NORTRIPTYLINE

THERAPEUTICS

Brands
• Sensoval, Aventyl, Pamelor, Norpress, Allegron, Nortrilen

Generic?
Yes

Class
• Tricyclic antidepressant (TCA)

Commonly Prescribed for
(FDA approved in bold)
• Depression
• Migraine prophylaxis
• Tension-type headache prophylaxis
• Diabetic neuropathy
• Post-herpetic neuralgia
• Other painful peripheral neuropathies
• Back or neck pain
• Phantom limb pain
• Fibromyalgia
• Bulimia nervosa
• Insomnia
• Anxiety
• Nocturnal enuresis
• ADHD
• Smoking cessation

How the Drug Works
• Blocks serotonin and norepinephrine reuptake pumps, increasing their levels within hours, but antidepressant effect takes weeks. Effect is more likely related to adaptive changes in serotonin and norepinephrine receptor systems over time
• It also has antihistamine properties, which most likely causes the sedation treating insomnia

How Long Until It Works
• Migraines – effective in as little as 2 weeks, but can take up to 3 months on a stable dose to see full effect
• Neuropathic pain – usually some effect within 4 weeks
• Depression – 2 weeks but up to 2 months for full effect
• Insomnia, anxiety, depression – may be effective immediately, but effects often delayed 2 to 4 weeks

If It Works
• Migraine – goal is a 50% or greater decrease in migraine frequency or severity. Consider tapering or stopping if headaches remit for more than 6 months or if considering pregnancy
• Neuropathic pain – the goal is to reduce pain intensity and symptoms, but usually does not produce remission
• Insomnia – continue to use if tolerated and encourage good sleep hygiene
• Depression – continue to use and monitor for AEs. Usually not first-line treatment for depression

If It Doesn’t Work
• Increase to highest tolerated dose
• Migraine: address other issues, such as medication overuse, other coexisting medical disorders, such as anxiety, and consider changing to another agent or adding a second agent
• Chronic pain: either change to another agent or add a second agent
• Insomnia: if no sedation occurs despite adequate dosing, stop and change to another agent

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 in combination with AEDs, antihypertensives, natural products, and non-medication treatments, such as biofeedback, to improve headache control
• Chronic pain: AEDs such as gabapentin, pregabalin, carbamazepine, and capsaicin, mexiletine are agents used for neuropathic pain. Opioids are appropriate for long-term use in some cases but require careful monitoring

Tests
• Consider checking ECG for QTc prolongation at baseline and when increasing dose, especially in those with a personal or family history of QTc prolongation, cardiac arrhythmia, heart failure or recent myocardial infarction. In patients on diuretics, measure potassium and magnesium at baseline and periodically
ADVERSE EFFECTS (AEs)

How Drug Causes AEs
• Anticholinergic and antihistaminic properties are causes of most common AEs. Blockade of alpha-1 adrenergic receptors may cause orthostasis and sedation

Notable AEs
• Constipation, dry mouth, blurry vision, increased appetite, nausea, diarrhea, heartburn, weight gain, urinary retention, sexual dysfunction, sweating, itching, rash, fatigue, weakness, sedation, nervousness, restlessness

Life-Threatening or Dangerous AEs
• Orthostatic hypotension, tachycardia, QTc prolongation, and rarely death
• Increased intraocular pressure
• Paralytic ileus, hyperthermia
• Rare activation of mania or suicidal ideation
• Rare worsening of existing seizure disorders

Weight Gain
• Common

Sedation
• Common

What to Do About AEs
• For minor AEs, lower dose or switch to another agent. If tiredness/sedation are bothersome, lower dose or consider desipramine or nortriptyline. For serious AEs, lower dose and consider stopping

Best Augmenting Agents for AEs
• Try magnesium for constipation. For migraine, consider using with agents that cause weight loss as an AE (e.g., topiramate)

Dosage Forms
• Capsules: 10, 25, 50, 75 mg
• Liquid solution: 10 mg/5 mL

How to Dose
• Initial dose 10–25 mg/day taken about 1 hour before retiring. Effective range from 10–150 mg but typically 100 mg or less

Dosing Tips
• Start at a low dose, usually 10 mg, and titrate up every few days as tolerated. Low doses are often effective for pain even though they are below the usual effective antidepressant dose. At doses of 100 mg or greater, monitor plasma levels of drug. Patients may choose to divide doses to 3–4 times daily dosing

Overdose
• Cardiac arrhythmias and ECG changes; death can occur. CNS depression, convulsions, severe hypotension, and coma are not rare. Patients should be hospitalized. Sodium bicarbonate can treat dysrhythmias and hypotension. Treat shock with vasopressors, oxygen, or corticosteroids

Long-Term Use
• Safe for long-term use

Habit Forming
• No

How to Stop
• Taper slowly to avoid withdrawal, including rebound insomnia. Withdrawal usually lasts less than 2 weeks. For patients with well-controlled pain disorders, taper very slowly (over months) and monitor for recurrence of symptoms

Pharmacokinetics
• Metabolized by CYP450 system, especially CYP2D6, 1A2. Half-life 18–44 h and time to reach steady-state 4–19 days

Drug Interactions
• CYP2D6 inhibitors (duloxetine, paroxetine, fluoxetine, bupropion), cimetidine, and valproic acid can increase drug concentration
• Phenothiazines increase tricyclic levels

DOSING AND USE

Usual Dosage Range
• Migraine/pain: 10–100 mg/day
• Depression, anxiety: 75–150 mg/day
**NORTRIPTYLINE** (continued)

- Enzyme inducers such as rifamycin, smoking, phenobarbital can lower levels. Carbamazepine use can also lower TCA levels
- Use with clonidine has been associated with increases in blood pressure and hypertensive crisis
- Tramadol increases risk of seizures in patients taking TCAs
- May reduce absorption and bioavailability of levodopa
- May alter effects of antihypertensive medications, and prolongation of QTc, especially problematic in patients taking drugs that induce bradycardia
- Quinolones, such as grepafloxacin and sparfloxacin, increase risk of cardiac arrhythmias when used with TCAs
- Use together with anticholinergics can increase AEs (e.g., risk of ileus)
- Methylphenidate may inhibit metabolism and increase AEs
- Use within 2 weeks of monoamine oxidase (MAO) inhibitors may risk serotonin syndrome

**Other Warnings/Precautions**
- May increase risk of seizure

**Do Not Use**
- Proven hypersensitivity to drug or other TCAs
- In acute recovery after myocardial infarction or uncompensated heart failure
- In conjunction with antiarrhythmics that prolong QTc interval
- In conjunction with medications that inhibit CYP2D6

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**SPECIAL POPULATIONS**

**Renal Impairment**
- Use with caution. May need to lower dose

**Hepatic Impairment**
- Use with caution. May need to lower dose

**Cardiac Impairment**
- Do not use in patients with recent myocardial infarction, severe heart failure, with a history of QTc prolongation or orthostatic hypotension

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**Elderly**
- More sensitive to AEs such as sedation, hypotension. Start with lower doses

**Children and Adolescents**
- Not as well studied but similar effectiveness compared with amitriptyline in children. In children less than 12, most commonly used at low dose for treatment of enuresis

**Pregnancy**
- Category D. Crosses the placenta and may cause fetal malformations or withdrawal. Generally not recommended for the treatment of pain or insomnia during pregnancy. For patients with depression or anxiety, selective serotonin-reuptake inhibitors (SSRIs) may be safer than TCAs

**Breast Feeding**
- Some drug is found in breast milk and use while breast feeding is not recommended

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**THE ART OF NEUROPHARMACOLOGY**

**Potential Advantages**
- Very effective in the treatment of multiple pain disorders. Useful for treatment of depression, anxiety, and insomnia, which are common in chronic pain disorders. Less sedation than tertiary amine TCAs (e.g., amitriptyline)

**Potential Disadvantages**
- AEs are often greater than SSRIs or SNRIs and many AEDs. Less effective for insomnia than tertiary amine TCAs (e.g., amitriptyline)

**Primary Target Symptoms**
- Headache frequency and severity
- Neuropathic pain

**Pearls**
- In patients with chronic pain, offers relief at doses below usual antidepressant doses
- For patients with significant anxiety or depressive disorders, as effective as newer drugs but much more AEs. Consider treatment of depression or anxiety with...
another agent and using a low dose of nortriptyline or other TCA for pain

• TCAs can often precipitate mania in patients with bipolar disorder. Use with caution
• Despite interactions, expert psychiatrists may use with MAO inhibitors for refractory depression. Combination with atypical neuroleptics is another option
• For post-stroke depression, may be superior to SSRIs and may even increase survival
• Many patients do not improve. The number needed to treat for moderate pain relief in neuropathic pain is 2–3
• Increases non-REM sleep time and decreases sleep latency. When starting, there is often an activating effect, and insomnia may temporarily worsen

Nortriptyline and other secondary amines (amoxapine, desipramine, protriptyline) have lower rates of sedation and orthostatic hypotension than tertiary amines (amitriptyline, clomipramine, doxepin, imipramine, trimipramine) and relatively more norepinephrine than serotonin blocking activity

• Previously used for ADHD before new treatments became available. May be useful as an adjunct for patients with pain and coexisting ADHD
• TCAs may increase risk of metabolic syndrome

Suggested Reading


