
FOR YOUR INPHARMATION



PHARMACY NEWSLETTER



Author: James Kim, BSc, BScPharm, PharmD
Reviewer: Jane Dumontet, BScPharm, BCPP, PharmD

Editor: James Kim, BSc, BScPharm, PharmD

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Is escitalopram, the “better half” of citalopram?

In order to appreciate the uniqueness of escitalopram (EC), its stereochemistry needs to be discussed. An enantiomer is one of a pair of three-dimensional compounds/structures/molecules having mirror images of each other. These mirror images of compounds which are identical in chemical composition cannot be superimposed. The R, S system is a general system used to specify configuration at an asymmetric carbon atom. R and S compounds interact differently with a specific (stereospecific) receptor and usually have different chemical/physical properties including pharmacodynamic and pharmacokinetic properties. A racemic mixture (or racemate) contains both the R and S form of a compound/drug. For example, thioridazine, trimipramine, mirtazapine, fluoxetine, venlafaxine and citalopram (to name a few) are racemic compounds that contain both R and S-enantiomer in equal proportions.

Escitalopram is a selective serotonin reuptake inhibitor (SSRI) comprised of just the S-enantiomer of citalopram, purportedly with better efficacy, faster antidepressant onset and less adverse reactions than citalopram. EC is the therapeutically active enantiomer. Hence, 10mg EC is theoretically equipotent to 20mg of citalopram. Other examples of pure enantiomers (one enantiomeric form) are paroxetine and sertraline.

The purpose of this newsletter is to review current literature on EC to examine its theoretical claim.

Pharmacodynamics

No single neurotransmitter theory can explain antidepressant action of various medications used for treatment of depression. Several neurotransmitter

systems (norepinephrine, serotonin & dopamine) appear to play a role in the treatment of depression. Serotonin augmentation is one of the options available at the present time. EC selectively blocks the reuptake of serotonin at the presynaptic neuron resulting in enhanced postsynaptic serotonergic transmission. It is hypothesized that increased serotonergic activity in the brain leads to the antidepressant action of EC.

The R form

EC and citalopram (but not R-citalopram) dose-dependently reduced firing of serotonin cells in the rat dorsal raphe nucleus (Bergqvist et al.).

Montgomery et al. observed that equivalent doses of EC and racemic citalopram did not produce equivalent results.

Sanchez et al. (a research scientist at Lundbeck) postulated that R-enantiomer (the inactive form in terms of inhibiting serotonin reuptake) of citalopram may interfere with the action of the active form by way of “negative” modulation. Normally EC would bind to the primary serotonin reuptake site at the presynaptic neuron. They proposed that binding by R-enantiomer at a nearby (modulatory) site on the presynaptic neuron would reduce the likelihood of the EC binding to its primary site, thereby making EC less effective at inhibiting serotonin reuptake.

R-enantiomer is also believed to have higher histamine binding properties resulting in higher incidence of fatigue compared to EC.

Clinical Studies

Depression

A U.S. randomized, double-blind, placebo-controlled, 8-week trial (Burke et al.) among 385 depressed outpatients compared efficacy of 10mg/day of EC, 20mg/day of EC or 40mg/day of citalopram to placebo. Several depression measuring scales were used including Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Rating Scale for Depression (HAM-D). Onset of therapeutic efficacy occurred rapidly at 2 weeks in both EC treatment groups. While this trial was not statistically powered to compare EC with citalopram, scores suggested that efficacy of 10mg/day of EC and 20mg/day of EC were at least as effective as treatment with 40mg/day of citalopram in alleviating symptoms of depression. At the endpoint, all active treatment groups were significantly superior to placebo.

A meta-analysis of three U.S. randomized, multicenter, 8-week clinical trials conducted by Gorman et al. showed that a statistically significant difference in the mean change in the MADRS scores versus the placebo first appeared at week 1 for EC (10-20mg/day) and week 6 for citalopram (20-40mg/day). However, each individual trial did not compare EC to citalopram. Therefore, based on this data, no conclusion can be drawn regarding comparison of efficacy of these two antidepressants.

A multinational, randomized, double-blind, flexible-dose (10-20mg/day of EC), 8-week study by Lepola et al. (sponsored by Lundbeck) showed that statistically significant difference in mean change in total MADRS scores was observed between EC and placebo after just 1 week.

In another double-blind, randomized, placebo-controlled, 8-week study (Wade et al.) involving 40 primary care centers in five countries, a statistically significant difference in total MADRS score emerged at Week 2 for 10mg/day EC group compared to the placebo group. EC also was well tolerated by the EC group.

A prospective, multicentre, randomized, double-blind trial (Moore et al funded by Lundbeck) directly comparing EC (20mg/day) with citalopram (40mg/day) over 8 weeks in outpatients showed that

the MADRS score was decreased by -22.4 ± 12.9 for the EC group versus -20.3 ± 12.7 for citalopram at $p < 0.05$. Although there is statistical difference in MADRS scores, the difference of 1 to 2 point in the MADRS score is clinically insignificant.

Adolescent Major Depression

Schaller JL et al. reported five successful cases of four girls (ages 14, 15, 16, 17) and one boy (age 15) with wide daily dose range (5-25mg) and minimal adverse reaction.

Panic Disorder (PD)/Social Anxiety Disorder (SAD)/Generalized Anxiety Disorder (GAD)

A randomized, double-blind, placebo-controlled, 10-week PD trial conducted by Stahl et al. showed that the EC (10-20mg/day) group had statistically significant improvement compared to placebo group as assessed by the Modified Sheehan Panic and Anticipatory Anxiety Scale.

A multinational, double-blind, placebo-controlled, flexible dose (10-20mg/day), 12-week SAD trial (Kasper et al.) funded by Lundbeck showed encouraging results of EC compared with placebo.

A randomized, flexible dose (10-20 mg/day), placebo-controlled GAD trial (Davidson et al.) demonstrated significant improvement in HAM-Anxiety scores by EC group compared to the placebo group.

Transvestic Fetishism/Obsessive Compulsive Disorder(OCD)

Praharaj describes a case report of a 15 year old boy who had recurrent thoughts and urges to collect female undergarments, and who derived sexual pleasure from cross-dressing. He had shown significant improvement after 4 weeks of EC at 10mg/day, with a decrease in recurrent thoughts and urges to pick up clothes.

Dosing

The recommended starting and maintenance dose of EC in adults is 10mg/day usually taken in the morning,

with or without food. The dose may be increased to 20mg/day after at least one week. Higher doses have not been shown to be more effective. The daily dose in the elderly and patients under 18 years has not been clearly established.

The recommended daily dose in hepatic impairment is 10mg/day.

A dose adjustment is not necessary in renal impairment if creatinine clearance is greater than 20 mL/min. If creatinine clearance is less than 20 mL/min, close monitoring with dose adjustment is warranted.

Adverse Drug Reactions (not inclusive)

Most commonly, EC may be associated with dizziness, anxiety, blurred vision, nausea, dry mouth, reversible sexual dysfunction (ejaculation delay, decreased libido, anorgasmia), increased sweating and fatigue.

Emergence of tics during EC treatment has been reported in one Turkish female patient after 8 weeks of 10mg/day of EC use (Altindag et al.).

SSRIs may cause bleeding by blocking serotonin uptake into platelets. Platelets cannot themselves synthesize serotonin, which is released from platelets in response to vascular injury and results in vasoconstriction and platelet aggregation. By blocking serotonin uptake, platelets have less serotonin reserve, leading to decreased ability to form clots and subsequent increased risk for bleeding. A case report describes development of mild hemorrhages in a 60-year old depressed man from his nose and rectum after two-month treatment with EC 20mg/day.

Potential hyponatremia related to SSRIs may also be associated with EC and citalopram. None of the studies reviewed reported hyponatremia. Monitoring electrolytes especially in the elderly may be advisable.

Moore et al. (funded by Lundbeck) reported that adverse events occurring in EC (N=142) and citalopram (N=152) were similar in both groups. Some of the slight differences were noted. For example, anxiety was observed in 4 EC patients and 1 citalopram patient. Somnolence in 3 citalopram patients and 0 in EC patients.

A letter to the editor describes a dramatic increase in weight (8 kg in over 1 month) with the introduction of EC in a 16-year old girl who was receiving quetiapine for over 5 months. Discontinuation of EC followed by topiramate treatment resulted in weight stabilization.

Pharmacokinetics & Drug Interactions

EC is primarily metabolized hepatically via cytochrome (CYP) P450 enzymes 2C19 (major), 3A4 (major) & 2D6 (minor) to an active metabolite, S-desmethylcitalopram. S-desmethylcitalopram is further metabolized to an active S-didesmethylcitalopram via CYP 2D6. The half life of EC is about 30 hours (with time to peak about 5 hours) and of S-desmethylcitalopram is about 60 hours (with time to peak about 14 hours). It is only bound approximately 55% to plasma proteins, reducing its potential for drug-drug interaction.

EC is a major substrate for CYP 2C19 and 3A4 and is a minor inhibitor of CYP P450 enzyme 2D6. In comparison, citalopram has the same metabolic properties as EC. In addition, citalopram is a minor substrate for CYP P450 enzyme 2D6 and is a minor inhibitor of CYP P450 enzyme 1A2, 2B6 and 2C19.

CYP 2C19 and 3A4 inhibitors can potentially increase the level/effects of EC. Fluconazole, delavirdine, fluvoxamine, gemfibrozil, isoniazid, and omeprazole are a sample of CYP 2C19 inhibitors. Ritonavir, isoniazid, clarithromycin, doxycycline and indinavir are examples of CYP 3A4 inhibitors.

It is important to note that although theoretical interaction exist between EC and various drugs, clinical interaction may not be observed. Gutierrez et al. found that 20mg EC as a single dose coadministered with ritonavir (600mg single dose) to 18 normal subjects did not appear to affect serum concentration of EC. However, one criticism of this study may be the fact that enzymatic inhibition (by ritonavir) may take time for a change so that a single dose would not have resulted in an enzymatic change.

CYP 2C19 and 3A4 inducers can potentially decrease the level/effects of EC. Some of these inducers are carbamazepine, phenytoin and rifampin.

As with other SSRIs, potential for severe reaction exists when EC is used with nonselective monoamine oxidase inhibitors (MAOIs) such as tranylcypromine, phenelzine, isocarboxazid and selegiline. EC should not be used with citalopram concurrently. A 5-week EC washout period (due to active metabolites) is advised before a MAOI is initiated and a 2-week MAOI washout period before EC is initiated.

Lithium may augment effects of EC and therefore it should be used with caution.

Pregnancy & Lactation Considerations

EC is Pregnancy Risk Category C. Teratogenic effects have not been noted in rat studies although lower fetal weight and delayed ossifications were observed. In comparison, citalopram has been reported to be teratogenic in some animal studies. There are no adequate studies in pregnant women. Risk versus benefit should be considered in pregnancy.

EC is known to be excreted in breast milk. Therefore, it should be used with caution.

Cost & Availability

Ciprallex® is marketed by Lundbeck in Canada. At the time of publication, the prices of 10mg and 20mg are \$1.66 per tablet and \$1.77 per tablet respectively. In comparison, the generic citalopram marketed by Apotex, Genpharm and Novopharm costs \$0.34 per 20mg tablet and \$0.46 per 40mg tablet. Both strengths

(20mg and 40mg) of the Celexa® brand, also marketed by Lundbeck in Canada, cost \$1.34 per tablet.

Summary & Conclusion

EC, the S-enantiomer of citalopram, may have some clinical advantages over racemic citalopram in terms of faster onset, less drug interaction potential and better tolerability. Further direct comparisons between EC and citalopram are needed to confirm these advantages.

Based on subtle differences in drug interactions and adverse drug reaction profile, clinical difference between EC and citalopram may be insignificant or irrelevant, in most patients. If a patient responds to citalopram but experiences intolerable adverse reactions such as severe fatigue, a trial of EC may be warranted.

Considering the difference in cost between the two drug forms, the use of EC may not be justified before a trial of citalopram in most patients. As in most treatments, the choice between EC and citalopram should be individualized to suit patient's needs. Please email jkim@bcmhs.bc.ca for any comments, questions or concerns with the content of the newsletter.

“For Your Inpharmation” is published quarterly and it is available on the Riverview Hospital website at http://www.bcmhs.bc.ca/library/content_handler.asp?content_file=Inpharmation/Inpharmation.asp

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