Eur Arch Psychiatry Clin Neurosci (1995) 244:309–316

Johan A. Den Boer · Irene M. van Vliet
Herman G. M. Westenberg

Recent developments in the psychopharmacology of social phobia

Received: 20 October 1994 / Accepted: 28 October 1994

Abstract The past 2 decades have witnessed an upsurge in the interest in anxiety disorders. Much research effort has been dedicated to panic disorder and obsessive – compulsive disorder. However, it is only very recently that we have begun to understand some of the basic principles about the psychopharmacology of social phobia. Drug classes thus far studied include beta-blockers, nonselective and irreversible monoamine oxidase inhibitors (MAOIs), and benzodiazepines. Beta blockers appear to be of use in specific social phobias, such as public speaking, whereas they are of little use in generalized social phobia. There is considerable evidence suggesting that MAOIs are effective in reducing both social anxiety as well as social avoidance in generalized social phobia. A disadvantage of the conventional irreversible MAOIs is their risk for hypertensive crises when combined with dietary tyramine. Thus far only a small number of studies with selective MAO-A inhibitors, such as moclobemide and brofaromine, have been conducted in social phobia, and the results indicate that both compounds are effective. Drugs exerting selective and specific actions on certain components of, for example, the serotonergic system, can now be studied, and it is hoped that the role of 5-hydroxytryptamine) and other neuronal systems in social phobia can be elucidated. In order to gain more information about selective serotonergic drugs, the first double-blind placebo-controlled study with fluvoxamine was recently published. Preliminary results indicate a reduction in social anxiety after a prolonged treatment period. Finally, the role of peptides in the treatment of social phobia is critically reviewed. The MSH/ACTH analog Org 2766 was investigated in patients suffering from social phobia. No anxiolytic effects of this peptide were observed.

Key words Social phobia · MAO-A inhibitors · SSRI's Peptides

Johan A. Den Boer (✉) · Irene M. van Vliet
Herman G. M. Westenberg
Department of Psychiatry, Academic Hospital, P.O. Box 85500, NL-3508 GA Utrecht, The Netherlands

Introduction

According to DSM-III-R criteria, social phobics are afraid of and avoid situations in which the individual is exposed to the scrutiny of other people because of fear of acting in an embarrassing way. In these situations such patients experience both subjective and somatic symptoms of anxiety including trembling, blushing, and sweating.

Epidemiological studies have suggested that this disorder is equally common in males and females (Marks and Gelder 1966; Solyom et al. 1986; Amies et al. 1983), and the lifetime prevalence is estimated at 2.8% (Regier et al. 1988). The age of onset is usually in late adolescence (Marks and Gelder 1966; Amies et al. 1983; Solyom et al. 1986).

Psychopharmacology of social phobia

It is only during the past decade that the psychopharmacology of social phobia has been subject to consistent investigation. The early experiences with beta-blocking drugs and irreversible nonselective monoamine oxidase inhibitors (MAOIs) provided sufficient evidence to suggest that pharmacotherapy could play a major role in the treatment of social phobia.

Benzodiazepines

Successful treatment of generalized anxiety disorder and panic disorder with the triazolobenzodiazepine alprazolam has prompted investigations into the efficacy of this compound in social phobia. In two open studies, alprazolam was found to be effective in reducing severity of social anxiety and avoidance behavior (Reich et al. 1988; Lydiard et al. 1988). However, the efficacy of MAOIs appeared to be superior to alprazolam (Gelernter et al. 1991).

One case report and two small controlled studies reported positive effects of clonazepam (Munjack et al.

Table 1 Controlled studies of MAO-I social phobia. IE instructions for exposure

Study	Patients	Design	Dose (mg)	Duration	Results
Tyrer et al. (1973)	Agoraphobia/ social phobia (n = 32)	Phenelzine Placebo	to 90	8 weeks	Phenelzine > Placebo
Solyom et al. (1973)	Agoraphobia/ social phobia (n = 30)	Flooding Phenelzine Placebo	to 45	3 months	Flooding + Phenelzine effective
Mountjoy et al. (1977)	Anxiety neurosis (n = 36) Social phobia/ Agoraphobia (n = 22)	Phenelzine Diazepam Placebo	to 75 15	4 weeks	In social phobia: phenelzine + diazepam > placebo
Solyom et al. (1981)	Agoraphobia social phobia (n = 40)	2 × 2 Phenelzine/placebo; Exposure VS no exposure	to 45	6 weeks	Phenelzine > placebo on anxiety in exposure No significant difference between exposure and phenelzine
Gelernter et al. (1991)	Social phobia (n = 65)	Phenelzine + IE Alprazolam + IE Placebo + IE Cognitive Behavioral therapy	to 90 to 7.3	12 weeks	All treatments effective Phenelzine > alprazolam
Liebowitz et al. (1992)	Social phobia (n = 74) DSM-III-R	Phenelzine Atanolol Placebo	60 100	8 weeks	Phenelzine > atenolol Atanolol > Placebo (n.s.)
Van Vliet et al. (1992)	Social phobia (n = 30) DSM-III-R	Brofaromine Placebo	150	12 weeks	Significant effect of brofaromine (> placebo) on social anxiety and avoidance
Versiani et al. (1992)	Social phobia (n = 78) DSM-III-R	Moclobemide Phenelzine Placebo	to 600 90	16 weeks	Both moclobemide and phenelzine led to a 25% reduction in Social phobia symptoms. After 16 weeks: 82% of moclobemide; 91% of Phenelzine-treated patients asymptomatic

1991; Reiter et al. 1990; Ontiveros and Fontaine 1990). In the largest study thus far, Davidson et al. (1991) reported that 22 of 26 social phobics (84.6%) showed good improvement with clonazepam. A major limitation of the latter study is that only the Clinical Global Impression scale was used; thus, no specific information on social phobic anxiety or avoidance could be deduced from their study.

It is important to note that benzodiazepines have strong sedative properties, and therefore it is not known whether the reductions in social anxiety and avoidance are due to this sedative effect or whether there is a specific anxiolytic effect leading to diminished avoidance behavior.

Beta-adrenergic blockers

The majority of studies with beta-blockers have been performed in patients with a subtype of social anxiety, i.e., performance anxiety. In several controlled studies in a variety of performing arts and sports, the use of beta-blockers has appeared to be helpful in reducing autonomic symptoms such as palpitations and tremors (Brantigan et al. 1982; Hartley et al. 1983; Gates et al. 1985; James and Savage 1984). As a secondary effect anxiety reduction is achieved. Because not all beta-blockers (e.g., atenolol) cross the blood-brain barrier, it is argued that the efficacy of beta-blockers in performance anxiety is related to an attenuation of autonomic symptoms, and not to a central reduction in anxiety.

In social phobia only a small number of studies using beta-blockers have been published. Propranolol was found to be ineffective in the treatment of social phobia (Falloon et al. 1981). In contrast, Gorman and coworkers (1985) reported a good treatment response in social phobics with atenolol. In subsequent double-blind studies with MAO inhibitors, the limited efficacy of beta-blockers in the treatment of generalized social phobia was further corroborated. In these studies no significant differences were found between placebo and atenolol (Liebowitz et al. 1991, 1992). In other anxiety disorders (e.g., panic disorder) beta-blockers appear to have only limited therapeutic value (Hayes and Schulz 1987).

MAO inhibitors in treatment of social phobia

In several studies beneficial effects of MAOIs in the treatment of social phobia have been reported. In most studies with the nonselective and irreversible MAOI phenelzine, a reduction in social anxiety has been reported (Kelly et al. 1970; Solyom et al. 1973, 1981; Tyrer et al. 1973; Tyrer and Steinberg 1975; Mountjoy et al. 1977; Liebowitz et al. 1985). There are, however, a number of methodological flaws with regard to the older studies with MAOIs.

Firstly, in most studies mixed patient groups of agoraphobic, simple phobic, and social phobic patients were used. Secondly, only small numbers of patients were studied. Thirdly, in the early studies vague diagnostic criteria were used (e.g., "phobic anxiety states"), and, moreover, low dosages were used as compared with those used in depressed patients (Tyrer et al. 1973; Solyom et al. 1973; Mountjoy et al. 1977; Solyom et al. 1981). It is thus impossible to determine whether the patients with social phobia, as a separate group, actually improved because of treatment with phenelzine (see Table 1).

More recent studies revealed that tranylcypromine led to a marked improvement in 60% of social phobia patients (Versiani et al. 1988). Phenelzine has also recently been investigated in well-designed studies. In the study by Gelernter et al. (1991) four treatment conditions were compared: alprazolam (plus instructions for exposure [IE]), phenelzine (plus IE), placebo (plus IE), and cognitive behavioral therapy. Results showed that 63% of the phenelzine-treated patients were responders, whereas the response rate was only 39% in the alprazolam treated group, 24% in the cognitive behavioral group, and 20% in the placebo group. The number of patients per group was too small to detect possible differences in treatment outcome; therefore, it was concluded that all four treatment conditions were effective in reducing social anxiety and distress. An important limitation of this study is the fact that the therapeutic gains might have been related to increased exposure, which was combined with all pharmacotherapeutic treatments.

In a study by Liebowitz et al. (1992) it was reported that phenelzine led to marked improvement in two-thirds of patients with social phobia, whereas atenolol could not be distinguished from placebo.

A major risk of the use of the conventional and irreversible MAOIs has been the development of hypertensive crises, due to potentiation of the tyramine pressor effect ("cheese effect"). The monoamine neurotransmitters, such as serotonin (5-hydroxytryptamine [5-HT]) and noradrenaline (NA), are preferentially deaminated by MAO-A, whereas other amines, such as phenylethylamine, are endogenous substrates for MAO-B (Robinson and Kurtz 1987). Tyramine, which was held responsible for the serious side effects of MAOIs, and dopamine are substrates for both types of enzymes. The MAO-I leaving the B-form of MAO intact allows this isoenzyme to deaminate tyramine, and thus no dietary measures are required during treatment with selective MAO-A inhibitors.

New findings with selective MAO-A inhibitors

Thus far the experiences with selective MAO-A inhibitors has been limited. Versiani et al. (1992) studied the effects of moclobemide and phenelzine in a double-blind, parallel-group, placebo-controlled, flexible-dose study. Moclobemide is the prototype of the new generation of selective and reversible MAO-A inhibitors. It increases the content of 5-HT, NA, and dopamine in the brain (for review see Haefely et al. 1992).

A total of 78 patients with social phobia, 26 on moclobemide (mean dose 580 ± 55 mg/day), 26 on phenelzine (67 ± 15 mg/day), and 26 on placebo, were included. It was found that on the social phobia scale, both phenelzine and moclobemide were significantly superior to placebo.

In our Hospital we investigated the efficacy of brofaromine in a double-blind, placebo-controlled design (Van Vliet et al. 1992). Similar to moclobemide, brofaromine selectively and competitively inhibits MAO-A, the enzyme responsible for the deamination of biogenic amines. In animal studies brofaromine has been shown to increase levels of NA, dopamine, and 5-HT dose-dependently in rat brain (Waldmeier and Baumann 1983). In addition to these effects brofaromine displayed weak 5-HT uptake inhibitory properties in synaptosomal preparations at doses approximately 30 times higher than those that inhibited MAO-A (Waldmeier and Stocklin 1989).

A group of 21 females and 9 males who fulfilled DSM-III-R criteria for social phobia were included. Patients were studied for 12 weeks in a double-blind, placebo-controlled design. If patients judged themselves to be improved they could continue their medication under double-blind conditions in a follow-up period that lasted another 12 weeks. The dose of brofaromine was gradually increased from 50 to 150 mg daily (75 mg. b.i.d.) in 3 weeks.

Efficacy of treatment was assessed using the Social Phobia Scale (SPS; Liebowitz 1987), the Spielberger State Anxiety Inventory (STAI; Van der Ploeg et al. 1981), the Hamilton Anxiety Scale (HAS; Hamilton 1967), and the Symptom Checklist 90-items (SCL-90). Plasma levels of brofaromine and 3-methoxy-4-hydroxyphenylglycol (MHPG) were assessed at baseline and at weeks 4, 8, and 12. Plasma levels of 5-hydroxyacetic acid (5-HIAA), melatonin, and homovanillic acid (HVA) were measured on admission and week 12.

Clinical results

Most notably we found a reduction in anxiety in social situations as well as a decrease in social avoidance as measured using the social phobia scale (Figs. 1 and 2). The SCL-90 revealed a reduction in interpersonal sensitivity and in subscore anxiety and phobic avoidance. Ten patients who continued their treatment during the follow-up period continued to benefit from treatment with brofaromine (Fig. 3).

Our results are similar to those obtained in previous studies in which (nonselective and irreversible) MAOIs were studied, and are in accordance with the results obtained with moclobemide. It should, however, be noted that the sample size is small, and thus larger numbers of patients need to be studied before firm conclusions about efficacy can be drawn. In keeping with the pharmacological profile of brofaromine, we found a decrease in plasma 3-methoxy-4-hydroxy phenylglycol, 5-hydroxy-indoleace-

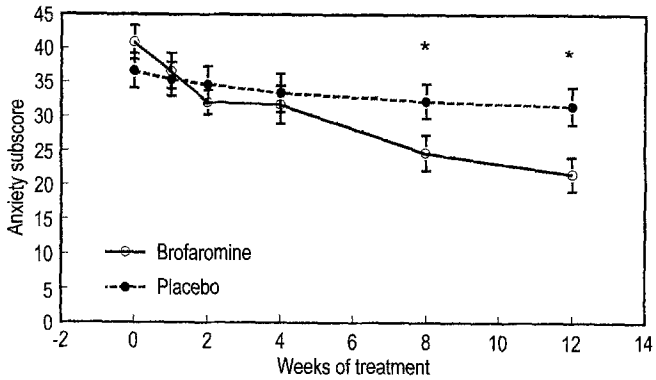

Fig. 1 Mean (± SEM) score on the anxiety subscale of the Social Phobia Scale SPS in patients with social phobia treated with brofaromine (n = 15) or placebo (n = 14). Brofaromine was found to be superior to placebo from week 8 ($P < 0.05$; from Van Vliet et al. 1992)

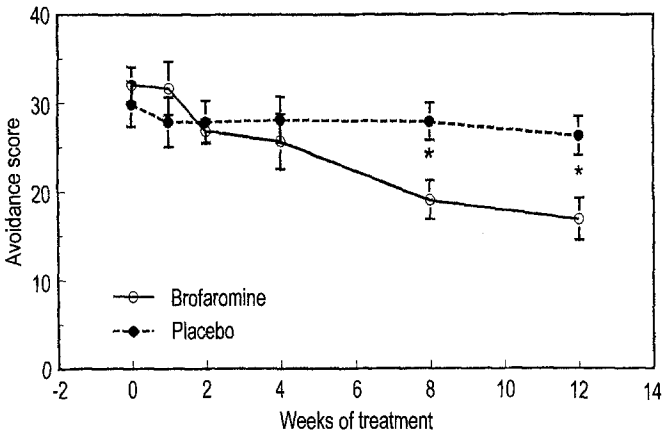

Fig. 2 Mean (± SEM) score on the avoidance subscale of the in patients with social phobia treated with brofaromine (n = 15) or placebo (n = 14). Brofaromine showed a statistically different treatment response from week 8 ($P < 0.05$; from Van Vliet et al. 1992)

tic acid, and HVA. Biochemical and neuroendocrine results are discussed in detail elsewhere (Van Vliet et al. 1992).

A comprehensive biological theory of social phobia is lacking. During normal social anxiety, such as public speaking, a two- to three fold increase in plasma adrenaline was found (Liebowitz et al. 1985). During an adrenaline challenge study in 11 social phobics, however, only 3 patients experienced anxiety (Liebowitz 1987). In addition, there is evidence indicating that a simple increase in plasma levels of adrenaline alone is inadequate to cause social anxiety (Papp et al. 1988).

It is not clear whether dopamine is involved in the pathogenesis of social phobia. Such a "dopaminergic theory" of social phobia is supported by the fact that MAOIs that have greater dopamine agonistic effects than tricyclic antidepressants (TCAs) are more effective in treating school phobias (Gittleman-Klein and Klein 1972, 1973). Further support was suggested by a study from King and coworkers (1986), who reported a positive correlation of

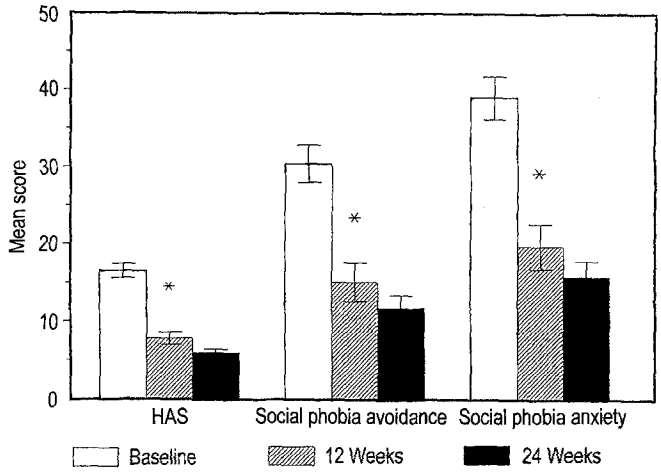

Fig. 3 Mean (± SEM) score on the Hamilton Anxiety Scale (HAS) and the avoidance and anxiety subscales of the SPS during follow-up period ($P < 0.05$)

cerebrospinal fluid (CSF) dopamine levels and self-reported extraversion in 16 social phobics. In addition, a recent study reported efficacy of the dopamine agonist bupropion (Emmanuel et al. 1991).

It is unlikely that treatment studies with MAO-A inhibitors will shed more light on underlying biological mechanisms involved in social phobia, because these drugs lead to increases in several monoaminergic systems. In order to shed more light on the dopaminergic theory, additional studies with more specific dopaminergic agents are required.

Is there a role for serotonin in social phobia?

There is only circumstantial evidence that antidepressants, such as clomipramine and imipramine, are effective in the treatment of social phobia (Gungras 1977; Beaumont 1977; Pecknold et al. 1982; Benca et al. 1986). Virtually no information is available with regard to the effects of selective serotonergic drugs in the treatment of social phobia. One open study reported the successful use of the 5-HT_{1A} agonist buspirone in social phobia, albeit the scales used in this study were not especially designed to measure social anxiety or avoidance; therefore, it remains inconclusive (Munjack et al. 1991). A recent open-label study in which the SPS was used reported only modest efficacy in the treatment of social phobia (Schneider et al. 1993). Clearly, confirmation of these preliminary findings in placebo-controlled studies is warranted.

There are some case reports that have documented the efficacy of fluoxetine in social phobia (Deltito and Stam 1990; Sternbach 1990; Schneier et al. 1992). Recently, two open studies were published reporting the efficacy of fluoxetine in patients with social phobia (Black et al. 1982; Van Ameringen et al. 1993), but well-designed studies are lacking.

In view of the fact that treatment with MAOIs affects two monoamine systems, no specific information can be

derived from these studies with regard to the involvement of serotonergic or noradrenergic neuronal systems in social phobia. With regard to other anxiety disorders there is abundant data suggesting involvement of 5-HT, particularly in panic disorder and obsessive–compulsive disorder (Den Boer and Westenberg 1988; 1990, 1991; Westenberg and Den Boer 1994).

In order to clarify the issue of serotonergic involvement in social phobia, we performed a study with the selective serotonin reuptake inhibitor (SSRI) fluvoxamine. A total of 30 outpatients (17 females and 13 males) suffering from social phobia according to the DSM-III-R were enrolled in a double-blind, placebo controlled 12-week study. Patients with other anxiety disorders or with a major affective disorder were excluded. A score of 15 or higher on the Hamilton Depression Scale was an exclusion criterion. The dosage of fluvoxamine used was 150 mg, gradually increasing from 50 mg in the first week.

Treatment efficacy was assessed by means of the SPS (anxiety and phobic avoidance subscales), the SCL-90, the HAS and the STAI. There were two dropouts. From the 28 patients who entered the statistical analysis, 15 were treated with fluvoxamine and 13 with placebo. If patients judged themselves to be improved they could continue their medication in a follow-up period that, lasted another 12 weeks. A total of 15 patients in the fluvoxamine group continued, and none in the placebo group.

Fluvoxamine was found to be superior to placebo on virtually all psychometric scales. Social anxiety as measured with the SPS showed a statistically significant decrease compared with baseline in the fluvoxamine groups but not in the placebo group. Social phobic avoidance was reduced in both groups, but there was a trend toward greater improvement in the fluvoxamine group. Taking a reduction on the anxiety scale of the SPS of 50% or more at endpoint as a criterion for clinically relevant improvement, 7 (46%) subjects on fluvoxamine and 1 (7%) on placebo were classified as responders to treatment.

The scores of all symptom factors of the SCL-90 (except the symptom factors Interpersonal Sensitivity [IS] and Somatization [SOM]) showed a statistically significant difference in favor of fluvoxamine. The results of the SCL-90 after treatment are depicted in Fig. 4.

During the follow-up period of another 12 weeks, during which patients who classified themselves as responders continued their treatment on fluvoxamine in an open-label follow-up study, a further improvement was found. General anxiety, social anxiety, and social phobic avoidance declined further (Fig. 5). These results suggest that a longer treatment period may be required.

In conclusion, the SSRI fluvoxamine has beneficial effects on social anxiety and reduces social phobic avoidance as assessed with the SPS in patients suffering from social phobia. The effects appear to require a longer treatment period, probably similar to the treatment period in depressed patients or patients with panic disorder. This study supports the notion that serotonergic neural systems may be implicated in the pathophysiology of social phobia (Van Vliet et al. 1994).

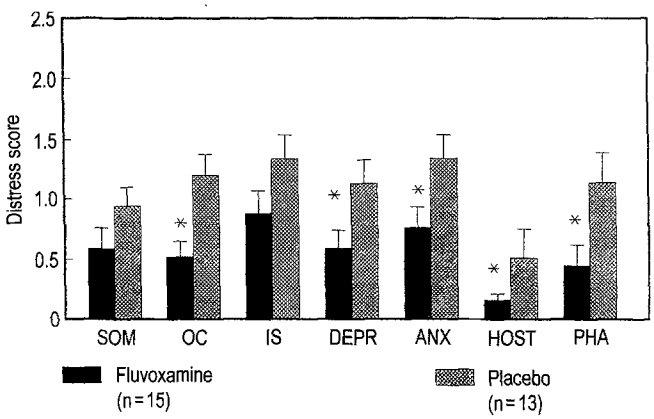

Fig. 4 Factor scores of the Symptom Checklist-90 in patients with social phobia treated with fluvoxamine or placebo at the end of the treatment period. Fluvoxamine was superior to placebo on the factors SOM, OC, DEPR, ANX, HOST, and PHA. SOM somatization; OC obsessive–compulsive; IS interpersonal sensitivity; DEPR depression; ANX anxiety; HOS hostility; PHA phobic anxiety ($P < 0.05$)

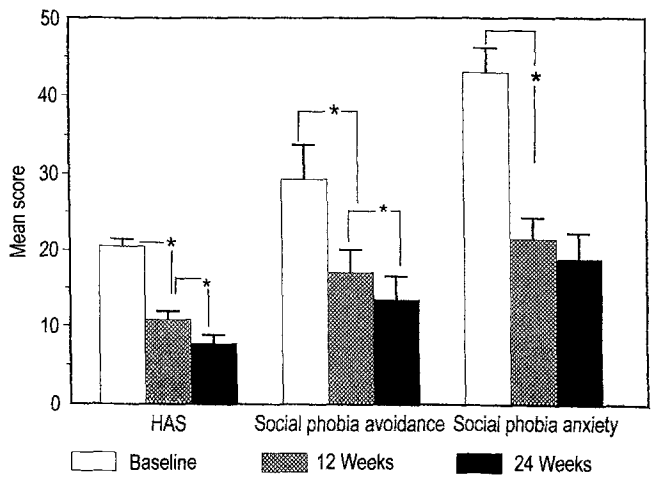

Fig. 5 Follow-up data of social phobic patients who continued their treatment for another 12 weeks (total 24 weeks) in an open-label treatment extension with fluvoxamine ($P < 0.05$)

It is difficult to explain why different anxiety disorders, such as panic disorder, obsessive – compulsive disorder, and social phobia respond to the same psychopharmacological treatment. There is a large body of evidence suggesting that SSRIs as well as MAOIs are effective in the treatment of panic disorder (Den Boer and Westenberg 1988; 1990). A parsimonious explanation as to why two different anxiety disorders respond to the same pharmacological treatment might be the fact that two subtypes of social phobia exist: generalized social phobia and discrete social phobia. The first type might show the greatest overlap with panic disorder patients and respond well to antidepressants and MAOIs. The second type, discrete social phobia, which is characterized by surges of autonomic activation, should respond to beta-adrenergic blockers. Another more liable explanation could be that certain symptom profiles and behavioral dimensions within different diagnostic entities respond to SSRIs and MAOIS irrespec-

Table 2 Assessment results of ORG 2766 in social phobia. HAM-A Hamilton Rating Scale for Anxiety; HAM-D Hamilton Rating Scale for Depression; SDS/ZUNG Zung's Self-Rating Depression Scale; STAI State-Trait Anxiety Inventory; GSI General Symptom Index of the 90-item symptom checklist

	Org 2766		Placebo	
	Baseline	Week 6	Baseline	Week 6
HAM-A	15.5 ± 2.7	11.7 ± 4.8	15.2 ± 1.2	12.5 ± 4.4
HAM-D total	7.3 ± 2.2	6.8 ± 1.7	6.7 ± 1.0	5.3 ± 2.3
SDS/ZUNG	44.3 ± 10.4	38.5 ± 13.8	38.5 ± 6.9	35.5 ± 9.7
STAI	47.7 ± 16.7	35.2 ± 16.8	41.0 ± 6.1	32.8 ± 9.5
GSI	1.2 ± 1.0	0.5 ± 0.4	0.7 ± 0.3	0.4 ± 0.3

tive of nosological diagnosis (Van Praag et al. 1987). It is well known that several psychiatric disorders such as bulimia, panic disorder, obsessive–compulsive disorder, and depressive disorders can be successfully treated with 5-HT uptake inhibitors. In depressive subtypes there is preliminary evidence that symptoms related to anxiety and aggression are the first symptoms to disappear with antidepressant treatment (Van Praag 1992).

It is conceivable, although presently still speculative, that the same reasoning could be applied to generalized social phobia. If the effect of fluvoxamine or other specific 5-HT uptake inhibitors is confirmed in other studies, then a more worthwhile approach would presumably be to look at common symptom profiles during treatment with 5-HT uptake inhibitors among patients suffering from, e.g., panic disorder, obsessive–compulsive disorder, and social phobia.

A peptide in the treatment of social phobia: preliminary findings

It has been suggested that peptides related to the pituitary adrenocorticotrophic hormone (ACTH), including the ACTH(4–9) analog Org 2766, increase the motivational value of environmental stimuli by inducing a state of arousal in limbic structures of the midbrain. The ACTH and related peptides may also be involved in behavior related to fear in animals. In the social-interaction model of anxiety, ACTH (1–24) and ACTH (4–10) have been shown to reduce active social contact in rats, which has been interpreted as an anxiogenic effect (File 1979). The social-interaction model is an example of a relatively new animal model of anxiety that is based on manipulation of novelty and uncertainty. It has been shown that the amount of time rats engage in active social interaction can be manipulated by varying the familiarity of the environment as well as the level of illumination. In this model a reduction of social interaction between pairs of male rats is observed when placed in a novel, well-lit environment (File and Hyde 1978; File 1980). This reduction in social interaction could be reversed by subacute administration of benzodiazepines (File and Velluci 1978). Interestingly, the MSH/ACTH(4–9) analog Org 2766 has effects similar to benzodiazepines in this model, in that this peptide increases social interaction.

Increased social interaction has been related to anxiolytic activity (File 1981; File and Hyde 1978), because chronic treatment with benzodiazepines, which have been shown to possess anxiolytic activity in humans, increases social interaction in rates (for review see Gardner and Guy 1984). Thus, based on the effects in this animal model, Org 2766 may have anxiolytic activity in humans.

In some clinical studies a reduced anxiety level has been described, e.g., in demented elderly patients following oral treatment with this peptide (Ferris et al. 1981; for review see Pigache and Rigter 1981). Most clinical studies, however, have studied the link between ACTH/MSH peptides and mood or cognition. In none of these studies was convincing evidence obtained for an antidementia or antidepressive efficacy, although decreases in feelings of tiredness and increases in alertness were reported (Gaillard 1981; Tinkelberg and Thornton 1983; Heuser et al. 1993).

In the present studies we studied the clinical efficacy of Org 2766 in a double-blind, placebo-controlled design in patients with anxiety disorders. Three groups of patients were investigated, suffering from panic disorder, generalized anxiety disorder, or social phobia, all according to DSM-III-R criteria (Den Boer et al. 1992). The results reported herein is confined to patients (n = 12) with social phobia.

Treatment with ORG 2766 and placebo resulted in a small decrease in both the "anxiety" and the "avoidance" subscales of the social phobia scale. The mean (± SD) anxiety score in the Org 2766 group was 41.3 ± 12.3 before, and 35.0 ± 13.9 after, treatment. In the placebo group the mean baseline anxiety score was 27.8 ± 13.0, and was 22.0 ± 8.1 at the end of treatment. The mean avoidance score in the Org 2766 group was 29.0 ± 16.1 and 29.2 ± 17.0 before and after treatment, respectively. In the placebo group the mean avoidance score was 17.8 ± 7.3 and 18.3 ± 8.5, respectively. Statistical analysis did not reveal significant differences. Other psychometric assessments are summarized in Table 2. No significant effects were present on any of the psychometric assessments. No side effects were reported.

In social phobia patients, Org 2766 did not result in a significant decrease in anxiety experienced in social situations, nor in a reduction in social avoidance. The social-interaction model has been used as a model predicting anxiolytic activity of benzodiazepines and other experimental compounds. The predictive value of the social-interaction test for newer compounds can only be critically assessed after clinical evaluation.

In the present study, however, no clear anxiolytic activity for Org 2766 could be observed, thus casting doubt

on the predictive value of the social interaction test as a predictor for anxiolytic activity in patients with anxiety disorders.

Summary and conclusions

There is increasing evidence that the new generation of reversible and selective MAO-A inhibitors, such as moclobemide and brofaromine, are of therapeutic value in the treatment of social phobic complaints, whereas beta-blockers appear to be only of limited value. Only one study has been published in which anxiolytic effects of the MSH/ACTH(4–9) analog Org 2766 has been investigated. The results indicate that there is no convincing evidence for anxiolytic effects of this experimental compound.

There is one controlled study indicating that social anxiety can be significantly reduced during treatment with the selective 5-HT uptake inhibitor fluvoxamine, although the effects on social avoidance was limited. A relatively long treatment period was required to achieve the observed anxiolytic effects.

In numerous clinical studies it has been established that MAO-A inhibitors, as well as 5-HT uptake inhibitors, are therapeutic in patients with depression and panic disorder. Recently, it has been shown that 5-HT uptake inhibitors such as clomipramine, fluvoxamine, and fluoxetine are also effective in the treatment of obsessive–compulsive disorder. These findings may argue for a common underlying mechanism, at least for those symptoms within different diagnostic categories, related to anxiety. The findings also provide empirical evidence suggesting that MAO-A inhibitors and 5-HT uptake inhibitors can be appropriate treatments for different disorders with overlapping symptom clusters.

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