An emerging role for escitalopram in the treatment of obsessive-compulsive disorder

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Abstract: Obsessive-compulsive disorder (OCD) is a common and severe neuropsychiatric disorder treated by both behavioral and pharmacologic techniques. Despite the availability of treatments for OCD, including the selective serotonin reuptake inhibitors (SSRIs), many OCD patients have an inadequate response to current treatments. As such, additional approaches to the management of OCD are required. A potential but little studied treatment for OCD is the SSRI escitalopram. Escitalopram is the S-enantiomer of citalopram, the preparation containing both S and R enantiomers of citalopram. Not only is escitalopram the most selective of the SSRIs, it is also devoid of R-citalopram, which may interfere with the effects of the S enantiomer. Escitalopram appears to be effective in depression and several anxiety disorders, including social anxiety disorder and generalized anxiety disorder, conditions in which it also appears reasonably well tolerated. Enantiomeric specificity, high serotonin reuptake selectivity, comparatively good tolerability and favorable pharmacokinetics, and preliminary evidence of efficacy in OCD suggest a potential role for the use of escitalopram in the treatment of OCD. Nevertheless, additional work including evaluating the use of escitalopram with behavioral interventions and in long-term treatment of OCD is needed to clarify its overall role in managing OCD.
Keywords: escitalopram, obsessive-compulsive disorder, pharmacotherapy

Introduction to management of obsessive-compulsive disorder

Characterized by obsessions, compulsions, considerable functional impairment, and once thought to be quite rare (Abramowitz 1997), obsessive-compulsive disorder (OCD) may occur in up to approximately 2.4% of the population in North America (Karno et al 1988) and typically presents in a person's early 20s (Abramowitz 1997). For many patients, OCD tends to be chronic, with many people experiencing features of OCD over decades (Skoog and Skoog 1999). People with OCD also suffer from a lower quality of life compared with healthy controls (Moritz et al 2005). Both psychotherapeutic and psychopharmacological approaches either singly or together are used in the treatment of OCD. The relationship between treatment response and quality of life in people with OCD is not entirely clear, but some data suggest that quality of life improves with treatment response (Moritz et al 2005).

Initially consisting of psychoanalysis, psychotherapy for OCD now uses the more effective exposure and response prevention techniques, cognitive therapy, or thought-stopping approaches (Abramowitz 1997). It is unknown, however, whether exposure and response prevention approaches and cognitive therapy work through separate mechanisms or via common factors, although Abramowitz (1997) concluded that these two therapies work through a similar mechanism due to lack of a differential response between cognitive and physiological features of OCD. Nevertheless, exposure and response prevention treatment not only appears helpful in the short-term treatment of OCD, but also seems to be associated with lower relapse rates compared with

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pharmacological interventions even after discontinuation (Simpson et al 2004).

Until the availability of the tricyclic antidepressant clomipramine, pharmacotherapy resulted in little, if any, improvement in OCD. The efficacy of clomipramine in OCD is now well established (Dell'Osso et al 2006), and its inhibition of serotonin reuptake guided attention to a possible role for serotonin in OCD (Abramowitz 1997). In fact, non-serotonergic antidepressants appear to have little efficacy in OCD (Fallon and Mathew 2000; Dell'Osso et al 2006). Since the introduction of clomipramine, other pharmacological approaches to treat OCD using medication have developed that predominantly include the use of selective serotonin reuptake inhibitors (SSRIs; Starcevic 2005). A 1997 meta-analysis comparing clomipramine with fluoxetine and sertraline found larger effect sizes for clomipramine; however, there were relatively few studies of fluoxetine and sertraline, and a large contrast in side effect profiles between clomipramine and placebo may have inflated the effect size for clomipramine (Abramowitz 1997). More recently, other work also has found that clomipramine tends to be slightly superior to other SSRIs in OCD (Ackerman and Greenland 2002; Dell'Osso et al 2006). Using meta-regression to control for factors such as clinical-trial length and OCD severity in their meta-analysis of placebo-controlled trials of clomipramine, fluvoxamine, sertraline, and paroxetine, Ackerman and Greenland (2002) found superiority for clomipramine. Monoamine oxidase inhibitors may have limited efficacy in OCD and a controlled, 6-week trial of buspirone suggested efficacy in OCD (Fallon and Mathew 2000). In a double-blind, placebo-controlled, multiple-crossover trial comparing clomipramine, clonazepam, and clonidine against each other in 6-week-long trials for the treatment of OCD, both clomipramine and clonazepam were effective in reducing symptoms (Hewlett et al 1992).

Generally, SSRIs antidepressants tend to be preferred over tricyclic antidepressants in treating anxiety disorders including OCD (Simpson et al 2004), a practice due to, in part, overall fewer side effects from SSRIs (Starcevic 2005). In placebo-controlled trials, citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline all appear effective in the short-term treatment of OCD (Fallon and Mathew 2000; Eddy et al 2004), and the SSRIs as a class are generally considered to be first-line drug treatment for OCD (Kaplan and Hollander 2003; Simpson et al 2004; Stein, Tonnoir et al 2007), despite the slight possible superiority of clomipramine in efficacy studies (Dell'Osso et al 2006). Case reports, open trials, and blinded trials comparing venlafaxine with active comparators preliminarily support the efficacy of venlafaxine (Phelps and Cates 2005), a dual serotonin and norepinephrine reuptake inhibitor, for OCD. However, a placebo-controlled trial of venlafaxine in OCD did not show clear superiority for venlafaxine (Phelps and Cates 2005). As such, more controlled trials are required to establish the place of venlafaxine in the treatment of OCD (Dell'Osso et al 2006).

Even with the efficacy of behavioral interventions and SSRIs, many patients with OCD continue to have OCD features (Fallon and Mathew 2000; Eddy et al 2004). Furthermore, OCD treatment outcome data for over a year are limited (Eddy et al 2004). To successfully treat OCD, long-term treatment appears to be required due to the chronic nature of OCD. For example, Simpson et al (2004) in a randomized trial investigated relapse rates after treatment discontinuation in patients who had responded to exposure and response therapy alone, to exposure and response therapy plus clomipramine, to clomipramine alone, and to placebo. They found a significant advantage at 12 weeks after treatment discontinuation for patients who had initially responded to exposure and response prevention alone or with clomipramine compared with clomipramine alone. In other words, successful drug treatment for OCD for many patients may require long-term treatment. Moreover, despite the use of SSRIs and psychotherapy, refractory OCD remains a particular challenge (McDougle et al 1993), resulting in several augmentation strategies.

One approach to managing treatment-resistant OCD is adding drugs that increase serotonin transmission to SSRIs (McDougle et al 2000). Clomipramine, for instance, has been combined with SSRIs, although this combination is poorly studied and requires careful monitoring of plasma clomipramine and desmethylclomipramine levels (Fallon and Mathew 2000). Drugs in addition to clomipramine have been added to SSRIs in refractory cases. However, a double-blind trial found little advantage using lithium to augment fluvoxamine in treatment-resistant OCD (McDougle et al 1991). Similarly, McDougle et al (1993) in a placebo-controlled trial found little advantage when buspirone was added to fluvoxamine in patients who had not responded to fluvoxamine alone. Other drugs that have been combined with an SSRI in an attempt to improve response in OCD include donepezil and gabapentin (Fallon and Mathew 2000), although these trials tended to be small and uncontrolled. The double-blind, placebo-controlled addition of the beta blocker pindolol to patients who had not responded to open treatment with paroxetine resulted in improvement as measured by the Yale-Brown Obsessive-Compulsive Scale (Dannon et al 2000). In

contrast, an earlier double-blind, placebo-controlled trial of pindolol or placebo in conjunction with fluvoxamine showed no differences between groups (Mundo et al 1998).

A second approach to treatment refractory OCD outlined by McDougle et al (2000) includes the use of low-dose dopamine antagonists added to existing regimens of SSRIs. Second-generation antipsychotics, for example, may improve the treatment response when added to an SSRI that is only producing a partially favorable response (Starcevic 2005). In a double-blind, placebo-controlled trial, McDougle et al (2000) found that low-dose risperidone was effective in reducing OCD features when added to an SSRI. Similarly, in a double-blind, placebo-controlled study of treatment-refractory subjects with OCD already taking fluoxetine, paroxetine, sertraline, or clomipramine, Bystritsky et al (2004) reported that the addition of the second-generation antipsychotic olanzapine to an SSRI in a double-blind, randomized trial was superior to the placebo group. Some controlled evidence supports the use of intravenous clomipramine for treatment-refractory OCD (Fallon and Mathew 2000). Finally, in some severe, treatment-refractory cases, stereotactic cingulotomy or other neurosurgical intervention can be associated with improvement in OCD, although these procedures tend to be reserved for extreme cases (Chang et al 2003; Cosgrove and Rauch 2003; Jung et al 2006).

Despite the use of both psychotherapy and pharmacotherapy in OCD, the response to treatment is often suboptimal (McDougle et al 1993), even with augmentation techniques (Bystritsky et al 2004). In fact, according to some estimates, approximately 40% (Dell'Osso et al 2006) to 60% (Fallon and Mathew 2000; Pallanti et al 2002) of patients with OCD have an inadequate response to SSRIs. Further, even some reduction in OCD features still may leave patients with considerable morbidity (Fallon and Mathew 2000). The prevalence of inadequate response to available OCD treatments argues for a need to consider alternative approaches to the management of OCD. One such potential treatment warranting consideration for use in adult OCD is the SSRI escitalopram.

Pharmacology and mechanism of action of escitalopram

The SSRI citalopram is a racemic preparation (Lader et al 2004) composed of both right (R) and left (S) stereoisomers (Burke and Kratochvil 2002) in a 1:1 ratio (Sanchez et al 2003). However, biochemistry in vivo appears to be enantiomer selective, possibly responding preferentially to only one stereoisomer (Burke and Kratochvil 2002), consistent with findings that it is the S-enantiomer of citalopram (ie, escitalopram) that inhibits serotonin reuptake (Hyttel et al 1992). In fact, citalopram's R-enantiomer appears to be relatively inactive (Dhillon et al 2006). Not only may it be inactive, but findings suggest that the R-enantiomer of citalopram may actually interfere with the action of the S-enantiomer. For example, Sanchez et al (2003) reported that R-citalopram significantly interfered with the anxiolytic-like effect of escitalopram in an animal model. The interference effect of R-citalopram may not extend to other SSRIs, as suggested by findings showing that R-citalopram did not appear to inhibit the behavioral effects of fluoxetine (Storustovu et al 2004). However, findings showing that R-citalopram can interfere with S-citalopram provide a rationale for the possibility that S-citalopram could have superior clinical efficacy compared with citalopram, which contains both R and S enantiomers. Moreover, the behavioral effect of escitalopram in the fear conditioned stress animal model of anxiety was greater than the behavioral effect of the dose-equivalent racemic preparation of citalopram, an observation providing additional evidence that the enantiomer specificity of escitalopram carries an advantage over citalopram, even though citalopram contains escitalopram (Sanchez et al 2003). Finally, equivalent doses of escitalopram increase frontal extracellular serotonin more than does citalopram (Baldwin and Nair 2005).

Used in adults for the treatment of depressive and anxiety disorders (Burke 2002), the SSRI escitalopram is simply the S-enantiomer of citalopram (Burke and Kratochvil 2002), a development designed to take advantage of physiological stereoisomer specificity by producing a drug preparation consisting of only one stereoisomer.

Like other SSRIs, escitalopram initiates its biological effects by binding to the serotonin transport molecule (Burke 2002) and increasing the concentration of serotonin in the synapse. A notable feature of escitalopram is that it is the most selective of all the SSRIs, having little or no affinity for 144 other binding sites (Sanchez et al 2003). In addition, escitalopram binds to both the primary, high-affinity site on the serotonin transporter protein, which inhibits serotonin reuptake, and to a low-affinity site that alters binding at the primary site (Dhillon et al 2006). Consistent with findings showing that R-citalopram is relatively inactive (Dhillon et al 2006), escitalopram binds more than 30 times more potently to the serotonin transporter receptor than does R-citalopram (Burke 2002), providing further support that stereoisomers have biological relevance. Other neurotransmitter receptors may be affected differently by R-citalopram and escitalopram. For example, Sanchez et al (2003) reported that citalopram

and R-citalopram have affinity for the histamine 1 receptor, whereas escitalopram does not.

It is likely that binding to the serotonin transporter initiates a series of effects in the brain beyond serotonin reuptake inhibition. Although little such data exist for escitalopram, functional neuroimaging data from citalopram are intriguing. In a study using single photon emission computed tomography, Carey et al (2004) found that citalopram treatment was associated with significant deactivation in the cingulate cortex, right thalamus, and left hippocampus in several anxiety disorders including OCD. Citalopram treatment may affect other metabolic factors in addition to cerebral blood flow. For example, citalopram use in OCD was associated with prefrontal and frontal white matter increases in N-acetylaspartate (Jang et al 2006), showing that citalopram can substantially alter brain function in various brain regions. While comparable data for escitalopram are not available, escitalopram may well cause cerebral blood-flow and metabolic effects similar to those reported with citalopram because of the racemic nature of citalopram.

Pharmacokinetics of escitalopram

In general, the pharmacokinetics of escitalopram appear favorable. For instance, the relationship between escitalopram dose and plasma concentrations is linear, which allows for plasma levels to be predicted from dose (Burke 2002). The absorption of escitalopram is not affected by food, and it reaches peak serum levels in three to four hours (Baldwin and Nair 2005). The half-life of escitalopram varies from approximately 27 to 32 hours (Burke 2002), enabling once daily dosing and eliminating the need for multiple daily doses. In people over age 65 though, the half-life can increase to 40 hours (Baldwin and Nair 2005), necessitating dosage adjustments in the elderly (Dhillon et al 2006). Steady state plasma concentrations in healthy volunteers occur in 7 to 10 days (Dhillon et al 2006). Like all other SSRIs, escitalopram undergoes extensive metabolism by cytochrome P450 enzymes, which convert escitalopram to S-desmethyl-citalopram and then to S-didesmethyl-citalopram (von Moltke et al 2001), neither of which metabolites appear to significantly affect serotonin reuptake (Dhillon, Scott and Plosker 2006). An in vitro study found that the cytochrome P450 enzymes 2C19, 2D6, and 3A4 accounted for 37%, 28%, and 35% respectively of the metabolism of escitalopram (von Moltke et al 2001). Drugs that inhibit these enzymes can increase escitalopram concentrations (Dhillon et al 2006). Compared with some other SSRIs, escitalopram may have weak or minimal interactions with the cytochrome P450 system (von Moltke et al 2001; Burke 2002), reducing the potential for cytochrome P450 drug–drug interactions (von Moltke et al 2001). In vivo work, in contrast, shows that escitalopram can inhibit cytochrome P450 2D6 (Dhillon, Scott and Plosker 2006), an effect that requires further study to more fully understand escitalopram's potential for drug-drug interactions.

Escitalopram efficacy studies

To date, escitalopram has shown efficacy in adult major depression (Burke 2002; Burke et al 2002), a condition in which it may have a faster antidepressant response than citalopram (Lepola et al 2003). A number of relatively short-term trials have found that escitalopram has efficacy for social anxiety disorder, panic disorder, and generalized anxiety disorder (Burke 2002). For example, in a double-blind, placebo-controlled trial over 12 and 24 weeks, Lader et al (2004) found escitalopram to be superior to placebo for the management of social anxiety disorder. Similarly, Kasper et al (2005) found escitalopram in a double-blind, placebo-controlled, randomized trial to be superior to placebo in social anxiety disorder, despite a high placebo response in this study. Investigating generalized social anxiety disorder in a double-blind, placebo-controlled, randomized trial, Montgomery et al (2005) found escitalopram to be effective and well tolerated over a 24 week study. Another double-blind, placebo-controlled study also found escitalopram to be effective in generalized anxiety disorder, with discontinuation rates from escitalopram not significantly different from those from placebo (Davidson et al 2004). In their review of the use of escitalopram for the treatment of generalized anxiety disorder, Baldwin and Nair (2005) note that escitalopram has shown efficacy in generalized anxiety for up to 6 months.

Despite findings that escitalopram appears to have efficacy in several anxiety disorders, little work so far has examined directly the efficacy of escitalopram in OCD. Several case reports suggest that escitalopram may be effective for conditions having either obsessive features or argued by some researchers to be related to OCD (Hollander, Friedberg, Wasserman et al 2005). For instance, in a case report of a 15-year-old male with transvestic fetishism thought by the authors to have a compulsive quality, the addition of escitalopram resulted in diminished recurrent thoughts (Praharaj 2004). Another case report found escitalopram use in a 10-year-old boy to be associated with a reduction of trichotillomania (Bhatia and Sapra 2004), a condition that shares some similarities with OCD and may be part of an

obsessive-compulsive spectrum (Hollander et al 2005). In an open-label trial followed by double-blind discontinuation of pathological gambling with anxiety, escitalopram appeared effective (Grant and Potenza 2006). Kirkcaldy et al (2004) reported a case of obsessive-compulsive disorder characterized by compulsive vomiting that appeared to respond favorably to escitalopram.

Stein et al (2006) conducted the only reported randomized, double-blind, placebo-controlled trial of escitalopram in OCD, a study that also included the active comparison drug paroxetine. After randomization to fixed doses of escitalopram 10 mg/day (n = 113), escitalopram 20 mg/day (n = 114), paroxetine 40 mg/day (n = 117), or placebo (n = 114) for 24 weeks, no significant differences in drop-out rates were found between the four groups, although fewer people dropped out of the two escitalopram groups compared with those dropping out of the placebo and paroxetine groups. In terms of efficacy, at 12 weeks, the escitalopram 20 mg/day group and paroxetine groups were superior to placebo, and the escitalopram 10 mg/day group was superior to placebo, albeit with a p value of only 0.052. Compared with placebo, week 12 effect sizes were 0.43 and 0.33 for escitalopram 20 mg/day and paroxetine, respectively. By week 24, both escitalopram groups and the paroxetine group were significantly superior to placebo in terms of treatment response rates. An analysis of remission, defined as a score on the Yale-Brown Obsessive-Compulsive Scale of less than or equal to 10, showed that only the escitalopram 20 mg group was reliably better than placebo in direct comparison to paroxetine 40 mg,

Comparing relapse rates in a large, multi-center study in OCD patients who had responded to 16 weeks of open-label treatment with escitalopram followed by randomized, double-blind treatment with either escitalopram (fixed dose of 10 or 20 mg) or placebo for up to an additional 24 weeks, Fineberg et al (2007) found that escitalopram doses at 10 and 20 mg daily were superior to placebo in preventing relapse. Drop-out rates not related to relapse were similar between the escitalopram and placebo groups. At the end of the open-label part of the study, the response rate (defined by a decrease in the Yale-Brown Obsessive-Compulsive Scale of greater than or equal to 25%) was 74%.

Escitalopram safety and tolerability

Both short- and long-term outcome are important when evaluating a drug for OCD (Starcevic 2005; Fineberg et al 2007). As such, drug tolerability requires careful consideration when evaluating a drug's role in the treatment of a disorder, particularly a chronic disorder such as OCD that often entails long-term treatment. One method of assessing tolerability is to evaluate discontinuation rates due to adverse effects in clinical trials. On this count, discontinuation from escitalopram in some trials tends to be approximately the same as discontinuation rates from placebo (Burke 2002; Fineberg et al 2007). Nonetheless, escitalopram is associated with several adverse effects that potentially can decrease a patient's quality of life, including dry mouth, insomnia, difficulty with ejaculation, nausea, diarrhea, drowsiness (Burke 2002), yawning (Lader et al 2004), fatigue, headache, dizziness, and increased sweating (Montgomery et al 2005).

Montgomery et al (2005) found more adverse effects early in their study of escitalopram for generalized social anxiety disorder than later in the study, implying the possibility that tolerance may occur to escitalopram's adverse effects. Furthermore, when these authors excluded adverse-effect data from the first two weeks of their study, they found that adverse effects were similar overall in the escitalopram and placebo groups.

Analyzing data for escitalopram tolerability in generalized anxiety disorder over six months of treatment (Davidson et al 2004), Baldwin and Nair (2005) found that the most commonly reported adverse effects were headache (25.5%), ejaculation disorder (16%), upper respiratory tract infection (15.4%), nausea (15.2%), and insomnia (14.8%). Baldwin and Nair (2005) concluded that in generalized anxiety disorder, escitalopram was better tolerated overall than paroxetine. Finally, withdrawal from escitalopram appears to be less severe than withdrawal from paroxetine (Montgomery et al 2005).

Conclusion – role of escitalopram in OCD

Based on currently available findings, few studies have evaluated the use of escitalopram in OCD and only one placebo-controlled, randomized study was conducted, limiting the conclusions that can be drawn about the efficacy of escitalopram in OCD. Several factors, however, suggest that escitalopram may have considerable clinical potential in the treatment of adult OCD. First, it is an SSRI, like other drugs that are considered to be first-line drug treatments for OCD (Eddy et al 2004). Second, escitalopram may possess unique advantages compared with other SSRIs in that it consists of not a racemic mixture but rather only the S isomer, a preparation that may target the organization of the nervous system more specifically than a racemic mixture. Third, escitalopram is the most selective of the SSRIs (Sanchez

et al 2003). Fourth, escitalopram has shown efficacy in other anxiety disorders including social anxiety disorder, panic disorder, and generalized anxiety disorder (Dhillon et al 2006). More importantly, the one well-designed, double-blind, placebo-controlled trial to date of escitalopram in OCD (Stein et al 2007) found that escitalopram was superior to placebo for the treatment of OCD. Finally, the evidence to date suggests that escitalopram is reasonably well tolerated and has favorable pharmacokinetics, important features for a drug used to treat a highly chronic condition. Nonetheless, given the few randomized, placebo-controlled trials of escitalopram for OCD to date, the role of escitalopram in the treatment of this condition will be better defined by data from additional controlled trials. Clearly, more clinical data are needed before the role of escitalopram in OCD can be defined. In addition to its clinical potential for the treatment of OCD, escitalopram may offer theoretical insight into the role of stereo-specific enantiomers in OCD. Together, these factors provide a rationale for additional trials of escitalopram in OCD. To further understand the role of escitalopram in the treatment of OCD, more data are required to evaluate its use with behavioral interventions such as exposure and response prevention treatment. Of equal importance is a better understanding of the role of escitalopram in the long-term treatment of OCD.

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