

# Current Concepts in the Treatment of Panic Disorder

David V. Sheehan, M.D., M.B.A.

Panic disorder is a prevalent psychiatric condition that often is chronic and rarely resolves without medical intervention. Many patients with panic disorder initially present with a variety of somatic symptoms, including chest pain, nausea, or dizziness, and patients frequently seek care in ambulatory care settings. Although panic disorder is classified as a single entity, it can have many dimensions and may be associated with significant morbidity. During the past 2 decades, there have been significant advances in the treatment of panic disorder, and a range of therapeutic choices is now available. Four classes of medications, including the selective serotonin reuptake inhibitors (SSRIs), high-potency benzodiazepines, tricyclic antidepressants, and monoamine oxidase inhibitors, may be considered for the management of patients with panic disorder. Emerging clinical data favor the SSRIs as first-line treatment for patients with panic disorder, and paroxetine and sertraline have been approved by the U.S. Food and Drug Administration for use in panic disorder. This article reviews the efficacy and safety of these treatments, as well as their relative merits and disadvantages, and assists the practicing clinician in choosing among the various pharmacotherapies to tailor therapy to each patient's individual needs.

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The prevalence of panic disorder is approximately 3.5% in the general population, and the disorder affects a larger percentage of women than men.<sup>1,2</sup> The age at onset typically is in the mid-20s, but some patients develop symptoms earlier in life.<sup>2</sup> Although panic disorder is classified as a single entity, it can have many dimensions, including anxiety, depression, obsessions, compulsions, and phobia, all of which may lead to disability. Many patients also present with somatic symptoms, such as palpitations, chest pain, nausea, trembling, and dizziness, which makes diagnosing panic disorder difficult.<sup>3</sup> Patients with panic disorder often seek medical care in the emergency department and frequently endure a variety of unnecessary tests before receiving an accurate diagnosis.<sup>4,5</sup> These patients rarely consider or obtain psychiatric care initially.

Panic disorder often occurs comorbidly with other anxiety and depressive disorders, and comorbidity is associ-

ated with poorer prognosis and an increased incidence of suicide.<sup>2</sup> It is more common for patients to have panic disorder comorbid with other psychiatric disorders than to have panic disorder alone.<sup>6</sup> Nearly 50% of patients with panic disorder develop comorbid depression, and 43% of patients with comorbid panic disorder and depression have attempted suicide.<sup>6,7</sup> The most commonly comorbid anxiety disorders include obsessive-compulsive disorder, post-traumatic stress disorder, and social anxiety disorder.<sup>8</sup> The incidence of substance abuse also is increased for patients with panic disorder. Panic disorder patients with comorbid illnesses may be less compliant with therapy and often have impaired response to treatment.<sup>6</sup>

Patients with panic disorder suffer from significant social and economic impairment. Many patients indicate that they have poor health and lowered quality of life because of the illness. On the basis of data from the Epidemiologic Catchment Area study, 12% of panic disorder patients reported that their marriage was dysfunctional and 25% of patients were divorced or separated.<sup>9</sup> Approximately 50% of patients with panic disorder are unable to maintain a full-time position and 25% are unemployed.<sup>10</sup> Not surprisingly, the incidence of financial dependency is high in this population.

## PHARMACOTHERAPY

Although most clinicians are familiar with the use of selective serotonin reuptake inhibitors (SSRIs) in the management of major depression, the scientific data support-

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*From the Department of Psychiatry, University of South Florida, USF Institute for Research in Psychiatry, Tampa, Fla. Presented at the symposium "New Treatments for Anxiety Disorders: Clinical Approaches for Successful Outcomes," which was held May 31, 1998, in Toronto, Ontario, Canada. This symposium was held in conjunction with the 151st annual meeting of the American Psychiatric Association and supported by an unrestricted educational grant from SmithKline Beecham Pharmaceuticals.*

*Reprint requests to: David V. Sheehan, M.D., M.B.A., Professor of Psychiatry, University of South Florida, USF Institute for Research in Psychiatry, 3513 E. Fletcher Ave., Tampa, FL 36613-4788 (e-mail: dsheehan@com1.med.usf.edu).*

Table 1. Comparison of the Effective Therapeutic Classes by Agent<sup>a</sup>

Area of Comparison	SSRIs					TCAs			Benzodiazepines	
	Citalopram <sup>b</sup>	Fluoxetine	Fluvoxamine	Paroxetine <sup>b</sup>	Sertraline <sup>b</sup>	Clomipramine	Imipramine	Lofepramine	Alprazolam	Clonazepam
Efficacy in panic disorder <sup>c</sup>	●	#	▸	●	#	●	●	▸	●	●
Efficacy in reducing panic attacks to zero <sup>c</sup>										
Short-term studies	●		▸	●		●	●	▸	●	●
Long-term studies				●		●	●		●	#
Efficacy data for all 5 domains (panic attacks, anxiety, phobias, well-being, disability) <sup>c</sup>			▸	●		●	●		●	
Onset of action (wk)	4	4	4	4	4	6	8	6	1	1
Efficacy in comorbid conditions <sup>c</sup>										
Depression	●	●	●	●	●	●	●	●		
OCD	#	●	▸	●	●	●				
Once-daily dosing <sup>c</sup>	●	●		●	●	●				
Good tolerability <sup>c</sup>	●	#	▸	●	#				●	●
Safety <sup>d</sup>										
In overdose	?	■	■	■	■				■	■
In driving		■		■	■					
Risk of dependence									■	■
Ease of withdrawal <sup>e</sup>	○	○	○	○	○	○	○	○		
Pharmacokinetics <sup>d</sup>										
Lack of active metabolites			■	■					■	
Half-life greater than 1 day	■	■								?

<sup>a</sup>Reprinted from reference 8, with permission. Abbreviations: OCD = obsessive-compulsive disorder, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

<sup>b</sup>SSRIs licensed for use in panic disorder.

<sup>c</sup>Efficacy and tolerability data from placebo-controlled studies: ● = large studies of over 100 patients; ▸ = small studies involving fewer than 100 patients; # = open, or nonpublished placebo-controlled data; blank = no published placebo-controlled data.

<sup>d</sup>Safety and pharmacokinetic data from published studies: ■ = the drug meets the criteria; ? = equivocal data; blank = not meeting criteria.

<sup>e</sup>○ = no addiction or dependence problems, but tapering of dose recommended; blank = not meeting criteria.

ing the use of SSRIs in the treatment of panic disorder are less well known. Medications for the treatment of panic disorder have evolved rapidly during the past 20 years. A significant range of choices is now available, including the SSRIs, high-potency benzodiazepines, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs)<sup>8,11</sup> (Table 1).

The SSRIs, either alone or in combination with high-potency benzodiazepines, are the treatment of first choice with most clinicians worldwide. In some regions, the use of benzodiazepines is limited, whereas in other countries the appropriate use of benzodiazepines in clinical practice is fully accepted. Because antidepressant medications typically take 3 to 6 weeks to achieve reliable, stable benefits, many patients (as many as 30% in some settings) become increasingly anxious during the first few weeks of therapy and stop taking the antidepressant before beneficial effects are achieved. Because of this practical limitation, it may be clinically appropriate to use the combination of an SSRI and a benzodiazepine.<sup>11,12</sup> By using this strategy, the benzodiazepine, which has a rapid onset of action, serves as a bridge during the first 4 to 6 weeks of SSRI therapy to control anxiety, agitation, and restlessness until the SSRI has an opportunity to work. After the patient is appropriately stabilized, the dose of benzodiazepine can be slowly tapered over several weeks and eventu-

ally discontinued. However, it should be noted that more than 50% of patients experience difficulty discontinuing benzodiazepine therapy.<sup>13</sup>

TCAs were the first antidepressants widely used for the management of panic disorder, and the efficacy of these agents is well established.<sup>14,15</sup> However, TCAs are associated with a number of anticholinergic and cardiovascular adverse effects that may affect patient compliance with therapy. Although clomipramine is more effective than other TCAs in the treatment of panic disorder,<sup>16</sup> it now appears that the TCAs, including imipramine, are probably the least effective of the classes of antipanic medications currently available.

Because of significant dietary restrictions and potential for severe adverse effects, the MAOIs are not considered medications of first choice in most situations. However, evidence from double-blind studies suggests that hydrazine MAOIs, such as phenelzine, are among the most powerful medications for panic disorder, particularly in severe cases associated with significant disability.<sup>16</sup> Although MAOIs are now used infrequently in clinical practice, these agents should not be forgotten and often are effective when other antipanic medications fail.

A variety of other medications have been used with some effect in panic disorder and could be included in a cluster of treatments loosely referred to as "other agents."

**Table 2. Studies Evaluating Fluvoxamine for the Treatment of Panic Disorder<sup>a</sup>**

Design	Duration		Results
	N	(wk)	
Fluvoxamine vs clomipramine	50	6	Clomipramine = fluvoxamine
Fluvoxamine vs ritanserin vs placebo	60	8	Fluvoxamine > ritanserin, placebo
Fluvoxamine vs placebo	50	8	Fluvoxamine > placebo
Fluvoxamine vs CBT vs placebo	66	8	Fluvoxamine > CBT > placebo
Fluvoxamine vs placebo vs exposure alone vs psychological panic management and exposure	96	12	All treatments effective Combination best

<sup>a</sup>Data from references 18–22.

Abbreviation: CBT = cognitive-behavioral therapy.

Notable among these are the anticonvulsants, particularly divalproex sodium or sodium valproate. Although these agents are used mainly in the treatment of seizures and bipolar disorders, anticonvulsants also have been shown to be effective for panic disorder in the absence of bipolar illness.<sup>17</sup> Patients with bipolar disorder, particularly those who have bipolar II disorder, who are rapid cyclers, or who have mixed-state bipolar disorder may present with panic attacks as a primary complaint, associated with increased anxiety, restlessness, insomnia, and agitation. Treating such patients with an SSRI or TCA for the panic attacks may induce rapid cycling and worsen anxiety and panic symptoms. Only the use of divalproex sodium, gabapentin, or lamotrigine will provide the necessary relief of both panic and anxiety symptoms.

### SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The SSRIs, including fluoxetine, fluvoxamine, paroxetine, citalopram, and sertraline, have been evaluated for the treatment of panic disorder and have well-established efficacy and safety profiles. These agents are well tolerated and are not associated with cardiovascular effects, orthostatic hypotension, or physical dependence. Consequently, many clinicians consider the SSRIs first-line therapy for the management of panic disorder. The SSRIs are also useful for panic disorder patients with comorbid conditions, including depression, social anxiety disorder, or obsessive-compulsive disorder.<sup>8</sup>

#### Fluvoxamine

Fluvoxamine was the first SSRI evaluated in a double-blind study in patients with panic disorder. In an 8-week study, den Boer and Westenberg<sup>18</sup> found that patients treated with fluvoxamine, 150 mg/day, experienced significantly greater reductions in Hamilton Rating Scale for Anxiety (HAM-A) scores compared with patients who received placebo or the serotonin-2 (5-HT<sub>2</sub>) antagonist ritan-

**Table 3. Studies Evaluating Fluoxetine for the Treatment of Panic Disorder**

Study	Duration		Results
	N	(wk)	
Gorman et al, 1987 <sup>23</sup>	25	52	76% improved
Schneier et al, 1990 <sup>26</sup>	20	8	43% responded
Pecknold et al, 1995 <sup>25</sup>	30	8	High dropout and modest efficacy rate

serin ( $p < .001$ ). Several placebo-controlled studies have demonstrated similar results<sup>18–22</sup> (Table 2). In the first head-to-head study comparing an SSRI with behavioral therapy, Black and associates<sup>19</sup> noted that patients treated with fluvoxamine had significantly greater reductions in clinical anxiety scale scores compared with patients treated with cognitive-behavioral therapy (CBT) or placebo ( $p < .005$ ). This finding, if replicated by others, may have important implications for clinical practice and reimbursement for effective treatments.

#### Fluoxetine

Although fluoxetine is widely used in clinical practice for the treatment of depressive and anxiety disorders, it is disappointing to find very few studies evaluating the efficacy of fluoxetine in panic disorder. There are no published double-blind, placebo-controlled studies assessing fluoxetine in panic disorder. During the past 10 years, only 4 open-label studies from 3 medical centers have evaluated the utility of fluoxetine in the treatment of panic disorder.<sup>23–26</sup> Three of the studies (Table 3) suggested that fluoxetine is effective approximately 50% of the time within 8 weeks, even with the modest doses used in these studies. In the fourth case series, an improvement rate of 76% was reported after 1 year of treatment, suggesting that rates may improve over time.<sup>23</sup>

The success rate with fluoxetine appears to be higher with longer treatment duration and higher doses. In patients with panic disorder, there was more anxiety and activation in the early weeks of treatment than was expected, and this may have contributed to a higher dropout rate.<sup>25</sup> Although fluoxetine appears to work for many patients with panic disorder, the initial activation and restlessness associated with the 20-mg dose may cause it to be less suitable as a starting dose for the acute management of panic disorder, especially in the early weeks, compared with other alternatives. Fluoxetine is available in a 10-mg capsule, but it is difficult to start patients with panic disorder on lower doses, such as 5 mg daily, without using the liquid formulation, which is expensive.

#### Sertraline

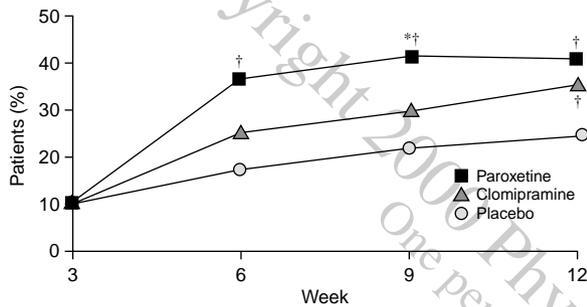
Sertraline was approved by the U.S. Food and Drug Administration (FDA) in 1997 for use in panic disorder. The studies that formed the basis for this approval are outlined in Table 4.<sup>27–30</sup> Two of these are fixed-dose studies,

**Table 4. Studies Evaluating Sertraline for the Treatment of Panic Disorder<sup>a</sup>**

Design	Duration		Results
	N	(wk)	
Sertraline vs placebo (fixed dose)	184	12	Sertraline > placebo (all doses)
Sertraline vs placebo (fixed dose)	157	12	Sertraline = placebo
Sertraline vs placebo	173	10	Sertraline > placebo
Sertraline vs placebo	178	10	Sertraline > placebo

<sup>a</sup>Data from references 27–30.

**Figure 1. Panic Attacks Reduced to Zero for Patients (N = 367) Treated With Paroxetine, Clomipramine, or Placebo<sup>a</sup>**



<sup>a</sup>Adapted from reference 33, with permission.

\*p < .05 vs. clomipramine.

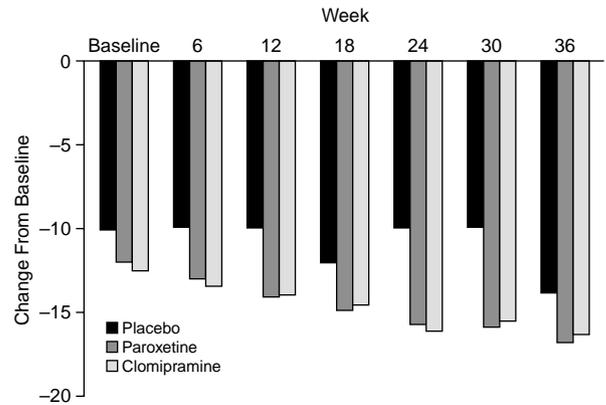
†p < .05 vs. placebo.

and 2 are flexible-dose studies.<sup>27,30</sup> In the fixed-dose studies, the individual doses did not separate from placebo using conventional methods for analyzing the primary outcome measure, so the minimum effective therapeutic dose of sertraline in panic disorder is unknown. In both of the flexible-dose studies, sertraline was significantly better than placebo.<sup>27,30</sup> In the flexible-dose studies, 130 mg/day was the mean effective dose of sertraline that was needed to achieve efficacy. A recent study evaluating sertraline (mean dose = 126 mg/day) in 168 patients with panic disorder also showed that sertraline was well tolerated and more effective compared with placebo.<sup>31</sup> These data suggest that low-dose sertraline, in doses less than 100 mg/day, is not expected to provide optimal relief of symptoms in the typical patient with panic disorder. To achieve beneficial effects in panic disorder, the dose of sertraline should be gradually increased to greater than 125 mg/day for the average patient.

**Paroxetine**

Paroxetine was the first SSRI to receive FDA indication for use in panic disorder, and it is the most well-studied SSRI in the management of panic disorder.<sup>32</sup> In a flexible-dose study comparing paroxetine, clomipramine, and placebo in 367 patients with panic disorder, the percentage of patients whose panic attacks were reduced to

**Figure 2. Reduction in Mean Hamilton Rating Scale for Anxiety Score From Baseline for Patients With Panic Disorder Treated With 36 Weeks of Paroxetine, Clomipramine, or Placebo<sup>a</sup>**

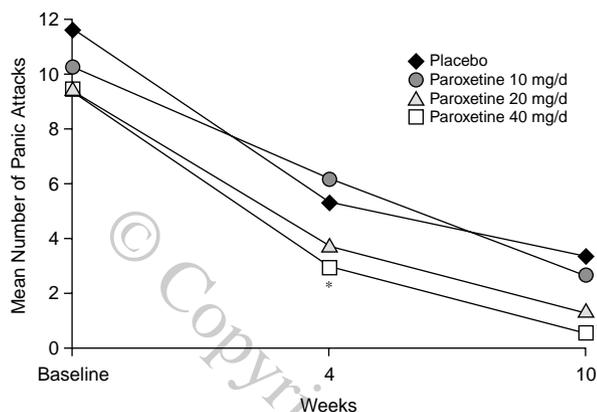


<sup>a</sup>Data from reference 34.

zero after 12 weeks of treatment was significantly higher in the paroxetine and clomipramine groups ( $p < .05$ )<sup>33</sup> (Figure 1). As might be expected from any SSRI, paroxetine was better tolerated and had fewer side effects compared with the TCA. Paroxetine was significantly more effective compared with placebo beginning at week 6. Patients who responded well in the acute phase of this study were invited to continue therapy in a 6-month follow-up study.<sup>34</sup> The 176 patients who received long-term therapy achieved continued reduction in mean HAM-A score (change from baseline) during the 9 months of treatment (Figure 2). Patients who received paroxetine or clomipramine not only maintained the improvement seen in the first 12 weeks, but also continued to show improvement during the additional 6 months of therapy.<sup>34</sup>

In a 10-week study evaluating paroxetine in the treatment of panic disorder, 278 patients were randomly assigned to paroxetine 10 mg, 20 mg, or 40 mg daily or placebo<sup>35</sup> (Figure 3). The analysis showed that patients treated with paroxetine, 10 mg and 20 mg, experienced a decreased mean number of panic attacks compared with placebo-treated patients. However, only the 40-mg dose was significantly better compared with placebo beginning at week 3 ( $p < .019$ ). A total of 86% of patients treated with paroxetine, 40 mg, attained a panic-free status at endpoint. In an extension of this study, patients who were previously maintained on paroxetine were invited to enter a 6-month follow-up study.<sup>36</sup> During the first 3 months, patients were maintained at the dose at which they had initially responded (i.e., 10 mg, 20 mg, or 40 mg daily). At the end of 3 months, the 105 patients who did not relapse were randomly assigned either to receive the same dose of paroxetine or to switch to placebo for an additional 3 months. By the end of the 3-month relapse-prevention study, 5% of patients who had continued on paroxetine

Figure 3. Reduction in Mean Number of Panic Attacks for Patients (N = 278) With Panic Disorder Treated With Paroxetine or Placebo<sup>a</sup>



<sup>a</sup>Data from reference 35.

\* $p < .019$  vs. placebo.

treatment relapsed, compared with 30% of those randomly assigned to placebo.<sup>36</sup> These studies suggest that long-term therapy with paroxetine may prevent relapse of panic disorder.

Oehrberg and colleagues<sup>37</sup> randomly assigned 129 patients to receive paroxetine 20 mg, 40 mg, or 60 mg daily or placebo. All patients received CBT during the 12-week period. A significantly higher percentage of patients receiving paroxetine with CBT had a 50% or greater reduction in panic attacks compared with patients receiving placebo with CBT ( $p = .006$ ).

### Miscellaneous Agents

The efficacy of citalopram, venlafaxine, and nefazodone also has been evaluated in patients with panic disorder.<sup>38-41</sup> Wade and associates<sup>41</sup> evaluated 475 patients in an 8-week, double-blind, placebo-controlled study of citalopram compared with clomipramine. Citalopram in doses of 20 mg to 30 mg or 40 mg to 60 mg daily, and clomipramine in doses of 60 mg to 90 mg daily, were significantly better compared with placebo. However, citalopram, 10 mg to 15 mg daily, had effects no different than placebo. Pollack and colleagues<sup>40</sup> found venlafaxine effective in the treatment of panic disorder, and Dassylva and associates<sup>38</sup> reported that nefazodone was superior to imipramine and placebo in a 6-week study.

### SSRIs VERSUS OTHER ANTIPANIC MEDICATIONS

As a class, how do the SSRIs compare with other classes of antipanic medications? Currently, there are no large class-to-class drug comparison studies to answer this question. In the meantime, a meta-analysis of 32 randomized, prospective, double-blind, placebo-controlled panic disorder studies using similar outcome measures and in-

volving more than 2348 patients provides a preliminary answer. In this meta-analytic study, Boyer<sup>42</sup> compared the effect sizes (i.e., difference between 2 treatments standardized to allow valid comparisons) and mean improvement ratios (i.e., proportion of patients who improved with placebo or active medication) of SSRIs, alprazolam, and imipramine in the treatment of panic disorder. The effect size for SSRIs as a class was significantly superior to the effect sizes for both imipramine and alprazolam. In addition, there is a significant relationship between dose and effect size. All pooled doses of SSRIs were superior to high doses of imipramine ( $p < .04$ ) and high doses of alprazolam ( $p < .005$ ). The mean improvement ratio was 3.0, 1.8, and 1.7 for SSRIs, alprazolam, and imipramine, respectively, indicating that the SSRIs are more effective. The author concluded that the SSRIs are, in aggregate, superior to alprazolam and to imipramine in the treatment of panic disorder. These data suggest that SSRIs not only are effective in the acute treatment of panic disorder but also are helpful in preventing relapse and maintaining benefit over at least a 9-month period.

### DURATION OF THERAPY

Because panic disorder is a chronic, recurring illness, it is not certain if medications should be discontinued in patients with panic disorder. There are many complications associated with stopping medications, including increased rates of recurrence, suicide, and morbidity. Patients who have experienced previous relapses or who have comorbid conditions should be considered for long-term therapy.<sup>43</sup> Based on long-term studies with paroxetine, it is evident that medication benefits persist after the acute period and that continued therapy prevents the occurrence of relapse.<sup>34,36</sup> In general, patients who have had a limited number of episodes ( $\leq 2$ ) should be treated for a minimum of 1 year and then may have their medications tapered over 4 to 6 months for a drug-free trial period. If the panic attacks recur, the medication should be restarted. Patients who have more than 2 episodes should be maintained on medications indefinitely.

### SUMMARY

Panic disorder is a common, chronic, disabling condition with a high suicide attempt rate. Patients with panic disorder frequently develop comorbid conditions and suffer from significant social and physical morbidity. Fortunately, once panic disorder is diagnosed, a number of treatment options are available, including the SSRIs, high-potency benzodiazepines, TCAs, and MAOIs. Based on proved efficacy in numerous clinical trials, the SSRIs are beneficial in the treatment of panic disorder, as well as a number of other anxiety and depressive disorders. A broad spectrum of action and improved tolerability compared

with older classes of medications make the SSRIs first-line agents for patients with panic disorder.

*Drug names:* alprazolam (Xanax and others), citalopram (Celexa), clomipramine (Anafranil and others), clonazepam (Klonopin and others), divalproex sodium (Depakote), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), lamotrigine (Lamictal), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), venlafaxine (Effexor).

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