Citalopram is metabolized by CYP 3A4 & 2C19; co-administration with a CYP2C19 inhibitor may increase the serum concentrations of citalopram and increase the risk of QT prolongation.

- The FDA recommends a maximum citalopram dose of 20 mg per day for patients taking concomitant CYP2C19 inhibitors.
- This interaction is largely theoretical based on the metabolic pathways of prescribed medications, and the clinical significance is unknown, especially with weak CYP2C19 inhibitors.

### Summary of Evidence on CYP2C19 Inhibitors that May Trigger a Drug Interaction Alert

<table>
<thead>
<tr>
<th>Name of Drug (2C19 Inhibitor)</th>
<th>Lexicomp Risk Rating</th>
<th>FDA</th>
<th>Comments on Interaction(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armodafinil</td>
<td>C: Monitor therapy</td>
<td>Weak</td>
<td>- No published reports of PK interaction with citalopram.</td>
<td>3</td>
</tr>
</tbody>
</table>
| Carbamazepine                 | D: Consider therapy modification | Weak | - Carbamazepine may decrease plasma concentrations of citalopram via CYP3A4 induction.  
- There is no evidence to support increased serum concentrations of citalopram due to 2C19 inhibition.  
- Lexicomp rating based on whether or not the SSRI is a strong CYP3A4 inhibitor or CYP1A2, 2C, or 3A4 substrate. | 3, 10, 11 |
| Chloramphenicol               | No interaction identified | Not listed | - Potent in vitro inhibition found. Possible cause of increase in phenytoin levels.  
- No published reports of PK interaction with citalopram.                                                                                                                                                 | 16        |
<p>| Cimetidine                    | C: Monitor therapy   | Weak      | - In vitro studies with escitalopram 20 mg and cimetidine led to 72% increase in escitalopram exposure. This increase is not clinically significant. The clinical significance of the DDI between citalopram and cimetidine is unknown. | 3, 8, 12  |
| Esomeprazole                  | C: Monitor therapy   | Moderate  | - In vitro comparison of CYP2C19 inhibition of S-mephenytoin metabolism: Lansoprazole&gt;rabeprazole thioether&gt;R-omeprazole&gt;esomeprazole&gt;rabeprazole&gt;pantoprazole.                                                                 | 3, 18, 5  |
| Ethinyl estradiol             | No interaction       | Weak      | - CYP2C19 inhibition is possible cause of potentiation of warfarin                                                                                                                                                       | 19        |</p>
<table>
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<tr>
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<tbody>
<tr>
<td>Etravirine</td>
<td>C: Monitor therapy</td>
<td>Weak</td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>C: Monitor therapy</td>
<td>Weak</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>D: Consider Therapy Modification</td>
<td>Strong</td>
<td>There are no case studies specific to the co-administration of fluconazole and citalopram. However, fluconazole alone has the potential to cause QT-prolongation in the high risk patient population.</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>D: Consider Therapy Modification</td>
<td>Moderate</td>
<td>Fluoxetine substantially inhibited the metabolism of CYP2C19 substrate, S-mephenytoin in vivo. QTc-prolonging agents may enhance the adverse/toxic effect of other QTc-prolonging agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. No published reports of PK interaction with citalopram.</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>D: Consider Therapy Modification</td>
<td>Strong</td>
<td>Likely cause of increased exposure of CYP2C19 substrate roflumilast N-oxide in vivo. Fluvoxamine increased levels of R- and S-citalopram, with some stereoselectivity of S-citalopram.</td>
</tr>
<tr>
<td>Garlic</td>
<td>D: Consider Therapy Modification</td>
<td>Weak</td>
<td>Allicin, a constituent of ground or crushed garlic, inhibited the metabolism of CYP2C19 substrate omeprazole in humans with certain CYP2C19 genotypes. No published reports of PK interaction with citalopram. Lexicomp rating based on antiplatelet properties of herbs.</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>D: Consider Therapy Modification</td>
<td>Not listed</td>
<td>No published reports of PK interaction with citalopram. Lexicomp rating based on enhanced antiplatelet activity of indomethacin.</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>C: Monitor therapy</td>
<td>Not listed</td>
<td>In vitro comparison of CYP2C19 inhibition of S-mephenytoin metabolism: Lansoprazole&gt;rabeprazole thioether&gt;R-omeprazole&gt;omeprazole&gt;esomeprazole&gt;rabeprazole&gt;pantoprazole.</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>X: Avoid combination</td>
<td>Moderate</td>
<td>Case reports of serotonin syndrome and death with concomitant use of moclobemide (MAOI) and citalopram.</td>
</tr>
<tr>
<td>Name of Drug (2C19 Inhibitor)</td>
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<td>FDA</td>
<td>Comments on Interaction(s)</td>
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<tr>
<td>------------------------------</td>
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</tr>
<tr>
<td>Modafinil</td>
<td>D: Consider Therapy Modification</td>
<td>See armodafinil</td>
<td>• No published reports of PK interaction with citalopram.</td>
</tr>
</tbody>
</table>
| Omeprazole                   | C: Monitor therapy | Moderate | • Omeprazole induces a loss of enantioselectivity in the citalopram pharmacokinetics because of the selective inhibition of (+)-(S)-citalopram metabolism.  
• In vitro comparison of CYP2C19 inhibition of S-mephenytoin metabolism: Lansoprazole>rabeprazole thioether>R-omeprazole>omeprazole>esomeprazole>rabeprazole>pantoprazole. | 3, 9, 17, 5 |
| Oxcarbazepine                | C: Monitor therapy | Not listed | • Carbamazepine and oxcarbazepine inhibited the CYP2C19 metabolism of phenytoin in vitro.  
• Case report of two patients with comorbid epilepsy, major depression, and panic disorder, whose serum citalopram levels increased and antidepressant response changed when concurrent carbamazepine treatment was substituted with oxcarbazepine.  
• Lexicomp rating based on CYP3A4 inhibition. | 3, 4, 25 |
| Pantoprazole                 | C: Monitor therapy | Not listed | • In vitro comparison of CYP2C19 inhibition of S-mephenytoin metabolism: Lansoprazole>rabeprazole thioether>R-omeprazole>omeprazole>esomeprazole>rabeprazole>pantoprazole.  
• PK studies show that pantoprazole is a weak CYP2C19 inhibitor, but there is no evidence to show how this might affect clinical outcomes. | 5 |
| Probenecid                   | No interaction identified | Not listed | • No published reports of PK interaction with citalopram. |     |
| Rabeprazole                  | C: Monitor therapy | Not listed | • One case report of a 60 y/o female with h/o gastritis on rabeprazole, untreated depression, cardiovascular risk factors (hyperlipidemia, cigarette smoking) who was admitted to the stroke unit due to sudden-onset weakness of her left arm. Patient had worsening depression s/p stroke and was started on escitalopram 5mg. Within 45 minutes of the first administration of escitalopram, patient had severe bradycardia, 20-30 bpm.  
** Concomitant therapy with rabeprazole and citalopram may increase cardiovascular risk in patients s/p a stroke event | 1, 3 |
<table>
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<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatropin</td>
<td>No interaction identified</td>
<td>Weak</td>
<td>• No published reports of PK interaction with citalopram.</td>
<td>3</td>
</tr>
</tbody>
</table>
| Ticlopidine                   | D: Consider Therapy Modification | Strong | • Ticlopidine inhibited the clearance of omeprazole in vivo, most likely due to inhibition of CYP2C19.  
• There was a case report of ticlopidine inhibition of phenytoin metabolism, likely due to inhibition of CYP2C19.  
• No published reports of PK interaction with citalopram. | 3, 7, 26, 27 |
| Topiramate                    | C: Monitor therapy | Not listed | • Nine of 12 patients experienced no clinically significant change in phenytoin levels with the addition of topiramate. Three patients experienced increases in phenytoin levels. An in vitro study found inhibition of metabolism of CYP2C19 substrate S-mephenytoin by topiramate at concentrations equivalent to five to 15 times higher plasma levels found with recommended dose range.  
• There was one case report of fatal intoxication with topiramate and citalopram, one case report of serotonin syndrome with topiramate and citalopram (suggested likely due to CYP2D6 inhibition by topiramate). | 28, 29, 30 |
| Voriconazole                  | D: Consider Therapy Modification | Moderate | • Lexicomp rating based on voriconazole QT prolongation.  
• No published reports of PK interaction with citalopram. | 3 |

Table compiled by Kaiser Drug Information Services

**Lexicomp Risk Rating**

**C**  
Monitor Therapy  
Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.

**D**  
Consider Therapy Modification  
Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes and choosing alternative agents.
**FDA Classification of In Vivo Inhibitors of CYP Enzymes.**

<table>
<thead>
<tr>
<th>Type</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak inhibitor</td>
<td>( \geq 1.25 ) but &lt; 2-fold increase in AUC or 20-50% decrease in clearance</td>
</tr>
<tr>
<td>Moderate inhibitor</td>
<td>( \geq 2 ) but &lt; 5-fold increase in AUC or 50-80% decrease in clearance</td>
</tr>
<tr>
<td>Strong inhibitor</td>
<td>( \geq 5 ) fold increase in AUC or &gt; 80% decrease in clearance</td>
</tr>
</tbody>
</table>

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**References**


