Predictors of Pharmacotherapy Response in Anxiety Disorders

*Damiaan Denys, MD, PhD*and Femke de Geus, MSc*

Address
*Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Center, B.01.206, PO Box 85500, 3508 GA, Utrecht, The Netherlands.
E-mail: D.A.J.P.Denys@azu.nl

Current Psychiatry Reports 2005, **7:**252–257
Current Science Inc. ISSN 1523-3812
Copyright © 2005 by Current Science Inc.

Although treatment with different compounds such as tricyclic antidepressants, selective serotonin reuptake inhibitors, high-potency benzodiazepines, and monoamine oxidase inhibitors has been proven effective in anxiety disorders, 20% to 40% of patients are nonresponders. Given the limited efficacy, the delayed onset of response (it takes several weeks before a clinical effect can be seen for most of these drugs), and the occurrence of side effects associated with pharmacotherapy, predicting response in anxiety disorders would be immensely valuable. This review surveys the literature over the past years on predictors of response to pharmacotherapy in obsessive-compulsive disorder, social anxiety disorder, panic disorder, and posttraumatic stress disorder. Prediction of treatment response may be founded on demographic and clinical variables, neurochemical and electrophysiologic parameters, imaging studies, and genetic markers.

Introduction

The current standard of care for anxiety disorders is to offer behavioral therapy and pharmacotherapy. Despite the general success of first-line pharmacologic treatments, no single drug seems to be effective for all patients with anxiety disorders. In obsessive-compulsive disorder (OCD), for example, approximately 50% of patients respond to an adequate drug trial with a mean decrease of 25% to 35% of symptoms. Low recovery rates have been reported in all anxiety disorders. Clearly, it would be immensely valuable to select patients at the beginning of treatment to target specific strategies and enhance treatment outcome. In this review, we report on recent literature that has investigated potential predictors of pharmacologic treatment in OCD, social anxiety disorder (SAD), panic disorder (PD), and posttraumatic stress disorder (PTSD). Prediction of treatment response may be based on 1) demographic and clinical variables such as age of onset of disease or clinical subtypes, 2) neurochemical and electrophysiological parameters such as plasma serotonin levels or event related potentials, 3) imaging studies such as positron emission tomography (PET) using brain glucose utilization, and 4) genetic markers.

Obsessive-compulsive Disorder

The current medications of choice for OCD are clomipramine and selective serotonin reuptake inhibitors (SSRIs), which allow 50% to 60% of patients to attain a moderate (25% to 45%) improvement in symptoms [1••]. A responder usually is defined as having a Clinical Global Impression (CGI) scale score of 1 ("very much improved") or 2 ("much improved") and/or a decrease of 25% to 35% on the Yale-Brown Obsessive-compulsive Scale [2,3].

Demographic and clinical variables

In the past, numerous studies have reported on the predictive value of demographic and clinical variables in response to SSRIs, but conclusions are equivocal and often contradicting [4•]. Recent studies have suggested that a symptom-based dimensional approach may prove to be valuable in identifying significant predictors of treatment response [5]. For instance, some studies have shown that patients with hoarding symptoms and patients with sexual and/or religious and somatic obsessions respond worse to serotonin reuptake inhibitors (SRIs) [6]. A common theme in these OCD symptom subtypes is the pronounced ego-syntonic nature with lack of insight, and a poorer motivation for treatment. Neziroglu *et al.* [7] reported a poorer outcome in the presence of overvalued ideation, and Ravi *et al.* [8] found poor insight (high baseline Brown Assessment of Beliefs Scale scores) to be highly predictive of poor treatment response. Denys *et al.* [4•] developed an easily applicable prediction method based on the joint predictive value of several clinical characteristics that can be evaluated at the beginning of the pharmacologic treatment. The absence of previous pharmacotherapies, moderate baseline severity of obsessive-compulsive symptoms (Yale-Brown Obsessive-compulsive Scale score < 23), and low Hamilton Depression scale (HAM-D) scores (6 to 15) were found to be prognostic determinants of good response to pharmacotherapy.

Neurochemical and neurophysiologic markers

Since the origin of the serotonin hypothesis in OCD, there has been a search for direct links between serotonin (5-HT)

concentrations and treatment response with SRIs. Elevated 5-HIAA concentrations in cerebrospinal fluid and higher platelet and whole blood 5-HT concentrations at baseline have been associated with a better clinical outcome after pharmacotherapy. Delorme *et al.* [9] confirmed recently in a small sample (n = 19) a positive relationship between pretreatment whole blood 5-HT concentrations and good response to SRIs. Bareggi *et al.* [10] found that plasma citalopram concentrations may be related to the clinical response in responders, but do not seem to account for the lack of clinical effect in nonresponders. Earlier reports have shown that baseline quantitative electroencephalography, such as increased alpha and beta activity, may predict better treatment outcome with SRIs, whereas nonresponders show decreased delta and theta activity [11•]. Recently, Hansen *et al.* [12] showed in a sample of 20 patients that responders had a strong baseline alpha activity that was normalized after paroxetine treatment. Relatively few patients have been studied with quantitative electroencephalography, and results need to be confirmed in larger samples. No study has been published since 1998 that relates event-related potentials to treatment outcome.

Neuro-imaging

Rauch *et al.* [13] found in contamination-related patients with OCD that lower pretreatment PET measures of regional cerebral blood flow (rCBF) within the orbitofrontal cortex and higher rCBF levels within the posterior cingulate cortex predicted symptom improvement after fluvoxamine treatment. The inverse relation between pretreatment rCBF in the orbitofrontal cortex and symptom improvement is remarkably consistent with results from three previous studies using clomipramine, fluoxetine, and paroxetine [11•]. However, Saxena *et al.* [14] observed with PET regional cerebral glucose uptake (rCMRglu) scans a significant correlation between higher pretreatment metabolism in the right caudate and symptom improvement after paroxetine treatment. They suggested that higher glucose metabolism reflects a greater release of glutamate in the caudate, which confirms an earlier finding reported by Rosenberg *et al.* [15]. With the same technique, Saxena *et al.* [14] also studied patients with SRI-refractory illness treated with adjunctive risperidone, and reported higher pretreatment rCMRglu in the right orbitofrontal cortex and bilateral thalamus in responders, but lower pretreatment rCMRglu in left parietal and bilateral dorsolateral prefrontal cortices. An important implication of this finding is that responders to an addition of atypical antipsychotics (patients with treatment-refractory OCD) may have different and opposite neurochemical underpinnings than responders to SRIs [11•].

Carey *et al.* [16] used hexamethylphosphoramide single photon emission computed tomography (SPECT) before and after a 12-week inositol treatment and found higher baseline perfusion levels in the left medial prefrontal region in responders. Hendler *et al.* [17] used a similar technique before and after a 6-month treatment with sertraline during a provoked symptomatic state and a relaxed condition. Responders showed significantly lower brain perfusion in the dorsal-caudal anterior cingulum and higher brain perfusion in the right caudate when compared with nonresponders during symptom provocation only. When pre- and posttreatment scans during symptom provocation were compared, responders showed increased perfusion in the left anterior temporal cortex and prefrontal cortex at 6 months' treatment.

In children with OCD, Castillo *et al.* [18] failed to detect baseline differences in rCBF with SPECT between responders and nonresponders after a 6-month clomipramine treatment, as did Diler *et al.* [19] after a 12 weeks treatment with paroxetine. Similarly, Szeszko *et al.* [20] failed to relate response to a 16-week paroxetine trial with amygdala volume changes.

Genetic markers

The paucity of pharmacogenetic research in OCD stands in sharp contrast with the abundance of genetic association studies. Three previous studies have investigated the role of the promoter region of the serotonin transporter gene (5-HTTLPR) and treatment response in OCD. McDougle *et al.* [21] found a trend for an association of the L-allele with poorer response to SRIs (clomipramine, fluvoxamine, fluoxetine, sertraline, and paroxetine) in a sample of 33 patients. Billet *et al.* [22] examined 72 patients retrospectively after a 10-week trial with SRIs and found no association; Di Bella *et al.* [23] failed to find a relation between response and 5-HTTLPR genotypes in a sample of 99 patients after 12 weeks of standardized fluvoxamine treatment. Pharmacogenetic studies are an unmet need in OCD, particularly given the success of addition trials with atypical antipsychotics [24].

Social Anxiety Disorder

Various drugs have been shown to be effective in SAD, including monoamine oxidase inhibitors, reversible monoamine oxidase inhibitors, benzodiazepines, and anticonvulsants, but first-line treatment of SAD currently consists of SSRIs, which allow 50% of patients with SAD to respond, with a mean decrease of symptoms of approximately 35% to 40% [25]. Response commonly is defined as a CGI improvement score of 1 ("very much improved") or 2 ("much improved") and/or a reduction on the fear/anxiety subscales of the Liebowitz Social Anxiety Scale by 50% or more.

Demographic and clinical variables

Versiani *et al.* [26] were among the first to evaluate treatment response in SAD, showing that alcohol abuse is a predictor of nonresponse to tranylcypromine. A follow-up study with moclobemide replicated this finding and also reported that high anxiety and depression scores were

predictive for good treatment response, whereas avoidant personality disorder (APD) predicted poor outcome [27]. However, in a clonazepam trial, a low level of pretreatment illness severity predicted better treatment response. Other variables such as gender, comorbidity, and duration of illness had no predictive value [28,29]. Sutherland *et al.* [30] found that older patients (older than 35 years) with SAD showed greater treatment effect after treatment with gabapentin. Numerous treatment studies looked for predictors of response with SRIs. Slaap *et al.* [31] showed that higher Hamilton Anxiety scale and HAM-D scores, and higher scores on the Symptom Checklist-90 (anxiety and interpersonal subscales) were indicative of nonresponse in a fluvoxamine and brofaromine comparison trial. In contrast, Montgomery [32] reported that patients with more severe SAD respond better to paroxetine treatment than do patients with moderate SAD.

The distinction between generalized and nongeneralized forms of SAD has received much attention with regard to pharmacotherapy and treatment response. Should generalized and nongeneralized forms of SAD be treated the same way? Stein *et al.* [33,34] pooled data from three paroxetine trials and found that paroxetine was equally effective in generalized and nongeneralized SAD, but responders were treated significantly longer compared with nonresponders. In a recent study, van Ameringen *et al.* [35] found that people with later onset tended to have a better response to treatment (which may not be explained by illness duration). Other variables such as age, gender, heart rate, blood pressure, symptom severity, disability, marital status, employment status, years of education, and comorbid APD had no predictive value in these studies. Another diagnostic issue is the high degree of overlap between the *Diagnostic and Statistical Manual of Mental Disorders* criteria of SAD and APD. Oosterbaan *et al.* [36] investigated the predictive value of APD in a trial comparing moclobemide, placebo, and cognitive therapy. As expected, he confirmed that patients with comorbid APD had a slightly slower onset of response to treatment, but this effect disappeared at 15-month follow-up.

Neurochemical and neurophysiologic markers

In the aforementioned study by Slaap *et al.* [31], higher heart rate and blood pressure levels characterized nonresponders to fluvoxamine. This finding parallels observations in PD, and suggests that nonresponders with PD and SAD have a disturbed autonomous nervous system, although Stein *et al.* [33] failed to replicate this finding in a sample of 829 patients with SAD.

Neuro-imaging

In a SPECT study, van der Linden *et al.* [37] found that treatment with citalopram led to significantly reduced activity in the left anterior and lateral temporal cortices, the left midfrontal cortex (anterior, lateral, and posterior parts), and the left cingulum. Nonresponders had higher activity at baseline in the anterior and lateral parts of the left temporal cortex and the lateral part of the left midfrontal regions compared with responders. In a study by Furmark *et al.* [38], rCBF was assessed by means of PET in 18 patients with SAD during an anxiogenic public speaking task before and after a 9-week citalopram trial, cognitive behavioral therapy, or a waiting list. Symptom improvement in both treatment groups, but not in the waiting list group, was accompanied by a decreased rCBF-response to the public speaking task in the amygdala, hippocampus, and the neighboring rhinal, parahippocampal, and periamygdaloid cortices. Favorable outcome after 1-year follow-up was associated with a greater initial attenuation of the subcortical rCBF.

Genetic markers

To the best of our knowledge, no studies using genetic markers as predictors for treatment response in SAD have been published.

Panic Disorder

Tricyclic antidepressants and SSRIs are equally effective in reducing the severity and number of panic attacks [39,40]. Because SSRIs have fewer side effects, they are the preferred choice of medication, leading to response rates of approximately 70% [41••]. In PD, response usually is defined as a panic-free period of 1 week or more, whether or not combined with a decrease in the Panic Disorder Severity Scale, the Hamilton Anxiety scale, or the Fear Questionnaire.

Demographic and clinical variables

Numerous previous treatment studies have used baseline variables to predict treatment outcome in PD. Although demographic variables, such as gender, age, and marital status often failed to show predictive value, one general consistent finding held up. More severely ill patients, defined by greater symptom severity, higher avoidance, and more comorbid disorders, have a lower chance of responding to treatment (for an excellent review, see Slaap *et al.* [41••]). In a recent study, Berger *et al.* [42] showed that response to paroxetine is poorer and slower in patients with a personality disorder or comorbid social phobia. A good predictor of endpoint remission status, which is an absence of panic attacks and a CGI score of 1 or 2, was the time of onset of response (a response at weeks 1, 2, and 3) [43]. A large naturalistic multicenter study in a group of primary care patients with PD was done to elucidate predictors of treatment response, defined as a 40% or greater decrease on the Panic Disorder Severity Scale [44]. The following factors were related to response: higher economic status (measures of income, employment, and ethnicity), better physical condition (measures of medical comorbidity, hospitalizations, and ER visits), and lower PD severity (measured by total phobia and agoraphobia scores). A surprising finding has been reported by Slaap *et*

al. [45]: one of the best predictors of nonresponse was a high baseline score on the blood-injury phobia subscale of the Fear Questionnaire. This finding was replicated by Overbeek *et al*. in 2004 [46] and explained as an expression of disturbed autonomous nervous system functioning or comorbid hypochondriac symptoms. Another good predictor of pharmacotherapy response seems to be the number of years of experience of the treating physician [47].

Neurochemical and neurophysiologic markers
Panic attack symptoms such as palpitations, chest pain, and shortness of breath are clearly linked to the autonomous nervous system (ANS). Slaap *et al*. [48] investigated the ANS functioning by measuring heart rate variability (HRV) and found that nonresponders to a 12-week treatment of mirtazapine showed a reduced HRV, which designates a decreased output of the ANS. However, Baker *et al*. [49] failed to find an effect of HRV on treatment response, but observed a normalization of sleep pattern in responders to clonazepam and placebo. Valença *et al*. [50,51] showed that patients taking clonazepam were less sensitive to the CO_2-challenge test (responded less frequently with a panic attack) and that this effect was related to clinical improvement.

Neuro-imaging
Currently, there are no neuro-imaging studies that have predicted treatment outcome in PD.

Genetic markers
Except for Woo *et al*. [52,53], who showed that the catechol-O-methyltransferase L/L genotype in patients with PD is associated with poor treatment response to paroxetine, no other study has been done regarding the predictive power of genetic markers in pharmacotherapy.

Posttraumatic Stress Disorder
First-line medication for PTSD treatment consists of SSRIs. Because many patients do not respond, combinations with other antidepressants or with other classes of psychotropic medication often are prescribed. Clinical response to treatment in PTSD usually is defined as a CGI-I rating of 1 or 2 and/or a decrease of 30% or greater in Clinician Administered PTSD Scale scores.

Demographic and clinical variables
Several studies [54–57] have suggested that SSRIs are more effective in civilian patients compared with combat veterans. Numerous explanations for this finding have been proposed such as gender, severity of illness, age, comorbidity with mood disorder, substance abuse, and previous treatments. Pooled data of six open-label nefazodone trials [58] showed higher response rates for the civilian trauma patients compared with the combat veterans. Predictors of response in this study were younger age, female gender, and civilian trauma. Martenyi *et al*. [55] found in a double-blind, placebo-controlled treatment study with fluoxetine a more favorable outcome in patients who were male, white, younger than 45 years old, suffered from combat-related trauma, had more than one traumatic event, and had no dissociative symptoms. In an open-label study comparing topiramate as monotherapy or augmentation therapy in civilian patients, Berlant [59] found that none of his predictors (bipolar comorbidity, duration of symptoms, age at onset, age, or gender) were significantly associated with symptom-reduction. Davidson *et al*. [60] examined the predictive value of improvement after sertraline treatment on anger outbursts, which are a prominent clinical feature in combat veterans with PTSD. They found that an increase in anger outbursts at week 1 predicted the likelihood of nonresponse.

Neurochemical and neurophysiologic markers
No studies using neurochemical or neurophysiologic markers as predictors for treatment response were found in PTSD.

Neuro-imaging
Recently, Seedat *et al*. [61] performed SPECT scans in patients with PTSD before and after 8 weeks of treatment with citalopram. Although a significant deactivation in the left medial temporal cortex was observed irrespective of clinical response, no significant pretreatment difference between responders and nonresponders was detected. Bremner and Vermetten [62] found that paroxetine treatment in patients with PTSD resulted in a 5% increase in hippocampal volume.

Genetic markers
In 2003, Lawford *et al*. [63] examined whether the allelic status of the dopaminergic TaqI A D2 dopamine receptor (DRD2) gene was associated with response to paroxetine. There was a significant effect of allele differentiation on the social dysfunction subscale of the General Health Questionnaire: A1+ allelic patients showed significantly more improvement on this scale than A1- allelic patients. Other subscales and the total General Health Questionnaire score showed no significant differences between the two groups.

Conclusions
Identification of predictors of pharmacotherapy outcome is important because they enable the physician to select and optimize treatment and to formulate a more accurate prognosis. Predictors are particularly useful in conditions in which the drugs have a very low expected efficacy and when a range of different drugs or groups of drugs are more or less equally efficacious, such as in anxiety disorders.

Clinical and demographic variables may be particularly helpful in prediction outcome because they are easy to assess and may be evaluated before treatment. Unfortunately, there is little consistency regarding clinical and demographic predictors. Duration, severity, and comorbidity generally seem to identify patients who are at risk for nonresponse to

treatment. Some studies suggest that patients with OCD with prominent egosyntonic symptoms (hoarding, religious obsessions, and overvalued ideas) are less prone to efficacious pharmacotherapy than patients with pronounced egodystonic symptoms. In PD and PTSD, more severely ill patients have a lower chance of responding. Currently, there are no reliable neurochemical and electrophysiologic predictors of outcome in anxiety disorders. There is some indication that nonresponders with SAD or PD have a disturbed autonomous nervous system. Surprisingly, there are no recent studies in anxiety disorders that relate immune function to treatment response. Imaging studies may help to identify predictors of treatment but are of limited use for the practicing clinician. In OCD there has been a profusion of imaging prediction studies and there seems to be some agreement on lower pretreatment PET measures of rCBF within the orbitofrontal cortex and higher activity in the caudate in predicting treatment response. With only three studies published in OCD, none in SAD, and one in PD and PTSD, there currently is a profound lack of pharmacogenetic studies in anxiety disorders.

Several studies have been done on the predictive value of clinical and neurobiological variables in response to pharmacotherapy in anxiety disorders, but conclusions are equivocal and sometimes contradicting. Possible reasons for divergent conclusions include the small sample size of some studies, differences in sample selection and definition of response, inhomogeneous samples with regard to the study factors of interest, and the use of inappropriate statistical procedures. Moreover, nonresponse often is poorly described in pharmacotherapy trials. A lower treatment outcome should be distinguished from drop-outs attributable to side effects or lack of compliance, comorbid personality disorders, or interpersonal difficulties with the treating clinician. Future research would benefit if consensus on definitions of response could be reached and nonresponse is better documented.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.•• Fineberg NA, Gale TM: **Evidence-based pharmacotherapy of obsessive-compulsive disorder.** *Int J Neuropsychopharmacol* 2005, **8:**107–129.

This is an excellent review on pharmacotherapy in OCD with critical notes and useful clinical comments.

2. Goodman WK, Price LH, Rasmussen SA, *et al.*: **The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability.** *Arch Gen Psychiatry* 1989, **46:**1006–1011.
3. Goodman WK, Price LH, Rasmussen SA, *et al.*: **The Yale-Brown Obsessive Compulsive Scale. II. Validity.** *Arch Gen Psychiatry* 1989, **46:**1012–1016.
4.• Denys D, Burger H, van Megen H, *et al.*: **A score for predicting response to pharmacotherapy in obsessive-compulsive disorder.** *Int Clin Psychopharmacol* 2003, **18:**315–322.

The authors propose a prediction rule on the joint predictive value of different clinical variables and include an exhaustive overview of response prediction studies in OCD.

5. Mataix-Cols D, Rosario-Campos MC, Leckman JF: **A multidimensional model of obsessive-compulsive disorder.** *Am J Psychiatry* 2005, **162:**228–238.
6. Mataix-Cols D, Rauch SL, Manzo PA, *et al.*: **The use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive-compulsive disorder.** *Am J Psychiatry* 1999, **156:**1409–1416.
7. Neziroglu F, Pinto A, Yaryura-Tobias JA, *et al.*: **Overvalued ideation as a predictor of fluvoxamine response in patients with obsessive-compulsive disorder.** *Psychiatry Res* 2004, **125:**53–60.
8. Ravi K, V, Samar R, Janardhan Reddy YC, *et al.*: **Clinical characteristics and treatment response in poor and good insight obsessive-compulsive disorder.** *Eur Psychiatry* 2004, **19:**202–208.
9. Delorme R, Chabane N, Callebert J, *et al.*: **Platelet serotonergic predictors of clinical improvement in obsessive compulsive disorder.** *J Clin Psychopharmacol* 2004, **24:**18–23.
10. Bareggi SR, Bianchi L, Cavallaro R, *et al.*: **Citalopram concentrations and response in obsessive-compulsive disorder. Preliminary results.** *CNS Drugs* 2004, **18:**329–335.
11.• Hurley RA, Saxena S, Rauch SL, *et al.*: **Predicting treatment response in obsessive-compulsive disorder.** *J Neuropsychiatry Clin Neurosci* 2002, **14:**249–253.

This is a short but thorough overview on response prediction in OCD, including mainly neuro-imaging studies.

12. Hansen ES, Prichep LS, Bolwig TG, *et al.*: **Quantitative electroencephalography in OCD patients treated with paroxetine.** *Clin Electroencephalogr* 2003, **34:**70–74.
13. Rauch SL, Shin LM, Dougherty DD, *et al.*: **Predictors of fluvoxamine response in contamination-related obsessive compulsive disorder: a PET symptom provocation study.** *Neuropsychopharmacology* 2002, **27:**782–791.
14. Saxena S, Brody AL, Ho ML, *et al.*: **Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression.** *Am J Psychiatry* 2003, **160:**522–532.
15. Rosenberg DR, MacMaster FP, Keshavan MS, *et al.*: **Decrease in caudate glutamatergic concentrations in pediatric obsessive-compulsive disorder patients taking paroxetine.** *J Am Acad Child Adolesc Psychiatry* 2000, **39:**1096–1103.
16. Carey PD, Warwick J, Niehaus DJH, *et al.*: **Single photon emission computed tomography (SPECT) of anxiety disorders before and after treatment with citalopram.** *BMC Psychiatry* 2004, **4:**30.
17. Hendler T, Goshen E, Tzila ZS, *et al.*: **Brain reactivity to specific symptom provocation indicates prospective therapeutic outcome in OCD.** *Psychiatry Res* 2003, **124:**87–103.
18. Castillo AR, Buchpiguel CA, de Araujo LA, *et al.*: **Brain SPECT imaging in children and adolescents with obsessive-compulsive disorder.** *J Neural Transm* 2005, In press.
19. Diler RS, Kibar M, Avci A: **Pharmacotherapy and regional cerebral blood flow in children with obsessive compulsive disorder.** *Yonsei Med J* 2004, **45:**90–99.
20. Szeszko PR, MacMillan S, McMeniman M, *et al.*: **Amygdala volume reductions in pediatric patients with obsessive-compulsive disorder treated with paroxetine: preliminary findings.** *Neuropsychopharmacology* 2004, **29:**826–832.
21. McDougle CJ, Epperson CN, Price LH, *et al.*: **Evidence for linkage disequilibrium between serotonin transporter protein gene (SLC6A4) and obsessive compulsive disorder.** *Mol Psychiatry* 1998, **3:**270–273.
22. Billett EA, Richter MA, King N, *et al.*: **Obsessive compulsive disorder, response to serotonin reuptake inhibitors and the serotonin transporter gene.** *Mol Psychiatry* 1997, **2:**403–406.
23. Di Bella DD, Catalano M, Cavallini MC, *et al.*: **Serotonin transporter linked polymorphic region in anorexia nervosa and bulimia nervosa.** *Mol Psychiatry* 2000, **5:**233–234.
24. Sareen J, Kirshner A, Lander M, *et al.*: **Do antipsychotics ameliorate or exacerbate Obsessive Compulsive Disorder symptoms? A systematic review.** *J Affect Disord* 2004, **82:**167–174.
25. Van Ameringen M, Mancini C, Pipe B, *et al.*: **Optimizing treatment in social phobia: a review of treatment resistance.** *CNS Spectr* 2004, **9:**753–762.

26. Versiani M, Mundim FD, Nardi AE, *et al.*: **Tranylcypromine in social phobia.** *J Clin Psychopharmacol* 1988, **8:**279–283.
27. Versiani M, Amrein R, Montgomery SA: **Social phobia: long-term treatment outcome and prediction of response—a moclobemide study.** *Int Clin Psychopharmacol* 1997, **12:**239–254.
28. Pande AC, Davidson JR, Jefferson JW, *et al.*: **Treatment of social phobia with gabapentin: a placebo-controlled study.** *J Clin Psychopharmacol* 1999, **19:**341–348.
29. Otto MW, Pollack MH, Gould RA, *et al.*: **A comparison of the efficacy of clonazepam and cognitive-behavioral group therapy for the treatment of social phobia.** *J Anxiety Disord* 2000, **14:**345–358.
30. Sutherland SM, Tupler LA, Colket JT, *et al.*: **A 2-year follow-up of social phobia. Status after a brief medication trial.** *J Nerv Ment Dis* 1996, **184:**731–738.
31. Slaap BR, van Vliet IM, Westenberg HG, *et al.*: **Responders and non-responders to drug treatment in social phobia: differences at baseline and prediction of response.** *J Affect Disord* 1996, **39:**13–19.
32. Montgomery SA: **Implications of the severity of social phobia.** *J Affect Disord* 1998, **50(Suppl 1):**S17–S22.
33. Stein DJ, Stein MB, Goodwin W, *et al.*: **The selective serotonin reuptake inhibitor paroxetine is effective in more generalized and in less generalized social anxiety disorder.** *Psychopharmacology (Berl)* 2001, **158:**267–272.
34. Stein DJ, Stein MB, Pitts CD, *et al.*: **Predictors of response to pharmacotherapy in social anxiety disorder: an analysis of 3 placebo-controlled paroxetine trials.** *J Clin Psychiatry* 2002, **63:**152–155.
35. Van Ameringen M, Oakman J, Mancini C, *et al.*: **Predictors of response in generalized social phobia: effect of age of onset.** *J Clin Psychopharmacol* 2004, **24:**42–48.
36. Oosterbaan DB, van Balkom AJ, Spinhoven P, *et al.*: **The influence on treatment gain of comorbid avoidant personality disorder in patients with social phobia.** *J Nerv Ment Dis* 2002, **190:**41–43.
37. Van der Linden G, van Heerden B, Warwick J, *et al.*: **Functional brain imaging and pharmacotherapy in social phobia: single photon emission computed tomography before and after treatment with the selective serotonin reuptake inhibitor citalopram.** *Prog Neuropsychopharmacol Biol Psychiatry* 2000, **24:**419–438.
38. Furmark T, Tillfors M, Marteinsdottir I, *et al.*: **Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioral therapy.** *Arch Gen Psychiatry* 2002, **59:**425–433.
39. Otto MW, Tuby KS, Gould RA, *et al.*: **An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder.** *Am J Psychiatry* 2001, **158:**1989–1992.
40. Bakker A, van Balkom AJ, Spinhoven P: **SSRIs vs. TCAs in the treatment of panic disorder: a meta-analysis.** *Acta Psychiatr Scand* 2002, **106:**163–167.
41.•• Slaap BR, Den Boer JA: **The prediction of nonresponse to pharmacotherapy in panic disorder: a review.** *Depress Anxiety* 2001, **14:**112–122.

This is an excellent review describing the predictors for nonresponse in short-term and long-term pharmacologic treatment in PD.

42. Berger P, Sachs G, Amering M, *et al.*: **Personality disorder and social anxiety predict delayed response in drug and behavioral treatment of panic disorder.** *J Affect Disord* 2004, **80:**75–78.
43. Pollack MH, Rapaport MH, Fayyad R, *et al.*: **Early improvement predicts endpoint remission status in sertraline and placebo treatments of panic disorder.** *J Psychiatr Res* 2002, **36:**229–236.
44. Roy-Byrne PP, Russo J, Cowley DS, *et al.*: **Unemployment and emergency room visits predict poor treatment outcome in primary care panic disorder.** *J Clin Psychiatry* 2003, **64:**383–389.
45. Slaap BR, van Vliet IM, Westenberg HG, *et al.*: **Phobic symptoms as predictors of nonresponse to drug therapy in panic disorder patients (a preliminary report).** *J Affect Disord* 1995, **33:**31–38.
46. Overbeek T, Buchold H, Schruers K, *et al.*: **Blood-injury related phobic avoidance as predictor of nonresponse to pharmacotherapy in panic disorder with agoraphobia.** *J Affect Disord* 2004, **78:**227–233.
47. Gorman JM, Martinez JM, Goetz R, *et al.*: **The effect of pharmacotherapist characteristics on treatment outcome in panic disorder.** *Depress Anxiety* 2003, **17:**88–93.
48. Slaap BR, Boshuisen ML, Van Roon AM, *et al.*: **Heart rate variability as predictor of nonresponse to mirtazapine in panic disorder: A preliminary study.** *Int Clin Psychopharmacol* 2002, **17:**69–74.
49. Baker B, Khaykin Y, Devins G, *et al.*: **Correlates of therapeutic response in panic disorder presenting with palpitations: heart rate variability, sleep, and placebo effect.** *Can J Psychiatry* 2003, **48:**381–387.
50. Valenca AM, Nardi AE, Nascimento I, *et al.*: **Early carbon dioxide challenge test may predict clinical response in panic disorder.** *Psychiatry Res* 2002, **112:**269–272.
51. Valenca AM, Nardi AE, Nascimento I, *et al.*: **Carbon dioxide test as an additional clinical measure of treatment response in panic disorder.** *Arq Neuropsiquiatr* 2002, **60:**358–361.
52. Woo JM, Yoon KS, Choi YH, *et al.*: **The association between panic disorder and the L/L genotype of catechol-O-methyltransferase.** *J Psychiatr Res* 2004, **38:**365–370.
53. Woo JM, Yoon KS, Yu BH: **Catechol O-methyltransferase genetic polymorphism in panic disorder.** *Am J Psychiatry* 2002, **159:**1785–1787.
54. van der Kolk BA, Dreyfuss D, Michaels M, *et al.*: **Fluoxetine in posttraumatic stress disorder.** *J Clin Psychiatry* 1994, **55:**517–522.
55. Martenyi F, Brown EB, Zhang H, *et al.*: **Fluoxetine versus placebo in posttraumatic stress disorder.** *J Clin Psychiatry* 2002, **63:**199–206.
56. Hertzberg MA, Feldman ME, Beckham JC, *et al.*: **Lack of efficacy for fluoxetine in PTSD: a placebo controlled trial in combat veterans.** *Ann Clin Psychiatry* 2000, **12:**101–105.
57. Zohar J, Amital D, Miodownik C, *et al.*: **Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder.** *J Clin Psychopharmacol* 2002, **22:**190–195.
58. Hidalgo R, Hertzberg MA, Mellman T, *et al.*: **Nefazodone in post-traumatic stress disorder: results from six open-label trials.** *Int Clin Psychopharmacol* 1999, **14:**61–68.
59. Berlant JL: **Prospective open-label study of add-on and monotherapy topiramate in civilians with chronic nonhallucinatory posttraumatic stress disorder.** *BMC Psychiatry* 2004, **4:**24.
60. Davidson J, Landerman LR, Clary CM: **Improvement of anger at one week predicts the effects of sertraline and placebo in PTSD.** *J Psychiatr Res* 2004, **38:**497–502.
61. Seedat S, Warwick J, van H, *et al.*: **Single photon emission computed tomography in posttraumatic stress disorder before and after treatment with a selective serotonin reuptake inhibitor.** *J Affect Disord* 2004, **80:**45–53.
62. Bremner JD, Vermetten E: **Neuroanotomical changes associated with pharmacotherapy in posttraumatic stress disorder.** *Ann N Y Acad Sci* 2004, **1032:**154–157.
63. Lawford BR, Young RM, Noble EP, *et al.*: **D2 dopamine receptor gene polymorphism: Paroxetine and social functioning in posttraumatic stress disorder.** *Eur Neuropsychopharmacol* 2003, **13:**313–320.