Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects

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INTRODUCTION

The use of tricyclic and tetracyclic antidepressants to treat depression began with reports in 1958 that imipramine was particularly effective for melancholic depression, marked by symptoms such as psychomotor retardation, anergia, dysphoria, hopelessness, and diurnal variation [1,2]. Many other cyclic antidepressants were subsequently developed, including the tricyclics amitriptyline, amoxapine, clomipramine, desipramine, doxepin, nortriptyline, protriptyline, and trimipramine, as well as the tetracyclic antidepressant maprotiline (not available in the United States). These cyclic compounds became first-line treatment for depression for the next 30 years, until the selective serotonin reuptake inhibitors were introduced.

Clinicians use tricyclic antidepressants to treat many other psychiatric disorders besides depression, including panic attacks, generalized anxiety disorder, post-traumatic stress disorder, bulimia nervosa, and smoking cessation. Tricyclics are used to treat a variety of chronic pain states such as chronic daily headache and neuropathy. See appropriate topic reviews.

This topic reviews the pharmacology, administration, and side effects of tricyclic and tetracyclic antidepressants. Switching and discontinuing antidepressants, the pharmacology, administration, and side effects of other antidepressant classes, choosing an antidepressant for

the initial treatment of depression and treatment of resistant depression, and management of tricyclic overdose are discussed separately.

- (See "Switching antidepressant medications in adults".)
- (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)
- (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)
- (See "Atypical antidepressants: Pharmacology, administration, and side effects".)
- (See "Serotonin modulators: Pharmacology, administration, and side effects".)
- (See "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)
- (See "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Tricyclic antidepressant poisoning".)

STRUCTURE OF CYCLIC ANTIDEPRESSANTS

The tricyclic antidepressants are named after their chemical structure, which consists of a three-ring central structure plus a side chain [3]. The tetracyclic maprotiline has a four-ring central structure plus a side chain. However, it is the nature of the side chain that is more important for their function and activity.

Tricyclics are subdivided into two categories [3]:

- Tertiary amines have two methyl groups at the end of the side chain. The five tertiary amines available in the US are amitriptyline, clomipramine, doxepin, imipramine, and trimipramine. They are generally more potent in blocking reuptake of serotonin compared with norepinephrine.

- Secondary amines have one methyl group at the end of the side chain. The three secondary amines are desipramine, nortriptyline, and protriptyline. Desipramine is the active (demethylated) metabolite of imipramine, and nortriptyline is the active (demethylated) metabolite of amitriptyline. Secondary amines are more potent in blocking reuptake of norepinephrine.

The tetracyclic maprotiline (also referred to as a heterocyclic) has a side chain identical to that of the secondary amines. Thus, it is more potent in blocking reuptake of norepinephrine.

Amoxapine has a three-ring central structure and a side chain that differs from the other tricyclics. It is a potent norepinephrine reuptake inhibitor and also blocks postsynaptic dopamine receptors. Thus, it is the only antidepressant that has antipsychotic effects.

Clinicians often avoid using tricyclics because of their adverse side effects, and tertiary amines generally cause more side effects compared with secondary amines. In particular, tertiary tricyclics cause more anticholinergic side effects (eg, constipation or blurred vision) and are also highly sedating because of their central affects on histamine. (See 'Side effects' below.)

PHARMACOKINETICS

The absorption, distribution, metabolism, and elimination of tricyclics are well-described [4-7].

Tricyclics are absorbed in the small intestine rapidly and nearly completely. The medication then enters the portal circulation and undergoes first-pass metabolism in the liver; for most tricyclics, approximately 50 percent of the drug is metabolized in this manner. The medication then enters the systemic circulation and binds to proteins, which for most tricyclics exceeds 90 percent. It is only the free fraction that is active. Tricyclics are widely distributed throughout the body, including the brain, because they are lipophilic.

Metabolism and elimination occurs largely in the liver. The hepatic CYP isoenzymes that metabolize the tricyclics include 2D6, 1A2, 3A4, 1C19, which demethylate the side chain of tertiary amines to secondary amines and hydroxylate the central ring structure. Many of the metabolites have antidepressant activity. As an example, the demethylated metabolite of amitriptyline is nortriptyline, and the demethylated metabolite of imipramine is desipramine.

The elimination half-life for the tricyclics and related drugs averages about 24 hours. The exception is amoxapine, which averages about eight hours.

PHARMACODYNAMICS

Each tricyclic and tetracyclic antidepressant inhibits reuptake of both serotonin and norepinephrine, which increases the amount of neurotransmitter in the synaptic cleft. These effects are thought to mediate the therapeutic benefit of cyclic antidepressants.

PRESCRIBING CYCLIC ANTIDEPRESSANTS

General principles — There are several basic points to review with patients prior to prescribing these medications [8]. Clinicians should describe potential common side effects, the need to take the medication as prescribed rather than on an as-needed basis, and to expect that response or remission may not occur until four or more weeks have elapsed after a therapeutic dose has been achieved.

The most commonly prescribed tricyclics in the United States are amitriptyline, imipramine, desipramine, and nortriptyline. Clomipramine is commonly used in Europe. The choice of cyclic antidepressant is often based upon side-effect profiles because these medications vary in their degree of side effects. Nortriptyline and desipramine tend to be the best tolerated.

Intramuscular forms of amitriptyline, imipramine, and clomipramine are available only outside of the United States, as is intravenous clomipramine. These parenteral formulations can be used for patients unable or unwilling to take oral medication, and can thus serve as an alternative to electroconvulsive therapy [8].

There are many other tricyclic antidepressants available outside of the United States in Europe and elsewhere. These include amitriptylinoxide, butriptyline, demexiptiline, dibenzepin, dimetacrine, dosulepin (formerly called dothiepin), imipraminoxide, iprindole, lofepramine, melitracen, metapramine, nitroxazepine, noxiptiline, pipofezine, propizepine, and quinupramine.

Dose — We suggest starting with a low dose in order to avoid side effects, and slowly increasing the dose. The initial and target doses of tricyclic antidepressants (table 1) can vary, depending upon factors such as body mass index, how rapidly the drug is metabolized, and tolerability of side effects (table 2). In addition to finding the right dose, which usually involves trial and error [8], it is important to prescribe antidepressants for a sufficient duration (eg, 6 to 12 weeks) before determining whether the medications have sufficiently relieved symptoms.

For depressed patients, lower doses of tricyclics can be effective. A meta-analysis of 14 randomized trials compared low doses (100 mg per day or less of amitriptyline, clomipramine, desipramine, doxepin, imipramine, or trimipramine; most studies involved amitriptyline or imipramine) with placebo in 807 patients for six to eight weeks [9]. Response (reduction of baseline symptoms ≥50 percent) occurred more often with low dose tricyclics than placebo (relative risk 1.5, 96% CI 1.1-1.9), but discontinuation of treatment due to side effects occurred more often with low dose tricyclics; heterogeneity across studies was significant.

However, depressed patients who do not respond to low doses of tricyclics may benefit from higher (standard) doses [10]. Higher doses may serve to optimize serum concentrations. (See

'Plasma levels and therapeutic response' below.)

Patients who recover from an acute episode of major depression generally receive maintenance treatment with the dose that successfully resolved the episode, rather than a lower dose. (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Dose'.)

Specific doses for each tricyclic and tetracyclic drug are described below. (See 'Amitriptyline' below and 'Amoxapine' below and 'Clomipramine' below and 'Desipramine' below and 'Doxepin' below and 'Imipramine' below and 'Maprotiline' below and 'Nortriptyline' below and 'Protriptyline' below and 'Trimipramine' below.)

Administration — The entire dose of a cyclic antidepressant is generally taken once a day because the elimination half-life averages about 24 hours [3]. Administration is usually at bedtime because these drugs are sedating. Patients who cannot tolerate a relatively large single dose of a tricyclic can be given doses divided evenly two or even three times per day, or given smaller daytime doses and a larger bedtime dose.

Plasma levels and therapeutic response — A relationship between plasma levels and response has been demonstrated for some tricyclic antidepressants given to patients with unipolar major depression [3]:

- Clomipramine (combined clomipramine plus metabolite norclomipramine) – >150 ng/mL
- Desipramine – >125 ng/mL
- Imipramine (combined imipramine plus metabolite desipramine) – >200 ng/mL
- Nortriptyline – 50 to 150 ng/mL

Serum levels are used to help establish the proper dose, especially in rapid or slow metabolizers [8]. Rapid metabolizers may present with lack of therapeutic response at typically high therapeutic doses, and slow metabolizers may present with intolerance at typically low therapeutic doses. Levels can also help assess adherence.

Response is less likely to occur at serum concentrations below the lower limit of the reference range, and tolerability decreases at concentrations above the upper limit [11]. In addition, serum concentrations above the upper limit are unlikely to further enhance therapeutic response.

Plasma levels should be drawn after the drug has achieved steady state, which is at least five days after a dose change, probably longer in older adults. The level should be drawn

approximately 12 hours after the last dose.

Serum levels may guide treatment for less severely ill outpatients with major depression, but there is no clear evidence that the same relationship exists between plasma levels and response in these patients.

Discontinuing tricyclics — Clinicians should taper tricyclics before stopping the drugs. Discontinuation of cyclic antidepressants is discussed separately. (See "Discontinuing antidepressant medications in adults", section on 'Tricyclics'.)

Specific cyclic drugs

Amitriptyline — We suggest an initial dose of 25 mg at bedtime, although starting doses as high as 100 mg may be used in closely supervised hospitalized patients. Patients sensitive to side effects and older adults can be started at a dose of 10 mg at bedtime.

The dose is generally increased by increments of 25 or 50 mg per day every few days or longer (eg, at intervals ≥1 week), although smaller increments of 10 mg per day may be necessary. Therapeutic doses are generally in the range of 100 to 300 mg per day, but some patients find it difficult to reach these doses due to sedation and other side effects.

The data that describe the relationship between serum concentrations of amitriptyline and response in depressive disorders are limited or conflicting [3].

Amitriptyline blocks reuptake of both serotonin and norepinephrine, but more potently blocks reuptake of serotonin. It also has a high affinity for histamine H1 and muscarinic M1 receptors; compared with other cyclic antidepressants, amitriptyline is highly sedating, associated with weight gain, and anticholinergic side effects (table 2).

Amitriptyline is demethylated in the liver to nortriptyline, which has antidepressant effects. (See 'Nortriptyline' below.)

Amoxapine — We suggest an initial dose of 25 mg at bedtime, but starting doses of 25 mg to 50 mg given two or three times per day are commonly used. Starting doses as high as 300 mg per day given in divided doses have been used [12].

The dose is usually increased over one to two weeks up to a target dose of 200 to 300 mg per day, usually taken in two or three divided doses, although a single bedtime dose may be effective. Total daily doses of 400 mg per day have been used in outpatients and 600 mg per day for inpatients, given in divided doses [12]. These larger doses are used in patients who do not respond to a total daily dose of 300 mg for at least two weeks and who do not have a

history of seizures. No single dose should exceed 300 mg. Increasing the total daily dose beyond 400 mg per day should be done cautiously only for closely supervised, hospitalized patients.

Amoxapine is unique among antidepressants because in addition to blocking reuptake of norepinephrine and to a lesser extent serotonin, it also blocks dopamine receptors and thus has antipsychotic activity.

Amoxapine is relatively well tolerated compared with other tricyclic and tetracyclic drugs (table 2).

Clomipramine — We suggest an initial dose of 25 mg at bedtime, although starting doses of 25 mg given three times per day have been used. The dose should be increased slowly over two weeks to about 100 mg per day. Clinicians can increase the dose to 250 to 300 mg per day over several more weeks, with the entire dose taken at bedtime. Doses may be increased more rapidly for inpatients and patients generally able to tolerate side effects.

The evidence suggests that a total serum level of clomipramine plus desmethylclomipramine (active metabolite) greater than 150 ng/mL is therapeutic [3].

Clomipramine blocks reuptake of both serotonin and norepinephrine, but more potently blocks reuptake of serotonin. It also has strong affinity for histamine H1 and muscarinic M1 receptors and thus causes sedation, weight gain, and anticholinergic side effects (table 2).

Desipramine — The usual starting dose of desipramine is 25 mg daily, given in the morning or at bedtime (patients may find the drug either activating or sedating). Patients sensitive to side effects and older adults can be started at dose of 10 mg. The dose can be increased by 25 to 50 mg every three to four days, as side effects allow, to a target dose range of 100 to 300 mg daily.

Patients tend to have a more robust antidepressant response if desipramine serum levels are greater than 125 ng/mL [3].

Desipramine blocks reuptake of norepinephrine and serotonin, but more potently blocks reuptake of norepinephrine. Its antidepressant effect is thought to be due to blocking reuptake of both neurotransmitters.

Desipramine has less affinity for histamine H1 receptors than any other cyclic antidepressant and is thus relatively less sedating. It also has less affinity for muscarinic M1 receptors than most cyclic antidepressants and thus fewer anticholinergic side effects (table 2).

Desipramine is an active metabolite of imipramine (see 'Imipramine' below).

Doxepin — We suggest an initial dose of 25 mg at bedtime, but starting doses up to 150 mg given once or in two or three divided doses have been used. Patients sensitive to side effects and older adults can start with a dose of 10 mg at bedtime. The dose can be increased by 25 to 50 mg every three to four days, as side effects allow, to a target dose range of 100 to 300 mg daily.

Doxepin has the strongest affinity for histamine H1 receptors among all cyclic antidepressants and is thus highly sedating, and associated with weight gain (table 2). The use of low dose doxepin (3 or 6 mg) for the treatment of sleep maintenance insomnia is discussed separately. (See "Pharmacotherapy for insomnia in adults", section on 'Antidepressants'.)

Imipramine — We suggest an initial dose of 25 mg at bedtime, but starting doses up to 150 mg given once or in divided doses have been used. Patients sensitive to side effects and older adults can start with a dose of 10 mg at bedtime. The dose can be increased by 25 to 50 mg every three to four days, as side effects allow, to a target dose range of 100 to 300 mg daily.

Patients tend to have a more robust antidepressant response if the total serum level of imipramine plus desipramine (the active metabolite) is greater than 200 ng/mL [3].

Imipramine is similar to amitriptyline in that they both block reuptake of serotonin and norepinephrine, but more potently blocks reuptake of serotonin. Its antidepressant effect is thought to be due to blocking reuptake of these neurotransmitters. It also has strong affinities for alpha-adrenergic, histamine H1, and muscarinic M1 receptors, which account for its side effects of orthostasis, sedation and weight gain, and anticholinergic effects. However, the intensity of these side effects is less than it is for amitriptyline (table 2).

Imipramine is demethylated in the liver to desipramine, which has antidepressant effects. (See 'Desipramine' above.)

Maprotiline — We suggest an initial dose of 25 mg at bedtime, but starting doses up to 150 mg have been used in severely ill hospitalized patients. The dose is usually increased by increments of 25 mg as tolerated to a target dose of 100 to 225 mg per day taken at bedtime. Maprotiline is not available in the United States.

Maprotiline potently blocks reuptake of norepinephrine, which is thought to be the source of its antidepressant activity. Maprotiline has a strong affinity for the histamine H1 receptor and is thus highly sedating (table 2).

Nortriptyline — Nortriptyline is approximately twice as potent as the other cyclic antidepressants. The usual starting dose of nortriptyline is 25 mg daily, given at bedtime.

Patients sensitive to side effects and older adults can be started at a dose of 10 mg. The dose can be increased by 25 to 50 mg every few days or longer (eg, at intervals ≥1 week), although smaller increments of 10 mg per day may be necessary. The target dose range for treating depression is 50 to 150 mg taken at bedtime. Occasional patients may tolerate and benefit from higher doses (eg, 200 mg/day).

Nortriptyline may have a therapeutic "window" of efficacy [3]. It is most effective at blood levels between 50 to 150 ng/mL and less effective at serum levels less than 50 ng/mL or greater than 150 ng/mL.

Nortriptyline is similar to desipramine in that they both block reuptake of norepinephrine and serotonin, but more potently block reuptake of norepinephrine. Its antidepressant effect is thought to be due to blocking reuptake of norepinephrine and serotonin.

Nortriptyline has relatively less affinity for histamine H1 and muscarinic M1 receptors compared with most cyclic antidepressants. It is thus tolerated as well or better than the other tricyclics (table 2).

Nortriptyline is an active metabolite of amitriptyline. (See 'Amitriptyline' above.)

Protriptyline — Protriptyline is the most potent cyclic antidepressant. We suggest a starting dose of 10 mg at bedtime, but starting doses of 5 or 10 mg given in three or four times per day have been used. Patients sensitive to side effects and older adults can be started at a dose of 5 mg at bedtime. The target dose is 15 to 60 mg, taken at bedtime.

Protriptyline blocks reuptake of norepinephrine and serotonin, but more potently blocks reuptake of norepinephrine. Its antidepressant effect is thought to be due to blocking reuptake of both neurotransmitters.

Protriptyline has relatively less affinity for histamine H1 and muscarinic M1 receptors compared with most cyclic antidepressants. It is thus tolerated as well or better than the other tricyclics (table 2).

Trimipramine — We suggest an initial dose of 25 mg at bedtime, although starting doses as high as 100 mg may be used in closely supervised hospitalized patients.

The dose is generally increased by increments of 25 or 50 mg per day every few days as tolerated. Therapeutic doses are generally in the range of 150 to 300 mg per day.

Trimipramine blocks reuptake of serotonin, which is thought to be the source of its antidepressant activity. It also has a high affinity for the histamine H1 receptor (only slightly less

than that of doxepin) and is thus highly sedating (table 2).

SIDE EFFECTS

Cyclic antidepressants tend to have dose-related side effects at therapeutic doses. These antidepressants are "broad spectrum" in that they interact with many neurotransmitter systems, which is the basis for both their antidepressant efficacy and their side effects. Tricyclics block muscarinic M1, histamine H1, and alpha-adrenergic receptors, and commonly cause cardiac effects, anticholinergic effects, antihistaminic effects, decreased seizure threshold, sexual dysfunction, diaphoresis, and tremor. In addition, cyclic antidepressants are dangerous in overdose. The side effects of tricyclic and tetracyclic antidepressants generally make them less tolerable compared with selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants [13]. Nevertheless, many patients use cyclic antidepressants safely.

The choice of cyclic antidepressant is usually based upon side-effect profiles, which vary between the different medications. The tertiary tricyclics amitriptyline, clomipramine, doxepin, imipramine, and trimipramine generally cause more side effects than other cyclic antidepressants. Nortriptyline and desipramine tend to have the best over-all tolerability. (table 2).

Depression itself causes somatic symptoms such as headache, constipation, and drowsiness, which is important to remember when assessing patients for side effects. Thus, clinicians should ask about physical symptoms prior to prescribing an antidepressant. This will enable the clinician to decide whether the medication has caused or exacerbated a physical symptom.

Overdose — Most concerning is that all of the tricyclic and tetracyclic antidepressants are dangerous in overdose. In contrast to the SSRIs, the cyclic antidepressants can be fatal in doses as little as 10 times the daily dose [3]. The toxicity is usually due to prolongation of the QT interval, leading to arrhythmias. Overdose of cyclic antidepressants can also cause anticholinergic toxicity and seizures. Furthermore, these medications are highly lipophilic and protein bound and are therefore not effectively removed by hemodialysis (see "Tricyclic antidepressant poisoning"). Thus, clinicians should avoid using cyclic antidepressants in outpatients who appear to be at high risk of intentional overdose.

Cardiac — All of the cyclic antidepressants are potentially cardiotoxic and should be avoided in susceptible individuals with heart disease [14]. (See 'Cardiac evaluation' below.)

At therapeutic serum levels, tricyclic antidepressants can cause orthostatic hypotension, which is one of the most common reasons for discontinuing them [15]. Orthostasis is most likely to

occur in patients with preexisting postural hypotension, is aggravated by concurrent antihypertensive medications and dehydration, and often occurs at low tricyclic serum levels. Blockade of alpha-adrenergic receptors is the primary cause.

Tricyclic antidepressants can cause electrocardiogram changes, benign or otherwise. The primary concern is prolongation of the QT interval, particularly when tricyclics are co-administered with other medications (eg, other psychotropic medications, certain antimicrobials, and antiarrhythmic drugs) that can prolong the QT interval (table 3). Patients with acquired long QT syndrome are at risk for ventricular arrhythmias, most notably polymorphic ventricular tachycardia, which may result in sudden cardiac arrest. The approach to the diagnosis and management of acquired long QT syndrome is discussed in detail separately. (See "Acquired long QT syndrome: Clinical manifestations, diagnosis, and management".)

Tricyclics can also reduce heart rate variability, slow intracardiac conduction, and cause various arrhythmias including tachycardia, ventricular fibrillation, and ventricular premature complexes. Tricyclics do not reduce cardiac contractility or output.

The decrease in cardiac conduction has been likened to the effects of Class 1A antiarrhythmics such as quinidine, and at therapeutic levels, tricyclics have mild antiarrhythmic effects on ventricular excitability and ventricular premature beats [3]. However, tricyclics can cause heart block in patients with preexisting conduction delay. Clinicians should avoid using these drugs in patients with underlying conduction system disease.

In patients with ischemic heart disease, tricyclics can increase cardiac work and decrease heart rate variability, possibly increasing the risk of sudden death [3]. Patients on high doses of cyclic antidepressants (300 mg or more amitriptyline or equivalent) may also be at increased risk for sudden cardiac death even in the absence of underlying heart disease [16]. In addition, tricyclic antidepressant users have a higher risk of myocardial infarction compared with SSRI users; it is not clear whether this is due to deleterious effects of the tricyclic antidepressants themselves, protective effects of SSRIs, or both [17].

It is not clear if tricyclics at therapeutic doses cause major cardiac complications in patients with normal hearts:

- In an eight-year, prospective observational study of adults with no known history of cardiovascular disease (n = 14,784, including 324 treated with tricyclics), several outcomes were evaluated after controlling for confounding factors [18]. Use of tricyclics was associated with a 35 percent increased risk of cardiovascular events (cardiovascular death,

nonfatal myocardial infarction, coronary surgical procedures, stroke, or heart failure). However, all-cause mortality was not associated with use of tricyclics.

- A study examined the association of tricyclics with ventricular arrhythmia or sudden cardiac death, using an administrative claims database that included patients treated with amitriptyline, doxepin, or nortriptyline (n >490,000) for different indications [19]. Patients treated with paroxetine (n >560,000) were the referent group due to its putatively favorable cardiovascular profile, and the analyses were adjusted for several potential confounds. The risk of ventricular arrhythmia or sudden cardiac death with each of the three tricyclics was comparable to that of paroxetine.

Seizures — All of the cyclic antidepressants can lower seizure threshold. Seizures are directly related to dose and serum level and are thus more likely to occur at higher doses (and in overdoses) [3]. As an example, clomipramine has a seizure rate of 0.5 percent at doses up to 250 mg/day, which increases to 1.7 percent at doses above 250 mg/day. Maprotiline (not available in the United States) has a seizure rate of 0.4 percent, which increases when doses exceed 225 mg/day. Imipramine has a seizure rate of 0.1 percent at doses up to 200 mg/day, and the rate increases to 0.6 percent at higher doses. Amitriptyline and doxepin have seizure rates of 1 to 4 percent at doses of 250 mg/day to 450 mg/day, depending upon the study.

Bone fractures — Observational studies have found an association between tricyclic use and bone fractures, which is discussed separately. (See "Drugs that affect bone metabolism", section on 'Antidepressants'.)

Anticholinergic — The tricyclics block muscarinic acetylcholine receptors and cause anticholinergic effects such as blurred vision, constipation, dry mouth (which may lead to dental caries), and urinary retention [3]. In addition, these anticholinergic effects can cause tachycardia, ocular crisis in patients with narrow-angle glaucoma, and confusion and delirium. Amoxapine, maprotiline (not available in the United States), desipramine, and nortriptyline are least likely to cause any of these problems.

Antihistaminic — The cyclic antidepressants block histamine receptors and cause sedation, increased appetite leading to weight gain, confusion, and delirium. The most potent antihistaminic drugs are maprotiline (not available in the United States) and the tertiary tricyclics amitriptyline, doxepin, and trimipramine. The sedative properties are sometimes harnessed for patients with insomnia, but more benign options are available.

Teratogenicity — Most studies indicate that tricyclics do not cause congenital defects. Use of tricyclics to treat depression during pregnancy is discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment".)

Other side effects — The cyclic antidepressants can cause a number of other side effects at therapeutic doses, most of which are dose dependent [3]:

- Sexual dysfunction including impaired arousal (especially in men) and orgasm is associated with more serotonergic drugs such as clomipramine, but occurs less often with tricyclics compared with SSRIs.
- Diaphoresis appears to be related to noradrenergic effects.
- Tremor.
- Acute hepatitis appears to be an allergic reaction that is uncommon but dangerous and potentially fatal. Elevated liver function tests should be followed with further tests for a few days. Hepatitis is reversible if the medication is discontinued.
- Amoxapine blocks dopamine and thus has neuroleptic properties that have caused rare cases of neuroleptic malignant syndrome and tardive dyskinesia.

BASELINE TESTING AND MONITORING FOR SAFETY

Cardiac evaluation — Cyclic antidepressants have been associated with heart block, ventricular arrhythmias, and sudden death. Before initiating treatment with any of the cyclic antidepressants, patients must be screened for cardiac conduction system disease, which precludes the use of these medications.

A typical history should include questions about known heart disease (including congenital or acquired long QT syndrome); any cardiac symptoms such as syncope, palpitations, dyspnea on exertion, shortness of breath, or chest pain; and the use of other drugs that can prolong the QT interval (table 3) [20]. In addition, clinicians should ask about a family history of heart disease, particularly sudden death, cardiac dysrhythmias, or cardiac conduction disturbances.

Baseline screening laboratory tests should include serum potassium to rule out hypokalemia (algorithm 1) [20]. In addition, a baseline electrocardiogram (ECG) is obtained for patients with any of the following:

- Age ≥40 years
- Cardiac symptoms
- Treatment with drugs that can prolong the QT interval

Tricyclics are generally contraindicated in patients with a corrected QT interval >500 milliseconds.

If patients have a history of or are at high risk for coronary heart disease, clinicians should avoid tricyclics [20].

The US Food and Drug Administration issued a warning specifically regarding desipramine [21]:

- Prescribe desipramine with extreme caution to patients with the family history described above
- Seizures precede cardiac dysrhythmias and death in some patients
- Overdose of desipramine has resulted in a higher death rate compared to overdose of other tricyclic antidepressants

After starting a tricyclic, clinicians should ask about new cardiac symptoms [20]. If new symptoms (eg, unexplained syncope, shortness of breath, dizziness, palpitations, or chest pain) occur, clinicians should obtain an ECG or refer the patient to cardiology.

Other monitoring — Although tricyclic antidepressants have been rarely associated with bone marrow and liver toxicity, we do not recommend checking blood counts or liver function tests either at baseline or as part of routine monitoring in the absence of specific concerns based on history or symptoms.

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Coping with high drug prices (The Basics)")

- Beyond the Basics topics (see "Patient education: Depression treatment options for adults (Beyond the Basics)" and "Patient education: Depression in adults (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)")

The National Institute of Mental Health also has educational material on the use of antidepressants, including tricyclic antidepressants, entitled "What Medications are used to Treat Depression" that is available online at the website. Material explaining the symptoms, causes, and treatment for depression is also available in a booklet entitled "Depression" that is available online at the website. Both publications can also be obtained through a toll-free number, 866-615-6464. The web site also provides references, summaries of study results in language intended for the lay public, and information about clinical trials currently recruiting patients.

The Depression and Bipolar Support Alliance (available at the website or 800-826-3632) is a national organization whose mission is to educate members about depression and how to cope with it. Other functions include increasing public awareness of the illness and advocating for more research and services. The organization is administered and maintained by patients and family members, and has local chapters.

The National Alliance on Mental Illness (available at the website or 800-950-6264) is a similarly structured organization devoted to providing education, support, and advocacy for patients with any mental illness. Depression is one of their priorities.

SUMMARY

- **Specific drugs** – There are nine tricyclic drugs available in the United States: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine. A related drug, the tetracyclic antidepressant maprotiline, is not available in the United States. (See 'Introduction' above.)

- **Structure** – The tricyclic antidepressants are named after their chemical structure, which consists of a three-ring central structure plus a side chain. The tetracyclic maprotiline has a four-ring central structure plus a side chain.

  Tricyclics are subdivided into two categories. Tertiary amines have two methyl groups at the end of the side chain. The tertiary amines are amitriptyline, clomipramine, doxepin, imipramine, and trimipramine. They are generally are more potent in blocking reuptake of serotonin compared with norepinephrine. Secondary amines have one methyl group at

the end of the side chain, and include desipramine, nortriptyline, and protriptyline. Secondary amines are more potent in blocking reuptake of norepinephrine. Tertiary amines generally cause more side effects compared with secondary amines. (See 'Structure of cyclic antidepressants' above.)

- **Pharmacokinetics** – Tricyclics are absorbed in the small intestine and undergo first-pass hepatic metabolism in the liver. They bind extensively to proteins and are widely distributed throughout the body. Metabolism and elimination occurs largely in the liver. Many of the tricyclic metabolites have antidepressant activity. (See 'Pharmacokinetics' above.)

- **Pharmacodynamics** – Each tricyclic and tetracyclic antidepressant inhibits reuptake of both serotonin and norepinephrine, which increases the amount of neurotransmitter in the synaptic cleft. These effects are thought to mediate the therapeutic benefit of cyclic antidepressants. (See 'Pharmacodynamics' above.)

- **Dose** – Finding the right dose involves a process of trial and error. We suggest starting with a low dose in order to avoid side effects and slowly increasing the dose. Patients who do not respond to low or medium doses may benefit from high doses. Patients who recover from an acute episode of major depression should receive maintenance treatment with the full dose that successfully resolved the episode, rather than a lower dose. (See 'Dose' above.)

- **Administration** – The elimination half-life for the tricyclics and related drugs averages about 24 hours. Thus, the entire dose of a cyclic antidepressant is generally taken once a day, usually at bedtime because of sedating side effects. (See 'Pharmacokinetics' above and 'Administration' above and 'Side effects' above.)

- **Adverse effects** – The side effects of cyclic antidepressants include cardiac effects, anticholinergic effects, antihistaminic effects, decreased seizure threshold, sexual dysfunction, diaphoresis, and tremor. These drugs are dangerous in overdose by suicidal patients. (See 'Side effects' above.)

- **Baseline testing and monitoring** – Cyclic antidepressants have been associated with heart block, ventricular arrhythmias, and sudden death. Before initiating treatment with any of the cyclic antidepressants, patients must be screened for cardiac conduction system disease, which precludes the use of these medications. We recommend that patients age 40 years or more have a baseline electrocardiogram (ECG) for this purpose (algorithm 1). Patients younger than 40 can be screened by history for evidence of cardiac disease and do not require an ECG if the history is negative and they are not

receiving drugs that can prolong the QT interval. (See 'Baseline testing and monitoring for safety' above.)

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