TRICYCLIC ANTIDEPRESSANTS (TCAs) Fact Sheet [G]

Bottom Line:
Not commonly used due to side effects and overdose toxicity risk; however, TCAs should be considered for appropriate patients who do not respond to other antidepressants.

FDA Indications:
Major depression.

Off-Label Uses:
Headache; migraine; neuropathic pain; fibromyalgia; anxiety disorders; insomnia; nocturnal enuresis; urinary incontinence.

Note: There are nine TCAs approved by the FDA for depression (amitriptyline, amoxapine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine) and one approved for OCD (clomipramine). We've selected six TCAs to cover in this book. Doxepin is in the Anxiolytic and Hypnotic Medications chapter, clomipramine is in this chapter, and in this sheet we include four of the more commonly prescribed TCAs.

Dosage Forms:
- Tertiary TCAs (more sedating):
  - **Amitriptyline tablets (G):** 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg.
  - **Imipramine tablets and capsules (G):** 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg.
- Secondary TCAs (less sedating):
  - **Desipramine tablets (Norpramin, [G]):** 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg.
  - **Nortriptyline capsules (Pamelor, [G]):** 10 mg, 25 mg, 50 mg, 75 mg, 10 mg/5 mL oral solution.

Dosage Guidance:
- Amitriptyline or imipramine: Start 25–50 mg QHS and ↑ by 25–50 mg/day intervals every two to three days to target dose 150–200 mg/day; max 300 mg/day.
- Desipramine: Start 25–50 mg QHS and ↑ by 25–50 mg/day intervals every two to three days to target dose 150–200 mg/day; max 300 mg/day.
- Nortriptyline: Start 25–50 mg QHS and ↑ by 25–50 mg/day intervals every two to three days to target dose 50–150 mg/day; max 150 mg/day.
  - Once you reach a dose of 100 mg/day, check nortriptyline serum level to maintain optimal therapeutic range of 50–150 ng/mL (check trough level and wait for steady state after a given dose, about five days).

Monitoring: ECG if history of cardiac disease. Nortriptyline level as described above.

Cost: $

Side Effects:
- Most common: Sedation, dry mouth, constipation, weight gain, sexual side effects, urinary hesitation, blurred vision.
- Serious but rare: Seizure; cardiac effects including orthostasis, arrhythmias, QT prolongation, AV block.
- Pregnancy/breastfeeding: Considered relatively safe.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Serotonin and norepinephrine reuptake inhibitors.
- Metabolized primarily through liver (limited data, though likely through oxidative CYP2D6 primarily); t ½: 18–44 hours.
- Avoid use with other serotonergic antidepressants or agents with hypotensive or anticholinergic effects.

Clinical Pearls:
- Using divided doses (BID to TID) may help with tolerability during initiation and titration; but can convert to QHS dosing to minimize daytime sedation.
- Tertiary amines amitriptyline and imipramine are metabolized to secondary amines nortriptyline and desipramine, respectively. Secondary amines are generally better tolerated.
- Value of serum level monitoring most clearly established for nortriptyline; utility of monitoring for other TCAs is controversial.
- Overdose toxicity with potentially serious cardiac effects or fatality with as little as 10-day supply.

Fun Fact:
Imipramine was the first antidepressant approved in the US, developed by tweaking the molecular structure of the antipsychotic Thorazine. It didn't work for psychosis, but it was the first "wonder drug" for depression and anxiety.