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SPECIAL SERIES

The evidence-based pharmacological treatment of social anxiety disorder

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Abstract

Social anxiety disorder (SAD) is a highly prevalent and often disabling disorder. This paper reviews the pharmacological treatment of SAD based on published placebo-controlled studies and published meta-analyses. It addresses three specific questions: What is the first-line treatment of SAD? How long should treatment last? What should be the management of treatment-resistant cases? Based on their efficacy for SAD and common comorbid disorders, tolerability, and safety, SSRIs should be considered as the first-line treatment for most patients. Less information is available regarding the optimal length of treatment, although individuals who discontinue treatment after 12–20 wk appear more likely to relapse than those who continue on medication. Even less empirical evidence is available to support strategies for treatment-resistant cases. Clinical experience suggests that SSRI non-responders may benefit from augmentation with benzodiazepines or gabapentin, or from switching to MAOIs, RIMAs, benzodiazepines or gabapentin. Cognitive–behavioural therapy may also be a helpful adjunct or alternative.

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Introduction

Social anxiety disorder (SAD) is characterized by a fear of negative evaluation in social or performance situations and a strong tendency for sufferers to avoid feared social interactions or situations. While the ECA study of the early 1980s suggested that SAD [as defined in DSM-III (APA, 1980)] affected 2–3% of women and 1–2% of men (Myers et al., 1984), the more recent National Comorbidity Survey using broader DSM III-R criteria found lifetime prevalence of SAD to be 13.3% in the USA (Kessler et al., 1994). In this study, SAD was the third most common mental disorder, following major depression and alcohol dependence. The 12-month prevalence of SAD was also high (7.9%).

SAD begins early (characteristically in the mid-teens) and follows a chronic, unremitting course (Amies et al., 1983; Marks, 1970; Öst, 1987). Impairments in vocational and social functioning are often substantial (Davidson et al., 1993; Schneier et al., 1992). Inability to work, attend school, socialize or marry are common in clinical samples (Liebowitz et al., 1985; Schneier et al., 1994; Wittchen and Beloch, 1996).

The DSM-IV describes a generalized subtype. Individuals with generalized SAD have distressing/disabling social fears in most social situations. It affects multiple aspects of life including social, familial and professional aspects. On the other hand, patients with non-generalized SAD typically fear only a few social/performance situations, most commonly public speaking.

Given the prevalence and degree of impairment associated with SAD, it is clear that its treatment is of great importance for public health. In this paper, we first review the available evidence for the pharmacological management of SAD focusing on the published randomized clinical trials, which are summarized in Table 1. In considering the individual studies, it is important to realize that initial studies were conducted at academic centres using relatively small samples, whereas more recent studies have generally been sponsored by the pharmaceutical industry and have tended to have larger sample sizes. Because there are few head-to-head comparisons of medication treatments, we rely on meta-analytical reviews to estimate and compare the relative efficacy of different medications.

In order to provide some foundations for evidence-based pharmacological treatment of SAD, we

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Table 1. Summary of placebo-controlled studies in the acute treatment of social anxiety disorder (SAD)

Drug class	Drug	Author	Sample size	Duration (wk)	Dose (mg/d)	Response rates (%)	
						Medication	Placebo
MAOIs	Phenelzine[a]	Liebowitz et al. (1992)	51	8	45–90	64	23
	Phenelzine[b]	Gelernter et al. (1991)	64	12	30–90	69	20
	Phenelzine[c]	Versiani et al. (1992)	52	8	15–90	81	27
	Phenelzine	Heimberg et al. (1998)	64	12	15–75	52	27
RIMAs	Moclobemide[b]	Versiani et al. (1992)	52	8	100–600	65	20
	Moclobemide	Katschnig et al. (1997)	578	12	300–600	44	32
	Moclobemide	Noyes et al. (1997)	506	12	75–900	35	33
	Moclobemide	Schneier et al. (1998)	75	8	100–400	18	14
	Moclobemide	Stein et al. (2002a)	390	12	450–750	43	30
	Brofaromine	van Vliet et al. (1992)	30	12	50–150	80	14
	Brofaromine	Fahlen et al. (1995)	77	12	150	78	23
	Brofaromine	Lott et al. (1997)	102	10	50–150	50	19
Benzodiazepines	Clonazepam	Davidson et al. (1993)	75	10	0.5–3	78	20
	Bromazepam	Versiani et al. (1997)	60	12	3–27	83	20
	Alprazolam[b]	Gelernter (1991)	65	12	2.1–6.3	38	23
SSRIs	Fluvoxamine	van Vliet et al. (1992)	30	12	150	46	7
	Fluvoxamine	Stein et al. (1999)	86	12	202, mean dose	43	23
	Paroxetine	Stein et al. (1998)	182	12	10–50	55	22
	Paroxetine	Baldwin et al. (1999)	290	12	20–50	66	33
	Paroxetine	Allgulander (1999)		12	20–50	70	8
	Paroxetine	Liebowitz et al. (2002)	384	12	20–60	66	28
	Sertraline[d]	Katzelnick (1995)	12	10	50–200	50	9
	Sertraline	Van Ameringen et al. (2001)	204	20	50–200	53	29
	Sertraline	Liebowitz et al. (2003)	211	12	50–200	47	26
	Fluoxetine	Kobak et al. (2002)	60	8	20–60	40	30
Beta blocker	Atenolol[a]	Liebowitz et al. (1992)	51	8	50–100	30	23
	Atenolol	Turner et al. (1994)	72	12	25–100	33	6
Other	Gabapentin	Pande et al. (1999)	69	14	900–3600	38	14
	Buspirone	van Vliet et al. (1997)	30	12	15–30	27	13

[a] Study had three arms: phenelzine, atenolol and placebo.
[b] Study had three arms: phenelzine, alprazolam and placebo.
[c] Study had three arms: phenelzine, moclobemide and placebo.
[d] Study had a cross-over design.

conducted a search using electronic databases (MEDLINE, PREMEDLINE and PsychInfo) for the years 1980–2002 using a search strategy that combined the terms (*social adj3* (*anxiety or phobi$*)) with (*control$ or randomized or clinical trial or placebo$ or blind$*). To complement the search strategy, we also consulted with other colleagues regarding published papers on trials involving medication for the treatment of SAD. In this review we attempt to provide evidence-based answers to three main questions:

(1) What should be the first-line pharmacological treatment of SAD?
(2) How long should this treatment last?
(3) What strategies can be used if first-line treatments fail?

The overwhelming majority of the published work on the pharmacological treatment of SAD is directed at answering the first question and, our review of the literature reflects this fact. However, we also examine the limited available information regarding duration of pharmacological treatment, and suggest strategies for management of treatment-resistant cases. We conclude the review by outlining some future directions.

What is the first-line treatment for SAD?

Summary of published clinical trials

Monoamine oxidase inhibitors (MAOIs)

Until recently, phenelzine was considered the best established treatment of SAD. Direct evidence of the efficacy of phenelzine in SAD has been provided by four double-blind, placebo-controlled trials. In the first study (Liebowitz et al., 1992), 85 patients meeting DSM-III criteria for SAD were randomly assigned to phenelzine, atenolol or placebo for 8 wk. Patients were excluded from the study if they had current major depression or other major Axis I disorders.

Patients were included in the statistical analysis ($n=74$) if they had completed at least 4 wk of medication with 2 wk at therapeutic dose (50 mg/d atenolol, or 45 mg/d phenelzine). Mean doses of medication used were: 75.7 mg/d phenelzine (S.D. = 16; range 45–90) and 97.6 mg/d atenolol (S.D. = 10.9; range 50–100). Using a Clinical Global Impression (CGI) Scale rating score (Guy, 1976) of 1–2 to define 'responders', the response rate was as follows: phenelzine 64% (16/25), atenolol 30% (7/23), and placebo 23% (6/26). Phenelzine was significantly superior to both atenolol and placebo, but there were no significant differences between those two groups.

In a second study, Gelernter et al. (1991) randomized 60 patients meeting DSM-III criteria for social phobia to 1 of 4 groups for 12 wk: phenelzine, alprazolam, placebo or cognitive–behavioural therapy (CBT). All patients assigned to medication (or placebo) received exposure instructions and were encouraged to engage in the feared situations. Medication dosages were increased until all social phobic symptoms had disappeared, until side-effects precluded further increases, or until the maximum medication dosage was reached. Mean doses at the end of the study were: 55 mg/d phenelzine (S.D. = 16) and 4.2 mg/d alprazolam (S.D. = 1.3). Phenelzine and alprazolam were superior to placebo on the Social Disability Scale (SDS; Sheehan, 1983), which was administered only to the patients in the medication groups, and phenelzine was better than all the other treatment groups on the State and Trait Anxiety Inventory (STAI; Spielberger et al., 1970). Response was defined as a final score on the SP subscale of the Fear Questionnaire (FQ) (Marks and Mathews, 1979) equal to or less than that established in the normative samples. Under that stringent criterion, 69% of patients on phenelzine were responders compared to 38% on alprazolam, 24% on CBT and 20% on placebo.

A third study, conducted by Versiani et al. (1992), compared phenelzine, moclobemide and placebo in 78 patients with SAD. The study was comprised of three phases each lasting 8 wk. Maximum allowed doses were 90 mg/d phenelzine or 600 mg/d moclobemide. Actual mean doses at the end of the study were: 67.5 mg/d phenelzine (S.D. = 15.0) and 570.7 mg/d moclobemide (S.D. = 55.6). At the end of the 8-wk acute phase phenelzine was found to be more efficacious than placebo on all measures of social anxiety and more efficacious than moclobemide on the social avoidance subscale of the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987), although not on the other measures of efficacy. The LSAS, the most widely used scale for the assessment of SAD severity in pharmacological trials, is a 24-item clinician-administered scale that rates the anxiety of individuals in a variety of social situations. Its value for total score is the sum of its two subscales ('Anxiety' and 'Avoidance') and ranges from 0 to 144. The scale has been shown to have good psychometric properties (Heimberg et al., 1999).

Most recently, Heimberg et al. (1998) randomized 133 patients to phenelzine, placebo, CBT (CBGT) group or an educational-supportive group. Efficacy was compared during a 12-wk acute trial, a 6-month maintenance phase for responders to phenelzine and CBGT during the acute phase, and a 6-month treatment discontinuation phase (Liebowitz et al., 1999). At the end of the 12-wk acute phase, both CBGT and phenelzine were significantly superior to the two control treatments in terms of rate of response and not different from each other (Heimberg et al., 1998). On dimensional ratings, however, phenelzine appeared superior to CBGT.

Reversible inhibitors of monoamine oxidase A (MAOA)

Concerns regarding side-effects and safety of the standard non-reversible MAOIs led to the development of the reversible inhibitors of MAOA (RIMAs), for which clinical experience has shown that dietary restrictions are unnecessary.

Moclobemide

Five double-blind, placebo-controlled studies of moclobemide have been published. The results of these studies indicate that while RIMAs are considerably safer than non-reversible MAOIs, their efficacy appears inferior to that of phenelzine. As mentioned in the previous section, the first study by Versiani et al. (1992) compared moclobemide at a mean dose of

581 mg/d (S.D. = 56) with phenelzine and placebo. Moclobemide and phenelzine showed similar improvement on most measures. Phenelzine was superior on the social avoidance subscale of the LSAS, but had more severe side-effects.

The second study, a large multicentre trial (Katschnig et al., 1997) randomized 578 patients to two doses of moclobemide (300 and 600 mg) or placebo in a 12-wk fixed-dose study. Patients were encouraged to confront anxiety-provoking situations, although formal psychotherapy or any other concurrent treatment for SAD was not allowed. The response rate was 47% in the 600-mg group, 41% in the 300-mg group, and 34% in the placebo group. The 600 mg dose was superior to placebo on all measures of SAD, general anxiety and disability. The 300 mg dose was superior to placebo on LSAS and Patient Impression of Change – Social Phobia scale. There were no differences in the side-effects of both groups of moclobemide.

In the third study (Noyes et al., 1997) patients were randomized to 1 of 5 different doses of moclobemide (75, 150, 300, 600, 900 mg) or placebo following a 12-wk double blind, fixed-dose, parallel study design. None of the doses of moclobemide was superior to placebo.

Schneier et al. (1998) conducted an 8-wk flexible-dose study in 77 social phobic patients of moclobemide vs. placebo. At week 8, only 7 out of 40 (17.5%) patients taking moclobemide and 5 out of 37 (13.5%) taking placebo were rated as 'much' or 'very much' improved in the CGI and considered responders, a non-significant difference.

In a recent study, Stein et al. (2002a) randomized 390 subjects with SAD to moclobemide or placebo for 12 wk. At week 12, 43% of patients in the moclobemide group and 31% in the placebo group were considered responders. Interestingly, exploratory analyses showed that the presence of a comorbid anxiety disorder was predictive of response. Subjects were offered the option of continuing for an additional 6 months of treatment. Moclobemide-treated patients continued to improve while some placebo-treated patients relapsed.

Brofaromine

Brofaromine differs from moclobemide in that, in addition to inhibiting MAO, it also inhibits the reuptake of serotonin. There are three published placebo-controlled studies of brofaromine for the treatment of SAD. In the first study, conducted by van Vliet et al. (1992) 30 patients with SAD were randomized to 12 wk of fixed-dose (150 mg/d) brofaromine or matching placebo. Brofaromine was found to be superior to placebo on the LSAS.

Fahlen et al. (1995) also used a 12-wk fixed-dose design to compare 150 mg/d brofaromine vs. placebo in 77 patients with SAD. The brofaromine group experienced significantly greater improvement than the placebo group in both the CGI and LSAS. At endpoint 78% of the patients in the brofaromine group were much or very much improved, compared to 23% in the placebo group.

In the third published trial, Lott et al. (1997) compared brofaromine ($n = 52$) with placebo ($n = 50$) in a 10-wk, flexible-dose design. Brofaromine was started at 50 mg/d and titrated up to 150 mg/d as clinically indicated. Brofaromine exceeded placebo in terms of response rates (50% vs. 19%). Similarly, mean LSAS scores were significantly more improved with brofaromine (from 81.8 at baseline to 62.6 at endpoint) than with placebo (from 79.8 to 70.7). However, the endpoint LSAS score for the brofaromine group was 62.6, still in the clinical range, suggesting the need for additional treatment.

Selective serotonin reuptake inhibitors* (SSRIs) *and venlafaxine

The efficacy and tolerability of SSRIs in the treatment of depression and other anxiety disorders encouraged researchers to systematically study the use of SSRIs in SAD.

Paroxetine

Paroxetine is at present the most extensively studied and together with sertraline and venlafaxine, the only FDA-approved medications for the treatment of SAD. There are four published placebo-controlled studies of paroxetine. The first study compared paroxetine up to 50 mg/d vs. placebo over 11 wk after a 1-wk single-blind, placebo run-in (Stein et al., 1998). On an intent-to-treat basis with 183 patients, response rates were 55.0% for paroxetine vs. 23.9% for placebo. Changes in total scores on the LSAS were 30.5 points for paroxetine vs. 14.5 points for placebo, a highly significant difference.

A second multicentre flexible-dose study conducted in Europe and South Africa involved 290 randomized patients in a 12-wk double-blind comparison of 20–50 mg/d paroxetine vs. placebo also after a 1-wk placebo run-in period. The response rate for paroxetine was 65.7% vs. 32.4% for placebo (Baldwin et al., 1999). Mean change on the total LSAS was 29.4 points for paroxetine vs. 15.6 points for placebo. Paroxetine

was statistically superior to placebo from week 4 onwards.

In a third study, conducted in Sweden by Allgulander (1999), 92 patients were randomized to paroxetine ($n=44$) or placebo ($n=48$) for 3 months. Patients were started at 20 mg/d paroxetine or placebo, and the dose increased by 10 mg/d every week. Similarly to the Baldwin et al. (1999) study, significant differences in efficacy between treatments were noted after 4 wk, and increased through the trial. At the end of the study 70% of the patients on paroxetine and 8% of the patients on placebo had a CGI of 'much improved' or 'very much improved' and were considered responders.

In a fourth study (Liebowitz et al., 2002), 384 patients meeting DSM-IV criteria for SAD were randomly assigned to receive fixed-dose paroxetine, 20 mg ($n=97$), 40 mg ($n=95$), 60 mg ($n=97$), or placebo ($n=95$) once daily in a 1:1:1:1 ratio for 12 wk, after a 1-wk single-blind, placebo run-in. Patients treated with 20 mg/d paroxetine, had significantly greater improvement on mean LSAS total scores compared to those receiving placebo ($p<0.001$), while the incidence of responders, based on the CGI-I rating, was significantly greater with 40 mg/d paroxetine than with placebo ($p=0.012$). Patients treated with paroxetine (20 and 60 mg), also had significantly better responses on the social item of the Sheehan Disability Scale than did patients treated with placebo ($p<0.019$).

Fluvoxamine

Two double-blind studies have investigated the efficacy of fluvoxamine in SAD. van Vliet et al. (1994) randomized 30 patients to 12 wk of fluvoxamine at 150 mg/d or placebo-controlled. Defining response as a reduction $\geqslant 50\%$ in LSAS, 7 patients on fluvoxamine (46%) and 1 (7%) on placebo were classified as responders at the end of week 12. The fluvoxamine group also did better than the placebo group in a variety of other dimensions such as generalized anxiety, sensitivity rejection, and hostility.

Stein et al. (1999) conducted a larger, multicentre placebo-controlled study ($n=92$) with a mean dose of 202 mg/d fluvoxamine (S.D. = 86). The results showed that 43% on fluvoxamine responded compared to 23% on placebo, a significant difference. LSAS decreased by 22.0 points for fluvoxamine vs. 7.8 points for placebo, a drug–placebo difference similar to the one found in the paroxetine trials. Fluvoxamine was also superior to placebo on the work functioning and family life/home functioning subscales but not the social life functioning subscale of the SDS.

Sertraline

The SSRI sertraline has been studied in four controlled trials. The first study consisted of a flexible-dose, cross-over, placebo-controlled trial that included 10 patients with generalized SAD. Statistically significant changes were seen on the LSAS with sertraline at a mean dose of 134 mg/d (S.D. = 69) but not placebo (Katzelnick et al., 1995). In a larger, controlled trial Van Ameringen et al. (2001) randomized 204 patients to sertraline or placebo for a period of 20 wk. Sertraline was started at 50 mg/d and increased by 50 mg/d every 3 wk after the fourth week of treatment. The maximum allowed dose was 200 mg/d. The mean dose of sertraline at the end of the study was 147 mg/d (S.D. = 57). Response was defined as a score of 'much improved' or 'very much improved' on the CGI. In the intent-to-treat sample, the response rate of sertraline (53%) was statistically superior to that of placebo (29%).

The third study (Blomhoff et al., 2001) investigated the efficacy of sertraline, exposure therapy or their combination administered alone or in combination in a general-practice setting. Patients ($n=387$) received 50–150 mg sertraline or placebo for 24 wk. Patients were additionally randomized to exposure therapy or general medical care. Combined sertraline and exposure and sertraline were significantly superior to placebo. In contrast, there were no significant differences observed between exposure- and non-exposure-treated patients.

In the most recent study, Liebowitz et al. (2003) randomly assigned 211 patients to sertraline or placebo using a flexible-dose design (maximum dose of 200 mg/d). At week 12, sertraline produced a significantly greater reduction in the LSAS compared to placebo. Using a CGI-I score of 2 or less as the criterion for response, more patients in the sertraline group (47%) than in the placebo group (26%) were considered responders at the end of the study.

Fluoxetine

To date there is only one placebo-controlled study of fluoxetine for SAD. Kobak et al. (2002) randomized 60 subjects to 14 wk double-blind of fluoxetine or placebo. Dose was fixed at 20 mg for fluoxetine during the first 8 wk of double-blind treatment; during the final 6 wk, the dose could be increased every 2 wk by 20 mg to a maximum of 60 mg/d. At the end of the study no

significant differences were found between fluoxetine and placebo. In this study a slightly higher than usual placebo response rate was found.

Venlafaxine

In a recent study (Liebowitz et al., unpublished observations), 279 adult outpatients with generalized SAD were randomized to venlafaxine extended release (ER) or placebo. The LSAS and the CGI were the primary outcome measures. Venlafaxine ER was superior to placebo on both measures. At week 12, the percentage of responders (defined as those patients who had a score of 1 or 2 on the CGI-I scale) and remitters (defined as individuals with an LSAS $\leqslant 30$) was significantly greater in the venlafaxine ER group than in the placebo group (response: 44% vs. 30%; remission: 20% vs. 7% respectively). Patients experienced no unexpected or serious adverse events.

There are at present other studies with SSRIs and venlafaxine that are at different stages in the prepublication process. Preliminary reports of those studies appear to largely confirm the findings presented here.

Benzodiazepines

Benzodiazepines have long been used for treatment of anxiety, although to date only clonazepam, alprazolam and bromazepam have been studied for SAD in the context of controlled clinical trials. Davidson et al. (1993) investigated the efficacy of clonazepam for the treatment of SAD in a 10-wk double-blind study with 75 patients. The mean dose of clonazepam at the end of the study was 2.4 mg/d. Seventy-eight per cent of the patients on clonazepam and 20% of those on placebo had a CGI of 'much improved' or 'very much improved' and were considered responders. The clonazepam group improved more than the placebo group in the LSAS and the work and social subscales of the SDS.

In the only published study of bromazepam for SAD, Versiani et al. (1997) randomized 30 patients to bromazepam (up to 36 mg/d) or placebo for 12 wk. Actual mean dose of bromazepam was 21 mg/d. At the end of the study, bromazepam was superior to placebo on the LSAS, CGI, Sheehan Disability Scale and other secondary outcome measures. The main side-effects were sedation and some degree of cognitive disturbance.

There has been only one double-blind study of alprazolam, in which Gelernter et al. (1991) compared phenelzine, alprazolam, placebo, and CBT (see section on non-reversible MAOIs). The mean alprazolam dose was 4.2 mg/d (S.D. = 1.3). Only 38% of patients on alprazolam were considered responders at 12 wk.

Other medications

Although most the research on the pharmacological treatment of SAD has investigated the efficacy of MAOIs, benzodiazepines, and SSRIs, there has also been some research on the efficacy of other medications. Pande et al. (1999) conducted 14-wk trial of gabapentin vs. placebo in 69 patients with SAD. Reductions in the LSAS were 27 points with gabapentin vs. 12 points with placebo, a 15-point difference that was statistically significant. Using a rating of 'much improved' or 'very much improved' as the criterion for response, 32% of patients in the gabapentin group were classified as responders compared to 14% in the placebo group. Sixty-two per cent of responders were on 3600 mg/d gabapentin, the highest allowed dose in the study, suggesting that high doses of gabapentin may be needed to achieve response in SAD.

Barnett et al. (2002) conducted an 8-wk, double-blind, placebo-controlled evaluation of olanzapine. Patients ($n = 12$) were randomized to either olanzapine ($n = 7$) or placebo ($n = 5$). An initial dose of 5 mg/d was titrated to a maximum of 20 mg/d. Primary measures included the Brief Social Phobia Scale (BSPS; Davidson et al., 1991) and Social Phobia Inventory (SPIN; Connor et al., 2001). Seven subjects completed all 8 wk of the study, 4 in the olanzapine group and 3 in the placebo group. In the intent-to-treat analysis, olanzapine yielded greater improvement than placebo on the primary measures: BSPS ($p = 0.02$) and SPIN ($p = 0.01$). Both treatments were well tolerated, although the olanzapine group had more drowsiness and dry mouth.

Beta-blockers are commonly used on an 'as needed' basis for non-generalized social phobia, based on anecdotal evidence and analogue studies of anxious performers. While the results of controlled trials suggest that beta-blockers are not effective in the treatment of the generalized type, the subsamples of patients with non-generalized subtype have been too small to perform meaningful analysis. Beta-blockers have minimal side-effects but should be avoided in patients with asthma, diabetes and certain heart diseases.

Finally, two studies with buspirone have failed to find differences from placebo for SAD patients (Clark and Agras, 1991; van Vliet et al., 1997), although a small open trial suggests that it might have some value as an augmentation strategy (Van Ameringen et al., 1996).

Use of the meta-analysis as a basis for evidence-based practice

Although clearly not a substitute for direct comparisons between medications within clinical trials, meta-analytical techniques can help resolve questions that individual studies might not be designed to answer. Meta-analysis is a statistical technique (or family of techniques) that allows the systematic combination and analysis of independent studies in order to obtain global estimates of the variable under investigation, such as medication efficacy. Meta-analytical techniques can provide more objective and precise (i.e. with smaller standard errors of the mean) estimates of group or subgroup treatment effects than narrative reviews of individual trials (Rosenthal, 1984). These techniques can assess the robustness of such estimates for each medication by testing for heterogeneity across studies and conducting sensitivity analyses (Greenhouse and Iyengar, 1994). They are more objective because they can eliminate the subjective differential weighting of studies that can occur in qualitative reviews. Meta-analytical techniques allow the comparison of individual studies and the comparison of a group of studies vs. a single study, and take into account the number of patients and studies when generating confidence intervals (CIs) for such comparisons. Comparisons involving smaller numbers of patients or studies tend to generate wider CIs, and are less likely to be statistically significant (Rosenthal, 1984; Wolf, 1986).

Meta-analysis of Gould et al. (1997)

The first meta-analysis to assess the efficacy of medication for SAD was carried out by Gould et al. (1997). They conducted a comprehensive computer-based search using relevant key terms such as social phobia/SAD, avoidant personality disorder and others. The authors established a priori that only trials that employed a control group would be included in the meta-analysis. The authors' search included unpublished articles reported in the Dissertation Abstract database or presented at relevant conferences. In addition, they reviewed the reference sections of articles located using the previous references. The authors initially identified 41 articles, but only 24 finally met inclusion/exclusion criteria. Reasons for exclusion were lack of adequate comparison group and use of mixed samples (i.e. study patients with SAD and patients with other anxiety disorders, such as agoraphobia or panic disorder). Of the 24 studies included, only 10 had a treatment arm that included medication, one of which was an interim report of a larger study.

Table 2. Meta-analysis of Gould et al. (1997)

Drug group	Effect size	Dropout rate (%)	No. of studies
MAOIs	0.64	13.8	5
Benzodiazepines	0.72	12	2
SSRIs	2.73	3	2
Beta blockers	−0.08	−22	3
Buspirone	−0.5	22	1

One of the problems encountered by Gould et al. (1997) was the variety of measures used to assess treatment outcome in studies of SAD. Those measures included behavioural avoidance tests, self-report questionnaires, blind and unblinded clinician-rated measures of change and physiological measures (e.g. heart rate or galvanic skin response). Following the recommendation of Rosenthal (1991), the authors decided to average across effect sizes when several dependent measures for the same construct were reported in a study. If a measure was mentioned in the Methods section but not presented in the Results section of a study, it was assumed to be non-significant and assigned a $p=0.5$, and an effect size was subsequently derived using conventional methods. Effect sizes used Glass's delta procedure. Glass's delta is identical to the more frequently used Cohen's d, except that in Glass's delta the denominator is the standard deviation of the control group, instead of the overall standard deviation of the treatment and control groups. In addition to calculation of effect sizes, the authors assessed the heterogeneity of effect sizes across studies using the χ^2 test (Wolf, 1986).

Gould et al. (1997) found that the mean effect size for pharmacotherapy of SAD was 0.62, with a 95% CI of 0.42–0.82. Because this CI did not include 0, it indicated that pharmacotherapy was superior to placebo. The overall dropout rate for all studies was 13.7%. The authors also reported effect sizes and dropout rates for groups of medications. The effect size of MAOIs (which included phenelzine and moclobemide) was 0.64, with a dropout rate of 13.8%. Benzodiazepines had an effect size of 0.72 and a dropout rate of 12%. The meta-analysis also included two studies conducted with SSRIs: the first study, conducted with fluvoxamine, had an effect size of 2.73 and a dropout rate of 3%, whereas the second one, a small cross-over of sertraline study had an effect size of 1.05, with zero dropout rate. In contrast atenolol and buspirone were not different from placebo. The results of this meta-analysis are summarized in Table 2.

One interesting feature of this meta-analysis is that the authors assessed the effect of gender on effect size. Simple regression analysis found no difference between sex distribution and effectiveness of treatment. However, it is important to note that the studies did not report results separately for males and females and the meta-analysis assessed the pharmacotherapy and psychotherapy studies together, possibly introducing confounders in the analysis.

The authors also included a separate meta-analysis of long-term treatment outcome. Only one pharmacotherapy study reported data on long-term follow up. Although those data suggested a limited continued improvement, they have to be interpreted with great caution due to the study's obvious limitations. Gould et al. (1997) also conducted a comparison of pharmacotherapy vs. cognitive–behavioral vs. combined treatment. They did not find any significant differences between the three conditions. However, given the differences in the control groups between pharmacotherapy and psychotherapy studies, and the limited statistical power of test of differences in effect sizes, those results are difficult to interpret.

Meta-analysis of Van der Linden et al. (2000)

A second meta-analysis was reported by Van der Linden et al. (2000). In that paper, the authors first reviewed the efficacy of the SSRIs for SAD using 25 reports of pharmacological clinical trials, 8 of which were placebo-controlled. In the second part of the paper, they used the data of the randomized trials to conduct a formal meta-analysis. They estimated the effect size of the SSRIs and also presented data on the effect size of placebo-controlled trials of MAOIs, RIMAs and clonazepam.

One innovative aspect of this meta-analysis is that it reported estimates using two measures of effect size, the odds ratio (OR) and Cohen's d (the mean difference between the treatments divided by the pretreatment standard deviation of the placebo and control groups combined), probably the two most commonly used measures in meta-analytical reviews. The OR was used to compare the percentage of responders in the drug and placebo drugs. Cohen's d was used to compare the improvement in LSAS scores between the active treatment and placebo groups.

Van der Linden et al. (2000) found a wide range in the estimates of effect size of the medications. However, with the exception of two moclobemide studies, all other studies showed superiority of drug over placebo. The results were consistent across the two measures of effect sizes used, increasing the credibility of their results. Although formal comparisons between drug classes were not performed, it appeared that SSRIs ($n=8$) and clonazepam ($n=1$) had the largest effect sizes.

One limitation of this study is that it did not report the search strategy, thus making it difficult to replicate. Similarly, inclusion and exclusion criteria were not clearly specified and might have been different from those used in the Gould study. However, the Van der Linden study confirmed the initial finding of the Gould meta-analysis of large effect sizes of SSRIs and benzodiazepines.

Meta-analysis of Fedoroff and Taylor (2001)

A third meta-analysis, conducted by Fedoroff and Taylor (2001), included both psychological and pharmacological treatment of social phobia. The authors used computerized searches complemented by manual searches and consultation with social anxiety researchers and relevant drug companies. Criteria used to identify eligible trials included: participants had received a DSM-III, DSM-III-R or DSM-IV diagnosis of generalized SAD; four or more patients had been included in the study; sufficient information was provided to calculate effect sizes; outcome measures were broad measures of SAD with acceptable levels of reliability and validity. The authors examined drug classes (e.g. SSRIs) rather than specific medications (e.g. paroxetine or sertraline). However, they conducted tests of heterogeneity to determine whether there were any outlying effect sizes within these treatment conditions. Treatment conditions were examined only if there were four or more trials in that condition, as the authors considered this the minimal number of trials needed to make meaningful comparisons across conditions.

Effect size was calculated using Cohen's d and individual effect sizes were weighted by the sample size to obtain overall estimates of effect size for each condition. This procedure, not reported in previous meta-analyses of SAD, allows for effect sizes of larger trials to make a greater contribution than effect sizes from small trials. Because intent-to-treat data were not available for many studies, the authors conducted their analyses based on completer data. In contrast to previous meta-analyses, which only included randomized trials, Fedoroff and Taylor also included uncontrolled trials.

One important innovation of this meta-analysis was the use of the random effect model, which assumes that studies analysed are a random sample of the studies that could have been conducted, allowing for a

generalization of the results. In contrast, the fixed effects model assumes that the studies included constitute the whole population of studies and thus does not allow for the generalization of the results beyond those studies (the random effects model is generally preferred at present). In addition, they conducted the first comparison of effect sizes across drug classes by the use of 95% CIs. Confidence intervals that do not overlap are indicative of significant differences between the two groups compared, whereas overlapping intervals indicate that the differences are not significant.

Because there are reports suggesting that observer-rated measures tend to yield larger effect sizes than self-report measures, the authors performed separate meta-analyses for the two types of measures. Similar to the procedure used by Gould et al. (1997) when several measures were reported in a trial, a composite measure was derived by averaging the effect sizes of the individual measures. Prior to constructing the combined effect sizes the authors tested for within-study differences in effect sizes using different outcome measures and found those differences were not significant.

Fedoroff and Taylor (2001) found a remarkable homogeneity of effect sizes within each drug class, with only three studies generating heterogeneity according to the χ^2 test for heterogeneity. In all three cases the effect sizes of the heterogeneous studies were greater than those of the other studies in their drug classes. The authors also found that the various drug treatments differed in terms of sex but not in terms of age. However, a one-way analysis of covariance (ANCOVA) using the (unweighted) effect size of the study as the outcome variable and the treatment condition and per cent of women in the study as covariates indicated that gender did not influence outcome.

Somewhat surprisingly the authors also found that the CIs of double-blind and non-double-blind, controlled vs. uncontrolled, and group vs. individual trials overlapped with one another, indicating no difference in effect size. Similarly, they also found that there were not differences in the rates of drop out by drug class. Consistent with the two previous meta-analyses, using self-report measures they found that the largest mean effect sizes for the acute treatment were for benzodiazepines and SSRIs, which were not significantly different from each other. However, when examining the 95% CI, there was no overlap between the CI of benzodiazepines and the CI of MAOIs, cognitive therapy or cognitive therapy with exposure, indicating a greater treatment efficacy for benzodiazepines. The CI of SSRIs, however, did overlap with these treatment conditions, indicating no difference between treatments. Results obtained using the observer-rated measures were in the same direction, but did not show any significant differences across treatment conditions.

Based on those results, Fedoroff and Taylor (2001) concluded that pharmacotherapies, particularly benzodiazepines and SSRIs, performed better than psychotherapies in the acute treatment of SAD. There were not enough available data to evaluate the long-term course of treatment with pharmacotherapy.

Blanco et al. (*In Press*)

We recently conducted a meta-analysis of the placebo-controlled studies of pharmacotherapy for social phobia using articles published between January 1980 and June 2001. In order to locate articles, we conducted computerized and manual searches of bibliographies in published manuscripts and consulted researchers in the treatment of SAD. Following suggested guidelines, two authors extracted data independently. Relevance of examined papers was assessed using a hierarchical approach based on title, abstract, and the full manuscript. When the reviewers disagreed on assignment, the study was included in the next screening level, except at the last level, where decisions were made by consensus.

In order to improve the comparability of the results, it was decided a priori to use the LSAS (Liebowitz, 1987) as the primary outcome measure for the meta-analysis. The proportion of responders (defined as a score of 1 or 2 on the CGI) in each study was used as a secondary measure. Effect sizes for the LSAS were estimated using Hedges' g, an unbiased measure of the difference between two means (Hedges and Olkin, 1985). Effect sizes for the proportion of responders were estimated using the OR (Fleiss, 1994).

For trials that included more than one dose of medication in their design (Katschnig et al., 1997; Noyes et al., 1997) a statistical adjustment was used to generate a unique effect size for each study (Glesser and Olkin, 1994). This adjustment compensates for the stochastic dependency of the effect sizes (one effect size per dose level) within each study to provide unbiased estimates of overall effect size within a study. Similar to Fedoroff and Taylor (2001), we used a random effects model for the estimation of effect sizes. The Q statistic was used to assess homogeneity across trials. Innovative features of this meta-analysis included the use of intent-to-treat data and the assessment of publication bias, i.e. testing whether studies

Table 3. Effect sizes of meta-analysis of Blanco et al. (In Press)

Drug	No. of studies	Effect size based on LSAS[a] (95% CI)	Heterogeneity (LSAS)	Effect size based on the CGI[b] (95% CI)	Heterogeneity based on the CGI
SSRIs	6	0.65 (0.50–0.81)	No	4.1 (2.01–8.41)	Yes
Benzodiazepines	2	1.54 (−0.03–3.32)	Yes	16.61 (10.18–27.39)	Yes
Phenelzine	3	1.02 (0.50–1.02)	Yes	5.53 (2.56–11.94)	Yes
Moclobemide	4	0.30 (0.00–0.6)	Yes	1.84 (0.89–3.82)	Yes
Brofaromine	3	0.66 (0.38–0.94)	No	6.96 (2.39–20.29)	No
Gabapentin[c]	1	0.78 (0.29–1.27)	na	3.78 (1.88–7.54)	na
Atenolol	2	0.10 (−0.44–0.64)	No	1.36 (0.87–2.12)	No
Buspirone[c,d]	1	0.02 (−0.70–0.73)	na	–	na

[a] LSAS, Liebowitz Social Anxiety Scale.
[b] CGI, Clinical Global Impression Scale.
[c] At least two studies are necessary to test for heterogeneity.
[d] Study did not use the CGI.
na, Not applicable.

with positive results were more likely to have been published than negative trials.

The authors also conducted a quality assessment of the clinical trials to evaluate whether standard procedures such as randomization of patients had been conducted, blind maintained throughout the trial and appropriate statistical analyses performed. Finally, another innovative aspect of this meta-analysis was the performance of power analyses for the comparison between treatments.

Overall, the quality of clinical trials was very high. Our analysis found that clonazepam, based on a single study, had the largest mean effect size of all medications. The effect sizes of SSRIs and phenelzine were similar to each other and numerically (but not statistically) smaller than those of clonazepam. Because we found heterogeneity of effect sizes between moclobemide and brofaromine we estimated mean effect sizes for both medications separately. While the effect size of brofaromine was similar to that of SSRIs and MAOIs, the effect size of moclobemide was substantially lower. There were no significant differences across the three SSRIs that had been tested in placebo-controlled studies: paroxetine, sertraline and fluvoxamine. Gabapentin, which had not been included in previous meta-analysis, had an effect size similar to that of the SSRIs, suggesting that further research on the efficacy of this medication for the treatment of SAD might be warranted. The results were consistent across measures, i.e. LSAS and proportion of responders using the CGI. The effect sizes of the Blanco et al. (In Press) meta-analysis are summarized in Table 3.

Surprisingly, there was no indication of publication bias, i.e. no evidence that papers reporting positive results had been published while those with negative results had been less likely to be published. Power was generally low, due mostly to relatively low number of studies in all categories, except the SSRIs (although power was also low to test individual SSRIs).

Choice of medication

The evidence from the reviewed clinical trials and meta-analyses suggests that a number of medications are efficacious in the treatment of SAD. Moreover, based on the meta-analysis of Fedoroff and Taylor (2001), they appear to be superior to psychotherapy, at least in the acute phase of the treatment. Those data are consistent with recent findings of a randomized study of phenelzine vs. cognitive–behavioural psychotherapy (Heimberg et al., 1998), although more direct comparison would be highly desirable to confirm those findings.

Despite the use of slightly different approaches and inclusion criteria for the clinical trials, the meta-analyses also consistently indicate that benzodiazepines are the medication with the largest effect size for the treatment of SAD independently of whether the analysis included only the placebo-controlled or also the open-label studies. Other medications with moderate to large side-effects included the SSRIs, phenelzine, brofaromine and gabapentin. Based on those results, what should the practising clinician do? We believe that choice of medication should be guided by three principles: (1) the highest efficacy, based on the effect size of the medication (or medication group); and its reproducibility (determined by number of clinical trials published and overall number of patients

in those clinical trials); (2) the lowest potential for side-effects of the drug, and (3) the ability to treat commonly comorbid conditions. In addition, special considerations pertaining to each individual patient, such as presence of specific comorbidity or contra-indications should always be taken into account.

Based on those considerations, we believe that at present SSRIs constitute the first-line medication treatment of SAD. They have been more extensively tested in clinical trials than any other medication for SAD, have a moderate effect size, are generally well tolerated and are efficacious for the treatment of other disorders that are frequently comorbid with SAD, including major depressive disorder and other anxiety disorders. It is important to note, however, that although double-blind studies support the efficacy of paroxetine, sertraline and fluvoxamine, there are no published placebo-controlled studies of citalopram, and a recent study found no significant differences between fluoxetine and placebo (Kobak et al., 2002). The SNRI venlafaxine also appears to have efficacy based on preliminary reports and FDA approval.

Benzodiazepines constitute a reasonable alternative to SSRIs as a first-line treatment for SAD. Clonazepam and bromazepam, considered separately, have shown large effect sizes in the individual randomized trials. However, as shown in our meta-analysis, the results of those two studies show heterogeneity of effect sizes. When combined into a single category, the CI for the effect size of clonazepam and bromazepam included 0, suggesting that the estimates of their effect sizes are unstable. In addition, the only published study of alprazolam did not show significant differences from placebo, raising further reservations to the use of benzodiazepines as first-line treatment, although it is possible that there might be intra-group differences in their efficacy for the treatment of SAD.

Part of the difficulty in assessing the effect size of benzodiazepines is that it is based on only three controlled trials that included a relatively low number of patients. Furthermore, benzodiazepines, in contrast with SSRIs, are not efficacious in the treatment of some of the psychiatric disorders, such as major depressive disorder, that are frequently comorbid with SAD. One additional consideration in the use of benzodiazepines is that epidemiological and clinical studies have shown high comorbidity of SAD with alcohol abuse and dependence. However, there is no evidence that use of prescribed benzodiazepines is associated with abuse liability in individuals without a history of substance abuse disorders. Overall, we think that these considerations make benzodiazepines a less preferred initial option for most patients.

Another alternative would be the use of phenelzine (or another irreversible MAOI, although those have been less systematically studied). Until relatively recently, phenelzine was considered the gold standard in the treatment of SAD. However, results from the meta-analyses suggest that its efficacy is not superior to that of the SSRIs or clonazepam, although it has never been directly compared to those medications. Phenelzine is often well tolerated, and as shown by the Gould meta-analysis, does not seem to be associated with higher dropout rates than other medications. The main barrier to treatment with phenelzine and other irreversible MAOIs is the need for the patient to follow a low tyramine diet, and the subsequent risk of hypertensive crisis if the diet is not followed. In addition, although clinical experience with MAOIs is extensive, relatively few patients with SAD have been treated in clinical trials using phenelzine compared to SSRIs. Thus, there is less systematic evidence to support the use of MAOIs than the use of SSRIs as first-line treatment.

Gabapentin showed an effect size similar to those of the SSRIs in the only published trial and it is safe and generally well tolerated. Therefore, it is a promising alternative to the other agents. However, the gabapentin trial is somewhat unusual in that response rates to placebo and drug were substantially lower than in other clinical trials of SAD. It is possible that the sample may have had some atypical characteristics that may account for this pattern of response. In any case, further studies to confirm the efficacy of gabapentin in SAD appear warranted.

The RIMA brofaromine also appeared as a promising alternative. Unfortunately, its development was stopped by the manufacturer prior to marketing, for reasons unrelated to its safety or efficacy in social anxiety. The results of our analyses suggest that brofaromine might have found a therapeutic niche in the treatment of social phobia. In contrast, the clinical trials of moclobemide provide much less support for its use, although it is probably efficacious in some patients.

How long should treatment last?

Although the research to date has provided answers to the most pressing questions regarding acute treatment of SAD, a number of questions remain unanswered. Only recently have researchers started to conduct the studies that can provide evidence-based answers for those questions. One important question, frequently asked by patients, is how long to continue in treatment once they respond to medication. A number of studies have looked at that question.

Versiani et al. (1992) reported 50% loss of treatment gains in the 2 months following discontinuation of phenelzine responders under double-blind conditions after 16 wk of treatment. Liebowitz et al. (1992) also reported relapse in one-third of patients over 2 months following discontinuation after 16 wk of phenelzine treatment. In our initial collaborative study, responders to 12 wk of acute treatment were maintained on phenelzine for an additional 6 months, during which there was a 23% relapse (Liebowitz et al., 1999). Continued responders were then discontinued from medication and followed for an additional 6 months, during which time there was an additional 30% relapse. Supporting the concept that concomitant CBT, may help maintain the gains following cessation of medication is the finding of Gerlernter et al. (1991), who reported no loss of phenelzine's effectiveness after 2 months of untreated follow up. In this study, unlike those of the Versiani or Liebowitz groups cited above, phenelzine was combined with detailed self-exposure instructions during acute treatment.

In the first study of discontinuation using an SSRI, patients were treated with paroxetine in an 11-wk open trial followed by 12 wk of double-blind, placebo-controlled discontinuation (Stein et al., 1996). Relapse rates were 13% with continued paroxetine vs. 63% with gradual switch to placebo. Given that the discontinuation of paroxetine was gradual, and placebo was substituted, the high relapse rate may indicate that 11 wk is too brief a treatment period for most patients. In a more recent study, Stein et al. (2002c) treated 437 patients for SAD with paroxetine for 12 wk. Of those, 323 responded and agreed to continue treatment for an additional 24 wk. Patients continuing treatment were randomized to paroxetine ($n=162$) or placebo ($n=161$). A total of 257 patients completed the study (136 paroxetine-treated and 121 placebo-treated). Significantly fewer patients relapsed in the paroxetine group than in the placebo group (14% vs. 39%; OR, 0.24; 95% CI, 0.14–0.43; $p<0.001$). Furthermore, at the end of the study, a significantly greater proportion of patients in the paroxetine group showed improvement as shown on the CGI-I rating compared to the placebo group (78% vs. 51%; OR, 3.66; 95% CI, 2.22–6.04; $p<0.001$).

In another study 203 patients were randomized to sertraline or placebo. Sertraline was superior to placebo with response rates of 53% vs. 29% in the intent-to-treat sample at the end of 20 wk (Van Ameringen et al., 2001). Responders to sertraline were entered into a 24-wk discontinuation trial, where they were randomized to continue on drug or switch abruptly to placebo (Walker et al., 2000). Relapse rates were 4% for patients continued on sertraline vs. 36% for those switched to placebo, a significant difference. An additional 20% of patients switched to placebo were prematurely discontinued due to adverse events vs. 0% for those continued on sertraline. Total premature discontinuation by the end of the 24-wk follow-up was 60% for patients switched to placebo vs. only 12% for those continued on sertraline, a highly significant difference. Thus, this data again suggest that even after 5 months of SSRI treatment, relapse rates are high after discontinuation.

Although data are still limited, the available evidence suggests that discontinuation of medication after 12–20 wk of treatment results in increased risk for relapse compared to maintenance on medication after that time period. Whether longer treatment periods with medication or the addition of psychotherapy can protect against such relapse is currently unknown. At present it appears reasonable to maintain treatment for at least 3–6 months after the patient responds to treatment, with longer periods considered in individuals cases, due to the lack of available systematic evidence.

What is the management of treatment-resistant cases?

The first question in the management of treatment-resistant cases is how to define them. Stein et al. (2002b) recently analysed pooled data from three placebo-controlled studies of paroxetine, including a total of 829 patients to determine predictors of response. Demographic, clinical, baseline disability, duration of treatment and trial variables were included. After adjusting for the other covariates, only duration of treatment was a predictor of treatment response. The authors found that 46 (27.7%) out of 166 non-responders to paroxetine at week 8 were responders at week 12. The authors concluded that an optimal trial of medications should continue beyond 8 wk. At present there is no information on the probability of response of patients who have not responded by week 12. It appears reasonable to try a new medication if the patient has not shown any response at that time. If there has been a partial response, it might be preferable to try to augment the response using another efficacious medication, such as a benzodiazepine or neurontin, although no study has systematically tested any of those strategies.

Reasons for treatment resistance

As with any other medical condition, the next step is to identify the sources of non-response. Again, there is a

paucity of information to guide this search. Probably an important source of therapeutic failure is non-adherence to treatment, which may have resulted in sub-optimal medication doses or duration of treatment. If that is the case, the reasons for departures from recommended treatment should be explored and remedied.

A second potential source of treatment resistance is the presence of a comorbid psychiatric disorder. Clinical trials tend to exclude patients with comorbid disorders. Those that allow for comorbidity do not report treatment response stratified by presence or absence of comorbidity. Thus, there is a lack of systematic knowledge regarding the influence of comorbidity on treatment response. We recently completed an open-label study of citalopram in patients with primary SAD and comorbid depression. Here 67% of patients completed the study, and the response rate was 67% for SAD and 76% for major depressive disorder (Schneier et al., 2003). Therefore, in that study response rates were similar to those found in clinical trials without comorbid depression. Whether presence or absence of other comorbid disorders will result in similar (lack of) impact is unknown.

Other specific reasons for decreased efficacy may include comorbid medical conditions or individual pharmacokinetic characteristics (such as in rapid metabolizers or drug interactions).

Management strategies

Augmentation with medication

To the best of our knowledge, only two studies have partially addressed augmentation strategies. In the first study, conducted by Van Ameringen et al. (1996), 10 patients with generalized social phobia and who had obtained only partial response to an adequate trial of an SSRI, were studied for 8 wk. At endpoint the mean dose of buspirone was 45.0 mg/d (S.D. = 10.8) and the dose range was 30–60 mg/d. Seven (70%) patients were considered responders with a CGI of 1 or 2, and three (30%) patients were considered non-responders. However, the small sample size and the lack of control condition limit the interpretability of this study.

Stein et al. (2001) reported a double-blind, placebo-controlled study about pindolol potentiation of paroxetine for SAD. Patients on paroxetine were randomly assigned to receive either 5 mg pindolol or placebo for 4 wk. Responders were identified by a CGI rating of change as 'very much improved' relative to the start of treatment. The results showed that pindolol was not superior to placebo for augmenting the actions of paroxetine. In this study pindolol was not used in treatment-resistant cases. However, the fact that it failed to increase response rates in non-resistant patients and that there are no clinical trials supporting the efficacy of beta-blockers in generalized SAD suggests that it might not be a first-line agent for augmentation.

Pharmacological alternatives for augmentation include any combination of drugs with demonstrated efficacy for SAD, provided their combined use is not contra-indicated. Thus, an SSRI plus clonazepam or gabapentin, or clonazepam plus phenelzine appear as reasonable options. In contrast, the combination of phenelzine and an SSRI is absolutely contra-indicated. However, these recommendations are purely based on clinical experience. There are no systematic data to evaluate the efficacy of those combinations.

Psychotherapy

Although not the topic of this review, there is substantial evidence demonstrating the efficacy of CBT for SAD. Therefore, it is intuitively appealing to combine, either simultaneously or sequentially, two treatments that are efficacious in their own right (medication and psychotherapy) and which probably have very different mechanisms of action. Very preliminary data from our group suggest that this may be a beneficial strategy. However, much more evidence is needed to confirm these initial findings.

The treatment of non-generalized SAD

This review has focused on the generalized subtype of SAD, which is most impairing and is the most common form among treatment-seeking patients. The non-generalized subtype, most commonly characterized by phobia of public speaking or other performance situations, has been much less studied. Prominent sympathetic nervous system symptoms of racing heart, tremor and sweating in anxious performers led early researchers to study the acute effects of beta-adrenergic blockers in these 'analogue' subjects, who were not formally assessed for SAD. Nearly a dozen small single-dose, placebo-controlled, cross-over studies in the 1970s and 1980s reported efficacy for propranolol and other beta-blockers for anxious musical performers, public speakers and students taking a test (see Potts and Davidson, 1995 for review). On this basis, beta-blockers are currently widely used on an 'as needed' basis for persons with non-generalized SAD, since as needed medication is often preferred by

patients who fear predictable and occasional performance situations. Benzodiazepines have also seen clinical use in this population, and may have the benefit of decreasing the anticipatory anxiety, such as not being able to sleep the night prior to a performance. However, some patients find that benzodiazepine effects of sedation or cognitive slowing may outweigh their anxiolytic benefits. Although SSRIs and MAOIs have not been studied in non-generalized subtype samples, clinical impressions suggest that, when used daily, they may also benefit performance anxiety.

Conclusion

Over the last few years the empirical basis for the pharmacological treatment of SAD has expanded substantially and there are now a number of medications with substantial evidence of treatment efficacy. Future, cumulative meta-analyses should continue to update our base of knowledge about the relative efficacy of different medications in the treatment of SAD. At the same time, there are still important gaps in our knowledge. Those gaps constitute important second-generation questions for research in SAD. Another area of future research should be the progressive linkage of biological findings and therapeutic strategies, so that treatment becomes not only evidence-based, but also theory-driven. Unfortunately, our understanding of the biology of SAD is quite limited.

Finally, although SAD often begins in childhood or adolescence, only one published randomized trial, recently completed by the Research Unit on Pediatric Psychopharmacology Anxiety Study Group (2002), has specifically addressed pharmacotherapy in these populations, although preliminary results from another study appear to confirm these findings (Wagner, 2003). Early treatment of SAD in children holds theoretical promise for reduction of long-term morbidity and comorbidity. Carefully designed studies are needed to assess the risks and benefits of medication treatment in SAD and to compare it to other alternatives such as age-adapted CBT.

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