**Brands**
- Anafranil
  see index for additional brand names

**Generic?**
Yes

**Class**
- Tricyclic antidepressant (TCA)
- Parent drug is a potent serotonin reuptake inhibitor
- Active metabolite is a potent norepinephrine/noradrenaline reuptake inhibitor

**Commonly Prescribed For**
(FDA approved in bold)
- Obsessive–compulsive disorder (OCD)
- Depression
- Severe and treatment-resistant depression
- Cataplexy syndrome
- Anxiety
- Insomnia
- Neuropathic pain/chronic pain

**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, clomipramine can increase dopamine neurotransmission in this part of the brain

**How Long until It Works**
- May have immediate effects in treating insomnia or anxiety
- Onset of therapeutic actions in depression usually not immediate, but often delayed 2 to 4 weeks
- Onset of therapeutic action in OCD can be delayed 6–12 weeks
- If it is not working for depression within 6–8 weeks, it may require a dosage increase or it may not work at all

**If It Works**
- The goal of treatment of depression 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
- Although the goal of treatment of OCD is also complete remission of symptoms, this may be less likely than in depression
- The goal of treatment of chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- 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 OCD may also need to be indefinite, starting from the time of initial treatment
- Use in other 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 patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other 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, especially behavioral therapy in OCD
- 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 (for depression and OCD)
- For the expert: consider cautious addition of fluvoxamine for treatment-resistant OCD
- Thyroid hormone (for depression)
- Atypical antipsychotics (for OCD)

Tests

- None for healthy individuals, although monitoring of plasma drug levels is potentially available at specialty laboratories for the expert
- 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, low-density lipoprotein (LDL) cholesterol and triglycerides; decreased high-density lipoprotein (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 MI; 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 and anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure
- 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 effect may develop with long-term use
### What to Do about AEs
- Wait
- 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

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### DOSING AND USE

#### Usual Dosage Range
- 100–200 mg/day

#### Dosage Forms
- Capsule 25 mg, 50 mg, 75 mg

#### How to Dose
- Initial 25 mg/day; increase over 2 weeks to 100 mg/day; maximum dose generally 250 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
- Patients treated for OCD may often require doses at the high end of the range (e.g. 200–250 mg/day)
- Risk of seizure increases with dose, especially with clomipramine at doses above 250 mg/day
- Dose of 300 mg may be associated with up to 7/1000 incidence of seizures, a generally unacceptable risk
- 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

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### Long-Term Use
- Limited data but appears to be efficacious and safe long-term

### 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, desmethyl-clomipramine, a predominantly norepinephrine reuptake inhibitor, by demethylation via CYP1A2
- Half-life approximately 17–28 hours

### 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 clomipramine to desmethyl-clomipramine, and increase clomipramine 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
- Use of TCAs with sympathomimetic agents may increase sympathetic activity
- TCAs may inhibit hypotensive effects of clonidine
- 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 clomipramine.

**Other Warnings/Precautions**
- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing clomipramine.
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI until 2 weeks after discontinuing clomipramine, but see *Pearls*.
- Use with caution in patients with history of seizures, 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 TCA 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 hyponatremia or who are taking drugs that can induce hypokalemia and/or hypomagnesemia (e.g., diuretics, stimulant laxatives, IV 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 AEs 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 MI.
- 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 MI, 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 clomipramine.
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
- 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
- Not recommended for use in children under age 10
- Several studies show lack of efficacy of TCAs for depression
- May be used to treat enuresis or hyperactive/impulsive behaviors
- Effective for OCD in children
- Some cases of sudden death have occurred in children taking TCAs
- Dose in children/adolescents should be titrated to a maximum of 100 mg/day or 3 mg/kg per day after 2 weeks, after which dose can then be titrated up to a maximum of 200 mg/day or 3 mg/kg per day

**Pregnancy**
- Risk Category C: some animal studies show adverse effects; no controlled studies in humans
- Clomipramine crosses the placenta
- Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations)
- Must weigh the risk of treatment (1st trimester fetal development, 3rd trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, worsening of OCD, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

**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 and worsening of OCD, especially in women who have had prior depressive episodes or OCD symptoms, so drug may need to be reinstituted late in the 3rd trimester or shortly after childbirth to prevent a recurrence or exacerbation 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

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**THE ART OF PAIN PHARMACOLOGY**

**Potential Advantages**
- Patients with insomnia
- Severe or treatment-resistant depression
- Patients with comorbid OCD and depression
- Patients with cataplexy

**Potential Disadvantages**
- Pediatric and geriatric patients
- Patients concerned with weight gain
- Cardiac patients
- Patients with seizure disorders

**Primary Target Symptoms**
- Depressed mood
- Obsessive thoughts
- Compulsive behaviors

**Pearls**
- The only TCA with proven efficacy in OCD
- Normally, clomipramine (CMI), a potent serotonin reuptake blocker, at steady state is metabolized extensively to its active metabolite desmethyl-clomipramine (de-CMI), a potent nonadrenaline reuptake blocker, by the enzyme CYP1A2
- 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 the SSRI and CYP1A2 inhibitor fluvoxamine blocks this conversion and results in higher CMI levels than de-CMI levels
- For the expert only: addition of the SSRI fluvoxamine to CMI in treatment-resistant OCD can powerfully enhance serotonergic activity, not only due to the inherent additive pharmacodynamic serotonergic activity of fluvoxamine added to CMI, but also due to a...
favorable pharmacokinetic interaction inhibiting CYP1A2 and thus converting CMI’s metabolism to a more powerful serotonergic portfolio of parent drug.

- One of the most favored TCAs for treating severe depression
- TCAs are no longer generally considered a first-line treatment option for depression because of their adverse effect profile
- TCAs continue to be useful for severe or treatment-resistant depression
- TCAs are often a first-line treatment option for chronic pain
- Unique among TCAs, clomipramine has a potentially fatal interaction with MAOIs in addition to the danger of hypertension characteristic of all MAOI–TCA combinations
- A potentially fatal serotonin syndrome with high fever, seizures, and coma, analogous to that caused by SSRIs and MAOIs, can occur with clomipramine and SSRIs, presumably due to clomipramine’s potent serotonin reuptake blocking properties
- 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
- Patients on TCAs should be aware that they may experience symptoms such as photosensitivity or blue-green urine
- SSRIs may be more effective than TCAs in women, and TCAs may be more effective than SSRIs in men
- Since tricyclic/tetracyclic antidepressants are substrates for CYP2D6, and 7% of the population (especially Caucasians) may have a genetic variant leading to reduced activity of CYP2D6, such patients may not safely tolerate normal doses of tricyclic/tetracyclic antidepressants and may require dose reduction
- Phenotypic testing may be necessary to detect this genetic variant prior to dosing with a tricyclic/tetracyclic antidepressant, especially in vulnerable populations such as children, elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe AEs at normal or low doses may have this phenotypic CYP2D6 variant and require low doses or switching to another antidepressant not metabolized by CYP2D6

Suggested Reading


