

# The therapeutic potential of escitalopram in the treatment of panic disorder

Mark H Townsend  
Erich J Conrad

Department of Psychiatry, Louisiana State University Health Sciences Center New Orleans, New Orleans, Louisiana, USA

**Abstract:** Panic disorder is a chronic and disabling condition that is often accompanied by other psychiatric and medical conditions. The serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been used effectively with panic disorder (PD) and conditions in which panic attacks frequently occur. Escitalopram is the most selective SSRI and a variety of evidence suggests it is of great value in the treatment of panic disorder. In this paper, we review the theoretical and practical implications of its use.

**Keywords:** panic disorder, escitalopram, antidepressant, serotonin

## Introduction

Panic disorder is a common and frequently chronic illness that often co-occurs with other psychiatric and medical conditions. For example, the National Comorbidity Survey-Replication study reported a 2.7% 12-month, and a 4.7% lifetime, prevalence (Kessler, Berglund et al 2005; Kessler, Chiu et al 2005). Panic disorder often accompanies general medical as well as psychiatric conditions (Simon and Fischmann 2005). Patients with panic disorder are at an increased risk for suicide (Goodwin and Roy-Byrne 2006), which appears to increase with comorbid depression (Black 1995). Panic disorder is also associated with autonomic instability, also worsened when depression is present (Townsend 1998).

Much evidence suggests that the selective serotonin uptake inhibitor (SSRI) escitalopram is effective in the treatment of panic disorder (PD). The tricyclic antidepressants (TCAs) and MAO inhibitors (MAOIs) are also effective in this population (Garakoni et al 1984). However, TCAs are associated with potentially fatal arrhythmias, either in monotherapy or in combination with fluoxetine (Witchel et al) and MAO inhibitors must be used with caution in many populations (Yamada and Yasuhara 2004). In this review, we consider neurobiological evidence that supports the use of escitalopram in PD and the clinical trials that have been performed with escitalopram in the treatment of anxiety.

## Neurobiological considerations

While numerous interacting neuroanatomical sites have been implicated in the pathogenesis of PD, a dysfunction of the serotonin (5-HT) system appears to play a crucial role in development and perpetuation of panic attacks (Grove 1997; Maron 2006). The selective SSRIs and the serotonin-norepinephrine reuptake inhibitors (SNRIs) have demonstrated efficacy in the treatment of panic disorder, as well as conditions frequently comorbid with it, including major depression, generalized anxiety disorder, post-traumatic stress disorder, social anxiety disorder and obsessive-compulsive disorder (Pollack 2005). SSRIs and SNRIs, in contrast with tricyclic antidepressants, monoamine oxidase inhibitors and benzodiazepines, hold more favorable side effect profiles and a lower likelihood of drug interaction (Lader 2005).

Correspondence: Mark H Townsend  
Department of Psychiatry, Louisiana State University Health Sciences Center New Orleans, 3450 Chestnut Street, 3rd Floor, New Orleans, Louisiana 70115, USA  
Tel +1 504 897 8558  
Fax +1 504 897 8327  
Email mtowns@lsuhsc.edu

Research into the mechanisms underlying fear and avoidance has implicated the serotonergic and noradrenergic systems in specific locations (Goddard 1997; Grove 1997; Gorman 2000; Ninan 2005). Several models integrate the panic response through the amygdala, with projections to the hypothalamus, locus ceruleus, periaqueductal gray region, parabrachial nucleus and thalamus (Gorman 2000). While the role of 5-HT in panic disorder is clearly important, researchers report conflicting evidence about whether the condition represents a state of 5-HT deficiency or excess (Maron 2006). Serotonin has an inhibitory effect within three brain systems: the noradrenergic activity of the locus ceruleus, the defense and escape behaviors mediated by the periaqueductal gray region, and the production of corticotrophin releasing factor (CRF) by the hypothalamus. SSRIs can produce an anti-panic activity through these mechanisms over time by reducing the “downstream manifestations of panic” (Gorman 2000).

Furthermore, the 5-HT<sub>1A</sub> auto-receptor is believed to play a role in counteracting the acute increase of serotonin after SSRI initiation, and it may be implicated in an elevated perception of somatic anxiety (Ceglia 2004; Sullivan 2005). Further research is needed to determine if escitalopram, highly potent at serotonin reuptake inhibition, is capable of producing a clinically significant anxiolytic effect more rapidly than other agents in the SSRI class.

### **Clinical trials with citalopram in panic disorder**

Although research into escitalopram as treatment for panic disorder per se has been relatively sparse, it has been shown to be effective in a number of anxiety disorders. Furthermore, escitalopram is the S-enantiomer of citalopram, a compound that is FDA-approved only for major depression, but which has demonstrated efficacy in panic disorder in several controlled trials (Wade et al 1997; Lepola et al 1998; Perna et al 2001).

In the 1997 Wade trial, for example, a large sample of PD subjects were randomized to placebo, citalopram, and the tertiary tricyclic clomipramine, the latter itself effective for PD (Cassano et al 1988). Subjects were followed for 8 weeks, and those given clomipramine at 60 or 90 mg/day and citalopram at doses between 20 to 60 mg/day had fewer panic attacks than on placebo. Interestingly, and perhaps suggestive of a negative effect of the R-enantiomer, citalopram at lower doses at end-of-trial had fewer panic attacks than the higher-dosed subjects. Some have suggested that the presence of the R-enantiomer reduces the efficacy of citalopram, whose anxiolytic and antidepressant effects are the result of escitalopram (Sanchez et al 2003).

Escitalopram itself is effective in generalized anxiety disorder (Davidson 2004; Baldwin and Nair 2005), which is frequently comorbid with panic disorder and in which panic attacks often occur. Social anxiety disorder is often accompanied by situational panic attacks, and escitalopram has been demonstrated to reduce social phobia symptoms (Lader et al 2004). In addition, studies of escitalopram in depression have shown a reduction in concurrent anxiety (Burke et al 2002; Olie et al 2006).

### **Clinical trials with escitalopram in panic disorder**

The literature contains three studies of varying rigor and intent that examine escitalopram in primary panic disorder (Stahl et al 2003; Sayer and Cetin 2004; Rampello et al 2006). The small, open-label Sayer and Cetin trial found escitalopram useful, but was presented as a poster and available only as an abstract. Both the Stahl and Rampello studies were designed to discriminate clinical outcome in PD patients taking either citalopram or escitalopram. In animal models, R-citalopram has appeared to counteract the antidepressant effect of escitalopram (Mansari et al 2007), thus the hypothesis that citalopram may be less effective than its S-enantiomer.

The Stahl study was a randomized, double-blind, placebo-controlled, 10-week trial with 366 adults with PD. Patients were randomized to escitalopram at 10 to 20 mg daily; citalopram, 20 to 40 mg daily; or placebo. While citalopram and escitalopram were more effective than placebo in reducing both anticipatory anxiety and the frequency and intensity of panic attacks, escitalopram subjects separated from placebo on one measure earlier than those taking citalopram. On the Panic and Agoraphobia scale, escitalopram showed significant improvement relative to placebo from week four onwards, whereas citalopram results did not obtain significance until week eight.

Although the Rampello study also attempted to show the superiority of escitalopram, it had fewer, older subjects than Stahl's and followed an open-label, naturalistic design. Forty men and women age 65 and older with panic disorder were assigned to either 10 mg escitalopram or 20 mg citalopram each day for 8 weeks. Although panic attack frequency was equivalently reduced in both groups, the escitalopram group showed fewer panic attacks at week 2, while the citalopram group separated from baseline panic attack numbers at week 4. The open-label nature of the Rampello trial hinders generalization of its results, however it does serve to underscore the effectiveness of both escitalopram and citalopram in this population.

## Safety and tolerability

Stahl confirmed the generally benign adverse event and safety profile of escitalopram demonstrated in depression trials (Hirschfeld 2004). The rate of discontinuation due to adverse events for escitalopram was 6.3% compared to 7.6% for placebo. Most treatment-emergency adverse events reported with escitalopram in major depression (Lexapro [package insert] 2007) are common to other SRIs. Sexual side effects, such as delayed ejaculation and anorgasmia, and gastrointestinal symptoms, including nausea and diarrhea, have been ascribed to SRI agonism at the 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors, respectively (Stahl 1998). As with all SRIs, clinicians must be alert to the possibility of iatrogenic mania (Goldberg and Truman 2003), as well as suicidal ideation or behavior, especially at treatment initiation (Bridge et al 2007).

## Conclusion

Many lines of evidence predict that a highly selective SSRI like escitalopram would be effective in PD, and several clinical trials with other anxiety disorders and in "anxious" depression support its first-line use. As PD often presents concurrently with other anxiety disorders and major depression, escitalopram has the potential to reduce numerous related symptoms. Its favorable tolerability predicts successful initiation and maintenance of treatment in PD, and its safety profile supports its use in individuals with concomitant general medical conditions.

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