Eur Arch Psychiatry Clin Neurosci (1997) 247:71–80

ORIGINAL PAPER

The International Multicenter Clinical Trial Group on Moclobemide in Social Phobia

Moclobemide in social phobia

A double-blind, placebo-controlled clinical study

Received: 29 January 1997 / Accepted: 18 February 1997

Abstract The primary objectives of this large multicenter study (n = 578) were to determine the efficacy and safety of moclobemide, 300 or 600 mg per day, for the treatment of social phobia. A double-blind fixed-dose parallel group study was conducted to compare the two different doses of moclobemide to placebo. After a 1-week placebo run-in period, patients were randomly assigned to one of the three treatment groups to receive the test compound for a 12-week period. Assessments were performed at screen, on baseline and on weeks 1, 2, 3, 4, 6, 8, 10, and 12. There were consistent, reliable and clinically meaningful drug effects and indications of a dose-response relationship. Statistical analysis of the results at both weeks 8 and 12 showed that 600 mg of moclobemide was effective and statistically significantly superior to placebo. The 300 mg dose also showed better efficacy than placebo on all measures of efficacy, and about half of them were statistically significantly different from placebo. Moclobemide was well tolerated. Adverse events, except for insomnia, were neither dose-related nor were there significant drug-placebo differences. The results indicate that 600 mg of moclobemide per day given b.i.d. is effective in social phobia, reducing the symptoms and the impairment associated with the disorder. The compound is well tolerated and safe.

Key words Moclobemide · Social phobia · Double-blind clinical study · Placebo · Dose-response

Investigators/centers:
Australia: Prof. G. Burrows, Austin Hospital, Heidelberg, Victoria; Dr. L. Evans, University of Queensland New Farm Clinic, Brisbane; *Austria*: Dr. U. Baumhackl, Allgemeines Oeffentliches Krankenhaus, St. Poelten; Dr. H. Hebenstreit, Private Practice, Amstetten; Prof. H. Katschnig, Psychiatrische Universitätsklinik, Wien; Dr. W. Schöny, Landesnervenklinik Wagner-Jauregg, Linz; Dr. H. Scholz, Allgemeines Oeffentliches Landeskrankenhaus, Villach, Kaernten; *Belgium*: Dr. J. Wilmotte, Hôpital Vincent van Gogh, Marchienne-Au-Pont, *Brazil*: Dr. J. Campos, Universidade Federal de Goias, Goiania, GO; Dr. D. Costa, Medicas de Minas Gerais, Belo Horizonte; Dr. A. Nardi. Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ; Prof. M. Versiani, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ; Dr. A. da Silva, Universidade Federal de Goias, Goiana, GO; *Canada*: DL R. Bowen, Royal University Hospital, Saskatoon, Saskatchewan; Dr. J. Bradwejn, St. Mary's Hospital, Montreal, Quebec; Prof. D. Johnston, Calgary General Hospital, Calgary, Alberta; Dr. J. Plamondon, Centre Hospitalier Universitaire Laval, Ste. Foy, Quebec; Dr. M. Stein, St. Boniface Hospital, Winnipeg, Manitoba; Dr. R. Swinson, Clarke Institute of Psychiatry, Toronto, Ontario; *France*: Dr. L. Chneiweiss, Stress and Anxiety French Institute. Paris; *Germany*: Dr. W. Bellaire, Private Practice, Homburg; Dr. M. Osterheider, Psychiatrische Universitätsklinik und Poliklinik, Wuerzburg; Dr. R. Sonntag, Private Practice, Olpe; *Great Britain*: Dr. J. Cookson, The London Hospital, London, England; Dr. C. Freeman, Royal Edinburgh Hospital, Edinburgh, Scotland; Prof. S. Hirsch, Charing Cross and Westminster Medical School, London, England; Dr. J. Mullin, De La Pole Hospital, Hull, England; Prof. R. Murray, Institute of Psychiatry, London, England; Prof. D. Nutt, The Medical School, Bristol, England. *Iceland*: Dr. H. Pétursson, Borgarspitalinn, Reykjavik. *Ireland*: Dr. F. O'Donoghue, St. Patrick's Hospital, Dublin. *The Netherlands*: Dr. J. Min. Centraal Militair Hospitaal, Utrecht. *Sweden*: Dr. C. Allgulander, Huddinge Sjukhus, Huddinge; Dr. S. Andersch, Lillhagens Sjukhus; Hisings Backa. *Switzerland*: Prof. R. Realini, Private Practice, Lugano. *Roche Staff*: Dr. J. L. Siegel, Nutley, USA, Dr. R. Buller, Basel, Switzerland.

H. Katschnig (✉)
Department of Psychiatry, University of Vienna,
Währinger Gürtel 18–20, A-1090 Vienna, Austria
Fax: 431 40400 3605

Introduction

Social phobia is one of the most frequent anxiety disorders and is characterized by a persistent fear of one or more social situations (e.g., speaking to others, eating or drinking in public). In these performance or interactional situations the person is exposed to possible scrutiny by others and fears that he or she may behave in a way that will be humiliating or embarrassing. Individuals with social phobia tend to avoid social situations, but when they force themselves to enter them, they will almost always experience symptoms of intense anxiety. There may be a vicious circle of anticipatory anxiety leading to fearful cognitions and anxiety symptoms in the feared situation,

which leads to actual or perceived poor performance and thus to embarrassment and increased anticipatory anxiety. The disorder is recognized by the ICD-10 (WHO 1992) and by the Diagnostic and Statistical Manual of Mental Disorders – DSM IV (APA 1994). Based on epidemiological studies the lifetime prevalence of social phobia ranges from 3 to 13%, depending on the definition and the threshold used to determine the presence of the condition (Myers et al. 1984; Kessler et al. 1994). The onset of social phobia is frequently during adolescence or early adulthood and may interfere with the successful completion of the individual's education or professional training. The course is often continuous, and there is substantial disability in work and social life (Liebowitz et al. 1985; Schneier et al. 1993). Severity of impairment may fluctuate with life stressors and demands.

Several studies have shown that social phobia is responsive to pharmacotherapy (Liebowitz et al.1988). The best evidence for efficacy in treating social phobia is, at present, with drugs that inhibit monoamine oxidase, including phenelzine (Liebowitz et al. 1986; Liebowitz et al. 1992; Gelernter et al. 1991), tranylcypromine (Versiani et al. 1988), and brofaromine (Van Vliet et al. 1992). In addition, there is some evidence for the efficacy of selective serotonin re-uptake inhibitors (Van Vliet et al. 1994; Katzelnick et al. 1995) and benzodiazepines (Davidson et al. 1993a).

A double-blind, parallel-group, single-center study of moclobemide, the first of a new class of reversible inhibitors of monoamine oxidase that are selective for the A form of the enzyme (RIMA), in social phobia showed that after 8 weeks of treatment both moclobemide and phenelzine were clinically and statistically significantly more effective than placebo in regard to symptom relief (Versiani et al. 1988). In addition, moclobemide was found to be much better tolerated than phenelzine. The efficacy of moclobemide in social phobia was further supported by the results of an open study (Bisserbe et al. 1994). Because of the selective and reversible inhibition of monoamine oxidase A, moclobemide has clear advantages over older irreversible MAO inhibitors since it does not show any clinically relevant potentiation of the tyramine pressor effect and therefore can be taken without dietary restrictions.

In light of these encouraging findings it was decided to undertake a large multicenter study to determine whether 300 mg or 600 mg moclobemide is more effective than placebo for the treatment of patients with social phobia and to determine the safety of moclobemide at the doses tested.

Methods

This was a multicenter trial conducted in 35 centers in 13 countries in Europe, Canada, Australia, and South America. It was designed as a randomized, double-blind, placebo-controlled, parallel-group study of two fixed doses of moclobemide and placebo in outpatients (n = 578) with social phobia.

Patient selection

Patients to be included in the study were adult men and non-pregnant, non-lactating women who satisfied the DSM IV criteria for social phobia (300.23). The diagnosis was made using a structured clinical interview (SCID-Ro), which was specifically adapted for the protocol from the structured clinical interview for DSM-IV (First et al. 1995) to provide a detailed evaluation of social phobia and any relevant comorbid conditions (including a single Axis II disorder-avoidant personality disorder).

The SCID-Ro has been shown to have excellent interrater reliability for the diagnosis of social phobia (percent agreement = 88%, κ = 0.73; A. L. Hazen, M. B. Stein, J. R. Walker, unpublished observations, 1993). The SCID-Ro also operationalizes the application of diagnostic *subtypes* of social phobia. First, the presence or absence of *performance* fears (e.g., public speaking, eating in front of others, writing in front of others) is documented. Then, the presence or absence of *interactional* fears (e.g., meeting new people, talking to strangers, asking for directions, going to parties) is documented. When social interactional fears occur in two or fewer situations, the individual is designated as having *limited interactional* fears; when they occur in three or more such situations, the individual is designated as having *generalized interactional* fears. By definition, persons meeting the SCID-Ro "generalized interactional" criterion also fulfill the DSM-IV criteria for the generalized subtype (Manuzza et al. 1995). Avoidant personality disorder was also assessed using a module derived from the SCID-II (Spitzer et al. 1990). This module has been shown to have acceptable inter-rater reliability for avoidant personality disorder (percent agreement = 86%, κ = 0.67; A. L. Hazen, M. B. Stein, J. R. Walker, unpublished observations, 1993).

Patients with any of the following disorders concurrently or within the prior 6 months were excluded from the study: panic disorder, agoraphobia, obsessive-compulsive disorder, or major depression. Patients who met SCID-Ro criteria for probable or definite substance abuse within the prior 6 months, as well as those who met lifetime criteria for bipolar disorder, schizophrenia or any other psychotic disorder, were also excluded. The patients were free of any significant unstable or uncontrolled medical disease, physical or psychological condition, medication, or treatment that might put them at risk or obscure or confound the effects of treatment.

Treatment

After a 1-week placebo run-in period, patients fulfilling the entry criteria were randomly assigned to one of the three treatment groups to receive either 300 mg moclobemide, 600 mg moclobemide, or placebo in two divided daily doses for a 12-week period. Patients were to take their tablets in the morning and in the evening after a meal. The patients of the 600 mg treatment group started with a reduced daily dose of 300 mg for the first 3 days, increasing to 600 mg on the 4th day. Moclobemide was supplied by F. Hoffmann-La Roche Ltd as an oval, cylindrical, biconvex, film-coated tablet light yellow in color and scored on one side, containing 150 mg moclobemide. Placebo tablets were identical both in appearance and composition, except that they contained denatonium benzoate instead of moclobemide.

No psychoactive substances were permitted other than chloral hydrate, promethazine, or diphenhydramine for use as a nighttime hypnotic, but for no more than 2 weeks of continuous use. Patients were also not permitted to take systemic corticosteroids, beta-blockers, clonidine, dextromethorphan, pethidine, or cimetidine. If ibuprofen or oral systemic indirect acting sympathomimetics were to be used, it was recommended that the dosage of these drugs be reduced. Patients were not permitted to continue or to undergo formal psychotherapy or any other treatment for their social phobia. They were, however, encouraged to expand their activities and start to participate in social activities that they may have avoided because of anxiety. As the likelihood of a hypertensive crisis, a complication of classical monoamine oxidase inhibitors, appears

to be very low with moclobemide, no stringent dietary restrictions were required.

Schedule of study procedures

At the screening visit (day 8), the patient's diagnosis was established, the patient's eligibility was evaluated, and demographic and background information were obtained. Baseline assessments were performed on the last day of the placebo run-in period (day 1). Study outcome for efficacy and safety was assessed on weeks 1, 2, 3, 4, 6, 8, 10, and 12.

The study was conducted according to the principles of the Declaration of Helsinki/Tokyo/Venice/Hong Kong and in full conformance with the laws and regulations of the country in which the research was conducted. The investigator obtained either witnessed verbal or written, informed consent. This study protocol and any accompanying written material provided to the patient were submitted by the investigators to their Ethics Review Committee.

Outcome measures

All investigators and raters were trained in the use of each efficacy parameter during training sessions at an investigators' meeting that preceded the start of the trial. They were also provided tapes for training of new staff at the site.

1. The Liebowitz Social Phobia Symptom Scale (LSPS) was designed to measure the severity of social phobia symptoms and consists of two major subscales to assess fear or anxiety and avoidance (Liebowitz 1987; Schneier et al. 1993). Within each subscale, an assessment is made separately for both performance and social interaction phobias. The ratings range from 0 (none) to 3 (severe) on levels of fear or anxiety, and from 0 (never, or 0%) to 3 (usually, or 68% to 100%) for avoidance of 24 different social situations.

2. The Clinical Impression of Change – Social Phobia (CIC-SP) evaluates the overall change in the patient's social phobia (exclusive of any comorbidity) and is a measure of clinical relevance. It is based on the widely used scale of change developed by the Early Clinical Drug Evaluation Unit (Guy 1976) and was rated by a psychiatrist at each assessment visit, the ratings ranging from 1 (very much improved) to 7 (very much worse). A score of 2 ("much improved") or of 1 ("very much improved") at weeks 8 or 12 was used to define a treatment responder, the variable chosen as the primary efficacy parameter. The scale also has four additional components to rate improvement on anxiety episodes, functional impairment, phobic avoidance, and anticipatory anxiety.

3. The Sheehan Disability Scale assesses the patient's quality of life (Sheehan 1983) and was used as a second measure of clinical relevance. Assisted by the investigator, the patient rates impairment and disability in three dimensions (work, social life/leisure activities, and family life/home responsibilities) on a scale of 0 (no impairment) to 10 (very severely impaired).

4. The Clinical Impression of Severity – Social Phobia (CIS-SP) is an anchored scale that evaluates the overall severity of the patient's social anxiety, exclusive of any comorbidity. The ratings range from 1 (normal, not ill) to 7 (among most severely ill) and are defined according to the presence or absence of specific symptoms of social anxiety and/or functional impairments. The scale is so constructed that a patient would require a severity score of at least 4 to meet diagnostic criteria for social phobia.

5. The Patient's Impression of Change – Social Phobia (PIC-SP) is based on the same scale as the CIC-SP; however, the patient rates the overall change in his or her illness compared to his/her condition at the screening visit.

6. The Hamilton Anxiety Scale (HAM-A) is a widely used rating scale for the severity of anxiety (Hamilton 1959). Fourteen items are rated on a scale of 0 (not present) to 4 (very severe).

7. The Montgomery and Asberg Depression Rating Scale (MADRS) is an evenly balanced rating scale for the severity of depression, sensitive to change (Montgomery and Asberg 1979). Ten items are rated on a scale from 0 to 6.

8. Adverse events were defined as any adverse change from the patient's baseline condition that occurred during the treatment. The investigator graded the intensity of the adverse event on a three-point rating scale (mild, moderate, severe) and evaluated its relationship to the study drug (not related, remote, possible, or probable). Adverse events are reported regardless of the investigator's assessed relationship to test drug.

Other assessments: Significant abnormal findings of the physical examinations were recorded by the investigator at the screening visit and at the final study visit. Body weight, heart rate, and blood pressure (supine and standing) were measured at each visit. Symptoms associated with orthostatic changes in blood pressure were reported as adverse events. The hematology and serum chemistry samples collected at screening and at the end of the study were analyzed at assigned laboratories using standard methodology.

Statistical analysis

The study was designed to assess the efficacy of moclobemide in comparison to placebo. A secondary goal was to assess the relative efficacy of the two doses. The primary efficacy criterion was the number of responders (i.e., patients with a rating of 'much improved' or 'very much improved' on the CIC-SP Overall Change Scale at weeks 8 and 12). The minimum sample size to detect a difference between the three groups was estimated at 450 patients for the intent-to-treat (ITT) population (two-sided significance level of 0.05; power of at least 0.80). This includes all patients who have been assessed at baseline and at least once after the initiation of treatment.

Demographic results presented in this paper are based on the ITT population. Efficacy results of weeks 8 and 12 were analyzed with the last observation carried forward in the case of missing observations (LOCF analysis).

Analysis of variance procedures (SAS PROC GLM) were used to evaluate the data of this study. For each analysis, a model containing terms for treatment effect, center effect, and treatment by center interaction were specified. If the variable to be analyzed had a baseline observation, then this observation was used as a covariate. Following the overall comparison, pairwise comparisons between moclobemide 300 mg and placebo, and between moclobemide 600 mg and placebo were carried out. All P-values are reported as determined and a 2-sided significance level of 0.05 was used for all variables.

Additional post-hoc analyses of variance were carried out to assess the influence of avoidant personality disorder, duration of illness and severity at baseline on the responder rates.

The adverse events were recorded in the case report form. The incidence is shown in terms of number of patients and not in terms of number of episodes.

Summary statistics for body weight, heart rate and blood pressure were calculated, by treatment group at all assessment visits, including distributions of maximum percent changes in mean heart rates and mean arterial pressure from baseline. Incidences of laboratory test abnormalities and changes from baseline were summarized by treatment group.

Results

Patients

The ITT population comprised 578 patients, who had received treatment and had at least one assessment after baseline; 445 patients completed the study through week

Table 1 Demographic characteristics of the three treatment groups and the entire study population

		Placebo (n = 194)	Moclobemide (300 mg daily; n = 191)	Moclobemide (600 mg daily; n = 193)	All patients (n = 578)
Gender	Male	120 (62%)	99 (52%)	110 (57%)	329 (57%)
	Female	74 (38%)	92 (48%)	83 (43%)	249 (43%)
Age	Mean years (SD)	36.6 (10.1)	36.6 (9.6)	36.2 (10.1)	36.4 (9.9)
Weight	Mean kg (SD)	70.0 (13.8)	70.0 (14.5)	70.1 (14.1)	70.0 (14.1)
Height	Mean cm (SD)	171.1 (9.5)	170.2 (9.8)	170.7 (9.0)	170.7 (9.4)
Marital status	Single	84 (43%)	79 (41%)	79 (41%)	242 (42%)
	Married	86 (44%)	84 (44%)	80 (42%)	250 (43%)
	Divorced	24 (12%)	26 (14%)	32 (17%)	82 (14%)
	Widowed	0	2 (1%)	2 (1%)	4 (1%)

Table 2 Baseline characteristics concerning social phobia and concurrent psychiatric illnesses of the three treatment groups and the entire study population

	Placebo (n = 194)	Moclobemide (300 mg daily; n = 191)	Moclobemide (600 mg daily; n = 193)	All patients (n = 578)
Age at onset of primary Diagnosis (mean years, SD)	20.0 (9.9)	19.8 (9.7)	19.8 (9.4)	19.9 (9.7)
Duration of illness (mean months, SD)	199 (136)	199 (145)	197 (143)	198 (141)
Social phobia subtype				
Performance subtype	179 (92%)	177 (93%)	175 (91%)	531 (92%)
Interactional subtype				
Limited	35 (18%)	33 (17%)	41 (21%)	109 (19%)
Generalized	154 (79%)	150 (79%)	147 (76%)	451 (78%)
Concurrent secondary psychiatric diagnosis				
Generalized anxiety disorder	20 (10%)	22 (12%)	30 (16%)	72 (13%)
Avoidant personality disorder	103 (53%)	88 (46%)	94 (49%)	285 (49%)

12. The most frequently cited reasons for discontinuation were insufficient therapeutic response (63 patients), withdrawal of consent (22 patients), and adverse events (19 patients). Attrition rates were similar among the three treatment groups (< 30%). The groups did not differ with respect to reasons for early termination, except that insufficient therapeutic response was somewhat more frequent in the placebo group (26 patients) than in the moclobemide 300 mg (18 patients) or 600 mg groups (19 patients).

The three treatment groups were similar with respect to their demographic data and baseline characteristics of social phobia and concurrent psychiatric illnesses (Tables 1, 2). Despite protocol requirements four patients with unspecified major depression were admitted to the trial. Overall, this was a relatively young (mean age of 36 years), white population with slightly more males (57%) than females. Almost 60% of the patients reported a decline in effectiveness of work performance over the past 3 years, and only 50% of the patients were fully employed at the time of the study. Almost 70% of the patients noted a decline in their social competence over the last 3 years. Twenty-nine percent of the patients reported previous treatment with medication for their social phobia during the three months before study entry, most commonly with benzodiazepines (15%), antidepressants (9%), and beta blockers (5%). Twenty-three percent of the patients had at least one concurrent medical illness at study entry, the most frequent being musculoskeletal diseases (3%). The treatment groups appeared comparable with respect to concurrent medical illnesses.

Treatment

Of the 578 patients in the ITT population, 194 received placebo, 191 received 300 mg moclobemide per day, and 193 received 600 mg moclobemide per day. The majority of patients in each treatment group received between 8 and 12 weeks of treatment. Forty-four percent of the patients received at least one concomitant medication during the course of the study. Medications that were most frequently administered were: drugs with combined analgesics and anti-inflammatory action (25%), hormones (8%), antibiotics (6%), and hypnotics/sedatives (5%). The treatment groups were comparable with respect to concurrent medications.

Table 3 Mean and 95% confidence interval of the efficacy parameters by treatment group at pre-treatment and at week 12. Treatments included moclobemide (*M*), 300 or 600 mg per day, or placebo (*LSPS* Liebowitz Social Phobia Symptom Scale, *CIC-SP* Clinical Impression of Change – Social Phobia, *CIS-SP* Clinical Impression of Severity – Social Phobia, *PIC-SP* Patient Impression of Change – Social Phobia, *HAM-A* Hamilton Anxiety Scale, *MADRS* Montgomery and Asberg Depression Rating Scale, *N/A* not applicable, *NS* not significant)

		Pre-treatment mean (SE)	Week 12 (LOCF) mean (95%-CI)	*P*-values	
				Overall	vs placebo
1. LSPS					
Total score	Placebo	81.3 (1.7)	61.4 (56.7–66.2)	0.0031	
	M, 300 mg	79.3 (1.8)	53.5 (48.9–58.2)		0.0443
	M, 600 mg	80.2 (1.8)	50.9 (46.2–55.7)		0.0007
Fear	Placebo	42.0 (0.8)	32.1 (29.8–34.4)	0.0024	
	M, 300 mg	41.0 (0.9)	28.3 (25.9–30.7)		0.0437
	M, 600 mg	41.7 (0.9)	27.1 (24.7–29.4)		0.0006
Avoidance	Placebo	39.3 (1.0)	29.4 (26.9–31.8)	0.0049	
	M, 300 mg	38.3 (1.0)	25.2 (22.9–27.6)		0.0492
	M, 600 mg	38.5 (1.0)	23.9 (21.4–26.4)		0.0012
2. CIC-SP					
Responders[a]	Placebo	N/A	34% (27%–40%)	0.0089	
	M, 300 mg	N/A	41% (34%–48%)		NS (0.2404)
	M, 600 mg	N/A	47% (40%–54%)		0.0024
Overall change	Placebo	N/A	3.1 (3.0– 3.3)	0.0003	
	M, 300 mg	N/A	2.9 (2.7– 3.1)		0.0231
	M, 600 mg	N/A	2.7 (2.5– 2.9)		0.0001
Anxiety episodes	Placebo	N/A	3.1 (2.9– 3.2)	0.0002	
	M, 300 mg	N/A	2.9 (2.7– 3.0)		NS (0.7350)
	M, 600 mg	N/A	2.6 (2.4– 2.8)		0.0001
Functional impairment	Placebo	N/A	3.2 (3.0– 3.3)	0.0002	
	M, 300 mg	N/A	2.9 (2.7– 3.1)		0.0205
	M, 600 mg	N/A	2.8 (2.6– 2.9)		0.0003
Phobic avoidance	Placebo	N/A	3.2 (3.0– 3.3)	0.0023	
	M, 300 mg	N/A	2.9 (2.7– 3.1)		NS (0.0710)
	M, 600 mg	N/A	2.8 (2.6– 2.9)		0.0005
Anticipatory anxiety	Placebo	N/A	3.1 (2.9– 3.3)	0.0004	
	M, 300 mg	N/A	2.9 (2.7– 3.0)		0.0433
	M, 600 mg	N/A	2.7 (2.5– 2.9)		0.0001
3. Sheehan disability scale					
Work	Placebo	6.8 (0.2)	5.1 (4.6– 5.5)	0.0068	
	M, 300 mg	6.7 (0.2)	4.4 (4.0– 4.8)		NS (0.0795)
	M, 600 mg	6.5 (0.2)	4.2 (3.7– 4.6)		0.0017
Social life and leisure activities	Placebo	7.2 (0.2)	5.2 (4.7– 5.6)	0.0016	
	M, 300 mg	7.2 (0.2)	4.7 (4.3– 5.1)		NS (0.2212)
	M, 600 mg	7.1 (0.2)	4.2 (3.7– 4.6)		0.0004
Family life and home responsibilities	Placebo	4.6 (0.2)	3.5 (3.1– 4.0)	0.0278	
	M, 300 mg	4.6 (0.2)	3.0 (2.6– 3.4)		NS (0.0844)
	M, 600 mg	4.5 (0.2)	2.8 (2.4– 3.2)		0.0085
4. CIS-SP	Placebo	5.1 (0.1)	4.1 (3.9– 4.3)	0.0005	
	M, 300 mg	5.2 (0.1)	3.8 (3.6– 4.1)		NS (0.0965)
	M, 600 mg	5.2 (0.1)	3.5 (3.3– 3.8)		0.0001
5. PIC-SP	Placebo	N/A	3.0 (2.8– 3.1)	0.0022	
	M, 300 mg	N/A	2.7 (2.5– 2.9)		0.0209
	M, 600 mg	N/A	2.6 (2.4– 2.8)		0.0006
6. HAM-A	Placebo	16.7 (0.6)	13.0 (11.6–14.3)	0.0422	
	M, 300 mg	17.2 (0.7)	12.0 (10.7–13.3)		NS (0.1667)
	M, 600 mg	17.0 (0.6)	11.1 (9.8–12.5)		0.0121
7. MADRS	Placebo	11.1 (0.5)	8.8 (7.7– 9.9)	NS (0.0550)	
	M, 300 mg	12.0 (0.6)	8.8 (7.7– 9.9)		NS (0.8332)
	M, 600 mg	11.5 (0.6)	7.5 (6.3– 8.6)		0.0291

[a] Responder: rating of "much improved" or "very much on the Clinical Impression of Change – Social Phobia

Efficacy

There was both a consistent and reliable drug effect and a dose-response relationship, which became apparent during the 2nd week of treatment. The results of the primary efficacy measure and the results of the secondary efficacy measures at week 12 reported here are representative of the data.

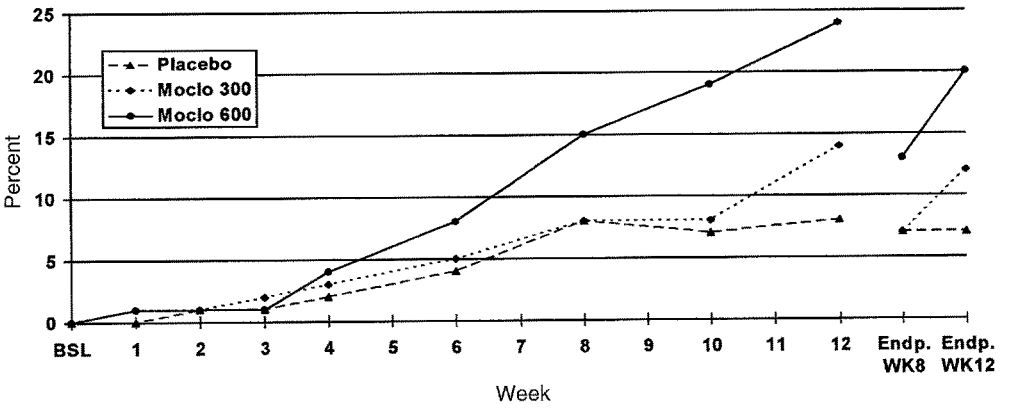

Fig. 1 Clinical impression of overall change – social phobia (CIC-SP): proportion of patients in each treatment group rated "very much improved" at each assessment and at last observation carried forward (LOCF) endpoints. Treatments included 300 or 600 mg of moclobemide per day, or placebo for 12 weeks

1. Liebowitz Social Phobia Symptom Scale (LSPS)

There was a significant overall treatment effect on the specific symptoms of social phobia as measured by the LSPS. The pairwise treatment comparisons versus placebo showed significant differences in favor of the 600 mg and the 300 mg dose for the total score as well as for the subscales. The results of the total score and both subscales ('Fear and Anxiety' and 'Avoidance') at baseline and week 12 are shown in Table 3.

2. Clinical Impression of Change – Social Phobia (CIC-SP)

The *overall change* scale of the CIC-SP was the primary measure of efficacy. The mean values of the overall change scores are summarized in Table 3. The percentages of patients in each treatment group who were considered to be responders at each visit and at LOCF endpoints at weeks 8 and 12 are shown in Fig. 1. Except for the 1st week, when the percentages of responders in the 300 mg and the 600 mg moclobemide dose group were equal, the percentage of responders in the 600 mg dose group was numerically higher than in the 300 mg dose group at each time point. There was a significant treatment effect at week 8 ($P = 0.0042$) and at week 12 ($P = 0.0089$). The response rates in the moclobemide 600 mg dose group were significantly higher than in the placebo group, both at week 8 (14%, $P = 0.0010$) and at week 12 (13%, $P = 0.0024$). The response rates in the 300 mg dose group were also higher than in the placebo group; however, these differences were not significant ($P = 0.0733$ and $P = 0.2404$, respectively). There was no significant treatment by center interaction.

The percentage of patients who were rated as "very much improved" (according to the CIC-SP) steadily increased in the 600 mg group through the course of the study, but appeared to reach a plateau in the placebo group after week 8 (see Fig. 1). At end-point week 12 (LOCF) the rate of patients with a rating of "very much improved" was almost three times higher in the 600 mg group (20%) than in the placebo group (8%).

The magnitude of the changes in the mean scores of the CIC-SP *subscales* (Anxiety Episodes, Functional Impairment, Phobic Avoidance and Anticipatory Anxiety) of patients in each of the treatment groups at week 12 were comparable to that seen in the overall score (Table 3). At week 12, the overall treatment effect was significant for all subscales. The 600 mg dose was significantly superior to placebo in all four subscales, while the 300 mg dose was only significantly superior to placebo on the 'Functional Impairment' and 'Anticipatory Anxiety' subscales. The response on the subscores are comparable to those seen on the global score and also show a dose response relationship.

3. Sheehan Disability Scale

The mean scores of the Sheehan disability scale for the work, social life and leisure, and family life and home responsibilities dimensions of functioning at week 12 are shown in Table 3. All three subscales showed significant treatment effects. The mean scores of all subscales were significantly lower with the 600 mg dose than with placebo, indicating a superior treatment effect. The mean scores with the 300 mg dose were also lower than those with placebo, but did not differ significantly.

4. Clinical Impression of Severity – Social Phobia (CIS-SP)

The mean CIS-SP scores at baseline and at week 12 are shown in Table 3. The overall treatment effect was statistically significant, and the mean score for the 600 mg dose was significantly lower than that for placebo.

5. Patient Impression of Change – Social Phobia (PIC-SP)

Patients' ratings also showed a significant overall treatment effect at week 12 (Table 3). The mean scores on the PIC-SP for both the 600 mg and the 300 mg dose were significantly lower than for placebo.

6. Hamilton Anxiety Scale (HAM-A)

At week 12, there was a significant overall treatment effect on the mean total score of the HAM-A (Table 3). The pairwise comparison versus placebo showed a significant difference in favor of the 600 mg dose, but not the 300 mg dose.

7. Montgomery and Asberg Depression Rating Scale (MADRS)

As the baseline evaluation, the MADRS showed very low depression scores, reflecting the exclusion of patients with a current major depression from the study (Table 3). There was no significant overall treatment effect on the depression scores of the MADRS.

8. Subgroup analyses

As shown in Table 4, post-hoc comparison of subgroups confirmed a more pronounced drug effect in patients with concurrent avoidant personality disorder, longer duration of illness or greater severity at entry into the study. Response to 600 mg of moclobemide was similar regardless of whether patients had an avoidant personality disorder (44.7% responders) or not (49.5% responders), but patients with avoidant personality responded less often to placebo (28.2% responders). The drug placebo difference was smaller in the subgroup without avoidant personality disorder. The group with a longer duration of illness likewise showed higher drug response and a lower placebo response. Patients with a more severe illness at baseline responded better to drug treatment and showed a smaller placebo response than milder cases. Significance levels are not given since the study was not powered to detect differences in the response rates among these subgroups.

Post-hoc analyses of variance procedures fitting for avoidant personality disorder showed a significant difference between 600 mg and placebo ($P = 0.0034$) but not between 300 mg and placebo ($P = 0.3318$). Similar results were seen when fitting for the duration of illness (600 mg versus placebo: $P = 0.0017$; 300 mg versus placebo: $P = 0.2546$) and when fitting for baseline severity (600 mg versus placebo: $P = 0.0022$; 300 mg versus placebo: $P = 0.2016$). These findings indicate that 600 mg of moclobemide is the best dose, independent of the presence of avoidant personality disorder, the duration of the illness, or the level of severity.

Safety

Adverse events

The frequencies and types of adverse events during treatment are summarized in Table 5. The majority of the patients of each treatment group experienced at least one adverse event. The average number of events per patient varied between 1.5 and 1.9. Among the patients treated with moclobemide, a slightly higher percentage showed adverse events than among the patients treated with placebo. There was no clear difference between the two moclobemide groups.

The most frequently reported adverse events were insomnia, headache, dizziness, and nausea (Table 5). For insomnia, there was a dose-response relationship, with a higher incidence in patients treated with moclobemide than placebo. For the adverse events headache, dizziness, and nausea there was no clear dose relationship, but their frequency was slightly higher in at least one of the moclobemide groups. Inspection of the other less frequent adverse events did not indicate a dose-response relationship or a drug-placebo difference.

The majority (92%) of adverse events were mild or moderate in intensity; of the 116 (8%) severe adverse events, 37 were reported in the 600 mg dose group, 45 in the 300 mg dose group, and 34 in the placebo group. There was no indication of a dose-response relationship, with the exception of severe insomnia and severe headache, which appeared more frequently in the moclobemide groups than in the placebo group. Twelve serious adverse events were reported. Among these were hospitalizations (for lumbago, lithotripsy, surgery of fibroma, diverticulitis, psy-

Table 4 Subgroup analyses – response to either placebo or moclobemide, 300 or 600 mg per day, in subgroups defined by presence or absence of avoidant personality disorder, duration of illness and severity at baseline

	Responders (%)		
	Placebo	Moclobemide (300 mg daily)	Moclobemide (600 mg daily)
Avoidant personality disorder			
With ($n = 285$)	29 (28.2%)	32 (36.4%)	42 (44.7%)
Without ($n = 291$)	36 (39.6%)	46 (44.7%)	48 (49.5%)
Duration of illness			
Long ($n = 287$)	28 (28.3%)	37 (39.4%)	49 (52.1%)
Short ($n = 289$)	37 (38.9%)	41 (42.3%)	41 (42.3%)
Severity of social phobia at baseline			
Moderate to marked ($n = 398$)	48 (34.8%)	56 (42.4%)	57 (44.5%)
Severe to most severe ($n = 178$)	17 (30.4%)	22 (37.3%)	33 (52.4%)

Table 5 Adverse events observed during the 12-week treatment with either placebo or moclobemide (300 or 600 mg per day)

	Placebo	Moclobemide (300 mg daily)	Moclobemide (600 mg daily)
Number of patients exposed	194	191	193
Total number of adverse events reported[a]	287	368	352
Mean number of adverse events per patient	1.5	1.9	1.8
Percentage of patients with at least one adverse event	59%	64%	63%
Most frequent adverse events (>10%)[b]			
Insomnia	28 (14.4%)	37 (19.4%)	59 (30.6%)
Headache	36 (18.6%)	31 (16.2%)	39 (20.2%)
Nausea	16 (8.2%)	25 (13.1%)	19 (9.8%)
Dizziness	15 (7.7%)	20 (10.5%)	15 (7.8%)

[a] If a patient had more than one occurrence of the same event, this event was only counted once in the computation of the total number of adverse events
[b] Number of patients experiencing an adverse event

chosis, and suicide attempt), one pregnancy, two intentional and three unintentional overdoses. No deaths occurred.

Other safety assessments

For each treatment group, blood pressure and heart rate remained stable and changes over time were minimal. There was no noticeable variation among groups for these three parameters at any time point and orthostatic hypotension was not observed. None of the treatment groups showed an appreciable mean change of body weight over the duration of the study, and no meaningful between-group difference emerged. A review of the hematological and chemical parameters showed very limited change over time for each dose group, and no clinically relevant group changes were evident.

Discussion

This multicenter study, so far the largest therapeutic trial in social phobia (n = 578), was designed and powered to test for differences between each of the two dose groups of moclobemide (300 and 600 mg per day) and placebo. Moclobemide showed the best efficacy with a dose of 600 mg per day. The drug reduced the intensity of social phobia symptoms and led to a clinically relevant overall response and a clear reduction in the patient's disability. The compound was well-tolerated and safe. The results of this study support the use of moclobemide as a first-line treatment for social phobia.

During the past few years social phobia has progressed from a 'neglected' (Liebowitz et al. 1985) to a fully recognized anxiety disorder (Stein 1996). However, the condition is still frequently underdiagnosed and undertreated. It has been estimated that less than 25% of the sufferers receive appropriate pharmacological or psychological treatment (Swinson et al. 1992). However, the severe disability, harmful coping strategies (like alcohol or drug abuse to reduce anxiety in social situations), and the development of significant comorbidity could be prevented by early intervention. While there is some evidence for the efficacy of some psychological treatments like behavior therapy or cognitive therapy, these are often only provided by specialist centers. This creates the need for efficacious, safe and well-tolerated pharmacological treatments that are readily available and easy to administer and therefore can be provided to the majority of patients without undue delays. Although several studies (Liebowitz et al. 1992; Versiani 1992) have shown that classical MAO inhibitors like phenelzine are effective in social phobia, the compounds are not well tolerated. In addition, patients must observe a special diet in order to avoid hypertensive crises due to potentiation of the tyramine pressor effect. This has significantly limited the use of MAO inhibitors and creates the need for better treatment alternatives. The newer reversible and selective inhibitors of monoamine oxidase A, like moclobemide, could meet that need since they have already been shown to be much safer and better tolerated in the treatment of depression (Stabl et al.1989; Versiani et al.1989), and treatment with these compounds does not require dietary restrictions.

The current study showed that treatment with moclobemide improved the symptoms of social phobia as measured by the Liebowitz Social Phobia Symptom Scale (LSPS). This improvement was clinically relevant as shown by a significantly higher moclobemide responder rate. Moclobemide at a dose of 600 mg per day was significantly superior to placebo on the primary efficacy variable (CIC-SP responders) and on the secondary efficacy measures. Although the 300 mg dose also showed numerically better results than placebo on all measures of efficacy, differences only reached statistical significance for approximately half of them. The findings clearly indicate that there was a consistent and reliable drug effect, and they suggest a dose-response relationship, which became apparent during the second week of treatment. Of note is the change in disability even during a treatment of only 12 weeks' duration. Moclobemide treatment resulted in an improvement on measures of disability in the areas of work, social life and leisure activities, and family life and home responsibilities. This also underscores the clinical relevance of the therapeutic effects.

After 12 weeks of treatment, the response rates were 47, 41, and 34% for moclobemide 600 mg, moclobemide 300 mg, and placebo, respectively. Thus, nearly half of the patients in the 600 mg group were rated as much improved or very much improved, which is a considerable response in a chronic disorder like social phobia. The re-

sponse rates in the moclobemide groups were somewhat lower than the rates reported in an earlier single center study (Versiani 1992), but this may be explained by the different study designs and by the fact that this was a multicenter trial. However, the response rate in the placebo group was somewhat higher than that seen in other drug trials in social phobia, which ranged from 7 to 25.6% (Liebowitz et al. 1992; Van Vliet et al. 1992, 1994; Versiani 1992; Fahlén et al. 1992; Davidson et al. 1993a; Gelernter et al. 1991). Most of these studies had small total sample sizes of between 30 and 85 patients and were carried out as single or dual center trials, which allow for tighter control of non-specific treatment effects. In multicenter trials there is often more variability in treatment outcome because of differences regarding the type of patients enrolled, the clinical setting and the experience of the investigators with the condition. Patients' expectations and the intensity of general psychological support may further increase placebo response. Patients entered into large placebo-controlled studies are often less severely impaired than patients entered into smaller trials. All these factors may limit the ability of a larger trial to discriminate between drug and placebo. A similar increase in placebo responsiveness in larger trials has also been observed for other anxiety disorders like obsessive compulsive disorder (Greist et al. 1995). The significant drug-placebo difference seen in the moclobemide study despite the raised placebo response rates provides good evidence of a specific pharmacological effect. Furthermore, subgroup analyses revealed that the placebo response was lowest and drug placebo differences were largest in the more severely ill patients, i.e., in those that are most in need of treatment.

The significant superiority of the 600 mg dose of moclobemide over placebo and the therapeutic dose-response are caused by a drug effect and not a consequence of unevenly distributed baseline characteristics, since the demographic and baseline disease characteristics of the patient sample did not differ substantially between treatment groups. Moreover, this sample of patients appears to be representative of the population of social phobics, since its characteristics are comparable to those described in previous epidemiological and clinical studies. The age of onset of social phobia in patients in this trial (mean of 20 years) is concordant with data from other studies, indicating that the typical age of onset occurs in the teenage years (Gelernter et al. 1992; Davidson et al. 1993b; Solyom et al. 1986; Schneier et al. 1992). Forty-two percent of patients in the current sample were never married, which is in line with rates of 29 to 44% reported elsewhere (Gelernter et al. 1992; Schneier et al. 1992; Amies et al. 1983; Kessler et al. 1994). The proportion of 57% males in this study is higher than in epidemiological reports (Davidson et al. 1993b; Schneier et al. 1992; Kessler et al. 1994), but is concordant with study reports of treatment-seeking patients with social phobia (Solyom et al. 1986; Amies et al. 1983; Liebowitz et al. 1992).

Consistent with previous social phobia trials (Versiani 1992; Liebowitz et al. 1992), patients in this study were markedly ill. The severity of the social phobia symptoms was confirmed by the fact that 78% of the patients were diagnosed as having a generalized subtype (the phobic stimuli included most social situations), while only 19% of patients had a limited interactional subtype (the phobic stimuli included no more than two socially interactive situations). The severity of the patients' psychopathology was also supported by the high prevalence of other psychiatric disorders. Consistent with epidemiological studies (Davidson et al. 1993b; Schneier et al. 1992; Magee et al. 1996), the majority (58%) of the patients in this study had one or more concurrent psychiatric diagnosis, most often avoidant personality disorder, followed by generalized anxiety disorder. The exclusion of patients with significant depressive symptomatology in this study is confirmed by the low mean score of the MADRS at baseline. Since moclobemide has proven antidepressant effects, and possibly antipanic effects, exclusion of these psychiatric conditions may have resulted in an underestimation of the drug's overall therapeutic effectiveness when used in the general clinical setting. In fact, the treatment effects and the drug placebo differences were more pronounced in patients who also met criteria for avoidant personality disorder or showed a longer duration of the illness or higher severity scores at baseline.

Since social phobia is a long-lasting condition, especially in cases where there is a need for chronic treatment better tolerability may be become relevant. Overall, the tolerability of moclobemide appeared excellent and hardly differed from placebo. Sixty-four percent of the patients on moclobemide and 59% of the patients on placebo experienced at least one adverse event. Four adverse events occurred in at least 10% of the patients in at least one moclobemide treatment group; one of them, insomnia, occurred somewhat more frequent with moclobemide (19% with the 300 mg dose, and 31% with the 600 mg dose) than with placebo (14%), but was not treatment limiting. Of note is the absence of sexual side effects, which compares well with the high frequency of these adverse effects observed during treatment with serotonin reuptake inhibitors, a class of compounds that may be efficacious in social phobia.

The absence of weight gains is especially important in patients who require prolonged treatment. The minimal drug effect on blood pressure and heart rate could not be differentiated from placebo, and very few patients had significant laboratory test abnormalities. There was no evidence of toxicity of moclobemide on the liver or the blood, and laboratory test abnormalities were few, did not appear to be dose-related, and none resulted in early discontinuation.

In conclusion, this study demonstrates the efficacy and safety of moclobemide and supports the compound's use as a first-line treatment of social phobia. Both clinical ratings and patients' self-assessment indicate that 600 mg moclobemide per day is an effective treatment, leading to substantial symptom relief and to reduced disability in such areas as work, social life, and family. Because of the benign side-effect profile treatment could start immedi-

ately with 600 mg of moclobemide given in two divided doses, although the study used a dose titration scheme reaching this dose after 3 days. The minimal treatment duration is 12 weeks, although hints at efficacy were observed already after 8 weeks. The therapeutic effect was consistent over time and appeared to be dose-related. Moclobemide was well tolerated, and adverse events, except insomnia, were not dose-related nor were there significant drug-placebo differences.

References

American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders (4th edn) (DSM-IV). American Psychiatric Association, Washington DC

Amies PL, Gelder MG, Shaw PM (1983) Social phobia: a comparative clinical study. Br J Psychiatry 142:174–179

Bisserbe J-C, Lépine J-P, GRP Group (1994) Moclobemide in social phobia: a pilot open study. Clin Neuropharmacol 17:88–94

Davidson JRT, Potts N, Richichi E, Krishnan R, Ford SM, Smith R, Wilson WH (1993a) Treatment of social phobia with clonazepam and placebo. J Clin Psychopharmacol 13:423–428

Davidson JRT, Hughes DL, George LK, Blazer DG (1993b) The epidemiology of social phobia: findings from the Duke Epidemiological Catchment Area Study. Psychol Med 23:709–718

Fahlén T, Humble M, Koczkas C, Nilsson HL (1992) Social phobia and its treatment with brofaromine. Efficacy regarding social phobia symptoms and personality traits. Clin Neuropharmacol 15:64B

First M, Spitzer RL, Williams JBW, Gibbon M (1995) Structured Clinical Interview for DSM-IV – Patient Edition (SCIP-P). American Psychiatric Press, Washington DC

Gelernter CS, Uhde TW, Cimbolic P, Arnkoff DB, Vittone BJ, Tancer ME, Bartko JJ (1991) Cognitive-behavioral and pharmacological treatments of social phobia. Arch Gen Psychiatry 48:938–945

Gelernter CS, Stein MB, Tancer ME, Uhde TW (1992) An examination of syndromal validity and diagnostic subtypes in social phobia and panic disorder. J Clin Psychiatry 53:23–27

Greist J, Chouinard G, DuBoff E, Halaris A, Kim SW, Koran L, Liebowitz M, Lydiard RB, Rasmussen S, White K, Sikes C (1995) Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. Arch Gen Psychiatry 52:289–295

Guy W (1976) Early Clinical Drug Evaluation Unit (ECDEU) assessment manual. US Department of Health, Education and Welfare, Washington DC, pp 217–222

Hamilton M (1959) The assessment of anxiety states by rating. Br J Med Psychol 32:50–55

Katzelnick DJ, Kobak KA, Greist JH, Jefferson JW, Mantle JM, Serlin RC (1995) Sertraline in social phobia: a double-blind, placebo-controlled crossover study. Am J Psychiatry 152: 1368–1371

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen H-U, Kendler KS (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Arch Gen Psychiatry 51:8–19

Liebowitz MR, Gorman JM, Fyer AJ, Klein DF (1985) Social phobia: review of a neglected anxiety disorder. Arch Gen Psychiatry 42:729–736

Liebowitz MR, Fyer AJ, Gorman JM, Campeas R, Levin A (1986) Phenelzine in social phobia. J Clin Psychopharmacol 6:93–98

Liebowitz MR (1987) Social phobia. Modern problems in pharmacopsychiatry 22:141–173

Liebowitz MR, Gorman JM, Fyer AJ, Campeas R, Levin AP, Sandberg D, Hollander E, Papp L, Goetz D (1988) Pharmacotherapy of social phobia: an interim report of a placebo controlled comparison of phenelzine and atenolol. J Clin Psychiatry 49:252–257

Liebowitz MR, Schneier F, Campeas R, Hollander E, Hatterer J, Fyer A, Gorman J, Papp L, Davies S, Gully R, Klein DF (1992) Phenelzine vs atenolol in social phobia: a placebo controlled comparison. Arch Gen Psychiatry 49:290–300

Magee WJ, Eaton WW, Wittchen HU, McGonagle KA, Kessler RC (1996) Agoraphobia, simple phobia, and social phobia in the National Comorbidity Survey. Arch Gen Psychiatry 53:159–168

Manuzza S, Schneier FR, Chapman TF, Liebowitz MR, Klein DF, Fyer AJ (1995) Generalized social phobia: reliability and validity. Reference for social phobia subtype. Arch Gen Psychiatry 52:230–237

Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389

Myers JK, Weissman MM, Tischler GL, Holzer CE, Leaf PJ, Orvaschel H, Anthony JL, Boyd JH, Burke JD, Kramer M, Stoltzman R (1984) Six month prevalence of psychiatric disorders in three countries. Arch Gen Psychiatry 41:959–967

Schneier FR, Johnson J, Hornig CD, Liebowitz MR, Weissman MM (1992) Social phobia. Comorbidity and morbidity in an epidemiological sample. Arch Gen Psychiatry 49:282–288

Schneier FR, Heckelman LR, Garfinkel R, Campeas R, Fallon BA, Gitow A, Street L, Del Bene D, Liebowitz MR (1993) Functional impairment in social phobia. J Clin Psychiatry 55:322–331

Sheehan DV (1983) The anxiety disease and how to overcome it. Schribner, New York, pp 148–149

Solyom L, Ledwidge B, Solyom C (1986) Delineating social phobia. Br J Psychiatry 149:464–470

Spitzer RL, Williams JBW, Gibbon M, First M (1990) Structured Clinical Interview for DSM-III-R – Patient Edition (SCIP-P). American Psychiatric Press, Washington DC

Stabl M, Biziere K, Schmid-Burgk W, Amrein R (1989) Review of comparative clinical trials: moclobemide vs tricyclic antidepressants and vs placebo in depressive states. J Neural Transm 45:77–90

Stein MB (1996) How shy is too shy? Lancet 347:1131–1132

Swinson RP, Cox BJ, Woszczyna CB (1992) Use of medical services and treatment for panic disorder with agoraphobia and for social phobia. Can Med Assoc J 147:878–883

Van Vliet IM, Boer JA den, Westenberg HGM (1992) Psychopharmacological treatment of social phobia: clinical and biochemical effects of brofaromine, a selective MAO-A inhibitor. Eur Neuropsychopharmacol 2:21–29

Van Vliet IM, Boer JA den, Westenberg HGM (1994) A novel psychopharmacological approach to social phobia; a double blind placebo controlled study with fluvoxamine. Psychopharmacology 115:128–134

Versiani M (1992) Pharmacotherapy of social phobia: a controlled study with moclobemide and phenelzine. Br J Psychiatry 161: 353–360

Versiani M, Mundim FD, Nardi AE, Liebowitz MR (1988) Tranylcypromine in social phobia. J Clin Psychopharmacol 8:279–283

Versiani M, Oggero U, Alterwain P, Capponi R, Dajas F, Heinze-Martin G, Marquez CA, Poleo MA, Rivero-Almanzor LE, Rossel L, Schmid-Burgk W, Ucha Udabe R (1989) A double-blind comparative trial of moclobemide vs imipramine and placebo in major depressive episodes. Br J Psychiatry 155:72–77

World Health Organisation (1992) Mental health and behavioral disorders (including disorders of psychological development). In: International classification of diseases, 10th rev. World Health Organisation, Geneva, Switzerland