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Pharmacotherapy for Social Anxiety Disorder: An Update

Michael Van Ameringen, MD, FRCP,[1, 2] Catherine Mancini, MD, FRCP,[1, 2]
Beth Patterson, BScN, RN, BEd,[2] and William Simpson, BSc[2]

1 *Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada*
2 *Anxiety Disorders Clinic, McMaster University Medical Center, Hamilton Health Sciences, Hamilton, Ontario, Canada*

Abstract: Since the emergence of social phobia into the diagnostic nomenclature, we have seen an exponential expansion in our knowledge regarding effective treatment of this disorder. The literature clearly supports the use of SSRIs and the SNRI venlafaxine ER as first line pharmacological agents in the treatment of GSAD. In this article, treatment studies of pharmacotherapy of social phobia are summarized. Additional issues such as comparative efficacy, treatment resistance and relapse-prevention are reviewed.

Introduction

Social Phobia (SP) first entered the diagnostic nomenclature in 1980 with the publication of the third edition of the Diagnostic and Statistical Manual (1). The characterization of social phobia, now also known as Social Anxiety Disorder (SAD), has evolved over the past 25 years, as has the associated prevalence rates. Preliminary epidemiological reports found lifetime rates of 2.4% in the Epidemiological Catchment Area study (ECA)(2) and, most recently, the National Comorbidity Survey – Revised for DSM-IV (NCS-R)(3) reported a rate of 12.1%. This report examines results from pharmacological treatment studies in social anxiety disorder, including short and long term, combination, augmentation and comparison (with psychological treatments) studies. Treatment resistance and relapse prevention will also be discussed.

Pharmacotherapy in Social Anxiety Disorder

Selective Serotonin Reuptake Inhibitors (SSRIs) are recognized as the first line treatment for generalized social anxiety disorder (GSAD) based on their efficacy, safety, tolerability and effectiveness in treating conditions commonly comorbid with GSAD. The efficacy of other agents such as the serotonin noradrenalin reuptake inhibitor (SNRI) venlafaxine, benzodiazepines, monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), anticonvulsants and other agents have also been demonstrated in the treatment of GSAD.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Fluvoxamine

Fluvoxamine was the first SSRI to show efficacy in controlled studies of social phobia. In a 12-week double-blind placebo-controlled study of fluvoxamine in 30 social phobics, 46% of the patients in the fluvoxamine group were considered responders (a 50% reduction in the Liebowitz Social Anxiety Scale [LSAS][4] score) at 12 weeks, versus 7% of patients taking placebo (5). In a larger, 12-week controlled study (6), fluvoxamine (mean dose of 202 mg/day) was compared to placebo in 92 patients with GSAD. At study endpoint, 43% of the patients in the fluvoxamine group versus 23% (placebo) were classified as responders according to the Clinical Global Impression – Improvement Scale (CGI-I) (7).

More recently, Asakura and colleagues (8) conducted a 10-week, randomized, placebo-controlled trial of fluvoxamine (150 mg/day or 300 mg/day) in a sample of 265 Japanese individuals with GSAD

Address for Correspondence: Michael Van Ameringan, MD, 3G – Outpatient Psychiatry McMaster University Medical Centre, Hamilton Health Sciences,1200 Main Street West, Hamilton, Ontario L8N 3Z5, Canada. E-mail: vanamer@mcmaster.ca

(179 male and 86 female). At the end of the double-blind phase, both doses of fluvoxamine were found to be significantly superior to placebo on the primary outcome measure, the LSAS-J (Japanese version of the LSAS) total score and revealed higher rates of response (CGI-I ≤ 2) (45.1% vs. 30.3% placebo, p = 0.0240).

Fluvoxamine-controlled release (CR) was examined in comparison to placebo in 279 generalized social phobics (9). The fluvoxamine CR group (mean daily dose 174 mg/day) displayed clinically and statistically significant reductions in social phobia symptoms compared to placebo based on the primary outcome measure (LSAS). Responders (cGI-I ≤ 2) were significantly greater in the fluvoxamine CR group (33.9%) as compared to placebo (16.7%) (p< .001).

Sertraline

Using a flexible-dose, crossover design, 12 patients meeting DSM-III-R (10) criteria for social phobia were randomized to either sertraline or placebo for ten weeks (11). Overall, based on the Liebowitz Panic and Social Phobic Disorders Rating Form (12), 50% of the sertraline group (versus 9% in the placebo group) were labelled responders. The mean change in the LSAS score from baseline in the sertraline phase was 22 and 5.5 for placebo (p < 0.05).

In a large Canadian 20-week, double-blind, multi-center study (13), sertraline (in flexible doses up to 200 mg/day) was compared to placebo in 204 patients with social phobia. At week 20, 53% of the sertraline group versus 29% of the placebo group were considered responders according to the CGI-I. Liebowitz and colleagues conducted a 12-week double-blind study of flexible dose sertraline in 415 individuals with severe generalized SAD (GSAD) (14). Patients who received sertraline (mean max. dose of 159 mg/day) experienced a clinically significant mean reduction in LSAS score by Week 12 of treatment (-31.0), compared to a -21.7 reduction in the placebo group. A significantly greater proportion of patients in the sertraline group achieved responder status (CGI-I< 2), compared to those taking placebo in the Week 12 Intent to treat (ITT)-LOCF analysis (46.8% vs. 25.5%; p<.001).

Paroxetine

Paroxetine has been the most studied SSRI in SAD. Stein and colleagues (15) compared paroxetine to placebo in a 12-week controlled trial of 187 patients with social phobia. Fifty-five percent of the paroxetine group versus 23% of the placebo group were considered to be responders with a CGI-I ≤ 2 (OR 3.88, 95% CI, 2.81–5.36). A statistically significant reduction in mean LSAS was reported for paroxetine (39%) versus a 17.4% drop in the placebo group (95% CI, 8.7%–34.7%).

In a 12-week multi-centered, double-blind, parallel-group, placebo-controlled trial, 290 patients with social anxiety disorder were randomized to paroxetine (20–50 mg/day; n = 139) or placebo (n = 151) (16). A clinically significant improvement was found in the paroxetine group as compared to placebo on primary efficacy measures of mean change in LSAS from baseline to endpoint, and in the proportion of responders having a CGI-I< 2.

Several subsequent randomized controlled trials (RCTs) with paroxetine (17, 18) and paroxetine controlled-release (paroxetine CR) (19) have yielded additional confirmatory evidence of efficacy.

Fluoxetine

In the first placebo-controlled study of fluoxetine in social phobia, (N = 60) the dose of fluoxetine and placebo was fixed at 20 mg/day for the first 8 weeks of double blind treatment (20). The final six weeks involved a flexible dose of fluoxetine, up to a maximum of 60 mg/day. No significant differences were found between fluoxetine and placebo in terms of LSAS score change from baseline (primary outcome measure), although a significant change in LSAS was found at Week 14 to baseline. The change in fluoxetine treatment response was similar to that reported with other SSRIs, however, the placebo response was greater. These results are important, as this is the first controlled study of an SSRI in social phobia to show lack of efficacy.

Escitalopram

A statistically superior therapeutic effect was found for escitalopram compared with placebo

in a 12-week double-blind comparison of flexible dose escitalopram (10–20 mg/day) and placebo (n = 358). This was based on total LSAS score (p = .005) with a significantly greater rate of response (54% for escitalopram vs. 39% with placebo; p<0.01; LOCF analysis) (21). Although a significant improvement was demonstrated, escitalopram only showed a significant separation from placebo at Week 12, which is later than found in most studies of SSRIs in GSAD (21).

Overall, there is overwhelming evidence for the efficacy of the SSRIs in GSAD. These agents have the additional benefit of treating comorbid conditions commonly seen with GSAD (22).

SNRIs: Venlafaxine

In a 12-week double-blind, placebo-controlled, parallel-group multi-site study 272 patients with DSM-IV (23) social phobia were randomized to either venlafaxine extended release (ER) (flexible doses, 75 to 225 mg/day) or placebo (24). At week 12, patients in the venlafaxine-ER group had a significantly lower LSAS total score than placebo (57.7 vs. 66.0, p≤.01). As well, significantly more patients were considered responders by CGI-I ≤ 2 at Week 12: 50% of venlafaxine ER patients versus 34% in the placebo group (p< .01; LOCF). These results have been supported by a 12-week flexible-dose, randomized-controlled trial of venlafaxine ER in 271 patients (25) and in a 28-week, double blind, multi-center design (N = 386) study was completed, in which patients were randomized into three treatment groups: venlafaxine at a fixed low dose (75 mg/day), venlafaxine ER at a flexible high dose (150–225mg/day) and placebo (26). In this latter study, no significant differences were found between low fixed-dose venlafaxine ER and the higher flexible dose.

Nefazodone

Nefazodone is a serotonergic antidepressant similar to an SSRI, but it also blocks post-synaptic 5-HT2A receptors (27). In the only RCT, where 105 patients were randomized to 14 weeks of nefazodone or placebo, nefazodone was found to be no better than placebo (28).

Tricyclic Antidepressants

There has been one reported study of an 8-week, placebo-controlled study of imipramine in the treatment of 41 patients with social phobia in which the efficacy of imipramine was found to be no better than placebo.

Monoamine Oxidase Inhibitors (MAOIs)

Phenelzine was the first drug in this class to demonstrate efficacy in placebo-controlled trials of social phobia (29–32). Gelernter and colleagues (31) found phenelzine to be superior to alprazolam, placebo and group cognitive behavioral treatment. In another landmark study, phenelzine, atenolol and placebo were compared in a controlled design in 74 individuals with social phobia (30). After 8 weeks of treatment, phenelzine was more effective than atenolol (p = .02) or placebo (p = .009) for relieving social phobic symptoms. Despite the robust efficacy demonstrated by MAOI's in GSAD, due to dietary restrictions, and risk of serious adverse events associated with the use of these agents, including the risk of hypertensive crisis, these medications are now reserved for those non-responsive to other drug treatments.

Reversible Inhibitors of Monoamine Oxidase Type A (RIMAs)

Randomized controlled trials of RIMAs have been equivocal. Brofaromine was shown to be effective in three placebo-controlled trials (33–35). This agent was withdrawn from the world market in 1994 for reasons unrelated to its safety or efficacy. Moclobemide was found to be no different in efficacy than placebo in three studies (36–38), but did show superiority to placebo in a long-term study (39). Given these inconsistent results and low effect sizes, these agents do not appear to be very potent as treatments for GSAD and should be reserved for use when trials of other agents have been unsuccessful.

Benzodiazepines

Benzodiazepines are thought to reduce anxiety by enhancing inhibitory GABA neurotransmission.

Positive randomized controlled trials of clonazepam (40), alprazolam (31) and bromazepam (41) have also been reported in SAD.

Davidson and colleagues (41) compared clonazepam to placebo in 75 social phobics. At endpoint, 78% of the clonazepam group and 20% of the placebo group were rated as improved by CGI-I ≤ 2 ($p = .0001$).

Benzodiazepines should not be considered first line therapy for this disorder due to their ineffectiveness in treating common comorbid conditions, as well as the potential for dependence in comorbid substance abusers, but should be reserved for use where adjunctive therapy may be needed or in cases where rapid onset of action is required.

Anticonvulsants

Anticonvulsants, or antiepileptics, are thought to modulate the glutamate – gamma-amino-butyric acid (GABA) neurotransmitter systems. Abnormalities in both GABA and glutamate have been associated with various anxiety disorders and supportive evidence for the use of anticonvulsants in social anxiety disorder is emerging in both open label and in randomized placebo – controlled trials (42) of topiramate (43), tiagabine and levetiracetam (44) and valproic acid (45).

Gabapentin

In a 14-week, double-blind, controlled study ($N = 69$), gabapentin (900 to 3600 mg/day) was compared with placebo in the treatment of social phobia (46). In the ITT analysis, 32% of those taking gabapentin vs. 14% taking placebo were found to be responders with a 50% reduction in LSAS scores, as well as 38% of the gabapentin group vs 17% of the placebo group being responders according to the CGI-I ≤ 2 ($p = .05$).

Pregabalin

In one controlled study of social phobia, 135 patients were randomized to pregabalin 150 mg/day or 600mg/day or placebo for 11 weeks (47). The primary efficacy measure of the LSAS (total score) was significantly decreased in the pregabalin 600 mg/day group as compared to placebo ($p = .03$), but pregabalin 150 mg/day showed no difference in LSAS total score reductions as compared to placebo. Response by CGI-I ≤ 2 was 42.6% in the 600 mg/day group versus 21.7% in the placebo group ($p = 0.03$).

Levetiracetam

Zhang and colleagues (48) conducted a 7-week randomized, double-blind, placebo-controlled study of levetiracetam (500–3,000 mg/day) in 18 subjects with social anxiety disorder. No significant difference was found between levetiracetam and placebo on the primary BSPS (ITT). Response rate by CGI-I ≤ 2 was 22% for levetiracetam versus 14.3% for placebo.

These anticonvulsants trials suggest that gabapentin and pregabalin could be alternative agents for the growing number of patients who are non-responsive to first line treatments. However, these conclusions are tentative as the efficacy of other anticonvulsant agents remains to be proven, and is yet unclear whether anticonvulsants will work in people where SSRIs or SNRIs fail.

Atypical Anti-Psychotics

Atypical anti-psychotic agents have been shown to have anxiolytic effects (49, 50). Quetiapine monotherapy has been examined in an open label trial in GSAD (51). In an 8-week, randomized, double-blind, placebo-controlled study in a sample of 12 patients with GSAD, flexible dose olanzapine resulted in significantly greater improvement on the primary outcome measures of the BSPS ($p = .02$) and the SPIN ($p = .01$) (52). Response rate by CGI-I ≤ 2 was 60% for olanzapine versus 0% for placebo ($p = .17$) These agents show promise as either adjunctive agents or in treatment resistance, although they have been associated with significant adverse events such as weight gain, diabetes, and high cholesterol (53). At this time, their side effect profile and the strength of the current data does not support their use as a first line treatment strategy.

Other Agents

Evidence from open label trials has shown selegiline (54) and reboxetine (55) to be of benefit in GSAD, while buproprion SR has had mixed results

(56–58). Mirtazepine and ondansetron have also been found to be of benefit in small RCTs (59).

Comparative Efficacy in Social Anxiety Treatment

Several recent meta-analyses have provided comparative efficacy data in the pharmacotherapy of GSAD. Effect sizes ranged from 0.19–2.095 for benzodiazepines, 0.3–2.2 for SSRIs, 0.75–1.02 for MAOIs, 0.7 for anticonvulsants and 0.66 for RIMAs (60–63). The consensus from these analyses was that based on efficacy and tolerability, SSRIs should be considered first line agents in the treatment of GSAD.

Drug vs. drug comparisons

The dose equivalent head to head antidepressant studies have not suggested a difference in efficacy thus far. The findings of these investigations are summarized in Table 1.

Treatment Resistance in Social Anxiety Disorder

Evidence is slowly emerging for the clinical management of treatment-resistant GSAD

To date, six open trials (64–69) and one double-blind, placebo-controlled, crossover study (70) have examined pharmacological agents in treatment-resistant social phobia.

In open-trials conducted by Altamura and colleagues (65) and Aarre (67) the effectiveness of switching to venlafaxine or phenelzine respectively, in patients resistant to traditional social phobia treatment was examined. Both investigations indicated significant reduction in social phobia symptoms with the switch in agents.

Augmentation strategies for non-responsive patients with SAD often involve the addition of a supplementary drug, usually from a different class. SSRI treatment has been augmented by the

Table 1: *Drug vs. Drug Comparisons*

Study	N	Duration (weeks)	Treatment	Outcome
Verisani et al. (78)	78	16	Moclobemide (MOC) Phenelzine (PHEN) Placebo (PBO)	MOC > PBO PHEN > PBO PHEN > MOC
Liebowitz et al. (30)	74	8	Atentolol	PHEN > PBO
Atmaca et al. (83)	71	8	MOC Citalopram (CIT)	MOC = CIT
Lader et al. (76)	899	24	Escitalopram (ECIT) Paroxetine (PAR) PBO	ECIT > PBO PAR > PBO ECIT 20mg > PAR 20mg
Allgulander et al. (84)	434	12	Venlafaxine ER (VEN) PAR PBO	VEN = PAR > PBO
Furmark et al. (85)	36	6	NKI Antagonist (GR205171) CIT PBO	GR205177 > PBO CIT > PBO

addition of benzodiazepines, anticonvulsants, as well as other agents (71) with positive open-label evidence for risperidone (73), aripiprazole (72), tiagabine (73) and buspirone (66).

In a small double-blind crossover study of paroxetine partial or non-responders, pindolol augmentation did not show any significant advantage over placebo (70).

A randomized study of 28 patients with GSAD compared open-label paroxetine (20–40 mg/day) with double-blind placebo or clonazepam (1 to 2 mg/day) for 10 weeks (74). At endpoint, only a trend favoring paroxetine/clonazepam treatment versus placebo was found (79% response rate for paroxetine vs. 43% placebo, $p < .06$), however there were no significant differences on other outcome measures.

At this time there are no controlled data to guide clinicians in the choice of next step treatments when a patient does not respond, or has a partial response to a standard, first line treatment.

Relapse Prevention and Long-Term Efficacy Investigations

Several long-term studies have been conducted to examine the issue of relapse prevention.Long-term studies using double-blind or open-label design or where there is a maintenance phase or long-term follow-up following an acute trial have been conducted with various agents including: moclobemide (39), phenelzine and CBT (32), sertraline and exposure therapy (75), fluvoxamine (8), paroxetine and escitalopram (76) and venlafaxine ER (26). Response rates in these studies range from 58% (venlafaxine ER [26]) – 88% (escitalopram [76]). Relapse-prevention studies in which subjects are generally randomized to long-term double blind, placebo-controlled treatment following an open-label treatment phase have been conducted using clonazepam (77), moclobemide and phenelzine (78), paroxetine (79), fluvoxamine CR (80), sertraline (81) and escitalopram (82), with rates of relapse ranging from 0% (clonazepam [77]) – 22% (escitalopram [82]) with placebo substitution. Long-term studies support long-term efficacy for SSRIs, benzodiazepines, MAOIs and RIMAs in the treatment of GSAD.

Summary

The current literature clearly supports the use of SSRIs (escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, sertraline) and the SNRI venlafaxine ER as first-line pharmacological agents in the treatment of GSAD. Second-line treatments would include the benzodiazepines (clonazepam, bromazepam and alprazolam) as well as the anticonvulsants (gabapentin and pregabalin). Nevertheless, there remains a paucity of data in a number of areas, which indicate a need for further randomized, controlled investigations. For example, treatment resistance is an area where the body of knowledge is increasing, but requires further enhancement. There appears to be a large number of patients who obtain a partial or non-response to first-line treatment, and more studies looking at next step treatments for these patients would be important to guide clinicians more effectively.

It would be of value for future research to examine these questions as well as the issue of comorbidity; does treatment of childhood GSAD prevent the occurrence of subsequent comorbid conditions which temporally follow the onset of GSAD?

One of the most promising developments in GSAD research is in our preliminary ability to look at genetic polymorphisms which may have future clinical utility. Identification of sub-groups of SAD through genetic polymorphisms and/or biological markers may be of benefit in the future by providing more reliable predictors of the clinical course and treatment response.

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