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Beyond depression: Other uses for tricyclic antidepressants

ABSTRACT

Tricyclic antidepressants (TCAs) were originally designed and marketed for treating depression, but over time they have been applied to a variety of conditions, mostly off-label. TCAs can serve as first-line or augmenting drugs for neuropathic pain, headache, migraine, gastrointestinal syndromes, fibromyalgia, pelvic pain, insomnia, and psychiatric conditions other than depression. This article reviews pharmacology, dosing, and safety considerations for these uses.

KEY POINTS

Amitriptyline is the most useful TCA for many painful conditions.

TCAs can be especially helpful for patients with a pain syndrome or insomnia with comorbid depression, although their benefits appear to be independent of antidepressant effects.

TCAs have long half-lives and so can be taken once a day.

Effective dosages for symptom control in many conditions are lower than for severe depression; dosage should start low and be gradually increased while monitoring efficacy and adverse effects.

TCAs should not be used concurrently with a monoamine oxidase inhibitor and by certain patient groups: the elderly, pregnant women, and patients with certain cardiac conduction abnormalities, epilepsy, or risk of suicide.

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Most tricyclic antidepressants (TCAs) have US Food and Drug Administration approval for treatment of depression and anxiety disorders, but they are also a viable off-label option that should be considered by clinicians in specialties beyond psychiatry, especially for treating pain syndromes. Given the ongoing epidemic of opioid use disorder, increasing attention has been drawn to alternative strategies for chronic pain management, renewing an interest in the use of TCAs.

This review summarizes the pharmacologic properties of TCAs, their potential indications in conditions other than depression, and safety considerations.

BRIEF HISTORY OF TRICYCLICS

TCAs were originally designed in the 1950s and marketed later for treating depression. Due to their adverse effects and lethality in overdose quantities, over time they have been largely replaced by selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) in depression management. However, TCAs have been applied to conditions other than depression with varying degrees of efficacy and safety.

TCA PHARMACOLOGY

Named for their chemical structure, TCAs contain 3 rings with 1 side chain. They are grouped into tertiary and secondary amine subtypes (**Table 1**).[1]

TCAs are absorbed in the small intestine and undergo first-pass metabolism in the liver. They bind extensively to proteins, leading to interactions with other protein-bound drugs. They are widely distributed throughout the

TABLE 1

Dosing and adverse effects of commonly prescribed tricyclic antidepressants

	Reuptake mechanism[b]	Adverse effects[a]					Initial/maximum dosing (for MDD)
		Sedation	Hypotension	Seizures	Weight gain	Cardiac	
Tertiary amine tricyclic antidepressants (TCAs)							
Amitriptyline	5-HT > NE	+++	+++	++	++	+++	25–75 mg/ 200 mg daily
Clomipramine	5-HT > NE	++	++	+++	+	++	25 mg/ 250 mg daily
Doxepin	5-HT = NE	++++	+	++	++	+	50–75 mg/ 300 mg nightly
Imipramine	5-HT = NE	++	+++	++	++	+++	50–100 mg/ 200 mg daily
Secondary amine TCAs							
Despiramine	NE > 5-HT	+	+	+	+	++	100–200 mg/ 300 mg daily
Maprotiline	NE > 5-HT	++	+	+	++	+	25–50 mg/ 225 mg nightly
Nortriptyline	NE > 5-HT	+	+	+	+	++	25–50 mg/ 150 mg daily

[a] Plus sign indicates potential severity of adverse effects.

[b] Tertiary amine TCAs tend to preferentially inhibit serotonin reuptake, resulting in greater synaptic serotonin levels, whereas secondary amine TCAs tend to preferentially inhibit norepinephrine reuptake, resulting in greater synaptic norepinephrine levels.

MDD = major depressive disorder; NE = norepinephrine; 5-HT = serotonin

systemic circulation because they are highly lipophilic, resulting in systemic effects including central nervous system manifestations.

Peak plasma concentration is at about 2 to 6 hours, and elimination half-life is around 24 hours for most agents, providing a long duration of action. Clearance depends on cytochrome P450 oxidative enzymes.[1]

MECHANISMS OF ACTION

TCAs inhibit reuptake of norepinephrine and serotonin, resulting in accumulation of these neurotransmitters in the presynaptic cleft. They also block postsynaptic histamine, alpha-adrenergic, and muscarinic-acetylcholine receptors, causing a variety of adverse effects, including dry mouth, confusion, cognitive impairment, hypotension, orthostasis, blurred vision, urinary retention, drowsiness, and sedation.[1]

Research suggests that TCAs relieve pain centrally through a descending pathway that inhibits transmission of pain signals in the spinal cord, as well as peripherally through complex anti-neuroimmune actions.[2] Norepinephrine appears to play a more important role in this process than serotonin, although both are deemed necessary for the "dual action" often cited in pain management,[1] which is also the rationale for widespread use of SNRIs to control pain.

Table 1 compares neurotransmitter reuptake mechanisms, adverse effect profiles, and typical dosages for depression for commonly prescribed TCAs.

POTENTIAL USES

Headache and migraine

TCAs have been shown to be effective for managing and preventing chronic headache syndromes.[3,4] Amitriptyline has been the most studied of the TCAs for both chronic daily and episodic migraine headache, showing the most efficacy among diverse drug classes (angiotensin II receptor blockers, anticonvulsants, beta-blockers, SSRIs) compared with placebo. However, in head-to-head trials, amitriptyline was no more effective than SSRIs, venlafaxine, topiramate, or propranolol.[4] Jackson et al[4] suggested that prophylactic medication choices should be tailored to patient characteristics and expected adverse effects, and specifically recommended that TCAs—particularly amitriptyline—be reserved for patients who have both migraine and depression.

Neuropathic pain

Neuropathic pain is defined as pain secondary to a lesion or disease of the somatosensory nervous system[5] and is the pathomechanistic component of a number of conditions, including postherpetic neuralgia,[6] diabetic and nondiabetic painful polyneuropathy,[7] posttraumatic or postsurgical neuropathic pain[8] (including plexus avulsion and complex regional pain syndrome[9]), central poststroke pain,[10] spinal cord injury pain,[11] and multiple sclerosis-associated pain.[12]

As a group, TCAs appear to have a role as first-line agents for managing these varied neuropathic pain syndromes. In a recent meta-analysis,[13] 16 (89%) of 18 placebo-controlled trials of TCAs (mainly amitriptyline at 25–150 mg/day) for these pain conditions were positive, with a combined number needed to treat of 3.6, suggesting a role for TCAs in these conditions. Of note, the TCAs desipramine[14] and nortriptyline[15] have demonstrated little evidence of efficacy in neuropathic pain syndromes.

Chronic low back pain

Chronic low back pain is a leading cause of loss of work, excessive healthcare expenditure, and disability in the United States. It can be due to numerous spinal conditions, including degenerative disk disease, spinal stenosis, lumbar spondylosis, and spinal arthropathy.

TCAs have been used to treat chronic low back pain for decades and have been repeatedly shown to be more effective than placebo in reducing pain severity.[16,17] A double-blind controlled trial[18] from 1999 compared the effects of the TCA maprotiline (up to 150 mg daily), the SSRI paroxetine (up to 30 mg daily), and placebo and found a statistically significant reduction in back pain with maprotiline compared with paroxetine and placebo. However, a 2008 meta-analysis suggested little evidence that TCAs were superior to placebo.[19]

Evidence of TCA efficacy for back pain was reported in 2018 with a well-designed 6-month double-blind randomized controlled trial[20] comparing low-dose amitriptyline (25 mg) with an active comparator (benztropine 1 mg). The authors reported that amitriptyline was effective in reducing pain and pain-related disability without incurring serious adverse effects. They suggested continued use of TCAs for chronic low back pain if complicated with pain-related disability, insomnia, depression, or other comorbidity, although they called for further large-scale studies. They also cautioned that patients started the trial with symptoms similar to the adverse effects of TCAs themselves; this has implications for monitoring of symptoms as well as TCA adverse effects while using these drugs.

Increasing attention has been drawn to alternative strategies for chronic pain management

Fibromyalgia and chronic widespread pain

Fibromyalgia is a common, frustrating, noninflammatory pain syndrome characterized by diffuse hyperalgesia and multiple comorbidities.[21] Although sleep hygiene, exercise, cognitive-behavioral therapy, some gabapentinoids (pregabalin), and a combination of these therapies have demonstrated efficacy, TCAs also offer robust benefits.

A meta-analysis of 9 placebo-controlled TCA trials showed large effect sizes for pain reduction, fatigue reduction, improved sleep quality, and reduced stiffness and tenderness, with the most significant of these improvements being for sleep.[22] A separate meta-analysis calculated that the number needed to treat with amitriptyline for a positive outcome is 4.9.[23] Recent systematic reviews have supported these findings, listing TCAs as second-line agents after pregabalin, duloxetine, and milnacipran.[24]

Of note, TCA monotherapy rarely produces a complete response in patients with moderate to severe fibromyalgia, chronic widespread pain, or significant comorbidities (depression, anxiety). Supplementation with cognitive-behavioral therapy, physical therapy, functional restoration, and other modalities is strongly recommended.

Abdominal and gastrointestinal pain

TCAs have been applied to a number of gastrointestinal syndromes with or without pain. Patients with irritable bowel syndrome have long been known to benefit from TCAs; the number needed to treat for symptomatic benefit over placebo is 3.5.[25,26]

Although there is no substantial evidence that TCAs are useful in reducing active inflammation in inflammatory bowel disease, a study involving 81 patients found that residual noninflammatory gastrointestinal symptoms (such as diarrhea and pain) responded to TCAs, including nortriptyline and amitriptyline, with greater benefit for ulcerative colitis than for Crohn disease.[27]

TCAs have also shown prophylactic benefit in cyclic vomiting syndrome, with a clinical response in over 75% of patients in controlled cohort studies.[28]

The elimination half-life is around 24 hours for most TCAs, providing a long duration of action

The efficacy of TCAs in other abdominal or gastrointestinal syndromes is unclear or modest at best.[29] However, few alternative treatments exist for these conditions. Amitriptyline may help symptoms of functional dyspepsia,[30] but nortriptyline has proven ineffective in gastroparesis.[31] Nonetheless, some authors[29] suggest considering TCAs on an individualized basis, with proper monitoring, in many if not most functional gastrointestinal disorders, especially when paired with behavioral therapies.

Pelvic and urogynecologic symptoms

Chronic pelvic pain affects up to 24% of women[32] and 5% to 10% of men.[33] TCAs have shown efficacy in treating chronic pelvic pain with or without comorbid depression.[34] Amitriptyline and to a lesser extent nortriptyline are the TCAs most often prescribed. Pain relief appears to be independent of antidepressant effects and may be achieved at low doses; initial dosing ranges from 10 to 25 mg at bedtime, which may be increased to 100 mg as tolerated.[34]

Based on a randomized, double-blind trial,[35] amitriptyline was recommended as a treatment option for interstitial cystitis or bladder pain, with the greatest symptom improvement in patients tolerating a daily dose of 50 mg.

Another study[36] randomized 56 women with chronic pelvic pain to amitriptyline or gabapentin, or a combination of the drugs for 24 months. Although each regimen resulted in significant reduction in pain, fewer adverse effects occurred with gabapentin than amitriptyline. Poor compliance and early discontinuation of amitriptyline were common due to anticholinergic effects.

In small uncontrolled studies,[37] about half of women with chronic pelvic pain became pain-free after 8 weeks of treatment with nortriptyline and imipramine.

Randomized controlled studies are needed to confirm potential benefits of TCAs in chronic urologic and pelvic pain.

Insomnia

Insomnia affects 23% to 56% of people in the United States, Europe, and Asia[38] and is the reason for more than 5.5 million primary care visits annually.[39] TCAs (especially doxepin, maprotiline, and amitriptyline[40]) have been shown to be an effective treatment, with an 82% increase in somnolence compared with placebo, as well as measurably improved total sleep time, enhanced sleep efficiency, reduced latency to persistent sleep, and decreased wake times after sleep onset.[38]

Dosing should be kept at a minimum to minimize harsh anticholinergic effects and avoid daytime sedation. Patients should be advised to take new doses or dose escalations earlier in the night to ensure less hangover sedation the next morning.

For patients with insomnia and comorbid depression, the American Academy of Sleep Medicine suggests the addition of a low dose (eg, 10–25 mg) of a TCA at nighttime to complement preexisting, full-dose, non-TCA antidepressants, while monitoring for serotonin syndrome and other potential but exceedingly rare drug-drug interactions.[41]

Psychiatric indications other than depression

Beyond the known benefits in major depressive disorder, TCAs have been shown to be

TABLE 2

Dosing guide for tricyclic antidepressants in conditions other than depression

Indication	Medications	Initial/ maximum dosing	Dose escalation	Adverse effect management
Headache or migraine	Amitriptyline	10–25 mg/ 100 mg nightly	Individualized: Increase by 10–25 mg every 5–14 days, assess for tolerability and adverse effects Amitriptyline side effects (dry mouth, orthostasis) often limit dose escalation above 100 mg; nortriptyline or maprotiline may be considered (better tolerated at higher doses)	Dry mouth and secretions: Pilocarpine 5 mg 2–3/day Constipation: Stool softeners, eg, docusate sodium, senna glycoside Weight gain: Consider augmenting with metformin 500–1,000 mg/day or topiramate 50–100 mg/day Seizures, QT interval prolongation, active suicidal risk, orthostasis, or falls: Discontinue the agent
Neuropathic pain	Amitriptyline	25–50 mg/ 150 mg nightly (or divided into twice-daily doses if frequent pain or symptom flares)		
Chronic low back pain	Amitriptyline, maprotiline	25–50 mg/ 150 mg nightly		
Fibromyalgia or chronic widespread pain	Amitriptyline, nortriptyline, maprotiline	25–50 mg/ 150 mg nightly (or divided into twice-daily doses if frequent pain or symptom flares)		
Irritable bowel syndrome	Amitriptyline, nortriptyline	10–25 mg/ 100 mg nightly		
Cyclic vomiting syndrome	Amitriptyline, nortriptyline	25–50 mg/ 100 mg nightly		
Chronic pelvic pain, interstitial cystitis, nocturia	Amitriptyline, nortriptyline, imipramine	10–25 mg/ 100 mg nightly		
Insomnia	Amitriptyline, maprotiline, doxepin	25–50 mg/ 150 mg nightly		

effective for obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, bulimia nervosa, and childhood enuresis.[42] Given the shortage of mental health clinicians and the high prevalence of these conditions, nonpsychiatrist physicians should be familiar with the therapeutic potential of TCAs for these indications.

ADVERSE EFFECTS

Adverse effects vary among TCAs. Common ones include blurred vision, dry mouth, constipation, urinary retention, hypotension, tachycardia, tremor, weight gain, and sexual dysfunction.[43] Tertiary amines are generally more sedating than secondary amines and cause more anticholinergic effects (**Table 1**).

Tolerance to some effects may develop over time. If adverse effects prove to be a problem, therapy may need to be stopped or doses adjusted. Alternatively, adjunctive medications to address adverse effects may be considered (eg, pilocarpine for dry mucous membranes, tamsulosin for urinary retention) (**Table 2**).

Despite widespread perceptions that TCAs are less tolerable than newer antidepressants, studies repeatedly suggest that they have an adverse-effect burden similar to that of SSRIs and SNRIs, although SSRIs have a greater tendency to produce nausea, whereas TCAs are more likely to cause constipation.[44]

Discontinuation syndrome

Abrupt discontinuation or unintentionally missed doses of TCAs have been associated

with a discontinuation syndrome in about 40% of users.[45] Patients should be warned about this possibility and the syndrome's potential effects: dizziness, insomnia, headaches, nausea, vomiting, flulike achiness, and restlessness. Rebound depression, anxiety, panic, or other psychiatric symptoms may also occur. Symptoms generally present within 2 to 5 days after dose discontinuation and last 7 to 14 days.[45]

However, all TCAs have a long half-life, allowing for sufficient coverage with once-daily dosing and thus carry a lower risk of discontinuation syndrome than many other antidepressants (78% with venlafaxine; 55% with paroxetine).[45]

To discontinue therapy safely, the dosage should be reduced gradually. As is pharmacologically expected, the greatest likelihood of discontinuation syndrome is associated with longer duration of continuous treatment.

CONTRAINDICATIONS

Cardiac conduction abnormalities

TCAs should not be prescribed to patients who have right bundle branch block, a severe electrolyte disturbance, or other cardiac conduction deficit or arrhythmia that can prolong the QTc interval and elevate the risk of lethal arrhythmia.[46,47] Cardiac effects from TCAs are largely dose-dependent. Nevertheless, a baseline electrocardiogram can be obtained to assess cardiac risk, and dose escalation can proceed if results are normal (eg, appropriate conduction intervals, QTc ≤ 450 ms).

TCAs may have a role as first-line agents for neuropathic pain syndromes

Advanced age

For elderly patients, TCAs should be prescribed with caution and sometimes not at all,[48] because anticholinergic effects may worsen preexisting urinary retention (including benign prostatic hyperplasia), narrow-angle glaucoma, imbalance and gait issues, and cognitive impairment and dementia. Dehydration and orthostatic hypotension are contraindications for TCAs, as they may precipitate falls or hypotensive shock.

Epilepsy

TCAs should also be used with caution in patients with epilepsy, as they lower the seizure threshold.

Concomitant monoamine oxidase inhibitor treatment

Giving TCAs together with monoamine oxidase inhibitor antidepressants should be avoided, given the risk of hypertensive crisis.

Suicide risk

TCAs are dangerous and potentially lethal in overdose and so should not be prescribed to suicidal or otherwise impulsive patients.

Pregnancy

TCAs are in pregnancy risk category C (animal studies show adverse effects on fetus; no adequate or well-controlled studies in humans; potential benefits may warrant use despite risks). Using TCAs during pregnancy has very rarely led to neonatal withdrawal such as irritability, jitteriness, and convulsions, as well as fetal QTc interval prolongation.[49]

The American College of Obstetricians and Gynecologists recommends that therapy for depression during pregnancy be individualized, incorporating the expertise of the patient's mental health clinician, obstetrician, primary healthcare provider, and pediatrician. In general, they recommend that TCAs should be avoided if possible and that alternatives such as SSRIs or SNRIs should be considered.[50]

TCAs are excreted in breast milk, but they have not been detected in the serum of nursing infants, and no adverse events have been reported.

OVERDOSE IS HIGHLY DANGEROUS

Severe morbidity and death are associated with TCA overdose, characterized by convulsions, cardiac arrest, and coma (the "3 Cs"). These dangers occur at much higher rates with TCAs than with other antidepressants.[43] Signs and symptoms of toxicity develop rapidly, usually within the first hour of overdose. Manifestations of overdose include prolonged QTc, cardiac arrhythmias, tachycardia, hypertension, severe hypotension, agitation, seizures, central nervous system depression, hallucinations, seizures, and coma.

Overdose management includes activated charcoal, seizure control, cardioversion, hydration, electrolyte stabilization, and other intensive care.

OFF-LABEL TCA MANAGEMENT

Dosing recommendations for off-label use of TCAs vary based on the condition, the medication, and the suggestions of individual authors and researchers. In general, dosing ranges for pain and other nondepression indications may be lower than for severe depression (**Table 2**).[1]

As with any pharmacologic titration, monitoring for rate-limiting adverse effects is recommended. We suggest caution, tailoring the approach to the patient, and routinely assessing for adverse effects and other safety considerations.

In addition, we strongly recommend supplementing TCA therapy with nonpharmacologic strategies such as lifestyle changes, dietary modifications, exercise, physical therapy, and mental health optimization.

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