



Tofranil and Tofranil-PM (imipramine)

Generic name: Imipramine

Available strengths: 10 mg, 25 mg, 50 mg tablets;

75 mg, 100 mg, 125 mg, 150 mg capsules (Tofranil-PM)

Available in generic: Yes

Drug class: Tricyclic antidepressant

General Information

Tofranil (imipramine) exerts its antidepressant action principally by inhibiting the reuptake of **serotonin** and, to a lesser extent, **norepinephrine**, two important neurotransmitters in the central nervous system, and thereby boosting neurotransmission. Tofranil also has other pharmacological effects, which are associated with its side effects. Depression and other mental disorders may be due to abnormally low levels of certain neurotransmitters in the brain. This abnormality may in turn produce changes in affected areas of the brain, resulting in psychiatric symptoms such as depression or anxiety. Tofranil exerts its antidepressant action presumably by boosting the levels of serotonin and norepinephrine. There is usually a time lag of 3–4 weeks for antidepressants to achieve their optimal effect, which may be the time needed for the brain to restore normal functioning before reducing the symptoms of the illness.

Tofranil was approved by the U.S. Food and Drug Administration (FDA) for the treatment of depression and for the treatment of bedwetting (enuresis) in children over 6 years of age. The use of a medication for its approved indications is called its *labeled use*. In clinical practice, however, physicians often prescribe medications for *unlabeled* (“off-label”) uses when published clinical studies, case reports, or their own clinical experiences support the efficacy and safety of those treatments. Unlabeled uses of Tofranil include treatment of chronic pain syndromes (e.g., migraine headaches, diabetic neuropathy, cancer pain), eating disorders (bulimia nervosa), panic disorder, premenstrual dysphoric disorder, posttraumatic stress disorder, and insomnia, and facilitation of cocaine withdrawal. Physicians may also use Tofranil in combination with another antidepressant, such as a **selective serotonin reuptake inhibitor** (SSRI), to augment the antidepressant effect. This augmentation strategy is often successful in treating refractory depression when response to a single antidepressant is inadequate.

Dosing Information

The recommended starting dosage is 75 mg/day, preferably taken at bedtime. The dosage is increased, as needed, to 150 mg/day in week 2 and may be taken in a single bedtime dose or in divided doses. If depressive symptoms persist, the physician may further increase the dosage up to a maximum of 300 mg/day or switch the patient's medication to another antidepressant. Seniors and adolescents generally require lower dosages of 25–100 mg/day, and dosages greater than 100 mg/day are not recommended for these patients.

Tofranil-PM sustained-release capsules offer the convenience of once-a-day dosing, preferably in the evening or at bedtime. A single dose at bedtime is convenient and will minimize daytime sedation and bothersome anticholinergic side effects. With higher dosages, a single dose of regular Tofranil produces high peak blood levels that may result in more side effects for most people. The sustained-release preparation of Tofranil-PM, however, may improve the tolerability of single daily dosing.

Common Side Effects

Because the tricyclic antidepressants (TCAs) inhibit **cholinergic neurons** in the nervous system, they frequently produce a cluster of symptoms called **anticholinergic** side effects, which include dry mouth and skin, blurred vision, constipation, and difficulty urinating. Usually, individuals become tolerant to these side effects, but excessive anticholinergic effects may lead to confusion and a psychiatric disorder called delirium if not monitored closely. Sometimes the physician may prescribe another medication to counteract the anticholinergic action of the antidepressant. For example, a physician may prescribe a 1% pilocarpine eyedrop to treat blurred vision and bethanechol (e.g., Urecholine), a cholinergic agent, to treat urinary difficulties. For constipation, an over-the-counter stool softener such as Colace (docusate) is usually helpful.

Individuals may experience dizziness from TCAs. Dizziness may be caused by the drugs' effect in momentarily dropping blood pressure; they block the body's compensatory response to maintain a stable blood pressure when a person moves from lying down to a sitting position or from sitting to standing. This reaction is known in medical terms as **orthostatic hypotension**. Seniors and those taking other medications to lower blood pressure may be more susceptible to orthostatic hypotension from these antidepressants.

Weight gain is another common problem. Most individuals gain several pounds while taking TCAs, including Tofranil. If the individual's weight does not stabilize, the physician may switch the patient's medication to one of the newer, weight-neutral antidepressants, such as the SSRIs.

Tofranil may also produce sexual difficulties, including impotence and ejaculatory difficulty in men and decreased sexual drive in both men and women. If this is a problem, the physician may switch the patient's medication to another antidepressant, such as bupropion (Wellbutrin SR or Wellbutrin XL), that does not interfere with sexual functioning.

Adverse Reactions and Precautions

Tofranil may cause significant drowsiness and blurred vision in some people. Patients should not drive, operate machinery, or perform other potentially hazardous tasks until they are certain that their vision, alertness, or coordination is not affected by the medication. Patients with a known allergy to Tofranil or who have experienced a severe reaction after taking it should not take Tofranil.

Tofranil may affect cardiac conduction by slowing the electrical impulses that travel across cardiac tissues, leading to a disturbance in heart rhythms called an arrhythmia. This side effect is common in seniors and in people with a history of arrhythmias or cardiovascular disease. Therefore, patients over 65 years of age and those with a history of heart disease should obtain a pretreatment electrocardiogram and periodic checks (at least annually). Moreover, because of the increased risk of cardiovascular complications and side effects, seniors may not tolerate single daily doses.

As previously stated, seniors and individuals taking medications to lower blood pressure may be susceptible to Tofranil-induced orthostatic hypotension. In such susceptible individuals, the sudden drop in blood pressure from rising too rapidly may cause fainting. To prevent this from occurring, the individual should rise slowly, allowing blood pressure to adjust gradually.

Use in Pregnancy and Breastfeeding: Pregnancy Category D

There have been reports of congenital malformations associated with Tofranil, and thus it is placed in a higher-risk category. The exposure of Tofranil during pregnancy in these women, however, was not confirmed as having a definite association with the defect. TCAs are *not* recommended during pregnancy, especially during the first 3 months. The anticholinergic side effects induced by TCAs may also affect the baby (these effects are known as **fetal anticholinergic syndrome**). Thus, use during pregnancy must be clearly weighed against the potential risk to the developing fetus. Women who are pregnant or may become pregnant should discuss this with their physician. Some women may experience a recurrence of their depression when they stop their antidepressant. In these circumstances it may be necessary to restart the medication or seek an alternative medication or treatment.

Nursing mothers should not take Tofranil, because small amounts will pass into breast milk and be ingested by the baby. If stopping the antidepressant is not an alternative, breastfeeding should not be started or should be discontinued.

Possible Drug Interactions

Combined use of Tofranil with certain medications may result in adverse drug interactions, because one medication may alter the blood levels of the other. The significant drug interactions with Tofranil are summarized below.

Selective serotonin reuptake inhibitors (SSRIs)	The combination of Tofranil and an SSRI may significantly increase the level of Tofranil, resulting in adverse or toxic reactions.
Tegretol (carbamazepine)	The combination of Tofranil and Tegretol may result in decreased levels of Tofranil and may lower its positive pharmacological effects; the combination may also increase Tegretol levels, resulting in more side effects and increased toxicity.
Coumadin (warfarin)	Tofranil may increase Coumadin levels and its anticoagulant effects, resulting in bleeding.
Catapres (clonidine)	The combination of Tofranil and Catapres may result in dangerous elevation of blood pressure and should be avoided.
Quinidine	The combination of Tofranil and quinidine, an antiarrhythmia medication, may increase the risk of arrhythmias and should be avoided.
Depakote, Depakote ER, or Depakene	The combination of Tofranil and Depakote, Depakote ER, or Depakene may elevate Tofranil levels, which may increase the likelihood of side effects.
Anticholinergic agents (e.g., Cogentin, Benadryl)	Anticholinergic side effects may increase when Tofranil is combined with an anticholinergic agent or another medication with anticholinergic side effects.
Antabuse (disulfiram)	The combination of Antabuse and TCAs has been reported to cause a rare but potentially serious reaction called <i>organic brain syndrome</i> , which affects mental function.

Antidepressants known as **monoamine oxidase inhibitors** (MAOIs) should not be taken together with Tofranil, because the combination may potentially produce a toxic reaction that includes elevated temperature, high blood pressure, and extreme excitation and agitation. Patients should consult their physician or pharmacist before taking any new medications, including over-the-counter medications and herbal supplements, with Tofranil.

Patients taking Tofranil should avoid alcohol or should consume it in moderation because the combination may worsen depression.

Overdose

Tofranil, like other tricyclic antidepressants (TCAs), is extremely lethal in acute overdose, especially in children. Overdoses may result in death, especially when the antidepressant is combined with other medications or alcohol. Disturbance of cardiac rhythm is usually the leading cause of death.

Any suspected overdose should be treated as an emergency. The person should be taken to the emergency room for observation and treatment. The prescription bottle of medication (and any other medication suspected in the overdose) should be brought as well, because the information on the prescription label can be helpful to the treating physician in determining the number of pills ingested.

Special Considerations

Most cases of major depression can be treated successfully, usually with medication, psychotherapy, or both. The combination of psychotherapy and antidepressants is very effective in treating moderate to severe depression. The medications improve mood, sleep, energy, and appetite, while therapy strengthens coping skills, deals with possible underlying issues, and improves thought patterns and behavior.

In general, antidepressants alone help about 60%–70% of those taking them. Although a few individuals may experience some improvement from antidepressants by the end of the first week, most people do not see significant benefits from their antidepressants until after 3–4 weeks, and it can sometimes take as long as 8 weeks for the medication to produce its full effects. Thus it is critical that patients continue to take their antidepressant long enough for the medication to be beneficial and that patients not get discouraged and stop their medication prematurely if they do not feel better immediately.

In short-term studies, antidepressants were found to increase the risk of suicidal thinking and behavior in children and adolescents with major depression and other psychiatric disorders. The FDA requires the prescriber to warn of this risk in children and adolescents when starting antidepressant therapy. According to the FDA findings, the risk of suicidal thoughts and behaviors associated with antidepressants is age-related. This phenomenon tends to occur in the younger population and is most likely to occur early in the course of treatment. In adults over 24 years of age, there did not appear to be an increased risk of suicidality with antidepressants compared with placebo. In patients over age 65, the findings showed that antidepressants had a “protective effect” against suicidal thoughts and behavior. Other studies have found that when more people in a community are taking antidepressants, the suicide rate is lower.

The risk of suicide is inherent in depression and may persist until the individual responds to treatment. After starting or changing antidepressant therapy, the person, especially a child or adolescent, should be closely observed for worsening signs of depression, and the family or caregiver should communicate any concerns to the physician.

- **Warning:** Always let your physician or a family member know if you have suicidal thoughts. Notify your psychiatrist or your family physician whenever your depressive symptoms worsen or whenever you feel unable to control suicidal urges or thoughts.

- Do not discontinue Tofranil without consulting with your physician. Tofranil should not be stopped abruptly, but gradually tapered down before discontinuation. Abrupt discontinuation of Tofranil may cause nausea, headache, and malaise.
- If you miss a dose, take it as soon as possible. If it is close to the next scheduled dose, skip the missed dose and continue on your regular dosing schedule. Do not take double doses.
- Tofranil may cause significant drowsiness. Until you are certain that your alertness and coordination are not affected by your medication, you should avoid driving and operating machinery.
- If you experience blurred vision, you should avoid driving, operating machinery, or performing potentially hazardous tasks. Consult your physician if you experience blurred vision.
- Do not take Tofranil if you have a known allergy to Tofranil or have experienced a severe reaction to it.
- Store the medication in its originally labeled, light-resistant container, away from heat and moisture. Heat and moisture may precipitate breakdown of your medication, and the medication may lose its therapeutic effects.
- Keep your medication out of reach of children. TCAs are extremely dangerous in acute overdose in young children.

If you have any questions about your medication, consult your physician or pharmacist.

Notes

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