PAROXETINE

Therapeutics

Brands: • Paxil
• Paxil CR
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 (paroxetine and paroxetine CR)
• Obsessive-compulsive disorder (OCD)
• Panic disorder (paroxetine and paroxetine CR)
• Social anxiety disorder (social phobia) (paroxetine and paroxetine CR)
• Posttraumatic stress disorder (PTSD)
• Generalized anxiety disorder (GAD)
• Premenstrual dysphoric disorder (PMDD) (paroxetine CR)
• Vasomotor symptoms (Brisdelle)

How the Drug Works
• Boosts neurotransmitter serotonin
• Blocks serotonin reuptake pump (serotonin transporter)
• Desensitizes serotonin receptors, especially serotonin 1A autoreceptors
• Presumably increases serotonergic neurotransmission
• Paroxetine also has mild anticholinergic actions
• Paroxetine may have mild norepinephrine reuptake blocking actions

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 for depression, it may require a dosage increase or it may not work at all

• By contrast, for generalized anxiety, onset of response and increases in remission rates may still occur after 8 weeks of treatment and for up to 6 months after initiating dosing
• 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

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doses since paroxetine 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

### 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

- Paroxetine’s weak antimuscarinic properties can cause constipation, dry mouth, sedation

**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, dose-dependent tremors, headache, dizziness)

**Weight Gain**

- Activation (short-term; patients with diagnosed or undiagnosed bipolar or psychotic disorders may be more vulnerable to CNS-activating actions of SSRIs)
- Autonomic (dose-dependent 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**

- Occurs in significant minority

**Sedation**

- Many experience and/or can be significant in amount
- Generally transient

**What to Do About Side Effects**

- Wait
- Wait
- Wait
- If paroxetine is sedating, take at night to reduce daytime drowsiness
- Reduce dose to 5–10 mg (12.5 mg for CR) until side effects abate, then increase as tolerated, usually to at least 20 mg (25 mg CR)
- 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
- Trazodone or a hypnotic for insomnia
- Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
**Usual Dosage Range**
- Depression: 20–50 mg (25–62.5 mg CR)
- Vasomotor symptoms: 7.5 mg at bedtime

**Dosage Forms**
- Tablets 10 mg scored, 20 mg scored, 30 mg, 40 mg
- Controlled-release tablets 12.5 mg, 25 mg
- Liquid 10 mg/5mL – 250 mL bottle

**How to Dose**
- Depression: initial 20 mg (25 mg CR); usually wait a few weeks to assess drug effects before increasing dose, but can increase by 10 mg/day (12.5 mg/day CR) once a week; maximum generally 50 mg/day (62.5 mg/day CR); single dose
- Panic disorder: initial 10 mg/day (12.5 mg/day CR); usually wait a few weeks to assess drug effects before increasing dose, but can increase by 10 mg/day (12.5 mg/day CR) once a week; maximum generally 60 mg/day (75 mg/day CR); single dose
- Social anxiety disorder: initial 20 mg/day (25 mg/day CR); usually wait a few weeks to assess drug effects before increasing dose, but can increase by 10 mg/day (12.5 mg/day CR) once a week; maximum 60 mg/day (75 mg/day CR); single dose

**Dosing Tips**
- 20-mg tablet is scored, so to save costs, give 10 mg as half of 20-mg tablet, since 10-mg and 20-mg tablets cost about the same in many markets
- Given once daily, often at bedtime, but any time of day tolerated
- 20 mg/day (25 mg/day CR) is often sufficient for patients with social anxiety disorder and depression
- Other anxiety disorders, as well as difficult cases in general, may require higher dosing
- Occasional patients are dosed above 60 mg/day (75 mg/day CR), but this is for experts and requires caution
- 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

**Paroxetine CR tablets not scored, so chewing or cutting in half can destroy controlled-release properties**
- Unlike other SSRIs and antidepressants where dosage increments can be double and triple the starting dose, paroxetine's dosing increments are in 50% increments (i.e., 20, 30, 40; or 25, 37.5, 50 CR)
- Paroxetine inhibits its own metabolism and thus plasma concentrations can double when oral doses increase by 50%; plasma concentrations can increase 2–7-fold when oral doses are doubled

**Main advantage of CR is reduced side effects, especially nausea and perhaps sedation, sexual dysfunction, and withdrawal**
For patients with severe problems discontinuing paroxetine, dosing may need to be tapered over many months (i.e., reduce dose by 1% every 3 days by crushing tablet and suspending or dissolving in 100 mL of fruit juice and then disposing of 1 mL while drinking the rest; 3–7 days later, dispose of 2 mL, and so on). This is both a form of very slow biological tapering and a form of behavioral desensitization (not for CR).

For some patients with severe problems discontinuing paroxetine, it may be useful to add an SSRI with a long half-life, especially fluoxetine, prior to taper of paroxetine; while maintaining fluoxetine dosing, first slowly taper paroxetine and then taper fluoxetine.

Be sure to differentiate between reemergence of symptoms requiring reinstition of treatment and withdrawal symptoms.

**Overdose**
- Rarely lethal in monotherapy overdose; vomiting, sedation, heart rhythm disturbances, dilated pupils, dry mouth

**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

- Withdrawal effects can be more common or more severe with paroxetine than with some other SSRIs
- Paroxetine’s withdrawal effects may be related in part to the fact that it inhibits its own metabolism
- Thus, when paroxetine is withdrawn, the rate of its decline can be faster as it stops inhibiting its metabolism

- Controlled-release paroxetine may slow the rate of decline and thus reduce withdrawal reactions in some patients
- Readaptation of cholinergic receptors after prolonged blockade may contribute to withdrawal effects of paroxetine

**Pharmacokinetics**
- Inactive metabolites
- Half-life approximately 24 hours
- Inhibits CYP450 2D6

**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 paroxetine
- 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 paroxetine
- May displace highly protein bound drugs (e.g., warfarin)
- There are reports of elevated theophylline levels associated with paroxetine treatment, so it is recommended that theophylline levels be monitored when these drugs are administered together
- May increase anticholinergic effects of procyclidine and other drugs with anticholinergic properties
- 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, paroxetine 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, paroxetine could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias.
Paroxetine increases pimozide levels, and pimozide prolongs QT interval, so concomitant use of pimozide and paroxetine is contraindicated.

- **Other Warnings/Precautions**
  - Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing paroxetine.
  - 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.
  - If patient is taking pimozide.
  - If patient is taking tamoxifen.
  - If there is a proven allergy to paroxetine.

**SPECIAL POPULATIONS**

- **Renal Impairment**
  - Lower dose [initial 10 mg/day (12.5 mg CR), maximum 40 mg/day (50 mg/day CR)].

- **Hepatic Impairment**
  - Lower dose [initial 10 mg/day (12.5 mg CR), maximum 40 mg/day (50 mg/day CR)].

- **Cardiac Impairment**
  - Preliminary research suggests that paroxetine 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**

- Lower dose [initial 10 mg/day (12.5 mg CR), maximum 40 mg/day (50 mg/day CR)].
- 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.
- Not specifically approved, but preliminary evidence suggests efficacy in children and adolescents with OCD, social phobia, or 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 (PLLKR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001.
- Not generally recommended for use during pregnancy, especially during first trimester.
- Epidemiological data have shown an increased risk of cardiovascular malformations (primarily ventricular and atrial septal defects) in infants born to women who took paroxetine during the first trimester (absolute risk is small).
• Unless the benefits of paroxetine to the mother justify continuing treatment, consider discontinuing paroxetine or switching to another antidepressant
• Paroxetine use late in pregnancy may be associated with higher risk of neonatal complications, including respiratory distress
• 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
• 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 paroxetine
• 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 anxiety disorders and insomnia
• Patients with mixed anxiety/depression

Potential Disadvantages
• Patients with hypersomnia
• Alzheimer/cognitive disorders
• Patients with psychomotor retardation, fatigue, and low energy

Primary Target Symptoms
• Depressed mood
• Anxiety
• Sleep disturbance, especially insomnia
• Panic attacks, avoidant behavior, re-experiencing, hyperarousal

Pearls
✶ Often a preferred treatment of anxious depression as well as major depressive disorder comorbid with anxiety disorders
✶ Withdrawal effects may be more likely than for some other SSRIs when discontinued (especially akathisia, restlessness, gastrointestinal symptoms, dizziness, tingling, dysthesias, nausea, stomach cramps, restlessness)
• Inhibits own metabolism, so dosing is not linear
✶ Paroxetine has mild anticholinergic actions that can enhance the rapid onset of anxiolytic and hypnotic efficacy but also cause mild anticholinergic side effects
• Can cause cognitive and affective “flattening”
• May be less activating than other SSRIs
• Paroxetine is a potent CYP450 2D6 inhibitor
• 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 anecdotal reports suggest greater weight gain and sexual dysfunction than some other SSRIs, but the clinical significance of this is unknown
• For sexual dysfunction, can augment with bupropion, sildenafil, tadalafil, or switch to a non-SSRI such as bupropion or mirtazapine
• Some postmenopausal women’s depression will respond better to paroxetine plus estrogen augmentation than to paroxetine alone
• Nonresponse to paroxetine in elderly may require consideration of mild cognitive impairment or Alzheimer disease
• CR formulation may enhance tolerability, especially for nausea
• Can be better tolerated than some SSRIs for patients with anxiety and insomnia and can reduce these symptoms early in dosing

Suggested Reading


