IMIPRAMINE

THERAPEUTICS

Brands
- Tofranil
  see index for additional brand names

Generic?
Yes

Class
- Tricyclic antidepressant (TCA); serotonin and norepinephrine/noradrenaline reuptake inhibitor

Commonly Prescribed For
(FDA approved in bold)
- Depression
- Enuresis
- Anxiety
- Insomnia
- Neuropathic pain/chronic pain
- Treatment-resistant depression
- Cataplexy syndrome

How the Drug Works
- Boosts neurotransmitters serotonin and norepinephrine/noradrenaline
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Presumably desensitizes both serotonin 1A receptors and beta-adrenergic receptors
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, imipramine can increase dopamine neurotransmission in this part of the brain
- May be effective in treating enuresis because of its anticholinergic properties

How Long until It Works
- May have immediate effects in treating insomnia or anxiety
- 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
- May continue to work for many years to prevent relapse of symptoms

If it Works
- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Treatment of chronic neuropathic pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression 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 and chronic pain may also need to be indefinite, but long-term treatment is not well studied in these conditions

If It Doesn’t Work
- Many depressed patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- 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
- Lithium, buspirone, thyroid hormone (for depression)
- Gabapentin, tiagabine, other antiepileptics, even opiates if done by experts while monitoring carefully in difficult cases (for chronic pain)
Tests

- None for healthy individuals
- Since tricyclic and tetracyclic antidepressants are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI >30)

Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–25 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management.

- Monitor weight and BMI during treatment
- While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant.
- ECGs may be useful for selected patients (e.g. those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
- Patients at risk for electrolyte disturbances (e.g. patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements.

ADVERSE EFFECTS (AEs)

How Drug Causes AEs

- Anticholinergic activity may explain sedative effects, dry mouth, constipation, and blurred vision.
- Sedative effects and weight gain may be due to antihistamine properties.
- Blockade of alpha-adrenergic-1 receptors may explain dizziness, sedation, and hypotension.
- Cardiac arrhythmias and seizures, especially in overdose, may be caused by blockade of ion channels.

Notable AEs

- Blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, heartburn, unusual taste in mouth, weight gain.
- Fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness.
- Sexual dysfunction, sweating.

Life-Threatening or Dangerous AEs

- Paralytic ileus, hyperthermia (TCAs + anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure, increased psychotic symptoms
- 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

- Common
- Many experience and/or can be significant in amount
- Can increase appetite and carbohydrate craving

Sedation

- Common
- Many experience and/or can be significant in amount
- Tolerance to sedative effects may develop with long-term use

What to Do about AEs

- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

Best Augmenting Agents for AEs

- Many AEs cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 50–150 mg/day
Dosage Forms
- Capsule: 75 mg, 100 mg, 125 mg, 150 mg
- Tablet: 10 mg, 25 mg, 50 mg

How to Dose
- Initial 25 mg/day at bedtime; increase by 25 mg every 3–7 days
- 75–100 mg/day once daily or in divided doses; gradually increase daily dose to achieve desired therapeutic effects; dose at bedtime for daytime sedation and in morning for insomnia; maximum dose 300 mg/day

Dosing Tips
- If given in a single dose, should generally be administered at bedtime because of its sedative properties
- If given in split doses, largest dose should generally be given at bedtime because of its sedative properties
- If patients experience nightmares, split dose and do not give large dose at bedtime
- Patients treated for chronic pain may only require lower doses
- Tofranil-PM(r) (imipramine pamoate) 100- and 125-mg capsules contain the dye tartrazine (FD&C yellow No. 5), which may cause allergic reactions in some patients; this reaction is more likely in patients with sensitivity to aspirin
- 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
- Death may occur; convulsions, cardiac dysrhythmias, severe hypotension, CNS depression, coma, changes in ECG

Long-Term Use
- Safe for long-term use

Habit Forming
- No

How to Stop
- Taper to avoid withdrawal effects
- Even with gradual dose reduction some withdrawal symptoms may appear within the first 2 weeks
- 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
- Substrate for CYP2D6 and CYP1A2
- Metabolized to an active metabolite, desipramine, a predominantly norepinephrine reuptake inhibitor, by demethylation via CYP1A2

Drug Interactions
- Tramadol increases the risk of seizures in patients taking TCAs
- Use of TCAs with anticholinergic drugs may result in paralytic ileus or hyperthermia
- Fluoxetine, paroxetine, bupropion, duloxetine, and other CYP2D6 inhibitors may increase TCA concentrations
- Fluvoxamine, a CYP1A2 inhibitor, can decrease the conversion of imipramine to desmethylimipramine (desipramine) and increase imipramine plasma concentrations
- Cimetidine may increase plasma concentrations of TCAs and cause anticholinergic symptoms
- Phenothiazines or haloperidol may raise TCA blood concentrations
- May alter effects of antihypertensive drugs; may inhibit hypotensive effects of clonidine
- Use with sympathomimetic agents may increase sympathetic activity
- Methylphenidate may inhibit metabolism of TCAs
- Activation and agitation, especially following switching or adding antidepressants, 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 imipramine

Other Warnings/Precautions
- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing imipramine
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI until 2 weeks after discontinuing imipramine, but see Pearls
- Use with caution in patients with history of seizure, urinary retention, narrow angle-closure glaucoma, hyperthyroidism
TCAs can increase QTc interval, especially at toxic doses, which can be attained not only by overdose but also by combining with drugs that inhibit its metabolism via CYP2D6, potentially causing torsade de pointes-type arrhythmia or sudden death.

Because TCAs can prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g. beta-blockers, calcium channel blockers, clonidine, digitalis).

Because TCAs can prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or hypomagnesemia (e.g. diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide).

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 recovering from myocardial infarction.
- If patient is taking agents capable of significantly prolonging QTc interval (e.g. pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin).
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure.
- If patient is taking drugs that inhibit TCA metabolism, including CYP2D6 inhibitors, except by an expert.
- If there is reduced CYP2D6 function, such as patients who are poor CYP2D6 metabolizers, except by an expert and at low doses.
- If there is a proven allergy to imipramine, desipramine, or lofepramine.

Hepatic Impairment

- Cautious use; may need lower dose.

Cardiac Impairment

- TCAs have been reported to cause arrhythmias, prolongation of conduction time, orthostatic hypotension, sinus tachycardia, and heart failure, especially in the diseased heart.
- Myocardial infarction and stroke have been reported with TCAs.
- TCAs produce QTc prolongation, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering imipramine.
- Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval.
- Avoid TCAs in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure.
- TCAs may cause a sustained increase in heart rate in patients with ischemic heart disease and may worsen (decrease) heart rate variability, an independent risk of mortality in cardiac populations.
- Since SSRIs may improve (increase) heart rate variability in patients following a myocardial infarction and may improve survival as well as mood in patients with acute angina or following a myocardial infarction, these are more appropriate agents for cardiac populations than tricyclic/tetracyclic antidepressants.
- Risk/benefit ratio may not justify use of TCAs in cardiac impairment.

Elderly

- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects.
- Initial 30–40 mg/day; maximum dose 100 mg/day.
- Reduction in 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.

SPECIAL POPULATIONS

Renal Impairment

- Cautious use; may need lower dose.

Hepatic Impairment

- Cautious use; may need lower dose.

Cardiac Impairment

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- 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 guardian of this risk so they can help observe child or adolescent patients. Used age 6 and older for enuresis; age 12 and older for other disorders. Several studies show lack of efficacy of TCAs for depression. May be used to treat hyperactive/impulsive behaviors. Some cases of sudden death have occurred in children taking TCAs. Adolescents: initial 30–40 mg/day; maximum 100 mg/day. Children: initial 1.5 mg/kg per day; maximum 5 mg/kg per day. Functional enuresis: 50 mg/day (age 6–12) or 75 mg/day (over 12).

**Pregnancy**

- Risk Category D (positive evidence of risk to human fetus; potential benefits may still justify its use during pregnancy)
- Crosses the placenta
- Should be used only if potential benefits outweigh potential risks
- Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations)
- Evaluate for treatment with an antidepressant with a better risk/benefit ratio

**Breast-Feeding**

- Some drug is found in mother’s breast milk
- Recommended either to discontinue drug or bottle feed
- 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 reinstated late in the 3rd 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

**Potential Advantages**

- Patients with insomnia
- Severe or treatment-resistant depression
- Patients with enuresis

**Potential Disadvantages**

- Pediatric and geriatric patients
- Patients concerned with weight gain
- Cardiac patients

**Primary Target Symptoms**

- Depressed mood
- Chronic pain

**Pearls**

- Was once one of the most widely prescribed agents for depression
- Probably the most preferred TCA for treating enuresis in children
- Preference of some prescribers for imipramine over other TCAs for the treatment of enuresis is based more upon art and anecdote and empiric clinical experience than comparative clinical trials with other TCAs
- TCAs are no longer generally considered a first-line treatment option for depression because of their AE profile
- TCAs may aggravate psychotic symptoms
- Alcohol should be avoided because of additive CNS effects
- Underweight patients may be more susceptible to adverse cardiovascular effects
- Children, patients with inadequate hydration, and patients with cardiac disease may be more susceptible to TCA-induced cardiotoxicity than healthy adults
- For the expert only: although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is to give a tricyclic/tetracyclic antidepressant other than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants. If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the...
**Suggested Reading**


