Abstract

What are the therapeutic advantages of escitalopram, the purified S-enantiomer of the racemate citalopram? The biological activity and therapeutic effects of citalopram, which has been used for over a decade to effectively treat depression and other psychiatric disorders, have been shown to reside exclusively in escitalopram. Escitalopram has been shown in vitro to be more than twice as potent as citalopram in the inhibition of serotonin uptake. It is the most selective agent in its class, with virtually no affinity for other neurotransmitters. The efficacy of escitalopram in the treatment of depression has been demonstrated in several clinical trials. Sustained improvement in symptoms of depression was first seen at 1–2 weeks, and continuing improvement and effective prevention of depressive relapse were observed during long-term studies. Further, escitalopram has also been shown to be an effective treatment for anxiety disorders such as panic disorder, generalized anxiety disorder, and social anxiety disorder. Escitalopram was safe and well-tolerated in these studies, with a low rate of discontinuation due to adverse events. Finally, escitalopram has the lowest propensity of all the selective serotonin reuptake inhibitors, including citalopram, for drug-drug interactions mediated by cytochrome P450. Together, these properties make escitalopram an ideal choice for the treatment of depression and other psychiatric disorders in primary care patients, in the elderly, and in patients with comorbid illness.

Introduction

The selective serotonin reuptake inhibitors (SSRIs) are widely accepted as first-line therapy for depression, as well as for anxiety disorders such as panic disorder (PD), generalized anxiety disorder (GAD), and social anxiety disorder (SAD). In addition, they have demonstrated utility in a variety of other conditions such as premenstrual dysphoric disorder, and some chronic pain syndromes and impulse control disorders. Thus, SSRIs are among the most prescribed pharmaceutical agents.1

Despite the great utility of the available SSRIs, research to develop improved antidepressants continues. Reported response rates in clinical trials with the older SSRIs have ranged from 50% to 60%, meaning that a proportion of patients may not adequately respond
to the first drug they try.1,2,4 Additional areas of unmet clinical need include better tolerability and long-term efficacy, faster onset of action, and better efficacy for difficult-to-treat conditions such as severe depression.5

One current area of research focuses on developing single-isomer products from racemic compounds. Approximately 80% of available medications are racemic compounds—mixtures of enantiomers, or stereoisomers that are nonsuperimposable images of one another. As one might expect, the biological activity of a compound is influenced by its stereochemical properties. For example, since many drugs act by adhering to specific receptors, it is no surprise a left-oriented isomer (“S”) may be a better fit in a particular receptor than a right-oriented isomer (“R”), or vice versa. Thus, single-isomer agents have the potential for an improved therapeutic index resulting from higher potency and selectivity, while removing any undesirable effects attributable to the less active enantiomer. This can result in a faster onset of action, improved duration of action, and decreased potential for drug-drug interactions. Other benefits could include a less complicated pharmacokinetic profile and a simplified relationship between plasma concentration and clinical effect.

Escitalopram oxalate is the S-enantiomer of the racemic SSRI antidepressant, citalopram hydrobromide. Citalopram has been demonstrated to effectively treat depression, PD, premenstrual dysphoric disorder, and obsessive-compulsive disorder.6-8 The biological activity and therapeutic effects of citalopram have been shown to reside exclusively in escitalopram. At physiologic concentrations, the R-enantiomer of citalopram has no activity to inhibit serotonin reuptake—the presumed mechanism underlying the antidepressant effect of citalopram. However, the R-isomer has been shown to have a weak affinity for histamine H1 receptors, and the demethyl metabolite of R-citalopram weakly inhibits cytochrome P450 (CYP) 2D6.9-12

This review summarizes published escitalopram data demonstrating the drug’s safety and efficacy in the treatment of depression and anxiety disorders, as well as its potential advantages over older SSRIs.

### Pharmacology

Escitalopram is more than twice as potent as citalopram in the inhibition of serotonin uptake in vitro binding studies,10 and is the most selective agent of its class.9,11,13,14 Escitalopram shows virtually no affinity for serotonin, norepinephrine, muscarinic, histaminic, and dopamine receptors (Table 1).

Escitalopram has been shown to be active in several animal models of depression. For example, chronic mild stress induces anhedonia in rats, as measured by a significant decrease in sucrose intake. Both escitalopram and citalopram reversed the effects of chronic mild stress, and the onset of effect in the escitalopram group was faster than in the citalopram group.15 Further, escitalopram and citalopram produced dose-dependent effects, while R-citalopram was inactive, as seen in Porsolt’s forced swim test in mice.9 Finally, escitalopram was at least twice as potent as citalopram in reducing aggressive behavior in an antagonistic behavior model in the rat.16

The anxiolytic activity of escitalopram has also been demonstrated using animal models.16,18 In the first model, stimulation of the dorsal periaqueductal grey matter in the rat leads to a panic-like aversive reaction that is considered one of the most reliable models of panic anxiety.18 In the second, foot shock induced ultrasonic vocalization in adult rats reflects aspects of panic disorder.17 Finally, the two-compartment black and white box test in mice and rats represents aspects of GAD.17 Escitalopram produced potent, dose-dependent anxiolytic-like effects in all three models, while R-citalopram was either inactive or showed weak activity.

### Pharmacokinetics

Metabolism of escitalopram to S-demethylcitalopram is mediated by three CYP isoforms in parallel (3A4, 2D6, and 2C19), with 3A4 becoming more dominant as escitalopram doses increase.12 Biotransformation of demethylcitalopram to didemethylcitalopram is mediated by CYP 2D6 and an unknown non-CYP-mediated reaction.12 The metabolites of escitalopram do not contribute to the clinical effects of the SSRI as they are present at much lower concentrations and are much weaker inhibitors of serotonin reuptake in vitro.12 Escitalopram is absorbed rapidly, with an average time to peak plasma concentration or serum concentrations of 4 hours. Food does not affect escitalopram absorption. Escitalopram does not bind strongly to plasma proteins, with approximately 56% of the compound being protein bound.19

Escitalopram exhibits linear kinetics that are dose-proportional across the therapeutic range. Terminal half-life in young healthy subjects is about 27–32 hours, consistent with once-a-day dosing.19 The metabolites of escitalopram do not have extended half-lives, so increased accumulation of drug is not observed. Steady state levels of escitalopram are achieved within 10 days. In a cross-over study comparing the single-dose pharmacokinetics of escitalopram 20 mg to those of citalopram 40 mg, the two SSRIs

### Table 1

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<tr>
<th>Receptor-Binding Affinities of SSRIs In Vitro</th>
<th>Ki (nM)</th>
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<tr>
<td>5-HT1A</td>
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<td>Human</td>
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<tr>
<td>Paroxetine</td>
<td>9,000</td>
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<tr>
<td>Sertraline</td>
<td>2,300</td>
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SSRIs = selective serotonin reuptake inhibitors; Ki (nM) = dissociation constant; 3H=tritiated hydrogen; NMS=N-methylscopolamine.

Primary Ps 40 mg/day, or placebo. 22 At both 491 depressed outpatients were ran
domized to escitalopram 10 mg/day, citalopram 20–40 mg/day, or placebo. Escitalopram has not been evaluated in pediatric patients. No dosage adjust-
ment is recommended for patients with reduced hepatic function, moderate renal function impairment, or on the basis of gender.21

**Efficacy in Depression**

Data from several large, randomized, placebo-controlled clinical trials indi-
cate that escitalopram is effective in the treatment of depression. These studies also indicate that the starting dose of 10 mg/day is an effective dose to which most patients respond, and that escitalopram treatment was significantly su-
perior to placebo in as little as 1–2 weeks.

**Fixed-Dose**

The safety and efficacy of escitalo-
pram has been demonstrated in two fixed-dose studies.22,23 In the first, an 8-week, placebo-controlled study conducted in the United States, 491 depressed outpatients were ran-
domized to escitalopram 10 mg/day, escitalopram 20 mg/day, citalopram 40 mg/day, or placebo.22 At both doses, escitalopram significantly improved depressive symptoms com-
pared to placebo as measured by the Montgomery-Asberg Depression Rating Scale (MADRS), the 24-item Hamilton Rating Scale for Depression (HAM-D), Clinical Global Impression (CGI) scales, and patient-rated quality of life (QOL) scales. Significant separation of escitalo-
pram from placebo was observed within 1 week of double-blind treatment, as measured by the CGI-Improvement scale (Figure 1, \( P < .01 \)). Citalopram also significantly improved depressive symp-
toms; however escitalopram 10 mg/day was at least as effective as citalopram 40 mg/day at endpoint. Anxiety symp-
toms and QOL were also significantly improved by escitalopram compared to placebo.

Another fixed-dose, 8-week, place-
bo-controlled, double-blind European trial (N=380) demonstrated that escitalopram 10 mg/day can be effectively used to treat depressed patients in a primary care setting.23 Escitalopram-treated patients experienced significant improvement by study endpoint relative to placebo on the MADRS total score (\( P = .002 \)). Further, escitalopram showed onset of action that was statistically superior to placebo from week 1 onward as measured by the CGI-Improvement scale, at week 2 as measured by MADRS total score, and from week 3 onward as measured by CGI-S. Response rates (defined as at least a 50% reduction in MADRS total score) were 55% for the escitalopram group versus 42% for placebo.

Montgomery and colleagues15 published results from the first 4 weeks of a European 8-week flexible-dose study conducted in primary care centers, during which the escitalopram and citalopram doses were fixed at 10 mg/day and 20 mg/day, respectively. At week 4, mean change in MADRS total score for escitalopram patients was significantly decreased versus placebo (\( P = .002 \)), and escitalopram was statistically superior to placebo on both CGI subscales. Further, escital-
pram but not citalopram produced a significantly superior effect versus placebo by week 1 on both the MADRS total score and CGI (\( P < .05 \)), which was sustained throughout the study.

**Flexible Dose**

Trivedi and Lepola24 reported the combined results of two 8-week, double-blind, placebo-controlled studies (including 8-week results from the European study described above15 and a study in the US of almost identical design) conducted by both specialists and primary care physicians.24 In these studies, 844 depressed out-
patients were randomized to receive placebo, escitalopram 10–20 mg/day, or citalopram 20–40 mg/day. Both active treatment groups experienced signifi-
cant changes from baseline in MADRS total score. Similar to the fixed-dose studies, the onset of action in the escitalopram group (1 week) was signifi-
cantly faster than the citalopram group, and changes in mean MADRS scores were larger for escitalopram than citalopram throughout the study. The mean change from baseline in CGI-S was significant for escitalopram at week 1 (\( P < .05 \)). By study end, 60% of escitalopram patients, 54% of citalo-
pram patients, and 46% of placebo patients were classified as respond-
ers (patients achieving a reduction in MADRS total score of at least 50%).

**Pooled Analysis**

Results from the previously described studies demonstrate that escitalopram at doses of 10–20 mg/day effectively

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**Figure 1**

**Mean Clinical Global Impression of Improvement Scores in Depressed Patients Treated With Escitalopram, Citalopram, or Placebo**

![Figure 1](image)

\( P < .05 \)

\( \dagger P < .01 \)


treats depression. However, none of the three studies employing both placebo- and citalopram-comparator arms was of sufficient sample size to detect a difference between active treatments. Therefore, Gorman examined pooled data from the three trials that included a citalopram arm in order to determine whether escitalopram represents an improved treatment for depression relative to citalopram. The similar design features (eg, patient characteristics, symptom measurement scales) of the three studies allowed for the pooling of data to provide a sample size adequate for statistical comparisons between the two active treatment groups.

At study endpoint, both the escitalopram 10–20 mg/day group (n=520) and the citalopram 20–40 mg/day group (n=403) experienced significantly improved depressive symptoms versus placebo (P≤.001). Escitalopram treatment significantly improved MADRS (Figure 2) and CGI scores within 1 week. At week 1 and week 8, escitalopram treatment led to statistically significantly greater improvement on the MADRS than citalopram treatment (Figure 2). Approximately 60% of patients treated with escitalopram were responders (defined as at least a 50% reduction in MADRS total score), while the response rates for citalopram and placebo were 53% and 41%, respectively.

Relapse Prevention

Continuation treatment with escitalopram in a long-term, double-blind, placebo-controlled study effectively prevented relapse and provided further improvement in depressive symptoms. Two hundred seventy-four patients who had completed 8 weeks of double-blind treatment with escitalopram, citalopram, or placebo were enrolled in this long-term extension study. The first phase of the continuation treatment was an 8-week, flexible-dose, open-label period in which all patients received escitalopram 10–20 mg/day (patients who had received escitalopram in the double-blind lead-in trials actually received a total of 16 weeks of escitalopram treatment prior to entering the placebo-controlled withdrawal phase). Responders during this 8-week treatment period were randomized in a 2:1 ratio to double-blind treatment with either escitalopram (at the same dose to which they had responded, n=181) or placebo (n=93) for 36 weeks (placebo-controlled withdrawal phase of the study). In the escitalopram group, time to relapse (defined as a MADRS total score ≥22, or discontinuation due to an insufficient therapeutic response) was significantly longer, and cumulative relapse rate was significantly lower than with placebo. In addition, continuing treatment with escitalopram produced further improvement in depression scores versus placebo.

Efficacy in Anxiety Disorders

Several animal models indicate that escitalopram has anxiolytic properties. Further, in clinical trials comparing the efficacy of escitalopram and citalopram in relieving anxiety symptoms associated with depression, escitalopram also had a rapid onset of action, which is consistent with the other efficacy findings determined for escitalopram in the treatment of depression. Results demonstrating the efficacy of escitalopram in the treatment of GAD, PD, and SAD are discussed in the following section.

Escitalopram 10–20 mg/day significantly improved symptoms of GAD in an 8-week, randomized, double-blind, placebo-controlled trial (N=252). The escitalopram-treated group experienced significant improvement over placebo on efficacy measures including the Hamilton Rating Scale for Anxiety (HAM-A) and the HAM-A psychic anxiety subscale, the Hospital Anxiety and Depression (HAD) subscale, and the CGI-Severity scale. Further, QOL measures improved, with statistically significant improvement observed in both the total scale and in individual items assessing overall life satisfaction and contentment, ability to function in daily life, and mood and overall sense of well-being.

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Figure 2

Mean Change From Baseline in MADRS Scores in Depressed Patients Treated With Escitalopram, Citalopram, or Placebo

MADRS=Montgomery-Asberg Depression Rating Scale; LOCF=last observation carried forward; vs=versus.
Escitalopram 10–20 mg/day was effective in the treatment of SAD in a 12-week, placebo-controlled, double-blind, multicenter study (N=358).30 Escitalopram was significantly superior to placebo (P<.01) on the primary efficacy parameter—mean change in Liebowitz Social Anxiety Score (LSAS) from baseline to endpoint. Superior therapeutic efficacy for the escitalopram group relative to placebo was also observed as measured by CGI scores, LSAS avoidance and fear/anxiety subscale scores, and the work and social life items on the Sheehan Disability Scale.

Safety and Tolerability

Adverse-Event Profile

Escitalopram is safe and well tolerated, with a low rate of discontinuation due to adverse events. According to a comprehensive safety database31 that include depressed patients from the efficacy studies described previously, the rates of discontinuation due to adverse events for escitalopram 10–20 mg/day (n=715) and placebo (n=592) are statistically indistinguishable (5.9% and 2.2%, respectively), while the package inserts for other SSRIs, including citalopram, report discontinuation rates due to adverse events in worldwide clinical trials of 15% to 20%.

The adverse events most commonly reported by escitalopram-treated patients in the safety database are shown in Table 2.31 Only one adverse event, nausea, occurred in >10% of patients treated with escitalopram and more frequently than with placebo. Point of prevalence estimates of nausea per day show the difference between escitalopram and placebo leveling off after 3–4 weeks of double-blind treatment.23 Escitalopram was not associated with central nervous system stimulant effects, as the only activation adverse event to occur at a rate greater than placebo was insomnia (9% versus 4%). Incidence of ejaculation disorder for male patients in the safety database is approximately 9% for escitalopram, and is similar to that reported for citalopram.31 Other sexual adverse events, such as decreased libido, impotence, and anorgasmia, were reported at 4%, 3%, and 2%, respectively.21

In all the studies reviewed, no clinically significant changes were noted for clinical laboratory parameters, electrocardiogram, or vital signs. Escitalopram treatment had no effect on body weight, unlike other SSRIs.

Patients can be reassured that, in cases where escitalopram data are limited, any concerns about tolerability or safety can be addressed by referring to published data on the racemate citalopram. For example, while there currently are no published data on the effects of escitalopram treatment during pregnancy, delivery outcomes recorded by the Swedish Birth Registry of women reporting the use of antidepressants (including citalopram, n=375) in early pregnancy were not significantly different from the rest of the registry, with the exception of a slightly shorter gestational duration.32

Drug-Drug Interactions

Inhibition of the CYP enzymes, which metabolize the majority of available medications, underlies many drug-drug interactions. Escitalopram is not a potent inhibitor of the CYP enzymes, which metabolize the majority of available medications. Therefore, no clinically significant drug-drug interactions are expected with escitalopram.30,31

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interactions. According to in vitro and in vivo data, escitalopram has little or no effect on the CYP pathways 1A2, 2C9, 2C19, 2D6, 3A4, and, 2E1 (Table 3). The weak inhibitory activity of escitalopram observed in vitro has been attributed to the demethyl metabolite of R-escitalopram. In vivo data on the drug interaction potential of escitalopram are limited; however, co-administration of escitalopram and ritonavir, a potent inhibitor of CYP 34A, in 21 healthy male and females produced no clinically significant effect.33

Although in vitro data indicate that escitalopram does not inhibit CYP 2D6, co-administration of a single dose of the 2D6 substrate, desipramine (50 mg), and escitalopram 20 mg/day for 21 days resulted in 40% increase in Cmax and a 100% increase in AUC of desipramine.21 The clinical significance of these results is not known. Although coadministration of escitalopram doubled blood levels of metoprolol in one single-dose study, no clinically significant effects on blood pressure or heart rate were observed.21 Clinical experience with the racemate citalopram indicates that coadministration with a variety of known CYP substrates and/or inhibitors, including antipsychotics,34,35 tricyclic antidepressants,36,37 theophylline 38 carbamazepine,39 ketoconazole,40 and triazolam,41 does not produce significant interactions. Citalopram also has a relatively low potential for drug-drug interactions via other mechanisms, such as interference with protein binding or renal elimination.32,43

As with all SSRIs, escitalopram should not be co-administered with monoamine oxidase inhibitors (MAOIs), or within 14 days of discontinuing an MAOI.

### Dosage and Administration

Escitalopram should be administered once daily in the morning or evening or without food at a starting dose of 10 mg/day. This is an effective dose to which most patients will respond; however, if needed, dosage can be increased to 20 mg/day. No adjustment of starting dose is required for special patient populations including elderly patients or those with renal or hepatic impairment. Escitalopram is available in 5-mg tablets and 10-mg or 20-mg scored tablets.

### Formulary Considerations and Conclusions

Escitalopram 10 mg/day is a selective and potent SSRI with little or no affinity for other neurotransmitter receptors. Several placebo-controlled clinical trials have demonstrated the drug's safety and efficacy in depression. Escitalopram also has been studied in the prevention of depression relapse, as well as anxiety disorders such as GAD, PD, and SAD. Sustained improvement in symptoms of depression was first seen at 1–2 weeks,22-25 and continuing improvement was noted during long-term studies.26 The drug is well tolerated, with rates of discontinuation due to adverse events that are indistinguishable from placebo. The low propensity of escitalopram for CYP-mediated drug-drug interactions is a potential advantage for the average adult patient, who will most likely tolerate more than one medication in the course of long-term therapy. It also is an advantage for the elderly, who tend to take more than one medication on a regular basis, as well as for those with chronic medical illnesses, which often require extensive polypharmacy. In conclusion, the data presented here support the use of escitalopram as a first-line antidepressant.

### References


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**Table 3**

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<th>Inhibition of CYP By SSRIs</th>
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