Easing the Burden of Social Anxiety Disorder

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the planning teleconference series "Easing the Burden of Social Anxiety Disorder," which was held in May and June 2008. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Jazz Pharmaceuticals.*

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Social anxiety disorder (SAD) is a common condition that often occurs comorbid with other disorders. The pathophysiology of SAD is not fully understood, but this disorder is chronic and appears to result from a combination of genetic and environmental factors. Although treatments are available to alleviate the burden of this disorder, SAD remains largely undiagnosed and undertreated.

In this ACADEMIC HIGHLIGHTS, Michael R. Liebowitz, M.D., introduced the following 3 essential topics: diagnosis, etiology and epidemiology, and treatment. Franklin Schneier, M.D., discussed conditions that have symptom overlap with SAD and conditions that are often comorbid with SAD, which are important components of the differential diagnosis. Dan J. Stein, M.D., Ph.D., reviewed the epidemiology of SAD and the neurocircuitry and neurotransmitters that may be involved in the etiology of SAD, which provide a basis for understanding how pharmacotherapy may help to ease social anxiety symptoms. Finally, Jonathan R. T. Davidson, M.D., elaborated on therapeutic interventions that have been shown to be effective in the treatment of SAD.

Differential Diagnosis of Social Anxiety Disorder and Common Comorbidities

Features of SAD

Dr. Schneier explained that the characteristic feature of SAD is marked and persistent fear of social and performance situations, specifically due to fear of embarrassment or humiliation in the situation (Table 1).[1] Exposure to a social situation usually provokes anxiety, which makes it a characteristic response, not an isolated one. Also, the person with SAD is aware that the fear is excessive or unreasonable and does not hold a delusional belief that the problem lies in other people. Feared situations are typically avoided or endured with distress, and this anxiety and avoidance must interfere with functioning or cause marked distress in order to distinguish it from normal anxiety.

According to Dr. Schneier, an important aspect of the differential diagnosis of SAD is recognizing the difference between trait social anxiety, which is a natural, normal shyness, and pathologic social anxiety disorder. In fact, social anxiety itself is not pathologic but adaptive. Social anxiety increases arousal and attention to social interactions.[2] It may inhibit aggressive or inappropriate social behavior, and moderate levels of social anxiety help motivate people to prepare for a social performance, providing energy to a presentation or a performance. However, the disorder occurs when the increased anxiety is excessive.

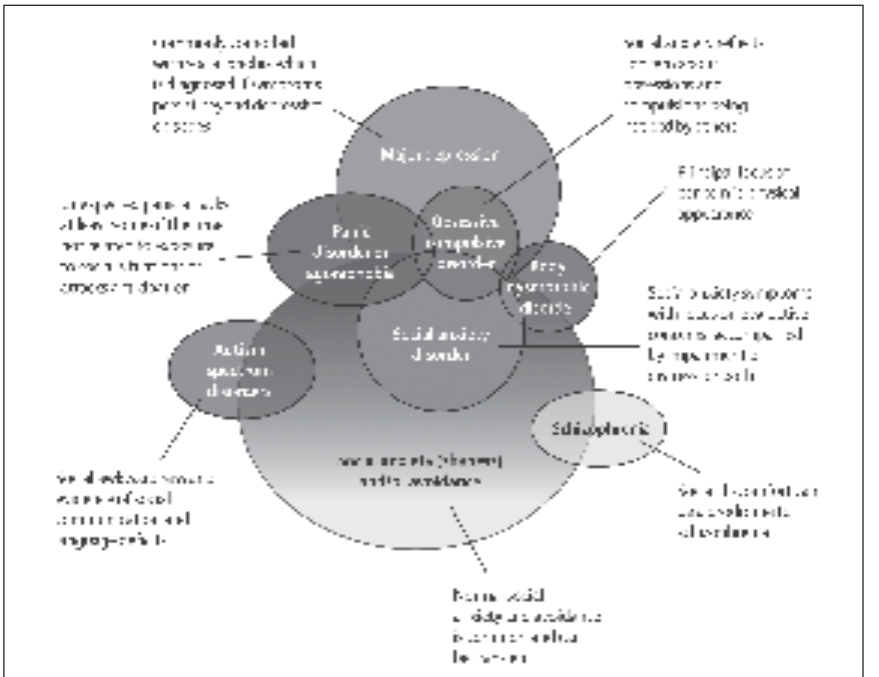
Prevalence rates of clinically significant social anxiety differ depending on how the distress or impairment threshold is defined. For example, Dr. Schneier described a study[3] using 3 systematically modified sets of criteria for social anxiety. When the threshold required moderate interference or distress, the prevalence rate was 18.7% in a community sample. When the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R)[4] criteria were used, which require marked interference or distress, the prevalence rate decreased to 7.1%. Limiting the threshold to only marked interference lowered the rate to 1.9%. In addition, higher prevalence rates have been found in studies that asked participants about more types of social situations.[2]

Table 1. DSM-IV Criteria for Social Anxiety Disorder (abbreviated)[a]

Persistent fear of 1 or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears he or she will act in a way (or show anxiety symptoms) that will be embarrassing and humiliating.
Exposure to the feared situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic attack.
The person recognizes that this fear is unreasonable or excessive.
The feared situations are avoided or else are endured with intense anxiety and distress.
The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the person's normal routine, occupational (academic) functioning, social activities or relationships, or there is marked distress about having the phobia.
In individuals under age 18 years, the duration is at least 6 months.
The fear or avoidance is not due to direct physiologic effects of a substance (e.g., drugs, medications) or a general medical condition.
The disturbance is not due to another mental disorder.

[a]Adapted with permission from the American Psychiatric Association.[1]

Figure 1. Conditions That Commonly Overlap With Social Anxiety Disorder[a]



[a]Reprinted with permission from Stein and Stein.[5]

The DSM-IV[1] recognizes 2 subsets of SAD, generalized and nongeneralized. The generalized subtype of SAD is defined by anxiety in most social situations. This subtype exhibits the most impairment and is more likely to exist with comorbid disorders. Most patients included in clinical trials of SAD have the generalized subtype of SAD. The remainder of patients with SAD who do not meet the criteria for generalized subtype may be diagnosed as having nongeneralized or discrete SAD or performance anxiety. Individuals with the nongeneralized subtype tend to have difficulty only with specific performance situations, most commonly public speaking. Some controversy exists over the distinction between 2 subtypes versus the concept of a continuum of social anxiety severity,[2] but the subtypes have some relevance for selecting treatments for patients.

Conditions That Share Symptoms of SAD

Dr. Schneier explained that some psychiatric disorders have criteria that overlap with SAD and should be considered in the differential diagnosis of SAD (Figure 1).[5] Most closely overlapping is avoidant personality disorder.[5] Severe SAD has so many similarities to avoidant personality disorder that there has been controversy over whether these should be considered separate diagnostic categories.[5,6] The *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (DSM-IV)[7] diagnosis for avoidant personality disorder requires that 4 of 7 criteria be met, and of the 7 criteria, 5 are related to social avoidance and 2 are related to cognitions about social rejection or inferiority, which are also features considered central to SAD. Studies comparing avoidant personality disorder to SAD tend to find differences in severity rather than qualitative distinctions.

Avoidance of social situations is not specific to SAD but can occur in patients with many other psychiatric conditions,[2] including generalized anxiety disorder (GAD), panic disorder with agoraphobia, posttraumatic stress disorder (PTSD), depressive disorders, and psychotic disorders. People with GAD, Dr. Schneier explained, worry about several different areas of their lives, and social anxiety may be an important part of those worries but not the predominant focus, as it is in SAD.

Patients with panic disorder with agoraphobia often initially fear uncued panics, which have no identified precipitant, but they may secondarily come to fear embarrassment when people witness their anxiety.[5] These patients may avoid social situations because of this indirect fear of embarrassment, but the primary diagnosis would be panic disorder with agoraphobia. Patients with SAD also may have panic attacks in social situations, although panic attacks are not required for, nor are they specific to, the diagnosis of SAD.[5] Dr. Schneier stated that the patient's perception of the cause of their panic attacks can be useful in diagnosis. If all panic attacks are cued by entering a social situation or thinking about a social situation, then they would be considered part of SAD.

Patients with panic disorder can first have unexpected panic attacks that then also come to be associated with social or performance situations without meriting a second diagnosis of SAD. However, patients with SAD can secondarily develop unexpected panic attacks that would then warrant an additional diagnosis of panic disorder. Distinguishing these disorders can be useful for treatment considerations, such as responsivity of panic disorder but not SAD to tricyclic antidepressants.

People with PTSD may also avoid social situations,[8] but typically they avoid what they experience as dangerous situations, particularly if they have had an interpersonal trauma such as an assault. Dr. Schneier suggested that these patients may also avoid social situations out of a loss of social interest—the emotional numbing that is characteristic of PTSD. The primary concern is rarely a fear of embarrassment or rejection in this case. Similarly, individuals with depressive disorders, most commonly major depression, may avoid social situations due to a loss of social interest, but here due to a general anhedonia or lack of energy rather than primary fear of embarrassment.[5] Those with psychotic disorders may also avoid interpersonal situations for a variety of reasons, for example, a delusional fear of being harmed by others.[5] Because avoiding social situations is an aspect of several other psychiatric disorders, Dr. Schneier recommended that clinicians inquire thoroughly about a patient's rationale for social avoidance as part of the differential diagnosis of SAD.

Common Comorbid Disorders

In addition to differentiating SAD from other disorders to determine a primary diagnosis, clinicians must consider whether a patient has co-occurring disorders. Dr. Schneier reported that 80% of patients with SAD in the community have lifetime comorbidity.[9] Specifically, 50% of those patients have other anxiety disorders. Rates of substance use disorders, particularly alcohol abuse and cannabis abuse, are also elevated in patients with SAD, as are rates of major depressive disorder (MDD), dysthymia, and bipolar disorder.[10]

Dr. Schneier noted that, in patients with SAD and comorbid disorders, SAD usually occurs first.[10] While earlier onset may be partially due to a typically early age at onset of SAD (usually in childhood or adolescence), SAD might also lead to secondary disorders as a consequence of the condition itself. For example, patients with major depression may report that the focus of their depressive ideation is their problem with social anxiety. Similarly, some patients with SAD report that they began to abuse alcohol for the purpose of self-medicating their social anxiety and that the alcohol use later became an ongoing problem of its own. Many patients will seek treatment only after developing a complication like depression or substance abuse. Dr. Schneier stressed that clinicians should inquire about preexisting social anxiety symptoms when patients present with these other conditions, as specific treatment may need to be directed at each condition present.

Some disorders that are accompanied by prominent fears of negative evaluation also tend to have high rates of comorbidity with SAD. These disorders include depression, particularly depression with atypical features such as sensitivity to rejection; selective mutism, in which children avoid speaking up in situations with strangers present; body dysmorphic disorder, in which persons focus on a particular part of their body that they feel appears abnormal; eating disorders, especially bulimia nervosa, which may include fear of being evaluated by others based on appearance; and a variety of medical conditions with physical symptoms that are visible to others and may be a source of embarrassment and heightened social anxiety. Dr. Schneier described these disorders in more detail.

Depression. Depression is highly comorbid with SAD, and, given that each is a common disorder, the comorbid state is also highly prevalent. A community survey found that 3.9% of the population had a lifetime prevalence of SAD combined with MDD.[11] In samples of depressed patients, about one quarter had comorbid SAD; the comorbidity of SAD and avoidant personality disorder was found more commonly in patients with atypical depression than typical depression.[12,13] Among primary care patients with SAD, 36% to 58% had comorbid MDD.[14,15]

Dr. Schneier explained that comorbid SAD is a marker for a more severe syndrome of depression. Specifically, comorbid SAD is associated with an increase in the number and duration of MDD episodes, increased suicidality, increased alcohol dependence, and presence of the atypical depressive trait of interpersonal sensitivity.[11,16,17]

Dr. Schneier then reviewed research about the influence of SAD on suicidal ideation and its relationship to comorbidity. The Epidemiologic Catchment Area (ECA) study[10] found that individuals with SAD were more likely to report suicidal ideation than were those without a psychiatric disorder, and persons with a psychiatric disorder and comorbid SAD had higher rates of suicidal ideation and suicide attempts than persons with the same psychiatric disorders without comorbid SAD. Dr. Schneier stated that SAD may be an added stressor in patients with depression in that it may limit the social network on which a person may rely.

Selective mutism. Studies[18,19] have reported that SAD has a high incidence of symptom overlap (fear of embarrassment and avoidance of social situations) with selective mutism. In a study[18] of 30 children with selective mutism, 97% had SAD or avoidant disorder of childhood or both. Of the subjects' first-degree relatives, 70% had a history of SAD. In another study,[19] all the patients with selective mutism (N = 50) also had SAD or avoidant disorder. Dr. Schneier added that medications known to be useful for SAD may be useful in selective

mutism, although further study is needed.

Body dysmorphic disorder and eating disorders. Body dysmorphic disorder shares the symptom of concern about social evaluation and comparison with SAD but also seems to overlap with obsessive-compulsive disorder (OCD). Between 34% and 50% of patients with body dysmorphic disorder have been found to meet diagnostic criteria for current or lifetime SAD.[20,21] Eating disorders share the symptom of fear of negative social comparison with SAD and are highly comorbid with SAD. Godart et al.[22] reported that 55% of patients with anorexia and 59% of patients with bulimia had lifetime SAD. Social anxiety disorder typically had an earlier age at onset than the eating disorders.

Medical conditions. A variety of potentially embarrassing medical conditions, such as stuttering, tremor related to movement disorders, hyperhidrosis, obesity, and conditions that cause disfigurement, share symptoms with SAD.[23] Dr. Schneier noted that, according to DSM-IV, a medical condition that is accompanied by social anxiety is not diagnosed as SAD if the medical condition is primary and if the social concerns are all related to embarrassing features of the medical condition. However, if these patients have prominent social anxiety, they might benefit from treatments directed at that symptom.

Dr. Schneier outlined a modified stress-diathesis model in which the diathesis is the person's individual vulnerability to social anxiety. A person who has no tendency toward social anxiety might be little affected by the social stressor of physical symptoms that call attention to the individual. However, patients who are predisposed toward social anxiety, but who ordinarily would not meet full criteria for SAD, might experience distress and impairment from social anxiety exacerbated by obvious, potentially embarrassing physical symptoms.

Paranoid conditions. Paranoid conditions may also co-occur with SAD. Typically, fear of harm and delusional fear have been considered distinct from the fear of embarrassment, but some studies have found correlations between them. In one epidemiologic study,[24] social anxiety appeared to be a potential risk factor for schizophrenia. Furthermore, Pallanti et al.[25] suggested that antipsychotic treatment, clozapine in particular, might increase SAD symptoms.

Dr. Schneier elaborated on another disorder called Taijin Kyofusho (TKS), an East Asian variant of SAD that is conceptualized as ranging from typical SAD symptoms to delusional symptoms. TKS is common in Japan and Korea and includes features that are characteristic of SAD like fear of embarrassment and fear of showing signs of anxiety.[26] However, TKS also includes several culture-specific features that may have a delusional intensity, such as a fear of offending others by making too-direct eye contact, experiencing a stiff facial expression, and emitting body odor. Some controversy exists as to whether this diagnosis should be brought into future diagnostic criteria for SAD.

Conclusion

Dr. Schneier reiterated 3 important clinical considerations for the differential diagnosis of SAD: (1) distinguish normal social anxiety from pathologic anxiety on the basis of functional impairment or distress; (2) recognize that avoidant personality disorder frequently overlaps with SAD, which may be due to similarities in their diagnostic criteria; (3) and assess the underlying basis for why people may express social fears or social avoidance.

Comorbidity of SAD with other disorders is extremely common, whether SAD is the primary or secondary diagnosis. Dr. Schneier stressed the importance of screening for SAD in patients with depression and SUD, and vice versa. Patients with other psychiatric disorders who also have SAD may benefit from specific treatments directed at their social anxiety. Dr. Schneier suggested that paying attention to comorbid secondary SAD in other patient populations may improve the treatment course of the primary disorder.

The Etiology, Epidemiology, and Functional Burden of Social Anxiety Disorder

Dr. Stein stated that SAD, also known as social phobia, is one of the most common psychiatric disorders. According to the U.S. National Comorbidity Survey Replication (NCS-R) study, the 12-month prevalence for social phobia is 6.8%,[27] and the lifetime prevalence is 12.1%.[28] Although prevalence estimates may vary across countries and studies because of different diagnostic criteria, certain epidemiologic patterns are relatively consistent, explained Dr. Stein. For example, prevalence rates are higher in females than males cross-culturally, and social phobia increases the risk of suicide in patients with comorbid psychiatric disorders.[29] The disorder usually begins in adolescence and precedes most comorbid psychiatric disorders. Further, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)[30] reported that over 80% of patients with SAD did not receive treatment, and SAD was associated with high rates of comorbidity.

Dr. Stein elaborated on an NCS-R study by Ruscio et al.[31] that found a high incidence of psychiatric comorbidity, role impairment, and treatment-seeking among respondents with social phobia. The study also found that each of these phenomena had a "dose-response" relationship with the number of social fears per individual—the more social fears in a given individual, the greater the comorbidity, role impairment, and treatment-seeking. However, among patients who received psychiatric treatment, social phobia was the focus of clinical attention in only half of cases. Among people with no comorbidity, those with more social fears were least likely to receive treatment for SAD.

Dr. Stein emphasized that functioning and quality of life decreased in individuals with SAD. Patients with SAD, compared with individuals without SAD, tend to have greater use of health care services, fewer years of schooling, lower income, and are more likely to be single.[10,15] According to Dr. Stein, the vulnerability of patients with SAD to other disorders and their lower quality of life amplify the need to detect and treat SAD as early as possible.

Neurocircuitry Associated With SAD

Dr. Stein stated that the advent of functional imaging has increased understanding of the neural circuitry involved in social cognition and how it can become dysfunctional.

Basic studies. Prather et al.[32] found that lesions in the neonatal amygdala of monkeys increased social fear but decreased fear of novel objects, suggesting that the amygdala plays an important role in social perception and mediation of fear. In humans, functional magnetic resonance imaging (fMRI) studies have found that the amygdala is activated by negatively or positively valenced facial expressions as opposed to neutral faces.[33] Another study[34] found that adults who had inhibited temperament as infants had greater fMRI signal response in the amygdala to novel versus familiar faces than adults who were not inhibited as infants.

Clinical studies. A range of studies have been conducted using fMRI to explore SAD. Birbaumer et al.[35] found that the amygdala is active during exposure to fear-relevant stimuli in patients with social phobia. Abnormal patterns of amygdala-hippocampal activation in patients with SAD during aversive conditioning have also been reported.[36] Using fMRI, Veit et al.[37] also found that social fear may be associated with an overactive frontolimbic system, while psychopathic fear may be associated with a hypoactive frontolimbic system.

One study[38] of single-photon emission computerized tomography (SPECT) scanning at rest found increased frontal perfusion in patients with SAD, and positron emission tomography (PET) showed an increase in the cerebral blood flow (rCBF) in the amygdala of patients with social phobia compared with healthy controls.[39] However, after treatment, there is a normalization of perfusion in both SPECT[40] and PET studies.[41]

Neurotransmitters Associated With SAD

Within the neuronal circuits are proteins such as neurotransmitter receptors. Dr. Stein reviewed 2 neurotransmitter systems that are likely involved in SAD, dopamine and serotonin.[42]

Dopamine. A range of studies have pointed to the role of dopamine in SAD. These include clinical studies that suggest an association between Parkinson's disorder and SAD,[43] and early biological studies indicating that patients with introverted depression, as well as SAD, had low dopamine metabolite levels in their cerebrospinal fluid.[44,45]

Grant et al.[46] found evidence of decreased striatal dopamine (D_2) binding in animals with subordinate behavior compared with those with dominant behavior. In humans, studies[46,47] have indicated that D_2 receptors may be associated with certain personality traits. For example, D_2 receptor polymorphisms have been found to be associated with schizoid or avoidant traits.[48]

Breier et al.[47] reported a relationship between decreased striatal D_2 binding and personal detachment in healthy subjects. Further, studies have found decreased density of striatal dopamine reuptake sites[49] and lower striatal D_2 binding potential[50] in patients with social phobia compared with healthy comparison subjects. Finally, the selective efficacy of monoamine oxidase inhibitors over tricyclic antidepressants in the treatment of SAD provides evidence for the role of dopamine in this disorder.[2,42]

Serotonin. Serotonin has also been implicated in SAD. Dr. Stein stated that serotonergic circuits are involved in the modulation of amygdala-mediated fear pathways, and increased serotonergic function may be associated with dominant versus submissive status.[42] Hollander et al.[51] found that patients with social phobia exhibited increased cortisol response after receiving the partial serotonin agonist *m*-chlorophenylpiperazine, compared with control subjects and patients with OCD. Tancer et al.[52] discovered an augmented cortisol response in patients with generalized social phobia compared with controls after they received the serotonin probe fenfluramine. Further, Furmark et al.[53] found that a functional polymorphism in the promoter region of the human serotonin transporter gene may be associated with increased levels of anxiety and differences in amygdala response to anxiety provocation.

Selective serotonin reuptake inhibitors (SSRIs) produce improvements in SAD,[54] which further suggests that serotonin may play a role in SAD. Dr. Stein cited one SPECT study[40] that showed decreased rCBF in insulae of patients with SAD after 8-week treatment with an SSRI or a reversible monoaminoxidase-A inhibitor. While both agents improved SAD symptoms and decreased rCBF in the insulae, patients treated with the SSRI also showed decreased rCBF in the superior cingulate, a region with many serotonin transporters. Furmark et al.[55] found that both SSRI treatment and cognitive-behavioral therapy (CBT) resulted in decreased rCBF in the amygdala, hippocampus, and neighboring cortical areas of patients with SAD who responded to treatment.

Neurogenetics of SAD

Neurogenetic exploration of SAD has revealed interesting finds, said Dr. Stein, such as a familial transmission of generalized SAD as seen in twin studies.[56] While a gene may not exist for social phobia per se, a gene or genes may exist for inhibited temperament or behavioral inhibition, which could develop into social anxiety.[57,58] According to Dr. Stein, it is interesting to

explore not only proximal mechanisms associated with SAD, such as neural circuitry and neurotransmitters, but also relevant distal mechanisms, which have come about over a process of evolution.[59] For example, blushing is an evolved response in humans, and blushing can be a core symptom of SAD. Exploring relevant neuro-evolutionary mechanisms may help to develop a better understanding of the etiology of anxiety disorders, such as SAD, Dr. Stein argued.

Conclusion

Dr. Stein concluded that SAD and SAD-spectrum disorders are highly prevalent, chronic conditions characterized by substantial morbidity and comorbidity. These conditions remain underdiagnosed in primary care, perhaps because shyness is so readily normalized. Further, these conditions are phenomenologically and biologically heterogeneous, which means that further exploration of the psychobiology of these disorders is important for understanding individual variations among patients.

Identifying Effective Treatments for Social Anxiety Disorder

The goal of treatment for patients with SAD is to reduce fear, avoidance, and physical symptoms such as sweating, blushing, and trembling. As well as treating these core features of the disorder, clinicians should focus on reducing the disability and comorbidity commonly associated with SAD. Several options exist for the treatment of SAD, including first- and second-line pharmacotherapeutic treatments, CBT, other medications that address common comorbidities, and agents for performance anxiety.

First-Line Treatments for SAD

Serotonin reuptake inhibitors (SRIs) are the preferred first-line treatment for patients with SAD (Table 2).[60–68] Of those, fluvoxamine controlled-release (CR), paroxetine CR and immediate release (IR), sertraline, and venlafaxine extended release (XR) are approved by the U.S. Food and Drug Administration (FDA) for the treatment of SAD. The remaining SRIs, such as fluoxetine, escitalopram, citalopram, and duloxetine have been approved for other anxiety disorders, and for some of these (fluoxetine, fluvoxamine IR, and escitalopram), there is supportive evidence for their benefit in SAD. Irreversible monoamine oxidase inhibitors (MAOI), such as phenelzine, are consistently effective, while reversible, selective MAOIs, such as moclobemide, are inconsistent in their effects; MAOIs will not be addressed in any great detail here. When prescribing any of these medications, clinicians should always be aware of and monitor for side effects and drug-drug interactions, especially when discontinuing agents.

Fluvoxamine. The first SSRI to be studied for SAD treatment, fluvoxamine has been shown to be effective in managing SAD symptoms. Most recently, 2 randomized, placebo-controlled trials[60,61] found that fluvoxamine CR was superior to placebo over the 12-week study periods, although Westenberg et al.[61] concluded that Clinical Global Impressions-Improvement scale (CGI-I) response rates were not significant between groups. Patients taking the active medication experienced improvements on both patient- and clinician-rated scales, and both studies concluded that fluvoxamine CR was a safe and effective treatment for patients with generalized SAD.

Paroxetine. In 1992, paroxetine IR became the first FDA-approved medication for the treatment of SAD. Stein et al.[62] conducted an 11-week, randomized, double-blind trial of paroxetine IR with the primary outcomes defined as response (much improved or very much improved on the CGI-I) and mean change from baseline on the Liebowitz Social Anxiety Scale (LSAS). Results showed that the paroxetine group achieved higher rates of response (55.0% vs. 23.9%, respectively, $p = .001$) and greater reductions on LSAS scores (39.1% vs. 17.4%, respectively, $p < .001$) than the placebo group. At endpoint, patients taking paroxetine experienced improvements in key SAD symptoms, including avoidance, fear, and anxiety, as well as improvements in their social, work, but not family, lives.

Dr. Davidson emphasized that SAD is a chronic illness, and patients who discontinue their medication are at risk for relapse. Stein et al.[63] followed patients who responded to paroxetine IR during an acute phase (12 weeks) study[62] and continued to treat those responders with either paroxetine IR or placebo over the subsequent 24 weeks. Significantly fewer patients who maintained paroxetine IR treatment relapsed than placebo-treated patients (14% versus 39%, respectively, $p < .001$),[63] illustrating the benefit of continuing pharmacotherapy after acute therapy has been successfully completed.

For paroxetine CR, a 12-week, double-blind, placebo-controlled study[64] reported that patients taking paroxetine CR had significantly greater remission rates (defined by ≥ 70% decrease in LSAS total score) compared with those taking placebo (24.3% versus 8.2%, respectively; $p < .001$). However, Dr. Davidson emphasized that the low remission rate for the paroxetine CR group highlights the fact that even first-line acute treatments for SAD may not provide optimal results for many patients, so clinicians must keep working toward the goal of remission with all patients.

Sertraline. The second FDA-approved agent for SAD, sertraline, has also been shown to be effective in managing the symptoms of SAD in both acute and maintenance phases. In a 20-week, double-blind study,[65] patients treated with sertraline demonstrated significant improvements over placebo-treated patients on all primary and secondary measurements at endpoint ($p \leq .001$), including fear, avoidance, and physiological response. Further, 53% of the sertraline group were

Table 2. Representative Studies of Serotonergic Antidepressants for Social Anxiety Disorder (SAD)

Drug	Study	Dosage	Duration	Endpoint Outcomes on Measurements: Significant Improvements[a]	Endpoint Outcomes on Measurements: Nonsignificant Improvements	Common Reported Side Effects
SRIs						
Fluvoxamine CR*	Davidson et al.[60]	100–300 mg/d, with 50 mg/d weekly increases as necessary	12 wk	LSAS, CGI-I, CGI-S, PGI-I, SDS	MADRS	Headache, nausea, somnolence, insomnia
	Westenberg et al.[61]	Flexible dose range of 100–300 mg/d	12 wk	LSAS, CGI-I, CGI-S, PGI-I, SDS	None	Nausea, headache, insomnia, asthenia, somnolence
Paroxetine IR*	Stein et al.[62]	20 mg/d with 10 mg/d weekly increases as necessary (up to 50 mg/d)	11 wk	LSAS (Avoidance, Fear/Anxiety), CGI-I, SADS, SDI (Social Life, Work)	SDI (Family Life)	Headache, delayed ejaculation, somnolence, nausea
	Stein et al.[63]	20 mg/d and titrated up to 50 mg/d	24 wk	LSAS, CGI-I, SCL-90, SDS, SPIN, EuroQol Visual Analog Scale	HAM-D	Abnormal ejaculation, nausea, headache, somnolence, insomnia, sweating
Paroxetine CR*	Lepola et al.[64]	Flexible dose range of 12.5–37.5 mg/d	12 wk	LSAS (Avoidance, Fear/Anxiety), CGI-I, CGI-S, SADS, SDS, (Family Life, Social Life, Work)	None	Nausea, asthenia, abnormal ejaculation, sweating, impotence, somnolence, insomnia, decreased libido
Sertraline*	Van Ameringen et al.[65]	Initial dose of 50 mg/d with flexible dose range of 50–200 mg/d	20 wk	BSPS (Fear, Avoidance, Physiologic response), CGI-I, CGI-S, Fear of Negative Evaluation Scale, Marks Fear Questionnaire, SADS, SDI (Social Life), SPIN	SDI (Family Life, Work)	Nausea, insomnia, dyspepsia, flu syndrome, delayed ejaculation, sweating
	Walker et al.[66]	50–200 mg/d	44 wk	BSPS (Fear, Avoidance), CGI-S, MADRS, Marks Fear Questionnaire, SDI (Work)	BSPS (Physiologic response), CAS, CGI-I, SADS, SDI (Family Life, Social Life), SPAI	Headache, flu-like symptoms
Venlafaxine XR*	Stein et al.[67]	Fixed dose of 75 mg/d or flexible dose range of 150–225 mg/d	28 wk	LSAS, SDS (Family Life, Social Life, Work), SPIN	WPAI	Nausea, somnolence, anorexia, asthenia, dizziness, dry mouth
Escitalopram	Lader et al.[68]	5 mg/d, 10 mg/d, or 20 mg/d	12 and 24 wk	LSAS (Avoidance, Fear/Anxiety), CGI-I, CGI-S, SDS (Family Life, Social Life, Work)	LSAS (Avoidance, Fear/Anxiety; for the 10 mg/d dose)	Nausea, fatigue, increased sweating, diarrhea, somnolence, ejaculation failure

[a]Statistical significance is defined as $p \leq .05$.
*Approved by the U.S. Food and Drug Administration for the treatment of SAD.
Abbreviations: BSPS = Brief Social Phobia Scale, CAS = Clinical Anxiety Scale, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = CGI-Severity scale, CR = controlled release, Ham-D = Hamilton Rating Scale for Depression, IR = immediate release, LSAS = Liebowitz Social Anxiety Scale, MADRS = Montgomery-Asberg Depression Rating Scale, SADS = Social Avoidance and Distress Scale, SCL-90 = Symptom Checklist-90, SDI/SDS = Sheehan Disability Inventory/Sheehan Disability Scale, SPAI = Social Phobia and Anxiety Inventory, SPIN = Social Phobia Inventory, WPAI = Work Productivity and Impairment questionnaire, XR = extended release.

much or very much improved on the CGI-I compared with 29% of the placebo group, leading Van Ameringen et al.[65] to determine that sertraline is safe and efficacious in the treatment of SAD.

A maintenance therapy study[66] was conducted after a 20-week lead-in, and patients who responded to sertraline treatment were then randomly assigned to receive either sertraline or placebo for 24 weeks. At endpoint, only 4% of sertraline-continued patients had relapsed versus 36% of the patients who switched to placebo, and the relative risk for relapse for the switch group was 10.2, which demonstrated the efficacy of sertraline as a relapse prevention agent over the long term.

Venlafaxine. A serotonin norepinephrine reuptake inhibitor (SNRI), venlafaxine XR has been shown to treat the symptoms of SAD. Stein et al.[67] conducted a randomized, double-blind study and reported response and remission rates of 58% and 31%, respectively, for the venlafaxine XR group versus 33% and 16%, respectively, for the placebo group. Again, the remission rate with active treatment was not high, pointed out Dr. Davidson. Additionally, improvement on the LSAS was substantially greater with the active medication (75 mg/day or 150–225 mg/day) over the 6-month trial. The researchers concluded, and Dr. Davidson concurred, that although venlafaxine XR is effective in treating SAD, this effect was not dose dependent, and the therapeutic result with venlafaxine XR may not necessarily be due to the increased reuptake blockade of norepinephrine. Overall, more research is needed on using SNRIs in the treatment of SAD.

Escitalopram. A randomized, placebo-controlled study[68] comparing the SSRIs escitalopram and paroxetine with placebo found that both active medications achieved higher response rates than that of placebo at the end of 12 weeks, and escitalopram, 5 mg/day and 20 mg/day, significantly improved LSAS scores over placebo ($p < .001$). Dr. Davidson stated that there was no evidence of a dose-dependent effect of the drug. As the study[67] progressed from weeks 12 to 24, patients further demonstrated improvements in LSAS scores, with all doses of escitalopram superior to placebo and escitalopram, 20 mg/day, superior to paroxetine, 20 mg/day. The 24-week endpoint results suggest that prolonging pharmacotherapeutic treatment beyond the acute phase will continue to improve patients' overall conditions.

Second-Line Treatments for SAD

If the available first-line treatments for SAD are ineffective at controlling patients' symptoms, other pharmacologic options such as benzodiazepines, $\alpha_2\delta$ calcium channel blockers, atypical antipsychotics, and combination therapies may be considered (Table 3).[69–75]

Benzodiazepines. Benzodiazepines can provide relief of anxious symptoms, as demonstrated by one such medication, clonazepam. A double-blind pilot study[69] showed that the response rate was 58.3% higher for clonazepam-treated patients compared with that of placebo-treated patients (78.3% and 20.0%, respectively), and clonazepam was well-tolerated. Dr. Davidson stated that this study illustrates the benefits of using a benzodiazepine in the treatment-resistant SAD population—benzodiazepines have a rapid onset of action, are effective, work reliably, and can be used as needed for situational anxiety. However, disadvantages of benzodiazepines like clonazepam or alprazolam include initial sedation, difficulty discontinuing the medication and abuse liability, and inefficacy for treating comorbid depression.

In a 44-week continuation therapy study,[70] patients who remained on clonazepam treatment for 5 months after responding to a 6-month treatment period had a 0% relapse rate, compared with a 21.1% relapse rate in patients who slowly down-titrated the medication, suggesting that clonazepam is effective over the long-term treatment of SAD. In the group who slowly tapered treatment, 27.7% experienced withdrawal symptoms.

$\alpha_2\delta$ Calcium channel blockers. Although originally developed as anticonvulsant agents, $\alpha_2\delta$ calcium channel blockers such as gabapentin and pregabalin have shown considerable efficacy for treating SAD. Pande et al.[71] found that patients who were administered flexibly dosed gabapentin had a significant reduction in social phobia symptoms compared with patients administered placebo over the 14-week period ($p < .05$). Additionally, gabapentin was well-tolerated and had a favorable risk-benefit analysis. Another study by Pande et al.[72] examined pregabalin, 150 mg/day and 600 mg/day, versus placebo, and showed that 600 mg/day of pregabalin 600 mg/day significantly decreased LSAS total scores ($p = .024$), including subscores on total fear, total avoidance, social fear, and social avoidance ($p \leq .05$). Dr. Davidson noted that the 150-mg/day dose was not significantly superior to placebo on any measures, and the response rates for both active medication groups were low. Levetiracetam and tiagabine are other anticonvulsants that may be effective, but Dr. Davidson stressed that more research is needed on these agents in order to make treatment recommendations.

Atypical antipsychotics. No atypical antipsychotic has been approved for the treatment of SAD, yet 2 have shown efficacy in treating the disorder in small preliminary trials. For example, an 8-week, double-blind pilot study[73] found that olanzapine produced superior results compared with placebo on Brief Social Phobia Scale scores and Social Phobia Inventory scores. Similarly, an 8-week controlled trial[74] of quetiapine showed that 40% of patients taking the active medication and 0% of patients taking placebo were much or very much improved according to the CGI-I. However, results indicated no significant difference between groups on number of responders, illustrating the need for further study on the use of atypical antipsychotics in the treatment of SAD.

Table 3. Representative Studies of Second-Line Medications for Social Anxiety Disorder (SAD)

Drug	Study	Dosage	Duration	Endpoint Outcomes on Measurements: Significant Improvements[a]	Endpoint Outcomes on Measurements: Nonsignificant Improvements	Common Reported Side Effects
Benzodiazepines						
Clonazepam	Davidson et al.[69]	Flexible dose range of 0.5–3 mg/d	10 wk	CGI-S, Fear of Negative Evaluation Scale, LSAS, Marks Fear Questionnaire SDS (Social, Work)	HAM-D, SDS (Family)	Unsteadiness, dizziness, anorgasmia, forgetfulness, poor concentration
	Connor et al.[70]	Flexible dose range of 1–2.5 mg/d	44 wk	BSPS, CGI-I, MSPSS (Avoidance, Fear)	None	Not reported
$\alpha_2\delta$ Calcium channel blockers						
Gabapentin	Pande et al.[71]	Flexible dose range of 900–3600 mg/d	14 wk	BSPS, HAM-D, LSAS, SPIN	HAM-A, Marks Fear Questionnaire	Dizziness, dry mouth, somnolence, nausea, flatulence, decreased libido
Pregabalin	Pande et al.[72]	150 mg/d or 600 mg/d	11 wk	BSPS (Fear), LSAS (Avoidance, Fear; for the 600 mg/d dose)	BSPS, CGI-S, HAM-A, HAM-D, LSAS, Marks Fear Questionnaire, SF-36, SPIN	Somnolence, dizziness, headache, abnormal thinking, asthenia
Atypical antipsychotics						
Olanzapine	Barnett et al.[73]	5 mg/d titrated up to 20 mg/d	8 wk	BSPS, SPIN	CGI-I, LSAS, SDS	Drowsiness, dry mouth, weight gain
Quetiapine	Vaishnavi et al.[74]	Flexible dose up to 400 mg/d	8 wk	None	BSPS, CGI-I, SDI, SPIN	Drowsiness, dizziness, nausea
Combination therapy						
Paroxetine + clonazepam	Seedat and Stein[75]	Paroxetine 20–40 mg/d + clonazepam 1–2 mg/d	10 wk	None	BSPS, BDI, CGI-I, LSAS, SDS	Somnolence, jitteriness, nausea, anxiety, sweating, restlessness, sexual side effects

[a]Statistical significance is defined as $p \leq .05$.
Abbreviations: BSPS = Brief Social Phobia Scale, BDI = Beck Depression Inventory, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = CGI-Severity scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, LSAS = Liebowitz Social Anxiety Scale, MSPSS = Marks-Sheehan Main Phobia Severity Scale, SDI/SDS = Sheehan Disability Inventory/Sheehan Disability Scale, SF-36 = 36-item short form health survey, SPIN = Social Phobia Inventory.

Combination therapy. An approach that may be useful for treating patients with SAD who have partially responded or who have not responded to SSRI monotherapy is to add a benzodiazepine. Seedat and Stein[75] found that the combination of paroxetine and clonazepam was superior to the paroxetine-placebo combination on CGI-I response rates (79% versus 43%, respectively) at endpoint (10 weeks), although this difference was not significant. The paroxetine-clonazepam combination did not lead to more rapid response. Dr. Davidson stated that few studies examining combination therapy for SAD exist, and, although this study did not examine treatment-resistant patients, future studies of this population may find combination treatment to be effective.

Cognitive-Behavioral Therapy for SAD

Cognitive-behavioral therapy for SAD consists of a set of techniques that help patients repeatedly confront their feared objects, situations, memories, and images, which reinforces patients' learning that the fear is unrealistic or exaggerated; Dr. Davidson stated that exposure can be in vivo or imaginal. In vivo exposure is a process in which patients confront feared situations in real life, for example, by going to a party or initiating conversations with strangers. Imaginal exposure entails patients imagining that they are confronting feared situations and feared negative consequences, such as giving a speech and being severely criticized by the audience.

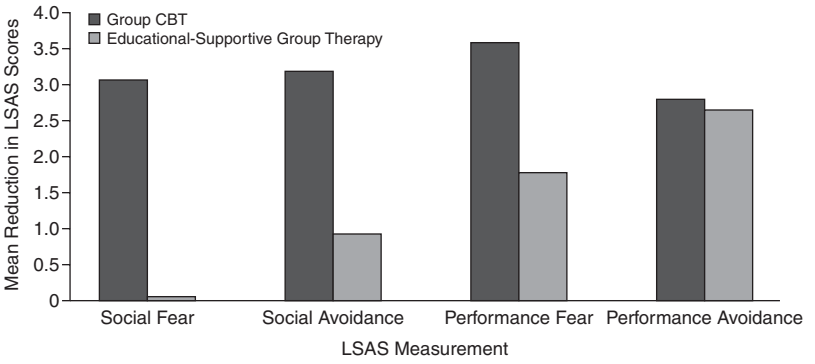
A 12-week trial[76] compared group CBT, the monoamine oxidase inhibitor phenelzine, a pill placebo, and educational-supportive group therapy (deemed a placebo version of CBT). At endpoint, rates of response were as follows: 75% for the CBT group (21 of 28), 77% for the phenelzine group (20 of 26), 41% for the placebo group (11 of 27), and 35% of the educational-supportive group (9 of 26; $p < .001$), showing that both CBT and phenel-

zine were superior to either of the other treatments and that no substantial difference existed between CBT and phenelzine. Further, decreases in LSAS scores demonstrated that not only were CBT and phenelzine more effective than the pill placebo treatments, but also that CBT produced more improvement than educational-supportive therapy (Figure 2).[76]

Davidson et al.[77] examined fluoxetine and CBT monotherapy, fluoxetine and CBT combination therapy, and CBT and placebo combination therapy in a 14-week trial of patients with generalized SAD. According to the CGI-I and the Brief Social Phobia Scale, all active treatments were more effective than placebo, yet no difference existed among the active treatment groups. Thus, Dr. Davidson concluded, CBT is a safe and effective treatment as monotherapy, and there is no evidence that its combination with medication is superior to either alone. Cognitive-behavioral therapy may, however, be an effective adjunctive strategy for those patients who do not respond well to medication monotherapy.

Recent evidence has shown that taking the antibiotic *d*-cycloserine before CBT sessions may help patients with SAD overcome their fears and anxiety. In a double-blind, placebo-controlled trial,[78] subjects receiving 50 mg of *d*-cycloserine 1 hour before each of 5 CBT sessions (either individual or group) reported significantly fewer social anxiety symptoms at posttreatment than those receiving placebo and CBT according to scores on the LSAS and the Social Phobia and Anxiety Inventory ($p = .02$ and $p = .006$, respectively). *d*-Cycloserine is a partial agonist at the *N*-methyl-D-aspartate glutamatergic receptor and appears to promote the extinction of feared responses, which, Dr. Davidson noted, may explain its efficacy. Because behavior therapy is primarily constructed around erasing patients' fears, which are replaced by more adaptive behaviors and cognitions, single doses of *d*-cycloserine in the context of the CBT session may be beneficial.

Figure 2. Mean Reductions in LSAS Scores for Completers With Social Anxiety Disorder Receiving Either Group CBT or Educational-Supportive Group Therapy[a]



[a]Data from Heimberg et al.[76]
Abbreviations: CBT = cognitive-behavioral therapy, LSAS = Liebowitz Social Anxiety Scale.

Treating SAD and Common Comorbidities

Patients with SAD frequently have co-occurring psychiatric conditions, such as depression and alcohol use disorder, although most research on SAD excludes patients with either comorbidity. One open study[16] had subjects who were diagnosed with primary generalized SAD and secondary MDD. Patients (N = 21) were treated for 12 weeks with a flexible dose of citalopram. At endpoint, 76.2% of patients had experienced response in depressive symptoms, and 66.7% of patients had a response in SAD symptoms. More than 12 weeks may be required to resolve SAD, particularly in patients with comorbid MDD.

Schneier et al.[79] examined patients with SAD and comorbid major depression (N = 20) who were treated with escitalopram, 10 mg/day to 20 mg/day. Patients' response rates were 45% for SAD and 75% for MDD over a 12-week naturalistic follow-up. Dr. Davidson stated that the larger response rates for depressive symptoms suggest that SAD may be a more complex condition to treat than MDD and may require additional treatment strategies.

For patients with SAD and alcohol use disorder, a pilot 8-week study[80] found a significant effect of paroxetine versus placebo on social anxiety symptoms as measured by the LSAS and the CGI-I ($p \leq .05$) and, although statistical significance was not shown for the quantity or frequency of drinking, 50% of the paroxetine group and only 11% of the placebo group experienced improvement on drinking measures. A subsequent and recently published 16-week, double-blind study[81] found that paroxetine substantially improved social anxiety over placebo as shown by the LSAS total scores and subscores, but there was no advantage for drug over placebo in drinking measures. The latter study provides the first placebo-controlled evidence of the efficacy of an SSRI in treating the SAD component of this dual diagnosis.

Treating Performance Anxiety

Unlike generalized social anxiety, in which the reuptake of serotonin alleviates many SAD symptoms, performance anxiety may require other agents, such as β-blockers, to temporarily calm a person for a specific situation. Evidence shows that using a β-blocker such as propranolol before performing surgery,[82] taking an examination,[83] going to the dentist,[84] and undergoing surgery[85] reduces anxiety and tremor, improves overall test scores, lessens self-reported anxiety and overall pain intensity, and reduces outpatients' anxiety, respectively. Dr. Davidson stressed that, although β-blockers may be effective in treating performance anxiety, they are not effective in treating generalized SAD.

Thus, physicians who prescribe β-blockers to a patient with SAD and do not observe an improvement in anxiety or fear should not be discouraged, but may need to re-evaluate the patient's diagnosis and treatment plan.

Conclusion

Dr. Davidson concluded that the first-line pharmacotherapeutic recommendation for the treatment of generalized SAD is using SRIs, based on the premise that these drugs have a broader efficacy spectrum than do most of the other drugs known to be effective in SAD. Moreover, inhibition of serotonin reuptake appears to best alleviate symptoms, and there is no evidence that norepinephrine reuptake inhibition provides any further enhancement of benefit. Cognitive-behavioral therapy is also a first-line option. Benzodiazepines and $\alpha_2\delta$ calcium channel blockers are presently the main second-line medication choices for SAD, and as atypical antipsychotics are better understood in the treatment of SAD, they may become a more widely-used therapeutic option, particularly for more severely impaired patients. Similarly, combining treatments is also a treatment option; however, Dr. Davidson stated that more research on efficacy and safety is necessary before making clinical recommendations about the use of drug combinations.

Residual morbidity remains the biggest challenge in treating SAD. Dr. Davidson emphasized that the primary treatment goal is to effectively alleviate patients' fear, phobic avoidance, physical symptoms, disability, and comorbidity, and if remission is achieved using medication, that agent should be maintained for at least 1 year to improve patients' overall outcomes as well as to prevent relapse.

Drug names: alprazolam (Xanax, Niravam, and others), citalopram (Celexa and others), clonazepam (Klonopin and others), clozapine (Clozaril, FazaClo, and others), cycloserine (Seromycin), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), gabapentin (Neurontin and others), levetiracetam (Keppra), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), pregabalin (Lyrica), propranolol (Inderal, InnoPran, and others), quetiapine (Seroquel), sertraline (Zoloft and others), tiagabine (Gabitril), venlafaxine (Effexor and others).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, alprazolam, citalopram, clonazepam, clozapine, cycloserine, duloxetine, escitalopram, fluoxetine, fluvoxamine, gabapentin, levetiracetam, moclobemide, olanzapine, phenelzine, pregabalin, propranolol, quetiapine, tiagabine, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of social anxiety disorder.

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