**FLUVOXAMINE**

**Therapeutics**

**Brands**
- Luvox
- Luvox CR

*see index for additional brand names*

**Generic?** Yes (not for fluvoxamine CR)

**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**
- Obsessive-compulsive disorder (OCD)
- Social anxiety disorder (fluvoxamine CR)
- Depression
- Panic disorder
- Generalized anxiety disorder (GAD)
- Posttraumatic stress disorder (PTSD)

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

*Fluvoxamine also binds at sigma 1 receptors*

**How Long Until It Works**
- Some patients may experience relief of insomnia or anxiety 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)
- Once symptoms 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**
- For the expert, consider cautious addition of clomipramine for treatment-resistant OCD
- Trazodone, especially for insomnia
- Bupropion, mirtazapine, reboxetine, or atomoxetine (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
FLUVOXAMINE (continued)

- Benzodiazepines
- If all else fails for anxiety disorders, consider gabapentin or tiagabine
- Hypnotics for insomnia
- Classically, lithium, buspirone, or thyroid hormone
- In Europe and Japan, augmentation is more commonly administered for the treatment of depression and anxiety disorders, especially with benzodiazepines and lithium
- In the USA, augmentation is more commonly administered for the treatment of OCD, especially with atypical antipsychotics, buspirone, or even clomipramine; clomipramine should be added with caution and at low doses as fluvoxamine can alter clomipramine metabolism and raise its levels

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
- Fluvoxamine’s sigma 1 antagonist properties may contribute to sedation and fatigue in some patients

Notable Side Effects
- Sexual dysfunction (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

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
- Patients may actually experience weight loss

Sedation
- Many experience and/or can be significant in amount

What to Do About Side Effects
- Wait
- Wait
- Wait
- If fluvoxamine is sedating, take at night to reduce drowsiness
- Reduce dose
- In a few weeks, switch 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
- Trazadone or a hypnotic for insomnia
- Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
- Bupropion for emotional flattening, cognitive slowing, or apathy
FLUVOXAMINE

**Dosing Tips**
- 50-mg and 100-mg tablets are scored, so to save costs, give 25 mg as half of 50 mg tablet, and give 50 mg as half of 100 mg tablet
- To improve tolerability of immediate-release formulation, dosing can either be given once a day, usually all at night, or split either symmetrically or asymmetrically, usually with more of the dose given at night
- Some patients take more than 300 mg/day
- Controlled-release capsules should not be chewed or crushed
- 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

**Overdose**
- Rare fatalities have been reported, both in combination with other drugs and alone; sedation, dizziness, vomiting, diarrhea, irregular heartbeat, seizures, coma, breathing difficulty

**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 9–28 hour half-life
- Inhibits CYP450 3A4
- Inhibits CYP450 1A2
- Inhibits CYP450 2C9/2C19

---

**Dosage Forms**
- Tablets 25 mg, 50 mg scored, 100 mg scored
- Controlled-release capsules 100 mg, 150 mg

**How to Dose**
- For immediate-release, initial 50 mg/day; increase by 50 mg/day in 4–7 days; usually wait a few weeks to assess drug effects before increasing dose further, but can increase by 50 mg/day every 4–7 days until desired efficacy is reached; maximum 300 mg/day
- For immediate-release, doses below 100 mg/day usually given as a single dose at bedtime; doses above 100 mg/day can be divided into two doses to enhance tolerability, with the larger dose administered at night, but can also be given as a single dose at bedtime
- For controlled-release, initial 100 mg/day; increase by 50 mg/day each week until desired efficacy is reached; maximum generally 300 mg/day

---

**Usual Dosage Range**
- 100–300 mg/day for OCD
- 100–200 mg/day for depression
- 100–300 mg/day for social anxiety disorder

---

- 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 fluvoxamine

---

**DOSING AND USE**

---

**Overdose**
- Rare fatalities have been reported, both in combination with other drugs and alone; sedation, dizziness, vomiting, diarrhea, irregular heartbeat, seizures, coma, breathing difficulty

**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 9–28 hour half-life
- Inhibits CYP450 3A4
- Inhibits CYP450 1A2
- Inhibits CYP450 2C9/2C19
Via CYP450 3A4 inhibition, fluvoxamine could theoretically increase the concentrations of pimozide, and cause QTc prolongation and dangerous cardiac arrhythmias.

Other Warnings/Precautions

Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing fluvoxamine.

Use with caution in patients with history of seizure.

Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent.

May cause photosensitivity.

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, pimozide, tizanidine, alosetron, or ramelteon.

If there is a proven allergy to fluvoxamine.

Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant.
- Can increase tricyclic antidepressant levels; use with caution with TCAs.
- 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 fluvoxamine.
- 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 1A2 inhibition, fluvoxamine may reduce clearance of theophylline and clozapine, thus raising their levels and requiring their dosing to be lowered.
- Fluvoxamine administered with either caffeine or theophylline can thus cause jitteriness, excessive stimulation, or rarely seizures, so concomitant use should proceed cautiously.
- Metabolism of fluvoxamine may be enhanced in smokers and thus its levels lowered, requiring higher dosing.
- Via CYP450 3A4 inhibition, fluvoxamine may reduce clearance of carbamazepine and benzodiazepines such as alprazolam and triazolam, and thus require dosage reduction.
- Via CYP450 3A4 inhibition, fluvoxamine could theoretically increase concentrations of certain cholesterol lowering HMG CoA reductase inhibitors, especially simvastatin, atorvastatin, and lovastatin, but not pravastatin or fluvastatin, which would increase the risk of rhabdomyolysis; thus, coadministration of fluvoxamine with certain HMG CoA reductase inhibitors should proceed with caution.

SPECIAL POPULATIONS

Renal Impairment

- Consider lower initial dose.

Hepatic Impairment

- Lower dose or give less frequently, perhaps by half; use slower titration.

Cardiac Impairment

- Preliminary research suggests that fluvoxamine is safe in these patients.
- 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**
- May require lower initial dose and slower titration
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older

**Children and Adolescents**
- Immediate-release approved for ages 8–17 for OCD
- 8–17: initial 25 mg/day at bedtime; increase by 25 mg/day every 4–7 days; maximum 200 mg/day; doses above 50 mg/day should be divided into 2 doses with the larger dose administered at bedtime
- Preliminary evidence suggests efficacy for other anxiety disorders and depression in 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

**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 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 fluvoxamine
- If child becomes irritable or sedated, breastfeeding 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 mixed anxiety/depression
- Generic is less expensive than brand name where available

Potential Disadvantages
- Patients with irritable bowel or multiple gastrointestinal complaints
- Can require dose titration and twice daily dosing

Primary Target Symptoms
- Depressed mood
- Anxiety

Pearls
- Often a preferred treatment of anxious depression as well as major depressive disorder comorbid with anxiety disorders
- Some withdrawal effects, especially gastrointestinal effects
- May have lower incidence of sexual dysfunction than other SSRIs
- Preliminary research suggests that fluvoxamine is efficacious in obsessive-compulsive symptoms in schizophrenia when combined with antipsychotics
- Not FDA approved for depression, but used widely for depression in many countries
- CR formulation may be better tolerated than immediate-release formulation, particularly with less sedation
- 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
- Actions at sigma 1 receptors may explain in part fluvoxamine’s sometimes rapid onset effects in anxiety disorders and insomnia
- Actions at sigma 1 receptors may explain potential advantages of fluvoxamine for psychotic depression and delusional depression
- For treatment-resistant OCD, consider cautious combination of fluvoxamine and clomipramine by an expert
- Normally, clomipramine (CMI), a potent serotonin reuptake blocker, at steady state is metabolized extensively to its active metabolite desmethyl-clomipramine (de-CMI), a potent noradrenergic reuptake blocker
- Thus, at steady state, plasma drug activity is generally more noradrenergic (with higher de-CMI levels) than serotonergic (with lower parent CMI levels)
- Addition of a CYP450 1A2 inhibitor, fluvoxamine, blocks this conversion and results in higher CMI levels than de-CMI levels
- Thus, addition of the SSRI fluvoxamine to CMI in treatment-resistant OCD can powerfully enhance serotonergic activity, not only due to the inherent serotonergic activity of fluvoxamine, but also due to a favorable pharmacokinetic interaction inhibiting CYP450 1A2 and thus converting CMI’s metabolism to a more powerful serotonergic portfolio of parent drug

Suggested Reading


