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Psychopharmacological treatment of social phobia; a double blind placebo controlled study with fluvoxamine

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Abstract. Previous studies have shown selective and non-selective monoamine oxidase inhibitors (MAOIs) to be effective in the treatment of social phobia. In this study we investigated the efficacy of selective serotonin reuptake inhibitors (SSRIs) in social phobia. Thirty patients with social phobia (DSM-IIIR) were treated with the SSRI fluvoxamine (150 mg daily) using a 12-week double-blind placebo controlled design. A substantial improvement was observed in seven (46%) patients on fluvoxamine and in one (7%) on placebo. Statistically significant effects were seen on measures of social anxiety and general (or anticipatory) anxiety in patients treated with fluvoxamine compared with placebo. The level of phobic avoidance decreased also but the difference at endpoint between fluvoxamine and placebo failed to reach statistical significance. It is concluded that treatment with the SSRI fluvoxamine has beneficial effects in patients suffering from social phobia, suggesting that serotonergic mechanisms might be implicated in social anxiety.

Key words: Social phobia – Psychopharmacology – Serotonin reuptake inhibitors – Fluvoxamine

Social phobia (SP) is a disorder with a high prevalence. Six-month and life-time prevalence rates of 2.7 and 3.8% were reported in a recent epidemiological study (Davidson et al. 1993). According to the DSM-IIIR, social phobic patients experience subjective and somatic symptoms of anxiety, like trembling, palpitations, blushing and sweating, in situations in which the individual is exposed to the scrutiny of other people due to fear of acting in an embarrassing way (American Psychiatric Association 1987). Social phobics are afraid of and avoid those situations. The distinction between different subtypes of social phobia has become a focus of recent investigations since these subtypes were included in the DSM-IIIR.

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Patients can be classified as suffering from the generalized subtype, if the phobic situation includes most social situations. The specific subtype according the DSM-IIIR requires fear of only specific situations (e.g. public speaking). Investigations of the validity of this social phobia subtype distinction revealed that these subtypes show significant differences in severity in social phobia and social anxiety as well as in the level of general distress (Turner et al. 1992). In general, patients with specific social phobia were less impaired in terms of social anxiety and showed lower levels of general distress than patients with the generalized subtype.

The treatment of SP has traditionally been the domain of psychoanalytic psychotherapy or behavior and cognitive therapies (Nichols 1974; Ost et al. 1980; Emmelkamp 1982; Brady 1984a, b; Marks 1985).

Psychopharmacological treatment of SP has not been extensively studied, in contrast to other anxiety disorders. Frequently, SP appears to be therapy resistant (Liebowitz 1987). There is circumstantial evidence that β-blockers might relieve some of the somatic symptoms of SP, like palpitations and trembling (Falloon et al. 1980; Gorman et al. 1980; Liebowitz et al. 1990, 1992), although this may be confined to specific social phobias like performance anxiety.

In several studies a beneficial effect of monoamine oxidase inhibitors (MAOIs) in the treatment of SP has been found.

In most studies a reduction in social anxiety is seen after treatment with phenelzine or tranylcypromine (Kelly et al. 1970; Tyrer et al. 1973; Tyrer and Steinberg 1975; Mountjoy et al. 1977; Solyom et al. 1973, 1981; Liebowitz et al. 1985, 1992; Versiani et al. 1988; Gelernter et al. 1992).

Recent studies with the selective monoamine oxidase-A inhibitors brofaromine and moclobemide in SP have shown these drugs to be effective in reducing social anxiety and social phobic avoidance (Van Vliet et al. 1992; Versiani et al. 1992).

Case studies and open studies have suggested that benzodiazepines like alprazolam (Lydiard et al. 1988)

and clonazepam (Versiani et al. 1989; Munjack et al. 1990; Versiani 1990), and the α_2-adrenoceptor agonist clonidine (Goldstein 1987) may also be effective.

Earlier investigations have shown that 5-HT uptake inhibitors are of value in the treatment of anxiety disorders like panic disorder (Den Boer et al. 1987; Den Boer and Westenberg 1988), supporting the hypothesis that serotonergic neural systems may be implicated in the pathophysiology of these anxiety disorders. Studies with selective serotonergic drugs in SP are sparse. Two open studies have reported beneficial effects with the 5-HT_{1A}-agonist buspirone in social phobia, albeit the scales used in these studies were not especially designed to measure social anxiety or avoidance (Schneier et al. 1990; Munjack et al. 1991). Therefore, these studies remain inconclusive. A recent open label study in which the Social Anxiety Scale (Liebowitz 1987) was used reported modest efficacy of buspirone in the treatment of social phobia (Schneier et al. 1993). Clearly, confirmation of these preliminary findings in placebo-controlled studies is warranted.

There are some case reports reporting the efficacy of fluoxetine in avoidant personality disorder and social phobia (Deltito and Stam 1989; Sternbach 1990; Schneier et al. 1992). Recently two open studies were published reporting efficacy of fluoxetine in patients with social phobia (Black et al. 1992; Van Ameringen et al. 1993), but well designed studies are lacking.

The aim of the present study was to evaluate the efficacy of the selective serotonin uptake inhibitor (SSRI) fluvoxamine in the treatment of SP.

Material and methods

Patients. Thirty patients were recruited from the outpatient clinic of the department of Biological Psychiatry of the University Hospital in Utrecht. The study was approved by the Ethics Committee of the Academic Hospital. Informed consent was obtained from all patients after full explanation of study procedures. Included in the study were patients suffering from social phobia according to DSM-IIIR criteria. Excluded were patients with another anxiety disorder, major affective disorder or psychotic disorder, alcohol or drug abuse, those patients suffering from medical problems on the basis of a complete medical evaluation and patients who were pregnant or lactating. A score of 15 or higher on the Hamilton Depression Scale was an exclusion criterion. Patients with personality disorders according to DSM-IIIR were also excluded. During treatment, the use of other psychotropic drugs was not allowed. Occasional use of oxazepam to a maximum of 30 mg daily was permitted, but only if required. There were 17 females and 13 males; the mean age was ($\pm$ SD) 35.2 $\pm$ 9.5 years (range 23–54) years. The mean duration of illness was 13.6 $\pm$ 8.9 years.

Patients were treated for 12 weeks using a double-blind placebo controlled design. Patients were randomly allocated to one of the two treatment groups. From the patients who were recruited one dropped out in the second week due to severe side effects (treated with fluvoxamine); another patient dropped out in week 8 due to lack of efficacy (treated with placebo).

From the 28 patients who entered the statistical analysis 15 were treated with fluvoxamine and 13 with placebo. The dose of fluvoxamine was gradually increased from 50 to 150 mg daily (50 mg t.i.d.) in 3 weeks.

Symptom assessments. Efficacy of the treatment was assessed using the Social Anxiety Scale (SAS; Liebowitz 1987) and the Hamilton Anxiety Scale (HAS; Hamilton 1959) on baseline and at weeks 1, 2, 4, 8 and 12. The SAS rates common social and common performance situations separately on four-point scales for anxiety and avoidance. At the outset and the end of the study period, patients completed the 90-item Symptom Checklist (SCL-90; Derogatis et al. 1973). The Hamilton Depression Scale (HDS; Hamilton 1967) was completed on baseline and at the end of treatment.

Adverse events were assessed by open questioning at weeks 1, 2, 4, 8 and 12.

Laboratory measurement. Blood samples for plasma drug levels were taken between 9.00 and 10.00 a.m. at weeks 8 and 12. The duration of time from the last dosage until the venepuncture was 12 h. Plasma fluvoxamine levels were measured by liquid chromatography using fluorometric detection. Blood pressure and body weight were assessed on baseline and at the end of weeks 1, 2, 4, 8 and 12.

Data analysis. The treatment effects as assessed with the HAS and SAS were analyzed by multivariate analysis of variance with repeated measures on the factor time. Between-group effects (mean group differences) and within-group effects (time and time by group interactions) were assessed. Bartlett's test for homogeneity of group variances was performed on all measures. In case of a significant time-by-group interaction, a post hoc pairwise comparison was made by time using the Tukey multicomparison test. The contrasts at the different time points are reported significant when the probability value was less than 5%. The HDS scores were evaluated by one-way analysis of variance and the SCL90 scores were tested by means of the Student *t*-test. The Systat statistical package was used for all analyses.

Results

Clinical variables

The two treatment groups did not differ in mean age, mean age of onset and sex. At baseline, there were no statistical differences between the groups for any of the outcome measures. With respect to the most conspicuous symptoms, patients were asked to rate the symptom they feared most. Ten patients suffered from anxiety about trembling, four patients from anxiety about blushing, eight patients suffered from a generalized form of social anxiety and eight patients had a combination of generalized and specific social phobia. Fifteen patients had relatives with SP. Sixteen patients reported taking alcoholic beverages before engaging in social situations to relieve social phobic anxiety.

Most patients had attended behavioral or cognitive therapy previously, but without any clinically relevant outcome.

At the outset of the study ten patients (six in the fluvoxamine group and four in the placebo group) took oxazepam (5–10 mg) occasionally. At the end of the study, three patients in the placebo group and two in the fluvoxamine group were still taking oxazepam if required.

Taking a reduction on the anxiety scale of the SAS of 50% or more at end point as criterion, seven (46%) subjects on fluvoxamine and one (7%) on placebo were classified as responders to treatment. The efficacy of treatment as assessed with the SAS scale is depicted in Figs 1 and 2. The subscores social anxiety and social phobic

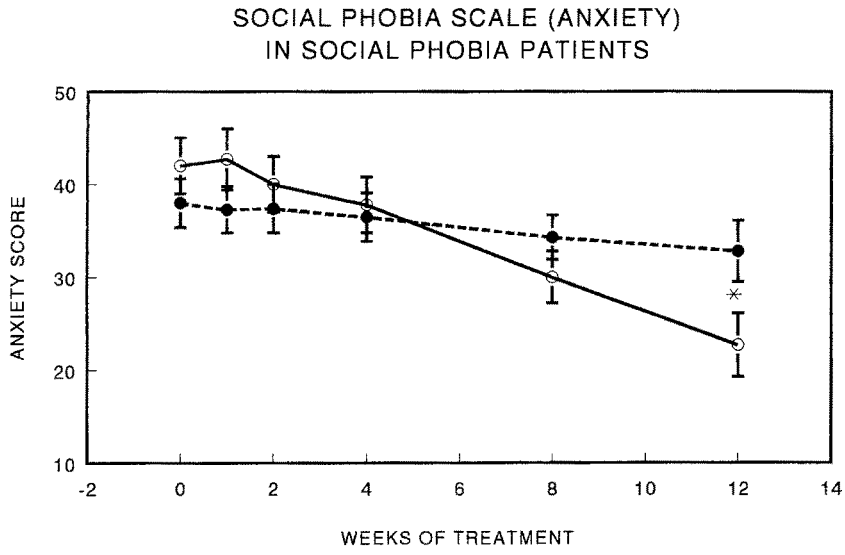

Fig. 1. Mean (± SEM) score on the anxiety subscale of the Social Phobia Anxiety in patients with social phobia treated with fluvoxamine ($n = 15$) or placebo ($n = 13$). The reduction in the fluvoxamine group was significantly greater than in the placebo group from week 12 (* $P < 0.001$). ○, fluvoxamine; ●, placebo

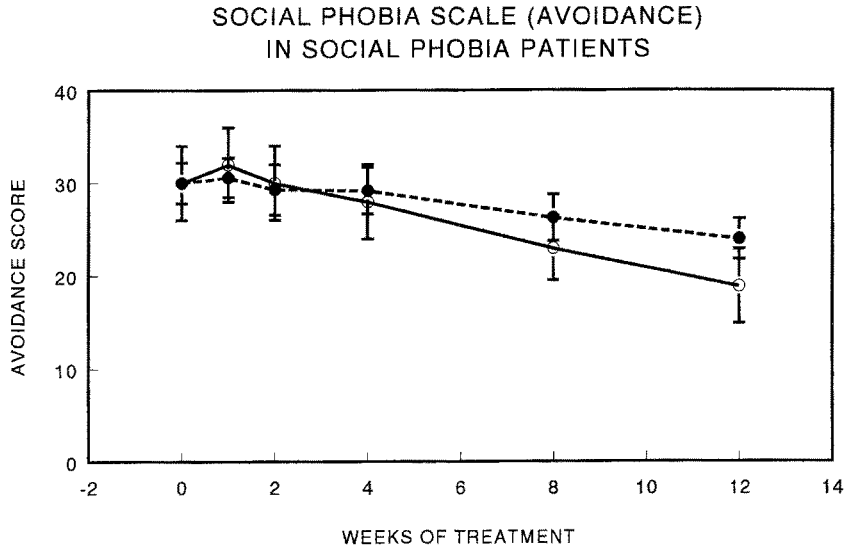

Fig. 2. Mean (± SEM) score on the avoidance subscale of the Social Anxiety Scale in patients with social phobia treated with fluvoxamine ($n = 15$) or placebo ($n = 13$). ○, fluvoxamine; ●, placebo

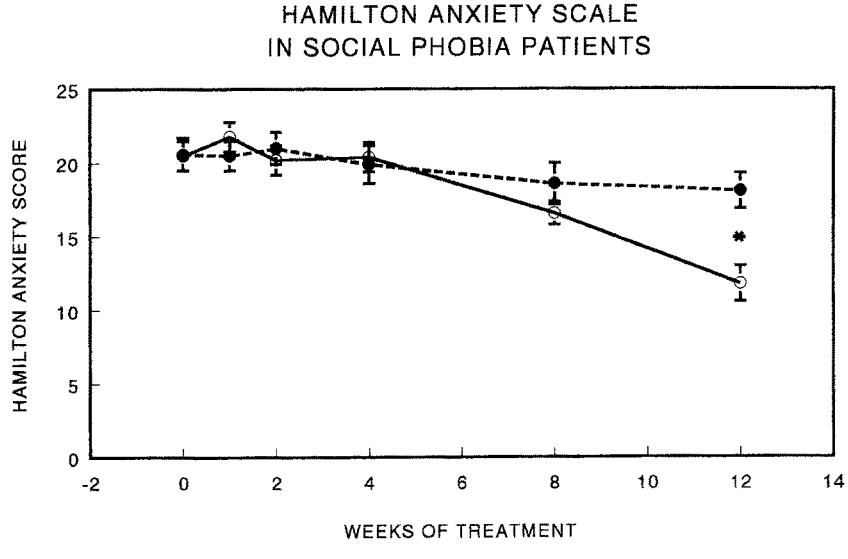

Fig. 3. Mean (± SEM) Hamilton Anxiety Score in patients with social phobia treated with fluvoxamine ($n = 15$) or placebo ($n = 13$). Fluvoxamine was superior to placebo from week 12 (* $P < 0.001$). ○, fluvoxamine; ●, placebo

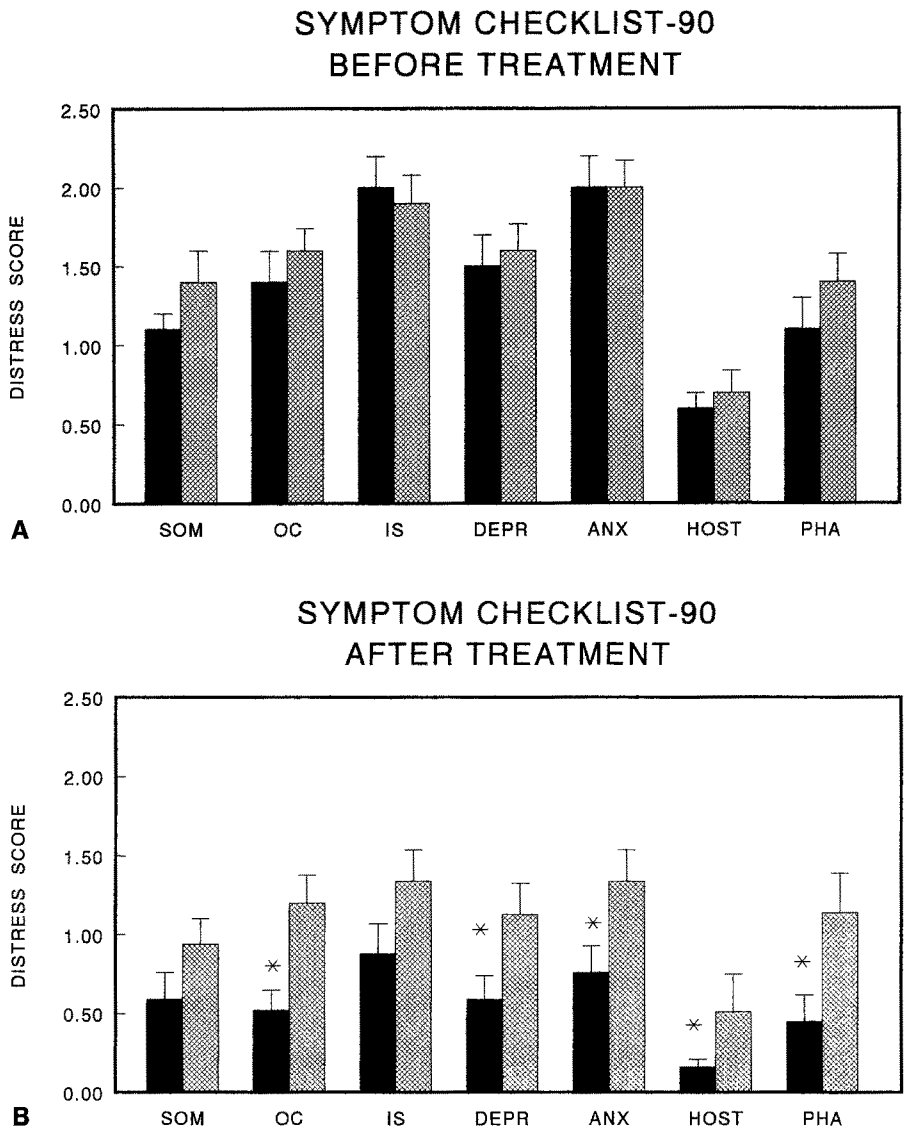

Fig. 4. Factor scores of the 90 Items Symptom Checklist in patients with social phobia treated with fluvoxamine or placebo at baseline (**A**) and at the end of week 12 (**B**). At the end of treatment fluvoxamine was superior to placebo on all subscores except SOM and IS; these factors just failed to reach statistical significance (see Results). Key: *SOM*, somatization; *OC*, obsessions and compulsions; *IS*, interpersonal sensitivity; *DEPR*, depression; *ANX*, anxiety; *HOS*, hostility; *PHA*, phobic anxiety. * $P < 00.5$. ■, fluvoxamine; ▩, placebo

avoidance were analyzed separately. At the outset of the study, the SP anxiety ratings (Fig. 1) were 42.1 ± 3.3 (mean ± SEM) and 38.0 ± 2.6 in the fluvoxamine and placebo group, respectively. During treatment these ratings gradually fell to 22.7 ± 3.4 in the fluvoxamine group and 32.8 ± 3.3 in the placebo group at week 12. Statistical analysis showed a significant time ($F = 20.8$; $df = 5.0$; $P < 0.001$) and time by group effect ($F = 6.7$; $P < 0.001$). Contrast analysis showed that the effect in the fluvoxamine group was superior to placebo at week 12.

SP avoidance ratings (Fig. 2) decreased gradually from 29.9 ± 4.1 to 18.9 ± 3.9 in the fluvoxamine group and from 30.1 ± 2.3 to 24.2 ± 2.2 in the patients receiving placebo. Statistical analysis indicated a significant time ($F = 13.4$; $P < 0.001$) but no time by group effect. Global anxiety as assessed with the HAS is depicted in Fig. 3. At baseline the ratings were 20.5 ± 0.9 in the fluvoxamine and 20.5 ± 1.1 in the placebo group. Following a slight exacerbation of symptoms in the fluvoxamine group in the first week of treatment, the ratings as measured with the HAS gradually declined subsequently. The increase in anxiety during the first week was present in patient's suffering from the generalized form, as well as in the patients who also fulfilled criteria for both subtypes. Statistical analysis showed a significant time effect ($F = 25.4$; $df = 5.0$; $P < 0.001$) and a significant time by group interaction ($F = 7.9$; $df = 5.0$; $P = <0.001$). Contrast analysis revealed that the reduction of symptoms as measured with the HAS was greater in the fluvoxamine group than in the placebo group at week 12.

The HDS ratings at baseline were 9.3 ± 0.6 and 9.6 ± 0.8 in the fluvoxamine and placebo groups, respectively (range 4–14). At endpoint these ratings were 5.4 ± 0.8 in the fluvoxamine and 8.6 ± 0.7 in the placebo group. With respect to the HDS scores a significant time effect ($F = 25.1$; $df = 1.0$; $P < 0.001$) and a significant time by group interaction was observed ($F = 5.0$; $df = 1.0$; $P < 0.05$), favoring fluvoxamine.

The results of the SCL-90 analyses are summarized in Fig. 4. As seen in this figure the pretreatment profiles of fluvoxamine and placebo show good comparability

(Fig. 4A). There were no statistically significant differences between the groups at baseline. The general symptom index (mean total score; GSI) fell from 1.3 ± 0.2 on baseline to 0.6 ± 0.2 at week 12 in the fluvoxamine group and from 1.4 ± 0.1 to 1.1 ± 0.2 in the placebo group. At endpoint, the score in the fluvoxamine group was significantly different from placebo ($T = 2.4$; $P < 0.05$). Subsequent analysis of the subscores revealed group effects for the following subscores: anxiety (ANX; $T = 2.1$; $P < 0.05$), depression (DEPR; $T = 2.1$; $P < 0.05$), hostility (HOST; $T = 2.2$; $P < 0.05$), obsessive compulsive (OC; $T = 3.1$; $P < 0.01$) and phobic anxiety (PHOB; $T = 2.4$; $P < 0.05$) (Fig. 4B). The factors somatization (SOM) and interpersonal sensitivity (IS) were not different at end point.

Drug concentrations

Plasma fluvoxamine concentrations at steady state were 175 ± 27 and 161 ± 23 ng/ml (mean ± SEM) at weeks 8 and 12, respectively.

Side effects

All patients but one in the fluvoxamine group (15 patients) and 3 patients in the placebo group (13 patients) experienced one or more side effects, most notably during the first 4 weeks of the treatment period. The most outstanding side effects in the fluvoxamine group were: increased anxiety in the first weeks (reported by eight patients in the fluvoxamine group and one in the placebo group), leading to panic attacks in one patient on fluvoxamine, nausea and stomach complaints (ten versus two patients), feeling sleepy and tiredness (seven versus one patients) and middle sleep disturbances (six versus two patients).

Blood pressure and body weight showed no clinical relevant changes during treatment in either group.

Discussion

The results of this study show that the SSRI fluvoxamine is effective in the treatment of social phobia. From the main efficacy measures, a marked reduction was found in general anxiety as measured with the HAS and anxiety in social situations as measured with the SAS. Seven out of 15 patients treated with fluvoxamine showed a clinically relevant improvement as defined by a reduction of 50% or more on the social anxiety scale. These subjects could resume their normal social lives to a large extent. The placebo effects were negligible in this respect. Although social avoidance decreased significantly during the study, no significant differences were seen between the treatment conditions. It is also noteworthy that a significant decrease in social anxiety was not reached until week 12. Apparently, social anxiety is much more treatment resistant that anxiety seen in patients with for instance panic disorder. In these patients beneficial effects are usually seen after the fourth week of treatment (Den Boer and Westenberg 1990). It is conceivable, therefore, that abatement of social avoidance behavior, which is considered to be a sequela of social anxiety, will appear at a later stage of treatment. Once the anxiety has ceased, patients will gradually learn to cope with social situations. On the other hand, possible flaws of the present study may also explain some of our results, in that firstly, the dosage of fluvoxamine may have been too low. In other anxiety disorders like obsessive compulsive disorder, dosages are used up to 300 mg. Nevertheless, in our previous studies in panic disorder we used similar dose levels as in the present study, and these dosages were high enough to achieve significant treatment effects (Den Boer and Westenberg 1988, 1990).

Secondly, SSRIs might simply be less effective in social phobia. In a previous study with the selective MAO-A inhibitor brofaromine we found that social anxiety as well as social avoidance tend to respond around week 8 (Van Vliet et al. 1992), whereas in the present study a reduction of social anxiety was not found until week 12. Moreover, MAOIs have been shown to improve symptoms of both social anxiety and social avoidance, whereas the efficacy of the SSRI fluvoxamine in the present study appears to be confined to social anxiety. Finally, the patient sample of the present study is relatively small; possibly a larger sample would yield statistically significant treatment effects with respect to social avoidance. Future studies in larger patient groups will hopefully resolve this issue.

The SCL-90 revealed a global reduction of all factors, with the exception of IS (excessive perception of and/or difficulty coping with criticism or rejection from others) and SOM. Interpersonal sensitivity is usually augmented in patients with SP. In a previous study from our group with brofaromine, a selective MAO-A inhibitor, a marked reduction of IS was found (Van Vliet et al. 1992).

The increase in anxiety in the first weeks of treatment with fluvoxamine (in one patient leading to panic attacks) is a relatively common observation in panic disorder patients treated with SSRIs (Den Boer and Westenberg 1988, 1990). Compared with these patients, the exacerbation seen in this study was less prominent. It is unlikely that this may have been due to comorbid panic disorder in this patient, since any other anxiety disorder was an exclusion criterion in the present study. Nevertheless, it may be that this patient was at risk for developing unexpected panic attacks, although she did not have unexpected panic attacks in her history.

The increase in global anxiety as measured with the HAS was not confined to patients suffering from either the generalized or the specific social phobia subtype. It needs to be emphasized, however, that only a very small number of patients suffered from the specific subtype.

Since stringent exclusion criteria were employed, excluding patients with major depression as well as those with depressed mood, it is unlikely that the treatment effects in the present study were secondary to an effect on depressive symptomatology. Although a statistically significant decrease in HDS score was observed, it is unlikely that the effects of fluvoxamine in social phobics were

obtained through the antidepressant effect, since the mean HDS score on baseline was less than 10.

Demographic and clinical features were quite similar to those of other samples (e.g. Amies 1983; Solyom et al. 1986; Liebowitz et al. 1990, 1992; Van Vliet et al. 1992). The male/female ratio in this study is somewhat lower than found in epidemiological studies (Marks 1970; Amies 1983). In keeping with previous reports, we found that social phobics had more relatives with the same disorder than normal controls (Reich and Yates 1988; Perugi et al. 1990). In a recent interview study of social phobia it was found that the relatives of social phobia probands were at increased risk for developing social phobia, but not other anxiety disorders (Fyer et al. 1993).

Available evidence suggests that the generalized subtype might benefit more from MAOIs like phenelzine, brofaromine and moclobemide, than the specific subtype for whom β-blockers like atenolol appear to be the treatment of choice (Liebowitz et al. 1992). Due to the relatively small sample size of the present study it cannot be decided whether there was a different treatment response to fluvoxamine for these subtypes. Only six patients fulfilled the criteria for specific social phobia. Of these, two were classified as non-responders to treatment, but they received placebo. The other patients with the specific subtype showed only a moderate response to fluvoxamine. Additional studies are required to answer the question whether the treatment response to fluvoxamine is confined to the generalized subtype.

Several studies have documented the efficacy of older nonselective irreversible MAOIs in patients with SP on (Liebowitz et al. 1985, 1992) or tranylcypromine (Versiani et al. 1988). Therapeutic results of the MAOI were also reported in a study with phenelzine versus atenolol (Liebowitz et al. 1992).

Recent studies using the new reversible and selective MAOIs, brofaromine and moclobemide, showed substantial clinical improvement with both drugs (Van Vliet et al. 1992; Versiani et al. 1992; for review see Den Boer et al. 1994).

Other antidepressants like clomipramine and imipramine might also be effective in the treatment of social phobia, although the studies reported are clinical anecdotes on the treatment of a few cases or uncontrolled studies using mixed patient populations (Beaumont 1977; Gungras 1977; Pecknold et al. 1982; Benca et al. 1986).

The findings of our study concur with case reports and open studies suggesting efficacy of the SSRI fluoxetine in social phobia (Deltito and Stam 1989; Sternbach 1990; Black et al. 1992; Schneier et al. 1992a, b; Van Ameringen et al. 1993). To the best of our knowledge this is the first study using a SSRI in social phobics under double-blind placebo-controlled conditions.

There is a large body of evidence that the SSRIs as well as MAOIs are effective in the treatment of other anxiety disorders like panic disorder and obsessive compulsive disorder. Why these drugs are also effective in social phobia cannot readily be explained yet. It is feasible that irrespective of their nosological diagnosis, certain symptom profiles within different diagnostic entities might respond to SSRIs and MAOIs (Van Praag et al. 1990). In depressive patients for example, there is preliminary evidence suggesting that symptoms related to anxiety and aggression are the first ones to disappear with antidepressant treatment (Van Praag 1992).

It is conceivable, although the present state of knowledge is still speculative, that the effects of fluvoxamine or other specific 5-HT uptake inhibitors in different psychiatric disorders are due to an effect on symptoms related to global anxiety and impulse dysregulation.

In conclusion, this study suggests that the selective 5-HT uptake inhibitor fluvoxamine is effective in the treatment of social phobia, reducing social and general anxiety, although the effects appear to require a longer treatment period.

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