, that will determine the expected response or nonresponse (Steketee and Chambless, 1992). Unfortunately, there is no consensus on how to measure response (Shear and Maser, 1994; Shear et al., 1998). The DSM-IV doesn’t offer criteria for response or remission and the literature on pharmacotherapy in PD abounds with many different scales which are used as criterion variables. Consequently, the studies in this review do not report on nonresponse in a uniform fashion. This problem hampers a methodologically flawless comparison of studies which investigated nonresponse to pharmacotherapy in PD. In this review nonresponse is defined in a general way as a lack of response to adequate treatment. Nonresponse can also mean that patients were unable to achieve remission (Pollack et al., 1990; Rickels et al., 1993; Warshaw et al., 1997; Toni et al., 2000). As the DSM-IV does not include a definition on remission in PD, remission is defined as an asymptomatic state with a duration of at least two (Pollack et al., 1990; Warshaw et al., 1997; Toni et al., 2000) or three months (Rickels et al., 1993).

Studies were also included if they investigated the effect on treatment outcome of a comorbid disorder, such as major depression or a personality disorder.

In order to investigate the strength of each predictor, we compared the number of studies which investigated a particular predictor with the number of studies which actually found that variable to predict nonresponse (Table 3).

In most short-term studies, treatments are pooled when predictors of nonresponse are investigated. An exception to this rule are studies which investigated a large number of patients; these studies reported on predictors of nonresponse for each treatment separately (Lesser et al., 1988; Maier et al., 1991; Keller et al., 1993; Pollack et al., 1994; Woodman et al., 1994; Hofmann et al., 1998). The larger sample sizes of these studies enabled the researchers to investigate possible differential effects of predictors of nonresponse. When pertinent these differential effects are discussed.

In long-term studies, treatment is often naturalistic, which means that for the prediction of nonresponse treatments are also pooled. In this review results are discussed for all pharmacological treatments, irrespective of the type.

**Predictors of nonresponse**

In Table 3 the most prominent baseline predictors are depicted. These are subdivided in three categories: demographic variables, illness variables and comorbidity. As can be seen in the table, it is clear that not all predictors are equally robust, or as widely investigated as others.

It has to be taken into account that these results may be biased. Demographic variables, for instance, were probably analysed in more studies than those who actually reported on these predictors. This means that the importance of some predictor variables could actually
be even less than some authors have suggested (Mavissakalian and Michelson, 1986; Faravelli et al., 1995).

**Demographic variables**

Demographic characteristics, such as gender, age or marital status do not appear to be predictors of nonresponse. In most studies these variables were investigated as potential predictors of nonresponse, but the results are inconsistent at best. Two studies have reported that gender is associated with nonresponse. In a short-term study, Mavissakalian and Michelson (1986) have found that male gender predicted a poor outcome. In contrast, Maier and Buller (1988) reported in a long-term study that female gender was a predictor of nonresponse.

In only one short-term study it was found that a younger age predicted nonresponse (Woodman et al., 1994). In a recent long-term study by Faravelli and co-workers (1995) the opposite was reported. Additionally, this study is also the only study that found marital status to be a predictor of nonresponse. A larger proportion of patients who were not married at baseline were doing well at follow-up, as compared to married patients.

Social-economic class may be the best demographic predictor, but is has not been widely investigated. In two long-term studies, Noyes, Jr. and co-workers (1990; 1993) investigated this predictor and in both studies they found that a lower social economic class predicted nonresponse. Recently, Warshaw et al. (1997) reported in a long-term study that they also found a lower social-economic class to predict nonresponse.

**Illness variables**

**Duration of illness and age at onset**

Duration of illness and age at onset have both been investigated thoroughly as likely predictors of nonresponse. A longer duration of illness has been found to predict nonresponse in more than half of the long-term studies (Noyes, Jr. et al., 1989; Noyes, Jr. et al., 1990; Noyes, Jr. et al., 1993; Pollack et al., 1993; Albus et al., 1995; Faravelli et al., 1995; Katschnig et al., 1995; Scheibe and Albus, 1997; Shinoda et al., 1999; Toni et al., 2000) (see Table 3). Noyes, Jr. et al. (1993) reported a mean (± SD) duration of illness for patients with a marked improvement of 7.7 (± 8.7) years and 12.5 (± 12.0) years for patients without marked improvement. Faravelli et al. (1995) reported an even more dramatic difference; patients who were fully recovered or improved had a mean duration of illness of 3.1 (± 3.8) years versus 10.7 (± 10.6) years for patients who had a recurrent course of illness or poor outcome.

This predictor does not seem to be as robust in short-term studies, since in only a minority of the studies a longer duration of illness was found to predict nonresponse (Mavissakalian and Michelson, 1986; Basoglu et al., 1994). It appears that the influence of a long duration of illness is less evident on the short-term treatment effect, indicating that...
chronic patients also benefit from short-term treatment. The effect of a longer duration of illness becomes more evident when the long-term treatment gains are investigated.

Age at onset appears to be a less important factor, since it was only found to predict nonresponse in a minority of the long-term studies (Noyes, Jr. et al., 1990; Scheibe and Albus, 1997; Warshaw et al., 1997; Toni et al., 2000). In these studies it was found that a younger age at onset was associated with nonresponse. Age at onset did not predict nonresponse in any of the short-term studies.

Global illness severity
Global illness severity, as measured by a global scale such as the Clinical Global Impression (CGI) (Guy, 1976), has been investigated primarily in short-term studies as a possible predictor of nonresponse. In two short-term studies it was found that a higher score on a global illness scale predicted nonresponse (Pollack et al., 1994; Pollack et al., 1993). Three other short-term studies did not show this relation (Liebowitz et al., 1986; Mavissakalian and Michelson, 1986; Ito et al., 1995). In long-term studies, this relation was only found in the study of Noyes, Jr. and co-workers (1989). Two other studies were unable to replicate this finding (Faravelli and Albanesi, 1987; Pollack et al., 1993).

Anxiety
Free-floating, chronic anxiety has been found to predict nonresponse in about half of the short-term (Liebowitz et al., 1986; Rosenberg et al., 1991a; Scheibe et al., 1992; Woodman et al., 1994; Sharp and Power, 1999) and long-term studies (Faravelli and Albanesi, 1987; Lelliott et al., 1987; Noyes, Jr. et al., 1990; Rickels et al., 1993; Albus et al., 1995). Nonresponders to pharmacotherapy tended to have higher baseline scores on scales such as the Hamilton Anxiety Scale (HAS) (Hamilton, 1959) or the Clinical Anxiety Scale (CAS) (Snaith et al., 1982). Whether these higher scores reflect a greater illness severity or a (sub-threshold) comorbid generalized anxiety disorder is difficult to determine since these scales measure both generalized anxiety and panic anxiety. Due to the high overlap of symptoms, these scales are not sufficiently specific to differentiate these two disorders (Bech et al., 1993).

Not only can differences in HAS scores be quite dramatic between responders and nonresponders, but also between studies. In a short-term study Liebowitz and co-workers (1986) reported that nonresponders had a baseline HAS score (mean ± SD) of 22.5 ± 5.3, whereas responders had 14.4 ± 5.6. In a long-term study Noyes, Jr. et al. (1990) reported a mean baseline HAS score of 14.6 for patients with high self-rated anxiety at follow-up, versus 8.3 for patients with low self-rated anxiety.

Phobic avoidance
As reported in epidemiological studies, about a third to one half of the patients with PD also have agoraphobia (Klerman et al., 1991; Eaton et al., 1994; Weissman et al., 1997). This percentage is substantially higher in clinical samples, and the studies reviewed here, where some 80% of the patients have PD and agoraphobia. Patients with PD and agoraphobia are
reported to be more ill than patients with PD only: they have more panic symptoms (Starcevic et al., 1993; Goisman et al., 1994) and a higher score on the HAS and the HDS (Lesser et al., 1988).

Phobic avoidance can be measured with scales such as the Fear Questionnaire (FQ) (Marks and Mathews, 1979) or derivatives like the Phobia Scale (Ballenger et al., 1988). Severity of phobic avoidance appears to be one of the most robust predictors of nonresponse, particularly in long-term studies. Almost all long-term studies have found that nonresponders have higher scores at baseline. Lelliott et al. (1987) and Faravelli et al. (1995) are the only researchers who did not find agoraphobic avoidance to predict nonresponse. Sample characteristics may explain why Lelliott and co-workers (1987) reported different findings. They investigated a sample of 40 patients with severe agoraphobia. Both responders and nonresponders alike, all had a very high score on the FQ, which makes it difficult, if not impossible, to find significant differences between these groups. The sample in the study Faravelli et al. (1995) was a mix of PD patients with and without agoraphobia: 38% of the patients had a diagnosis of PD without agoraphobia. Since the authors themselves made no attempt, an explanation to these deviant findings is cumbersome.

In a majority of short-term studies, it was found that severity of agoraphobic avoidance predicted nonresponse (Mavissakalian and Michelson, 1986; Rosenberg et al., 1991a; Pollack et al., 1994; Basoglu et al., 1994; Woodman et al., 1994; Sharp and Power, 1999). Slaap et al. (1995) could not replicate this finding, but they did find that nonresponders had a higher score on the blood-injury phobia subscale of the FQ, indicative of phobic avoidance of another type.

Two studies reported on differential effects of phobic avoidance on pharmacotherapy. Maier et al. (1991) reported that alprazolam and imipramine were more effective than placebo, particularly in patients with severe phobic avoidance. In terms of patients with less severe avoidance, active medication was about as effective as placebo. In contrast, Pollack et al. (1994) reported opposite differential effects: in patients with severe agoraphobic avoidance they found no evidence of superiority of alprazolam or imipramine over placebo. The samples of both studies are not directly comparable, as in the study of Pollack et al. (1994) only PD patients with agoraphobic avoidance were included. Furthermore, this study had a much smaller sample size (n=126 vs. n=1134) which influences the power of such comparisons. In conclusion: the relation between severity of agoraphobic avoidance and outcome of pharmacotherapy is very robust, although possibly not as strong in short-term studies.

Frequency & intensity of panic attacks
The accurate measurement of the frequency and intensity of panic attacks is one of the challenges PD researchers encounter. It has been noted that not only large variations in panic frequency exist between patients, but also within patients (Shear and Maser, 1994; Bouchard et al., 1997). This phenomenon reduces the power to discriminate between
treatments and makes the frequency and intensity of panic attacks a less attractive efficacy measure (Bandelow et al., 1995a).

This variable has been studied as a possible predictor of nonresponse to pharmacotherapy. It appears that nonresponders are characterized by a greater panic frequency or intensity at baseline in about half of the short-term (Mavissakalian and Michelson, 1986; Rosenberg et al., 1991a; Woodman et al., 1994; Slaap et al., 1995; Sharp and Power, 1999) and long-term studies (Noyes, Jr. et al., 1989; Noyes, Jr. et al., 1990; Noyes, Jr. et al., 1993; Rickels et al., 1993). The aforementioned problems with the measurement of panic frequency and intensity, together with differences in patient samples, may explain why this predictor was not found in more studies.

**Comorbidity**

**Comorbid Depression**

The prevalence of comorbid depression in patients with PD ranges between 23% and 53% (Klerman, 1990; Gorman and Coplan, 1996; Pelissolo and Lepine, 1998). The average reported lifetime occurrence of major depression in patients with PD is also high: between 40% and 50% (Lydiard, 1991; Gorman and Coplan, 1996; Pelissolo and Lepine, 1998). In large epidemiological studies, such as the National Comorbidity Study (NCS) (Kessler et al., 1998; Roy Byrne et al., 2000) and the World Health Organization (WHO) Collaborative Study on Psychological Problem in General Health Care (Lecrubier and Ustun, 1998), and in several clinical studies (Grunhaus et al., 1994; Chambless and Gracely, 1988), it has been reported that comorbid patients tend to have more severe symptoms and more impairment. An important question is whether this implies less response to treatment.

In short-term studies, a comorbid depression has been found to predict nonresponse in two out of the six studies which investigated this predictor (Reich, 1988; Pollack et al., 1993). The results of the study of Reich (1988) need to be interpreted carefully, because in his study the outcome of treatment of only four PD patients with a secondary depression is compared to the outcome of 45 patients without depression. Four other short-term studies, with larger patient samples, did not find a relation between a comorbid depression and treatment outcome (Lesser et al., 1988; Keller et al., 1993; Basoglu et al., 1994; Rosenberg et al., 1991b). Rosenberg and co-workers (1991b) reported that some 20% of their sample met the DSM-III criteria for a diagnosis of current or past depression. These patients were more ill at baseline, but their improvement was not significantly different after eight weeks of treatment with either alprazolam or imipramine.

In about half of the long-term studies, a comorbid depression was found to predict nonresponse (Maier and Buller, 1988; Nagy et al., 1989; Noyes, Jr. et al., 1990; Albus and Scheibe, 1993; Noyes, Jr. et al., 1993; Albus et al., 1995). Maddock and Blacker (1991) reported, that as a group, patients with a comorbid diagnosis of current or lifetime history of depression improved as much as the patients without depression. This did not apply to all patients; the patients with a primary depression, who had their first episode before the onset
of panic disorder, had a worse outcome. Pollack and co-workers (1993) reported that a comorbid diagnosis of dysthymia was not a predictor of long-term treatment response, while it did predict nonresponse to short-term treatment (see above). In another study, Pollock and co-workers (1990) reported that there was no relation between a lifetime or current diagnosis of depression and failure to achieve remission (Pollack et al., 1990). They did find that a diagnosis of comorbid depression was associated with other predictors of nonresponse, for example a high panic frequency or a comorbid anxiety disorder. This suggests that there is a relation between a comorbid depression and nonresponse, albeit not a direct relation.

In long-term studies which found that a comorbid depression was a predictor of nonresponse, patients were more ill at follow-up. These patients had higher HAS and HDS scores (Nagy et al., 1989; Albus et al., 1995), more disability (Noyes, Jr. et al., 1990; Albus and Scheibe, 1993) and more panic symptoms (Noyes, Jr. et al., 1993). Albus and co-workers (1995) remark in their study that patients with a comorbid depression had a poorer outcome. However, no differences were found on several relevant illness variables, such as agoraphobic avoidance and the number of panic attacks. The authors speculate that this finding may be due to the fact that 45% of the patients in the comorbid group and 33.3% of the pure panic group were still on medication.

Three studies investigated whether depressed patients with a comorbid panic disorder had a worse prognosis that those with depression only (Grunhaus et al., 1986; Grunhaus et al., 1988; Coryell et al., 1988). In both short-term studies (Grunhaus et al., 1986; Grunhaus et al., 1988) and the long-term study (Coryell et al., 1988), depressed patients with a comorbid PD had a worse treatment outcome.

It appears that the combination of PD and depression, irrespective of primary diagnosis, is a factor to be reckoned with. Comorbid patients seem to have a reduced chance of getting well. However, there is evidence that the effect of comorbidity on the short-term treatment effect is less robust, meaning that patients with a comorbid condition may equally benefit from pharmacotherapy, as compared to patients with a single diagnosis.

Comorbid Anxiety Disorder

The available literature on comorbidity suggests that a significant percentage of patients with PD has an additional diagnosis. The percentage of PD patients with a diagnosis of an additional anxiety disorder ranges between 44% (Di Nardo and Barlow, 1990) and 83.3% (Starcevic et al., 1992). In the above cited studies, as well as in other papers (Brown and Barlow, 1992; de Ruiter et al., 1989; Sanderson et al., 1990; Marshall, 1996; Hoffart et al., 1995) it appears that generalized anxiety disorder, social phobia and simple phobia are the most frequently occurring additional diagnoses in PD patients. Percentages ranging between 19% (Hoffart et al., 1995) and 51.9% (Starcevic et al., 1992) have been reported for a comorbid generalized anxiety disorder. For a comorbid social phobia the percentages vary between 9.6% (de Ruiter et al., 1989) and 40.7% (Starcevic et al., 1992) The percentages for a comorbid simple phobia vary between 6.3% (Brown and Barlow, 1992) and 46.6% (de
Ruiter et al., 1989). Differences in reported percentages reflect differences in diagnostic criteria and differences between samples.

In two short-term studies the influence of a comorbid anxiety disorder on outcome was investigated (Pollack et al., 1993; Pollack et al., 1994). Both studies reported that the presence of a comorbid social phobia or generalized anxiety disorder did not influence treatment outcome.

In long-term studies the opposite has been found: in three studies the presence of a comorbid anxiety disorder predicted nonresponse (Pollack et al., 1990; Pollack et al., 1993; Scheibe and Albus, 1997). Pollack and co-workers (1990) reported that the presence of any comorbid anxiety disorder predicted failure to achieve remission. The same group, in another study, reported that a comorbid diagnosis of social phobia predicted nonresponse (Pollack et al., 1993). This diagnosis did not influence short-term treatment success, see above. Scheibe and Albus (1997) recently reported that a comorbid generalized anxiety disorder was the most robust predictor of nonresponse in their sample. Warshaw et al. (1997) were surprised by their own contradictory findings: in their study, patients with a comorbid social phobia were more likely to have experienced periods of remission.

The study of Toni and co-workers (2000) has to be interpreted with care. They did not investigate whether the presence of a comorbid anxiety disorder influenced the likelihood of achieving remission. They investigated whether comorbid anxiety disorders influenced the total time spent in remission. In their study, the presence of these comorbid conditions, diagnosed at baseline, had no effect on the duration of remission. Predicting the total time spent in remission is different from predicting the likelihood of achieving remission. It is imaginable that patients with a comorbid condition have a much reduced chance of achieving remission, while the duration of the period of remission is not shorter than in patients without this comorbid condition. This makes it hard to compare the results of this study with other studies.

Only a few studies have investigated the influence of a comorbid anxiety disorder on the effect of pharmacotherapy in PD. Nevertheless, it appears that a comorbid anxiety disorder may have a great influence on treatment outcome in the long term. More studies are needed to verify this tentative conclusion.

Comorbid Personality Disorder

Personality disorders are not uncommon in PD patients: using categorical measures, incidence rates have been reported ranging from 27% to over 50% (Mavissakalian and Hamann, 1986; Reich et al., 1987; Friedman et al., 1987; Green and Curtis, 1988; Reich, 1988; Mavissakalian and Hamann, 1988). These estimates greatly exceed those of the general population, which range from 5.9% to 18% (Zimmerman and Coryell, 1989; Reich et al., 1989; Samuels et al., 1994; Lenzenweger et al., 1997). Differences in instruments used and investigated populations probably caused the variation in estimates (Noyes, Jr. et al., 1991).

In PD it has been repeatedly found that a certain amount of covariation exists between the severity of personality disorder characteristics and severity of illness (Mavissakalian and
Hamann, 1986; Mavissakalian and Hamann, 1987; Wittchen et al., 1991; Hofmann et al., 1998). The impairment in personality functioning may worsen on an exacerbation of PD symptoms and may improve on effective treatment of PD. This suggests that personality disorder characteristics are in part state dependent, because they can change significantly with effective treatment (for a overview see Hofmann et al., 1998). The measurement of personality disorder characteristics in acute PD patients is therefore not independent of illness severity, as they are likely to show more Axis II traits or diagnoses, compared to when they are in remission.

The influence of a comorbid personality disorder on the outcome of pharmacotherapy has been investigated in ten studies. Both personality traits and personality disorder diagnoses have been investigated. In these studies a diagnosis is established by means of a structured clinical interview, such as the Structured Interview for DSM-III Personality Disorders (SIDP) (Pfohl et al., 1982), or by means of a self-report questionnaire such as the Personality Diagnostic Questionnaire (PDQ) (Hyler et al., 1983), or the Wisconsin Personality Disorders Inventory (WISPI) (Klein et al., 1990). Traits can be established by using scales such as the Minnesota Multiphasic Personality Inventory (MMPI) (Hathaway and McKinley, 1945).

The presence of a comorbid personality disorder, or even traits, is one of the most robust predictors of nonresponse in PD. Almost all studies that have investigated the role of this predictor have found it to predict nonresponse, in both short-term (Mavissakalian and Hamann, 1987; Green and Curtis, 1988; Reich, 1988; Ito et al., 1995) and long-term studies (Faravelli and Albanesi, 1987; Noyes, Jr. et al., 1990; Lydiard et al., 1992; O'Rourke et al., 1997).

There are two notable exceptions: a short-term study of Hofmann and co-workers (1998) and a long-term study by Toni et al.(2000). Hofmann and co-workers (1998) did not find that personality disorder characteristics, as measured by the WISPI, predicted nonresponse to either 12 weeks of imipramine or 11 sessions of individual cognitive-behavior therapy. The authors acknowledge that their study is limited by the fact that it is unclear whether the WISPI is a valid instrument to assess and diagnose personality disorder. Toni and co-workers (2000) did not find any influence of personality disorder characteristics on the total time spent in remission. As discussed above, the design of their study hampers direct comparison with other studies.

Ito et al. (1995), in a short-term study, and Faravelli and Albanesi (1987), in a long-term study, investigated MMPI traits as possible predictors of nonresponse. Both groups reported that nonresponder had higher scores on the Psychopathic Deviate and the Hysteria scales. The authors merely state that these personality traits are associated with nonresponse, but an interpretation of these results is not given.

Most studies that have investigated the influence of a comorbid personality disorder on outcome reported that any personality disorder would interfere with treatment, irrespective of cluster or exact diagnosis. This applies to studies that used structured clinical interviews, e.g. the SIDP (Noyes, Jr. et al., 1990; Green and Curtis, 1988; Reich, 1988), or self-report
questionnaires, e.g. the PDQ (Pollack et al., 1990; O'Rourke et al., 1997; Mavissakalian and Hamann, 1987; Reich, 1988). Both Green and Curtis (1988) and O'Rourke et al. (1997) have reported that comorbid disorders of the anxious-fearful cluster were most prominent in nonresponders. Reich (1988) reported that nonresponders were most notably characterized by personality disorders of the dramatic cluster.

Discussion

In this review evidence has been presented for several factors which have a negative influence on the outcome of pharmacotherapy in PD patients. These factors are present before treatment and exert their influence on short-term and long-term treatment outcome. There does not appear to be much evidence for the existence of factors which specifically predict nonresponse to a particular treatment. Six short-term studies investigated possible treatment specific predictors of nonresponse. Two studies reported a differential predictive effect of agoraphobia, albeit in opposite directions. All other predictors, investigated in these studies, failed to show any differential effects. Based on the scantily available data, it appears more probable that factors exist which hamper pharmacotherapy, irrespective of type.

Two questions were addressed in this review: is there consensus in respect to predictors of nonresponse, and are there any differences between short-term and long-term predictors? It appears that patients who are more ill at baseline, and who have been ill for a long time, have a worse prognosis. The severity of illness is evident from higher scores on scales that measure phobic avoidance, anxiety, panic frequency and from the presence of comorbid disorders. The CGI, a global measure of illness severity, was able to detect differences between responders and nonresponders in only two short-term studies which investigated this predictor. The CGI is probably not sensitive enough to detect differences in illness severity between responders and nonresponders at baseline.

Illness variables, such as panic frequency, anxiety and phobic avoidance appear to exert their detrimental influence on both short-term and long-term treatment outcome. Anxiety and panic frequency (or intensity) predicted nonresponse in about half of the studies which investigated these predictors. Agoraphobic avoidance predicted nonresponse in a majority of the short-term studies and in almost all long-term studies. It is not clear whether the influence of severe agoraphobia is less substantial on short-term treatment success; further research is needed to make a definite statement about this. It does seem to be the case that severe agoraphobia is not controlled by the treatments offered in the studies in this review.

Several variables do not appear to influence short-term treatment success, but show their harmful influence when the long-term treatment effect is evaluated. A longer duration of illness, a comorbid anxiety disorder, and probably a comorbid depression, do not appear to disrupt the short-term treatment effect. These variables did predict nonresponse to treatment in a majority of the long-term studies. This suggests that chronic patients, and/or patients with a comorbid affective disorder, equally benefit from pharmacotherapy in the short-term, as compared to patients without these conditions. However, in the long-term,
the treatment gains of these patients are not sustained. The mechanism, by which a chronic condition and/or comorbidity disrupts long-term treatment outcome is unclear and warrants further research. Also of note is the relative lack of studies which investigated the influence of comorbid anxiety disorders. This condition often co-occurs in PD patients, yet only a few studies have investigated its influence on treatment outcome.

A comorbid diagnosis of a personality disorder, or even personality traits, is possibly the most robust predictor of nonresponse in this review. Almost all studies which investigated this predictor found it to predict nonresponse. This is a worrisome conclusion, and similar findings have been reported on the influence of personality disorders on the treatment of Axis-I disorders in general (Reich and Green, 1991; Reich and Vasile, 1993). Standard treatment for PD is clearly less effective against PD with a comorbid personality disorders, or even traits, which makes it evident that these patients should receive alternative treatments, or a combination of treatments, to reduce the influence of this comorbid condition.

Roy-Byrne and Cowley (1994) have reviewed follow-up studies in PD and have meticulously described some of the methodological problems involved. These problems also apply to the prediction of nonresponse and all deal with differences between studies. These differences make comparison cumbersome and definitive conclusions of predictors of nonresponse to remain tentative.

To name the most prominent problems involved in the comparison of studies on the prediction of nonresponse:

The lack of consensus on how to measure response to treatment in panic disorder, meaning that a variety of instruments is used.

The patient samples differs between studies; not only in size, but also in different inclusion and exclusion criteria.

To date, all studies used a retrospective prediction. In other words, at the end of the study, after the data had been collected, investigators examined the association between potential predictors and outcome.

Future research would benefit greatly if consensus on definitions of response and remission could be reached. Consensus would make a vast difference in this field, as it would make methodologically flawless generalization of findings possible. In spite of all the problems mentioned above, it is our firm belief that the tentative conclusions from this review are of value, in the absence of more definitive prospective studies. The clinical issue here is predicting poor treatment response and the next step, based on the tentative conclusions of this paper and others, would be a prospective trial, in which these hypotheses can be tested. Ultimately, studies are essential which test whether it is possible to intervene, based on baseline predictor variables, in an attempt to increase response to pharmacotherapy.
References


Springer Verlag. p 209-220.

WA, Winokur G. 1988. Depression and panic attacks: the significance of overlap as re-

Cowley DS, Ha EH, Roy Byrne PP. 1997. Determinants of pharmacologic treatment failure

the anxiety disorders. J Anxiety Disord 3:57-68.

den Boer JA, Westenberg HGM. 1990. Serotonin function in panic disorder: a double blind
placebo controlled study with fluvoxamine and ritanserin. Psychopharmacology 102:85-94.

Di Nardo PA, Barlow DH. 1990. Syndrome and symptom comorbidity in the anxiety dis-


Compr Psychiatry 28:481-487.

Faravelli C, Paterniti S, Scarpato A. 1995. 5-year prospective, naturalistic follow-up study of

Feighner JP. 1999. Overview of antidepressants currently used to treat anxiety disorders. J

Personal Disord 1:132-135.

Goisman RM, Warshaw MG, Peterson LG, Rogers MP, Cuneo P, Hunt MF, Tomlin-
Agoraphobia, and Panic Disorder with Agoraphobia - Data from a Multicenter Anxiety Disorders Study. J Nerv Ment Dis 182:72-79.

Psychiatry 57:34-43.

Green MA, Curtis GC. 1988. Personality disorders in panic patients: response to termina-


Hofmann SG, Shear MK, Barlow DH, Gorman JM, Hershberger D, Patterson M, Woods SW. 1998. Effects of panic disorder treatments on personality disorder characteristics. Depress Anxiety 8:14-20.


Klein MH, Benjamin LS, Treece C, Rosenfeld R, Greist J. 1990. The Wisconsin Personality Disorder Inventory (Available from: M.H. Klein, Department of Psychiatry, University of Wisconsin, School of Medicine, Madison, WI 53706).


**Table 1**: An overview of short-term studies which investigated nonresponse to pharmacotherapy in PD.

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (weeks)</th>
<th>n</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liebowitz et al. (1986)</td>
<td>12</td>
<td>30</td>
<td>alprazolam</td>
</tr>
<tr>
<td>Mavissakalian and Michelson (1986)</td>
<td>12</td>
<td>62</td>
<td>imipramine or flooding, combined with programmed practice or placebo</td>
</tr>
<tr>
<td>Mavissakalian and Hamann (1987)</td>
<td>16</td>
<td>33</td>
<td>antidepressants and exposure</td>
</tr>
<tr>
<td>Green and Curtis (1988)</td>
<td>8</td>
<td>30</td>
<td>alprazolam, imipramine or placebo</td>
</tr>
<tr>
<td>Lesser et al. (1988)</td>
<td>8</td>
<td>481</td>
<td>alprazolam or placebo</td>
</tr>
<tr>
<td>Reich (1988)</td>
<td>8</td>
<td>52</td>
<td>alprazolam or diazepam</td>
</tr>
<tr>
<td>Buller et al. (1991)</td>
<td>8</td>
<td>1168</td>
<td>alprazolam, imipramine or placebo</td>
</tr>
<tr>
<td>Maier et al. (1991)</td>
<td>8</td>
<td>1134</td>
<td>alprazolam, imipramine or placebo</td>
</tr>
<tr>
<td>Rosenberg et al. (1991a; 1991b)</td>
<td>8</td>
<td>123</td>
<td>alprazolam, imipramine or placebo</td>
</tr>
<tr>
<td>Scheibe et al. (1992)</td>
<td>8</td>
<td>103</td>
<td>alprazolam, imipramine or placebo</td>
</tr>
<tr>
<td>Keller et al. (1993)</td>
<td>16</td>
<td>126</td>
<td>alprazolam, imipramine or placebo</td>
</tr>
<tr>
<td>Pollack et al. (1993)</td>
<td>6</td>
<td>59</td>
<td>alprazolam, clonazepam or placebo</td>
</tr>
<tr>
<td>Basoglu et al. (1994)</td>
<td>8</td>
<td>144</td>
<td>alprazolam or placebo, combined with exposure or relaxation</td>
</tr>
<tr>
<td>Pollack et al. (1994)</td>
<td>16</td>
<td>126</td>
<td>alprazolam, imipramine or placebo</td>
</tr>
<tr>
<td>Woodman et al. (1994)</td>
<td>8</td>
<td>506</td>
<td>alprazolam or placebo</td>
</tr>
<tr>
<td>Ito et al. (1995)</td>
<td>8</td>
<td>33</td>
<td>imipramine, clomipramine or placebo</td>
</tr>
<tr>
<td>Slaap et al. (1995)</td>
<td>12</td>
<td>44</td>
<td>brofaromine or fluvoxamine</td>
</tr>
<tr>
<td>Hofmann et al. (1998)</td>
<td>12</td>
<td>93</td>
<td>imipramine or cognitive behavioral therapy</td>
</tr>
<tr>
<td>Sharp and Power (1999)</td>
<td>12</td>
<td>149</td>
<td>fluvoxamine or placebo, alone or combined with cognitive behavioral therapy (CBT), CBT alone</td>
</tr>
</tbody>
</table>
Table 2: An overview of long-term studies which investigated nonresponse to pharmacotherapy in PD.

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (years)</th>
<th>n</th>
<th>Treatment a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faravelli and Albanesi (1987)</td>
<td>1</td>
<td>53</td>
<td>antidepressants, alprazolam or benzodiazepines; psychotherapy if needed</td>
</tr>
<tr>
<td>Lelliott et al. (1987)</td>
<td>5</td>
<td>40</td>
<td>imipramine or placebo, combined with exposure or relaxation for 28 weeks</td>
</tr>
<tr>
<td>Maier and Buller (1988)</td>
<td>1</td>
<td>77</td>
<td>benzodiazepines or antidepressants</td>
</tr>
<tr>
<td>Nagy et al. (1989)</td>
<td>2.5</td>
<td>60</td>
<td>behavioral group therapy and alprazolam for 16 weeks, alprazolam if necessary during follow-up</td>
</tr>
<tr>
<td>Noyes, Jr. et al. (1989)</td>
<td>1-4</td>
<td>107</td>
<td>tricyclic antidepressants, sometimes combined with a benzodiazepine</td>
</tr>
<tr>
<td>Noyes, Jr. et al. (1990)</td>
<td>3</td>
<td>89</td>
<td>alprazolam, diazepam, placebo for 8 weeks (up to 6 months)</td>
</tr>
<tr>
<td>Pollack et al. (1990)</td>
<td>2</td>
<td>100</td>
<td>benzodiazepines or antidepressants</td>
</tr>
<tr>
<td>Maddock and Blacker (1991)</td>
<td>1</td>
<td>30</td>
<td>naturalistic treatment</td>
</tr>
<tr>
<td>Albus and Scheibe (1993)</td>
<td>2</td>
<td>52</td>
<td>imipramine or doxepin for 8 weeks, supportive psychotherapy for 6 to 8 months, as needed</td>
</tr>
<tr>
<td>Noyes, Jr. et al. (1993)</td>
<td>7</td>
<td>69</td>
<td>naturalistic treatment</td>
</tr>
<tr>
<td>Pollack et al. (1993)</td>
<td>1.5</td>
<td>59</td>
<td>alprazolam, clonazepam or placebo for 6 weeks</td>
</tr>
<tr>
<td>Rickels et al. (1993)</td>
<td>1</td>
<td>48</td>
<td>alprazolam, imipramine or placebo for 8 months</td>
</tr>
</tbody>
</table>
**Table 2: continued**

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (years)</th>
<th>n</th>
<th>Medication a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albus et al. (1995)</td>
<td>5</td>
<td>50</td>
<td>imipramine or doxepin for 8 weeks,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>supportive psychotherapy for 6 to 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>months, as needed</td>
</tr>
<tr>
<td>Faravelli et al. (1995)</td>
<td>5</td>
<td>99</td>
<td>naturalistic treatment</td>
</tr>
<tr>
<td>Katschnig et al. (1995)</td>
<td>4</td>
<td>423</td>
<td>alprazolam, imipramine or placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>for 8 weeks</td>
</tr>
<tr>
<td>O'Rourke et al. (1997)</td>
<td>5.3</td>
<td>68</td>
<td>lofepramine, clomipramine or placebo</td>
</tr>
<tr>
<td>Scheibe and Albus (1996)</td>
<td>5</td>
<td>50</td>
<td>imipramine or doxepin for 8 weeks,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>supportive psychotherapy for 6 to 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>months, as needed</td>
</tr>
<tr>
<td>Scheibe and Albus (1997)</td>
<td>2</td>
<td>53</td>
<td>antidepressants for 8 weeks,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>supportive psychotherapy for 6 to 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>months, as needed</td>
</tr>
<tr>
<td>Warshaw et al. (1997)</td>
<td>5</td>
<td>412</td>
<td>naturalistic treatment</td>
</tr>
<tr>
<td>Shinoda et al. (1999)</td>
<td>1</td>
<td>65</td>
<td>naturalistic treatment</td>
</tr>
<tr>
<td>Toni et al. (2000)</td>
<td>3</td>
<td>326</td>
<td>naturalistic treatment</td>
</tr>
</tbody>
</table>

**Legend:** a In most studies a protocolized treatment is given initially. After this period treatment is naturalistic, unless otherwise stated.
### Table 3: Baseline clinical predictors of nonresponse to pharmacotherapy in panic disorder a.

<table>
<thead>
<tr>
<th>Predictor of nonresponse</th>
<th>Short-term treatment (6 –16 weeks)</th>
<th>Long-term treatment (1 - 7 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>0/7 b</td>
<td>1/12</td>
</tr>
<tr>
<td>Higher age</td>
<td>0/7</td>
<td>1/11</td>
</tr>
<tr>
<td>Married</td>
<td>0/3</td>
<td>1/6</td>
</tr>
<tr>
<td><strong>Illness variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longer duration of illness</td>
<td>2/9</td>
<td>10/15</td>
</tr>
<tr>
<td>Lower age at onset</td>
<td>0/3</td>
<td>4/10</td>
</tr>
<tr>
<td>Higher CGI score</td>
<td>2/5</td>
<td>1/3</td>
</tr>
<tr>
<td>Higher Anxiety score</td>
<td>5/9</td>
<td>5/9</td>
</tr>
<tr>
<td>Higher Phobic Avoidance score</td>
<td>7/10</td>
<td>13/15</td>
</tr>
<tr>
<td>Higher Panic score</td>
<td>5/9</td>
<td>4/11</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid depression</td>
<td>2/6</td>
<td>6/11</td>
</tr>
<tr>
<td>Comorbid anxiety disorder</td>
<td>0/2</td>
<td>3/5</td>
</tr>
<tr>
<td>Comorbid personality disorder</td>
<td>4/5</td>
<td>4/5</td>
</tr>
</tbody>
</table>

**Legend:** a: variables reported on in three or more studies; b: 0/7 means that this variable was investigated in seven studies, but in none of the studies it was found to be a predictor of nonresponse.