Pharmacotherapy for social anxiety disorder in adults

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INTRODUCTION

Social anxiety disorder (SAD), also known as social phobia, is a condition marked by extreme fear of situations that involve possible scrutiny by others. The individual is concerned that embarrassment or humiliation will result, and so they avoid such situations or endures them with intense anxiety.

SAD is a prevalent condition, estimated to affect between 4 and 10 percent of the adult United States population over a 12-month period. SAD typically begins in childhood or adolescence and, untreated, can be associated with the subsequent development of major depression, substance use disorder, and other mental health problems. The disorder can be associated with extensive functional impairment and reduced quality of life [1].

This topic addresses the pharmacologic treatment of SAD. Discussed separately are epidemiology, pathogenesis, clinical manifestations, and diagnosis of SAD; psychotherapy for SAD; and fears and specific phobias in children. (See "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis" and "Social anxiety disorder in adults: Psychotherapy" and "Overview of fears and phobias in children and adolescents".)

APPROACH TO TREATMENT

Our approach to selecting among treatments for social anxiety disorder, including the use of pharmacotherapy and psychotherapy, is discussed separately. (See "Approach to treating social

anxiety disorder in adults".)

TYPES OF SOCIAL ANXIETY DISORDER

In the transition from the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) to DSM-5, the subtypes of generalized and nongeneralized social anxiety disorder (SAD) were replaced by SAD and SAD, performance only, respectively [2]. The guidance that follows applies to SAD. Pharmacotherapy for performance-only SAD is discussed separately, later in the topic. (See 'Social anxiety disorder, performance only' below.)

MONOTHERAPY

Several classes of drugs are used to treat social anxiety disorder (SAD), including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and benzodiazepines. Pharmacologic treatment is quite different for the performance-only version of SAD compared with the general form of SAD (known prior to DSM-5 as nongeneralized and generalized SAD).

Whenever pharmacotherapy is prescribed for SAD, it is good clinical practice to recommend to the patient that they enter previously feared social situations to "test out" the effects of the medication and to learn that these situations are safe and can be tolerated. Although there are no research data to support this claim, there is some reason to believe that those patients who do the most "practicing" and "expanding of their social horizons" while on medication are the ones who have the best longer-term outcomes.

Selective serotonin reuptake inhibitors — A meta-analysis of seven trials that compared SSRIs with placebo in a total of 896 patients with SAD found that SSRIs resulted in greater symptom reduction compared with placebo and had a moderate effect size [3]. SSRIs are the best studied and the most commonly prescribed of the medication treatments for SAD [4]. The SSRI paroxetine was the first medication to receive approval from the Food and Drug Administration (FDA) in the United States for SAD [5].

As an example, a clinical trial randomly assigned 183 patients with SAD to receive paroxetine (20 to 50 mg) or placebo for 11 weeks. Patients receiving paroxetine were more likely to be "much improved" or "very much improved" at the end of treatment with paroxetine compared with patients on placebo (55 versus 24 percent). The mean score on the Liebowitz Social Anxiety

Scale was reduced in the paroxetine group compared with the placebo group (39 versus 17 percent).

The clinical effects of SSRI treatment for SAD typically require four to six weeks to have a significant impact; maximal benefit can require as long as 16 weeks [6]. Patients should be encouraged to "try out" the medication by engaging in social situations that typically result in anxiety and to report back about their response. One of the first indications of response is the patient's report of feeling less "self-conscious" in typical social situations. Higher doses of SSRIs typically result in better outcomes, so the dose is usually pushed to the maximum tolerated by the individual (unless an excellent response is attained at a lower dose, at which point the dose would be held there to ascertain stability of the response).

Although some SSRIs have been more extensively studied than others in the treatment of SAD, there is no evidence of superiority of one SSRI over another. As examples:

- Paroxetine can be started at 10 mg/day taken orally and increased to a therapeutic dose of 20 mg/day after a few days. If the patient does not respond after a six-week trial, the dose can be increased in 10 mg increments every few weeks to a maximum of 60 mg/day.

- Sertraline can be started at 50 mg/day taken orally and, if the patients does not respond after six weeks, can be increased in 50 mg increments every few weeks to a maximum of 250 mg/day.

Common side effects of SSRIs include restlessness, agitation, headache, diarrhea, nausea and insomnia. SSRIs also cause sexual dysfunction in as many as 50 percent of patients. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects" and "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Management".)

Many of the side effects can be reduced or avoided by starting the medication at lower doses and increasing it gradually. See table for standard and lower initial doses as well as the range of therapeutic doses for SSRIs (table 1).

Serotonin-norepinephrine reuptake inhibitors — Although less well studied than the SSRIs, the SNRI venlafaxine extended release appears to be equally effective for SAD on the basis of a comparable effect size compared with various SSRIs in meta-analysis [7-10].

As an example, a clinical trial randomly assigned 440 patients with SAD to treatment with venlafaxine (75 to 225 mg daily extended release), paroxetine (20 to 50 mg daily), or placebo [8]. After 12 weeks, response rates were similar in the venlafaxine and paroxetine groups, both of which were superior to placebo (59 and 63 versus 36 percent response, respectively).

Medication discontinuation rates were similar with venlafaxine and paroxetine, but adverse events leading to a reduction in dosage were more common with venlafaxine (16 versus 8 percent).

Venlafaxine can be started at 37.5 mg/day taken orally and increased to a dose within the therapeutic range, between 75 and 225 mg/day (table 1). SSRI recommendations regarding gradual titration, trial duration, and dose increases apply to SNRIs as well.

The most common side effects of venlafaxine are nausea, dizziness, insomnia, sedation, and constipation. Venlafaxine may cause elevations in blood pressure. Though usually small, the increases can be significant in some patients. The medication should be avoided in patients with hypertension, and blood pressure should be monitored during use. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)

There are no published data from controlled trials on the use of another marketed SNRI, duloxetine, in the treatment of SAD.

Monoamine oxidase inhibitors — The MAOIs have the longest track record of use for SAD, having been essentially the only pharmacotherapy available (though never FDA approved) for SAD prior to the advent of the SSRIs. However, side effects and dietary restrictions limit their use. MAOIs are generally reserved for SAD refractory to other treatments. Some practitioners feel that MAOIs are more effective than SSRIs or SNRIs, though no comparative efficacy trials have been conducted to substantiate this belief. (See "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

Several randomized trials have found that phenelzine is an efficacious treatment for SAD, with approximately one-half of patients responding with a clinically significant reduction in symptoms [3]. A 2010 randomized trial that included a phenelzine arm found a response rate of 54 percent for phenelzine compared with 33 percent for placebo [11]. Phenelzine is typically started at 15 mg once or twice daily, and increased to a total dose of 60 to 90 mg/day based on response. It can take four to six weeks for a response to occur, and longer for maximal response to be attained.

MAOIs cause inhibition of the MAO enzyme. Irreversible MAOIs, such as phenelzine, are incompatible with certain foods and medications (eg, cheese, aged meats, alcohol, over-the-counter cold preparations). A potentially fatal hypertensive reaction can occur if users of MAOIs consume food containing tyramine; thus, use of irreversible MAOIs must be accompanied by a low tyramine diet. Their use is also contraindicated with other antidepressants, and over-the-counter or prescribed medications containing sympathomimetic stimulants or dextromethorphan.

Other adverse effects common at therapeutic doses include postural hypotension, insomnia, paradoxical daytime sedation, sexual dysfunction, and weight gain. In many instances, these side effects can be dose limiting.

Benzodiazepines — Two, small randomized trials found the high-potency benzodiazepines, alprazolam [12] and clonazepam [13], to be efficacious as monotherapy in the reduction of SAD symptoms. Clonazepam, a longer-acting agent with a slower rate of onset, seems to be more commonly used for SAD than other benzodiazepines. Sedation, the principal dose-limiting adverse effect, can be minimized by starting with low doses and titrating upwards slowly until a satisfactory response is achieved. As either monotherapy or in augmenting a serotonin reuptake inhibitor, clonazepam can be started at 0.25 to 0.50 mg twice daily, and increased to a maximum of 2 mg twice daily.

Benzodiazepines and SUD history — Sedation and the potential for misuse and physiologic dependence limit the usefulness of these agents, which are generally avoided in patients with a history of a substance use disorder (SUD). If other agents are not effective, however, patients with history of an SUD could be judiciously prescribed a benzodiazepine, provided that the SUD was not active and the patient's use of the medication were carefully monitored.

Gabapentin — Gabapentin (an anticonvulsant) has demonstrated modest effectiveness (response rates <45 percent) for SAD [14] in a randomized clinical trial. Sixty-nine patients were randomly assigned to receive double-blind treatment with either gabapentin (dosed flexibly between 900 and 3600 mg daily in three divided doses) or placebo for 14 weeks. Patients receiving gabapentin experienced reduced SAD symptoms compared with patients receiving placebo. Adverse events were consistent with the known side effect profile of gabapentin (eg, dizziness, dry mouth, somnolence).

Based upon case reports and human studies, the United States Food and Drug Administration issued a safety alert in 2019, warning that gabapentin may be associated with respiratory depression when administered to patients receiving central nervous system depressants or patients with underlying respiratory impairment [15]. In prescribing gabapentin to patients with these risk factors, it is prudent to start the drug at a relatively low dose (eg, 100 mg three times daily) and monitor patients for symptoms of respiratory depression (eg, unusual dizziness, dyspnea, or extreme sedation).

Pregabalin — Pregabalin, a compound related to gabapentin, has demonstrated modest effectiveness (response rates <45 percent) for DSM-IV generalized SAD [16]. Pregabalin was approved in 2006 for the treatment of anxiety in Europe [17,18]. The medication inhibits calcium currents via high-voltage-activated channels containing the a2d-1 subunit, though the

relationship of this mechanism to its efficacy for anxiety is not known. Side effects include sedation and dizziness. Tolerance, withdrawal, and dependence are possible, but pregabalin is generally better tolerated than benzodiazepines. Doses of pregabalin for SAD typically range from 150 to 600 mg per day.

The United States Food and Drug Administration issued a safety alert in 2019, warning that gabapentinoids may be associated with respiratory depression. (See 'Gabapentin' above.)

Other agents — Other medications have yielded mixed or negative results in clinical trials, or have not been sufficiently tested:

- **Moclobemide** – Moclobemide, a reversible MAOI selective for inhibition of MAO-A, has shown, at best, mixed results in randomized controlled trials of SAD [19-21]. Moclobemide is not marketed in the United States, but is available in many other countries. In contrast to non-reversible MAOIs (such as phenelzine or tranylcypromine), moclobemide does not require a low tyramine diet, and generally has fewer adverse effects overall.

- **Mirtazapine** – Mirtazapine has shown mixed results in patients with SAD. In a randomized trial of 66 women with SAD, mirtazapine (30 mg a day) was found to be efficacious for SAD compared with placebo [22]. In a more recent randomized controlled trial of 60 males and females with generalized SAD randomized to either 30 to 45 mg/day of the medication or placebo for 12 weeks, mirtazapine was no more effective than placebo (13 versus 13 percent response rate).

- **Beta-blockers** – Beta-blockers are not an effective treatment for SAD [23,24], but are effective for the performance-only SAD subtype. (See 'Social anxiety disorder, performance only' below.)

- **Tricyclic antidepressants (TCAs)** – The TCAs have not been well studied in clinical trials of patients with SAD. A small open-label trial of imipramine suggested that it was not effective. It is possible that TCAs with more potent serotonergic reuptake blockade (eg, clomipramine) might be useful, but this is unknown.

- **Second-generation antipsychotics** – Very small randomized controlled trials of olanzapine and quetiapine suggested that these atypical (or "second-generation") antipsychotics might be effective for SAD [25,26]. Considerable further study is needed as well as consideration of metabolic side effects of these agents [27].

- **Buspirone** – The limited available data suggest that buspirone is ineffective as monotherapy for SAD [28].

- **Atomoxetine** – Atomoxetine, an SNRI (marketed for the treatment of attention deficit disorder/hyperactivity [ADHD]), was not shown to be effective for DSM-IV generalized SAD in a small randomized controlled trial [29]. However, there is some evidence from a trial in adults with comorbid ADHD and SAD [30] that atomoxetine may be helpful for both ADHD and SAD symptoms in patients who have both.

- **Oxytocin** – Intranasal oxytocin (24 international units) versus placebo has been shown to improve some social behaviors and anxious appearance in 40 patients with SAD [31], but an effect on symptoms or overall functioning was not observed in that study [31] or in an earlier placebo-controlled trial [32].

AUGMENTATION

A substantial number of patients with social anxiety disorder (SAD) respond only partially to monotherapy [4], leading to clinical trials in DSM-IV generalized SAD of medications augmenting selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) with other agents:

- **Buspirone** – A small uncontrolled trial found that 7 of 10 patients partially responsive to SSRIs appeared to benefit from augmentation with buspirone [33].

- **Clonazepam** – Randomized trials have found some evidence in support of augmentation of an SSRI with clonazepam [34,35]. As an example, in the larger trial, 181 patients with social anxiety disorder who had no more than a partial response to 10 weeks of sertraline were randomly assigned to 12 weeks of continuation on sertraline augmented by either clonazepam or placebo [35]. (A third arm, in which patients were switched from sertraline to venlafaxine, is described separately.) (See "Approach to treating social anxiety disorder in adults", section on 'No substance use disorder history'.)

  The proportion of patients responding to treatment (defined as a Liebowitz Social Anxiety Scale [LSAS] score <50) was greater in patients receiving sertraline plus clonazepam compared to the other two groups. Patients receiving sertraline plus clonazepam had a clinically significant decrease in LSAS severity compared to patients receiving sertraline plus placebo. A numerical advantage favoring a higher rate of remission (an LSAS score ≤30) in patients receiving sertraline plus clonazepam compared with patients continuing on sertraline plus placebo and to patients switched to venlafaxine (27 versus 17 and 19 percent); the results did not reach statistical significance.

The use of benzodiazepines in patients with a history of a substance use disorder is described above. (See 'Benzodiazepines and SUD history' above.)

- **Other**

  - **Pindolol** – A small randomized trial did not show a benefit of augmenting paroxetine with the beta-blocker pindolol compared to placebo augmentation [36].

  - **Monoamine oxidase inhibitors** – Monoamine oxidase inhibitors should not be combined with other antidepressants due to the risk of serotonin syndrome. (See "Serotonin syndrome (serotonin toxicity)".)

  - **Ketamine** – A small randomized clinical trial of a single dose of intravenous ketamine (0.5 mg/kg over 40 minutes) versus placebo in 18 adults with SAD found that patients were more likely to exhibit a treatment response (defined as >35 percent reduction on the LSAS) after ketamine relative to placebo in the first two weeks following infusion (33.3 versus 0 percent) [37]. The response rate to both treatments is low. More work is needed to determine the efficacy and safety of ketamine infusions for SAD.

SOCIAL ANXIETY DISORDER, PERFORMANCE ONLY

In the transition from DSM-IV to DSM-5, the subtypes of generalized and nongeneralized social anxiety disorder (SAD) were replaced by SAD and SAD, performance only (specifier) [38].

Medication treatment is often prescribed on an "as needed" basis for performance-only SAD. We suggest benzodiazepines or beta-blockers as first-line medication treatment. Administering a test dose prior to treatment, at the same dose intended to be used prior to the performance situations(s), can be useful to assess the drug's effects.

Benzodiazepines — Benzodiazepines can also be used on an "as needed" basis to treat performance-only SAD [39]. Clonazepam 0.25 to 1 mg or lorazepam 0.5 to 2 mg can be given 30 to 60 minutes before the performance. Tolerance and physical dependence are not a concern with occasional use. But the potential for misuse, highest in persons with a history of alcohol or other substance use, should also limit their use in this context.

Sedation can be a side effect of benzodiazepines, particularly at higher doses. For this reason, the patient should be encouraged to try out the medication in advance of a potentially precipitating event to determine how well it is tolerated and to see if it is efficacious. The prescribing physician may need to fine-tune the dose for the individual. Patients may have used

alcohol in the past to cope with similar situations and should be explicitly cautioned not to mix alcohol with benzodiazepines.

Beta-adrenergic blockers — There is no evidence from clinical trials on the effectiveness of beta-blockers (such as propranolol) in the treatment of performance-only SAD [40]. Beta-blockers are nonetheless used at times for the management of performance anxiety; clinical experience suggests that only half (or fewer) people find as-needed beta-blockers useful for performance anxiety.

Beta-adrenergic blockers may be most useful for patients who have prominent awareness of physiological symptoms such as tachycardia or tremor.

Propranolol can be taken orally 30 to 60 minutes prior to the anxiety-inducing situation, at an initial dose of 10 or 20 mg. The patient should be encouraged to try out the medication in advance of a potentially precipitating event to determine how well it is tolerated and to see if it is efficacious. If tolerated but not sufficiently effective, increase the dose next time by 10 or 20 mg. Some patients may eventually require a dose of 60 mg. Contraindications to the prescription of beta-blockers include: a history of beta-blocker intolerance or allergy, diabetes, and certain cardiac conditions (eg, conduction problems). (See "Major side effects of beta blockers".)

Cannabinoids — A small, randomized, double-blind study of 600 mg cannabidiol (n = 12) versus placebo (n = 12) never-treated patients with SAD found that cannabidiol reduced anxiety during a public speaking task [41]. More recently, cannabidiol 300 mg oral (n = 39) versus placebo (n = 41) did not enhance the effects of exposure therapy on outcomes in a study that included patients with SAD and panic disorder with agoraphobia [42].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Anxiety and anxiety disorders in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given

condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topic (see "Patient education: Social anxiety disorder (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Monotherapy** – Several classes of drugs are effective in the treatment of social anxiety disorder (SAD), including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and benzodiazepines. (See 'Monotherapy' above.)
  - **SSRIs** – Although some SSRIs have been more extensively studied than others in the treatment of SAD, there is no evidence of superiority of one SSRI over another. (See 'Selective serotonin reuptake inhibitors' above.)
  - **SNRIs** – Although less well studied than the SSRIs, the SNRI venlafaxine extended release appears to be equally effective for SAD on the basis of a comparable effect size compared with various SSRIs. (See 'Serotonin-norepinephrine reuptake inhibitors' above.)
  - **MAOIs** – The MAOIs have the longest track record of use for SAD; however, side effects and dietary restrictions limit their use. MAOIs are generally reserved for SAD refractory to other treatments. (See 'Monoamine oxidase inhibitors' above.)
  - **Benzodiazepines** – The high-potency benzodiazepines, alprazolam and clonazepam, have been found to be efficacious as monotherapy in the treatment of symptoms of SAD. For individuals with a history of benzodiazepine use or substance use disorder (SUD) we avoid treatment with benzodiazepines and use gabapentin or pregabalin as alternative treatment. (See 'Benzodiazepines' above and 'Benzodiazepines and SUD history' above.)

- **Other agents with limited or mixed supporting data** – Moclobemide, mirtazapine, beta blockers, tricyclic antidepressants, buspirone, second-generation antipsychotics, atomoxetine, and oxytocin have mixed or limited data supporting their use in the treatment of SAD. (See 'Other agents' above.)

SSRIs, SNRIs, and MAOIs may take four to six weeks for an initial response and 12 to 16 weeks to achieve their full effect. We typically continue these and other medications for SAD for at least 6 to 12 months to decrease the likelihood of relapse. Some patients may need continuing treatment to maintain the gains achieved. (See 'Monotherapy' above.)

- **Augmentation** – A substantial number of patients with SAD respond only partially to monotherapy. Clinical trials have found limited evidence supporting clonazepam, buspirone, and ketamine as augmenting agents. (See 'Augmentation' above.)

- **SAD, performance only** – In the transition from American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) to DSM-5, the subtypes of generalized and nongeneralized SAD were replaced by SAD and SAD, performance only (specifier). (See 'Social anxiety disorder, performance only' above.)

  - We suggest **not treating** performance-only SAD with medication. However, medication is a reasonable alternative if preferred by the patient or if a therapist trained to provide cognitive-behavioral therapy were not available.

  - When medication is used to treat SAD, performance-only specifier, we suggest treatment with a benzodiazepine in patients who lack a history of an SUD (**Grade 2C**).

  - For patients with an SUD history or who experience sedation with a benzodiazepine, a beta-blocker is a reasonable alternative unless the patient has a contraindication to their use.

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