Cyclic antidepressants were the first-generation of drugs developed to treat depression. Their use for treating depression has declined greatly as safer agents have been developed. Cyclic antidepressants are now occasionally used to treat obsessive-compulsive disorder, attention-deficit disorder, panic and phobia disorders, anxiety disorders, and a variety of other conditions.

In 2013, cyclic antidepressants were the most commonly identified antidepressants associated with overdose-related deaths. Roughly half of all cyclic antidepressant exposures involve other drugs as well, and most co-ingestants increase the incidence and severity of cyclic antidepressant overdose toxicity.

Eight cyclic antidepressants are currently available in the United States (Table 177-1), with more agents available in other countries. Therapy is initially started at the lowest therapeutic level and slowly increased until the desired therapeutic response is achieved. This approach allows patients to become acclimated to adverse effects such as sedation and dry mucous membranes. Two related antidepressants, amoxapine and maprotiline, have structural differences from traditional cyclic antidepressants but have similar toxicity in overdose. Cyclobenzaprine is a muscle relaxant that is almost structurally identical to amitriptyline but lacks antidepressant activity, and serious toxicity from overdose is rare.
### TABLE 177-1

**Cyclic Antidepressants and Related Drugs**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Typical Adult Outpatient Daily Dose (milligrams)</th>
<th>Recommended Maximal Adult Outpatient Daily Dose (milligrams)</th>
<th>Active Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>75–150</td>
<td>300</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Amoxapine*</td>
<td>50–300</td>
<td>400</td>
<td>7-Hydroxyamoxapine (minor)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8-Hydroxyamoxapine (major)</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>25–50</td>
<td>250</td>
<td>Desmethylclomipramine</td>
</tr>
<tr>
<td>Cyclobenzaprine*</td>
<td>15–30</td>
<td>30</td>
<td>None</td>
</tr>
<tr>
<td>Desipramine</td>
<td>75–200</td>
<td>300</td>
<td>None</td>
</tr>
<tr>
<td><strong>Doxepin</strong></td>
<td>75–300</td>
<td>300</td>
<td>Desmethyldoxepin</td>
</tr>
<tr>
<td>Imipramine</td>
<td>75–200</td>
<td>300</td>
<td>Desipramine</td>
</tr>
<tr>
<td>Maprotiline*</td>
<td>75–150</td>
<td>225</td>
<td>Desmethylmaprotiline</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>75–150</td>
<td>150</td>
<td>None</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>15–60</td>
<td>60</td>
<td>None</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>75–200</td>
<td>300</td>
<td>Desmethylintrimipramine</td>
</tr>
</tbody>
</table>

*See text for clarification.

Cyclic antidepressant–related drug toxicity can occur at therapeutic dosages from one or more of seven possible mechanisms (Table 177-2).
TABLE 177-2
Mechanisms for Cyclic Antidepressant Drug Toxicity at Therapeutic Dosages

-Administration of high therapeutic dosages to naive individuals
-Drug interactions with medications sharing similar pharmacologic actions
-Elevated levels of cyclic antidepressants due to genetically slow hepatic metabolism
-Drug interactions with other medications that inhibit hepatic metabolism (cytochrome P-450 system)
-Additional toxicity from other active ingredients (e.g., antipsychotics) contained in some combination cyclic antidepressant formulations
-Preexisting cardiovascular or CNS disease that predisposes patients to toxicity
-Development of serotonin syndrome, usually in combination with serotoninergic medications

PHARMACOLOGY

The cyclic antidepressants are named after their chemical structure, which consists of a three-ring central structure plus a side chain, thus the common term tricyclic antidepressants. Maprotiline is a tetracyclic (also termed a heterocyclic), with a four-ring central structure plus a side chain. Cyclic antidepressants are subdivided into two categories: tertiary and secondary amines. Tertiary amines have two methyl groups at the end of the side chain. The five tertiary amines—amitriptyline, clomipramine, doxepin, imipramine, and trimipramine—are generally more potent in blocking reuptake of serotonin compared with norepinephrine. Tertiary tricyclics also cause more anticholinergic side effects (e.g., constipation or blurred vision) and are also highly sedating because of their central effects on histamine receptors.

Secondary amines—desipramine, nortriptyline, and protriptyline—have one methyl group at the end of the side chain and are more potent in blocking reuptake of norepinephrine. Desipramine is the active (demethylated) metabolite of imipramine, and nortriptyline is the active (demethylated) metabolite of amitriptyline. The tetracyclic maprotiline 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 and can produce seizures with minimal warning and normal QRS complex.

Cyclic antidepressants are nonselective agents with multiple pharmacologic effects (Table 177-3) with considerable variation in potency at therapeutic dosages. However, these differences become less important at the higher plasma levels typically seen in overdose. Inhibition of amine reuptake (norepinephrine, serotonin) and antagonism of postsynaptic serotonin receptors are believed to produce the therapeutic effects of these agents. The remaining pharmacologic actions are seemingly without therapeutic benefit in treating major depression but significantly contribute to cyclic antidepressant–related adverse effects and overdose toxicity.
### Pharmacologic Profile of Cyclic Antidepressants

<table>
<thead>
<tr>
<th>Pharmacologic Activity</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antagonism of postsynaptic histamine receptors</td>
<td>Sedation</td>
</tr>
<tr>
<td>Antagonism of postsynaptic muscarinic receptors</td>
<td>Sedation, coma, agitation, confusion, hallucinations, ataxia, seizures, mydriasis, dry mucous membranes, dry skin, flushed skin, tachycardia, mild hypertension, hyperthermia, ileus, urinary retention, tremor</td>
</tr>
<tr>
<td>Antagonism of postsynaptic α-adrenergic receptors</td>
<td>Sedation, miosis, orthostatic hypotension, reflex tachycardia</td>
</tr>
<tr>
<td>Inhibition of norepinephrine reuptake</td>
<td>Agitation, mydriasis, diaphoresis, tachycardia, early hypertension</td>
</tr>
<tr>
<td>Inhibition of serotonin reuptake</td>
<td>Sedation, mydriasis, myoclonus, hyperreflexia (see later discussion of inhibition of amine reuptake and chapter 178, “Atypical and Serotonergic Antidepressants”)</td>
</tr>
<tr>
<td>Inhibition of voltage-gated sodium channels</td>
<td>Impaired conduction, wide QRS complex, other conduction abnormalities; impaired cardiac contractility; wide-complex tachycardia, Brugada pattern, ventricular ectopy</td>
</tr>
<tr>
<td>Inhibition of voltage-gated rectifier potassium channels</td>
<td>Prolongation of QT interval, ventricular ectopy, torsades de pointes</td>
</tr>
</tbody>
</table>

### ANTIHISTAMINIC EFFECTS

Cyclic antidepressants are potent inhibitors of peripheral and central postsynaptic histamine receptors. Antagonism of central histamine receptors produces sedation and contributes significantly to the depressed level of consciousness and coma frequently seen in cyclic antidepressant overdose.

### ANTIMUSCARINIC EFFECTS

Cyclic antidepressants are competitive inhibitors of acetylcholine at central and peripheral muscarinic receptors but not at nicotinic receptors. Thus, they are antimuscarinic agents and not truly anticholinergic drugs. Central antimuscarinic symptoms vary from agitation to delirium, confusion, amnesia, hallucinations, slurred speech, ataxia, sedation, and coma. Peripheral antimuscarinic symptoms include dilated pupils, blurred vision, tachycardia, hyperthermia, hypertension, decreased oral and bronchial secretions, dry skin, ileus, urinary retention, increased muscle tone, and tremor. Antimuscarinic symptoms are especially common when cyclic antidepressants are combined with other medications that also have antimuscarinic activity, such as antihistamines, antipsychotics, antiparkinsonian drugs, antispasmodics, and some muscle relaxants. Antimuscarinic
symptoms and signs are common findings in cyclic antidepressant overdose, making them an important clinical marker for toxicity, but these effects are not directly responsible for cyclic antidepressant–related deaths, and they do not require specific therapy other than supportive care.5

INHIBITION OF α-ADRENERGIC RECEPTORS

Inhibition of postsynaptic central and peripheral α-adrenergic receptors is a characteristic action of most cyclic antidepressants.4 Cyclic antidepressants have a much greater affinity for α₁-adrenergic than for α₂-adrenergic receptors. Inhibition of α₁-receptors produces sedation, orthostatic hypotension, and pupillary constriction. This action frequently offsets pupillary dilatation induced by antimuscarinic activity. Thus patients with cyclic antidepressant toxicity can present with mid-sized or small pupils despite having other antimuscarinic signs. Orthostatic hypotension is often associated with reflex tachycardia. The antihypertensive effect of clonidine can be negated by cyclic antidepressants because of their ability to block the binding of clonidine to α₂-receptors.

INHIBITION OF AMINE REUPTAKE

Inhibition of amine reuptake is believed to be the most important mechanism for treating depression.6 Cyclic antidepressants are potent inhibitors of norepinephrine and serotonin reuptake but produce little inhibition of dopamine reuptake, except for amoxapine, which does inhibit dopamine reuptake. Inhibition of neurotransmitter reuptake leads to increased synaptic levels and subsequent augmentation of the neurotransmitter response. Inhibition of norepinephrine reuptake is thought to produce the early sympathomimetic effects occasionally seen in some cyclic antidepressant overdoses and may contribute to the development of cardiac dysrhythmias. Myoclonus and hyperreflexia are attributed to increased serotonin activity. Serotonin syndrome results from increased serotonin brainstem activity that can be produced by cyclic antidepressants that are particularly potent serotonin uptake inhibitors, such as clomipramine and amitriptyline (see chapter 178). In general, cyclic antidepressants produce serotonin syndrome only when used in combination with other serotonergic agents.

SODIUM CHANNEL BLOCKADE

Cyclic antidepressant–induced cardiotoxicity is the most important factor contributing to patient mortality.7 Cardiac conduction abnormalities occur during cyclic antidepressant poisoning because inhibition of the fast sodium channels in the His-Purkinje system and myocardium decreases conduction velocity, increases the duration of repolarization, and prolongs absolute refractory periods. Severe sodium channel blockade culminates in depressed myocardial contractility, hypotension, various types of heart blocks, cardiac ectopy, bradycardia, widening of the QRS complex, and/or the Brugada pattern. Mechanisms that contribute to hypotension during overdose include decreased contractility from reduced calcium release during depolarization within the ventricular myocytes and peripheral vasodilatation from blockade of α₁-adrenergic receptors. Rapid influx of sodium is necessary for the release of intracellular calcium stores and subsequent myocardial contractility. Some of the negative chronotropic effects of sodium channel blockade can be attenuated by the sinus tachycardia secondary to antimuscarinic activity.

Cyclic antidepressant cardiotoxicity produces ECG changes, such as prolongation of the PR interval and QRS duration, frontal plane right axis deviation, and the Brugada pattern (incomplete right bundle-branch block with ST-segment elevation in leads V₁ to V₃).7,8 The right axis deviation is most pronounced in the terminal 40 milliseconds of limb leads, demonstrated by a terminal R wave in ECG lead aVR and an S wave in ECG lead I. The Brugada pattern is seen in approximately 10% to 15% of all patients with significant cyclic antidepressant overdose admitted to an intensive care unit but is rarely seen in other types of overdose.8,9 Therefore, the Brugada pattern strongly suggests a cyclic antidepressant overdose.
Slow electrical conduction can produce various types of heart blocks. Local changes in electrical conduction can predispose to ventricular dysrhythmias by establishing reentry loops. Bradycardia, when accompanied by QRS complex widening, indicates profound sodium channel blockade.

**POTASSIUM CHANNEL ANTAGONISM**

Cyclic antidepressants block myocardial potassium channels and inhibit the efflux of potassium during repolarization. This effect is seen on the ECG as QT interval prolongation, which is more pronounced at slower heart rates. Torsades de pointes is rarely seen in cyclic antidepressant overdoses in the presence of sinus tachycardia, which is partially protective against severe QT interval prolongation and after-potential generation.

**PHARMACOKINETICS**

All cyclic antidepressants share similar pharmacokinetic properties. They are highly lipophilic, readily cross the blood–brain barrier, and achieve peak plasma levels between 2 and 6 hours after ingestion at therapeutic doses. In overdose, GI absorption can be prolonged because of the antimuscarinic effect on gut motility. Bioavailability is only 30% to 70% because of extensive first-pass hepatic metabolism. Cyclic antidepressants are highly protein bound to \( \alpha_1 \)-acid glycoproteins, with a large apparent volume of distribution, ranging from 10 to 50 L/kg. Tissue cyclic antidepressant levels are commonly 10 to 100 times greater than plasma levels, and only 1% to 2% of the total body burden of cyclic antidepressants is found in the blood. These pharmacokinetic properties explain why it is unproductive to attempt removal of cyclic antidepressants by hemodialysis, hemoperfusion, peritoneal dialysis, or forced diuresis.

Cyclic antidepressants are eliminated almost entirely by hepatic oxidation, which consists of \( N \)-demethylation of the amine side-chain groups and hydroxylation of ring structures. The removal of a methyl group from the tertiary amine side chain usually produces an active metabolite designated by the desmethyl prefix (Table 177-1). Clinical toxicity from cyclic antidepressants usually lasts longer than explained by the activity of the parent drug because of the production of active metabolites. These active metabolites often have different pharmacologic activities compared with the parent compounds. Secondary amines such as desipramine, nortriptyline, and protriptyline are not believed to have active metabolites. Amoxapine and maprotiline both have active metabolites. Some cyclic antidepressants undergo enterohepatic circulation prior to their eventual oxidation, conjugation, and renal elimination, but this does not significantly contribute to their toxicity.

The average elimination half-life of cyclic antidepressants is approximately 24 hours (range, 6 to 36 hours) at therapeutic dosages, but this can increase to 72 hours after overdose. Inhibition of cyclic antidepressant metabolism by other drugs that use the same hepatic enzymes can prolong the half-life of cyclic antidepressants.

Cyclic antidepressants undergo significant postmortem drug redistribution. Plasma levels can increase significantly after death as tissue binding sites release cyclic antidepressants back to the blood. This is a time-dependent process, and therefore, the diagnostic accuracy of postmortem cyclic antidepressant levels is inversely proportional to the time after death at which the measurement sample was obtained, among other factors.

**TOXICITY**

Therapeutic dosages of cyclic antidepressants are variable, generally ranging from 1 to 5 milligrams/kg per day (Table 177-1). Ingestions of <1 milligram/kg are generally nontoxic. Life-threatening symptoms usually occur with ingestions of >10 milligrams/kg in adults, and fatalities are commonly associated with ingestions of >1 gram. Children are particularly susceptible to antimuscarinic effects and show clinical toxicity at lower dosages. The majority of adult intentional ingestions and pediatric accidental exposures of >2.5 milligrams/kg are expected to result in some clinical toxicity based on the low therapeutic index of cyclic antidepressants. In addition, patients at higher risk for cyclic antidepressant toxicity include patients who have co-
ingested cardiotoxic or sedative-hypnotic medications, geriatric patients, and patients with underlying heart or neurologic
disease.

Desipramine is the most potent sodium channel blocker among the cyclic antidepressants and is able to precipitate severe
cardiotoxicity (e.g., wide QRS complex, hypotension) without producing significant antimuscarinic symptoms. It is associated
with a higher case-fatality rate than the other cyclic antidepressants. Amoxapine and maprotiline have historically been
associated with greater toxicity than other cyclic antidepressants, especially in regard to causing seizures.

Quantitative measurement of plasma levels of cyclic antidepressants is helpful in monitoring long-term drug therapy, but results
are rarely available during the time of patient evaluation. Patients with a combined plasma level of parent cyclic antidepressant
and metabolite of >1000 nanograms/mL (>3500 nmol/L) are at greater risk for developing seizures and cardiotoxicity. However,
the severity of clinical toxicity does not always correlate with the degree of plasma cyclic antidepressant elevation. Serious
toxicity rarely develops at therapeutic levels, typically 75 to 300 nanograms/mL (300 to 1000 nmol/L) for most agents.

**CLINICAL FEATURES**

The clinical presentation of cyclic antidepressant toxicity varies from mild antimuscarinic symptoms to severe cardiotoxicity
secondary to sodium channel blockade. Antimuscarinic symptoms commonly serve as markers for cyclic antidepressant toxicity
(e.g., dry mouth and axillae, sinus tachycardia), but they alone are rarely responsible for fatalities. Moreover, antimuscarinic
symptoms are not uniformly present in cyclic antidepressant toxicity. Altered mental status is the most common symptom
reported after cyclic antidepressant exposure. A Glasgow coma scale score of <8 in the ED is a strong predictor of serious
complications such as seizures and cardiac dysrhythmias. Sinus tachycardia is the most frequent dysrhythmia noted in cyclic
antidepressant toxicity, occurring in up to 70% of symptomatic patients.

Mild to moderate cyclic antidepressant toxicity presents as drowsiness, confusion, slurred speech, ataxia, dry mucous
membranes and axillae, sinus tachycardia, urinary retention, myoclonus, and hyperreflexia. Antimuscarinic syndrome is
classically associated with decreased bowel sounds and ileus, but bowel function is fairly resistant to inhibition, so the presence
of active bowel sounds does not exclude antimuscarinic syndrome. Mild hypertension is occasionally present and rarely requires
treatment. Overflow urinary incontinence may be mistaken for normal micturition in diaper-dependent children or older adults.

Most cyclic antidepressant overdose fatalities occur within the initial hours after ingestion, often before the patient reaches the
hospital. If serious toxicity is going to occur, it almost always is seen within 6 hours of ingestion and consists of the following
features: coma, cardiac conduction delays, supraventricular tachycardia, hypotension, respiratory depression, ventricular
tachycardia, and seizures. Secondary complications from serious toxicity include aspiration pneumonia, pulmonary edema,
anoxic encephalopathy, hyperthermia, and rhabdomyolysis. Seizures are more commonly reported in maprotiline and
trimipramine overdoses. Seizures are usually generalized, of brief duration, and occur with other signs of serious toxicity. The
exception to this rule is amoxapine overdoses; this agent can cause status epilepticus without warning or QRS complex widening.
Cyclobenzaprine overdoses are usually characterized by prolonged CNS sedation and antimuscarinic toxicity with minimal
cardiotoxicity compared to amitriptyline.

**DIAGNOSIS**

Cyclic antidepressant toxicity is diagnosed using a combination of four criteria: history of exposure, clinical symptomatology,
characteristic ECG findings, and positive cyclic antidepressant urine drug screen results. Other toxic exposures may produce
similar symptoms, signs, and ECG changes; the essential point is that the initial treatment for toxicity due to any of these
medications is identical and should not be delayed until definitive drug test results become available. At least half of all cyclic
antidepressant exposures involve co-ingestion of other substances, which can significantly increase or alter toxic manifestations.
False-positive results on qualitative cyclic antidepressant urine drug screens occur for carbamazepine, cetirizine, cyclobenzaprine, cyproheptadine, diphenhydramine, hydroxyzine, quetiapine, and phenothiazines (e.g., thioridazine). The false-positive cyclic antidepressant screen result is generally dose dependent and is more common following a supratherapeutic dose of these medications. Most of these medications are structurally similar to cyclic antidepressants, producing the same ECG abnormalities and clinical toxicity in overdose as cyclic antidepressants. Conversely, false-negative results on cyclic antidepressant drug tests are extremely unusual with clinical toxicity.

ECG abnormalities are common with cyclic antidepressant toxicity and are useful in identifying patients at increased risk for seizures and ventricular dysrhythmias. The classic ECG with cyclic antidepressant toxicity shows sinus tachycardia, right axis deviation of the terminal 40 milliseconds, and prolongation of the PR, QRS, and QT intervals (Figure 177-1). Right axis deviation is demonstrated as a positive terminal R wave in lead aVR and a negative S wave in lead I (Figure 177-1). This classic ECG pattern is seen frequently in moderate to severe cyclic antidepressant toxicity, but its absence does not eliminate the possibility of toxicity, and life-threatening complications can occur in the absence of significant ECG abnormalities, especially following amoxapine ingestion. Moderate prolongation of the QT interval is noted frequently, even at therapeutic cyclic antidepressant dosages. Nonspecific ST-segment and T-wave abnormalities are observed commonly in cyclic antidepressant overdose. Less common ECG abnormalities include right bundle-branch block and high-degree atrioventricular blocks. The Brugada pattern is seen in roughly 10% to 15% of patients with cyclic antidepressant poisoning who require intensive care unit admission.

FIGURE 177-1.
Twelve-lead ECG showing classic cyclic antidepressant ECG abnormalities: sinus tachycardia; prolonged PR, QRS, and QT intervals; and right axis deviation of the terminal 40 milliseconds of the QRS complex.
complex in lead aVR are usually seen together but can occur independently of each other. The development of right axis deviation of the terminal 40 milliseconds and/or QRS complex widening appear to be less predictive of cyclic antidepressant-induced cardiotoxicity in young children because pediatric ECGs tend to have a wider range of acceptable variant features, and this complicates the identification of cyclic antidepressant toxicity on the ECG.

**ECG abnormalities develop within 6 hours of ingestion and typically resolve over 36 to 48 hours.** These ECG abnormalities in isolation are not 100% specific for cyclic antidepressant toxicity, so because prior ECGs may not be available for comparison, any observed ECG abnormalities should be assumed attributable to cyclic antidepressant exposure and managed accordingly.

**TREATMENT**

Evaluate patients for alterations of consciousness, hemodynamic instability, and respiratory impairment. Establish an IV line, initiate continuous cardiac rhythm monitoring, and obtain serial ECGs. Suggested laboratory studies include serum electrolytes, creatinine, and glucose. To identify co-ingestants, obtain serum acetaminophen and salicylate levels. Blood gas measurement is required for symptomatic patients. In patients with antimuscarinic symptoms, urinary catheterization may be required to prevent urinary retention, and a nasogastric tube may be needed if ileus is present. **Patients who are initially asymptomatic may deteriorate rapidly and therefore should be monitored closely for 6 hours.** Treatment recommendations (Table 177-4) are based primarily on cohort or case-control studies resulting in only moderate strength of evidence for those measures discussed below.21
TABLE 177-4

Treatment of Cyclic Antidepressant Overdose

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Indication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI decontamination</td>
<td>Activated charcoal 1 gram/kg PO</td>
<td>Within 1 h of ingestion as long as airway is stable and patient is awake</td>
<td>Do not give multidose charcoal; do not do whole-bowel irrigation</td>
</tr>
<tr>
<td>Initial treatment of hypotension</td>
<td>Sodium bicarbonate, 1–2 mEq/kg IV bolus;</td>
<td>For dysrhythmias, conduction abnormalities (QRS &gt;100 ms), or hypotension</td>
<td>Keep blood pH 7.50–7.55</td>
</tr>
<tr>
<td>or dysrhythmias</td>
<td>repeat bolus or add 150 mEq in 1 L 5%</td>
<td>refractory to IV fluid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dextrose in water at 2–3 mL/kg per hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Replace potassium as needed</td>
<td>Serum potassium &lt;3.5 mEq/L</td>
<td>Bicarbonate will decrease potassium</td>
</tr>
<tr>
<td>Seizures or agitation</td>
<td>Benzodiazepines for seizures or agitation</td>
<td></td>
<td>Do not give physostigmine, flumazenil, or phenytoin</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Treat hypotension with normal saline, up</td>
<td>Use norepinephrine or epinephrine if refractory to IV normal saline</td>
<td>Case reports of glucagon, 1 milligram IV bolus</td>
</tr>
<tr>
<td></td>
<td>to 30 mL/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torsades de pointes and refractory</td>
<td>Magnesium sulfate 2 grams IV; 3% saline</td>
<td>Consider lipid emulsion for refractory dysrhythmias, but no convincing</td>
<td>Do not give class I antiarrhythmics (i.e., procainamide, lidocaine,</td>
</tr>
<tr>
<td>dysrhythmias</td>
<td>1–3 mL/kg IV over 10 min; overdrive</td>
<td>evidence of effectiveness</td>
<td>phenytoin, flecainide, β-blockers, calcium channel blockers, or class</td>
</tr>
<tr>
<td></td>
<td>pacing</td>
<td></td>
<td>III antiarrhythmics (i.e., amiodarone, sotalol, ibutilide)</td>
</tr>
</tbody>
</table>

**GI DECONTAMINATION**

Do not use ipecac syrup or gastric lavage.\(^{13,22,23,24}\) Give a single 1 gram/kg dose of activated charcoal PO if patients are awake, have a patent airway, and arrive within 1 hour of ingestion.\(^{13,25}\) Activated charcoal effectively binds cyclic antidepressants and decreases absorption. Neither multidose activated charcoal nor whole-bowel irrigation is warranted.\(^{22,26}\) Asymptomatic patients with reliable histories of minimal cyclic antidepressant ingestion can be treated with activated charcoal alone and observed for toxicity.

**SODIUM BICARBONATE**

Sodium bicarbonate is used to treat cardiac conduction abnormalities, ventricular dysrhythmias, or hypotension refractory to IV fluid.\(^{21}\) Administer sodium bicarbonate as an initial IV bolus of 1 to 2 mEq/kg, and repeat until patient improvement is noted or
until blood pH is between 7.50 and 7.55 (Figure 177-2). Additional alkalization beyond this point can be deleterious to oxygen extraction and serum electrolytes.

**FIGURE 177-2.**
ECG before and after bicarbonate treatment. **A,** Cardiac rhythm strip of a patient with a wide QRS complex recorded 3 hours after ingestion of amitriptyline. **B,** Narrowing of the QRS complex in the same patient after administration of an IV bolus of sodium bicarbonate.

As an alternative of repeat boluses, continuous infusions of sodium bicarbonate can be administered as 150 mEq added to 1 L of 5% dextrose in water (or 100 mEq added to 5% dextrose in 0.45% saline, creating a slightly hypertonic solution with the sodium bicarbonate added) and infused IV at a rate of 2 to 3 mL/kg per hour. Adjustments in the IV rate are made based on blood pH measurements and clinical response to therapy. Monitor serum electrolytes during the sodium bicarbonate infusion. Hypernatremia is not of particular concern using this dose of sodium bicarbonate. Serum potassium will decrease during sodium bicarbonate therapy, and IV potassium supplementation may be required.

### Altered Level of Consciousness

Antagonism of postsynaptic muscarinic, histaminic, and α-adrenergic receptors contributes to the development of depressed mentation in cyclic antidepressant overdose. Coma from cyclic antidepressant toxicity typically is rapid in onset and is a predictive factor for cardiotoxicity and/or seizures. Pulmonary aspiration is common among comatose cyclic antidepressant overdose patients. Agitation is observed commonly prior to the onset of coma, as well as during awakening. Agitation is best controlled with reassurance, decreased environmental stimulation, and benzodiazepines. **Do not give flumazenil or physostigmine for mixed cyclic antidepressant–benzodiazepine or cyclic antidepressant–anticholinergic overdoses, respectively.**

### Seizures
Most seizures occur within the first 3 hours following ingestion and are typically generalized and of brief duration. Multiple seizures are reported in approximately 10% to 30% of cases of cyclic antidepressant overdose. Focal seizures and status epilepticus are atypical and should prompt further neurologic evaluation. Seizures are especially common with maprotiline and amoxapine ingestions and require aggressive management, because status epilepticus is frequently associated with these two particular antidepressants. Benzodiazepines (e.g., diazepam, lorazepam) are the anticonvulsants of choice to stop seizure activity. Barbiturates (e.g., phenobarbital) are indicated to treat seizures resistant to benzodiazepines. The initial IV dose of phenobarbital is 10 to 15 milligrams/kg, but this can be increased in patients with continued seizure activity and adequate blood pressure. Other therapy for refractory seizures includes continuous-infusion midazolam or propofol. Hypotension is a major side effect of IV phenobarbital administration.

Endotracheal intubation and respiratory support are typically required when benzodiazepines are combined with barbiturates or propofol. Phenytoin, sodium bicarbonate, and physostigmine do not stop cyclic antidepressant–induced seizures. Neuromuscular blockers will stop the physical manifestations of seizures and their secondary effects, which include metabolic acidosis, hyperthermia, rhabdomyolysis, and renal failure, but they do not stop brain seizure activity. Therefore, following the induction of muscle paralysis, continue anticonvulsant therapy and consider electroencephalographic monitoring.

**HYPOTENSION**

Hypotension should be treated initially with isotonic crystalloid fluids in IV boluses in increments of 10 mL/kg to a maximum of 30 mL/kg. With impaired cardiac contractility, pulmonary edema can develop if excessive fluids are administered. Hypotension that does not improve with appropriate fluid challenges should be treated with sodium bicarbonate (regardless of QRS complex duration). Vasopressors should be used when hypotension is unresponsive to fluids and sodium bicarbonate therapy.

Norepinephrine and epinephrine are the most effective vasopressors because they directly compete with the cyclic antidepressants at the α-adrenergic receptors. Start the IV infusion at 1 microgram/min and titrate according to blood pressure.

Vasopressin can be tried if there is no response to norepinephrine or epinephrine. Dopamine is less effective than norepinephrine in reversing cyclic antidepressant–induced hypotension because it has primarily indirect α-adrenergic agonist activity and, at lower dosages, promotes vasodilation through its β-adrenergic and dopaminergic actions.

Placement of a pulmonary artery catheter for monitoring in patients whose hypotension is refractory to fluid, sodium bicarbonate, and vasopressor therapy may precipitate life-threatening conduction abnormalities and ventricular dysrhythmias as the catheter passes through the right ventricle. Mechanical support of the circulation with cardiopulmonary bypass, overdrive pacing, or aortic balloon pump assistance may be warranted in patients with refractory hypotension, although no studies document the effectiveness of these measures. There are isolated case reports suggesting that glucagon administered as 1 milligram IV boluses might be effective in patients with refractory cyclic antidepressant–induced hypotension.

**CARDIAC CONDUCTION ABNORMALITIES AND DYSRHYTHMIAS**

Cyclic antidepressants frequently alter cardiac rate, conduction, and contractility. These negative cardiac effects are increased with acidosis, which occurs in patients with respiratory depression or seizures. Asymptomatic patients with sinus tachycardia, isolated PR interval prolongation, or first-degree atrioventricular block do not require specific pharmacologic therapy. Conduction blocks greater than first-degree atrioventricular block are worrisome because they can progress rapidly to complete heart block secondary to impaired infranodal conduction.

The controversial issue is whether asymptomatic or mildly toxic patients with isolated QRS complex prolongation should be treated with sodium bicarbonate therapy. There are no controlled human trials demonstrating benefits in otherwise asymptomatic patients with QRS complex prolongation. Nonetheless, many physicians use sodium bicarbonate therapy in asymptomatic or minimally toxic patients with cyclic antidepressant overdose if the QRS duration is >100 milliseconds.
Hyperventilation represents a reasonable alternative to sodium bicarbonate therapy in the setting of renal failure, pulmonary edema, or cerebral edema, although hyperventilation is less effective in reversing toxicity.  

Ventricular dysrhythmias should be treated with sodium bicarbonate. Consider 3% hypertonic saline, 1 to 3 mL/kg IV over 10 minutes, to decrease ventricular ectopy or dysrhythmia in a patient with cardiotoxicity refractory to sodium bicarbonate therapy.

Torsades de pointes should be treated initially with 2 grams of IV magnesium sulfate. Identify and treat electrolyte disorders that are associated with torsades de pointes. Overdrive pacing may be considered for refractory tachydysrhythmias. Older case reports indicate that IV isoproterenol may be of some benefit when overdrive pacing is not available. The following medications are contraindicated in the treatment of cyclic antidepressant–induced dysrhythmias: all class I antiarrhythmic agents, β-blockers, calcium channel blockers, and all class III antiarrhythmic agents. Lidocaine, a sodium channel blocker, has unclear benefits in cyclic antidepressant–induced dysrhythmias, and there are no convincing data to support its effectiveness.

**LIPID EMULSION**

Cyclic antidepressants are highly lipid soluble, and it has been postulated that intravenous lipid emulsion creates a "lipid sink" that sequesters the drug and prevents toxicity. Case descriptions report both benefit and complications. Currently, there is no consensus or convincing evidence for the use of lipid emulsion in cyclic antidepressant toxicity. In patients with cardiotoxicity refractory to other measures, it seems reasonable to infuse a 20% lipid emulsion in an amount based on that recommended for local anesthetic systemic toxicity: 100 mL IV bolus (1.5 mL/kg) over 2 to 3 minutes, followed by an infusion of 18 mL (0.25 mL/kg) per minute to a total dose of 10 mL/kg.

**DISPOSITION AND FOLLOW-UP**

Patients who remain asymptomatic after 6 hours of observation do not require hospital admission for toxicologic reasons. All symptomatic patients require hospital admission to a monitored bed. Patients demonstrating signs of moderate to severe toxicity should be admitted to an intensive care unit. Hospitalized patients can be cleared medically after 24 hours if they are asymptomatic, with a normal or baseline ECG, normal mental status, and resolution of all antimuscarinic symptoms. Patients with an intentional overdose require mental health evaluation.

**REFERENCES**


