**TRANYLCYPROMINE**

**THERAPEUTICS**

**Brands**  •  Parnate  
*see index for additional brand names*

**Generic?**  Yes

**Class**  
- Neuroscience-based Nomenclature: serotonin, norepinephrine, dopamine multimodal enzyme inhibitor (SN-MM)  
- Monoamine oxidase inhibitor (MAOI)

**Commonly Prescribed for**  *(bold for FDA approved)*  
- Major depressive episode without melancholia  
- Treatment-resistant depression  
- Treatment-resistant panic disorder  
- Treatment-resistant social anxiety disorder

**How the Drug Works**  
- Irreversibly blocks monoamine oxidase (MAO) from breaking down norepinephrine, serotonin, and dopamine  
- This presumably boosts noradrenergic, serotonergic, and dopaminergic neurotransmission  
- As the drug is structurally related to amphetamine, it may have some stimulant-like actions due to monoamine release and reuptake inhibition

**How Long Until It Works**  
- Some patients may experience stimulant-like actions early in dosing  
- 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)

**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  
- 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**  
- Augmentation of MAOIs has not been systematically studied, and this is something for the expert, to be done with caution and with careful monitoring  
- A stimulant such as d-amphetamine or methylphenidate (with caution; may activate bipolar disorder and suicidal ideation; may elevate blood pressure)  
- Lithium  
- Mood-stabilizing anticonvulsants  
- Atypical antipsychotics (with special caution for those agents with monoamine reuptake blocking properties, such as ziprasidone and zotepine)

**Tests**  
- Patients should be monitored for changes in blood pressure  
- Patients receiving high doses or long-term treatment should have hepatic function evaluated periodically
**SIDE EFFECTS**

**How Drug Causes Side Effects**
- Theoretically due to increases in monoamines in parts of the brain and body and at receptors other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of norepinephrine on vascular smooth muscle causing hypertension, etc.)
- Side effects are generally immediate, but immediate side effects often disappear in time

**Notable Side Effects**
- Agitation, anxiety, insomnia, weakness, sedation, dizziness
- Constipation, dry mouth, nausea, diarrhea, change in appetite, weight gain
- Sexual dysfunction
- Orthostatic hypotension (dose-related); syncope may develop at high doses

**Life-Threatening or Dangerous Side Effects**
- Hypertensive crisis (especially when MAOIs are used with certain tyramine-containing foods or prohibited drugs)
- 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)
- Seizures
- Hepatotoxicity

**Weight Gain**
- Occurs in significant minority

**Sedation**
- Many experience and/or can be significant in amount
- Can also cause activation

**What to Do About Side Effects**
- Wait
- Wait
- Wait
- Lower the dose

**DOSING AND USE**

**Usual Dosage Range**
- 30 mg/day in divided doses

**Dosage Forms**
- Tablet 10 mg

**How to Dose**
- Initial 30 mg/day in divided doses; after 2 weeks increase by 10 mg/day each 1–3 weeks; maximum 60 mg/day

**Dosing Tips**
- Orthostatic hypotension, especially at high doses, may require splitting into 3–4 daily doses
- Patients receiving high doses may need to be evaluated periodically for effects on the liver

**Overdose**
- Dizziness, sedation, ataxia, headache, insomnia, restlessness, anxiety, irritability; cardiovascular effects, confusion, respiratory depression, or coma may also occur

**Long-Term Use**
- May require periodic evaluation of hepatic function
- MAOIs may lose efficacy long-term

**Habit Forming**
- Some patients have developed dependence to MAOIs
**How to Stop**
- Generally no need to taper, as the drug wears off slowly over 2–3 weeks

**Pharmacokinetics**
- Clinical duration of action may be up to 14 days due to irreversible enzyme inhibition

**Drug Interactions**
- Tramadol may increase the risk of seizures in patients taking an MAOI
- Can cause a fatal “serotonin syndrome” when combined with drugs that block serotonin reuptake, so do not use with a serotonin reuptake inhibitor or for 5 half-lives after stopping the serotonin reuptake inhibitor (see Table 1 after Pearls)
- Hypertensive crisis with headache, intracranial bleeding, and death may result from combining MAOIs with sympathomimetic drugs (e.g., amphetamines, methylphenidate, cocaine, dopamine, epinephrine, norepinephrine, and related compounds methyldopa, levodopa, L-tryptophan, L-tyrosine, and phenylalanine)
- Do not combine with another MAOI, alcohol, or guanethidine
- Adverse drug reactions can result from combining MAOIs with tricyclic/tetracyclic antidepressants and related compounds, including carbamazepine, cyclobenzaprine, and mirtazapine, and should be avoided except by experts to treat difficult cases
- MAOIs in combination with spinal anesthesia may cause combined hypotensive effects
- Combination of MAOIs and CNS depressants may enhance sedation and hypotension

**Other Warnings/Precautions**
- Use requires low tyramine diet (see Table 2 after Pearls)
- Patient and prescriber must be vigilant to potential interactions with any drug, including antihypertensives and over-the-counter cough/cold preparations
- Over-the-counter medications to avoid include cough and cold preparations, including those containing dextromethorphan, nasal decongestants (tablets, drops, or spray), hay-fever medications, sinus medications, asthma inhalant medications, anti-appetite medications, weight reducing preparations, “pep” pills (see Table 3 after Pearls)
- Hypoglycemia may occur in diabetic patients receiving insulin or oral antidiabetic agents
- Use cautiously in patients receiving reserpine, anesthetics, disulfiram, metrizamide, anticholinergic agents
- Tranylcypromine is not recommended for use in patients who cannot be monitored closely
- 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 meperidine (pethidine)
- If patient is taking a sympathomimetic agent or taking guanethidine
- If patient is taking another MAOI
- If patient is taking any agent that can inhibit serotonin reuptake (e.g., SSRIs, sibutramine, tramadol, milnacipran, duloxetine, venlafaxine, clomipramine, etc.)
- If patient is taking diuretics, dextromethorphan
- If patient has pheochromocytoma
- If patient has cardiovascular or cerebrovascular disease
- If patient has frequent or severe headaches
- If patient is undergoing elective surgery and requires general anesthesia
- If patient has a history of liver disease or abnormal liver function tests
- If patient is taking a prohibited drug
- If patient is not compliant with a low-tyramine diet
- If there is a proven allergy to tranylcypromine
**SPECIAL POPULATIONS**

**Renal Impairment**
- Use with caution – drug may accumulate in plasma
- May require lower than usual adult dose

**Hepatic Impairment**
- Tranylcypromine should not be used in patients with history of hepatic impairment or in patients with abnormal liver function tests

**Cardiac Impairment**
- Contraindicated in patients with any cardiac impairment

**Elderly**
- Initial dose lower than usual adult dose
- Elderly patients may have greater sensitivity to adverse effects
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older

**Children and Adolescents**
- Not generally recommended for use in children under age 18
- 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

**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 (PLLRR 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
- Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

**Breast Feeding**
- Some drug is found in mother’s breast milk
- Effects on infant unknown
- 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
- Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

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**THE ART OF PSYCHOPHARMACOLOGY**

**Potential Advantages**
- Atypical depression
- Severe depression
- Treatment-resistant depression or anxiety disorders

**Potential Disadvantages**
- Requires compliance to dietary restrictions, concomitant drug restrictions
- Patients with cardiac problems or hypertension
- Multiple daily doses

**Primary Target Symptoms**
- Depressed mood
- Somatic symptoms
- Sleep and eating disturbances
- Psychomotor retardation
- Morbid preoccupation

**Pearls**
- MAOIs are generally reserved for second-line use after SSRIs, SNRIs, and combinations of newer antidepressants have failed
Although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is for an expert to give a tricyclic/tetracyclic antidepressant other than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants.

Use of MAOIs with clomipramine is always prohibited because of the risk of serotonin syndrome and death.

Amoxapine may be the preferred tricyclic/tetracyclic antidepressant to combine with an MAOI in heroic cases due to its theoretically protective 5HT2A antagonist properties.

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 most common side effects of MAOI and tricyclic/tetracyclic combinations may be weight gain and orthostatic hypotension.

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Table 1. Drugs contraindicated due to risk of serotonin syndrome/toxicity

<table>
<thead>
<tr>
<th>Do Not Use:</th>
<th>Drugs of Abuse</th>
<th>Opioids</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td>MDMA (ecstasy)</td>
<td>Meperidine</td>
<td>Non-subcutaneous sumatriptan</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Cocaine</td>
<td>Tramadol</td>
<td>Chlorpheniramine</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Methamphetamine</td>
<td>Methadone</td>
<td>Brompheniramine</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>High-dose or injected amphetamine</td>
<td>Fentanyl</td>
<td>Dextromethorphan</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Procarbazine?</td>
</tr>
</tbody>
</table>
Table 2. Dietary guidelines for patients taking MAOIs

<table>
<thead>
<tr>
<th>Foods to avoid*</th>
<th>Foods allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried, aged, smoked, fermented, spoiled, or improperly stored meat, poultry, and fish</td>
<td>Fresh or processed meat, poultry, and fish; properly stored pickled or smoked fish</td>
</tr>
<tr>
<td>Broad bean pods</td>
<td>All other vegetables</td>
</tr>
<tr>
<td>Aged cheeses</td>
<td>Processed cheese slices, cottage cheese, ricotta cheese, yogurt, cream cheese</td>
</tr>
<tr>
<td>Tap and unpasteurized beer</td>
<td>Canned or bottled beer and alcohol</td>
</tr>
<tr>
<td>Marmite</td>
<td>Brewer’s and baker’s yeast</td>
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<tr>
<td>Sauerkrat, kimchee</td>
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<tr>
<td>Soy products/tofu</td>
<td>Peanuts</td>
</tr>
<tr>
<td>Banana peel</td>
<td>Bananas, avocados, raspberries</td>
</tr>
<tr>
<td>Tyramine-containing nutritional supplement</td>
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</tbody>
</table>

*Not necessary for 6-mg transdermal or low-dose oral selegiline

Table 3. Drugs that boost norepinephrine: should only be used with caution with MAOIs

<table>
<thead>
<tr>
<th>Use With Caution:</th>
<th>Decongestants</th>
<th>Stimulants</th>
<th>Antidepressants with norepinephrine reuptake inhibition</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine</td>
<td>Amphetamines</td>
<td>Methylphenidate</td>
<td>Most tricyclics</td>
<td>Phentermine</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>Methylphenidate</td>
<td>NRIs</td>
<td>Local anesthetics containing vasoconstrictors</td>
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<tr>
<td>Cocaine</td>
<td>NDRIs</td>
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<tr>
<td>Methamphetamine</td>
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<tr>
<td>Modafinil</td>
<td>Tapentadol</td>
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<tr>
<td>Armodafinil</td>
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Suggested Reading


