Chapter 22

Psychopharmacology for Social Anxiety Disorder

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Established treatments for social anxiety disorder include psychotherapy and pharmacotherapy. In this chapter we focus on pharmacological strategies.

Although some patients may be surprised by the idea of taking medication for a problem that they see as a long-standing personality trait, pharmacotherapy is a reasonable option for many individuals with social anxiety disorder, given the degree of associated impairment, and the efficacy of established medication treatments for the disorder. Pharmacological approaches to social anxiety disorder have been shown to substantially reduce avoidance and psychological distress. Furthermore, both cognitive and physical symptoms of anxiety can interfere with optimal performance and ultimately lead to avoidance of feared situations. Thus, medications that can directly decrease anxiety and physical symptoms typical of social anxiety disorder may help improve performance in social or professional situations. Finally, predisposition towards shyness and excessive concerns about social comparisons are likely to be strongly biologically based, given the early onset of behaviorally inhibited temperament, evidence of a significant genetic contribution from twin and family studies, and the biological salience of social hierarchies in the evolution of humans as a group-living species. These findings support the utility of biologically-based treatments.

A number of medications have been studied for the treatment of social anxiety disorder. Early reports suggested the potential value of monoamine oxidase inhibitors (MAOI), reversible inhibitors of MAO-A (RIMAS) and benzodiazepines. Over the last two decades, research has focused on the effects of SSRIs and SNRIs, although other medications, such as anticonvulsants and atypical antipsychotics have also been examined. Most clinical trials have included predominantly or exclusively patients with the generalized type of social anxiety disorder, as defined in DSM-III-R and DSM-IV (American Psychiatric Association, 1980, 2000). We present a review of the research progress on pharmacotherapy for social anxiety disorder over time, focused mainly on controlled trials.

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MEDICATION TREATMENTS

Irreversible, Nonselective Monoamine Oxidase Inhibitors

MAOIs were the first antidepressants to be widely studied as a treatment for social anxiety disorder. The suggestion that monoamine oxidase inhibitors (MAOIs) might have efficacy in the treatment of social anxiety disorder came from two different sources. One line of evidence came from studies of the use of phenelzine in atypical depression, whereas the second line consisted of four placebo-controlled studies of phenelzine on mixed phobic populations.

Five double-blind, placebo-controlled trials have studied the efficacy of phenelzine in social anxiety disorder. Liebowitz and colleagues (1992) randomized 85 patients to an eight-week trial of phenelzine, atenolol, or placebo. Mean doses of medication used were: phenelzine, 75.7 mg/day (SD = 16; range = 45–90 mg/day); and atenolol, 97.6 mg/day (SD = 10.9; range = 50–100 mg/day). Response rates, defined as a Clinical Global Impression Clinic Improvement (CGI-I) scale score ≤ 2, were: phenelzine, 64%; atenolol, 30%; and placebo, 23%. Both social and performance anxiety were reduced, and social and work function improved on phenelzine.

Gelernter and colleagues (1991) randomly assigned 65 patients to one of four groups: (1) cognitive-behavioral therapy (CBT), (2) phenelzine (range = 30–90 mg/day; mean = 55 mg/day), (3) alprazolam (range = 2.1–6.3 mg/day; mean = 4.2 mg/day), or (4) placebo. Duration of the trial was 12 weeks for all treatments. All pharmacotherapy patients were also given exposure instructions. Medication dosages were increased until all symptoms of social anxiety had disappeared, until the maximum medication dosage was reached or until side effects precluded further increases. Patients were considered responders if their final social anxiety disorder scores on the Fear Questionnaire (FQ; Marks and Matthews, 1979) were equal to or below a cut-off score based upon normative samples. According to that criterion, 69% of the patients taking phenelzine were responders, compared with 38% of those taking alprazolam, 24% of those receiving CBT, and 20% of those taking placebo.

In the third study, Versiani et al. (1992) treated 78 patients with social anxiety disorder with phenelzine, moclobemide, or placebo. The trial included three eight-week phases. In the acute phase, patients given phenelzine were titrated up to 90 mg/day or the highest tolerated dose (mean = 67.5 mg/day; SD = 15.0), and those given moclobemide were titrated up to 600 mg/day or the highest tolerated dose (mean = 570.7 mg/day; SD = 55.6). At week 8, phenelzine was superior to placebo on all global and social anxiety disorder measures. After the first eight weeks, non-responders, defined as those whose CGI did not change or worsened from baseline, were withdrawn from the study. All other patients entered the second eight-week phase, in which they continued with the same treatment. At the end of phase II, participants responding to placebo and those who relapsed in any of the active treatment groups were withdrawn from the study. Ninety-one percent and 82% of patients completing 16 weeks of treatment with

phenelzine and moclobemide respectively, were considered responders. For patients who continued to respond to active drugs, half continued on active treatment in phase III, and the other half were blindly switched to placebo. Patients in the active treatment group who were switched to placebo in the third phase of the study had an increase in the mean scores of all parameters at week 24, indicating that some patients relapse when treatment is discontinued. Moclobemide was also superior to placebo in this study (see section on Reversible Inhibitors of Monoamine Oxidase-A, below).

In the fourth study, Heimberg et al. (1998) compared phenelzine, placebo, an educational supportive group, or group CBT for 12 weeks (n = 133). Phenelzine and CBT were superior to the other groups, and phenelzine was also superior to CBT on some measures.

In the most recent study, Blanco et al. (2010) randomized 128 patients to phenelzine, CBT, combined CBT plus phenelzine, or placebo. There was a specific order of effects across treatments, with the largest reductions in social anxiety symptoms for the combined group, followed by each monotherapy, and the least reduction in the placebo group. Response rates followed the same pattern.

Two open trials studying the effect of the MAOI tranylcypromine on social anxiety disorder have been published. In the first one, Versiani et al. (1988) treated 32 patients with social anxiety disorder for up to one year. Of the 29 patients who completed at least one month of treatment, 62% showed marked improvement, 17% showed moderate improvement, and 21% showed no improvement. In all responders, improvement was maintained throughout the year. When tranylcypromine was discontinued, 62% of the patients relapsed to baseline within three months, and an additional 22% had a partial return of their symptoms. In a second study, an eight-week open trial that included 81 patients, Versiani et al. (1989) found statistically significant reductions in both CGI Scale severity and Liebowitz Social Anxiety Scale (LSAS) scores. Mean CGI Scale severity scores went from 5.2 (SD = 0.9) to 1.5 (SD = 1.0). LSAS scores changed from 90.4 (SD = 18.7) to 28.2 (SD = 17.9).

An open trial has examined the efficacy of oral selegiline, an irreversible MAOI, marketed for treatment of Parkinson's disease, which is selective for the MAO-B isozyme. Simpson et al. (1998b) administered 10 mg of selegiline divided into two oral doses of 5 mg a day to 16 individuals with social anxiety disorder. The group showed an average improvement of 33% in the LSAS total score and less than 20% (three out of 16) were considered respondents, suggesting limited efficacy of selegiline for social anxiety disorder.

Overall, substantial evidence shows that phenelzine and probably other irreversible, nonselective MAOIs are highly effective in the treatment of many patients with social anxiety disorder. However, the MAOI side-effect profile, particularly the risk of hypertensive crisis if a low-tyramine diet and related precautions are not strictly followed, led researchers to focus their attention and research efforts into other medications.

Reversible Inhibitors of Monoamine Oxidase-A (RIMAs)

The limitations of nonreversible MAOIs stimulated the development of the reversible inhibitors of MAO-A (RIMAs). RIMAs have a significantly lower ability to potentiate the depressor effect of tyramine, which allows for relaxation or total elimination of dietary restrictions. Other MAOIs' side effects such as fatigue and hypotension also seem to be much less common when RIMAs are used. Unfortunately, RIMAs appear to be less effective than MAOIs and are not available in the United States. Moclobemide and brofaromine (which is an SSRI in addition to a RIMA) are the only RIMAs that have been studied in the treatment of social anxiety disorder.

3Moclobemide

Five double-blind, placebo-controlled studies of moclobemide have produced mixed results. In the aforementioned study by Versiani and colleagues (1992), moclobemide was superior to placebo on a number of measures at the end of week 8. Fourteen (67%) of the 21 responders at week 8 who entered a continuation phase, were classified as responders at the end (week 16). Moclobemide was as effective as phenelzine on all measures, except on the social avoidance subscale of the LSAS and showed similar rates of side effects to those of placebo, especially in the second phase of the study.

In a much larger multicenter study, Katschnig and co-workers (1997) compared two doses of moclobemide (300 and 600 mg) with placebo using a double-blind design over a 12-week period. The 600 mg moclobemide group was superior to the placebo group on all measures, whereas the 300 mg moclobemide group was superior to placebo on the LSAS and Patient Impression of Change–Social Phobia scale. However, effect sizes were much smaller than those initially found by Versiani. In another large multicenter study, Noyes et al. (1997) found no significant improvement with five doses of moclobemide (75, 150, 300, 600, and 900 mg/day) compared to placebo in a 12-week double-blind study.

In a double-blind, flexible-dose study, Schneier et al. (1998) administered moclobemide (mean dose = 728 mg) or placebo to 77 patients with social anxiety disorder. At week eight, seven of the 40 (18%) moclobemide patients and five of the 37 (14%) placebo patients were considered responders. Moclobemide was superior to placebo on only two of 10 secondary outcome measures. Patients at least improved minimally on the CGI Scale after the eight weeks (n = 21) were offered eight additional weeks of the same treatment. Although some further improvement occurred on the CGI Scale in the moclobemide group, neither group showed significant changes on any continuous measures.

In the fifth study, Stein et al. (2002b) randomized 390 subjects with social anxiety disorder to moclobemide or placebo for 12 weeks. At week 12, 43% of patients in the moclobemide group and 31% in the placebo group were

considered responders, a statistically significant difference. Subjects were offered the option of participating in a continuation phase. Fifty patients on moclobemide and 40 on placebo continued with the same treatment for an additional six months. Moclobemide-treated patients continued to improve, whereas some placebo-treated patients relapsed. At the ninth month, in the moclobemide group 86% were considered responders, compared to 58% in the placebo group.

In summary, placebo-controlled studies of moclobemide have shown mixed results. Moclobemide appears better tolerated, but it is clearly less efficacious than phenelzine in the treatment of social anxiety disorder.

Brofaromine

Despite its classification as a reversible and selective type-A monoamine oxidase inhibitor (MAOI), brofaromine also has serotonin reuptake inhibitory properties. Three studies on brofaromine were conducted, as summarized in Table 22.1. Taken together, the studies suggested that brofaromine was efficacious in the treatment of social anxiety disorder. However, the development of brofaromine was stopped for reasons unrelated to its efficacy in social anxiety disorder and is not available for clinical purposes.

Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

SSRIs and SNRIs are currently considered the first-line treatment for social anxiety disorder based on their efficacy, safety and tolerability compared with other medication studied in earlier years, as well as their efficacy in the treatment of depression and other anxiety disorders. More than a dozen placebo-controlled trials have shown that SSRIs are highly efficacious in the treatment of social anxiety disorder and seven meta-analyses have supported their efficacy (Blanco et al. 2003; Canton J, 2012; Fedoroff & Taylor 2001; Gould et al. 1997; Hedges et al. 2007; Stein et al. 2004; van der Linden et al. 2000).

Although most patients can tolerate regular antidepressant starting doses, medication is frequently initiated at half or even a quarter of the usual effective dose, as seeking a rapid response is rarely the priority in this chronic condition, with further dose increases after the first week of treatment. Since some patients appear to benefit from higher doses, it is a common practice to increase the dose as tolerated in those who have no response after four weeks of treatment.

Although controlled trials have been reported for all the SSRIs, at present, paroxetine (immediate release and controlled-release), sertraline, venlafaxine ER (extended-release) and fluvoxamine (controlled-release) are the SSRIs and the SNRI approved by the Food and Drug Administration (FDA) for the treatment of social anxiety disorder. Trials comparing SSRIs with one another have not demonstrated that any one medication is superior to the others in the treatment of social anxiety disorder.

TABLE 22.1 Randomized Controlled Trials in the Treatment of Social Anxiety Disorder

Drug Class	Drug	Author	Sample Size	Duration	Dose Range	Dose Mean	Outcome Measure	Response Rates (%)	
					(mg/day)	(mg/day)		Med	Placebo
MAOIs	Phenelzine	Liebowitz et al., 1992	51	8 weeks	45–90	75.7	CGI-I	64	23
	Phenelzine	Gelernter et al., 1991	64	12 weeks	30–90	55	FQ	69	20
	Phenelzine	Versiani et al., 1992	52	16 weeks	15–90	67.5	CGI-I	91	27
	Phenelzine	Heimberg et al., 1998	64	12 weeks	15–75	59.64	SPDSC	52	27
	Phenelzine	Blanco et al., 2010	84	24 weeks	15–90	65.9	CGI-I	48	33
RIMAs	Moclobemide	Versiani et al., 1992	52	8 weeks	100–600	580.7	CGI-I	65	20
	Moclobemide	Katschnig et al., 1997	578	12 weeks	300 or 600	Fixed dose	CIC-SP	44	32
	Moclobemide	Noyes et al., 1997	506	12 weeks	75–900	Not given	CGI-I	35	33
	Moclobemide	Schneier et al., 1998	77	8 weeks	100–800	728	CGI-I	18	14
	Moclobemide	Stein et al., 2002	390	12 weeks	450–750	630	CGI-I	43	30
	Brofaromine	van Vliet et al., 1992	30	12 weeks	150	150	SPS	80	14
	Brofaromine	Fahlen et al., 1995	77	12 weeks	150	150	CGI-I	78	23
	Brofaromine	Lott et al., 1997	102	10 weeks	50–150	107.2	CGI-I	50	19

(Continued)

Drug Class	Drug	Author	Sample Size	Duration	Dose Range (mg/day)	Dose Mean (mg/day)	Outcome Measure	Response Rates (%) Med	Placebo
SSRIs/SNRIs	Paroxetine	Stein et al., 1998	182	12 weeks	20–50	36.6	CGI-I	55	22
	Paroxetine	Baldwin et al., 1999	290	12 weeks	20–50	34.7	CGI-I	66	33
	Paroxetine	Allgulander, 1999	92	12 weeks	20–50	Not given	CGI-I	70	8
	Paroxetine	Liebowitz et al., 2002	384	12 weeks	20–60	Fixed dose	CGI-I	66	28
	Paroxetine	Stein et al., 2002	323	24 weeks	20–50	37.21	CGI-I	78	51
	Paroxetine (CR)	Lepola et al., 2004	370	12 weeks	12.5–37.5	32.3	CGI-I	57	30
	Paroxetine	Allgulander et al., 2004	260	12 weeks	20–50	44.2	CGI-I	66	36
	Paroxetine	Lader et al., 2004	335	24 weeks	20	20	CGI-I	80	66
	Paroxetine	Liebowitz et al., 2005	280	12 weeks	25–50	46	CGI-I	63	36
	Sertraline	Katzelnick, 1995	12	10 weeks	50–200	133.5	LSAS	50	9
	Sertraline	Van Ameringen et al., 2001	204	20 weeks	50–200	146.7	CGI-I	53	29
	Sertraline	Walker et al., 2000	50	24 weeks	50–200	148	CGI-I	96	64
	Sertraline	Blomhoff et al., 2001	191	24 weeks	50–150	Not given	CGI-I	35	21
	Sertraline	Liebowitz et al., 2003	211	12 weeks	50–200	158.8	CGI-I	47	26
	Escitalopram	Lader et al., 2004	670	24 weeks	5, 10, 20	Fixed dose	CGI-I	76-88	66
	Escitalopram	Kasper et al., 2005	358	12 weeks	10–20	17.6	CGI-I	54	39

(Continued)

TABLE 22.1 Randomized Controlled Trials in the Treatment of Social Anxiety Disorder *(cont.)*

Drug Class	Drug	Author	Sample Size	Duration	Dose Range (mg/day)	Dose Mean (mg/day)	Outcome Measure	Response Rates (%) Med	Placebo
	Escitalopram	Montgomery et al., 2005	371	24 weeks	10, 20	Fixed dose	LSAS	78	50
	Citalopram	Furmark et al., 2005	24	6 weeks	40	40	CGI-I	50	8.3
	Fluvoxamine	Van Vliet et al., 1994	30	12 weeks	150	150	LSAS	47	7
	Fluvoxamine	Stein et al., 1999	86	12 weeks	50–300	202	CGI-I	43	23
	Fluvoxamine (CR)	Westenberg et al., 2004	300	12 weeks	100–300	209	CGI-I	48	44
	Fluvoxamine (CR)	Davidson et al., 2004a	279	12 weeks	100–300	174	CGI-I	34	17
	Fluoxetine	Kobak et al., 2002	60	8 weeks	20–60	38.3	CGI-I	40	30
	Fluoxetine	Davidson et al., 2004b	117	14 weeks	10–60	43.6	CGI-I	51	32
	Fluoxetine	Clark et al., 2003	40	16 weeks	20–60	Not given	SP Composite	33	16
	Venlafaxine (ER)	Rickels et al., 2004	272	12 weeks	75–225	178	CGI-I	50	34
	Venlafaxine (ER)	Allgulander et al., 2004	434	12 weeks	75–225	192.4	CGI-I	69	36
	Venlafaxine (ER)	Liebowitz et al., 2005a	271	12 weeks	75–225	165	CGI-I	44	30

(Continued)

Drug Class	Drug	Author	Sample Size	Duration	Dose Range	Dose Mean	Outcome Measure	Response Rates (%)	
					(mg/day)	(mg/day)		Med	Placebo
	Venlafaxine (ER)	Liebowitz el al., 2005b	440	12 weeks	75–225	201.7	CGI-I	59	36
	Venlafaxine (ER)	Stein et al., 2005	395	28 weeks	75–225	72.2 & 213.7	CGI-I	58	33
Other Anti-depressants	Mirtazapine	Muehlbacher et al., 2005	66	10 weeks	30	30	SPIN	26	5.4
	Mirtazapine	Schutters et al., 2010	60	12 weeks	30–45	Not given	CGI-I	13	13
	Nefazodone	Van Ameringen, 2007	105	14 weeks	300–600	493.9	CGI-I	31	24
Benzodiaz-epines	Alprazolam	Gelernter, 1991	65	12 weeks	2.1–6.3	4.2	FQ	38	23
	Clonazepam	Davidson et al., 1993	75	10 weeks	0.5–3	2.4	CGI-I	78	20
	Clonazepam	Munjack et al., 1990	23	8 weeks	0.5–6	2.75	CGI-I	90	10
	Clonazepam	Ontiveros el al., 2008	27	16 weeks	Not given	3.4	CGI-I	65	30
	Bromazepam	Versiani et al., 1997	60	12 weeks	3–27	21	CGI-I	83	20
Beta-blockers	Atenolol	Liebowitz et al., 1992	51	8 weeks	50–100,	97.6	CGI-I	30	23
	Atenolol	Turner et al., (1994)	72	12 weeks	25–100	Not given	CGI-I	13.3	6
Other	Buspirone	Clark et al., 1991	17	6 weeks	15–60	32	PRCAP	57	60
	Buspirone	Van Vliet et al., 1997	30	12 weeks	15–30	28.3	CGI-I	27	13

(Continued)

TABLE 22.1 Randomized Controlled Trials in the Treatment of Social Anxiety Disorder *(cont.)*

Drug Class	Drug	Author	Sample Size	Duration	Dose Range	Dose Mean	Outcome Measure	Response Rates (%)	
					(mg/day)	(mg/day)		Med	Placebo
Anticonvulsants	Gabapentin	Pande et al., 1999	18	7 weeks	500–3600	Not given	CGI-I	22	14
	Pregabalin	Pande et al., 2004	135	10 weeks	150 & 600	Fixed dose	CGI-I	29	10
	Pregabalin	Feltner et al., 2011	69	14 weeks	300, 450, 600	Fixed dose	LSAS	38	14
	Levetiracetam	Zhang et al., 2005	329	7 weeks	500–3000	2279	CGI-I	22	14
Atypical Antipsychotics	Olanzapine	Barnett et al., 2002	12	8 weeks	5–20	9	CGI-I	60	0
	Quetiapine	Vaishnavi et al., 2007	15	8 Weeks	400	400	CGI-I	20	0
Novel Treatments	Cannabidiol	Bergamaschi et al., 2011	24	1 session	600	600	**	**	**
	D-Cycloserine	Hofmann et al., 2006	27	4 weeks	50	50	SPAI	26	9
	D-Cycloserine	Guastella et al., 2008	56	4 weeks	50	50	SPAI	†	†
	D-Cycloserine	Hofmann et al., 2013	169	12 weeks	50	50	CGI-I	79.3	73.3

Notes: ** Multiple symptoms measured at different time points during a public speaking session. † Data not reported. CGI-I = Clinical Global Impression—Improvement Scale. FQ = Fear Questionnaire. SPDSC = Social Phobic Disorders Severity and Change Scales. CIC-SP = Clinical Impression of Change—Social Phobia Scale. SPS = Social Phobia Scale. LSAS = Liebowitz Social Anxiety Scale. SP Composite = Social Phobia Composite. SPIN = Social Phobia Inventory. SPAI = Social Phobia and Anxiety Inventory.

Paroxetine

Stein et al. (1998) randomized 187 patients with generalized social anxiety disorder to paroxetine of placebo for a 12-week trial. The initial dose of paroxetine was 20 mg/day, with weekly increases of 10 mg permitted after the second week of treatment, up to a maximum of 50 mg/day. The proportion of responders was higher in the paroxetine than in the placebo group (55% versus 24%) as determined by a CGI score of 1 or 2. Patients taking paroxetine (n = 94) had also greater mean improvement from baseline than did those taking placebo (n = 93) on secondary outcome measures.

Similar results were obtained by another large multicenter 12-week trial. Baldwin et al. (1999) in a double-blind, placebo-controlled study (N = 290), found a response rate of 66% in the paroxetine group and 32% in the placebo group.

In Sweden, Allgulander and colleagues (1999) conducted the third randomized controlled study of paroxetine. Ninety-two patients were randomized to paroxetine or placebo for 12 weeks. Patients were started at 20 mg/day of paroxetine or placebo, and the dosage was increased by 10 mg/day every week. At the end of the study, 70% of the patients on paroxetine and 8% of the patients on placebo were considered respondents, based on CGI scores.

In order to better determine the effectiveness and safety of various daily dosages of paroxetine, Liebowitz and colleagues (2002) conducted a 12-week double-blind, placebo-controlled trial. They randomly assigned 384 patients to receive either: 20 mg/day, 40 mg/day, or 60 mg/day of paroxetine or placebo. Although Liebowitz and colleagues, adopting a very conservative statistical approach, only considered the 20 mg/day dose to be superior to placebo, patients treated with paroxetine at any dosage showed significantly greater improvement compared with those receiving placebo on LSAS scores.

An additional study examined the long-term effects of paroxetine. Stein et al. (2002c) conducted a placebo-controlled study comprising an initial 12-week single-blind acute treatment phase and a subsequent 24-week randomized, double-blind maintenance treatment phase for respondents in the initial phase. Four hundred and thirty-seven adult patients with social anxiety disorder entered the acute phase, and 323 continued into the maintenance phase (162 in the paroxetine group and 161 in the placebo group). Significantly fewer patients relapsed in the paroxetine group than in the placebo group. Paroxetine treatment was also associated with decreased disability and increased well-being.

In a reanalysis of three randomized controlled trials, Stein et al. (2002a) studied the time course of response (ratings of much or very much improvement on the CGI) to paroxetine. Among responders by the 4th week in the paroxetine group, 84% remained responders at week 12. Of those considered responders at week 4 in the placebo group, 71% remained that way at week 12. Moreover, out of 166 patients classified as nonresponders at week 8, 28% became responders at week 12 after continuing treatment with paroxetine. Among non-responders

at week 8 in the placebo group, only 8.2% of subjects became responders at week 12, suggesting that an initial trial should last 12 weeks.

Additionally, Lepola et al. (2004) conducted a 12-week double-blind, placebo-controlled randomized trial comparing the controlled-release (CR) formulation of paroxetine (flexible dose of 12.5–37.5 mg/day) (n = 186) with placebo (n = 184). Statistically significant differences in favor of paroxetine CR compared with placebo were observed in the change from baseline to week 12 last-observation-carried-forward (LOCF) in LSAS total score and response rates (CGI $\leq$2).

In addition to these, two trials compared paroxetine with venlafaxine (Allgulander et al. 2004; Liebowitz et al. 2005b), one trial compared paroxetine with escitalopram (Lader et al. 2004), and one trial was conducted in children and adolescents (Wagner et al., 2004). These trials are described below in the venlafaxine, escitalopram, and children and adolescent sections.

Sertraline

Katzelnick et al. (1995) conducted the first controlled trial of sertraline for social anxiety disorder. Twelve patients were randomized to sertraline (dose range = 50–200 mg/day; mean dose = 133.5 mg/day; SD = 68.5) or placebo using a crossover design. Patients were assigned to receive a flexible dose of sertraline or placebo for 10 weeks, followed by taper and no treatment for two weeks, and finally crossed over to the other treatment for another 10 weeks. A statistically significant improvement on the LSAS was found in the sertraline group only.

In a larger, double-blind placebo-controlled trial, Van Ameringen et al. (2001) randomized 204 patients to sertraline (mean dose = 146.7 mg/day; SD = 57) or placebo for a period of 20 weeks. At the end of the 20-week period, 53% of sertraline-treated patients versus 29% of the placebo-treated patients were considered respondents as determined by the CGI-I score.

In order to examine the ability of sertraline to prevent relapse, the study included a continuation phase (Walker et al., 2000). Among sertraline-treated patients, those considered responders at the end of week 20 were randomly assigned again in a double-blind fashion to either continue sertraline or switch to placebo, whereas responders in the placebo group continued to receive double-blind placebo for 24 additional weeks. Significantly fewer patients in the sertraline-continuation group than in the placebo-switch group relapsed at study endpoint (4% versus 36%). Overall, the risk for relapse on placebo was ninefold the risk for relapse on sertraline.

In another study, Liebowitz et al (2003) randomly assigned 211 patients to sertraline (flexible dose up to 200 mg/day) or placebo. The authors reported a significant decrease in LSAS scores and higher response rates in the sertraline group compared to placebo at week 12 as determined by CGI criteria (47% versus 26%).

In a general-practice setting, Blomhoff et al. (2001) compared the efficacy of sertraline (dose range = 50-150 mg), exposure therapy or their combination administered alone or combined for 24 weeks. Patients were further randomized to either exposure therapy or general medical care. The combined treatment and sertraline alone were significantly superior to placebo. A reanalysis of those data (Blanco et al., 2010), suggested a gradation of increasing response from placebo, to exposure therapy alone, sertraline alone and combined treatment.

Escitalopram and Citalopram

Lader et al. (2004) conducted a randomized, double-blind, placebo-controlled, fixed-dose trial that compared placebo, escitalopram 5 mg, 10 mg, 20 mg, and paroxetine 20 mg for 24 weeks. At week 12, both 5 and 20 mg doses of escitalopram and paroxetine were significantly more efficacious compared to placebo. At week 24, escitalopram was superior to placebo at all doses, and 20 mg escitalopram was significantly superior to paroxetine from week 16 onwards.

Kasper et al. (2005) conducted a 12-week placebo-controlled trial in 358 patients who were randomized to receive 10-20 mg escitalopram (mean dose of 17.6 mg/day at week 12) or placebo. By the end of week 12, the response rate (54% versus 39%) and the decrease in LSAS scores was greater in the escitalopram group than in the placebo group.

A study conducted by Montgomery et al. (2005) examined the ability of maintenance treatment with escitalopram to decrease rates of relapse among responders to acute escitalopram treatment. In the first phase of the study, 517 patients entered an open-label, flexible-dose trial of escitalopram (10-20 mg/day) for 12 weeks. Patients who responded were then randomized to 24 weeks of either escitalopram, continuing the dose level administered at the end of the open trial, or placebo. There was a 22% relapse rate in the escitalopram group versus 50% rate in the placebo group, a statistically significant difference.

Pallanti et al. (2006) conducted a study of subjects with at least one previously unsuccessful course of treatment with paroxetine ($\geq$60 mg/day for $\geq$12 weeks). Patients meeting criteria for other Axis I diagnosis, including concurrent major depressive episode and marked depressive symptoms were excluded. Twenty-nine patients received open label escitalopram (mean dose = 18.5 mg/day) for 12 weeks. Low-dose benzodiazepines for insomnia were permitted. At the end of week 12, 48% of the patients were considered responders on the basis of the CGI-I score and reduction of >35% compared to baseline on the LSAS.

Some of these studies (Kasper et al., 2005; Lader et al., 2004a; Montgomery et al., 2005) were used for further analyses of the effect of escitalopram on different patient subgroups and symptom dimensions. Stein et al. (2004a) did an exploratory factor analysis of the LSAS and found that escitalopram was significantly superior to placebo on all six factors of the LSAS: social interaction, eating/drinking in public, speaking in public, assertiveness, observation fear, and partying. The analysis also found escitalopram to be effective regardless of

gender, severity and chronicity of the disorder, and the presence of comorbid depressive symptoms.

In contrast to the amount of information available on escitalopram, to date, only one small RCT of citalopram (dose = 20-40 mg/ day) for the treatment of social anxiety disorder has been published. It included 24 participants randomized 1:1 to citalopram or placebo. At the end of six weeks of treatment, the citalopram group had a significantly higher rate of improvement on the CGI than the placebo group (50% versus 8%) (Furmark et al., 2005). A smaller open-label trial of citalopram (mean dose = 55 mg; SD = 12.7 mg/day) included ten patients with generalized social anxiety disorder, of whom six had failed to respond or had not tolerated a prior medication treatment. Citalopram was well tolerated and patients improved significantly on all outcome measures (Simon et al., 2002).

Fluvoxamine

In a 12-week placebo-controlled study of fluvoxamine in 30 patients with social anxiety disorder van Vliet et al. (1994) found that fluvoxamine (50-150 mg/day) was superior to placebo. Forty-seven percent of patients taking fluvoxamine and 7% of those taking placebo were classified as responders to treatment (as determined by a 50% reduction in the LSAS). Among those taking fluvoxamine, 93% entered an additional 12-week continuation phase in which further improvement was observed.

In a multicenter randomized trial, Stein et al. (1999) found that fluvoxamine (dose range = 50-300 mg/day; mean dose = 202 mg/day; SD = 86) was superior to placebo. From week 8 onward, fluvoxamine was superior to placebo on all social anxiety disorder rating scales and at week 12. A greater number of patients in the fluvoxamine group than in the placebo group were considered as responders (43% versus 23%).

The controlled-release (CR) form of fluvoxamine was also investigated in a randomized controlled trial lasting 12 weeks (Westenberg et al., 2004). Fluvoxamine CR at flexible doses (dose range = 100–300 mg/day; mean dose = 209 mg/day) was significantly superior to placebo in almost all outcome measures. In a second, 12-week randomized control trial of fluvoxetine CR, Davidson et al. (2004a) confirmed the superiority of fluvoxamine (dose range = 100–300 mg/d) over placebo in a sample of 279 patients. Treatment with fluvoxamine CR resulted in significant improvements in symptoms associated with social anxiety disorder as early as week 4.

Fluoxetine

Early uncontrolled studies of fluoxetine also suggested that it could be efficacious in the treatment of social anxiety disorder (Black et al., 1992; Schneier et al., 1992; Sternbach, 1990; Van Ameringen et al., 1993). However, in a randomized study, Kobak et al (2002) found no significant difference between those receiving 14 weeks of fluoxetine (20–60 mg/day) or placebo. In a second

study, Clark et al. (2003) randomly assigned 60 patients to fluoxetine plus self-exposure, placebo plus self-exposure, or cognitive therapy in a 16-week trial. All three treatments resulted in significant improvement. Cognitive therapy was superior to fluoxetine plus self-exposure and placebo plus self-exposure from mid-treatment to the end of the booster period and at 12-month follow-up. There were no differences between fluoxetine plus self-exposure and placebo plus self-exposure.

In a third study, Davidson et al. (2004b) examined the efficacy of fluoxetine in a 14-week randomized, double-blind, placebo-controlled trial. In this two-site study, patients were randomized to fluoxetine alone, comprehensive cognitive behavioral therapy (CCBT) alone, placebo alone, fluoxetine plus CCBT or placebo plus CCBT. All active treatments were significantly better than placebo, but did not differ from each other. In the fluoxetine group, 50.9% were considered responders, 51.7% in the CCBT, 52.4% in the fluoxetine plus CCBT group, 50.8% in the CCBT plus placebo group, and 31.7% in the placebo group. Overall, these findings suggest that fluoxetine may have some efficacy in the treatment of social anxiety disorder, but the results appear less robust than those of other SSRIs.

Venlafaxine

Large randomized controlled trials have supported the efficacy of venlafaxine, an SRNI, for social anxiety disorder. Rickels et al. (2004) randomized 272 patients to venlafaxine extended-release (ER) at flexible doses (75 to 225 mg/day) or placebo for a 12-week period. As early as week 4, venlafaxine ER was superior to placebo on total LSAS scores and additional outcome measures. Subsequently, Liebowitz et al. (2005a) also found significantly greater rates of response (44% versus 30%) and remission (20% versus 7%) in the venlafaxine ER than in the placebo group.

Stein et al. (2005) conducted a 28-week multicenter randomized double-blind controlled trial. Three hundred and ninety-five subjects with generalized social anxiety disorder were randomized to either venlafaxine ER in a fixed low dose (75 mg/day), venlafaxine ER flexible higher dose (150–225 mg/day), or placebo. A greater and sustained improvement (58% versus 33%) and higher rates of remission (31% versus 16%) were observed in the venlafaxine ER groups (both 75 mg/day and 150–225 mg/day) compared to placebo. There were no significant differences in response and remission rates between the low and higher venlafaxine ER dosage groups.

As described before, two randomized trials of venlafaxine ER have included paroxetine as an active comparator in addition to placebo. In the first trial, Allgulander et al. (2004), randomly assigned patients to venlafaxine ER (75–225 mg/day), paroxetine (20–50 mg/day), or placebo for a 12-week period. Response rates of the venlafaxine ER and paroxetine groups were both significantly greater than those of the placebo group as early as week 3. However, a significant difference in remission rates emerged earlier in the venlafaxine group (week 4) than in paroxetine (week 8).

In the second trial, Liebowitz et al. (2005b) randomized a total of 440 patients with generalized social anxiety disorder to receive either: venlafaxine ER, paroxetine, or placebo for 12 weeks. Significantly greater reduction in LSAS mean score was observed for both venlafaxine and paroxetine groups when compared to placebo. Moreover, response rates for both the venlafaxine ER (58.6%) and the paroxetine group (62.5%) were significantly greater than those for the placebo group (36.1%).

Duloxetine

Simon et al. (2010) treated 39 individuals with social anxiety disorder for six weeks with open-label duloxetine 60 mg/day. Those with an LSAS score >30 at week 6 were randomized to an additional 18 weeks of duloxetine 60 mg/day or to duloxetine 120 mg/day. Duloxetine was associated with a significant LSAS reduction at week 6 and randomized participants overall continued to improve at week 24, but there were no differences between individuals whose dose increased to 120 mg/day compared to those who continued taking 60 mg/day. Although these data are promising, further studies are needed to establish the efficacy of duloxetine for social anxiety disorder.

In conclusion, a large number of randomized controlled trials have established the efficacy of both SSRIs and SNRIs in the treatment of generalized social anxiety disorder, although they have not been shown in direct comparisons to be superior to other medications or psychotherapy alone. No SSRIs and SNRIs have been established as superior in efficacy or acceptability to the others, although the published data on fluoxetine (Clark et al., 2003; Davidson et al., 2004b; Kobak et al., 2002), probably make it the less preferred medication in this class.

Other Antidepressants

Mirtazapine

Mirtazapine is a presynaptic adrenoceptor antagonist. In an early open label trial, Van Veen et al. (2002) treated 14 patients with generalized social anxiety disorder and no comorbid depression with mirtazapine 30 mg/day for 12 weeks. There was a 41.7% rate of response to mirtazapine and significant reductions on secondary outcome measures. Mirtazapine was generally well tolerated. Subsequently, Muehlbacher et al. (2005) randomly assigned 66 female patients to mirtazapine (fixed dose of 30 mg/day) or placebo in a 10-week trial. Mirtazapine was significantly superior to placebo on primary and secondary outcome measures and was relatively well tolerated by all patients. In a second randomized controlled trial, 60 participants with generalized social anxiety disorder were randomized to either mirtazapine (30–45 mg/day) or placebo for 12 weeks. No difference was found between groups on either reduction in LSAS score or the CGI (Schutters, Van Megen, Van Veen, Denys, & Westenberg, 2010). Overall, the evidence for the efficacy of mirtazapine for social anxiety disorder appears limited.

Bupropion

Bupropion is a weak dopamine and norepinephrine reuptake inhibitor that has generated mixed results in two small open trials. Emmanuel et al (2000) administered bupropion sustained-release (SR) (dose range = 200 and 400 mg/day) to ten patients with generalized social anxiety disorder in a 12-week open label trial. Five patients (50%) were considered to be responders. Bupropion was generally well tolerated in this study. However, others have reported negative results in a limited number of patients (Potts and Davidson, 1995).

Nefazodone

Nefazodone has been reported to have both 5-HT reuptake and 5-HT_{2A} receptor blockade properties. To date, only one randomized, placebo-controlled trial on the efficacy of nefazodone for social anxiety disorder has been published, with negative results. Van Ameringen et al. (2007) randomized a total of 105 patients to nefazodone (range dose = 300–600 mg/day; mean dose = 493.9 ± 128.1 mg/day) or placebo for 14 weeks. Comorbid secondary major depressive disorder was permitted if baseline scores on the MADRS were ≤19 and no risk of suicide was present. No differential improvement between the nefazodone and the placebo group was observed. Difference of remission and response rates in the nefazodone-treated group with the placebo group was not significant (31.4% versus 23.5%).

Reboxetine

Reboxetine is an antidepressant with selective norepinephrine reuptake properties not currently marketed in the U.S. The only open label study (Atmaca, 2003) examining the efficacy of reboxetine (dose range = 4–8 mg/day) in social anxiety disorder found statistically significant reductions in the mean Hamilton Anxiety Rating Scale (HAM-A) and total LSAS scores from baseline to the end-point assessment at week 8. Additionally, at week 8, 63.6% were considered responders. Reboxetine was well tolerated in general.

Tricyclic Antidepressants

Based on its efficacy in the treatment of panic disorder, imipramine was studied in mixed phobias and in social anxiety disorder. However, the results of these trials failed to demonstrate efficacy (Simpson et al. (1998a); Zitrin et al. 1983). Tricyclic antidepressants do not appear particularly useful in the treatment of social anxiety disorder.

Benzodiazepines

The anxiolytic properties of benzodiazepines were initially shown to be useful in the treatment of generalized anxiety disorder and panic disorder. Therefore, a logical extrapolation was to assess their efficacy in social anxiety disorder.

Clinical trials have been conducted for standing-dose treatment only, although clinical experience suggests that benzodiazepines may also be used on an as-needed basis for performance fears.

Alprazolam and clonazepam are the most studied benzodiazepines. There have been two open trials and one double-blind study of alprazolam in social anxiety disorder. In the first open trial, Lydiard and colleagues (1988) administered alprazolam to four patients in dosages ranging from 3 to 8 mg/day. All patients had moderate to marked reduction of their symptoms. One of the patients, who had an initial partial response to alprazolam, had a full response when phenelzine was added. Reich and Yates (1988) treated fourteen patients over eight weeks with alprazolam (dose range = 1–7 mg/day; mean dose = 2.9 mg/day). At the study endpoint, 14 patients were considered respondents according to the CGI-I Scale. One week after drug discontinuation, however, symptoms returned to baseline. It was unclear whether that was due, at least in part, to withdrawal symptoms from alprazolam. In the only double-blind study of alprazolam (described in the MOAI section), Gelernter et al. (1991) compared phenelzine, alprazolam (mean dose = 4.2 mg/day; SD = 1.3), placebo, and CBT. Only 38% of the patients taking alprazolam were considered responders after 12 weeks. When patients were reassessed two months after discontinuation of alprazolam, symptoms had returned in most cases, suggesting the low durability of already limited gains. Given the time lapsed since the discontinuation of the drug, it is unlikely that those symptoms represented benzodiazepine withdrawal.

In contrast to alprazolam, several open trials with clonazepam have obtained positive results. Versiani et al. (1989) treated 40 patients with social anxiety disorder over eight weeks. Statistically significant decreases in the CGI severity Scale and LSAS scores were noted between baseline and post-treatment assessment. Munjack and colleagues (1990) compared the effects of clonazepam versus placebo in 10 patients with social anxiety disorder, matching them for baseline severity. Of the clonazepam patients, three were very much improved and three were much improved. Although the clonazepam group also was superior to the no-treatment group on the LSAS and self-ratings of social anxiety, scores of social disability did not change.

Davidson et al. (1991) conducted an open trial with 26 patients treated for an average of 11.3 months (range = 1–20 months). At the end of the trial, 42% of the patients were very much improved, 42% were much improved, and 15% were minimally or not improved. Subsequently, the same group examined for the efficacy of clonazepam showed efficacy in a 10-week placebo-controlled study of 75 patients (Davidson et al. 1993). At the end of the treatment, 78% of the patients taking clonazepam (range = 0.5–3 mg/day; mean = 2.4 mg/day) were classified as responders according to the CGI Scale, compared with 20% of those taking placebo. In a more recent placebo-controlled trial, 53 patients were randomly assigned to either clonazepam (mean dose = 3.4 mg/day; SD = 4.9) or placebo for 16 weeks. The clonazepam group showed significantly greater improvement on the CGI than the placebo group (65.3% versus 29.6%) (Ontiveros, 2008).

Use of bromazepam, a benzodiazepine marketed outside the U.S., has been also reported in the treatment of social anxiety disorder. In the first study, Versiani et al. (1989) treated 10 patients in an eight-week open trial with bromazepam (mean dose = 26.4 mg/day; SD = 4.9). CGI severity scale scores decreased from 5.0 (SD = 0.8) at baseline to 1.3 (SD = 0.5) and LSAS score improved from a baseline 69.3 (SD = 20.5) to 15.8 (SD = 9.1) at the end of treatment. In a subsequent study (Versiani et al., 1997), bromazepam (dose up to 36 mg/day) was superior to placebo in a 12-week randomized study.

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 statistically significant ($p = 0.06$) in this small sample. This maximum dose of clonazepam in this study was 2.0 mg/day, rather than 3.0 mg used in the Davidson et al. (1993) trial. A large randomized study is currently examining the efficacy of clonazepam as an augmentation strategy for patients who do not respond completely to an initial SSRI trial and its results should be highly informative for clinical practice.

In summary, all open trials suggest that benzodiazepines are useful in the treatment of social anxiety disorder. In double-blind studies, clonazepam and bromazepam, but not alprazolam, have been superior to placebo. Whether those differences are due to true differential efficacy or are related to study design and sampling requires further examination. Benzodiazepines also may be helpful on an as-needed basis for performance anxiety. The benefit of decreased anxiety must be balanced with the risk of sedation interfering with the quality of performance. It is not uncommon for patients with social anxiety disorder to present with comorbid psychiatric disorders such as depression. Benzodiazepines are not recommended as monotherapy for patients with concomitant major depression, and must be used with caution in patients with a history of substance use disorders.

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-blockers in nonclinical samples of performers with high levels of anxiety, many of whom would probably be currently diagnosed as having social anxiety disorder performance type. The results of those trials seemed to indicate that β-blockers were successful in decreasing performance anxiety.

Gorman et al. (1985) conducted an open trial of atenolol in 10 patients with social anxiety disorder. Five patients had a marked reduction in social anxiety disorder symptoms, and four reported moderate reduction, as assessed by clinicians and patients. However, a subsequent randomized trial (Liebowitz et al., 1992;

described in the MAOI section above) did not find differences between the rates of response to atenolol (30%) and placebo (23%).

More promising results were obtained by Turner et al. (1994), who randomized 25 patients to atenolol (25–100 mg/day), 26 to flooding and 21 to placebo for 12 weeks. Patients who received behavior therapy received a total of twenty 90-minute sessions of each distributed as follows: twice a week for the first eight weeks and once a week for the last four weeks. Improvement rates were higher among patients who received flooding (89%) than in the group that received atenolol (47%) or placebo (44%). All of those who were assessed six months post-treatment had maintained most of the gains.

β-Blockers have not been proven superior to placebo in any controlled clinical trial. However, anecdotal experience and studies of analogue samples of anxious performers suggests that they are effective for specific and circumscribed performance anxiety. β-Blockers have the advantage over benzodiazepines of rarely impairing concentration or coordination. Nonselective β-blockers (affecting both β_1 receptors in the heart and β_2 receptors that mediate tremor), such as propranolol or nadolol, may in theory be more effective than those selective for the β_1 receptor, such as atenolol or metoprolol, although this remains to be empirically tested (Schneier, 1995).

Before using a β-blocker in a performance situation, patients should try a test dose at home, to ensure that the degree of β-blockade is sufficient and that untoward side effects will not develop during the performance. Most individuals tolerate propranolol well, especially because the hypotensive effects will be partially balanced with the sympathetic arousal of anxiety. Propranolol (dose range = 10–40 mg) taken 45–60 minutes before the performance is sufficient for most patients.

Other Medications

Buspirone

Buspirone is an azapirone that acts as a full agonist on the serotonin 1A ($5HT_{1A}$) autoreceptor and as a partial agonist on the postsynaptic 5-HT_{1A} receptor. Positive results of the trials with SSRIs for social anxiety disorder stimulated further research with drugs that have a serotonergic effect.

Clark and Agras (1991) randomized 34 musicians with social anxiety disorder to receive either six weeks of buspirone, six weeks of placebo, five sessions of group CBT plus buspirone, or CBT with placebo. The average dose of buspirone was 32 mg. There was no difference between buspirone and placebo, whereas CBT was superior to both buspirone and placebo without psychotherapy. Munjack et al. (1991) conducted a 12-week open trial of buspirone (mean dose = 48 mg/day) in 17 patients with generalized social anxiety disorder. The overall response rate was 53% of the intent-to-treat sample.

Schneier et al. (1993) conducted another 12-week open trial with 21 patients with similar response rates (47%) to those obtained in Munjack and colleagues'

study. Seventeen patients completed at least two weeks of treatment and were included in the analysis. Interestingly, responders received a higher average dose of buspirone than did nonresponders (56.9 vs. 38.3 mg/day). Van Vliet et al. (1997) investigated further the efficacy of fixed-dose buspirone (30 mg/day) versus placebo in a 12-week placebo-controlled study of 30 patients with social anxiety disorder. Only one patient receiving buspirone and another taking placebo were classified as responders. There were no statistically significant differences between the two treatment groups on any of the outcome measures.

In contrast with the promising results of the open trials neither of the two controlled trials of buspirone was able to show its efficacy as monotherapy for social anxiety disorder. Additionally, the dosage of buspirone needed seems to be in the upper range (60 mg/day), at which its usefulness may be limited by side effects, such as nausea or headache. Although buspirone has not proven to be superior to placebo as monotherapy, a small trial conducted by Van Ameringen et al. (1996) studied buspirone (doses range = 30-60 mg/day; mean dose = 45 mg/day) as an augmenting agent on 10 patients with generalized social anxiety disorder with a partial response to an adequate trial of an SSRI during eight weeks. Although seven patients (70%) were considered responders according to CGI criteria, this approach has not been further studied.

Pergolide

Only one small open trial of pergolide has been conducted to date. Villarreal et al. (2000) treated four subjects openly with pergolide (25–600 mcg/day) but only two completed the 12 weeks of the study. Conclusions could not be drawn from such a small sample.

Anticonvulsants

Gabapentin

Gabapentin, approved since 1993 for use as adjunctive in the treatment of refractory partial epilepsy, is thought to work through voltage-gated calcium channels and to have GABAergic effects. In the only published placebo-controlled trial of gabapentin for social anxiety disorder, Pande et al. (1999) randomized 69 patients with low levels of comorbidity to gabapentin (dose range 900–3600 mg/day) or placebo for 14 weeks. Significantly higher rates of response were observed among patients on gabapentin than on placebo (32% versus 14%) in the intent-to-treat sample. Patients over 35 years old exhibited a greater degree of effect than younger patients. Dizziness and dry mouth were among the most common side effects.

Pregabalin

The anticonvulsant pregabalin has been shown to have analgesic, anxiolytic, and anticonvulsant properties. Pande et al. (2004) randomly assigned 135 patients

to pregabalin 600 mg/d, pregabalin 150 mg/d, or placebo in a 10-week double-blind trial. Pregabalin 600 mg/day, but not pregabalin 150 mg/day was superior to placebo at endpoint. Although a total of 19 patients withdrew from the study due to adverse events, these were of mild or moderate intensity and no serious adverse event was considered related to study medication.

Feltner et al. (2011) conducted an 11-week controlled trial randomizing 329 patients to pregabalin 300 mg/d, 450 mg/d, 600 mg/d, or placebo. As in the previous trial, only the 600 mg/d group was superior to placebo at post-treatment on the CGI-I (53% versus 25%). A controlled trial investigating discontinuation found that 450 mg/day pregabalin significantly lowered the rate of relapse as compared to placebo (Greist, Liu-Dumaw, Schweizer, & Feltner, 2011). Further studies are needed to define the optimal dose, magnitude of the effect, and long-term effect.

Topiramate

This glutamatergic and GABAergic anticonvulsant has been used for a variety of psychiatric disorders (Dursun et al., 2001; Johnson et al., 2005; Tata et al., 2006); Vasudev et al., 2006. Van Ameringen et al. (2004a) conducted a 16-week open trial to examine the efficacy of topiramate (dose range = 25–400 mg/day; mean dose = 222.8 ± 141.8 mg/day) in generalized social anxiety disorder. The trial included 23 outpatients who could have comorbid anxiety disorders, major depressive disorder, or attention deficit hyperactivity disorder. Of the 12 subjects who completed the trial, nine (75%) were considered responders according to CGI-I criteria at study endpoint. However, in the intent-to-treat analysis, only 48% were considered responders and 35% remitters, as by CGI-I scores. All patients experienced adverse effects, which included weight loss, paresthesias, headache, cognitive impairment, anorexia, gastrointestinal upset, tiredness, lightheadedness, agitation, and metallic taste.

Levetiracetam

Levetiracetam is an anticonvulsant that modulates voltage-gated calcium channels in the CNS. In a first, open-label flexible dose study, Simon et al. (2004) treated 20 patients with generalized social anxiety disorder with levetiracetam (dose range = 500–3000 mg/day; mean dose = 2013 ± 948 mg/day) for eight weeks. Comorbid depressive and other anxiety disorders were permitted as long as they were considered secondary disorders for that patient. At week 8, the study found a 20-point decrease in LSAS scores. There were also decreases in CGI-S and Hamilton Rating Scale for Anxiety scores. Levetiracetam was generally well tolerated with mild and transient side effects in this study. Later on, Zhang et al. (2005) randomized 18 subjects to receive either placebo or levetiracetam at flexible doses (dose range = 500–3000 mg/day; mean dose = 2279 mg/day) in a small seven-week placebo-controlled pilot study. Two subjects from the levetiracetam group dropped out because of early side effects and an additional

two subjects in this group had a relative poor tolerance to the drug. The study found no differences on a number of outcome measures.

Valproic acid

The anticonvulsant valproic acid (VPA) may have anxiolytic properties mediated by its enhancement of GABA activity in the CNS. Kinrys et al. (2003) conducted a 12-week flexible-dose, open trial of valproic acid (range dose = 500–2500 mg/day; mean dose = 1985 ± 454 mg/day) in 17 patients with social anxiety disorder. Mean reduction in the LSAS was 19.1 points for all participants. Results of the study showed 41% response rate. Side effects of VPA were mild, and no severe adverse events were reported during the study.

Tiagabine

There is only one open trial of the selective GABA reuptake inhibitor tiagabine for patients with social anxiety disorder. Dunlop et al. (2007) treated 54 patients in a 12-week open-label tiagabine (dose range = 4–16 mg/day; mean dose = 12.2 ± 4.0 mg/day). At study endpoint, 63% of the completer sample and 40.7% of the intent-to-treat sample were considered responders.

Atypical antipsychotics

Few antipsychotics have been tested for the treatment of social anxiety disorder and none of them have been tested in large trials. These include olanzapine (Barnett et al. 2002), quetiapine (Schutters et al. 2005), and risperidone (Simon et al. 2006). Some of these studies have shown promise, but larger studies will be needed in order to clarify their effects.

Novel Treatments

Cannabidiol

Bergamaschi and colleagues investigated the anxiolytic efficacy of cannabidiol (CBD), a compound derived from the *cannabis sativa* plant, during a simulated public speaking task. Twenty-four treatment-naïve participants diagnosed with social anxiety disorder were randomized to either placebo or CBD and significant group differences were found on anxiety and related constructs (Bergamaschi et al., 2011). Though promising, further research is needed to investigate cannabidiol and its anxiolytic effects.

D-Cycloserine

D-Cycloserine (DCS), a partial NMDA receptor agonist, has been investigated as an augmenting agent for exposure therapy in social anxiety disorder. Two separate randomized trials have found that study groups receiving DCS one hour prior to an exposure session, showed significantly more improvement at

posttreatment than those receiving placebo. Effect sizes were medium to large for both studies (Guastella et al., 2008; Hofmann et al., 2006). A recent multicenter study (n = 169) found that although rates of response and remission did not differ between those taking DCS or placebo at the end of the 12-week treatment, individuals receiving DCS one hour prior to exposure therapy improved faster, suggesting that DCS is more likely to accelerate than to amplify exposure procedures (Hofmann et al., 2013).

Pharmacotherapy in children and adolescents

Although children and adolescents with social anxiety disorder often have great impairment in their social and family relationships and academic life, this often goes underdiagnosed and undertreated. Few studies of pediatric social anxiety disorder have examined the efficacy of treatment modalities, making the role of pharmacotherapy for treatment of this disorder 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 social anxiety disorder.

Only two studies have investigated the efficacy of benzodiazepines in this population. In a six-week open label study, Simeon and Ferguson (1987) treated 12 children with avoidant and overanxious disorders with alprazolam (mean dose = 1.5 mg/day). Both child- and parent-rated anxiety symptoms as well as cognitive functioning decreased for both diagnostic groups. In a subsequent study, Simeon et al. (1992) randomized 30 children with avoidant and overanxious disorders to alprazolam or placebo. The maximum dosage permitted was 0.04 mg/kg/day. Differences between groups did not reach significance, possibly due to the relatively small size of the groups.

In contrast to the scarcity of studies conducted on benzodiazepines, more data is available in the efficacy of SSRIs. Several placebo-controlled trials have been conducted, providing substantial evidence of the efficacy of SSRIs and SNRIs in children six to 17 years of age. However, the increasing concern about studies, most of them 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.

Fairbanks et al. (1997) used fluoxetine to treat a group of children with mixed anxiety disorders that had not responded to psychotherapy. Treatment was started at 5 mg/day and increased weekly by 5–10 mg/day for six to nine weeks until improvement occurred, or to a maximum of 40 mg in children younger than 12 years, or 80 mg in adolescents, was administered. Eight of the 10 children with social anxiety disorder were considered respondents as assessed by CGI criteria.

Rynn et al. (2001) randomized 22 children with social anxiety disorder to either sertraline (maximum dose of 50 mg/day) or placebo for nine weeks. CGI-I scores at post-treatment showed the sertraline group to have significantly more improvement than placebo (90% versus 10%) (Rynn, 2001).

In the first large study on the treatment of anxiety disorders in children and adolescents (Research Unit on Pediatric Psychopharmacology Anxiety Study Group, 2001), 128 individuals aged six to 17 who met criteria for social anxiety disorder, separation anxiety disorder, or generalized anxiety disorder (GAD) and showed no improvement after receiving psychological treatment for three weeks were randomized to either placebo or fluvoxamine (dose range = 50–300 mg/day). After eight weeks of treatment, patients in the fluvoxamine group showed significantly greater improvement than those in the placebo group. Fluvoxamine was well tolerated with mild adverse events and no reports of suicidal ideation.

In another trial, Birmaher et al. (2003) randomized subjects seven to 17 years old that met criteria for GAD, separation anxiety disorder, and/or social anxiety disorder with significant impairment. Seventy-four patients were randomized to fluoxetine or placebo. Fifty-four percent of the sample had social anxiety disorder. Subjects with current social anxiety disorder on fluoxetine had a 76% response rate vs. 21% on placebo, and 45.5% of children in the fluvoxamine group versus 10.5% in the placebo group showed significant increase in functional improvement measures.

Beidel et al. (2007) randomized 139 patients with social anxiety disorder aged seven to 17 to fluoxetine, placebo or social effectiveness therapy for children (SET-C). More patients in the SET-C group (79%) than either those in the fluoxetine group (36%) or placebo group (6.3%) were considered responders as assessed by the CGI score. Furthermore, fluoxetine was also shown to be significantly superior to placebo. At one-year follow-up, all treatment gains were maintained and fluoxetine and SET-C treated patients showed continued improvement.

An eight-week open label trial of sertraline was conducted in 14 adolescents aged 11-17 with social anxiety disorder specifically (Compton et al., 2001). At the study end-point 36% were considered responders, while an additional 29% were considered partial responders.

Wagner et al. (2004) conducted a randomized double-blind controlled multicenter trial of paroxetine (10–50 mg/day) that included 322 youths with social anxiety disorder. Significantly more patients taking paroxetine were considered responders (77% versus 38%) and achieved remission (47.2% versus 13.3%). Although no suicide attempts were reported, four of the children treated with paroxetine expressed suicidal ideation or threatened suicide.

Isolan et al. (2007) conducted a 12-week open trial of escitalopram (mean dose = 13 mg ± 4.1) in twenty children and adolescents (aged between 10 and 17 years old) with social anxiety disorder. In the intent-to-treat analysis at week 12, 65% of the sample achieved response criteria. In addition, scores of self-report and parent report measures decreased significantly as early as week 8, with further improvement by week 12. Nevertheless, a substantial number of patients remained symptomatic at the end of the trial. Adverse effects of escitalopram were transitory and well tolerated. The most common side effects were somnolence and insomnia. No patient developed suicidal ideation.

In another large trial, March et al. (2007) randomized 293 patients aged eight to 17 with generalized social anxiety disorder to venlafaxine ER (dose range = 37.5–225 mg/day) or placebo for 16 weeks. Using a CGI-I of 1 or 2 as the criterion for response, 56% of subjects treated with venlafaxine ER responded compared to 37% on placebo, a statistically significant difference. Adverse effects included nausea, anorexia, asthenia, and mydriasis. Three subjects (two during the course of treatment and one during the taper phase) in the venlafaxine ER group versus none in the placebo group developed suicidal ideation, but there were no suicide attempts.

In an eight-week open-label pilot study Mrakotsky et al. (2008) administered mirtazapine (mean dose = 28.8 mg/day; S.D. = 12.4) to children with social anxiety disorder aged eight to 17 years. Fifty-six percent (10/18) responded to treatment and 17% (3/18) of the patients treated with mirtazapine achieved full remission. Social anxiety disorder symptoms improved significantly during the first two weeks of treatment, as did comorbid symptoms of depression and anxiety. Eleven patients (61%) did not complete all eight weeks of treatment. Four patients (22%) discontinued due to adverse effects including fatigue and irritability, whereas the others discontinued due to study-burden (28%), insufficient response (6%), or to pursue herbal treatment (6%). Mirtazapine treatment resulted in a significant increase in weight (mean of 3.3 kg; S.D. = 2.6).

In summary, 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%. Reports of occasional emergence of suicidal ideation during treatment suggest the need for close monitoring of these treatments in this population.

RECOMMENDATIONS

Before initiating pharmacotherapy, it is essential to conduct a thorough assessment of the scope of social anxiety disorder symptoms, and to help set reasonable expectations for response. In the short term, we expect to see symptomatic relief and improved social relatedness and performance. Over the long term, we hope to see decreased avoidance, increased vocational or educational functioning and improved capacity for more satisfying relationships. Although some patients ultimately achieve a complete remission of symptoms, more commonly seen is a substantial reduction that improves quality of life without altering the typical patient's self-perception of being a shy person.

Predictors of response to a particular treatment are lacking. To date, only later age of onset (in adulthood) of social anxiety disorder (Van Ameringen, 2004b) and duration of treatment (Stein et al. 2002a) have been shown to predict treatment response. The choice of a pharmacological agent for a specific patient depends on the diagnostic subtype of social anxiety disorder, presence of comorbidity, and patient preference.

Anxiety-provoking situations in the generalized type of social anxiety disorder are frequent and largely unpredictable. Since as-needed use becomes impractical for patients with generalized type, standing daily doses of medication are warranted. At present, SSRIs constitute the first-line medication treatment for generalized social anxiety disorder. They have been most extensively tested, are generally well tolerated, and treat comorbid depression. Double-blind studies support the efficacy of drugs like paroxetine, sertraline, fluvoxamine and escitalopram with efficacy rates ranging from 50% to 80% after eight to 12 weeks of treatment. Studies on fluoxetine have had inconsistent results, making it a less preferred treatment. The SNRI venlafaxine can also be considered as first-line therapy due to response characteristics similar to SSRIs.

Benzodiazepines remain a reasonable alternative for the treatment of the generalized type of social anxiety disorder. These are commonly used in patients who cannot tolerate SSRIs or venlafaxine side effects or are unresponsive to these medications. The relatively long-acting clonazepam has shown efficacy in several studies. The role of alprazolam remains inconclusive. Benzodiazepines are not efficacious in the treatment of some of the comorbidities commonly associated with this disorder (e.g., major depressive disorder) and they should generally be avoided in most patients with a history of substance use disorders, which are moderately comorbid with social anxiety disorder. In most patients, tolerance to the sedative effects of benzodiazepines develops rapidly, in most cases without loss of anti-anxiety efficacy.

Phenelzine has been the most studied MAOI in the treatment of social anxiety disorder. It has proven to be efficacious, but the risk of hypertensive reaction and related need to follow dietary restrictions is an important limitation for its use. It is generally well tolerated as demonstrated by several studies, and it can be reserved for patients with refractory disease. Gabapentin and pregabalin have also shown some promising data. Preliminary results have suggested moderate efficacy, but empirical support for their use is more limited than for SSRIs, benzodiazepines or MAOIs. The antidepressant mirtazapine has also shown efficacy in one of two controlled trials in adults.

Cases of non-generalized social anxiety disorder, in which feared performance situations arise only occasionally and predictably (e.g., recitals and professional presentations), can be treated initially with β-blockers such as propranolol used on an as-needed basis about an hour before a performance. If β-blockers are ineffective or are contraindicated, an alternative is the use of a benzodiazepine. The doses needed to control anxiety may interfere with functioning when the demands of the performance are high, and may sometimes cause sedation. When performance situations arise more frequently, treatments used for generalized social anxiety disorder might be preferable for most patients.

Little empirical data are available to guide subsequent treatment of patients who show minimal or no improvement, or of patients who show much improvement but still exhibit meaningful symptoms and impairment. The first step in

managing treatment-resistant patients is to identify possible causes. Several reasons for resistance exist. For example, therapeutic failure may be caused by nonadherence to treatment resulting in sub-optimal medication levels or treatment duration. The presence of a comorbid psychiatric disorder may be another reason for resistance. These are very common in patients with social anxiety disorder, and are often exclusion criteria in clinical trials. The lack of information about the influence of comorbidity on treatment response can also be due to the fact that trials that allow comorbid disorders do not usually report treatment response stratified by their presence or absence of these conditions. Comorbid medical conditions and individual pharmacokinetic characteristics (drug interactions, rapid metabolizers) may be other sources contributing to resistance. Partial responses to a maximal tolerated dose of an SSRI or a SNRI may be augmented with a benzodiazepine, gabapentin or pregabalin (although the combination of an SSRI or a SNRI with an MAOI is absolutely contraindicated due to the risk of development of a serotoninergic syndrome). The study by Blanco et al. (2010) as well as data from Blomhoff et al. (2001) indicate that combined CBT and medication treatment is superior to medication alone, suggesting that it may a reasonable strategy for patients who do not respond to medication alone. However, data on sequential treatment, particularly randomized trials that compare different sequential strategies, are needed to further improve the treatment of social anxiety disorder.

Another important question often raised by patients is related to the length of treatment. The available data suggest that discontinuation of medication, even after several months of treatment, can result in relatively high rates of relapse. It appears reasonable to recommend treatment for at least six to 12 months, and then to re-evaluate with the patient the advantages and disadvantages of a longer treatment versus medication discontinuation. In many cases, patients prefer to continue on medication, whereas in others, patients choose a slow taper period to evaluate whether a lower dose or full discontinuation are viable alternatives. Preliminary findings suggest that the use of concomitant CBT may help maintain the gains following medication cessation, but replication of these findings are needed. Important progress over the last two decades has yielded pharmacological treatments that clearly improve the prognosis of the patient with social anxiety disorder, yet remaining questions demonstrate substantial need for further research.

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