PROPRANOLOL

**Therapeutics**

**Brands**
- Inderal
- Inderal LA
- InnoPran XL

*see index for additional brand names*

**Generic?**
- Yes

**Class**
- Beta blocker, antihypertensive

**Commonly Prescribed for**
*Bold for FDA approved*
- Migraine prophylaxis
- Essential tremor
- Hypertension
- Angina pectoris due to coronary atherosclerosis
- Cardiac arrhythmias (including supraventricular arrhythmias, ventricular tachycardia, digitalis intoxication)
- Myocardial infarction
- Hypertrophic subaortic stenosis
- Pheochromocytoma
- Akathisia (antipsychotic induced)
- Parkinsonian tremor
- Violence, aggression
- PTSD, prophylactic
- Generalized anxiety disorder (GAD)
- Prevention of variceal bleeding
- Congestive heart failure
- Tetralogy of Fallot
- Hyperthyroidism (adjunctive)

**How the Drug Works**
- For migraine, proposed mechanisms include inhibition of the adrenergic pathway, interaction with the serotonin system and receptors, inhibition of nitric oxide synthesis, and normalization of contingent negative variation
- For tremor, antagonism of peripheral beta 2 receptors is the proposed mechanism
- For PTSD, blockade of beta 1 adrenergic receptors may theoretically prevent fear conditioning and reconsolidation of fear
- For violence/aggression, the mechanism is poorly established; presumed to be related to central actions at beta adrenergic and serotonin receptors

**How Long Until It Works**
- For migraine, can begin to work within 2 weeks, but may take up to 3 months on a stable dose to see full effect
- For tremor, can begin to work within days

**If It Works**
- For migraine, the goal is a 50% or greater decrease in migraine frequency or severity; consider tapering or stopping if headaches remit for more than 6 months
- For tremor, can cause reduction in the severity of tremor, allowing greater functioning with daily activities and clearer speech
- For PTSD, may theoretically block the effects of stress from prior traumatic experiences
- For aggression, may reduce aggression, agitation, or uncooperativeness

**If It Doesn’t Work**
- Increase to highest tolerated dose
- For migraine, address other issues such as medication overuse or other coexisting medical disorders; consider changing to another drug or adding a second drug
- For tremor, coadministration with primidone up to 250 mg/day can augment response; second-line medications include benzodiazepines, gabapentin, topiramate, methazolamide, nadolol, and botulinum toxin (useful for voice and hand tremor); alternative treatments include caffeine and hand weights
- For patients with truly refractory tremor, thalamotomy or deep brain stimulation of the ventral intermediate nucleus of the thalamus is an option
- For PTSD, consider initiating first-line pharmacotherapy (SSRI, SNRI) and psychotherapy
- For violence/aggression, switch to another agent, e.g., valproate or an antipsychotic

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- Migraine: for some patients, low-dose polytherapy with 2 or more drugs may be better tolerated and more effective than high-dose monotherapy; may use propranolol in combination with antimetics, antidepressants, natural products, and non-pharmacologic
treatments, such as biofeedback, to improve headache control
• For tremor, can combine with primidone or second-line medications
• For aggression and violence, can combine with valproate and/or antipsychotics

Tests
• None for healthy individuals

SIDE EFFECTS
How Drug Causes Side Effects
• By blocking beta adrenergic receptors, it can cause dizziness, bradycardia, and hypotension

Notable Side Effects
• Bradycardia, hypotension, hyper- or hypoglycemia, weight gain
• Bronchospasm, cold/flu symptoms, sinusitis, pneumonias
• Dizziness, vertigo, fatigue/tiredness, depression, sleep disturbances
• Sexual dysfunction, decreased libido, dysuria, urinary retention, joint pain
• Exacerbation of symptoms in peripheral vascular disease and Raynaud’s syndrome

Life-Threatening or Dangerous Side Effects
• In acute congestive heart failure, may further depress myocardial contractility
• Can blunt premonitory symptoms of hypoglycemia in diabetes and mask clinical signs of hyperthyroidism
• Non-selective beta blockers such as propranolol can inhibit bronchodilation, making them contraindicated in asthma, severe COPD
• Do not use in pheochromocytoma unless alpha blockers are already being used
• Risk of excessive myocardial depression in general anesthesia

Weight Gain
• Many experience and/or can be significant in amount

Sedation
• Many experience and/or can be significant in amount

What to Do About Side Effects
• Lower dose, change to an extended-release formulation, or switch to another agent

Best Augmenting Agents for Side Effects
• When patients have significant benefit from beta blocker therapy but hypotension limits treatment, consider alpha agonists (midodrine) or volume expanders (fludrocortisones) for symptomatic relief
• Many side effects cannot be improved with an augmenting agent

DOSING AND USE
Usual Dosage Range
• 40–400 mg/day

Dosage Forms
• Tablet 10 mg, 20 mg, 40 mg, 60 mg, 80 mg, 90 mg
• Extended-release capsule 60 mg, 80 mg, 120 mg, 160 mg
• Oral solution 4 mg/mL, 8 mg/mL
• Injection 1 mg/mL

How to Dose
• Migraine: initial dose 40 mg/day in divided doses or once daily in extended-release preparations; gradually increase over days to weeks until effective dose is reached; maximum dose 400 mg/day
• Tremor: initial dose 40 mg twice per day; dosage may be gradually increased as needed to 120–320 mg/day in 2 to 3 divided doses
• PTSD: effective dose varies greatly; up to 240 mg/day have been used
• Aggression: same as migraine; up to 400 mg/day if tolerated and effective

Dosing Tips
• For extended-release capsules, give once daily at bedtime consistently, with or without food
Doses above 120 mg had no additional antihypertensive effect in clinical trials.

High doses may be effective in some patients with tremor, migraine, or aggression/violence.

**Overdose**

- Bradycardia, hypotension, low-output heart failure, shock, seizures, coma, hypoglycemia, apnea, cyanosis, respiratory depression, and bronchospasm

**Other Warnings/Precautions**

- May elevate blood urea, serum transaminases, alkaline phosphatase, and lactate dehydrogenase (LDH)
- Rare development of antinuclear antibodies (ANAs)
- May worsen symptoms of myasthenia gravis
- Can lower intraocular pressure, interfering with glaucoma screening test

**Do Not Use**

- If patient has bradycardia, greater than first-degree heart block, or cardiogenic shock
- If patient has bronchial asthma or severe COPD
- If there is a proven allergy to propranolol

- Doses above 120 mg had no additional antihypertensive effect in clinical trials
- High doses may be effective in some patients with tremor, migraine, or aggression/violence

- Bradycardia, hypotension, low-output heart failure, shock, seizures, coma, hypoglycemia, apnea, cyanosis, respiratory depression, and bronchospasm

**Drug Interactions**

- Cimetidine, oral contraceptives, ciprofloxacin, hydralazine, hydroxychloroquine, loop diuretics, certain SSRIs (with CYP 2D6 metabolism), and phenothiazines can increase levels and/or effects of propranolol
- Use with calcium channel blockers can be synergistic or additive, use with caution
- Barbiturates, penicillins, rifampin, calcium and aluminum salts, thyroid hormones, and cholestyramine can decrease effects of beta blockers
- NSAIDs, sulfipyrazone, and salicylates inhibit prostaglandin synthesis and may inhibit the antihypertensive activity of beta blockers
- Propranolol can increase adverse effects of gabapentin and benzodiazepines
- Propranolol can increase levels of lidocaine, resulting in toxicity, and increase the anticoagulant effect of warfarin

**SPECIAL POPULATIONS**

**Renal Impairment**

- No dose adjustment necessary

**Hepatic Impairment**

- Use with caution with severe impairment; dose reduction may be necessary

**Cardiac Impairment**

- Do not use in acute shock, myocardial infarction, hypotension, and greater than first-degree heart block, but indicated in clinically stable patients post-myocardial infarction to reduce risk of re-infarction starting 1–4 weeks after event

**Elderly**

- Use with caution
- May increase risk of stroke
PROPRANOLOL (continued)

**Children and Adolescents**

- Usual dose in children is 2–4 mg/kg in 2 divided doses; maximum 16 mg/kg/day
- Clinical trials for migraine prophylaxis did not include children

**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
- May reduce perfusion of the placenta
- Use only if potential benefits outweigh the potential risks to the fetus

**Breast Feeding**

- Some drug is found in mother’s breast milk
- Due to high lipid solubility, propranolol is found in breast milk more than many other beta blockers
  - Recommended either to discontinue drug or bottle feed unless the potential benefit to the mother justifies the potential risk to the child

**THE ART OF PSYCHOPHARMACOLOGY**

**Potential Advantages**

- Patients who do not respond to or tolerate other options
- Patients with autonomic hyperactivity

**Potential Disadvantages**

- Multiple potential undesirable adverse effects, including bradycardia, hypotension, and fatigue

**Primary Target Symptoms**

- Migraine frequency and severity
- Tremor
- Effects of stress from prior traumatic experience
- Aggression, agitation

**Pearls**

- Often used in combination with other drugs in migraine, which may allow patients to better tolerate medications that cause tremor, such as valproate
- May worsen depression, but helpful for anxiety
- 50–70% of patients with essential tremor receive some relief, usually with about 50% improvement or greater
- Propranolol may theoretically block the effects of stress from prior traumatic experiences, but this is unproven and data thus far are mixed

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**Suggested Reading**


