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

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Summary and concluding remarks

Panic disorder is an anxiety disorder with a lifetime prevalence of about 3%. The occurrence of unexpected panic attacks is the most prominent feature of this disorder. These panic attacks are defined as discrete periods of intense fear or discomfort, in which various symptoms develop rapidly, such as palpitations, shortness of breath, chest pain, nausea, intense fear of losing control, going crazy or dying. Patients frequently start avoiding places or situations where they think panic attacks are likely to occur and from which escape might be difficult. This agoraphobic avoidance, together with the constant anticipatory anxiety of having another panic attack, and of course the panic attacks themselves, leads to significant impairment in social and vocational functioning and decrease in overall quality of life.

Consensus has been reached on how panic disorder patients should be treated. Effective treatment for panic disorder should consist of either panic-focused cognitive behavioral therapy or pharmacotherapy. Currently it is not known whether a combined antipanic treatment of cognitive behavioral therapy and medication is superior to either treatment alone. Considering pharmacotherapy, antidepressants or benzodiazepines have been shown to be effective treatments for panic disorder. For many patients, the selective serotonin reuptake inhibitors (SSRI’s) are likely to have the most favorable balance between adverse effects and benefit.

This thesis focuses on a known problem in the treatment of panic disorder: nonresponse to pharmacotherapy. Even in properly diagnosed patients who receive adequate pharmacotherapy, some 20% to 40% of patients do not respond at all. Considering the fact that it may take several weeks of treatment before a clinical effect can be expected, and the side effects associated with pharmacotherapy, it is an important clinical task to identify factors which can predict nonresponse to pharmacotherapy in panic disorder.

In this thesis several studies are described which investigated variables, measured before treatment, as possible predictors of nonresponse to pharmacotherapy. In chapter 1 a review is presented on both short-term and long-term studies which investigated the prediction of nonresponse to pharmacotherapy in panic disorder. 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? It appears that several factors, indicative of the severity of illness, are predictors of nonresponse. 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.
In chapters 2 and 3 a study is described which investigated predictive factors to treatment with fluvoxamine, an SSRI, or brofaromine, a selective and reversible monoamine oxidase inhibitor (MAOI), in a sample of 44 panic disorder patients. A strict definition of non-response was used to find patients who did not respond at all after 12 weeks of treatment. Patients were considered nonresponders when they fulfilled two criteria: they did not show a 50% reduction of agoraphobic avoidance and they still experienced panic attacks at endpoint. Using this definition 15 patients (32.6%) were considered non-responders. These patients were characterized by a higher score on the Blood-Injury subscore of the Fear Questionnaire and they more often had high scores on several Fear Questionnaire subscores, indicative of comorbid phobic symptoms.

In the same group heart rate, blood pressure, plasma cortisol and the plasma concentration of 3-methoxy-4-hydroxyphenylglycol (MHPG) were also investigated as possible predictors of nonresponse. Nonresponders were characterized at baseline by a higher plasma MHPG concentration and a higher heart rate.

In chapter 4 a preliminary study is described in social phobia. This study was undertaken to see if predictive variables, reported in our studies with panic disorder, would also be predictive of nonresponse to fluvoxamine or brofaromine in social phobia. The data of 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. Similar to our study in panic disorder patients, nonresponders were characterized at baseline by a higher heart rate. Furthermore, these patients also had a higher blood pressure and higher scores on several psychometric scales, indicative of a greater illness severity.

There is evidence that the autonomous nervous system functioning may be disturbed in patients with panic disorder. The elevated heart rate at rest, which we found in nonresponders to pharmacotherapy, might be indicative of a higher autonomic arousal in nonresponders. Recent studies have used the analysis of heart rate variability (HRV) as a tool to study the functioning of the autonomous nervous system. In chapter 5 HRV is investigated as a possible predictor of nonresponse to mirtazapine, a dual action antidepressant, which we investigated in PD patients. Five-minute ECG recordings were obtained before treatment and were analysed using spectral analysis. Twenty-eight medication free panic disorder patients participated in this 12 week open label treatment study. The total spectrum and low frequency power of responders to mirtazapine were significantly higher than those of nonresponders. The findings of this preliminary study suggest that nonresponders to short term mirtazapine treatment are characterized at baseline by a lowered output of the autonomous nervous system.

In chapter 6 we present data on a large scale comparison of HRV data in patients with panic disorder, obsessive compulsive disorder and age matched normal controls. This study was undertaken to investigate whether drug free patients with obsessive compulsive disorder are also characterized by autonomous nervous system abnormalities, as has been
reported in patients with panic disorder. Standardized HRV measurements were carried out in 24 panic disorder patients, 26 patients with obsessive compulsive patients and 24 age matched normal controls. It appeared that the HRV of both panic disorder and obsessive compulsive disorder patients did not differ from normal controls. To verify this measurement, we enlarged the samples of panic disorder patients and normal controls, but again no differences in HRV parameters were evident. Thus, HRV analysis in a large sample of patients with panic disorder or obsessive compulsive disorder showed that these patient groups were not characterized by autonomous nervous system abnormalities, as no evidence was found of diminished HRV.

In this thesis, nonresponse to pharmacotherapy in panic disorder was investigated from several viewpoints: from high above in a review of the domain, from the perspective of psychometric scales and from the perspective of biological parameters. In reviewing studies on nonresponse to pharmacotherapy, a methodological obstacle was encountered which forced conclusions on predictors of nonresponse to remain tentative. The impediment was a total lack of consensus on key definitions such as response and remission, and the absence of these definitions in the DSM-IV. This made comparisons of studies on nonresponse methodologically cumbersome. The various incarnations of the DSM have provided us with consensus on diagnoses and consequently both patient care and scientific research have benefited greatly from this consensus. Both groups would benefit again if consensus would be reached on clear, standardized definitions of response and remission.

The review also made it clear that it is pointless to label a patient a nonresponder when it has not been established that this patient was treated adequately. The non-triviality of this statement is made clear by several recent studies which showed that a large number of panic disorder patients are still not treated adequately.

From the perspective of psychometric scales as predictors of nonresponse, it seems clear that these instruments can yield information on patients at risk of nonresponse to standard pharmacotherapy. Several factors can be measured before treatment which are clearly predictive of nonresponse. This implies that it should be possible to identify these patients before treatment and that alternative treatment strategies need to be devised for these patients who have a reduced chance of getting well and staying well.

The biological perspective shows that a lot of research needs to be done in this field. Compared to the wealth of studies using psychometric scales, only a handful of studies are known which investigated biological predictors of nonresponse. Clinicians would have great use for biological markers of nonresponse, but to date no solid markers were reported.

Our preliminary studies, which reported on plasma MHPG and reduced HRV as predictors of nonresponse, are in need of replication, considering the small sample sizes used. The need for replication with larger samples sizes became strikingly clear when we failed to replicate HRV abnormalities in panic disorder patients which several others had found in small patient samples. Panic disorder patients were reported to be characterized by a reduced HRV, indicative of a disturbed balance between the vagal and the sympathetic branches of
the autonomous nervous system. In our HRV study we found no evidence whatsoever of this autonomous nervous system dysfunction in our HRV study with the largest sample to date.

The efforts needed to further investigate the prediction of nonresponse to pharmacotherapy in panic disorder are considerable. A drawback of this kind of research is that many patients must be treated, in order to get enough nonresponders to test the alternative treatments for nonresponders. A hundred panic disorder patients must be treated, in order to get some thirty nonresponders. This means that a large multi-center study is probably the only viable way of studying the early identification and treatment of nonresponders to standard pharmacotherapy.