Medication Treatments for Social Anxiety Disorder

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Abstract: Social anxiety disorder or social phobia (SP) is defined as "the intense fear of becoming humiliated in social situations, specifically of embarrassing yourself in front of other people" (National Institute of Mental Health, 2000). It affects between 6% and 15% of the general U.S. population (1), is the third most common psychiatric disorder, and is extremely debilitating to those who have it. Individuals with SP are extremely fearful and avoid social situations (APA, 2000). The fear is caused primarily by feelings that they will be humiliated or embarrassed. The onset of SP is usually in childhood or adolescence, and the disorder occurs more often in women than in men. Many people are so affected by it that they cannot work and cannot start or maintain personal or professional relationships; in addition, an unusually high rate of comorbid depression is seen in individuals with SP. More recently, interest has focused on the development course of SP, leading to a reconceptualization of the disorder as a chronic neurodevelopment illness rather than one manifesting for the first time in adulthood (2). In recent years, our knowledge of SP has included important advances in the understanding of the epidemiology, neurobiology, and neural circuitry of SP. In this clinical synthesis, we will review the diagnosis, psychopharmacological treatment, and recent questions and controversy regarding this debilitating, yet treatable, disorder. DSM-IV-TR criteria for social anxiety disorder are listed in Table 1.

Clinical context

SP is the third most prevalent psychiatric disorder in the United States following major depression and alcoholism. SP often appears in adolescence with a mean age of onset of 15 years with a slightly higher prevalence in women than in men (3, 4). Despite its high prevalence, barriers in both identifying and treating social anxiety symptoms cause many individuals with social anxiety symptoms to experience delays in obtaining treatment (5). Many individuals with SP are unaware that they have a treatable condition. Other barriers include avoidance in seeking treatment because of the fear and stigma of the illness and, in those individuals who do seek treatment, the possibility of being either underdiagnosed or misdiagnosed by clinicians. Many clinicians may lack knowledge about SP and view it as a normal variant of shyness and something many people "will simply outgrow." Moreover, because of the high comorbidity of SP with both depression and alcohol use, the assessment and treatment may focus on these comorbid conditions (6). Major depression is one of the most frequent comorbid conditions associated with SP. The risk for subsequent depression was twice that in patients with SP compared with that in those individuals without SP (7). The importance of identifying and treating SP is underscored by findings that the suicide attempt rate for individuals with comorbid SP is 16-fold greater than that of those depressed individuals without SP (8); moreover, another study demonstrated that social anxiety disorder was associated with almost one and one-half times the risk of having suicidal thoughts (9).

Diagnostic approach to SP

Quick screening tool

A quick tool for screening for SP is shown in Table 2.

CME Disclosure

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Table 1. DSM-IV-TR Diagnostic Criteria for Social Anxiety Disorder

1. The person has a marked and persistent fear of one or more social or performance situations involving exposure to unfamiliar people or possible scrutiny by others.
2. The person fears that he or she will act in a way (or show symptoms of anxiety) that will be humiliating or embarrassing.
3. Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a panic attack.
4. The person recognizes that the fear is excessive or unreasonable.
5. The feared social or performance situations are avoided or endured with intense anxiety or distress.
6. The condition interferes significantly with the person's normal routine, occupational (or academic functioning), or social activities or relationships, or there is marked distress about having the phobia.
7. The fear of avoidance is not due to the direct physiological effects of a substance or a general medical condition and is not better accounted for by another mental disorder.
8. If a general medical condition or another mental disorder is present, the social or performance fear is unrelated to it (e.g., the fear is not of trembling in Parkinson's disease.

DIFFERENTIAL DIAGNOSIS

The initial approach to diagnosis of SP begins with a general screening for anxiety symptoms, which often includes a simple question: "Do you feel anxious?" If the answer is "yes," it is then important to rule out medical induced anxiety disorders such as (but not limited to) hypothyroidism, hypoglycemia, and mitral valve prolapse. It is also imperative to screen for current use of substances that might induce anxiety including stimulants, for example, cocaine or ephedrine. After these "medical and substance use" causes have been ruled out, the clinician can then narrow the focus to the predominant anxiety disorder the patient currently has. An anxiety screening question that incorporates the core features of SP including feeling embarrassment when speaking or being in front of others is often a logical next step. The differential diagnosis of SP includes generalized anxiety disorder (GAD), panic disorder with agoraphobia (PD), and avoidant personality disorder (which will be discussed in the later section on controversies and questions). Unlike panic disorder, which begins in the 20s or 30s, the onset of SP is often in the early to mid teens. Moreover, the somatic symptoms of SP include blushing, sweating, and tremors, whereas those in PD involve shortness of breath and palpitations. The principle differences between SP and PD involve the cognitions and triggers. In PD, the cognitions involve a sense of impending doom and the triggers include a feeling of "wanting to escape." In contrast, in SP, the cognitions involve fear and humiliation, and the triggers involve being scrutinized and being "the center of attention." GAD is another anxiety disorder that is often in the differential diagnosis with SP. However, the onset of GAD is also somewhat later than that of SP, beginning in an individual's early 20s. Also, in contrast to SP, the somatic symptoms include chronic discomfort and muscle tension and often involve multiple organ systems; the cognitions in GAD involve excessive and chronic worry over minor matters and the triggers involve work, school, and social events.

Table 2. Mini-SPIN Items*

1. Fear of embarrassment causes me to avoid doing things or speaking to people.
2. I avoid activities in which I am the center of attention.
3. Being embarrassed or looking stupid is among my worst fears

* Optimum efficiency at a cutoff score of three for each item. SPIN, Social Phobia Inventory.
From Connor KM, Kobak KA, Churchill LE, Katzelnick D, Davidson JR: Mini-SPIN: a brief screening assessment for generalized social anxiety disorder. Depress Anxiety 2001; 14:137–140. Reprinted with permission.

TREATMENT STRATEGIES

SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

The current U.S. Food and Drug Administration-approved medications for the treatment of social anxiety disorder include fluvoxamine (Luvox CR), venlafaxine (Effexor XR), paroxetine (Paxil), Paxil CR, and sertraline (Zoloft). Similar to that for other anxiety disorders, the first-line pharmacotherapy includes the selective serotonin reuptake inhibitors (SSRIs) with paroxetine, sertraline, and fluvoxamine CR all approved for the treatment of SP (10, 11). The serotonin-norepinephrine reuptake inhibitors (SNRIs) (specifically venlafaxine) have also been demonstrated to be quite effective in treating individuals with this disorder (12, 13). It appears that the SSRIs and venlafaxine have roughly equivalent efficacy for SP (10). Large double-blind trials in a head-to-head comparison of venlafaxine and paroxetine found that both were equally effective (12, 14, 15). Benzodiazepines are considered a second-line treatment for SP with longer-acting agents such as clonazepam being preferred over shorter-acting medications such as alprazolam (16–18). Unlike in panic disorder, the

tricyclic antidepressants have demonstrated little efficacy in treating individuals with SP (19). Other agents such as bupropion and mirtazapine have shown some promise in early open-label studies, but more large, controlled studies are needed to evaluate their effectiveness for treating SP (20). Mirtazapine (a $5HT_2$, $5HT_3$, and α_2-adrenergic receptor antagonist), in particular, showed efficacy in a single placebo-controlled trial with only female subjects at 30 mg/day (21, 22).

OTHER ANTIDEPRESSANTS

There have been no randomized control trials to date demonstrating the efficacy of bupropion in individuals with SP although open-label studies suggest some benefit (20). For those individuals with nongeneralized social anxiety (performance anxiety), β-blockers (such as atenolol) have been demonstrated to be quite effective in alleviating some of the symptoms (23, 24).

MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase inhibitors (MAOIs) (irreversible) have also been shown to be quite effective in the treatment of social anxiety disorder stemming from earlier studies demonstrating both effectiveness in mixed phobic disorders (25) as well as improvement of interpersonal sensitivity in individuals with atypical depression (24). Phenelzine, in particular, has been shown to be effective in four double-blind placebo-controlled trials examining the efficacy of the MAOIs for social anxiety disorder (21). The reversible MAOIs have also been studied for the treatment of social anxiety disorder. Moclobemide has been shown to have generally positive results in studies in social anxiety disorder (14); however, one double-blind study demonstrated no statistical significance for moclobemide over placebo at the end of the 12-week study (14). Although it has not been marketed in the United States, another reversible MAOI, brofaromine, has demonstrated efficacy in SP in three placebo-controlled trials (14).

ANTICONVULSANTS: GABAPENTIN AND PREGABALIN

These medications have been postulated to work through binding to the $\alpha_2\delta$ subunit of voltage-sensitive calcium channels (21). There have been only a few studies with mixed results. Whereas in a 14-week placebo-controlled flexible dose study (26), gabapentin did reduce severity of symptoms as shown on the Liebowitz Social Anxiety Scale (LSAS), there was a significant dropout rate due to side effects and only one-third of the patients had greater than a 50% reduction in symptoms. A 10-week placebo-controlled trial of pregabalin (27) demonstrated a greater decrease in the LSAS score at higher doses (600 mg/day) but not at lower doses, compared with controls. This result was supported by a more recent double-blind placebo-controlled fixed-dose study, which showed that higher dose treatment (600 mg) with pregabalin significantly improved LSAS scores among subjects with social anxiety disorder (28). Levetiracetam has unfortunately demonstrated disappointing results for the treatment of social anxiety disorder in several studies (29).

ANTIPSYCHOTICS AND SOCIAL ANXIETY DISORDER

There has been recent interest in investigating the efficacy of augmentation with atypical antipsychotics in both treatment-resistant depression and treatment-refractory obsessive compulsive disorder. There have been relatively few studies looking at atypical antipsychotics in the treatment of social anxiety disorder. In particular, in a small study olanzapine as a monotherapy treatment appeared effective and tolerated between 2.5 and 20 mg/day (30). Another study involving quetiapine in which 15 patients were randomly assigned to 400 mg of quetiapine or placebo demonstrated no significant differences on the primary measures with the exception of Clinical Global Impression scales (40%–0%) (31). Moreover, another study looking at quetiapine given before public speaking exposures also did not yield significant results (32).

D-Cycloserine

D-Cycloserine is an antibiotic used to treat tuberculosis. It works as a partial agonist at the glycine modulatory site of the *N*-methyl-D-aspartate receptor and in preclinical studies has been shown to safely enhance learning and memory in several animal models (33). There have been several clinical studies investigating D-cycloserine in combination with exposure therapy in the treatment of anxiety disorders, all with promising results with the caveat that all the studies had relatively small sample sizes (34, 35).

QUESTIONS AND CONTROVERSY

DISCRETE VERSUS GENERALIZED SP

What exactly is SP? The vast majority of the studies involving SP view the disorder under one

major category. This category encompasses both generalized SP, in which individuals are fearful of most social situations and hypersensitive to criticism, and discrete SP (performance anxiety), in which individuals are fearful of speaking or performing in public. There is growing controversy as to whether it is appropriate to distinguish between these two subtypes. A recent review concluded that there was insufficient evidence to distinguish between the two and the symptoms of social anxiety disorder fell along a "continuum of severity based on the number of fears" (36). However, other earlier studies have illuminated the differences in transmission between these two subtypes. In one study, it was shown that the rates of familial transmission were 16% for generalized SP compared with a substantially lower transmission rate of 6% for patients with discrete SP (37). Another study examining the transmission of SP found that subjects with generalized social phobia and persons with avoidant personality disorder had a 10 times higher rate of familial transmission compared with control subjects, whereas they found no significant difference between individuals with discrete social phobia and the control population (38). Another area that has always intrigued researchers studying SP has been the different response to pharmacological treatment exhibited by the two subtypes of SP. Generalized social phobia seems to respond quite effectively to SSRIs (39), irreversible MAOIs such as phenelzine (Nardil) (40) and benzodiazepines (16), whereas discrete social phobia responds particularly well to β-blockers such as atenolol (23). Thus, the findings from both genetic transmission and pharmacological studies converge in demonstrating significant differences between the two subtypes of SP and, in turn, lead to the theory that there may be separate neurotransmitters and distinct neural circuitry involved in generalized social phobia and discrete social phobia.

ARE SOCIAL ANXIETY DISORDER AND AVOIDANT PERSONALITY DISORDER THE SAME DISORDER?

Another area of controversy involves whether to classify SP and avoidant personality disorder as two separate entities or whether they are essentially the same disorder. Although some reviews have shown no consistent clinical differences in symptom presentation (41), more recent studies have demonstrated qualitative differences between the two disorders; specifically, they have shown that the symptoms of avoidant personality disorder are more severe and broader in nature (42). Other studies examining differences in genetics (43) and treatment response (both behavioral and pharmacological) showed no compelling evidence that they should be viewed as two separate disorders.

SUMMARY

In summary, social anxiety disorder is an extremely prevalent and disabling disorder but also a disorder that can be effectively treated with medications including SSRIs, SNRIs, MAOIs, and benzodiazepines. Promising novel medications include atypical antipsychotics, anticonvulsants, and the *N*-methyl-D-aspartate agonist D-cycloserine. There is still research to be conducted to help determine whether both SPs should be viewed as one disorder or two separate entities and whether avoidant personality disorder should be also viewed as a separate disorder.

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