International Journal of Neuropsychopharmacology (2013), **16**, 235–249. © CINP 2012
doi:10.1017/S1461145712000119

REVIEW

The evidence-based pharmacotherapy 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 pharmacological 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 co-morbid disorders, tolerability and safety, selective serotonin reuptake inhibitors (SSRIs) and venlafaxine should be considered 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 monoamine oxidase inhibitors, reversible inhibitors of monoamine oxidase A, benzodiazepines or gabapentin. Cognitive-behavioural is a well-established alternative first line therapy that may also be a helpful adjunct in non-responders to pharmacological treatment of SAD.

Received 24 May 2011; Reviewed 22 June 2011; Revised 16 December 2011; Accepted 18 January 2012; First published online 21 March 2012

Key words: Pharmacological treatment, social anxiety disorder, social phobia.

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. Recent epidemiological studies suggest that the lifetime prevalence of SAD may be as high as 12% (Grant *et al.* 2005; Kessler *et al.* 1994, 2005*a*). SAD generally begins in the mid-teens, is associated with substantial impairments in vocational and social functioning (Davidson *et al.* 1993; Schneier *et al.* 1992*a*, *b*) and often follows a chronic, unremitting course (Amies *et al.* 1983; Marks, 1970; Öst, 1987). The DSM-IV (APA, 2000) describes a generalized subtype, characterized by distressing or disabling fears in most social situations. By contrast, individuals with the non-generalized subtype typically fear only a few performance situations, most commonly, public speaking.

The current review updates a previous one published in 2003 (Blanco *et al.* 2003*a*, *b*). We first summarize the available evidence for the pharmacological management of SAD, focusing on the published randomized clinical trials, which are summarized in Table 1. Because there are few head-to-head comparisons of medication treatments, we rely primarily on meta-analytic reviews to estimate and compare the relative efficacy of different medications.

In order to provide a foundation for identifying evidence-based pharmacological treatments of SAD, we conducted a search using electronic databases (Medline, PreMedline and PsychINFO) for the years 1980–2010 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 consulted with other colleagues regarding published manuscripts on trials involving medication for the treatment of SAD, as well as recent published guidelines for evidence-based treatment of SAD (Baldwin *et al.* 2005;

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

Drug class	Drug	Author	Sample size	Duration	Dose (mg/d)	Response rates (%)	Medication placebo
MAOIs	Phenelzine[a]	Liebowitz *et al.* (1992)	51	8 wk	45–90	64	23
	Phenelzine[b]	Gelernter *et al.* (1991)	64	12 wk	30–90	69	20
	Phenelzine[c]	Versiani *et al.* (1992)	52	8 wk	15–90	81	27
	Phenelzine	Heimberg *et al.* (1998)	64	12 wk	15–75	52	27
	Phenelzine	Blanco *et al.* (2010*a*, *b*)	128	24 wk	15–90	49	33
RIMAs	Moclobemide[b]	Versiani *et al.* (1992)	52	8 wk	100–600	65	20
	Moclobemide	Katschnig *et al.* (1997)	578	12 wk	300–600	44	32
	Moclobemide	Noyes *et al.* (1997)	506	12 wk	75–900	35	33
	Moclobemide	Schneier *et al.* (1998)	75	8 wk	100–400	18	14
	Moclobemide	Stein *et al.* (2002 *a*, *b*, *c*)	390	12 wk	450–750	43	30
Benzodiazepines	Clonazepam	Davidson *et al.* (1993)	75	10 wk	0.5–3	78	20
	Clonazepam	Munjack *et al.* (1990)	23	8 wk	0.5–6	90	10
	Clonazepam	Ontiveros *et al.* (2008)	27	16 wk	3.4 mean dose	65	30
	Bromazepam	Versiani *et al.* (1997*a*, *b*)	60	12 wk	3–27	83	20
	Alprazolam[b]	Gelernter *et al.* (1991)	65	12 wk	2.1–6.3	38	23
SSRIs	Fluvoxamine	van Vliet *et al.* (1993)	30	12 wk	150	46	7
	Fluvoxamine	Stein *et al.* (1999)	86	12 wk	202 mean dose	43	23
	Fluvoxamine (CR)	Westenberg *et al.* (2004)	300	12 wk	100–300	48	44
	Fluvoxamine (CR)	Davidson *et al.* (2004*a*)	279	12 wk	100–300	34	17
	Paroxetine	Stein *et al.* (1998)	182	12 wk	10–50	55	22
	Paroxetine	Baldwin *et al.* (1999)	290	12 wk	20–50	66	33
	Paroxetine	Allgulander (1999)	92	12 wk	20–50	70	8
	Paroxetine	Liebowitz *et al.* (2002)	384	12 wk	20–60	66	28
	Paroxetine	Stein *et al.* (2002*a*, *b*, *c*)	323	24 wk	20–50	78	51
	Paroxetine	Seedat & Stein (2004)	28	10 wk	20–40	79	43
	Paroxetine (CR)	Lepola *et al.* (2004)	370	12 wk	12.5–37.5	57	30
	Paroxetine	Allgulander *et al.* (2004)	434	12 wk	20–50	66	36
	Paroxetine	Lader *et al.* (2004)	839	24 wk	20	80	66
	Paroxetine	Wagner (2003)	322	16 wk	10–50	78	38
	Paroxetine	Liebowitz *et al.* (2005*a*, *b*)	440	12 wk	25–50	63	36
	Sertraline[d]	Katzeknick *et al.* (1995)	12	10 wk	50–200	50	9
	Sertraline	van Ameringen *et al.* (2000)	204	20 wk	50–200	53	29
	Sertraline	Walker *et al.* (2000)	50	24 wk	50–200	96	64
	Sertraline	Blomhoff *et al.* (2001)	387	24 wk	50–150	40	24
	Sertraline	Liebowitz *et al.* (2003)	211	12 wk	50–200	47	26
	Fluoxetine	Kobak *et al.* (2002)	60	8 wk	20–60	40	30
	Fluoxetine	Davidson *et al.* (2004*b*)	295	14 wk	10–60	51	32
	Fluoxetine	Clark *et al.* (2003)	60	16 wk	20–60	33	16
	Escitalopram	Lader *et al.* (2004)	839	24 wk	5–20	54	39
	Escitalopram	Kasper *et al.* (2005)	358	12 wk	10–20	54	39
	Escitalopram	Montgomery *et al.* (2005)	371	24 wk	10–20	78	50
	Venlafaxine (ER)	Rickels *et al.* (2004)	272	12 wk	75–225	50	34
	Venlafaxine (ER)	Allgulander *et al.* (2004)	434	12 wk	75–225	69	36
	Venlafaxine (ER)	Liebowitz *et al.* (2005*a*)	271	12 wk	75–225	44	30
	Venlafaxine (ER)	Liebowitz *et al.* (2005*b*)	440	12 wk	75–225	59	36
	Venlafaxine (ER)	Stein *et al.* (2005)	395	28 wk	75–225	58	33
β-blocker	Atenolol[a]	Liebowitz *et al.* (1992)	51	8 wk	50–100	30	23
	Atenolol	Turner *et al.* (1994)	72	12 wk	25–100	33	6

Table 1 (*cont.*)

Drug class	Drug	Author	Sample size	Duration	Dose (mg/d)	Response rates (%)	Medication placebo
Other	Buspirone	van Vliet *et al.* (1997)	30	12 wk	15–30	27	13
	Buspirone	Clark & Agras (1991)	34	6 wk	32 mean dose	57	60
Other antidepressants	Nefazodone	van Ameringen *et al.* (2007)	105	14 wk	300–600	31	24
	Mirtazapine	Muehlbacher *et al.* (2005)	66	10 wk	30	26	5.4
	Mirtazapine	Schutters *et al.* (2010)	60	12 wk	30–45	13	13
Anticonvulsants	Gabapentin	Pande *et al.* (1999)	69	14 wk	900–3600	38	14
	Levetiracetam	Zhang *et al.* (2005)	18	7 wk	500–3000	22	14
	Pregabalin	Pande *et al.* (1999)	135	10 wk	150–600	43	22
	Pregabalin	Feltner *et al.* (2011)	329	11 wk	300, 450, 600	29.8	19.7
Atypical antipsychotics	Olanzapine	Barnett *et al.* (2002)	12	8 wk	5–20	60	0

MAOIs, Monoamine oxidase inhibitors; RIMA, reversible inhibitors of MAOI-A; SSRIs, selective serotonin reuptake inhibitors.
[a] Study had three arms: phenelzine; atenolol; placebo.
[b] Study had three arms: phenelzine; alprazolam; placebo.
[c] Study had three arms: phenelzine; moclobemide; placebo.
[d] Study had a cross-over design.

Bandelow *et al.* 2008). In this brief review we attempt to provide evidence-based answers to three main questions: (1) What should be the first-line pharmacological treatment? (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*)

MAOIs were the first medications to be widely studied as a treatment for SAD. Six double-blind, placebo-controlled trials have consistently demonstrated the efficacy of phenelzine in the treatment of SAD, resulting in symptomatic and functional improvement (Blanco *et al.* 2010*a*; Gelernter *et al.* 1991; Guastella *et al.* 2008; Heimberg *et al.* 1998).

Overall, substantial evidence shows that phenelzine and probably other irreversible, non-selective MAOIs are highly effective in the treatment of many patients with SAD. However, concerns regarding side-effects and safety of the non-reversible MAOIs, particularly the risk of hypertensive crisis if a low-tyramine diet and related precautions are not strictly followed, led to the development of the reversible inhibitors of MAOI-A (RIMAs).

RIMAs

Compared to non-reversible MAOs, RIMAs have a significantly lower risk of potentiating the dangerous pressor effect of tyramine, which allows for relaxation or total elimination of dietary restrictions. Other MAOI side-effects such as fatigue and hypotension also occur less often with RIMAs. Unfortunately, RIMAs appear to be less effective than MAOIs and are not available in the United States. Moclobemide is currently the only RIMA available for the treatment of SAD.

Moclobemide. Five double-blind placebo controlled studies of moclobemide have produced mixed results, suggesting modest efficacy in the treatment of SAD. The results of these studies indicate that whereas moclobemide appears better tolerated and safer than phenelzine, it is clearly less efficacious in the treatment of SAD (Versiani *et al.* 1992).

Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

SSRIs and SNRIs have been studied widely because of their efficacy, safety and tolerability compared to earlier medications. More than 20 placebo-controlled trials have shown that SSRIs are highly efficacious in the treatment of SAD and six meta-analyses have supported their efficacy (Blanco *et al.* 2003*a*, *b*; Fedoroff & Taylor, 2001; Gould *et al.* 1997; Hedges *et al.* 2007; Seedat & Stein, 2004; van der Linden *et al.* 2000). In conjunction with their favourable side-effect profile and their efficacy for co-morbid depression, these findings have established SSRIs as a first-line medication for SAD. Paroxetine (immediate release and extended release), sertraline, extended-release fluvoxamine and extended-release venlafaxine are the only medications that are FDA-approved for the indication of SAD.

Paroxetine. There are 11 published placebo-controlled studies of paroxetine and all have found it to be superior to placebo for the treatment of SAD (Allgulander, 1999; Baldwin *et al.* 1999; Lader *et al.* 2004; Lepola *et al.* 2004; Liebowitz *et al.* 2002, 2005*a*, *b*; Seedat & Stein, 2004; Stein *et al.* 1998, 2002*a*, *b*, *c*; Wagner, 2003).

Fluvoxamine. Four double-blind studies have investigated the efficacy of fluvoxamine in SAD. Results from these studies indicate that fluvoxamine is superior to placebo for reduction of SAD symptoms, including anxiety, sensitivity to rejection and hostility, and for increase in overall functioning (Davidson *et al.* 2004*b*; Stein *et al.* 1999; van Vliet *et al.* 1994; Westenberg *et al.* 2004).

Sertraline. Five placebo-controlled studies have demonstrated the efficacy of sertraline (Blomhoff *et al.* 2001; Katzelnick *et al.* 1995; Liebowitz *et al.* 2003; van Ameringen *et al.* 2001; Walker *et al.* 2000). Furthermore, sertraline is more effective than placebo in preventing relapse (Walker *et al.* 2000). A recent re-analysis of the Blomhoff *et al.* (2001) study suggested that sertraline and exposure therapy may have an additive effect (Blanco *et al.* 2010*a*, *b*).

Fluoxetine. Early uncontrolled studies of fluoxetine also suggested that it could be efficacious in the treatment of SAD (Black *et al.* 1992; Schneier *et al.* 1992*a*; Sternbach, 1990; van Ameringen *et al.* 1993). However, results from more recent studies are mixed (Clark *et al.* 2003; Davidson *et al.* 2004*a*; Kobak *et al.* 2002) Overall, these findings suggest that fluoxetine may have some efficacy in the treatment of SADs, but the results appear less robust that those of other SSRIs.

Escitalopram and citalopram. Results from placebo-controlled trials of escitalopram have found it to be superior to placebo in reducing SAD symptoms and preventing relapse (Kasper *et al.* 2005; Lader *et al.* 2004; Montgomery *et al.* 2005). A small placebo-controlled study also found that citalopram was well tolerated and superior to placebo (Furmark *et al.* 2005).

Venlafaxine. Five large, placebo-controlled trials have supported the efficacy of venlafaxine, a SNRI, for SAD (Allgulander *et al.* 2004; Liebowitz *et al.* 2005*a*, *b*; Rickels *et al.* 2004; Stein *et al.* 2005). At doses typically prescribed, SSRIs and SNRIs have similar pharmacological properties, safety profiles and efficacy, so they share the established role in the treatment of SAD as the first-line pharmacological agents.

Other antidepressants

A placebo-controlled study provided initial support for the efficacy of mirtazapine, a presynaptic adrenoceptor antagonist, in the treatment of SAD (Muehlbacher *et al.* 2005). However, another recent study (Schutters *et al.* 2010) failed to confirm that finding. Nefazodone, which has both 5-HT reuptake and 5-HT_{2A} receptor blockade properties, had negative results in the only published placebo-controlled study of this medication (van Ameringen *et al.* 2007). Tricyclic antidepressants do not appear particularly useful in the treatment of SAD either (Simpson *et al.* 1998; Zitrin *et al.* 1983).

Benzodiazepines. Two studies of clonazepam have reported significant improvement as compared to placebo (Davidson *et al.* 1993; Munjack *et al.* 1990). Davidson and colleagues examined the efficacy of clonazepam in a placebo-controlled study of 75 patients, where 78% of the treatment group were classified as responders *vs.* 20% of the placebo group (Davidson *et al.* 1993). In the only published placebo-controlled study of alprazolam for SAD, only 38% of patients were considered responders, which did not differ significantly from the response rate with placebo, and symptoms had returned 2 months after discontinuation of alprazolam (Gelernter *et al.* 1991). Use of bromazepam, a benzodiazepine marketed outside the US, has also been reported to be efficacious

for the treatment of SAD (Versiani *et al.* 1997*a*). The most common adverse effect of benzodiazepines is sedation, which can interfere with the quality of performance. Benzodiazepines can also impair cognition and they have been associated with falls in the elderly. Because these medications have abuse potential, they should be avoided in persons with a history or substance abuse and dosage should be carefully monitored.

In summary, in double-blind studies, clonazepam and bromazepam, but not alprazolam, have been superior to placebo. Benzodiazepines also may be helpful on an as-needed basis for performance anxiety. The benefit of decreased anxiety must be balanced with the risks associated with benzodiazepine use.

β-Adrenergic blockers

Studies showing a connection between anxiety, signs and symptoms of peripheral arousal (i.e. tremor, palpitation and sweating) and increased plasma levels of norepinephrine led to early trials of β-adrenergic antagonists (β-blockers) in non-clinical samples of performers with high levels of anxiety. Many of these subjects would probably be currently diagnosed as having non-generalized SAD. The results of those trials indicate that β-blockers were successful in decreasing the autonomic manifestations of anxiety in performance situations.

Anecdotal experience also suggests that β-blockers are effective for non-generalized, circumscribed performance anxiety. However, β-blockers have not been proven superior to placebo in any controlled clinical trial for the treatment of diagnosed SAD. Thus, at present, they cannot be considered an evidence-based treatment for SAD.

Other medications

Buspirone. Buspirone is an azaspirone that acts as a full agonist on the 5-HT_{1A} autoreceptor and as a partial agonist on the post-synaptic 5-HT_{1A} receptor. Neither of the two controlled trials of buspirone in SAD demonstrated efficacy for it as monotherapy (van Vliet *et al.* 1997). Additionally, the dosage of buspirone that is possibly more efficacious appears to be in the upper range (60 mg/d), which may limit its usefulness on the basis of side-effects, such as nausea or headache (Schneier & Saoud, 1993).

Anticonvulsants. Gabapentin is thought to act as an $\alpha\,\delta$ calcium channel and reduce glutamate, although the exact mechanism of action is unknown. In the only published placebo-controlled trial of gabapentin for SAD, a significantly higher rate of response was observed among patients on gabapentin than on placebo (Pande *et al.* 1999).

In two randomized, double-blind trials, 600 mg/d pregabalin was superior to placebo (Feltner *et al.* 2011; Pande *et al.* 1999). Further studies will be needed to define the optimal dose, magnitude of the effect and long-term effect of pregabalin for SAD.

Levetiracetam is a novel anticonvulsant that modulates voltage-gated calcium channels in the central nervous system. A small randomized, placebo-controlled study by Zhang *et al.* (2005) found no differences in efficacy as compared to placebo.

Atypical antipsychotics

Some antipsychotics, including olanzapine (Barnett *et al.* 2002), quetiapine (Schutters *et al.* 2010) and risperidone (Simon *et al.* 2002), have been tested for the treatment of SAD in small studies. Some of these studies have suggested promise for these medications, but larger studies will be needed in order to clarify their effects, especially given their potential side-effect burden, including weight gain and metabolic syndrome.

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

To date, seven meta-analyses have examined the efficacy of medication for the treatment of SAD.

Meta-analysis of Gould et al. (1997)

The first meta-analysis to assess the efficacy of medication for SAD was carried out by Gould and colleagues and looked at 24 studies involving a control group (Gould *et al.* 1997). Effect sizes were found using Glass's δ procedure and heterogeneity of effect sizes across studies were calculated using the χ^2 test (Wolff, 1986).

Gould *et al.* found that the mean effect size for pharmacotherapy of SAD was 0.62. The effect size of MAOIs (which included phenelzine and moclobemide) was 0.64, whereas benzodiazepines had an effect size of 0.72. The meta-analysis also included two studies conducted with SSRIs. The first study, conducted with fluvoxamine, had an effect size of 2.73 whereas the second one, a small crossover of sertraline study, had an effect size of 1.05. A linear regression analysis found no gender differences in efficacy. The results of this meta-analysis are summarized in Table 2.

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

Drug group	Effect size	Drop-out rate	Number of studies
MAOIs	0.64	13.8%	5
Benzodiazepines	0.72	12%	2
SSRIs	2.73	3%	2
β-blockers	−0.08	22%	3
Buspirone	−0.5	22%	1

MAOIs, Monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors.

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

van der Linden *et al.* (2000) reviewed the efficacy of the SSRIs for SAD based on 25 clinical trials, eight of which were placebo-controlled, and used the data of the randomized trials to conduct a formal meta-analysis.

With the exception of two moclobemide studies, all studies showed superiority of drug over placebo. SSRIs ($n=8$) and clonazepam ($n=1$) had the largest effect sizes, confirming the initial finding of the Gould meta-analysis.

Meta-analysis of Fedoroff & Taylor (*2001*)

Fedoroff & Taylor (2001) included both psychological and pharmacological treatment of SAD and examined drug classes (e.g. SSRIs) rather than specific medications. Uncontrolled trials were also included in the meta-analysis.

The authors performed separate meta-analyses for observer-rated and self-report measures. Federoff & Taylor 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. Consistent with the findings of Gould and colleagues, the authors found no overall gender differences in treatment efficacy.

Federoff & Taylor also found that the confidence intervals (CI) of double-blind and non-double-blind trials overlapped with one another, indicating no difference in effect size. 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.

Blanco et al. (*2003a, b*)

We conducted a meta-analysis of the placebo-controlled studies of pharmacotherapy for SAD using studies published between January 1980 and June 2001. The Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) was used as the primary outcome measure and proportion of responders [defined as a score of 1 or 2 in the Clinical Global Impression Scale (CGI)] in each study was used as a secondary measure. Effect sizes were estimated using Hedges' *g* (Hedges & Olkin, 1985) for the LSAS and odds ratio for proportion of responders (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 & Olkin, 1994).

Quality assessment of the clinical trials was conducted to evaluate whether standard procedures such as randomization of patients had been conducted, blind maintained throughout the trial and appropriate statistical analyses performed. 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, phenelzine and clonazepam were not significantly different. Because we found heterogeneity of effect sizes between moclobemide and brofaromine, we estimated mean effect sizes for both medications separately. Whereas 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 between the three SSRIs that had been tested in placebo-controlled studies: paroxetine; sertraline; fluvoxamine. Gabapentin, which had not been included in previous meta-analyses, had an effect size similar to that of the SSRIs. The results were consistent across measures, i.e. LSAS and proportion of responders using the CGI. The effect sizes of the Blanco *et al.* meta-analysis are summarized in Table 3.

Hedges et al. (*2007*)

Hedges *et al.* sought to investigate the efficacy of selective SSRIs for the treatment of adult SAD and

Table 3. Effect sizes of meta-analysis of Blanco *et al.* (2003*a*, *b*)

Drug	No. of studies	Effect size based on LSAS (95% CI)	Heterogeneity (LSAS)	Effect size based on the CGI (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 to 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[a]	1	0.78 (0.29–1.27)	n.a.	3.78 (1.88–7.54)	n.a.
Atenolol	2	0.10 (−0.44 to 0.64)	No	1.36 (0.87–2.12)	No
Buspirone[b,c]	1	0.02 (−0.70 to 0.73)	n.a.	–	n.a.

LSAS, Liebowitz Social Anxiety Scale; CGI, Clinical Global Impression Scale; CI, confidence intervals; SSRIs, selective serotonin reuptake inhibitors.

[a] At least two studies are necessary to test for heterogeneity.

[b] Study did not use the CGI.

included 15 published randomized, double-blind, placebo-controlled trials using SSRIs (Hedges *et al.* 2007).

Effect sizes were measured with Cohen's *d*. The Q statistic was used to assess heterogeneity across studie, and a funnel-plot analysis was used to examine publication bias.

Results indicated that all SSRIs studies were significantly more efficacious than placebo. Furthermore, no significant differences were found between LSAS scores for the drugs paroxetine, sertraline, fluvoamine and fluoxetine.

Hansen et al. (*2008*)

This meta-analysis focused on the comparative efficacy of SSRIs and venlafaxine. Confirming findings from previous meta-analyses, it did not find significant differences in the efficacy of these medications.

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 & Taylor, they appear to be superior to psychotherapy, at least in the acute phase of the treatment. Those data are consistent with recent findings from two randomized trials of phenelzine *vs.* cognitive-behavioural psychotherapy (Blanco *et al.* 2010*a*, *b*; Heimberg *et al.* 1998). Two direct comparisons of psychotherapy *vs.* fluoxetine have failed to show superiority of medication over psychotherapy (Clark *et al.* 2003; Davidson *et al.* 2004*a*, *b*). However, as reviewed above, fluoxetine may be less efficacious than other SSRIs in the treatment of SAD. Additional direct comparisons of medication *vs.* psychotherapy 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, although this is based on a small number of trials. 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) highest efficacy, based on the effect size of the medication or medication group, and its reproducibility as determined by the number of clinical trials published and overall number of patients in those clinical trials; (2) lowest potential for side-effects of the drug; (3) ability to treat commonly co-morbid conditions. Furthermore, special considerations pertaining to each individual patient, such as presence of specific co-morbidity, contraindications or patient preference, should always be taken into account.

Based on those considerations, we believe that, at present, SSRIs constitute the first-line medication treatment of SAD for most patients. 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 co-morbid with SADs, including major depressive disorder (MDD) and other anxiety disorders. It is important to note, however, that, although double-blind

studies support the efficacy of paroxetine, sertraline, escitalopram, citalopram and fluvoxamine, evidence for the efficacy of fluoxetine appears to be weaker than for other SSRIs (Kobak *et al.* 2002). The SNRI venlafaxine appears to have similar efficacy to SSRIs, although it has been less extensively studied, and there are no published placebo-controlled studies of duloxetine. Most clinical trials for SAD have used dose ranges similar to those used for the treatment of MDD and, similar to findings in MDD, there is no clear evidence for a dose-relationship between SSRIs or SNRIs and treatment response (Liebowitz *et al.* 2002; Stein *et al.* 2005). Similarly, although there are no controlled comparisons of differences in response between MDD and SAD, an open trial reported that MDD symptoms responded more rapidly than SAD symptoms (Schneier *et al.* 2003).

Benzodiazepines constitute a reasonable alternative in cases when SSRIs are not efficacious or well tolerated. 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 (Blanco *et al.* 2003*b*). Furthermore, the only published study of alprazolam did not show significant differences from placebo, although all patients in that study also received exposure instructions. These heterogeneous findings may reflect differences in study design or patient samples. It is also possible that there may be within-group differences in benzodiazepine efficacy for the treatment of SAD.

Part of the difficulty in assessing the effect size of benzodiazepines is that it can be 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 MDD, that are frequently co-morbid with SAD. One additional concern about the use of benzodiazepines is that epidemiological and clinical studies have shown high co-morbidity 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. However, results from the meta-analyses suggest that its efficacy is not superior to that of the SSRIs or clonazepam. Although irreversible MAOIs are often well tolerated, the need to follow a low tyramine diet and the subsequent risk of hypertensive crisis if the diet is not followed constitute an important inconvenience for most patients. Furthermore, there is less systematic evidence to support the use of MAOIs than the use of SSRIs as first-line treatment. Gabapentin and pregabalin are also reasonable alternatives in cases when the previous medications fail.

How long should treatment last?

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 double-blind drug discontinuation in phenelzine responders 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). Persistent 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 cognitive behavioural therapy (CBT) may help maintain the gains following cessation of medication is the finding of Gelernter *et al.* (1991), who reported no loss of phenelzine's effectiveness after 2 months of untreated follow-up. Stein *et al.* (2002*a*, *b*, *c*) treated 437 SAD patients 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 or placebo. Significantly fewer patients relapsed in the paroxetine group than in the placebo group. Furthermore, at the end of the study, a significantly greater proportion of patients in the paroxetine group showed improvement as shown on the CGI rating compared to the placebo group.

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, these 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 unknown at present. Given the existing data, it appears reasonable to maintain treatment for at least 3–6 months after the patient responds to treatment, with longer periods considered in individual 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.* (2002*a*, *b*, *c*) 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 response using another efficacious medication, such as a benzodiazepine or gabapentin, 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. Probably an important source of therapeutic failure is non-adherence to treatment, which may have resulted in suboptimal 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 co-morbid psychiatric disorder. Clinical trials tend to exclude patients with co-morbid disorders (Blanco *et al.* 2008, 2010*b*). Thus, there is a lack of systematic knowledge regarding the influence of co-morbidity on treatment response. In an open label study of citalopram in patients with primary SAD and co-morbid depression, 67% of patients completed the study and the response rate was 67% for SAD and 76% for MDD (Schneier *et al.* 2003). In that study, response rates were similar to those found in clinical trials without co-morbid depression. Whether presence or absence of other co-morbid disorders will result in a similar lack of impact is unknown.

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

Management strategies

Augmentation with medication. A small number of studies have investigated augmentation strategies, although only one study has specifically examined treatment-resistant cases. In that study, conducted by van Ameringen *et al.* (1996), 10 patients with generalized SAD, who had obtained only partial response to an adequate trial of an SSRI, were studied for 8 wk after adding buspirone. Seven (70%) patients were considered responders with a CGI of 1 or 2. However, the small sample size and the lack of control condition limit the interpretability of this study.

Stein *et al.* (2001) conducted a placebo-controlled study of pindolol potentiation of paroxetine for SAD. Pindolol was not superior to placebo when used as an augmenting agent to paroxetine. In this study pindolol was not used in treatment-resistant cases and was started at the same time as paroxetine. 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 β-blockers in generalized SAD suggests that it might not be a first-line agent for augmentation.

Clonazepam has also been studied as treatment augmentation of paroxetine. Seedat & Stein (2004) randomized 28 patients to paroxetine plus clonazepam or paroxetine plus placebo. More clonazepam patients (79%) than placebo patients (43%) were classified as CGI responders, but the effect only approached

Table 4. Summary of placebo-controlled studies in the acute treatment of paediatric anxiety disorders

Drug class	Drug	Author	Sample size	Duration	Dose (mg/d)	Response rates (%)	Medication placebo
Benzodiazepines	Alprazolam	Simeon *et al.* (1992)	30	4 wk	0.25–3.5	88	61
	Clonazepam	Graae *et al.* (1994)	15	8 wk	0.25–2.0	75	25
SSRI	Fluoxetine	Black & Uhde (1994)	15	12 wk	0.6	67	11
	Fluoxetine	Birmaher *et al.* (2003)	74	12 wk	20	61	35
	Sertraline	Rynn *et al.* (2001)	22	9 wk	25–50	90	10

SSRI, Selective serotonin reuptake inhibitor.

significance ($p = 0.06$) in this small sample. Again, an important limitation of this study was its lack of focus on treatment-resistant cases. Nevertheless, clonazepam deserves further study as an augmentation or alternative treatment for patients who do not respond completely to an initial SSRI trial.

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

Psychotherapy. Recent work by our group has suggested that the combination of phenelzine and CBT is superior to either treatment alone (Blanco *et al.* 2010*a*, *b*). Therefore, providing CBT to treatment-resistant cases appears to be a reasonable strategy. However, more evidence is needed to confirm these initial findings and to see if they extend to other medication groups.

Similarly, preliminary studies have looked at D-cycloserine, a partial agonist at the NMDA receptor, as a possible augmenting agent for fear reduction in exposure therapy (Hofmann *et al.* 2006). Preliminary evidence has shown D-cycloserine to have a significant effect as compared to placebo in enhancing the effectiveness of an attenuated course of exposure therapy for the treatment of SAD (Guastella *et al.* 2008; Hofmann *et al.* 2006).

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 as well as in the general population (Grant *et al.* 2005). The non-generalized subtype, most commonly characterized by fear of public speaking or other performance situations, has been much less studied. Nearly a dozen small single-dose, placebo-controlled crossover studies in the 1970s and 1980s reported efficacy for propranolol and other β-blockers for anxious musical performers, public speakers and students taking a test (Potts & Davidson, 1995). On this basis, β-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. Similarly, although no published studies have directly examined the efficacy of SSRIs for non-generalized SAD, an analysis of three pooled paroxetine studies found no differences in response rates between generalized and non-generalized subtypes of SAD, suggesting that paroxetine may be efficacious for the non-generalized subtype. Whether this result extends to other SSRIs is unknown.

Although there is no published literature on this issue, benzodiazepines are also used in this population, based on clinical experience and may have the benefit of decreasing 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 impression suggests that, when used daily, they may also benefit performance anxiety.

Treatment of SAD in children

Although children and adolescents with SAD often have great impairment in their social and family relationships and academic life, this often goes

undiagnosed and untreated. Few studies of paediatric SAD have examined the efficacy of treatment modalities, so the role of pharmacotherapy for treatment of this disorder is less established than for adults. The first group of studies conducted in children included a wide range of anxiety disorders and some of them concentrated on selective mutism, a condition shown to greatly overlap with SAD (Birmaher *et al.* 1998; Black & Uhde, 1994; Dummit *et al.* 1996; Fairbanks *et al.* 1997; Golwyn & Sevlie, 1999; Kutcher *et al.* 1992). Only two studies have investigated the efficacy of benzodiazepines in this population (Graae *et al.* 1994; Simeon *et al.* 1992). Slightly more data are available on the efficacy of SSRIs. Several placebo-controlled trials have been conducted, providing substantial evidence of the efficacy of SSRIs and SNRIs in children aged 6–17 yr (Birmaher *et al.* 2003; Rynn *et al.* 2001; Williams & Miller, 2003). These are depicted in Table 4. The increasing concern about studies, mostly in depression, reporting an increased risk of suicidal ideation among adolescents treated with SSRIs or SNRIs led the FDA to add a warning in regard to the use of antidepressants in this population (Bridge *et al.* 2007). However, substantial evidence has shown that the increase in suicidal ideation is more linked to children with depressive disorders rather than anxiety (Gibbons *et al.* 2006).

Although replication is still needed and long-term effects are still unknown, a growing body of literature supports the efficacy of pharmacological treatments in children and adolescents. SSRIs and SNRIs are the pharmacological treatment of choice in this population, with response rates ranging from 36 to 77%, but concerns regarding the emergence of suicidal ideation suggest the need for close monitoring of these treatments in this population (Williams & Miller, 2003).

Conclusion

There are several medications with substantial evidence of treatment efficacy for SAD. 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, as pointed out in the second section of this review, 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.

Acknowledgements

Supported by NIH grants DA019606, DA020783 and DA023200 (to Dr Blanco) and by the New York State Psychiatric Institute (to Dr Blanco and Dr Schneier).

Statement of Interest

Dr Liebowitz reports the following potential conflict of interests. Equity ownership: ChiMatrix LLC, electronic data capture and Liebowitz Social Anxiety Scale. Consulting: Astra Zeneca, Wyeth, Pfizer, Takeda, Pherin, Lilly, Otsuka, Eisai. Licensing software or LSAS: GSK, Pfizer, Avera, Tikvah, Endo, Lilly, Indevus, Servier. Recent or current clinical trial contracts: Allergan, Pfizer, GSK, Astra Zeneca, Forest, Tikvah, Avera, Eli Lilly, Novartis, Sepracor, Horizon, Johnson and Johnson. Pherin, PGX Health, Abbott, Jazz, MAP, Takeda, Wyeth, Cephalon, Indevus, Endo, Ortho-McNeil, Gruenthal, Otsuka, Gruenthal. Dr Schneier reports consulting for GlaxoSmithKlein.

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