Overview of Panic and Social Anxiety Disorders

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Panic disorder and social anxiety disorder are often-overlooked but debilitating disorders that share some common symptoms and treatments. Patients with panic disorder experience unexpected panic attacks and then worry about having more attacks. Those with social anxiety disorder fear doing or saying something embarrassing in social situations. The prevalence of these conditions is about 3% for panic disorder and 13% for social anxiety disorder in the United States and is higher in women than in men. Both disorders are thought to have a familial link and to be related to dysregulation of neurotransmitter systems. Panic and social anxiety disorders are often comorbid with other psychiatric disorders. Medication treatment and/or cognitive-behavioral therapy might need to be continued over the long term to prevent relapse. *(J Clin Psychiatry 2004;65[suppl 14]:22–26)*

Although anxiety is experienced by everyone and, at appropriate levels, can be beneficial, excess anxiety that interferes with functioning may qualify as an illness such as panic disorder or social anxiety disorder. These disorders, which share some symptoms and are improved by several of the same treatments, are often underdiagnosed.

PRESENTATION, PREVALENCE, AND COMORBIDITY

Panic disorder is the occurrence of unexpected panic attacks and the consequent worry of having more attacks or experiencing mental, physical, or social impairment related to the attacks, which may alter behavior. During a panic attack, patients experience sudden physical or emotional symptoms, such as chest pain, shortness of breath, hot flushes or chills, nausea, fear of going crazy, and fear of dying, that peak within 10 minutes. Panic disorder is commonly accompanied by agoraphobia. Patients with agoraphobia avoid or experience great distress and/or need a companion during situations or in places in which they fear being embarrassed or unable to escape or get help if a panic attack occurs.

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Social anxiety disorder is the fear of doing or saying something embarrassing or humiliating in social situations. Patients with social anxiety often isolate themselves from or endure social interaction with great distress and exhibit physical symptoms such as blushing and tremor. The 2 subtypes of social anxiety disorder are generalized and nongeneralized. Patients with the generalized form fear most social situations, but patients with the nongeneralized form fear specific social situations, such as public speaking.

Panic and social anxiety disorders may cause social, occupational, and academic impairment. For example, because these patients fear a panic attack or social scrutiny by others, they may stay at home and suffer isolation from friends, financial loss from missed work, or lower grades from missed school. The impairments associated with these disorders often arise during the teenage years to the mid-30s—when educational, interpersonal, and occupational development is particularly important.

In the United States, the rate of lifetime diagnosis was found to be 3% for panic disorder (about 71% of those diagnosed were women and 29% men)[1] and 13% for social anxiety disorder (with a rate of 16% in women and 11% in men).[2] In Europe, the 12-month prevalence was 0.8% for panic disorder and only 1.1% for social anxiety disorder, and all anxiety disorders were 2 to 3 times more common in women than men.[3]

In a study of comorbidity in 360 patients with panic disorder, current comorbid conditions included major depressive disorder (23%), generalized anxiety disorder (16%), social anxiety disorder (15%), and obsessive-compulsive disorder (7%).[4] Substance abuse may be comorbid in about 10% to 20% of patients with panic-related anxiety disorders.[5] In the National Comorbidity Survey,[6] 56% of the patients who had panic disorder had a lifetime history of major depressive disorder. The survey[2] also showed that 81% of patients with social anxiety disorder had another psy-

chiatric condition such as another anxiety disorder (57%), major depressive disorder (37%), alcohol dependence (23%), and drug dependence (15%). Comorbid conditions, especially alcohol or drug dependence, can mask panic or social anxiety disorder. For example, patients with social anxiety may self-medicate with alcohol to ease nervousness before social situations.

ETIOLOGY

Both panic and social anxiety disorders appear to have a familial link. In a meta-analysis[7] of family and twin studies, first-degree relatives of patients with panic disorder were at greater risk for the disorder than first-degree relatives of controls (10% vs. 2%); genetics appeared to account for 48% of the contribution to panic disorder. Similarly, first-degree relatives of patients with generalized social anxiety have been found to be substantially more likely to have social anxiety than relatives of controls[8] or relatives of patients with specific social anxiety.[9]

Research on the neurobiology of panic disorder has implicated both serotonin and norepinephrine dysregulations. Patients with panic disorder are more sensitive than controls to administration of α_2-adrenoceptor agonists[10] and antagonists,[11] and they have a markedly elevated 3-methoxy-4-hydroxyphenylglycol (MHPG) volatility, which normalizes after fluoxetine treatment.[12] On the other hand, the selective norepinephrine reuptake inhibitor maprotiline is not effective in treating patients with panic disorder,[13] whereas the efficacy of imipramine, a mixed serotonin/norepinephrine reuptake inhibitor, correlates with the plasma level of the parent compound but not with its major metabolite, desipramine, which has predominantly norepinephrine reuptake properties.[14] Serotonin receptor agonists may cause anxiety and greater increases in cortisol or prolactin levels in people with panic disorder than in controls.[15] Selective serotonin reuptake inhibitors (SSRIs), on the other hand, are among the agents that most effectively reduce panic symptoms. Direct evidence for the role of serotonin was recently presented by Neumeister et al.,[16] who reported a reduced density of the 5-HT_{1A} receptor in patients with panic disorder. Benzodiazepine receptors have been implicated by findings that agonists such as alprazolam and clonazepam are highly effective in reducing panic and that antagonists may cause panic in patients with panic disorder but not in controls.[17] Neuropeptide cholecystokinin receptor agonists are more likely to result in panic attacks in patients with panic disorder than in controls,[18] while antagonists may reduce the effect.[19] Finally, carbon dioxide[20] and lactate[21] are also more likely to induce panic symptoms in patients with panic disorder than in controls.

In social anxiety disorder, the neurobiology of the generalized form versus that of the specific form differs. Specific social anxiety disorder is more strongly associated with autonomic nervous system dysregulations because β-blockers, which may reduce autonomic symptoms of social anxiety, appear to be effective for only the specific form.[22,23] Also, patients with the specific subtype had greater heart rate acceleration during a public speaking test than patients with the generalized subtype.[24]

Generalized social anxiety disorder is thought to be influenced largely by dopamine and serotonin function. The role of dopamine has been implicated by a variety of sources. Neuroleptics have been shown to induce social anxiety disorder when given to certain patient groups.[25] Also, social anxiety is more prevalent in patients with Parkinson's disease than in the general population[26]; Parkinson's disease is associated with low levels of dopamine in the striatum.[27] And social anxiety shares characteristics with detached personality,[28] which is associated with a low level of the dopamine-2 receptor.[29] Dopamine transporter binding density may be different in the basal ganglia of patients than controls; some findings suggest a lower rate[30] and others, a higher rate (H. Stevens, Ph.D.; F. van Veen, M.D.; N. J. A. van der Wee, M.D.; et al., manuscript submitted). These findings suggest the involvement of dopamine in the pathophysiology of social anxiety, but the precise mechanism is still to be determined.

The idea that serotonin plays a role in social anxiety disorder comes from several findings. Long-term treatment with SSRIs may increase the sociability of healthy controls,[31] and increased serotonin availability may speed recognition of social cues such as facial expressions.[32] Also, cortisol response to partial serotonin receptor agonists may be greater in patients with social anxiety disorder than controls.[33] Further, the long allele of the serotonin transporter promoter region 44 base pair deletion/insertion polymorphism may be associated with social anxiety disorder.[34] Finally, a study found that patients with social anxiety disorder had greater serotonin transporter binding density in the thalamus and right orbital frontal cortex than did healthy controls (H. Stevens, Ph.D.; F. van Veen, M.D.; N. J. A. van der Wee, M.D.; et al., manuscript submitted).

TREATMENT

Selection of a single treatment or a combination of treatments should be influenced by the possibility for drug interactions and the presence of comorbid conditions that may be affected.

Antidepressants

SSRIs are first-line therapy for panic and social anxiety disorders. The SSRIs found efficacious in panic disorder are citalopram,[35] fluoxetine,[36] fluvoxamine,[37] paroxetine,[38] and sertraline.[39] For social anxiety disorder, fluoxetine may have little effect,[40] but fluvoxamine,[41] paroxetine,[42] and sertraline[43] have been found efficacious. Physicians

should tell patients that the therapeutic effect may take 2 to 3 weeks to be reached.

Tricyclic antidepressants (TCAs) may improve symptoms of panic disorder and prevent relapse.[44] Clomipramine may be more efficacious than desipramine[45] and imipramine[46] for panic. In social anxiety disorder, imipramine—the only TCA studied—had little effect in a small open trial.[47] Many patients may find TCA side effects intolerable.

Overall, the monoamine oxidase inhibitors (MAOIs) have good evidence of efficacy in panic and social anxiety disorders. Phenelzine may improve panic and social anxiety disorder.[22] Tranylcypromine may be effective for social anxiety.[48] Moclobemide has been found as effective as the TCA clomipramine[49] and the SSRI fluoxetine[50] for panic disorder but has mostly poor results for social anxiety disorder.[51,52] MAOI side effects may outweigh the benefits.

Venlafaxine has shown promise for alleviating panic and social anxiety symptoms in small trials.[53,54] Studies[55,56] of bupropion in panic disorder show mixed results. In the single published study[57] of bupropion in social anxiety disorder, 5 of the 10 patients responded.

Anxiolytics

Benzodiazepines, the classic anxiolytics, often improve panic and social anxiety disorders. In controlled studies,[58,59] clonazepam substantially reduced symptoms of both disorders. Alprazolam appears effective in panic disorder.[58] However, in the only controlled trial[60] of alprazolam in social anxiety disorder, the agent was not significantly more effective than placebo, possibly because both treatment groups included self-exposure, which may be effective alone. Because some patients may abuse benzodiazepines, these agents may be best used in patients without comorbid substance abuse. The anxiolytic buspirone may not be more effective than placebo for either panic or social anxiety disorder.[61,62]

Anticonvulsants

The few studies of anticonvulsants in panic and social anxiety disorder have shown some efficacy. In a placebo-controlled trial[63] of gabapentin in panic disorder, symptoms were substantially reduced in only the severely ill patients. In a social anxiety disorder study,[64] the entire gabapentin-treated group experienced significantly greater improvement than the placebo group, but scores remained high after 14 weeks of treatment. Pregabalin[65] and valproic acid[66,67] have shown promise in both disorders in unpublished or open trials. A possible drawback of anticonvulsants is daytime sedation.

β-Blockers

One trial[68] of propranolol in panic disorder found the agent effective, but most other trials[69,70] have shown no significant improvement in panic. For example, in one study,[70] propranolol given prior to lactate infusions in panic patients lowered heart rate but did not block induced panic symptom. In social anxiety, although atenolol was not significantly more effective than placebo in 74 patients, 76% of whom had the generalized subtype,[22] β-blockers may relieve specific social anxiety associated with public performance.[23]

Cognitive-Behavioral Therapy

A large body of research supports the efficacy of cognitive-behavioral therapy (CBT) in panic and social anxiety disorders, although whether CBT is as effective as pharmacotherapy remains unclear. In a meta-analysis[71] of panic disorder studies, improvements were greater with CBT alone than with pharmacotherapy alone or CBT and pharmacotherapy, a finding that has been controversial.[72] In a meta-analysis[73] of social anxiety treatment studies, CBT produced much greater improvement than placebo or a waiting list condition, and the benefits of CBT continued after discontinuation. More comparisons of CBT with efficacious medication are needed.

CONCLUSION

Because panic and social anxiety disorders cause substantial impairment, physicians must be aware of the symptoms and comorbid conditions that may point to the presence of these disorders. Patients should generally receive an effective medication such as an SSRI or a benzodiazepine; CBT may also benefit patients, especially those who are taking medication but have residual symptoms. Treatments might need to be continued over the long term to prevent relapse.

Drug names: alprazolam (Xanax and others), atenolol (Tenormin and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa), clomipramine (Anafranil and others), clonazepam (Klonopin and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), gabapentin (Neurontin and others), imipramine (Tofranil and others), paroxetine (Paxil and others), phenelzine (Nardil), propranolol (Inderal, Innopran XL, and others), sertraline (Zoloft), tranylcypromine (Parnate), valproic acid (Depakene, Myproic Acid, and others), venlafaxine (Effexor).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, bupropion, desipramine, paroxetine, valproic acid, venlafaxine, and maprotiline are not approved by the U.S. Food and Drug Administration for the treatment of panic disorder; atenolol, citalopram, gabapentin, tranylcypromine, and pregabalin are not approved for the treatment of social anxiety disorder; and alprazolam, buspirone, clomipramine, clonazepam, fluoxetine, imipramine, phenelzine, propranolol, fluvoxamine, and moclobemide are not approved for the treatment of panic disorder or social anxiety disorder.

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