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Escitalopram for the Treatment of Depression in Adolescents Marcia L. Buck, Pharm.D., FCCP

Escitalopram, a selective serotonin reuptake inhibitor (SSRI), has been available in the United States since August 2002.¹ Since its approval, it has become one of the most widely used antidepressants in adults. In a recent consensus paper, escitalopram, clomipramine, and venlafaxine, were found to have demonstrated superiority over other antidepressants in both randomized clinical trials and meta-analyses.² On March 19, 2009, the Food and Drug Administration (FDA) extended the indications for escitalopram to include treatment of major depressive disorder in adolescents between 12 and 17 years of age. This action makes escitalopram only the second SSRI to be approved by the FDA for use in teens, following the earlier approval of fluoxetine.^{1,3} This issue of *Pediatric Pharmacotherapy* will describe the clinical trials which supported the FDA approval and review the pharmacology of escitalopram, highlighting information needed for safe use in pediatric patients.

Mechanism of Action

Escitalopram is the S-enantiomer of citalopram. It is approximately 100 times as potent as the R-enantiomer. Like racemic citalopram, escitalopram inhibits neuronal reuptake of serotonin (5-HT). It is highly selective for 5-HT and has minimal effects on dopamine or norepinephrine. Escitalopram has no activity at muscarinic, histaminergic, adrenergic, or GABA receptors.^{3,4} Occupancy of serotonin reuptake transporters by escitalopram occurs in a dose-dependent manner, increasing from 60±6% with 5 mg to 75±5% with 20 mg.⁴

Pharmacokinetics

After oral administration, escitalopram is nearly completely absorbed, with a bioavailability of 80%. Food does not alter absorption. Peak serum concentrations occur within 5 hours, with steady-state concentrations achieved within 1 week. The volume of distribution in adults is

approximately 12 L/kg, with 56% of the drug bound to serum proteins. Escitalopram is metabolized via hepatic cytochrome P450 3A4 and 2C19 to S-demethylcitalopram (S-DCT), the primary metabolite, and S-didemethylcitalopram (S-DDCT). Both of the metabolites are pharmacologically active, but are much less potent than the parent compound and do not contribute significantly to its effects. Less than 10% of an oral escitalopram dose is excreted unchanged in the urine. The terminal half-life in adults is approximately 27-32 hours.^{1,3}

A comparison of the pharmacokinetic profile of escitalopram in adolescents and adults was conducted by Periclou and colleagues.^{5,6} Twelve adolescents (12-17 years of age) and twelve adults were enrolled in this open-label single dose study. The subjects were given 10 mg of escitalopram and underwent blood sampling at regular intervals for up to one week. Eleven teens and all 12 adults completed the study.

The mean maximum concentration was slightly higher in the adolescent group, but the difference was not statistically significant (13.1±2.76 ng/mL in adolescents, compared to 10.39±1.92 ng/mL in adults, p=0.0621). The time to maximum escitalopram concentration was shorter in adolescents (2.9±0.5 hours versus 4.5±2.2 hours in adults, p=0.0249), as was the mean elimination half life (19±6.4 hours in adolescents, compared to 28.9±9.4 hours in adults, p=0.0275). Area under the time-concentration curve, however, was not significantly different between the groups (311.7±105 ng•hr/mL in adolescents, compared to 387.1±157 ng•hr/mL in adults). The authors concluded that the minor differences in pharmacokinetic parameters identified in the study were not clinically significant and did not warrant adjustment in the dose of escitalopram based on patient age.^{5,6}

Treatment Guidelines

In November 2007, guidelines for the treatment of pediatric depression were published in both *The Journal of the American Academy of Child and Adolescent Psychiatry* and *Pediatrics*.⁷⁻⁹ Both provide in-depth recommendations for the diagnosis and treatment of depression, including the use of antidepressants. These guidelines can also serve as a useful review of the utility and limitations of conducting antidepressant trials in children and adolescents, including an explanation of the high response rate in placebo-treated patients and its impact on study results.

Clinical Trials in Children and Adolescents

In 2006, Wagner and colleagues published the results of a randomized, double-blind, placebo-controlled trial of escitalopram in 264 children and adolescents with depression.¹⁰ The patients (6-17 years of age) were randomized to receive either escitalopram, starting at 10 mg/day and increasing to 20 mg/day if needed, or placebo for 8 weeks. The primary outcome measure was the mean change from baseline Children's Depression Rating Scale-Revised (CDRS-S) score, with a decrease representing improvement. Eighty-two percent of the patients completed the study. When evaluated as a whole, there was no significant difference in CDRS-R scores between the treatment and placebo groups (least squares mean difference -1.7, $p=0.31$). However, analysis of just the adolescent patients (those between 12 and 17 years of age) revealed a significantly greater improvement in CDRS-S scores the escitalopram group (least squares mean difference -4.6, $p=0.047$).

Emslie and colleagues published a second randomized, double-blind, placebo-controlled trial of escitalopram in adolescent major depressive disorder.¹¹ This study, published in July 2009, enrolled 312 patients between the ages of 12 and 17 years. As in the previous study, patients received either escitalopram 10-20 mg/day or placebo for 8 weeks and were assessed by CDRS-S scores. Eighty-three percent of the patients completed the study. There was a significant difference in the final CDRS-S score, -22.1 in the escitalopram group versus -18.8 in the placebo group ($p=0.022$). The authors of both studies concluded that escitalopram was effective in the treatment of adolescents with depression.

The efficacy of escitalopram has also been studied in children and adolescents with social anxiety disorder. Isolan and colleagues enrolled 20 pediatric patients between 10 and 17 years of age in a 12 week open-label trial.¹² Outcome was assessed by the change from baseline in Clinical Global Impression-Improvement scale

(CGI-I) scores, as well as several other standard rating scales. Thirteen of the 20 patients (65%) had CGI-I scores ≤ 2 , where scores range from 1 (no symptoms) to 7 (severe) by the end of the study. All testing measures, including CGI-I, showed statistically significant improvement over baseline ($p<0.0001$).

Contraindications and Precautions

On October 15, 2004, the FDA issued a statement requiring manufacturers to add a black box warning to all antidepressants calling attention to the risk for suicidal ideation (suicidal thinking or behavior, also referred to as suicidality) when used in children and adolescents.¹³ The warning came as the result of an investigation into the risk for these behaviors after interim analysis of a study being conducted with paroxetine in adolescents revealed a small, but statistically significant, increase the treatment group. The risk of suicide in depressed adolescents is known to be high, with recent studies suggesting that 7% of depressed adolescents commit suicide by adulthood; and antidepressants have long been acknowledged to be an additional risk factor, particularly in the early phase of treatment.

Several meta-analyses have been conducted to determine the relative risk of suicidal ideation with antidepressant use. In 2007, Bridge and colleagues published the results of their meta-analysis of 27 clinical trials of antidepressants in pediatric patients, the largest analysis conducted to date.¹⁴ Data from 13 trials for major depressive disorder, with 2,910 patients, revealed a pooled absolute rate of suicidal ideation or suicide attempts of 3% in the antidepressant-treated group and 2% in the patients given placebo. The pooled risk difference was 1% (95% CI -0.1% to 2%, $p=0.08$), resulting in a number needed to harm (NNH) of 112. Six studies were conducted in pediatric patients with obsessive-compulsive disorder. A total of 705 children were enrolled. The pooled absolute rate for suicidal ideation/attempt was 1% for the treated patients and 0.3% in the placebo group, resulting in a pooled risk difference of 0.5% (95% CI -1% to 2%, $p=0.57$) and a NNH of 200. In the studies conducted in 1,136 children with non-obsessive-compulsive anxiety disorders, the pooled absolute rate of suicidal ideation/attempt was 1% in the treatment group and 0.2% in the controls. The pooled risk difference was 0.7% (95% CI -0.4% to 2%, $p=0.21$), with a NNH of 143. There were no completed suicides in any of the pediatric trials evaluated. Overall, the results from this analysis showed a small increase in the risk of treatment-emergent suicidal ideation or attempts, similar to the earlier analysis conducted by the FDA.

As a result of this information, it is recommended that all patients be carefully screened prior to initiating therapy and that patients and family members be made aware of the risk for suicide and the need for close monitoring. Family members should report any signs of agitation, irritability, impulsivity, insomnia, or other changes in mood or behavior. All patients starting antidepressant therapy should also be evaluated for bipolar disorder. Treatment with an antidepressant may precipitate a manic episode. Mania has also been reported after SSRI use in patients without an underlying mood disorder. Kul and colleagues described an 11 year old girl diagnosed with a manic episode after receiving one week of escitalopram 10 mg/day for generalized anxiety disorder.¹⁵ She experienced a full recovery three days after discontinuation of escitalopram.

Adverse Effects

Escitalopram is generally well tolerated. In studies of adults being treated for depression, the most common adverse effects reported were: insomnia (in 9% of patients), diarrhea (8%), somnolence or dry mouth (each in 6%), dizziness, fatigue, rhinitis, diaphoresis, or flu-like symptoms (5%), decreased appetite, decreased libido, sinusitis, indigestion, or constipation (3%), and abdominal pain (2%). In studies of adults treated for anxiety, results were similar, except for higher rates of headache (24%), nausea (18%), and somnolence (13%).^{1,3}

Studies conducted in adolescents have shown similar results. In the Wagner study, the most frequently reported adverse effects were headache (22.9% in the escitalopram group and 21.8% in the controls), abdominal pain (10.7% and 5.3%, respectively), and nausea (7.6% and 4.5%).¹⁰ The discontinuation rate was 1.5% for both groups. Reasons for discontinuation in the escitalopram group were stomach upset in one patient and nausea, insomnia, and shaking in the other. Suicidal ideation was present in one patient in the treatment group and two controls.

Similar adverse effects were observed in the Emslie study.¹¹ The most frequently reported were headache (25% in both groups), insomnia (10.3% in the escitalopram group and 6.4% in the controls), and nausea (10.3% and 6.4%, respectively). The rate of discontinuation was 2.6% in the treatment group and 0.6% in the controls (p=0.21). Suicidal tendency was reported in one patient in each group. The study by Isolan and colleagues produced similar results.¹² In addition to these clinical trial results, enuresis has been reported in several pediatric patients receiving escitalopram.¹⁶

Serious, but infrequent, adverse effects associated with escitalopram include hypersensitivity reactions and renal dysfunction. Renal failure has been reported in a 17 year old patient after 10 months of escitalopram 10-20 mg/day.¹⁷ Abrupt discontinuation of an SSRI may result in a withdrawal-like syndrome, with anxiety or mood changes, irritability, agitation, dizziness, headache, lethargy, or insomnia. Some patients may experience transient paresthesias. A gradual reduction in dose is recommended when discontinuing therapy to avoid these symptoms.^{1,3}

Drug Interactions

Serotonin syndrome may occur in patients given other serotonergic drugs, including the L-tryptophan, linezolid, tramadol or the triptans (sumatriptan and related compounds used for the treatment of migraines) or drugs that impair serotonin metabolism (monoamine oxidase inhibitors). These drugs should be discontinued at least two weeks prior to starting escitalopram. Symptoms of serotonin syndrome may include mental status changes (including agitation, hallucinations, and eventually coma), autonomic instability (hyperthermia, hypertension, and tachycardia), neuromuscular disturbances (hyperreflexia), along with nausea, vomiting, and diarrhea. Patients with these symptoms should seek immediate medical attention.^{1,3}

Administration of escitalopram is contraindicated in patients taking pimozide. This combination may place patients at significant risk for cardiac arrhythmias. Carbamazepine may decrease escitalopram concentration by inducing hepatic metabolism. Cyproheptadine may also decrease escitalopram concentrations. Conversely, administration of cimetidine or desipramine with escitalopram may increase escitalopram maximum concentrations by approximately 40%. Escitalopram may decrease the serum concentration of ketoconazole when the two are given together. It may increase the concentration of metoprolol, producing a 50% increase in the maximum concentration.^{1,3}

Administration of lithium in patients taking escitalopram should be undertaken with caution. The effect of escitalopram may be increased by lithium. In addition, escitalopram may increase serum lithium concentrations and predispose the patient to toxicity. If the combination is necessary, serum lithium concentrations should be closely monitored. Escitalopram may increase the antiplatelet or anticoagulant effects of aspirin, non-steroidal anti-inflammatory drugs, or warfarin. Patients should be advised of

the increased risk for bleeding and monitored appropriately.^{1,3}

Dosing Recommendations

The typical starting dose for escitalopram in adolescents or adults is 10 mg taken once daily. It may be taken in the morning or evening, with or without food. In patients who do not respond to the initial regimen, the dose may be increased to 20 mg after at least a week of treatment. Doses above 20 mg have not produced additional benefit in clinical trials. Dosage adjustment is not needed in patients with renal dysfunction. Patients with hepatic impairment should receive no more than 10 mg/day.^{1,3,10-12}

Availability and Cost

Escitalopram is marketed as Lexapro® by Forest Laboratories, Inc. It is available in 5, 10, and 20 mg tablets. Both the 10 and 20 mg tablets are scored. Escitalopram is also available as a peppermint-flavored 1 mg/mL oral solution. The average wholesale price for a 100 tablet bottle is \$322.65 for the 5 mg tablets, \$337.36 for the 10 mg tablets, and \$352.04 for the 20 mg tablets. The price for the oral solution is approximately \$120 for an 8 ounce bottle.^{1,3,18}

Summary

Escitalopram is one of the most widely used antidepressants in adults. It has also been extensively used off-label in adolescents. New studies, conducted as part of the FDA approval process, have demonstrated its efficacy in adolescents and provide information on the relative risk for adverse effects, including suicidal ideation. While the recent action by the FDA offers pediatric health care providers a second approved SSRI to treat adolescents with depression, more long-term research is needed to define the benefits and risks of therapy in this patient population.

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Formulary Update

The next meeting of the Pharmacy and Therapeutics Committee will be held on 9/25/09.

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