Tricyclics

Still solid performers

Tricyclics played an important therapeutic role in the past and are still valuable treatments for depression, anxiety, pain syndromes, and other disorders. It's time to re-examine TCAs and prescribe them when appropriate.

Current PSYCHIATRY

for the savvy psychiatrist

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Recent practice guidelines generally do not position tricyclic antidepressants (TCAs) as first-line therapies because of concerns about side effects and safety issues.[1-3] Yet these agents have important clinical uses—both for approved and off-label indications—and diverse pharmacologic properties that distinguish them from each other as well as from many of the "newer antidepressants."

Eleven TCAs are available in the United States (*Table 1*). Here's what the evidence says about when and how to use them to treat a variety of psychiatric disorders, along with our recommendations on how to reduce the risk of side effects.

Indications and off-label uses

TCAs' pharmacologic properties make them very versatile (*Box 1*).[4] Major depression and anxiety disorders (such as obsessive compulsive disorder [OCD]) are the principal FDA-approved indications for TCAs. Other approved indications are anxiety (doxepin) and childhood enuresis (imipramine). Common off-label uses supported by scientific literature include panic disorder, social phobia, insomnia, posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), attention-deficit/hyperactivity disorder (ADHD), migraine headache, chronic pain syndromes, premature ejaculation, substance abuse disorders, and eating disorders, to name a few.

Major depression To treat major depressive disorder, the American Psychiatric Association recommends selective serotonin reuptake inhibitors (SSRIs), bupropion, venlafaxine, and the secondary amine TCAs desipramine and nortriptyline as "optimal" first-line therapy for most patients.[1] The Texas Medication Algorithm Project recommends SSRIs, bupropion, nefazodone, venlafaxine, or mirtazapine as first-

Table 1
THERAPEUTIC DOSAGE RANGE

Generic name	Brand names	Therapeutic dosage range (mg/d)
Amitriptyline	Elavil, Endep	150-300
Amoxapine	Asendin	150-450
Clomipramine	Anafranil	100-250
Desipramine	Norpramin, Pertofane	150-300
Doxepin	Sinequan Adapin	150-300
Imipramine	Tofranil, Tofranil PM Janimine, Sk-Pramine	150-300
Maprotiline	Ludiomil	150-200
Nortriptyline	Pamelor Aventyl	50-150
Protriptyline	Vivactil	15-60
Trimipramine	Surmontil	150-300
Trazodone	Desyrel	50-600

* Dosage ranges are approximate. Dosage needs to be tailored by individual patient needs. The elderly, children, and the medically compromised may require lower dosages.

Box 1

DUAL REUPTAKE INHIBITION OF TCAs

The tricyclic antidepresants are a broad class of drugs that can be divided, based on the number of rings in their nucleus, into tricyclics and tetracyclics. The tricyclics can be further classified into tertiary and secondary amines, based on the number of methyl groups on the side chain. In addition, some clinicians include trazodone—an antidepressant chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents—in the broad class of TCAs.

TCAs were initially hypothesized to block the reuptake of norepinephrine (NE) or serotonin (5HT), thereby increasing the levels of these neurotransmitters at the postsynaptic receptor. More recent theories include effects on pre- and postsynaptic receptors and other neurotransmitters, such as histamine and acetylcholine, which explain the various side effects of TCAs.

The relative norepinephrine-reuptake-blocking effects versus serotonin-reuptake-blocking effects of the TCAs and each drug's biochemical effects are summarized in Table 2. Except for clomipramine, TCAs are relatively weak 5HT reuptake blockers.

line therapy and lists TCAs as second- or third-line therapy for patients with partial or no response to initial therapy.[2]

Although recommended as first-line therapies, SSRIs and other newer antidepressants exhibit no greater efficacy than TCAs in treating major depression.[5,6] Three major meta-analyses[7-9] reported no significant difference in efficacy between the two antidepressant classes. In the largest,[9] published by the U.S. Department of Health and Human Services, 50% of inpatients and 52% of outpatients responded to TCAs, whereas 54% of inpatients and 47% of outpatients responded to SSRIs. Compared with SSRIs, TCAs also may be associated with higher rates of remission.[7,8]

Clomipramine—approved for OCD—has been used for decades to treat depression and resistant depression. Two meta-analyses by the Danish University Antidepressant Group[7,8] showed that clomipramine produced a "significantly better therapeutic effect" compared with citalopram and paroxetine. In three major studies,[5,7,8] TCAs showed greater effectiveness than SSRIs in treating melancholic depression.

The anticholinergic side effects of TCAs have been perceived to cause higher patient dropout and discontinuation rates, but studies have shown mixed results. In one meta-analysis comparing SSRIs and TCAs, the difference in dropout rates due to adverse effects was less significant than previously reported. When total dropout rates for any reason were examined, the difference was less than was originally expected.[10]

OCD In clinical practice, most patients with OCD are started on an SSRI. Clomipramine is another valuable option, however, especially for patients who fail one or more therapeutic trials with SSRIs. Clomipramine may produce significant therapeutic benefit in patients with OCD, possibly because of its potent 5-HT reuptake properties. In one study, patients with OCD symptoms who received clomipramine improved more than those receiving SSRIs when each class was compared with placebo.[11]

Panic disorder Although not approved for panic disorder, imipramine and desipramine provide effective treatment, even in nondepressed patients.[12] Doses and plasma levels are the same as those used for treating depression. Start low (e.g., imipramine, 10 to 20 mg/d; desipramine, 10 to 25 mg/d) and increase gradually over several weeks to typical therapeutic dosages (*Table 1*). Do not escalate too rapidly, as this may increase anxiety or precipitate a panic attack.

Uses in children TCAs have been used to treat children with ADHD, OCD, enuresis, and depression. The American Academy of Child and Adolescent Psychiatry (AACAP) does not recommend TCAs as first-line treatment for youths requiring pharmacotherapy for depressive disorders but acknowledges that some youths with depression may respond better to TCAs than to other medications.[3]

> Imipramine and desipramine provide effective treatment of panic disorder, even in nondepressed patients

Imipramine is the only TCA indicated for nocturnal enuresis, but its exact mechanism of action is not known. The benefit may be secondary to imipramine's anticholinergic effect or to changes in sleep architecture. Recommended bedtime doses for children with enuresis are:

- 25 to 50 mg under age 12;
- up to 75 mg age 12 and older.

TCAs are an option for children with ADHD, especially if ADHD is present with comorbid depression or anxiety

disorder. However, because at least four cases of sudden cardiac death have been reported in children taking desipramine, it is prudent to monitor cardiac function when children are started on TCAs. AACAP guidelines recommend obtaining a baseline ECG, resting blood pressure, and pulse (supine or sitting, then standing), with regular monitoring of the child's weight during TCA therapy.

Combination therapy Few controlled studies have tested TCAs as combination therapy. Trazodone can be used as an adjunct to SSRIs and monoamine oxidase inhibitors (MAOIs) for patients with insomnia. TCAs are used as an adjunct to treat resistant depression and OCD[13,14] (e.g., clomipramine added to fluvoxamine to treat OCD).[15] Serum level monitoring is recommended when TCAs are used as adjuncts.

Other uses TCAs play a role in the prophylactic treatment of premature ejaculation and migraine headaches, probably because of their serotonergic (5HT2) effect. In patients with migraine and depression, a trial of a TCA such as amitriptyline may be warranted.

TCAs are widely used to manage neuropathic pain,[16] although the exact mechanism of action is unknown. Because depression is commonly associated with pain, the effect may result from the agents' action on depression, or TCAs may possess direct analgesic action.

Trazodone, 25 to 100 mg at bedtime, is widely used for insomnia, alone or as an adjunct with other classes of antidepressants—even in combination with MAOIs. Nortriptyline has been shown to be safe and effective for post-stroke and geriatric types of depression.[17]

TCAs are also used for a host of other medical, psychiatric, and neurologic problems, such as social phobia, PTSD, GAD, substance abuse disorders, and eating disorders.[18] Only a few controlled studies have tested TCAs for these indications.

Side effects

Although TCAs have shown efficacy in many clinical situations, their use is associated with potentially serious side effects, which may include anticholinergic effects, sedation, weight gain, CNS toxicity, orthostatic hypotension, cardiovascular toxicity, delirium, and risk of suicide by overdose. The risk of side effects can be reduced with careful prescribing practices (*Box 2*).

Anticholinergic effects, sedation TCAs vary in their anticholinergic activity (*Table 2*). Tertiary amine TCAs such as amitriptyline and protriptyline may cause dry mouth, constipation, urinary hesitancy, and blurred vision in some patients, and confusion in elderly or demented patients. Secondary amine TCAs such as nortriptyline or desipramine are less anticholinergic and less likely to cause these side effects.

Peripheral anticholinergic side effects can be managed with bethanacol—a cholinergic drug—in dosages of 25 to 50 mg tid or qid. Dry mouth can be treated with pilocarpine, 5 mg bid to qid, or oral bethanacol (5- to 10-mg tablets sublingually), artificial saliva drops, sugarless candy/gum, or mouthwash.

Sedation is a common side effect caused by the antihistaminic properties of some TCAs (*Table 2*). Agents with this

Box 2

TIPS FOR SAFER USE OF TCAs

- Obtain a baseline ECG for patients of all ages before starting TCA therapy.
- When dosing TCAs, start low and go slow to maximize efficacy and minimize side effects, especially in the elderly patient.
- In the elderly, avoid highly anticholinergic TCAs such as amitriptyline or protriptyline, which can cause delirium. Choose a TCA with low anticholinergic properties, such as desipramine or nortriptyline.
- For patients who are intolerant of the anticholinergic and sedative properties of amitriptyline or protriptyline, consider switching to desipramine or nortriptyline.
- If a patient develops a toxic effect mediated by either the cardiovascular or central nervous system, discontinue the TCA or reduce the dosage.
- In patients at risk for suicide by overdose, consider dispensing less than a 2-week supply. In case of overdose, cardiac monitoring for at least 24 hours may be indicated.

Table 2

BIOCHEMICAL EFFECTS OF TRICYCLICS AND OTHER ANTIDEPRESSANTS

	POTENCY				SIDE EFFECTS	
	NE reuptake blockade	5HT reuptake blockade	DA reuptake blockade	5HT blockade	Muscorinic blockade	Histamine blockade
TCAs						
Tertiary amines						
Amitriptyline	◆◆	◆◆	○	◆	◆◆◆	◆◆
Imipramine	◆◆◆	◆◆◆	○	○	◆◆	◆
Doxepin	◆◆	◆◆	○	◆	◆◆	◆◆◆
Clomipramine	◆◆*x*	◆◆◆	○	◆	◆	◆◆
Trimipramine	◆	◆	○	◆	◆◆	◆◆◆
Secondary amines						
Nortriptyline	◆◆	◆◆	○	◆	◆	◆
Desipramine	◆◆◆	◆	○	-	◆	◆
Protriptyline	◆◆◆	◆	○	◆	◆◆◆	◆
Tetracyclics						
Maprotiline	◆◆	◆	○	○	◆	◆◆
Amoxapine	◆◆	◆	○	◆◆◆	◆	◆
Other						
Trazodone	○	◆	○	◆◆	○	○
SSRIs						
Fluoxetine	○	◆◆◆	○	○	○	○
Sertraline	○	◆◆◆	◆	○	○	○
Paroxetine	◆	◆◆◆	○	○	◆	○
Fluvoxamine	○	◆◆◆	○	○	○	○
Citalopram	○	◆◆◆	○	○	○	○
Receptor modulators/reuptake inhibitors						
Nefazodone	◆/○	◆	○	◆◆◆	○	○
Mirtazapine	◆*	◆	○	◆◆◆	○	◆◆◆
Norepinephrine/dopamine modulators						
Bupropion	◆/○	○	◆/○	○	○	○
Serotonin/norepinephrine reuptake inhibitors						
Venlafaxine	◆◆*	◆◆◆	◆*	○	○	○

Strength effect on a scale from ○ (no effect) to ◆◆◆ (marked effect); ◆/○ (marginal effect)
NE: norepinephrine; 5HT: serotonin; DA: dopamine * Dose-dependent *x* Includes metabolite, desmethyl clomipramine

Table 3

APPROXIMATE THERAPEUTIC PLASMA LEVEL RANGES

TCA	Blood level (ng/ml)
Amitriptyline	100-250
Amoxapine	Unknown
Clomipramine	Unknown
Desipramine	Unknown
Doxepin	120-250
Imipramine	150-300
Maprotiline	150-250
Nortriptyline	50-150
Protriptyline	75-250
Trimipramine	Unknown
Trazodone	Unknown

+ Only nortriptyline has a clear therapeutic window. The others are either approximate or unknown.

effect (e.g., doxepin), when given once daily at bedtime, can benefit patients with concomitant sleep disturbance.

Weight gain Patients being treated with TCAs often gain weight, most likely because of carbohydrate craving associated with H2 blockade. Patient education, monitoring of weight, and dietary counseling may be necessary during TCA use. Regular exercise is recommended, although depressed patients often lack the motivation and energy to exercise.

Cardiovascular toxicity All TCAs have potential cardiovascular effects (*Table 3*), which are seen on an ECG as increased PR, QRS, or QTc intervals, especially at higher dosages or in patients with pre-existing cardiac disease.[19] Orthostatic hypotension is among the most common cardiovascular side effects, particularly in the elderly, and may result in falls or other injuries.

A baseline ECG is recommended before starting TCA therapy, especially in depressed patients with cardiac conduction delays (primary or secondary to concomitant medications). Routine ECGs should be used to monitor patients:

- with pre-existing cardiac disease;
- taking higher-than-recommended dosages of a TCA;
- taking other medications that may affect cardiac conduction.

When in doubt, obtaining a cardiology consultation is recommended.

CNS effects Signs of CNS toxicity include confusion, memory impairment, delirium, seizures, coma, and eventual respiratory depression.[20] Risk factors include toxic TCA plasma levels, elderly patient age, and concomitant use of other medications, such as psychotropics (neuroleptics), anticholinergics, and antihistamines. CNS toxicity may be difficult to diagnose, as it may initially resemble worsening of depressed mood. Confusion or worsening of memory or cognitive function are predictors of CNS toxicity.

A patient with anticholinergic-related delirium should be monitored on a medical unit. A trial of physostigmine may be warranted to confirm the diagnosis.

Neurologic symptoms Maprotiline and clomipramine have been associated with an increased risk of seizures. Use reduced dosages in patients with a history of seizures or concomitant use of medications that may increase maprotiline or clomipramine levels or decrease the seizure threshold (e.g., other antidepressants, withdrawal from benzodiazepines). Amoxapine has been associated with extrapyramidal symptoms secondary to a neuroleptic metabolite.

Overdose The severity of adverse side effects often depends upon drug concentration. An overdose of as little as a 2-week supply of a TCA can cause potentially fatal arrhythmias.

A baseline ECG is recommended before starting TCA therapy, especially in depressed patients with cardiac conduction delays

Priapism Trazodone has been associated with priapism, which has an incidence rate of 1/6,000 in patients taking this drug. Priapism is a medical emergency that requires prompt treatment.

Administration

TCAs are well-absorbed following oral administration and reach peak plasma levels in 2 to 6 hours. The average half-life of approximately 24 hours often allows therapeutic levels to be achieved with once-daily dosing at bedtime (*Table 3*).

TCAs are metabolized primarily by the cytochrome P-450 2D6 (CYP2D6) isoenzyme. Patients differ by a factor of 30- to 40-fold in their rate of metabolism of some TCAs, depending on individual genotypes.

The 7 to 9% of Caucasians classified as poor metabolizers at CYP2D6 require much lower-than-usual dosages of

secondary amine TCAs.[21] The 50% of Asians who are intermediate metabolizers require one-half the usual dosage. Tailor therapy to the individual patient, starting low, checking plasma levels, and monitoring for side effects.

For patients who would benefit from TCAs' H1 anxiolytic effects, start with bid or tid dosing and later switch to once daily after achieving efficacy.

When using TCAs, start low and go slow to maximize efficacy and minimize side effects, especially in the elderly patient. The goal is to treat the patient, not to achieve target serum levels. The most favorable results have been demonstrated when patients are maintained at the dosages to which they respond when their disorder is in the acute stage.[17]

Symptoms usually improve after 2 weeks of TCA therapy, and up to 6 weeks may be required for a clinically significant effect. For many depressed patients, symptoms of insomnia, anxiety, and poor appetite improve within the first few days.

Monitoring serum levels

Serum levels are useful for monitoring treatment, compliance, and toxicity.[22] Because the most accurate TCA serum levels are found at steady state, check the level after the patient has been on TCA therapy for at least 5 days and 8 to 12 hours after the last dose. Serum levels may also guide dosage increases in patients who exhibit a partial response to therapy.

Nortriptyline has a therapeutic window between 50 and 150 ng/mL. Patients who do not respond to serum levels higher than 150 ng/mL may respond when the dosage is reduced and the serum level falls to within that range. If response is adequate and without side effects, however, there is no need to reduce the dose. Other, less clear therapeutic windows have been described for other TCAs (*Table 3*).

TCA metabolism is affected by age and interaction with other drugs. Closely monitor serum levels in elderly and medically compromised patients, especially during dosage increases. Pay particular attention to other medications that may affect serum levels[23] (*Table 4*). SSRIs, particularly fluoxetine and paroxetine, may affect TCA plasma levels because of their potent inhibition of CYP2D6.

Individualize dosing and serum level monitoring. For example, the patient who is clinically tolerating a TCA and has a normal ECG does not require a serum level measurement, unless medically indicated.

Table 4

DRUGS THAT INTERACT WITH TCAs

- Anticholinergic agents
- Barbiturates
- Cimetidine
- Disulfiram
- ETOH
- Flecainide
- Guanethidine
- Haloperidol
- MAOIs
- Methylphenidate
- Phenothiazines
- Phenytoin
- Propafenone
- Quinidine
- SSRIs (e.g., fluoxetine, sertraline, paroxetine)
- Sympathomimetic drugs (e.g., norepinephrine, epinephrine)
- Warfarin

Discontinuing tricyclics

When discontinuing a TCA, taper the dosage no more rapidly than 25 to 50 mg every 2 to 3 days. Abrupt discontinuation can cause cholinergic rebound, with symptoms such as nausea, cramping, headache, vomiting, and sweating. "Rebound hypomania" or "mania" have been reported with abrupt cessation of TCAs,[24] especially in patients with bipolar disorder. If the etiology of rebound symptoms is unclear (i.e., medical versus psychiatric), re-administering the discontinued TCA should relieve the symptoms and confirm a diagnosis of discontinuation.

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Bottom Line

Tricyclic antidepressants remain an effective and valuable treatment for many patients with depression, OCD, and other psychiatric disorders. TCAs may have a broader therapeutic range, higher rates of remission, and possibly more rapid onset of efficacy than other antidepressant classes.

Related resources

- Schatzberg AF, Cole JO, DeBattista C. Antidepressants. *Manual of clinical psychopharmacology* (3rd ed). Washington, DC: American Psychiatric Press, 1997.
- Janicak PG, Davis JM, Preskorn SH, Ayd Jr. FJ. *Principles and practice of psychopharmacotherapy* (2nd ed). Baltimore: Lippincott Williams & Wilkins, 1997.
- *PDR Psychotropic Prescribing Guide* (2nd ed). Montvale, NJ: Medical Economics, 1999.
- National Library of Medicine, MedlinePlus Health Information: *Antidepressants, tricyclics* (http://www.nlm.nih.gov/medlineplus/druginfo/antidepressantstricyclicsystem202055.html)

DRUG BRAND NAMES

See table 1 for tricyclic drug brand names. Others mentioned in this article include:

Bupropion • Wellbutrin
Cimetidine • Tagamet
Citalopram • Celexa
Disulfiram • Antabuse
Fluoxetine • Prozac
Fluvoxamine • Luvox
Guanethidine • Ismelin
Methylphenidate • Concerta, Ritalin
Mirtazapine • Remeron
Nefazodone • Serzone
Paroxetine • Paxil
Phenytoin • Dilantin

DISCLOSURE

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