## THERAPEUTICS

**Brands**  • Celexa  
*see index for additional brand names*

**Generic?**  Yes

**Class**  
• Neuroscience-based Nomenclature: serotonin reuptake inhibitor (S-RI)  
• SSRI (selective serotonin reuptake inhibitor): often classified as an antidepressant, but it is not just an antidepressant

**Commonly Prescribed for**  
(bold for FDA approved)  
• Depression  
  - Premenstrual dysphoric disorder (PMDD)  
  - Obsessive-compulsive disorder (OCD)  
  - Panic disorder  
  - Generalized anxiety disorder (GAD)  
  - Posttraumatic stress disorder (PTSD)  
  - Social anxiety disorder (social phobia)

### How the Drug Works

- Boosts neurotransmitter serotonin  
- Blocks serotonin reuptake pump (serotonin transporter)  
- Desensitizes serotonin receptors, especially serotonin 1A autoreceptors  
- Presumably increases serotonergic neurotransmission  

\*Citalopram also has mild antagonist actions at H1 histamine receptors  
\*Citalopram’s inactive R enantiomer may interfere with the therapeutic actions of the active S enantiomer at serotonin reuptake pumps

### How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks  
- If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all  
- May continue to work for many years to prevent relapse of symptoms

### If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses  
- Treatment most often reduces or even eliminates symptoms, but not a cure

since symptoms can recur after medicine stopped  
• Continue treatment until all symptoms are gone (remission) or significantly reduced (e.g., OCD, PTSD)  
• Once symptoms are gone, continue treating for 1 year for the first episode of depression  
• For second and subsequent episodes of depression, treatment may need to be indefinite  
• Use in anxiety disorders may also need to be indefinite

### If It Doesn’t Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating in depression)  
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory  
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”  
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent  
- Consider psychotherapy  
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)  
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

### Best Augmenting Combos for Partial Response or Treatment Resistance

- Trazodone, especially for insomnia  
- Bupropion, mirtazapine, reboxetine, or atomoxetine (add with caution and at lower doses since citalopram could theoretically raise atomoxetine levels); use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation  
- Modafinil, especially for fatigue, sleepiness, and lack of concentration  
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, treatment-resistant depression, or treatment-resistant anxiety disorders
CITALOPRAM (continued)

- Benzodiazepines
- If all else fails for anxiety disorders, consider gabapentin or tiagabine
- Hypnotics for insomnia
- Classically, lithium, buspirone, or thyroid hormone

Tests
- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects
- Theoretically due to increases in serotonin concentrations at serotonin receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of serotonin in the gut causing diarrhea, etc.)
- Increasing serotonin can cause diminished dopamine release and might contribute to emotional flattening, cognitive slowing, and apathy in some patients
- Most side effects are immediate but often go away with time, in contrast to most therapeutic effects which are delayed and are enhanced over time

- Citalopram’s unique mild antihistamine properties may contribute to sedation and fatigue in some patients

Notable Side Effects
- Sexual dysfunction (dose-dependent; men: delayed ejaculation, erectile dysfunction; men and women: decreased sexual desire, anorgasmsia)
- Gastrointestinal (decreased appetite, nausea, diarrhea, constipation, dry mouth)
- Mostly CNS (dose-dependent insomnia but also sedation, agitation, tremors, headache, dizziness)
- Activation (short-term; patients with diagnosed or undiagnosed bipolar or psychotic disorders may be more vulnerable to CNS-activating actions of SSRIs)
- Sweating (dose-dependent)
- Bruising and rare bleeding
- Rare hyponatremia (mostly in elderly patients and generally reversible on discontinuation of citalopram)
- SIADH (syndrome of inappropriate antidiuretic hormone secretion)

Life-Threatening or Dangerous Side Effects
- Rare seizures
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain
- Reported but not expected
- Citalopram has been associated with both weight gain and weight loss in various studies, but is relatively weight neutral overall

Sedation
- Occurs in significant minority

What to Do About Side Effects
- Wait
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- Wait
- Take in the morning if nighttime insomnia
- Take at night if daytime sedation
- In a few weeks, switch to another agent or add other drugs

Best Augmenting Agents for Side Effects
- Often best to try another SSRI or another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia
- Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
- Bupropion for emotional flattening, cognitive slowing, or apathy
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Benzodiazepines for jitteriness and anxiety, especially at initiation of treatment and especially for anxious patients
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time).

Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of citalopram.

**Overdose**

Rare fatalities have been reported with citalopram overdose, both alone and in combination with other drugs.

- Vomiting, sedation, heart rhythm disturbances, dizziness, sweating, nausea, tremor
- Rarely amnesia, confusion, coma, convulsions

**Long-Term Use**

- Safe

**Habit Forming**

- No

**How to Stop**

- Taper not usually necessary
- However, tapering to avoid potential withdrawal reactions generally prudent
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

**Pharmacokinetics**

- Parent drug has 23–45 hour half-life
- Weak inhibitor of CYP450 2D6
- Metabolized by CYP450 3A4 and 2C19

**Drug Interactions**

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can increase TCA levels; use with caution with TCAs
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or at least for 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing citalopram
- May displace highly protein bound drugs (e.g., warfarin)
- Can rarely cause weakness, hyperreflexia, and incoordination when combined with

**DOSING AND USE**

**Usual Dosage Range**

- 20–40 mg/day

**Dosage Forms**

- Tablets 10 mg, 20 mg scored, 40 mg scored
- Orally disintegrating tablet 10 mg, 20 mg, 40 mg
- Capsule 10 mg, 20 mg, 40 mg

**How to Dose**

- Initial 20 mg/day; increase by 20 mg/day after 1 or more weeks; maximum 40 mg/day; single dose administration, morning or evening

**Dosing Tips**

- Citalopram should no longer be prescribed at doses greater than 40 mg/day because if can cause abnormal changes in the electrical activity of the heart
- Some controversy with FDA dosage limit of 40 mg/day, and higher doses may be prescribed by experts
- Tablets are scored, so to save costs, give 10 mg as half of 20-mg tablet or 20 mg as half of 40-mg tablet, since the tablets cost about the same in many markets
- Many patients respond better to 40 mg than to 20 mg
- Given once daily, any time of day when best tolerated by the individual
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

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- Can rarely cause weakness, hyperreflexia, and incoordination when combined with
sumatriptan or possibly other triptans, requiring careful monitoring of patient
• Possible increased risk of bleeding especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
• NSAIDs may impair effectiveness of SSRIs
• Should not be dosed above 20 mg/day in patients taking a CYP450 2C19 inhibitor (e.g., cimetidine) due to risk of QT prolongation
• Via CYP450 2D6 inhibition, citalopram could theoretically interfere with the analgesic actions of codeine, and increase the plasma levels of some beta blockers and of atomoxetine
• Via CYP450 2D6 inhibition, citalopram could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias

Other Warnings/Precautions
• Use with caution in patients with history of seizures
• Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
• When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart
• Distribute the brochures provided by the FDA and the drug companies
• Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
• Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use
• If patient is taking an MAOI
• If patient is taking thioridazine or pimozide
• If there is a proven allergy to citalopram or escitalopram

SPECIAL POPULATIONS

Renal Impairment
• No dose adjustment for mild to moderate impairment
• Use cautiously in patients with severe impairment

Hepatic Impairment
• Should not be used at doses greater than 20 mg/day
• May need to dose cautiously at the lower end of the dose range in some patients for maximal tolerability

Cardiac Impairment
• May cause abnormal changes in the electrical activity of the heart at doses greater than 40 mg/day
• Treating depression with SSRIs in patients with acute angina or following myocardial infarction may reduce cardiac events and improve survival as well as mood

Elderly
• Doses greater than 20 mg/day should not be used in patients over age 60 years
• May need to dose at the lower end of the dose range in some patients for maximal tolerability
• Risk of SIADH with SSRIs is higher in the elderly
• Citalopram may be an especially well-tolerated SSRI in the elderly
• Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older

Children and Adolescents
• Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart
• Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
• Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
• Not specifically approved, but preliminary data suggest citalopram is safe and effective in children and adolescents with OCD and with depression

**Pregnancy**

• Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLRL or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
• Controlled studies have not been conducted in pregnant women
• Not generally recommended for use during pregnancy, especially during first trimester
• Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
• At delivery there may be more bleeding in the mother and transient irritability or sedation in the newborn
• Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
• For many patients, this may mean continuing treatment during pregnancy
• Exposure to SSRIs early in pregnancy may be associated with increased risk of septal heart defects (absolute risk is small)
• SSRI use beyond the 20th week of pregnancy may be associated with increased risk of pulmonary hypertension in newborns, although this is not proven
• Exposure to SSRIs late in pregnancy may be associated with increased risk of gestational hypertension and preeclampsia
• Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertension, hyperreflexia, tremor, jitteriness, irritability, and constant crying

**Breast Feeding**

• Some drug is found in mother’s breast milk
• Trace amounts may be present in nursing children whose mothers are on citalopram
• If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
• Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstituted late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
• Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
• For many patients, this may mean continuing treatment during breast feeding

**THE ART OF PSYCHOPHARMACOLOGY**

**Potential Advantages**

• Elderly patients
• Patients excessively activated or sedated by other SSRIs

**Potential Disadvantages**

• May require dosage titration to attain optimal efficacy
• Can be sedating in some patients

**Primary Target Symptoms**

• Depressed mood
• Anxiety
• Panic attacks, avoidant behavior, reexperiencing, hyperarousal
• Sleep disturbance, both insomnia and hypersomnia

**Pearls**

• May be more tolerable than some other antidepressants
• May have less sexual dysfunction than some other SSRIs
CITALOPRAM (continued)

- May be especially well tolerated in the elderly
- May be less well tolerated than escitalopram
- Documentation of efficacy in anxiety disorders is less comprehensive than for escitalopram and other SSRIs
- Can cause cognitive and affective “flattening”
- Some evidence suggests that citalopram treatment during only the luteal phase may be more effective than continuous treatment for patients with PMDD
- SSRIs may be less effective in women over 50, especially if they are not taking estrogen
- SSRIs may be useful for hot flushes in perimenopausal women
- Nonresponse to citalopram in elderly may require consideration of mild cognitive impairment or Alzheimer disease

Suggested Reading

