Panic disorder and social phobia: Current treatments and new strategies

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Panic disorder and social phobia are two common anxiety disorders that affect many adults in the United States today. It has been estimated that 3.5% of adults in the United States will suffer from panic disorder at some time in their lives,[1] and that 13% will experience social phobia.[1] Left untreated, the ultimate outcome of these pathologic reactions can be devastating: significant impairment can occur in several realms, including perceived physical and emotional deterioration, reduced productivity, increased absenteeism, onset of alcohol abuse, marital discord, and even suicide.

Treatment for panic disorder and social phobia can dramatically improve patient functioning and quality of life. A combination of psychotherapy and pharmacotherapy is most often used to control anxiety symptoms and enable patients to resume a normal routine and productive lifestyle. Until the 1980s, benzodiazepines were the pharmacologic agents of choice for anxiety disorders: they were considered highly effective and largely safe. As the associated cognitive impairment and abuse potential became apparent, however, scientists searched for newer agents with improved safety profiles.

In the last decade, several classes of compounds with anxiolytic efficacy without the risk for cognitive impairment, abuse, or dependence observed with benzodiazepines have been identified. The most promising of these agents are the selective serotonin reuptake inhibitors (SSRIs) and anticonvulsants. The roles for these compounds in panic disorder and social phobia are reviewed here, particularly in the historical context of benzodiazepine use and its inherent benefits and risks.

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PANIC DISORDER

Cost benefits of therapy

The benefit of successful treatment for panic disorder has been documented in an analysis of clinical status and health care utilization among patients before and after successful treatment for panic disorder. In Spain, Salvador-Carulla and coworkers[2] collected data on 61 patients with panic disorder from 12 months before diagnosis for comparison with data for 12 months after their treatment was initiated. In the year before therapy, the patients had lost more than 1,000 workdays; in the 12 months after diagnosis and during therapy, all were back at work, with only 190 sick days accumulated overall.

This substantial improvement in productivity translated into a significant financial benefit. Although direct health care costs due to medical care were about one-third greater in the year after diagnosis than in the 12 months before (per-patient costs of $478 versus $758, respectively), the indirect costs—eg, measures of lost productivity, employer costs—were almost 80% lower in the year after treatment (per-patient costs of $1,076 versus $228, respectively) resulting in an overall cost reduction associated with effective therapy for panic disorder. The substantial overall cost savings warrants a public health effort to properly diagnose and treat panic disorder.

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TABLE 1
CHARACTERISTICS OF MAJOR HIGH-POTENCY BENZODIAZEPINES USED IN THE TREATMENT OF PANIC DISORDER AND SOCIAL PHOBIA

	Alprazolam	Clonazepam
Efficacy	Yes	Yes
Dose range	2–9 mg/day	1–4 mg/day
Dose frequency	3–4 times daily	1–2 times daily
Half-life	6–27 hours	18–50 hours

Treatment goals in panic disorder

The goals of therapy for panic disorder are well defined: prevention of panic attacks; reduction of anticipatory anxiety; elimination of phobic avoidance behavior; and control of common comorbid conditions. Meeting these goals often requires long-term intervention, since terminating treatment, particularly when done early in the course of the disease, results in a high relapse rate.[3] Continuous and long-term treatments are safe and the most effective approaches to panic disorder; therapy is the most reliable way to improve patients' quality of life.

Treatment for panic disorder is a multifaceted effort. Every patient should be educated about the causes and course of his or her condition, without stigmatizing the diagnosis. Cognitive-behavioral or other psychosocial therapies also can be instituted to teach patients skills for altering their maladaptive behavior. Pharmacotherapy—treatment with tricyclic antidepressants, benzodiazepines, monoamine oxidase inhibitors (MAOIs), SSRIs, and anticonvulsants—is used for the expeditious elimination of panic symptoms, and for effective maintenance of control over these symptoms.

Historical review of treatment for panic

In 1964, Klein[4] reported success in treating panic attacks with the tricyclic antidepressant imipramine. Imipramine eliminated panic attacks in a group of patients who had not responded to treatment with phenothiazines or sedative agents. Although this was a revolutionary observation at the time, the use of tricyclics—including clomipramine, desipramine, and nortriptyline, in addition to imipramine—was supplanted by the next generation of anxiolytic drugs, the benzodiazepines.

The benzodiazepines rapidly became standard therapy for panic disorder because they were highly effective and easy to use. Alprazolam and clonazepam are the benzodiazepines most commonly administered for panic disorder, and both have been proven to effectively control panic attacks (*Table 1*). Alprazolam is effective at higher doses and must be given more frequently than clonazepam, which can be administered only once or twice a day. The notable activity of clonazepam was documented recently by Rosenbaum and colleagues.[5] In a multicenter, parallel-group, placebo-controlled, fixed-dose trial, 413 patients with panic disorder were randomized to one of five daily doses of clonazepam (0.5 mg, 1.0 mg, 2.0 mg, 3.0 mg, and 4.0 mg) or placebo. Although the 0.5-mg clonazepam dose did not significantly reduce the number of panic attacks compared with placebo, daily doses of 1.0 mg or higher all provided equivalent efficacy and superiority to placebo in controlling panic symptoms.

Although long-term use of benzodiazepines in the treatment of panic disorder is generally effective and safe, there are two main concerns with their use. First, dose-dependent side effects such as somnolence, irritability, and ataxia may increase to the point where they detract from the patient's sense of well-being. In addition, although tolerance levels necessitating dose increases are unusual, dependence can be a concern with long-term benzodiazepine use.[5] Discontinuation of benzodiazepine therapy, therefore, must be approached as a slow, deliberate process in order to lessen the risk of rebound—the transient worsening of panic symptoms—and withdrawal symptoms. The occurrence of a withdrawal syndrome marked by symptoms ranging from irritability, headache, and tremor to delirium and even seizures is a function of several factors which include the duration of drug use, the characteristics of the specific drug, and the tapering schedule. Several studies have shown that a gradual discontinuation program and/or simultaneous cognitive-behavior therapy can increase the success rate and the ease of terminating benzodiazepine use.[6,7] This is an important benefit for the significant number of patients who, after long-term benzodiazepine use, have found it difficult to discontinue the drug.

Identification of newer agents

As it became clear that the tricyclic antidepressants and benzodiazepines had significant shortcomings in the long-term therapy for panic disorder, an

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effort was made to identify effective agents with improved safety profiles and less risk for abuse. In this setting, the SSRIs have proven to be effective alternatives for the treatment of panic disorder. Although only paroxetine and sertraline have formal indications for management of this disorder,[8,9] fluoxetine and fluvoxamine also have been shown in open-label or double-blind, placebo-controlled trials to successfully improve panic symptoms.[10–14]

TABLE 2
ADVANTAGES AND DISADVANTAGES OF SSRI DRUGS IN THE TREATMENT OF PANIC DISORDER

Advantages	Disadvantages
Broad-spectrum efficacy	Slow onset
Abuse-free	Overstimulation
Beneficial for comorbid depression	Activation of sexual and gastrointestinal side effects
	Interaction with drugs metabolized by the cytochrome P450 isoenzyme system

Paroxetine and sertraline have both been shown to decrease the number of full- and limited-symptom panic attacks, to reduce the intensity of attacks, and to improve the quality of life in patients with panic disorder with and without agoraphobia,[15–18] without any risk for abuse or dependence (*Table 2*). The onset of action of SSRIs is relatively slow, requiring 6 to 12 weeks for full efficacy. In addition, a significant complication of SSRI use is agitation occurring early in the course of therapy, particularly with the use of high initial doses. This side effect can be very distressing to the patient, who may on occasion decide to discontinue treatment prematurely. Slow titration up to an effective dose may minimize the risk of this outcome but can also delay the time to full drug activity. Other potential side effects of SSRI therapy include somnolence, insomnia, constipation, nausea, diarrhea, sweating, and sexual difficulties, especially impaired orgasm. These reactions may lead to discontinuation.

With the side effects and difficulties associated with the use of benzodiazepines and antidepressants, there obviously was room for improvement in the form of another category of medication. Anticonvulsant agents were identified as a class of drugs with much to offer. First, there are a number of phenomenologic similarities between panic attacks and features of complex partial seizures, in that panic episodes and depersonalization can sometimes be seen in the latter. The GABA-ergic activity and antikindling effects of anticonvulsants might also provide some benefit in the treatment of panic attacks.

There is little formal experience with the use of anticonvulsant drugs in the treatment of panic disorder, but studies performed to date are suggestive of activity. Lum and colleagues[19] found that the intensity and duration of panic attacks in 12 patients with diagnosed panic disorder responded to treatment with valproate. Woodman and Noyes[20] reported results from a 6-week open clinical trial of valproate involving 12 patients with panic disorder. They noted marked improvement in 75% of patients; among 11 patients who elected to continue therapy, all showed sustained improvement at 6 months' follow-up. Although the numbers of subjects in these trials were small, there was a clear trend suggesting that anticonvulsant therapy is beneficial in the treatment of panic disorder.

Keck et al[21] examined the efficacy of valproate in panic disorder in an interesting prospective, open-label trial. They observed 16 patients treated with a 28-day regimen of valproate following lactate infusion to induce panic symptoms and compared the data with results derived from a subsequent lactate rechallenge. Of the 14 patients completing the trial, 71% experienced a > 50% reduction in the frequency of attacks, including 6 patients who had complete remissions. On lactate rechallenge, valproate blocked symptoms in 83% of individuals who had experienced symptoms on the initial infusion. These findings support the concept that valproate can meaningfully and effectively correct some of the underlying psychobiologic disturbances in panic disorder, possibly including increased GABA-ergic neurotransmission or antikindling activity.

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Gabapentin is of clear theoretical relevance for the treatment of panic disorder, and the results of a recent controlled trial are currently undergoing analysis.

SOCIAL PHOBIA

Social phobia is defined as the pathologic fear of scrutiny by other people in social settings, particularly a marked and persistent fear of performance situations or social settings that are potentially embarrassing or humiliating. The fear causes disabling distress, leading to avoidance of the threatening setting. This relatively common anxiety disorder affects between 10% and 15% of the US population at some time in their life; similar rates have been observed in European countries as well.[1,22]

Generalized social phobia, wherein fears pervade almost all areas of interpersonal functioning, is the most common clinical manifestation of this diagnosis, as well as the most disabling. Performance or nongeneralized social phobia is less commonly seen in clinical settings and its pharmacotherapy is less well understood.

Treatment goals in social phobia

As in panic disorder, the treatment goals for social phobia center on eliminating episodes of anxiety and returning the patient to a "normal" level of daily functioning and interpersonal relations. Two forms of treatment have been found to be effective in meeting these goals. Psychosocial therapies involving exposure, cognitive restructuring, and cultivation of social skills provide a solid basis for relearning behavioral responses. Pharmacotherapy is also useful for treating social phobia, and the range of agents used in the treatment of this disorder have included beta-blockers, MAOIs, benzodiazepines, tricyclic antidepressants, and SSRIs. One study suggests that the best outcome is achieved with a combination of psychotherapy plus pharmacotherapy.[23]

Among the original pharmacologic agents examined for the treatment of social phobia, beta-blockers have been found to show no efficacy[24] for generalized social phobia. The MAOIs, although effective, are difficult drugs to use, requiring dietary restrictions and carrying the risk of significant side effects, such as hypertensive crisis and intracranial bleeding.[24,25] The selective, reversible inhibitor of MAO-A, moclobemide, is of some benefit at daily doses of 600 mg,[26] although another major trial showed no effect for the drug.[27] The benzodiazepine drug, clonazepam was shown to be highly effective in predominantly generalized social phobia.[28]

The next section will focus on further effective and practical drug-treatment options for social phobia. These include the SSRIs and, as of recently, the anticonvulsant agent gabapentin.

DRUG OPTIONS FOR THE TREATMENT OF SOCIAL PHOBIA

SSRIs

There are both controlled and anecdotal reports describing the efficacy of the SSRIs in the treatment of social phobia.[29–35] The most extensively studied SSRI and the first of this class to be approved for use in this indication is paroxetine.[35,36]

In a randomized, double-blind, multicenter study, Stein and coworkers[36] compared the efficacy of paroxetine versus placebo in the treatment of 187 patients with generalized social phobia. At the end of the 12-week trial, 50 (55%) of 91 persons taking paroxetine were significantly improved according to the Clinical Global Impression (CGI) Global Improvement Item, compared with 22 (23.9%) of 92 patients receiving placebo ($P = .001$). Mean scores on the Liebowitz Social Anxiety Scale (LSAS) fell by 39.1% and 17.4% in the paroxetine and placebo groups, respectively ($P < .001$). This representative study established the efficacy of paroxetine in reducing the symptoms and disability of social phobia.

Similarly, positive results have been reported with sertraline[37] and fluvoxamine.[38] No placebo-controlled experience with fluoxetine in the treatment of social phobia has been reported to date.

Gabapentin: A novel anticonvulsant agent

Gabapentin is the first anticonvulsant agent to be tested for the treatment of social phobia in a double-blind, randomized, placebo-controlled study. In this 14-week trial, 60 patients > 18 years of age with a clinical diagnosis of social phobia were randomly assigned to treatment with 900 to 3,600 mg/day of gabapentin, or placebo, as described in the report by Pande et al (1998).[39] All patients had LSAS scores of > 50 and Hamilton Depression Scale (HamD) scores of < 2 on Item 1, were not current alcohol or

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substance abusers, and provided written informed consent.

Baseline measures of LSAS, Brief Social Phobia Scale (BSPS), Marks' Fear Questionnaire (MFQ), Social Phobia Inventory (SPIN), and CGI were recorded and followed at regular intervals during treatment (1, 2, 3, 4, 6, 8, 10, 12, and 14 weeks). Vital signs and laboratory measures were assessed, and adverse event histories were recorded at each visit.

TABLE 3
ADVERSE EVENTS ASSOCIATED WITH GABAPENTIN THERAPY IN THE TREATMENT OF SOCIAL PHOBIA (INCIDENCE > 5%)

Adverse Event	No. Pts (%) Gabapentin (n=34)	No. Pts (%) Placebo (n=35)	Fisher's Exact Test (*P*)
Dizziness	8 (24)	2 (6)	.05
Somnolence	7 (21)	3 (9)	.19
Dry mouth	4 (12)	0 (0)	.05
Flatulence	3 (9)	0 (0)	.11
Decreased libido	3 (9)	0 (0)	.11

At the last follow-up visit, the response rate, based on CGI scores, was greater in the gabapentin group compared with the placebo group (39% vs 19%, respectively; $P < .05$). The effect size—which is a measure of the magnitude of the drug treatment effect—approached 0.7 on the BSPS and CGI-I. (A score of 0.5 is considered a moderate treatment effect, making 0.7 a relatively strong measure of drug impact.) A more modest, but still meaningful, effect size of 0.4 was observed on the LSAS.

Side effects of gabapentin therapy were moderate and did not impair the safety or tolerability of treatment (*Table 3*). Dizziness (24% vs 6% with gabapentin and placebo, respectively) and dry mouth (12% vs 0%, respectively) were the only side effects that occurred with statistically significant greater frequency with gabapentin compared with placebo therapy.

The results of this trial indicate that gabapentin is a well-tolerated, effective alternative for the treatment of social phobia, with a moderate to good effect size on clinical measures of anxiety symptomatology. Higher baseline scores of severity on the SPIN scale, as well as more severe physiologic symptoms and agoraphobic avoidance behavior as determined by the MFQ scale, predicted better response to gabapentin therapy. This is especially important because phobic avoidance is one of the more difficult-to-treat aspects of social phobia. Gabapentin is a promising new approach to the pharmacotherapy of social phobia without many of the complications associated with SSRI and benzodiazepine treatment.

SUMMARY

Panic disorder and social phobia are among the most disabling of the anxiety disorders. The emotional cost to the patient suffering from these diagnoses is exceeded only by the very real economic costs to the community because of reduced productivity, lost workdays, and increased health care costs for associated physical complaints. It is imperative, therefore, that the medical community focus on the accurate diagnosis and effective treatment of these potentially devastating conditions.

Pharmacologic treatments for panic disorder and social phobia have been available since the early 1960s. The limited efficacy and significant side effects of the early medications, however, led to a search for new treatment options. For many years, the benzodiazepines were the principal first-line therapy for treatment of these illnesses. Yet, their potential for cognitive impairment, physiological dependence, abuse, and withdrawal phenomena warranted a continued search for newer agents with an improved safety profile. In the last 10 years, several treatments have been identified that may fill this need.

Controlled trials and/or anecdotal reports have shown SSRIs and anticonvulsants to be effective treatments for the symptoms of panic disorder and social phobia. However, although SSRIs are emerging as a leading treatment for generalized social phobia, it is not at all clear whether they can benefit nongeneralized social phobia. Their side-effect profile, while a marked improvement over earlier antidepressant drugs, still can cause significant dis-

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comfort. The anticonvulsants are now emerging as a very important group of drugs in the anxiety disorders, with gabapentin having been the most extensively studied in social phobia.

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