Key Words: paroxetine, paroxetine CR, panic disorder

Treatment of Panic Disorder: Focus on Paroxetine

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ABSTRACT *~ Panic disorder is a chronic and disabling condition associated with significant morbidity. Treatment of panic disorder has evolved significantly in the past 20 years with the availability of serotonergic antidepressants, including the selective serotonin reuptake inhibitors (SSRIs). Of these, paroxetine was the first to receive an indication for treatment of panic disorder and has been extensively studied in this area. A series of randomized, double-blind, placebo-controlled studies have demonstrated the efficacy and safety of paroxetine treatment of panic disorder, with a majority of patients achieving panic-free status during 12-week studies. Continued treatment with paroxetine results in sustained rates of remission compared with placebo. The combination of paroxetine and cognitive behavioral therapy appears to offer benefits of efficacy and sustained therapeutic response.* Psychopharmacology Bulletin. *2003;37(Suppl 1):53-63.*

INTRODUCTION

Panic disorder is a common, typically chronic anxiety disorder associated with significant distress and disability in affected individuals. It is characterized by recurrent panic attacks, consisting of episodes of intense fear or anxiety associated with symptoms of autonomic arousal that peak within 10 minutes.[1] The panic attacks are complicated by the development of *anticipatory anxiety*, persistent concerns about having additional attacks and fear of the meaning and consequences of these attacks (eg, "I'm having a heart attack"). The majority of patients with panic disorder, particularly in treatment-seeking populations, have accompanying *agoraphobia*, the fear and avoidance of situations in which attacks have previously occurred or of any situation in which assistance might be unavailable or easy escape difficult. Panic disorder is relatively common, with the National Comorbidity Survey reporting a

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lifetime prevalence of 3.5% in the United States.[2] The condition is reported more commonly in women than in men, with a 2:1 female:male ratio for uncomplicated panic and a 3:1 ratio in patients with comorbid agoraphobia. Whether this gender distribution is the result of differences in hormonal milieu or other biological factors, psychosocial issues such as culturally sanctioned modes for expression of distress in men and women, or some other combination of factors, is unknown.[3]

Panic disorder is a chronic condition for many affected individuals, with converging sources of data suggesting that panic and other anxiety disorders in adulthood represent manifestations of a lifelong constitutional predisposition or vulnerability to anxiety that tends to be familial, first emerges in childhood, and is variably expressed during the course of a lifetime.[4] Whereas the usual age of onset of panic disorder is in the third or fourth decade of life, more than half of affected patients report a history of some form of anxiety dating back to childhood.[5] This constitutional vulnerability to anxiety may be mediated in part by dysregulation in the limbic system and other components of the central nervous system, and exacerbated or diminished by environmental factors such as trauma, early life experiences and conditioning, and modeling of peer or parental behavior.[4] The underlying neurobiology of panic disorder is an area of active study, with data from a variety of sources implicating dysfunction in brain monoamine (including norepinephrine and serotonin), neuropeptide, GABA, and hypothalamic-pituitary axis systems, as well as dysregulation in central structures mediating the fear network, including the amygdala, hippocampus, and medial prefrontal cortex.[6] Perhaps not surprisingly, given the evidence of an innate vulnerability to anxiety, the available evidence from naturalistic and follow-up studies suggests that panic disorder may be a chronic and persistent condition, with relapse not uncommon following treatment discontinuation.[7-9]

Panic disorder exerts a significant negative impact on overall quality of life, including dysfunction in marital, social, and vocational spheres of activity. In addition, the adverse effect on physical function associated with panic disorder is comparable to and sometimes greater than that seen with many other chronic medical conditions.[10-12] Panic disorder appears to be associated with increased mortality in both men and women,[13] with the increased risk of mortality in men primarily attributable to cardiovascular causes. Although the reason for this association is unclear, men with high levels of phobic anxiety may have an increased risk for fatal coronary events because of decreased heart-rate variability predisposing to the development of malignant dysrhythmias.[14] Although tricyclic antidepressants (TCAs) decrease heart-rate variability, paroxetine normalized heart-rate variability in a study of patients with panic disorder[15]; this effect might be expected to reduce the risk of adverse

cardiac events, although this hypothesis has not been confirmed to date. In addition, panic disorder increases the risk of suicide in both men and women, particularly when associated with comorbid depression and personality disorders.[16]

Patients with panic disorder are 5 to 8 times more likely to be high utilizers of medical services than individuals without panic.[17] Panic disorder appears to be overrepresented among patients with chest pain and negative findings on angiography,[18] and among patients with chronic obstructive pulmonary disease,[19] irritable bowel dysfunction,[20] and dizziness.[21] There is some evidence suggesting that the diagnosis and treatment of panic disorder result in reduction in medical service utilization and increased productivity, as well as symptomatic improvement, leading to an overall reduction in costs associated with the disorder.[22]

TREATMENT OF PANIC DISORDER

Since the recognition of panic disorder as a discrete entity by Donald Klein in the 1960s,[23] the primary pharmacologic treatments for panic disorder through the early 1990s were the TCAs, with imipramine[24] and clomipramine[25] being the most well studied. Monoamine oxidase inhibitors (MAOIs), although demonstrably effective for panic,[26] were not widely used for this indication because of their adverse-event profile, the need for careful dietary restrictions, and associated risks of hypertensive reactions and serotonin syndrome. A series of studies with the high-potency benzodiazepine, alprazolam,[27,28] demonstrated that benzodiazepines could be effective for panic disorder as well as for generalized anxiety. The longer-acting agent, clonazepam,[29] subsequently became widely used for this indication as well, particularly in psychiatric settings. It has since been demonstrated that lower-potency benzodiazepines, at equipotent doses, could be effective for panic disorder as well.[30] However, although both the TCAs and the benzodiazepines were clearly effective, the use of the former was limited by their adverse-event profile, and the use of the latter limited by issues related to dependence, abuse, liability, and lack of efficacy against common comorbidities, including depression.

The selective serotonin reuptake inhibitors (SSRIs), including citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, have been studied in patients with panic disorder and proven effective for this condition.[31] During the past decade, the SSRIs have become the first-line pharmacotherapy for panic disorder because of their demonstrated efficacy and generally favorable adverse-event profile, including lack of significant cardiovascular, orthostatic, and anticholinergic effects, and their relative safety in overdose as compared with the TCAs. The SSRIs are not associated with the concerns about dependence and abuse liability that complicate use of the benzodiazepines. In addition, as agents

with a broad spectrum of activity, the SSRIs proved useful for the treatment of panic disorder in patients with comorbid conditions, including depression, social anxiety disorder, posttraumatic stress disorder, and obsessive-compulsive disorder. Although the SSRIs are generally better tolerated than the older classes of antidepressants, their administration may be associated with a number of treatment-emergent adverse events, including sexual dysfunction, gastrointestinal disturbances, activation, and sedation. Two recently introduced SSRIs, controlled-release paroxetine (paroxetine CR) (Sheehan DV, unpublished data) and escitalopram,[32] as well as the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine,[33] have also demonstrated efficacy for panic disorder.

In addition to pharmacotherapies, psychosocial treatments, particularly cognitive-behavioral therapy (CBT), have demonstrated efficacy for the treatment of panic disorder. The theoretical underpinnings of CBT derive from a model of panic that focuses on the role of fears of bodily sensations, catastrophic cognitions, and avoidance behavior in the genesis and subsequent maintenance of panic disorder.[34] Components of effective CBT interventions involve provision of information about self-perpetuating patterns that maintain the disorder, cognitive restructuring, both interoceptive and in vivo exposure, and anxiety-management skills, including breathing techniques and muscle relaxation. Studies document the comparable efficacy of CBT and pharmacotherapy for panic disorder and suggest that combined treatment may be more effective than either intervention alone for some patients.[35] CBT has the advantage of lack of treatment-emergent side effects and persistence of benefit for some patients after discontinuation. Widespread use of CBT is limited by the increased work required on the part of the patient and the lack of providers trained to deliver this intervention.

PAROXETINE FOR PANIC DISORDER

Paroxetine, which was the first SSRI to receive an indication for panic disorder from the US Food and Drug Administration, is the most extensively studied SSRI for the treatment of panic disorder. Table 1 lists a number of the randomized, controlled trials examining the efficacy of paroxetine for treatment of panic disorder.[36-45] The findings of a multicenter, placebo-controlled, randomized trial of paroxetine and clomipramine in 367 patients with panic disorder demonstrated comparable efficacy for the 2 agents. Both paroxetine and clomipramine were significantly more effective in reducing the number of panic attacks than placebo, and paroxetine was generally better tolerated than the TCA.[40] A group of 176 patients, who responded positively during the initial 12 weeks of treatment in that study, continued to experience a

reduction in anxiety on paroxetine and clomipramine during a 6-month follow-up study.[41]

In a 10-week, placebo-controlled, randomized, fixed-dose study of paroxetine 10 mg, 20 mg, or 40 mg per day, patients receiving paroxetine in each of the dosing arms experienced a reduction in the mean number of panic attacks. However, significant differences from placebo were achieved only in the 40-mg group, with separation from placebo occurring at week 3.[37] Of the patients receiving 40 mg/day, 86% achieved "panic-free" status by study endpoint ($P<.02$). One hundred and thirty-eight responders to acute treatment with paroxetine in this study entered into a 3-month, double-blind maintenance period in which they were maintained on the same treatment received during the acute trial. One hundred and five patients with sustained response during the maintenance period (ie, no relapse) were randomly assigned to continue either the same dose of paroxetine or switch to placebo for an additional 3 months. Paroxetine was significantly effective in preventing relapse. At the end of the 3-month relapse prevention phase, only 5% of patients in the paroxetine group relapsed compared with 30% of those randomized to placebo ($P=.002$).[38]

The efficacy and tolerability of the controlled-release formulation of the drug, paroxetine CR, has been assessed in 3 identically designed, flexible-dose studies of 444 adults with panic disorder (Sheehan DV, unpublished data). At the 12-week study end point, 73% of patients in the paroxetine CR group and 60% of patients in the placebo group achieved panic-free status ($P<.005$).

A number of studies have examined the use of paroxetine in conjunction with CBT for panic disorder. In one 12-week study, Oehrberg and colleagues[42] randomly assigned 129 patients to treatment with paroxetine 20 mg, 40 mg, or 60 mg/day, or placebo, with all patients receiving CBT. The combination of paroxetine and CBT resulted in a significantly greater proportion of patients experiencing at least a 50% reduction in panic attacks (82%) compared with those receiving placebo and CBT (51%; $P=.001$).

In a pilot study to test whether the addition on an SSRI would enhance the efficacy of a very brief CBT intervention, Stein and colleagues[45] examined 33 patients with panic disorder who were randomized to receive flexibly dosed paroxetine (10-50 mg/d) or placebo, with a brief CBT intervention added at weeks 5 and 7 of treatment and supplemented by educational and directive reading material. Both treatment groups improved significantly on most measures during the 10-week acute treatment trial; however, the proportion of patients who were "panic free" at end point was significantly greater in the paroxetine-treated group versus the placebo group (80% versus 25%, respectively) as was the proportion of patients rating themselves as "very much

TABLE 1

RANDOMIZED CONTROLLED TRIALS OF PAROXETINE TREATMENT OF PANIC DISORDER

Study	Medication	Dose	N
Bakker et al.[36]	Paroxetine	20-60 mg/d	32
	Clomipramine	50-150 mg/d	32
	Cognitive therapy	12 sessions	35
	Placebo		32
Ballenger et al.[37]	Paroxetine	10 mg/d	67
	Paroxetine	20 mg/d	70
	Paroxetine	40 mg/d	72
	Placebo		69
Burnham et al.[38]	Paroxetine	10 mg	31
	Paroxetine	20 mg	29
	Paroxetine	40 mg	39
	Placebo		37
Kampman et al.[39]	CBT + paroxetine	20-40 mg/d	19
	CBT + placebo		19
Lecrubier et al.[40]	Paroxetine	20-60 mg/d	123
	Clomipramine	50-150 mg/d	121
	Placebo		123
Lecrubier et al.[41]	Paroxetine	20-60 mg/d	68
	Clomipramine	50-150 mg/d	63
	Placebo		45
Oehrberg et al.[42]	CBT + paroxetine	20-60 mg/d	55
	CBT + placebo		52
Perna et al.[43]	Paroxetine	20-50 mg/d	25
	Citalopram	20-50 mg/d	27
Pollack et al.[44]	Paroxetine + placebo	10-40 mg/d	22
	Paroxetine + clonazepam maintenance	10-40 mg/d 0.5-2.0 mg/d	20
	Paroxetine + clonazepam taper	10-40 mg/d 0.5-2.0 mg/d	18
Stein et al.[45]	Paroxetine + vbCBT	10-50 mg/d	17
	Placebo + vbCBT		16

CBT=cognitive behavioral therapy; vbCBT=very brief cognitive therapy.

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Duration	Outcome
12 weeks	65% of paroxetine patients vs 34% of placebo patients were "panic-free" at end point (*P*=.012)
10 weeks	86% of patients receiving 40 mg/d of paroxetine vs 50% of placebo patients were panic-free at end point
3 months	5% of paroxetine maintenance patients vs 30% of placebo patients experienced relapse (*P*=.002)
8 weeks	74% of CBT + paroxetine patients vs 47% of CBT + placebo patients were "panic-free" at end point (*P*<.1)
12 weeks	50.9% of paroxetine patients vs 36.7% of clomipramine patients (*P*=.04) vs 31.6% of placebo patients (*P*=.004) reported a reduction to zero full panic attacks at end point
36 weeks	84.6% of paroxetine patients vs 59.1% of placebo patients reported a reduction to zero or one attack at end point (*P*=.004)
12 weeks	82% of paroxetine patients vs 50% of placebo patients experienced a ≥50% reduction in panic attacks at end point (*P*=.001)
2 months	Equivalent efficacy on most measures; 50% of paroxetine patients vs 24% of citalopram patients reported a reduction to zero one attack at end point (*P*=.07)
12 weeks	Panic-free rates at end point ranged from 60%-70% and were not significantly different between groups
10 weeks	80% of paroxetine patients vs 25% of placebo patients were "panic-free" at end point (*P*<.007)

improved" (60% versus 13% of paroxetine- and placebo-treated patients, respectively). Kampman and colleagues[39] examined the efficacy of adjunctive paroxetine for patients remaining symptomatic despite initial treatment with CBT. Of 161 patients receiving an initial 15-session course of CBT, 43 were unimproved and included in a subsequent double-blind study in which patients continued CBT and were randomized to paroxetine 40 mg/d or placebo. Analysis across a range of measures demonstrated significant improvement for the combined CBT plus paroxetine group compared with the CBT plus placebo group. The efficacies of paroxetine flexibly dosed from 20 to 60 mg/day and clomipramine 50 to 150 mg/day were compared with those of placebo and cognitive therapy (CT) in a 12-week trial.[36] In the intent-to-treat analysis, the mean dose of paroxetine was 36.2 ± 16.4 mg/day, and the mean dose for clomipramine was 90.6 ± 36.9 mg/day. A significantly greater proportion of paroxetine-treated patients (65%) but not clomipramine-treated patients (53%) compared with those receiving CT (40%) and placebo (34%) were panic free at end point.

The common strategy of combining treatment with an SSRI and benzodiazepine for panic disorder was examined with paroxetine in a 12 week, double-blind study, in which all patients were randomized at initiation of treatment to 1 of 3 arms: paroxetine (up to 40 mg/d) and placebo, paroxetine coadministered with clonazepam followed by a tapered benzodiazepine discontinuation phase, and ongoing combination treatment.[44] Similar to prior studies of combined treatment,[46] initiation with combined treatment led to a faster reduction in distress. However, this study extended the findings from previous reports by demonstrating that continued combined treatment did not confer ongoing superior efficacy; by end point all 3 treatment groups demonstrated significant improvement. There was no differential benefit beyond the initial few weeks of therapy for the group receiving combined treatment with paroxetine and clonazepam compared with those on paroxetine plus placebo, or those tapering off the benzodiazepine. Results from this study suggested that the strategy of initiating combined treatment followed by benzodiazepine taper after a few weeks might provide early benefit while avoiding the potential adverse consequences of long-term combination therapy.

There have been relatively few studies comparing the efficacy of different SSRIs for any anxiety indication, including panic disorder. However, one single-blind study, without placebo control, compared the efficacy of paroxetine flexibly dosed up to 50 mg/day and citalopram also dosed up to 50 mg/day for 60 days in 58 patients with panic disorder.[43] Both drugs were effective, with response rates of 84% and 86%, respectively, and no significant differences in primary efficacy measures, although there was a trend in this small study toward a

higher proportion of panic-free patients at end point on paroxetine compared with citalopram (50% versus 24%, *P*=.07).

Given the evidence suggesting that the majority of patients with panic disorder begin manifesting anxiety difficulties in childhood,[47] there has been increasing interest in the treatment of anxiety disorders in children. It is hoped that early intervention may reduce not only acute morbidity but also, perhaps, alter the course of illness and decrease the development of long-term complications. A recent naturalistic study examined the efficacy and safety of paroxetine in the treatment of children and adolescents with panic disorder.[48] Patients were treated with an initial dose of 5 to 10 mg/day and titrated up to 40 mg/day, with a mean of 24 mg/day during the 12 months of treatment. Eighty-three percent of those treated were considered responders, and the medication was generally well tolerated. Although this was a retrospective case series, these data do suggest a role for paroxetine in the treatment of panic disorder in children and adolescents. Treatment of anxiety in children is an issue of critical importance that is receiving increasing systematic study.

CONCLUSION

Panic disorder is a common and chronic psychiatric condition that is associated with significant distress and disability. Affected individuals often experience the onset of anxiety difficulties in childhood, and manifest with a variety of affective symptomatology during the course of their lifetime. Panic disorder is associated with elevated rates of psychiatric and medical comorbidities and panic patients tend to be high utilizers of medical services. A variety of effective pharmacologic and psychosocial treatments for panic disorder are available, with the SSRIs becoming first-line pharmacotherapy because of their broad spectrum of efficacy and favorable adverse-event profile compared with earlier classes of medication. As the first SSRI with an indication for panic disorder, paroxetine has emerged as a prototypic agent for the treatment of panic, with a large body of data documenting its efficacy and safety and widespread experience demonstrating its effectiveness alone and in combination with CBT for individuals affected by this distressing condition. ✤

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