

Social anxiety disorder (social phobia)

S Seedat

1. Introduction

According to epidemiological studies, rates of social anxiety disorder (SAD) or social phobia range from 3% to 16% in the general population.^[1,2] Social phobia and specific phobias have an earlier age of onset than other anxiety disorders. The median age of onset for the disorder is 13 years with an onset after age 25 relatively uncommon. The disorder typically persists throughout adult life and is associated with significant functional impairment.^[3-5] Individuals with SAD are more likely to be females; however in clinical samples SAD seems to be more equally distributed among men and women.^[4]

2. Diagnosis and clinical characteristics

SAD is characterised by an exaggerated and persistent fear of being negatively evaluated in social and performance situations.^[6] The disorder is associated with physical, cognitive and behavioural disturbances. The generalised subtype consists of fears of most interactional and performance situations, while the non-generalised (or circumscribed) subtype is restricted to a few specific situations, such as public speaking or dating.^[4,5] The generalised subtype or generalised social anxiety disorder (GSAD) is associated with greater comorbidity, chronicity, and functional impairment.^[7] The avoidance of feared situations impacts on daily routine, work, academic and social activities and relationships. More than 80% of patients with SAD have a lifetime history of at least one other psychiatric disorder, most commonly major depression, panic disorder, generalised anxiety disorder, agoraphobia and substance use disorders.^[5-7] There is also considerable overlap between SAD and avoidant personality disorder.^[6,7]

SAD generally runs a chronic course and precedes mood, anxiety and substance use disorders. Even in the absence of comorbidity, SAD is associated with significant distress, including financial problems, increased suicidal thoughts, reduced work and school performance, poor social support and greater use of psychotropic medications.^[5] Despite significant suffering, only 50% of patients with SAD ever seek treatment and when they do, it is usually when a comorbid condition develops and necessitates treatment.^[8]

3. Assessment

There are several aspects of the clinical presentation of patients with SAD that may impact on treatment decisions.

First, it is important to assess the level of disability to help distinguish social phobia from shyness.^[9]

Second, SAD may be complicated by comorbid major depression, which is usually responsive to first-line therapy options (e.g. selective serotonin reuptake inhibitors (SSRIs) and dual-acting serotonin-norepinephrine reuptake inhibitors (SNRIs)). Conversely, social anxiety symptoms should be excluded in patients presenting with depression, panic attacks restricted to social situations, or alcohol misuse.

Third, in patients with alcohol and substance use disorders it is generally advisable to detoxify first, prior to commencing pharmacotherapy for SAD.

Fourth, in women, pregnancy and lactation considerations may necessitate the use of a non-pharmacological intervention (e.g. cognitive-behavioural therapy) as first-line.

Fifth, the presence of comorbid medical disorders and the prescription of concurrent medications must be borne in mind when using an anti-anxiety agent, particularly in view of the potential for drug-drug interactions and the potential impact of pharmacotherapy for SAD on underlying medical conditions.

4. Treatment

4.1 Treatment goals

The need for treatment is determined by the severity and persistence of symptoms, the presence of comorbid psychiatric disorder or physical illness, the level of disability and impact on social functioning, concomitant medication, and a history of good response to, or poor tolerability of, previous treatment approaches. In line with this, the main goals of treatment in SAD are to treat core symptoms and comorbidities, reduce functional impairment and avoidance, and improve the quality of life.

4.2 General aspects of treatment

Several treatment guidelines are available including those from the World Federation of Societies of Biological Psychiatry,^[10] World Council on Anxiety,^[11] the British Association for Psychopharmacology^[9] and the Canadian Psychiatric Association.^[12] Broadly speaking, these guidelines advocate for both pharmacological and non-pharmacological approaches in the management of SAD.

4.3 Acute treatment

Current evidence clearly supports the use of SSRIs (escitalopram, fluvoxamine, fluvoxamine controlled release (CR), paroxetine, sertraline) and the SNRI venlafaxine extended release (ER) as first-line pharmacological agents in the treatment of GSAD. Improvement in symptoms should become manifest by week 4; however, up to 12 weeks of treatment are needed to more definitively assess efficacy. In terms of psychotherapy, cognitive-behavioural therapy (CBT) is the treatment of choice. There is no conclusive evidence that pharmacotherapy is more effective than CBT or vice versa and the evidence in favour of the combination of pharmacotherapy and CBT is also limited.

4.4 Maintenance treatment

Drug treatment should be continued for a minimum period of 6 months in patients who have responded at 12 weeks. Several long-term studies (double-blind and open-label) have been conducted to examine the issue of relapse prevention.^[13] These studies have evaluated moclobemide, phenelzine and CBT, sertraline and exposure therapy, fluvoxamine, paroxetine and escitalopram and venlafaxine ER. Response rates in these studies range from 58% for venlafaxine ER to 88% for escitalopram.

4.5 Pharmacological treatment

Evidence from controlled trials indicates that SAD is responsive to a wide range of medication treatments.^[4] Drugs recommended as first-line treatment include SSRIs (escitalopram, fluvoxamine, paroxetine and sertraline) and the SNRI, venlafaxine. In a meta-analysis of efficacy of the SSRIs, which examined outcomes from 15 separate controlled studies (including trials of escitalopram, sertraline, paroxetine, fluoxetine and fluvoxamine), all agents with the exception of a single trial of fluoxetine (which did not separate from placebo), showed efficacy in ameliorating symptoms of SAD.^[14] Venlafaxine has also been widely studied and venlafaxine ER has regulatory approval for SAD in a number of countries.^[4] In a head-to-head comparison of venlafaxine and paroxetine, venlafaxine ER was as effective as paroxetine, and both drugs were better than placebo.^[15] The efficacy of venlafaxine ER in SAD does not appear to be dose-related, i.e. lower (75 mg/day) and higher (150 - 225 mg/day) doses have produced similar therapeutic effects in trials.^[16] The other SNRI, duloxetine, has not been studied in controlled trials for SAD.

In addition to the SSRIs and venlafaxine, the monoamine oxidase inhibitor (MAOI) phenelzine and the reversible inhibitor of monoamine oxidase (RIMA) moclobemide have controlled evidence for efficacy. Phenelzine is not widely used because of its requirement of a low tyramine diet to prevent a hypertensive crisis. Moclobemide has demonstrated comparable effectiveness among patients with and without a comorbid anxiety disorder, as well as among patients with different SAD subtypes (generalised and non-generalised SAD).^[17]

There is preliminary evidence from randomised controlled trials for the efficacy of pregabalin and gabapentin. Open trials of other anticonvulsants (e.g. levetiracetam, tiagabine, topiramate) and the antipsychotic olanzapine show some promise as acute treatments, but adequate randomised controlled trials (RCTs) are lacking.^[4,10]

Evidence for the efficacy of benzodiazepines (bromazepam and clonazepam) in SAD is mixed.

Treatments with *unproven* efficacy in generalised social phobia include the tricyclic antidepressant imipramine, buspirone, and the beta-blocker, atenolol.^[18]

4.6 Non-pharmacological treatment

The non-pharmacological treatment of choice for SAD is CBT or exposure therapy alone. CBT for social phobia includes techniques of psycho-education, in-session and *in vivo* exposure to feared situations, and techniques intended to modify maladaptive or irrational thinking patterns. Other techniques in the CBT umbrella are applied relaxation and social skills training. The relative efficacy of CBT vs exposure therapy is unclear, with some studies indicating comparable efficacy while other studies show somewhat greater efficacy for CBT.^[4,10] In a recent meta-analysis of 32 RCTs that examined a variety of non-pharmacological approaches, CBT was consistently shown to result in significantly greater improvements in SAD symptoms than other 'placebo' conditions, such as supportive group therapy, self-exposure, being wait-listed (i.e. waiting for an intervention) or pill placebo.^[19]

4.7 Special populations

4.7.1 Pregnancy and lactation

The risks of drug treatment during pregnancy need to be weighed against the risks of withholding treatment for SAD. During the

first trimester, SSRIs do not increase the risk of birth defects; the exception to this is paroxetine which is associated with a 1.5-fold increased risk of congenital heart defects.^[20] Clinical guidelines recommend that paroxetine be discontinued during pregnancy. SSRIs taken after 20 weeks of gestation may be associated with an increased risk of persistent pulmonary hypertension in the neonate, and all antidepressants administered in the third trimester may cause discontinuation effects (e.g. increased muscle tone, irritability, disrupted sleep, jitteriness) although these tend to be mild and self-limiting. There are no data, other than a single case report, on the safety of moclobemide during pregnancy, while there are limited data on the safety of the MAOIs. As animal studies are suggestive of teratogenicity and use of MAOIs necessitates dietary modifications, MAOIs are not considered first-line treatments for SAD in pregnancy. Newer antidepressants, such as venlafaxine, have been associated with poor neonatal adaptation syndrome (tremors, irritability, shivering, feeding disturbances, increased muscle tone, respiratory difficulties) although it is unclear whether this is the result of medication withdrawal or toxicity. Treatment is supportive and symptoms usually resolve within 2 weeks. In general, venlafaxine is considered to be moderately safe in pregnancy. Benzodiazepine use during pregnancy has been associated with neonatal morbidity, some congenital malformations such as orofacial cleft, and may be associated with an increased risk for preterm birth, low birth weight, floppy infant syndrome, and neonatal withdrawal symptoms. Clonazepam monotherapy, specifically, has not been associated with an increased risk of major malformations. Gabapentin has been shown to be teratogenic in mice; its safety in pregnant women has not been established and is best avoided during pregnancy.^[20]

Long-term safety data on the use of antidepressants in pregnancy are lacking. Factors that are important to consider include the time between medication administration and feeding, and infant size and infant metabolism. Most SSRIs do not attain detectable levels in breast milk and are not associated with disturbed infant development or neuropathology. Sertraline and paroxetine may be good choices for lactating women as these SSRIs have specifically been associated with undetectable levels in infants. Benzodiazepines, such as clonazepam, diazepam and lorazepam, are excreted in breast milk. However, published data indicate that the levels detected in breast milk are low; thus the nursing infant is unlikely to ingest significant amounts of the drug in this way. Breastfeeding is possible, but the infant should be carefully monitored for any adverse effects.

4.7.2 Children and adolescents

Shyness in young children may be a precursor to SAD in adulthood. In children, common fears include fears about performance situations such as speaking or performing in front of people, social interactional fears such as joining in or starting a conversation, and interacting with same-age peers.^[21] Unlike adults, children with SAD are seen as generally anxious and may experience more somatic symptoms, such as headaches, stomach aches and nausea, as a result of their anxiety. Impairments range from low self-esteem, social skills deficits, few friendships to scholastic underachievement. Among adolescents, typical fears include formal and informal social interactions, public observation and performance, and situations requiring assertive behaviour. In addition, adolescents seem to have more pervasive patterns of fear and

avoidance, as well as higher levels of social distress than either children or adults. SAD in childhood and adolescence is highly comorbid with depression. Comorbidity with anxiety and substance use disorders is also common.^[21]

Compared with adults, there is relatively less information available on the safety, efficacy and long-term outcomes (relapse rates) of SSRI or SNRI treatment. Open-label and double-blind placebo-controlled studies have shown response rates ranging from 36% to 100%.^[9-12] Fluoxetine, fluvoxamine, paroxetine and venlafaxine ER have been evaluated in RCTs. These agents have been well tolerated in children and adolescents in doses comparable to the adult dose. Antidepressants, in particular SSRI use, have come under the spotlight in recent years owing to concerns about their potential to increase suicidal ideation and attempts.^[21] While the safety profile of SSRIs and other antidepressants specifically in children and adolescents with SAD is not yet known, a review of 24 short-term (4 - 16 weeks) trials involving nine antidepressant medications (including SSRIs) in more than 4 400 youth with major depressive disorder, obsessive-compulsive disorder, and other psychiatric disorders, documented a 4% rate of suicidal ideation and suicidal behaviours in patients treated with antidepressants compared with a 2% rate in patients treated with a placebo.^[22] It is important to note that there were no completed suicides in any of these studies.

CBT, as a 16-session treatment, has been shown to be an effective strategy in both children and adolescents with SAD, with continued improvement or maintenance of gains over a 1-year period.^[21] The benefits of combining CBT and medication for childhood SAD have yet to be established.^[21]

4.7.3 The elderly

The prevalence of SAD tends to decline in older adults (55 years of age and older). SAD is more common in elderly patients who have other psychiatric disorders, in particular major depression. Both pharmacological treatments (e.g. SSRIs, venlafaxine) and CBT are indicated for use in older adults with SAD; however, the standard of practice has been to infer from data in younger patients and assume their efficacy in older adults.^[23]

Several factors should be considered when selecting a medication for an older patient with SAD. Prior treatment response, target symptoms, concurrent physical illness and medications, and drug tolerability should all be taken into account. In order to reach the optimal dose for an older patient without causing intolerable side-effects, it is well worth remembering the adage 'start low and go slow'.^[23] Important considerations in pharmacological treatment in the elderly include heightened sensitivity for anticholinergic drug effects, increased sensitivity for extrapyramidal symptoms, an increased risk for orthostatic hypotension and electrocardiograph changes, and the possibility of paradoxical reactions (e.g. aggression) to benzodiazepines. SSRIs have been shown to be relatively safe and recommended doses of SSRIs for SAD are the same as for younger adults. However, the potential for SSRIs to cause gastrointestinal and other bleeds, hyponatraemia, postural hypotension and falls needs to be borne in mind in this age group.

4.8 Managing partial and non-responders

See steps 3 and 4 of algorithm below.

4.9 Algorithm

Step 1. Initiating treatment with pharmacotherapy/psychotherapy

Choose an evidence-based pharmacological or psychological therapy for the acute treatment of SAD.^[9] Take account of patient clinical features, needs and preference when choosing treatment. If the decision is to start pharmacological treatment with an SSRI or SNRI, the starting dose can be low (sertraline 25 - 50 mg; paroxetine 10 - 20 mg; venlafaxine 37.5 - 75 mg; fluvoxamine 25 - 50 mg; escitalopram 5 - 10 mg), with titration up to a maximally tolerated therapeutic dose (Table 1). Although routine prescription of higher doses of SSRIs is not recommended,^[9] individual patients may benefit from higher doses. For patients with comorbid mood (or anxiety) disorders, SSRIs may be preferred because of their broad spectrum of action. There is some evidence to suggest that major depressive disorder symptoms tend to resolve before an improvement in SAD symptoms is seen.^[24]

Evidence of symptom improvement should manifest by week 4. However, patients should be advised that treatment periods of up to 12 weeks are needed to assess efficacy, as there is some evidence from double-blind controlled trials to suggest that non-responders to treatment at 8 weeks become responders with 4 further weeks of double-blind treatment.^[25]

Step 2. Maintaining a response and preventing relapse

Double-blind studies indicate that continuing SSRI or SNRI treatment from 12 weeks to 24 weeks (i.e. up to 6 months after initiation) is associated with an increase in overall treatment response rates.^[9] Placebo-controlled relapse-prevention studies in patients who have responded to previous acute treatment also reveal

Table 1. Recommended daily drug doses for social anxiety disorder^{[10]*}

Selective serotonin reuptake inhibitors (SSRIs)
Escitalopram 10 - 20 mg
Paroxetine 20 - 50 mg
Sertraline 50 - 150 mg
Fluvoxamine 100 - 300 mg
Citalopram 20 - 40 mg
Fluoxetine 20 - 40 mg
Serotonin-norepinephrine reuptake inhibitors (SNRI)
Venlafaxine 75 - 225 mg
Monoamine oxidase inhibitor (MAOI)
Phenelzine 45 - 90 mg
Benzodiazepines
Clonazepam 1.5 - 8 mg
Anticonvulsant
Gabapentin 600 - 3 600 mg
Reversible inhibitor of monoamine oxidase (RIMA)
Moclobemide 300 - 600 mg

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a significant advantage for staying on active medication (clonazepam, escitalopram, paroxetine, sertraline) for up to 6 months, compared with switching to placebo.^[18] Therefore, continue drug treatment for at least another 6 months in patients who are responding at 12 weeks (i.e. show at least a 50% improvement in symptoms). Several of the guidelines recommend continuing treatment for at least 12 months. In patients at a high risk of relapse, it may be prudent to consider cognitive therapy after an adequate response to drug treatment. It is also vital that efficacy and tolerability are regularly monitored during long-term treatment.^[9]

Step 3. Managing partial response

If after 12 weeks, there is only a 25 - 50% reduction in symptoms or a less than 25% reduction in symptoms, consider switching to venlafaxine after non-response to acute treatment with an SSRI. There is no clear evidence for the benefit of dose escalation after an initial non-response. Switching between treatments with proven efficacy is preferable. Alternative treatment strategies include a switch to non-SSRI antidepressants, anticonvulsants and benzodiazepines, as discussed above.

Open-label augmentation of SSRI treatment with buspirone^[26] has been reported as beneficial but placebo-controlled trials of pindolol augmentation and clonazepam augmentation, respectively, were not associated with greater treatment efficacy.^[27,28]

Step 4. Managing non-response

If there is still no response, re-evaluate the diagnosis and reassess for comorbid substance use disorders, undetected medical conditions, comorbid personality disorders, psychosocial stressors and poor compliance. Consider combining evidence-based pharmacological treatments only where there are no contraindications to doing so. An alternative strategy is to combine drug treatment with CBT. There is some preliminary evidence for the usefulness of this approach.^[29] A recent randomised, double-blind placebo-controlled trial to determine whether combined medication and cognitive behavioural group treatment (CBGT) was superior to either monotherapy or pill placebo found that combined phenelzine and CBGT treatment was superior to either treatment alone and to placebo in terms of rates of response and remission.^[30] D-cycloserine, a partial N-methyl-D-aspartate (NMDA) receptor agonist that facilitates fear extinction, has been documented in several trials to be useful as an augmentation to CBT in patients with SAD.

5. Summary points

- SAD is highly responsive to evidence-based acute treatments:
 - *Pharmacological*: most SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), venlafaxine, phenelzine, moclobemide, some benzodiazepines (clonazepam), anticonvulsants (gabapentin, pregabalin) and olanzapine.
 - *Psychological*: cognitive-behavioural therapy (CBT).
- There is no conclusive evidence that pharmacotherapy is more effective than CBT for the treatment of social phobia.
- Treatment duration of up to 12 weeks is needed to assess efficacy.
- Drug treatment should be continued for at least a further 6 months in patients who have responded at 12 weeks.

- Cost should be factored into the choice of medication; the most affordable medication should preferably be selected to allow for funding of the minimum period of suggested pharmacotherapy.
- In the longer term, consider CBT as this may reduce relapse rates better than drug treatment.
- Monitor efficacy and tolerability regularly during long-term treatment.
- Combining a drug and psychological approach is recommended during the initial phase of treatment.
- Consider switching to venlafaxine after non-response to acute treatment with an SSRI.
- Consider combining evidence-based pharmacological treatments if there is non-response but only where there are no contraindications to do so.

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