**FLUOXETINE**

**THERAPEUTICS**

**Brands**
- Prozac
- Prozac weekly
- Sarafem

*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 (ages 8 and older)
- Obsessive-compulsive disorder (OCD) (ages 7 and older)
- Premenstrual dysphoric disorder (PMDD)
- Bulimia nervosa
- Panic disorder
- Bipolar depression [in combination with olanzapine (Symbyax)]
- Treatment-resistant depression [in combination with olanzapine (Symbyax)]
- Social anxiety disorder (social phobia)
- 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
- Fluoxetine also has antagonist properties at 5HT2C receptors, which could increase norepinephrine and dopamine neurotransmission

**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
- For anxiety disorders and bulimia, treatment 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
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
- 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
- Possible weight loss, especially short-term

Sedation

- Reported but not expected

What to Do About Side Effects

- Wait
- Wait
- Wait
- If fluoxetine is activating, take in the morning to help reduce insomnia
- Reduce dose to 10 mg, and either stay at this dose if tolerated and effective, or consider increasing again to 20 mg or more if tolerated but not effective at 10 mg
- 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

Fluoxetine has been specifically studied in combination with olanzapine (olanzapine-fluoxetine combination) with excellent results for bipolar depression, treatment-resistant unipolar depression, and psychotic depression.

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
- Fluoxetine’s unique 5HT2C antagonist properties could contribute to agitation, anxiety, and undesirable activation, especially early in dosing

Bupropion, mirtazapine, reboxetine, or atomoxetine (add with caution and at lower doses since fluoxetine 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 unipolar depression, and psychotic depression
- 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

Fluoxetine’s unique 5HT2C antagonist properties could contribute to agitation, anxiety, and undesirable activation, especially early in dosing.
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 fluoxetine

Overdose
• Rarely lethal in monotherapy overdose; respiratory depression especially with alcohol, ataxia, sedation, possible seizures

Long-Term Use
• Safe

Habit Forming
• No

How to Stop
• Taper rarely necessary since fluoxetine tapers itself after immediate discontinuation, due to the long half-life of fluoxetine and its active metabolites

Pharmacokinetics
• Active metabolite (norfluoxetine) has 2 week half-life
• Parent drug has 2–3 day half-life
• Inhibits CYP450 2D6
• Inhibits CYP450 3A4

Drug Interactions
• Tramadol increases the risk of seizures in patients taking an antidepressant

DOSING AND USE

Usual Dosage Range
• 20–80 mg for depression and anxiety disorders
• 60–80 mg for bulimia

Dosage Forms
• Capsules 10 mg, 20 mg, 40 mg, 60 mg
• Tablet 10 mg
• Liquid 20 mg/5 mL–120 mL bottles
• Weekly capsule 90 mg

How to Dose
• Depression and OCD: initial dose 20 mg/day in morning, usually wait a few weeks to assess drug effects before increasing dose; maximum dose generally 80 mg/day
• Bulimia: initial dose 60 mg/day in morning; some patients may need to begin at lower dose and titrate over several days

Dosing Tips
• The long half-lives of fluoxetine and its active metabolites mean that dose changes will not be fully reflected in plasma for several weeks, lengthening titration to final dose and extending withdrawal from treatment
• Give once daily, often in the mornings, but at any time of day tolerated
• Often available in capsules, not tablets, so unable to break capsules in half
• Occasional patients are dosed above 80 mg
• Liquid formulation easiest for doses below 10 mg when used for cases that are very intolerant to fluoxetine or for very slow up and down titration needs

For some patients, weekly dosing with the weekly formulation may enhance compliance
• 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 an atypical antipsychotic
• Can increase TCA levels; use with caution with TCAs or when switching from a TCA to fluoxetine
• 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 weeks after discontinuing fluoxetine
• 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, 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, fluoxetine could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias
• May reduce the clearance of diazepam or trazodone, thus increasing their levels
• Via CYP450 3A4 inhibition, may increase the levels of alprazolam, buspirone, and triazolam
• Via CYP450 3A4 inhibition, fluoxetine 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 fluoxetine with certain HMG CoA reductase inhibitors should proceed with caution
• Via CYP450 3A4 inhibition, fluoxetine 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 5 weeks after discontinuing fluoxetine
• Use with caution in patients with history of seizure
• 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
• If patient is taking pimozide
• If patient is taking tamoxifen
• If there is a proven allergy to fluoxetine

SPECIAL POPULATIONS

Renal Impairment
• No dose adjustment
• Not removed by hemodialysis

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

Cardiac Impairment
• Preliminary research suggests that fluoxetine 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
**FLUOXETINE**

**Elderly**
- Some patients may tolerate lower doses 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
- Approved for OCD and depression
- Adolescents often receive adult dose, but doses slightly lower for children
- Children taking fluoxetine may have slower growth; long-term effects are unknown

**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
- Current patient registries of children whose mothers took fluoxetine during pregnancy do not show adverse consequences

**Breast Feeding**
- Some drug is found in mother’s breast milk
- Trace amounts may be present in nursing children whose mothers are on fluoxetine
- 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

**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
THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- Patients with atypical depression (hypersomnia, increased appetite)
- Patients with fatigue and low energy
- Patients with comorbid eating and affective disorders
- Generic is less expensive than brand name where available
- Patients for whom weekly administration is desired
- Children with OCD or depression

Potential Disadvantages
- Patients with anorexia
- Initiating treatment in anxious, agitated patients
- Initiating treatment in severe insomnia

Primary Target Symptoms
- Depressed mood
- Energy, motivation, and interest
- Anxiety (eventually, but can actually increase anxiety, especially short-term)
- Sleep disturbance, both insomnia and hypersomnia (eventually, but may actually cause insomnia, especially short-term)

Pearls
- May be a first-line choice for atypical depression (e.g., hypersomnia, hyperphagia, low energy, mood reactivity)
- Consider avoiding in agitated insomniacs
- Can cause cognitive and affective “flattening”
- Not as well tolerated as some other SSRIs for panic disorder and other anxiety disorders, especially when dosing is initiated, unless given with co-therapies such as benzodiazepines or trazodone
- Long half-life; even longer lasting active metabolite
- Actions at 5HT2C receptors may explain its activating properties
- Actions at 5HT2C receptors may explain in part fluoxetine’s efficacy in combination with olanzapine for bipolar depression and treatment-resistant depression, since both agents have this property
- For sexual dysfunction, can augment with bupropion, sildenafil, vardenafil, or tadalafil, or switch to a non-SSRI such as bupropion or mirtazapine
- Mood disorders can be associated with eating disorders (especially in adolescent females) and be treated successfully with fluoxetine
- 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
- Some postmenopausal women’s depression will respond better to fluoxetine plus estrogen augmentation than to fluoxetine alone
- Nonresponse to fluoxetine in elderly may require consideration of mild cognitive impairment or Alzheimer disease
- SSRIs may not cause as many patients to attain remission of depression as some other classes of antidepressants (e.g., SNRIs)
- A single pill containing both fluoxetine and olanzapine is available for combination treatment of bipolar depression, psychotic depression, and treatment-resistant unipolar depression

Suggested Reading


