Sertraline

**Brands**  • Zoloft  
*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)  
• Major depressive disorder  
• Premenstrual dysphoric disorder (PMDD)  
• Panic disorder  
• Posttraumatic stress disorder (PTSD)  
• Social anxiety disorder (social phobia)  
• Obsessive-compulsive disorder (OCD)  
• Generalized anxiety disorder (GAD)

**How the Drug Works**  
• Boosts neurotransmitter serotonin  
• Blocks serotonin reuptake pump (serotonin transporter)  
• Desensitizes serotonin receptors, especially serotonin 1A receptors  
• Presumably increases serotonergic neurotransmission  

❄ Sertraline also has some ability to block dopamine reuptake pump (dopamine transporter), which could increase dopamine neurotransmission and contribute to its therapeutic actions  
• Sertraline also binds at sigma 1 receptors

**How Long Until It Works**  
❄ Some patients may experience increased energy or activation early after initiation of treatment  
• 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  
• In the USA, sertraline (Zoloft) is commonly augmented with bupropion (Wellbutrin) with good results in a combination anecdotally called “Well-loft” (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)
• Mirtazapine, reboxetine, or atomoxetine (add with caution and at lower doses since sertraline 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
• 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

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### 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, although this could theoretically be diminished in some patients by sertraline’s dopamine reuptake blocking properties
- 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
- Sertraline’s possible dopamine reuptake blocking properties could contribute to agitation, anxiety, and undesirable activation, especially early in dosing

#### Notable Side Effects

- Sexual dysfunction (dose-dependent; men: delayed ejaculation, erectile dysfunction; men and women: decreased sexual desire, anorgasmia)
- Gastrointestinal (decreased appetite, nausea, diarrhea, constipation, dry mouth)
- Mostly CNS (insomnia but also sedation, agitation, tremors, headache, dizziness)
- Note: patients with diagnosed or undiagnosed bipolar or psychotic disorders may be more vulnerable to CNS-activating actions of SSRIs
- Autonomic (sweating)
- Bruising and rare bleeding
- Rare hyponatremia (mostly in elderly patients and generally reversible on discontinuation of sertraline)
- Rare hypotension
- 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
- Some patients may actually experience weight loss

#### Sedation

- Reported but not expected
- Possibly activating in some patients

#### What to Do About Side Effects

- Wait
- Wait
- Wait
- If sertraline is activating, take in the morning to help reduce insomnia
- Reduce dose to 25 mg or even 12.5 mg until side effects abate, then increase dose as tolerated, usually to at least 50 mg/day
- In a few weeks, switch or add other drugs
**DOSING AND USE**

### Usual Dosage Range
- 50–200 mg/day

### Dosage Forms
- Tablets 25 mg scored, 50 mg scored, 100 mg
- Oral solution 20 mg/mL

### How to Dose
- Depression and OCD: initial 50 mg/day; usually wait a few weeks to assess drug effects before increasing dose, but can increase once a week; maximum generally 200 mg/day; single dose
- Panic, PTSD, and social anxiety: initial 25 mg/day; increase to 50 mg/day after 1 week thereafter, usually wait a few weeks to assess drug effects before increasing dose; maximum generally 200 mg/day; single dose
- PMDD: initial 50 mg/day; can dose daily through the menstrual cycle or limit to the luteal phase
- Oral solution: mix with 4 oz of water, ginger ale, lemon/lime soda, lemonade, or orange juice only; drink immediately after mixing

### 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 sertraline

### Dosing Tips
- All tablets are scored, so to save costs, give 50 mg as half of 100-mg tablet, since 100-mg and 50-mg tablets cost about the same in many markets
- Give once daily, often in the mornings to reduce chances of insomnia
- Many patients ultimately require more than 50 mg dose per day
- Some patients are dosed above 200 mg
- Evidence that some treatment-resistant OCD patients may respond safely to doses up to 400 mg/day, but this is for experts and use with caution
- The more anxious and agitated the patient, the lower the starting dose, the slower the titration, and the more likely the need for a concomitant agent such as trazodone or a benzodiazepine
- 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 atypical antipsychotic
- Utilize half a 25-mg tablet (12.5 mg) when initiating treatment in patients with a history of intolerance to previous antidepressants

### Overdose
- Rarely lethal in monotherapy overdose; vomiting, sedation, heart rhythm disturbances, dilated pupils, agitation; fatalities have been reported in sertraline overdose combined with other drugs or alcohol

### Long-Term Use
- Safe

### Habit Forming
- No
How to Stop
• Taper to avoid withdrawal effects (dizziness, nausea, stomach cramps, sweating, tingling, dysesthesias)
• 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 22–36 hour half-life
• Metabolite half-life 62–104 hours
• Inhibits CYP450 2D6 (weakly at low doses)
• Inhibits CYP450 3A4 (weakly at low doses)

Drug Interactions
• Tramadol increases the risk of seizures in patients taking an antidepressant
• Can increase TCA levels; use with caution with TCAs or when switching from a TCA to sertraline
• Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 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 sertraline
• May displace highly protein bound drugs (e.g., warfarin)
• Can rarely cause weakness, hyperreflexia, and incoordination when combined with sumatriptan or possibly with 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
• Via CYP450 2D6 inhibition, sertraline 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 sertraline could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias

Other Warnings/Precautions
• Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing sertraline
• 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 pimozide
- If patient is taking thioridazine
- Use of sertraline oral concentrate is contraindicated with disulfiram due to the alcohol content of the concentrate
- If there is a proven allergy to sertraline

Approved for use in OCD
- Ages 6–12: initial dose 25 mg/day
- Ages 13 and up: adult dosing
- Long-term effects, particularly on growth, have not been studied

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 (PLLR 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

Renal Impairment
- No dose adjustment
- Not removed by hemodialysis

Hepatic Impairment
- Lower dose or give less frequently, perhaps by half

Cardiac Impairment
- Proven cardiovascular safety in depressed patients with recent myocardial infarction or angina
- 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
- Some patients may tolerate lower doses and/or slower titration better
- Risk of SIADH with SSRIs is higher 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

SPECIAL POPULATIONS

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
include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, 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 sertraline
• Sertraline has shown efficacy in treating postpartum depression
• 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
• Patients with atypical depression (hypersomnia, increased appetite)
• Patients with fatigue and low energy
• Patients who wish to avoid hyperprolactinemia (e.g., pubescent children, girls and women with galactorrhea, girls and women with unexplained amenorrhea, postmenopausal women who are not taking estrogen replacement therapy)
• Patients who are sensitive to the prolactin-elevating properties of other SSRIs (sertraline is the one SSRI that generally does not elevate prolactin)

Potential Disadvantages
• Initiating treatment in anxious patients with some insomnia
• Patients with comorbid irritable bowel syndrome
• Can require dosage titration

Primary Target Symptoms
• Depressed mood
• Anxiety
• Sleep disturbance, both insomnia and hypersomnia (eventually, but may actually cause insomnia, especially short-term)
• Panic attacks, avoidant behavior, re-experiencing, hyperarousal

Pearls
★ May be a type of “dual action” agent with both potent serotonin reuptake inhibition and less potent dopamine reuptake inhibition, but the clinical significance of this is unknown
• Cognitive and affective “flattening” may theoretically be diminished in some patients by sertraline’s dopamine reuptake blocking properties
★ May be a first-line choice for atypical depression (e.g., hypersomnia, hyperphagia, low energy, mood reactivity)
• Best documented cardiovascular safety of any antidepressant, proven safe for depressed patients with recent myocardial infarction or angina
• May bind to sigma 1 receptors, enhancing sertraline’s anxiolytic actions
• Can have more gastrointestinal effects, particularly diarrhea, than some other antidepressants
• May be more effective treatment for women with PTSD or depression than for men with PTSD or depression, but the clinical significance of this is unknown
• 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
• For sexual dysfunction, can augment with bupropion, sildenafil, vardenafil, tadalafil, or switch to a non-SSRI such as bupropion or mirtazapine
• Some postmenopausal women’s depression will respond better to sertraline plus estrogen augmentation than to sertraline alone
• Nonresponse to sertraline in elderly may require consideration of mild cognitive impairment or Alzheimer disease
• Not as well tolerated as some SSRIs for panic, especially when dosing is initiated,
unless given with co-therapies such as benzodiazepines or trazodone
• Relative lack of effect on prolactin may make it a preferred agent for some children, adolescents, and women

• Some evidence suggests that sertraline treatment during only the luteal phase may be more effective than continuous treatment for patients with PMDD

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**Suggested Reading**


