Comorbidity, Neurobiology, and Pharmacotherapy of Social Anxiety Disorder

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Social anxiety disorder is a common psychiatric illness that imposes persistent functional impairment and disability on persons who have the disorder. The disorder is characterized by a marked and persistent fear of social or performance situations in which embarrassment may occur. It is the most prevalent of any anxiety disorder and is the third most common psychiatric disorder after depression and alcohol abuse. Social anxiety disorder typically begins during childhood with a mean age at onset between 14 and 16 years and is sometimes preceded by a history of social inhibition or shyness. Persons who have social anxiety disorder either endure or avoid social situations altogether because the fear of embarrassment causes such intense anxiety; such avoidance may ultimately interfere with occupational and/or social functioning and lead to significant disability. The duration of social anxiety disorder is frequently lifelong, and there is a high degree of comorbidity with other psychiatric disorders. Social anxiety disorder is a serious illness that frequently runs a chronic course and is associated with significant morbidity. Patients should be treated aggressively using pharmacotherapeutic agents that can be tolerated over the long term. Cognitive-behavioral therapy should also be considered in treatment planning. Efforts to increase the recognition of social anxiety disorder as a common, distressing, and disabling condition are critical. This article discusses the comorbidity, neurobiology, and pharmacotherapy of social anxiety disorder. *(J Clin Psychiatry 2001;62[suppl 12]:24–29)*

Social anxiety disorder is a common psychiatric illness that imposes persistent functional impairment and disability on persons who have the disorder. Social scrutiny almost always provokes an immediate anxiety response in these patients. To differentiate normal shyness from social anxiety disorder, DSM-IV refers to the intensity of the experience in terms of distress and the recognition (even by the patient) that the fear is excessive or unreasonable. Impairment in work function—i.e., missed workdays, decreased productivity at home, and overall occupational impairment—places a personal burden on the individual and a burden on society because of lost work productivity. Persons who have social anxiety disorder either endure or avoid social situations altogether because the fear of embarrassment causes such intense anxiety; such avoidance may ultimately interfere with occupational and/or social functioning and lead to significant disability. Disability in these patients is a critical clinical issue that can cause enormous distress. Disability can also complicate the understanding of the neurobiological mechanisms of the disorder because the pathologic state is, to some extent, defined by social, political, and cultural norms. Thus, the ability to tease out underlying neurobiological mechanisms may in part depend on the patient's perceived distress and disability and their impact on treatment-seeking behavior. In an effort to increase the recognition of social anxiety disorder as a common, distressing, and disabling condition, this article will discuss the comorbidity, neurobiology, and pharmacotherapy of social anxiety disorder.

Social anxiety disorder is commonly conceptualized as having 2 distinct subtypes, generalized and nongeneralized.[1] The nongeneralized subtype is predominantly associated with performance anxiety (e.g., public speaking), whereas patients who have the generalized subtype are anxious in most social situations. Persons with generalized social anxiety have increased social and occupational impairment, are more disabled, and tend to have a higher incidence of comorbid depression or alcohol abuse than those with the nongeneralized subtype.[1]

PREVALENCE OF SOCIAL ANXIETY DISORDER

The National Comorbidity Survey (NCS) has established that social anxiety disorder is the most prevalent of any anxiety disorder and is the third most common psychiatric disorder after depression and alcohol abuse.[2] Social anxiety disorder has a lifetime prevalence of 13.3% in the

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United States and is more common in women (15.5%) than men (11.1%). Perhaps because of traditional gender roles and social expectations, it seems that more men than women tended to seek treatment for the disorder in the past. Shyness, lack of assertiveness, and inhibition are qualities that limit vocational achievements and social satisfaction. The increased participation and assertiveness of women in these domains over the years parallels an apparent increase in women seeking treatment for social anxiety disorder, although these gender issues warrant further study. Social anxiety disorder is commonly underdiagnosed and undertreated. However, recent attempts at public awareness campaigns—supported by industry as well as the National Institute of Mental Health and the Anxiety Disorders Association of America—have increased recognition and treatment of social anxiety disorder.

By the time most clinicians diagnose social anxiety disorder, a majority of patients have been struggling with anxiety in one form or another since childhood. In many adult patients, social anxiety disorder represents a manifestation of an anxious temperament and behavioral inhibition that emerged early and variably throughout their lifetime. The link between adult and childhood social anxiety disorder appears greatest in patients who have the generalized subtype. Social anxiety disorder begins predominantly in childhood with a mean age at onset between 14 and 16 years[3] and is sometimes preceded by a history of social inhibition or shyness. My colleagues and I[4] conducted a study in which over 80% of 100 adult patients with social anxiety disorder described the onset of anxiety difficulties prior to age 18 years (Table 1). Almost half of the patients reported a history of overanxious behavior, and others reported avoidant personality, separation anxiety, and agoraphobia. A recent study[5] focused on potential psychosocial factors that may contribute to social anxiety disorder. In a total of 1047 adolescents, aged 14 to 17 years, a strong association was noted between parental social anxiety disorder and social anxiety disorder among their offspring (odds ratio [OR] = 4.7). Parenting style, specifically parental overprotection and rejection, was also associated with increased social anxiety disorder in offspring.

Different social norms as determined by culture may affect the diagnosis of social anxiety disorder.[6] For instance, certain social behavior, e.g., assertiveness, may be less of a cultural norm in some traditional Asian cultures than in Western society. Social anxiety arising in such contexts may not be as disabling or distressing and thus might not be considered a disorder. Research in both the prevalence and presentation of symptoms of social anxiety disorder across different cultures is needed.

COMORBIDITY OF SOCIAL ANXIETY DISORDER

Social anxiety disorder exhibits a high degree of comorbidity with other psychiatric disorders. Because social anxiety disorder has an early onset, it precedes other comorbid conditions in more than 70% of patients.[7] Common comorbidities include agoraphobia, simple phobia, major depression, substance abuse disorders, and obsessive-compulsive disorder.[7] In a sample of 2096 patients in France, Lecrubier and Weiller[8] reported that the most frequent comorbid condition was depression, which affected 70% of patients with social anxiety disorder of early onset (< 15 years). Additionally, more than 70% of patients in the comorbid group (i.e., social anxiety and depression) had moderate or severe disability in domains relating to adjustment to daily routine and impact on daily activities. In the group of patients with social anxiety disorder without depression, the proportion of patients with the same level of disability was closer to 30%.[8]

Recent NCS data[9] of lifetime comorbidities between social anxiety disorder and mood disorders showed strong associations between lifetime social anxiety disorder and major depressive disorder (OR = 2.9), dysthymia (OR = 2.7), and bipolar disorder (OR = 5.9). In one study,[10] the prevalence and clinical impact of comorbid anxiety disorders were observed in 255 depressed adult outpatients. Comorbid anxiety disorders were present in 50.6% of the depressed patients, and social anxiety disorder was diagnosed in 27% of patients with comorbidity. Social anxiety disorder preceded the first episode of major depression in 65% of the patients. Depressed patients with comorbid anxiety disorders tended to be younger during the index episode and had an earlier onset of major depressive disorder than patients with major depression alone.

Table 1. Rates of Childhood Anxiety Disorders in 100 Patients With Social Anxiety Disorder[a]

Disorder	%
Social anxiety disorder	80
Overanxious behavior	47
Avoidant personality	25
Separation anxiety	13
Agoraphobia	10
Any anxiety disorder	82
Any anxiety disorder excluding social anxiety disorder	54
2 or more anxiety disorders excluding social anxiety disorder	25

[a]Data from Otto et al.[4]

NEUROBIOLOGY OF SOCIAL ANXIETY DISORDER

The neurobiology of social anxiety disorder is a relatively new field of research, and understanding of the biological causes underlying the condition is evolving. The symptoms of social anxiety disorder presumably reflect perturbations of various neurotransmitter systems including the serotonergic, noradrenergic, dopaminergic, corticotropin-releasing factor, and γ-aminobutyric acid (GABA) systems. While current treatments for social anxiety disorder target the serotonergic system, different social fears are likely to have different developmental roots and may be based on quite different neurobiological systems.[11] Moreover,

some neurotransmitter systems may be more amenable to manipulation by currently available pharmacologic agents than others.[12]

The clinical effectiveness of selective serotonin reuptake inhibitor (SSRI) treatment for social anxiety disorder suggests that serotonin has a role in the etiology of social anxiety disorder. Increased serotonin is associated with dominant social status and affiliated behavior in animal models. When hierarchical relationships are uncertain, serotonergic mechanisms may mediate the behaviors that permit a male to attain high dominance status.[13] Decreased serotonin may be associated with subordinate status, which may have parallels in human social anxiety. Consistent with this, another study[14] of social interaction in animals showed that paroxetine, an SSRI, had anxiolytic effects; however, the mechanisms of action were unclear.

Norepinephrine appears to modulate serotonergic and dopaminergic release and arousal. The major noradrenergic nucleus in the brain is the locus ceruleus.[15] Noradrenergic neurons give rise to diffuse axonal projections that innervate virtually all areas of the brain. Projections from noradrenergic neurons to the prefrontal cortex and the hippocampus may play a particularly important role in the symptoms of depression, but the noradrenergic system has also been implicated in the pathophysiology of anxiety.[15] Norepinephrine release is associated with orienting to novel stimuli, selective attention, vigilance, and autonomic arousal.

The dopaminergic system modulates approach behavior, and dopaminergic dysfunction may also be related to social anxiety disorder. Tiihonen et al.[16] conducted a study of 11 patients who had social anxiety disorder and 11 healthy comparison subjects who were age- and gender-matched to the patients for analysis. Blind quantitative analysis revealed that striatal dopamine reuptake site densities were markedly lower in the patients who had social anxiety disorder than in the age- and gender-matched comparison subjects. In a study[17] of 10 unmedicated subjects who had generalized social anxiety disorder and 10 healthy age- and gender-matched comparison subjects, mean dopamine (D_2) receptor binding potential was significantly lower in the patients who had social anxiety disorder than in the comparison subjects.

Corticotropin-releasing factor (CRF) is produced by the hypothalamus in response to stress and activates the release of adrenocorticotropic hormone (ACTH) and cortisol. CRF systems in the brain have a unique role in mediating behavioral responses to diverse stressors.[18] These systems may be particularly important in situations where an organism must mobilize both the pituitary adrenal system and the central nervous system in response to environmental challenge.[18] Intraventricular administration of CRF results in behavioral stress responses that are mediated through the amygdala (with a high density of CRF receptors) and the bed nuclei of the stria terminalis.[19]

Table 2. Pharmacologic Agents for Treatment of Social Anxiety Disorder

Selective serotonin reuptake inhibitors
Monoamine oxidase inhibitors
High-potency benzodiazepines
β-Blockers
Other agents
Gabapentin
Venlafaxine
Nefazodone
Augmentation
Buspirone
Ropinirole
Pramipexole

The GABAergic system is ubiquitous and represents an inhibitory neurotransmitter system that has diffuse and generalized anxiolytic effects.[20] The ability of alcohol to reduce anxiety and lessen social inhibition is believed to be mediated at least in part via enhancement of GABA neurotransmission.[21] Additionally, benzodiazepines, which facilitate GABA transmission, have shown efficacy in the treatment of social anxiety disorder.[22] GABA agonists show considerable promise in the future treatment of social anxiety disorder.[11]

PHARMACOTHERAPY OF SOCIAL ANXIETY DISORDER

Social anxiety is a serious illness that is associated with significant morbidity; therefore, patients should be treated aggressively once the diagnosis is established. Because social anxiety disorder is a chronic condition, pharmacotherapy should be chosen that can be tolerated over long periods to enhance compliance. A number of pharmacologic agents appear effective for the treatment of social anxiety disorder (Table 2). These agents include the SSRIs, monoamine oxidase inhibitors (MAOIs), high-potency benzodiazepines, and β-blockers. Other useful therapeutic agents include gabapentin, venlafaxine, nefazodone, and augmentation with buspirone, ropinirole, or pramipexole. Tricyclic antidepressants are unlikely to be useful for the treatment of social anxiety disorder.[23] Although not the focus of this discussion, cognitive-behavioral therapy is also clearly effective for the treatment of social anxiety disorder and should be considered in treatment planning. Although most patients improve with currently available therapies, a sizeable proportion do not remit, and further work is warranted to improve outcome in these individuals.

Selective Serotonin Reuptake Inhibitors

The SSRIs have become first-line pharmacotherapy for the treatment of social anxiety disorder. Stein et al.[24] studied the efficacy of fluvoxamine versus placebo in 92 patients with social anxiety disorder; 42.9% of the patients responded to treatment. In a small crossover study

(N = 12) by Katzelnick et al.,[25] approximately half of the patients responded to sertraline treatment.

Paroxetine has demonstrated efficacy in the treatment of social anxiety disorder. A large dataset of 187 patients who had generalized social anxiety disorder were studied in a 12-week, multicenter, randomized, double-blind trial of paroxetine versus placebo.[26] The 2 main outcome measures were number of responders—based on the Clinical Global Impressions-Improvement (CGI-I) scale (much improved or very much improved)—and the mean change from baseline on the Liebowitz Social Anxiety Scale (LSAS) total score. The mean change from baseline on the LSAS total score was more than twice as large in the paroxetine group than in the placebo group. When the number of responders at endpoint was measured by CGI-I items, 55.0% of paroxetine-treated patients and 23.9% of placebo patients were much improved or very much improved at the end of treatment.

Lydiard and Bobes[27] reviewed the outcomes of 3 large multicenter clinical trials in which 861 subjects with social anxiety disorder were randomly selected to receive paroxetine versus placebo for 12 weeks. In 2 studies, patients received a flexible dose of paroxetine (20–50 mg/day) or placebo; in the fixed-dose study, patients received paroxetine 20 mg/day, 40 mg/day, or 60 mg/day, or placebo. In each of the 3 studies, 45% to 66% of patients who received paroxetine were rated as responders (very much improved or much improved) on the CGI-I items; paroxetine treatment also improved the symptoms of social anxiety, as measured by the LSAS. Differences between paroxetine and placebo groups were statistically significant and were clinically relevant within each study for the dose ranges examined.

Monoamine Oxidase Inhibitors

Until the advent of the SSRIs, the MAOIs were considered to be the mainstay of pharmacotherapy for patients who had social anxiety disorder. MAOIs have demonstrated efficacy in controlled trials[28,29] and have shown marked acute benefits even in highly disabled patients with generalized social anxiety disorder.[1] A recent study by Heimberg et al.[30] compared the MAOI phenelzine with cognitive-behavioral group therapy (CBGT) and placebo. After 12 weeks, patients on both phenelzine therapy and CBGT demonstrated marked positive responses. Phenelzine therapy was superior to CBGT on some acute measures, and CBGT demonstrated some more persistent gains, with both treatment strategies more efficacious than placebo. Although MAOIs are clearly effective for social anxiety, the potential interaction of MAOIs with tyramine-containing foods and the need for careful dietary monitoring limit their treatment utility.

High-Potency Benzodiazepines

High-potency benzodiazepines have also demonstrated efficacy for the treatment of patients who have social anxiety disorder. Davidson et al.[31] reported that 78% of clonazepam-treated patients experienced significant improvement compared with 20% of placebo-treated patients. Alprazolam was compared with phenelzine and CBGT treatment in a placebo-controlled study.[28] Although comparably improved on most measures, phenelzine-treated patients were rated by clinicians as more improved on a measure of work and social disability than alprazolam-treated patients or placebo patients. The overall advantages of benzodiazepine treatment include efficacy, rapid onset of effect, feasibility of rapid dose adjustments, and situational or as-needed dosing. Disadvantages include side effects—such as sedation, ataxia, and cognitive impairment—and discontinuation-related difficulties, abuse, and dependence liability in predisposed individuals as well as lack of efficacy in those with comorbid depression.

β-Blockers

β-Blockers are more effective for discrete performance anxiety than for generalized social anxiety disorder. β-Blockers can be taken 1 to 2 hours before a performance to decrease the autonomic symptoms of tachycardia, tremors, and sweating. These agents have the advantages of as-needed use, they rarely impair concentration or coordination, and they do not induce dependence.[12] However, they are not effective for generalized social anxiety, in which their use is best confined to an adjunctive role.

Other Pharmacologic Agents

A variety of other pharmacologic agents have been used for the treatment of social anxiety disorder. Gabapentin, a non-benzodiazepine GABA analog, was shown to be effective in 69 patients with social anxiety disorder during a 14-week double-blind, placebo-controlled study.[32] The flexible dose range was between 900 mg/day and 3600 mg/day given in 3 divided doses. A significant reduction in symptoms of social anxiety disorder was observed among patients taking gabapentin compared with placebo, as evaluated by both clinician- and patient-rated scales.

Venlafaxine, a dual norepinephrine and serotonin reuptake inhibitor, has also been reported to be effective in patients with social anxiety disorder, including those patients who fail to respond to SSRIs.[33] Altamura et al.[34] evaluated the clinical response to venlafaxine in 12 patients with social anxiety disorder who were nonresponders to SSRIs; the study also judged the treatment response of patients with comorbid avoidant personality disorder. Venlafaxine improved the symptoms of social anxiety disorder and symptoms of avoidant personality disorder as demonstrated by a decrease in LSAS total scores including reduction in phobic avoidant behavior; depression and general anxiety symptoms also improved.

Nefazodone, a serotonin-2 antagonist/reuptake inhibitor, was evaluated in a 12-week open trial as treatment for generalized social anxiety disorder in 23 patients.[35] A total of 16 patients (69.6%) were considered to be responders (mod-

erate or marked improvement). Measures of social anxiety, phobic avoidance, depression, and social functioning showed a statistically significant change at endpoint.

Buspirone, an antianxiety agent, has not demonstrated efficacy as monotherapy for social anxiety disorder, but may be useful as augmentation in patients who show a partial response to SSRIs.[36] In addition, consistent with reports of decreased dopaminergic activity in patients with social anxiety disorder, anecdotal experience suggests the potential utility of augmentation of SSRIs with dopaminergic agonists such as ropinirole (0.5–2.0 mg b.i.d. or t.i.d.) or pramipexole (0.25–1.0 mg b.i.d. or t.i.d.).[37]

Response and Remission

Most patients with social anxiety disorder, though improved, do not remit after short-term treatment. Ongoing therapy is often necessary to effect and maintain optimal response. Recognizing the limitations of defining treatment outcome, the Consensus Group on Depression and Anxiety[3] formulated the following definitions for response and remission in patients with social anxiety disorder. Response is defined as a stable, clinically meaningful improvement, such that the patient no longer has the full range of symptoms but has more than minimal symptoms. Full remission is defined as almost complete resolution of symptoms across the 3 domains (symptoms, functionality, and well-being/overall severity of illness), which should be maintained for a period of 3 months. The consensus group recommends maintenance of pharmacotherapy for a minimum of 12 months[3] following response, although many patients require ongoing treatment to maintain the benefit.

CONCLUSION

Social anxiety disorder is a common, distressing, and disabling condition that is frequently comorbid with other psychiatric illnesses. A number of neurotransmitter systems may be involved in the etiology of the disorder, which is characterized by an early onset and chronic course. Although many patients improve using the currently available pharmacotherapeutic agents, sizable numbers of patients fail to achieve remission. Further research is warranted to improve outcomes in affected patients with social anxiety disorder.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar), clonazepam (Klonopin and others), fluvoxamine (Luvox), gabapentin (Neurontin), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), pramipexole (Mirapex), ropinirole (Requip), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, alprazolam, buspirone, clonazepam, fluvoxamine, gabapentin, nefazodone, phenelzine, pramipexole, ropinirole, sertraline, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of social anxiety disorder.

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