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## **The embarrassed brain : towards a neurobiology of generalized social anxiety disorder**

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### **Citation**

Veen, J. F. van. (2010, October 28). *The embarrassed brain : towards a neurobiology of generalized social anxiety disorder*. Retrieved from <https://hdl.handle.net/1887/16086>

Version: Corrected Publisher's Version

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**Note:** To cite this publication please use the final published version (if applicable).

# **Mirtazapine in social anxiety disorder: a pilot study**

International Clinical Psychopharmacology 2002;17:315-317

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## **Abstract**

Fourteen patients with social anxiety disorder (generalized type), according to DSM-IV criteria, were treated with mirtazapine 30 mg for 12 weeks. Twelve patients completed the study. Two patients (14.3%) dropped out due to side-effects. Generally, mirtazapine was well tolerated. Five out of twelve patients (41.7%) were classified as responders, based on a Clinical Global Improvement score of 1 or 2 and a reduction of the Liebowitz Social Anxiety Scale (LSAS) of 40%. The mean total score on the LSAS, as well as the anxiety and avoidance subscores, decreased significantly. This open pilot study suggests that further investigations are warranted to prove the efficacy of mirtazapine in generalized social anxiety disorder.

## Introduction

Social anxiety disorder (SAD), or social phobia, is one of the most common, but still underrecognized, psychiatric disorders. The majority of the epidemiological studies found lifetime prevalence rates of between 1.7% and 16.1%, using DSM-III, or -IV criteria (Brunello et al, 2000). An epidemiological survey found lifetime prevalence rates for the generalized type and the specific type of 5.9% and 7.0%, respectively (Stein and Kean, 2000). The essential feature of SAD is the fear of being negatively evaluated by others, resulting in avoidance of social situations or marked distress. Exposure to the feared situation provokes an immediate anxiety response, with symptoms such as trembling, blushing and sweating, and may even take the form of a situationally predisposed panic attack. Social anxiety and avoidance interferes significantly with the person's daily routine, social or occupational functioning. Treatment options for SAD are cognitive behavioural therapy and drug treatment.

The selective serotonin reuptake inhibitors (SSRIs) are the firstline drug treatment for SAD. Other treatment options include monoamine oxidase inhibitors (MAOIs) and benzodiazepines (Westenberg, 1999a). Information on other antidepressants, such as venlafaxine (Van Vliet et al., 1997; Altamura et al, 1999) and clomipramine (Van Vliet and Westenberg, 1999), suggest that they might also be effective in SAD, but data from controlled studies are lacking. Mirtazapine is an antidepressant with a novel mechanism of action. It has shown to block the  $\alpha_2$ -adrenergic autoreceptors, resulting in a stimulation of both noradrenergic and serotonergic pathways. In addition, mirtazapine also blocks the 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors. By virtue of its antihistaminergic properties, sedation and weight gain may occur (De Boer, 1996).

Several small open label studies with mirtazapine have been performed in anxiety disorders. These studies in anxiety states (Sitsen and Moors, 1994), panic disorder (Carpenter et al, 1999), post-traumatic stress disorder (Connor et al, 1999), major depression with comorbid generalized anxiety disorder (Goodnick et al, 1999) and major depression with anxiety symptoms (Fawcett and Barkin, 1998) suggest mirtazapine has anxiolytic properties.

The aim of the present study was to assess the possible efficacy of mirtazapine in patients suffering from SAD and to evaluate whether large controlled studies with this drug are warranted.

## Methods

### *Subjects*

The present study was performed in the outpatient clinic of the University Medical Center Utrecht, the Netherlands. Patients meeting DSM-IV criteria for SAD, generalized type, who were aged 18-65 years, were included in the study. Patients with other axis I disorders, and pregnant or nursing women were excluded.

### Study design

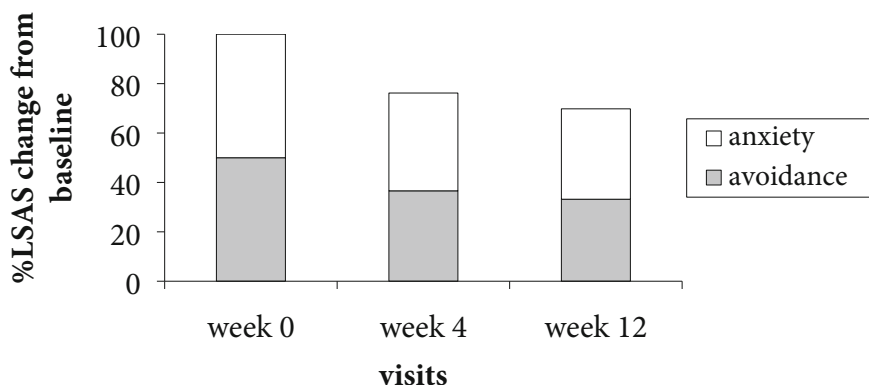
Subjects were treated with mirtazapine, 30 mg a day, fixed dose, for 12 weeks. They were evaluated at baseline, and at weeks 4 and 12. Responders were treated for another 12 weeks and evaluated at week 24. None of the patients had used psychotropic medication other than incidental use of oxazepam for more than a year prior to the study. Concomitant psychotropic medication was not allowed during the course of the study, except for oxazepam 10 mg, with a maximum of 20 mg a day.

The primary outcome measure was the Liebowitz Social Anxiety Scale (LSAS), comprising 24 items, in which anxiety and avoidance are rated in different social situations on a 0 – 3 points scale.

The other efficacy measures were the Clinical Global Improvement scale (CGI), and the Hamilton Depression Rating Scale (HDRS). The LSAS, and the HDRS were performed at baseline, LSAS and CGI were performed at week 4, and the LSAS CGI and HDRS were performed at week 12. Patients with a reduction of 40% or more on the LSAS total score and a CGI score 'improved' (2) or 'much improved' (1) were considered responders to treatment. Information on side-effects was collected by open questioning.

### Statistical analysis

Multivariate analysis of variance with repeated measures (ANOVA) was used to evaluate the LSAS score in completers. Student's paired t-test was used to determine significant differences between baseline and endpoint on the LSAS and HDRS.



**Figure 1.** The mean Liebowitz Social Anxiety Scale (LSAS) total score of all patients (n=14), divided in an anxiety and an avoidance subscore, is shown as percent change from baseline. Statistical analysis revealed a significant change in anxiety and in avoidance subscores over time ( $P<0.005$ , d.f.=2,12,  $F=8.85$ ;  $P<0.001$ , d.f.=2,12,  $F=15.13$ ). The changes from baseline were already statistically significant as of week 4 ( $P<0.005$ ,  $t=4.00$ ;  $P<0.001$ ,  $t=7.03$ ). Analysis with last observation carried forward also showed a significant change in anxiety and avoidance subscores from baseline to week 12 ( $P<0.01$ ,  $t=3.14$ ;  $P<0.005$ ,  $t=3.98$ )

## Results

Fourteen patients (11 males and three females), aged 23-44 years, who were suffering from the generalized type of SAD, were included in this study. The mean age was 35.5 years. The mean

age of onset of SAD was 13.4 years, and the mean duration of illness was 22 years. Previous drug treatment with antidepressant medication, mostly SSRIs, was reported in 28.6% of patients. Previous cognitive behavioural therapy was applied in 35.7% of the patients, and 64.3% had a family history of SAD. Mirtazapine was well tolerated in the majority of the patients. The most frequently reported side-effects were sedation and weight gain. Other side-effects reported were a dry mouth, muscle cramps, dizziness, insomnia and restless sleep. Two patients used oxazepam 10 mg occasionally. Two patients dropped out after 4 weeks due to weight gain and sedation. All responders to treatment continued taking mirtazapine after completion of the study.

The mean LSAS total score at baseline was  $72.6 \pm 5.11$ , and decreased to  $48.3 \pm 8.18$  at week 12. The change in mean LSAS score is shown in figure 1. Statistical analysis revealed a significant change in LSAS score over time ( $P < 0.001$ , d.f.=2,12,  $F=12.33$ ), and this was already statistically significant by week 4 ( $P < 0.001$ ,  $t=5.25$ ). Analysis with last observation carried forward (LOCF) also showed a significant change in LSAS score from baseline to week 12 ( $P < 0.05$ ,  $t=3.59$ ). Five out of 12 (41.7%) completers were classified as responders to treatment, with a mean LSAS total score of 67.6 at baseline ( $n=5$ ), and 24.5 at week 12. No further improvement was seen at week 24. The mean HDRS score decreased from 7.4 at baseline to 5.0 at week 12 ( $P < 0.05$ ,  $t=3.62$ ).

## Discussion

This open pilot study suggests that mirtazapine is a clinically effective treatment for SAD of the generalized type. Mirtazapine was generally well tolerated. Using a stringent criterion for response, 41.7% of the patients were classified as responders. Because no comorbidity, such as depression, was allowed in this study, these effects of mirtazapine appear to be specific, and cannot be attributed to the antidepressant effect of the drug.

The present study is the first study to describe the effects of mirtazapine in SAD. The pharmacological properties of mirtazapine are quite different from SSRIs, the treatment of choice for SAD thus far. Mirtazapine is an  $\alpha_2$ -adrenergic receptor antagonist with additional antagonistic activity at the 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors. Unlike SSRIs, mirtazapine has no direct stimulatory effects on the serotonergic system. According to its different mechanism of action, mirtazapine has a side-effect profile that completely differs from SSRIs. Mirtazapine is devoid of side-effects common to all SSRIs, such as nausea, sleep disturbances and sexual dysfunction, which might influence patient's compliance and lead to treatment discontinuation (Westenberg and Den Boer, 2001). Mirtazapine lacks these side-effects because it blocks the 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors, and even shows sleep improvement (Thase et al, 2001). In contrast to SSRIs, the most prominent side-effects of mirtazapine are daytime sedation and weight gain (De Boer, 1996). The efficacy of SSRIs in SAD is well documented. Studies with SSRIs using a similar response criterion as that in the present study, generally show an efficacy of between 50% and 60%, which is slightly higher than the response of 42% seen in the present study (Westenberg, 1999b). However, it should be noted that this was a fixed dose study and that no information is available on the optimal dose of mirtazapine in SAD. In conclusion, double-

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blind research is clearly warranted to confirm the efficacy of mirtazapine in SAD. By virtue of its different pharmacological profile, mirtazapine might be an alternative treatment option for those patients who can not tolerate, or are unresponsive to SSRIs.

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