Tricyclic antidepressant poisoning

Author
Steven D Salhanick, MD

Section Editor
Stephen J Traub, MD

Deputy Editor
Jonathan Grayzel, MD, FAAEM

All topics are updated as new evidence becomes available and our peer review process is complete. Literature review current through: Jul 2016. | This topic last updated: Jun 07, 2016.

INTRODUCTION — Between the late 1950s and the late 1980s, tricyclic antidepressants (TCAs) were used extensively in the management of depression and other psychiatric disorders. Although selective serotonin reuptake inhibitors (SSRIs) and other agents have supplanted TCAs as first line therapy in the management of depression, TCAs are still used for depression and other indications. Consequently, TCA poisoning, which can be life-threatening, remains a significant clinical issue.

The diagnosis and management of TCA poisoning is reviewed here. A summary table to facilitate the emergent management of TCA overdose is provided (table 1). The management of SSRI poisoning and a general clinical approach to the patient with known or suspected drug poisoning are discussed separately. (See "Selective serotonin reuptake inhibitor poisoning" and "General approach to drug poisoning in adults" and "Initial management of the critically ill adult with an unknown overdose".)

PHARMACOLOGY — Inhibition of presynaptic neurotransmitter reuptake (norepinephrine and serotonin) is the primary mechanism for the therapeutic effects of tricyclic antidepressants (TCAs).

Following overdose, the following cellular effects often produce important clinical consequences:

- Blockade of cardiac fast sodium channels
- Antagonism of central and peripheral muscarinic acetylcholine receptors
- Antagonism of peripheral alpha-1 adrenergic receptors
- Antagonism of histamine (H1) receptors
- Antagonism of CNS gamma-aminobutyric acid (GABA) A receptors

In therapeutic use, TCAs are rapidly absorbed from the gastrointestinal tract, reaching maximal plasma concentrations within two to eight hours. TCAs are lipophilic and thus have a large volume of distribution (Vd). The fraction of the drug found in the plasma is usually highly bound to alpha-1 acid glycoprotein. TCAs are primarily metabolized by the liver, undergoing phase one metabolism primarily via CYP 2D6 and phase 2 glucuronidation. Many phase one metabolites are pharmacologically active and may persist in the plasma for 12 to 24 hours [1-3]. Depending upon the TCA, the half-life of the parent compound can range from 7 to 58 hours. Approximately 70 percent of the total dose is renally excreted as inactive metabolites; the remainder is eliminated primarily via the biliary system, with a small amount excreted unchanged in the urine. Enterohepatic recirculation can delay final elimination of a large fraction of the drug [4,5].

Important changes make it impossible to extrapolate overdose kinetics from kinetics measured during therapeutic dosing. Absorption may be delayed, largely due to decreased gut motility from anticholinergic effects. Bioavailability may be increased as metabolic pathways become saturated, reducing the first pass metabolism. Acidemia, which frequently complicates overdose, may increase the amount of free drug due to effects on plasma glycoprotein binding. Genetic polymorphisms of CYP2D6 resulting in a decreased rate of elimination, may become more relevant following overdose. The sum total of these effects is often delayed absorption, an increased proportion of active drug, and delayed excretion.

CARDIOVASCULAR PATHOPHYSIOLOGY — Cardiac conduction abnormalities occur during tricyclic antidepressant (TCA) poisoning because TCAs inhibit the fast sodium channels in the His-Purkinje system and myocardium. This inhibition decreases conduction velocity, increases the duration of repolarization, and prolongs absolute refractory periods (figure 1) [6,7]. These effects are similar to those of the class IA antiarrhythmic drugs such as quinidine. Mechanisms that contribute to hypotension during overdose include decreased contractility from reduced calcium influx into ventricular myocytes, blockade of rapid sodium channels, and peripheral vasodilatation from
**History** — It is important to learn the particular tricyclic antidepressant (TCA) ingested and the amount, and whether the patient took any other agents. In the event of mental status changes, information can be obtained from emergency medical personnel, police, family, friends, pharmacists, psychiatrists, and primary care clinicians. (See "General approach to drug poisoning in adults", section on 'History'.)

**Overview of physical findings** — Signs of TCA poisoning typically include sedation, but may also include confusion, delirium, or hallucinations. Cardiac conduction delays, arrhythmias, hypotension, and anticholinergic toxicity (eg, hyperthermia, flushing, dilated pupils) are also common ([table 1](#))[2,3,9,10]. The clinical course of patients with TCA poisoning can be unpredictable, and patients who present immediately after ingestion may initially be well-appearing, only to deteriorate rapidly, due to the variable absorption kinetics described above. In most cases, acute TCA ingestions of 10 to 20 mg/kg lead to significant cardiovascular and central nervous system (CNS) toxicity [11]. (See 'Pharmacology' above and "General approach to drug poisoning in adults".)

**Cardiac toxicity** — Sinus tachycardia is common in TCA overdose, likely due to anticholinergic (vagolytic) hemodynamic decompensation causing a reflex tachycardia. Hypotension is common following significant TCA poisoning, and mortality from TCA overdose is due largely to refractory hypotension [12,13]. Cardiac conduction abnormalities may contribute to hypotension. Ventricular tachycardia and ventricular fibrillation (VT and VF) occur in approximately 4 percent of TCA overdose cases [14]. VT and VF are more common in severe poisonings (eg, severe acidosis, hypotension), particularly those involving extreme QRS prolongation.

**CNS toxicity** — Mental status changes, such as a decreased level of consciousness (due to antihistaminic effects) or, less frequently, delirium (due to anticholinergic effects), are common following TCA overdose.

TCA poisoning can cause seizures, likely due to the antagonist effects of TCAs on the GABA-A receptor [15,16]. Most seizures are brief and self-limited, but some are associated with cardiovascular deterioration, including hypotension and ventricular arrhythmia [17,18]. Maprotiline has been associated with a greater frequency of seizures and arrhythmias than other TCAs [19].

**Anticholinergic toxicity** — TCAs have anticholinergic effects and signs of TCA poisoning can include hyperthermia, flushing, dilated pupils that respond poorly to light, delirium, intestinal ileus, and urinary retention. (See "Anticholinergic poisoning", section on 'Clinical features of overdose'.)

**DIAGNOSTIC TESTING**

**General approach** — Laboratory studies and other diagnostic testing are directed toward establishing the diagnosis, estimating the severity of intoxication, and ruling out additional toxicities. (See "General approach to drug poisoning in adults".)

Routine laboratory evaluation of the poisoned patient should include the following:

- An electrocardiogram, to assess for cardiac conduction abnormalities (this is particularly important in tricyclic antidepressant [TCA] ingestions)
- Fingerstick glucose, to rule out hypoglycemia as the cause of any alteration in mental status
- **Acetaminophen** and salicylate levels, to rule out these common coingestants
- Pregnancy test in women of childbearing age

**Electrocardiogram**

**Monitoring and overview of conduction abnormalities** — Cardiac conduction abnormalities are common in patients with TCA poisoning. Therefore, obtaining an electrocardiogram (ECG) immediately upon presentation is essential in patients with known or suspected TCA poisoning ([table 1](#)). Arrhythmias from a TCA overdose can develop quickly and ECGs should be obtained frequently until the patient has been free of any symptoms or signs of cardiac toxicity for several hours. We suggest obtaining an ECG approximately every hour, but more frequent studies are needed if the patient manifests signs of cardiotoxicity or conduction abnormalities are evident on the initial ECG or a cardiac monitor.
• Abnormal size and ratio of the R and S waves in lead AVR: R wave in AVR >3 mm; R to S ratio in AVR >0.7

These signs are used as important tools in diagnosis, risk stratification, and management (waveform 2A-D). However, none is completely reliable in the individual patient, and significant toxicity can occur despite falsely reassuring indices [20]. Preexisting conduction delay may also complicate interpretation. We view prolongation of the QRS duration >100 msec as a sign of potential cardiac toxicity, and as an indication for a trial of therapy with intravenous sodium bicarbonate. (See 'Sodium bicarbonate for cardiac toxicity' below.)

Other possible ECG findings with TCA poisoning include prolongation of the PR and QT intervals, block within the His-Purkinje system, and intraventricular conduction delay (eg, bundle branch block). Because of its relatively longer refractory period, the right bundle branch is especially sensitive to block from TCA overdose [21]. Several reports have described a Brugada type pattern following TCA overdose, with the incidence ranging from 2.3 to 15 percent of overdose [22,23]. These conduction system abnormalities may contribute to the hypotension seen in TCA poisoning. Although QT prolongation is common in TCA overdose, the polymorphic ventricular tachycardia associated with QT prolongation, Torsade de Pointes (TdP), is not.

**QRS duration** — The most prominent electrocardiographic manifestation of TCA toxicity is widening of the QRS interval. In one prospective series, patients with a QRS duration less than 100 msec did not suffer a seizure or a ventricular arrhythmia; those with a QRS duration >100 msec had a 26 percent chance of seizure; and those with a QRS duration >160 msec had a 50 percent chance of a ventricular arrhythmia [24]. Although some authors have questioned the utility and reproducibility of QRS duration analysis [20,25,26], other studies confirm the predictive value of QRS duration for seizure and ventricular arrhythmia [27-29]. In the setting of a TCA overdose, we consider a QRS interval duration greater than 100 msec an indication for bicarbonate therapy. (See 'Sodium bicarbonate for cardiac toxicity' below.)

**Terminal frontal plane QRS vector** — Delayed right ventricular activation from intra and interventricular conduction delays in the setting of TCA overdose has been shown to cause a rightward shift in the terminal 40 msec of the frontal plane QRS vector [21,27,28,30]. Precise measurement of this parameter can be performed but is complex and rarely done at the bedside. In qualitative terms, this conduction delay manifests as a deep, slurred S wave in leads I and AVL, and an R wave in lead AVR (waveform 1 and waveform 2A). (See "Basic approach to delayed intraventricular conduction".)

As a result of this differential conduction delay, R wave amplitude in lead AVR (RAVR) and the ratio of R:S wave amplitude in AVR (R/SAVR) are significantly higher in patients with a TCA overdose compared to matched controls [28]. One cohort study noted that the risk of seizures and ventricular arrhythmias was significantly increased in patients with RAVR >3 mm, R/SAVR >0.7, and QRS duration >100 msec [28].

**Measurement of TCA concentrations** — Qualitative (urine) and quantitative (serum) TCA testing have limited therapeutic and prognostic utility in the acute setting. Significant illness can occur at drug concentrations not classically described as toxic, especially in children and in patients taking TCAs on a chronic basis [27,31,32]. In addition, a positive qualitative test only indicates use, not overdose, and multiple drugs, including carbamazepine, diphenhydramine, cyclobenzaprine, and quetiapine cross-react with qualitative immunoassays, potentially yielding false positive results [33-36]. Quantitative serum concentrations are not only poor predictors of systemic toxicity, due to the kinetic changes described above, but are usually not available within a clinically relevant time frame [24]. (See 'Pharmacology' above.)

For all these reasons, we do not advocate the use of any numerical level to gauge toxicity. The clinical picture dictates the need for therapy in TCA overdose; clinicians should not be falsely reassured by a low serum drug concentration, nor should they initiate therapy solely on the basis of a high serum drug concentration.

**DIAGNOSIS** — Although a definitive diagnosis of tricyclic antidepressant (TCA) overdose can be made using serum measurements, such testing is typically not available to clinicians in a timely fashion and seldom plays a role in patient management. Clinically, the diagnosis of TCA poisoning is made based upon a history of ingestion, symptoms and signs consistent with the diagnosis, and characteristic ECG findings.

Signs of TCA poisoning typically include sedation, but may also include confusion, delirium, or hallucinations. Sinus tachycardia and other arrhythmias, hypotension, cardiac conduction delays, and anticholinergic toxicity (hyperthermia, flushing, dilated pupils, intestinal ileus, urinary retention, and sinus tachycardia) are also common. Of note, patients...
ECG findings suggestive of cardiotoxicity include: prolongation of the QRS >100 msec; abnormal morphology of the QRS (eg, deep, slurred S wave in leads I and AVL); and, abnormal size and ratio of the R and S waves in lead AVR (R wave in AVR >3 mm; R to S ratio in AVR >0.7), or possibly a Brugada pattern.

**DIFFERENTIAL DIAGNOSIS** — The differential diagnosis of patients presenting with toxicity from tricyclic antidepressants (TCAs) is broad given the range of clinical findings (decreased level of consciousness, seizures, anticholinergic effects, hypotension, and widening of the QRS interval) associated with this poisoning. In addition to being common in TCA toxicity, these findings are associated with a number of other poisonings:

- Decreased level of consciousness may be caused by sedative-hypnotic drugs, anti-epileptic drugs, alcohols, opioids and opiates, carbon monoxide, cyanide and hydrogen sulfide, and antipsychotics;
- Seizures may be seen with cocaine, salicylates, methylxanthines (eg, caffeine and theophylline), metals (lead), and other therapeutic agents such as bupropion, tramadol, propoxyphene and baclofen;
- Anticholinergic effects (primarily muscarinic) may be sequelae of poisoning from diphenhydramine and other antihistamines, carbamazepine, cyclobenzaprine, amantadine, clozapine, phenothiazines, procainamide, quinidine, and trihexyphenidyl, among others;
- Hypotension with reflex tachycardia may result from poisoning from various antihypertensives, such as alpha-adrenoreceptor antagonists, nitrates, and dihydropyridine calcium channel antagonists (such as nifedipine, nimodipine, amlodipine and felodipine);
- QRS widening may be due to other sodium channel antagonists, such as diphenhydramine, phenytoin, propoxyphene, cocaine and the class 1A and 1C Vaughan Williams antiarrhythmics.

Generally speaking, it is the constellation of the above findings (particularly depressed mental status, peripheral anticholinergic signs, and evidence of sodium channel antagonism on ECG) that strongly suggests TCA poisoning. Other drugs that can mimic this specific clinical picture include diphenhydramine and possibly carbamazepine, although the former is less known for depressed mental status and controversy exists regarding the risk of fatal arrhythmias [37].

**MANAGEMENT**

**Initial resuscitation** — Initial management of the patient with a tricyclic antidepressant (TCA) overdose centers on evaluating and, if necessary, securing the patient's airway, breathing, and circulation. TCA poisoned patients are frequently moribund and require intubation for airway protection and ventilation. In hypotensive patients, avoid induction agents that may worsen hypotension. Supplemental oxygen should be administered as needed. A summary table to facilitate the emergent management of TCA overdose is provided (table 1).

Initial resuscitation includes the following measures:

- **Sodium bicarbonate** to treat cardiac toxicity, as manifested by a prolonged QRS complex or ventricular arrhythmia. (See 'Sodium bicarbonate for cardiac toxicity' below.)
- Isotonic saline given as intravenous (IV) boluses to treat hypotension. IV boluses of 250 to 500 mL can be given and repeated based upon patient response.
- Benzodiazepines for control of agitation. We suggest lorazepam (1 mg IV) or diazepam (5 mg IV), repeated at 5 to 10 minute intervals as needed. Benzodiazepines should be used judiciously, as agitation can rapidly give way to profound sedation (from antihistaminic effects).

Despite prominent anticholinergic toxicity in some patients with TCA poisoning, physostigmine is contraindicated as it is associated with cardiac arrest in the setting of TCA toxicity [38]. (See 'Unhelpful and contraindicated therapies' below.)

Frequent reassessment of patients with known or suspected TCA intoxication is essential, as their level of alertness can change quickly. Patients may manifest psychomotor agitation and delirium in the initial hours after ingestion, only to develop progressive obtundation and coma in later stages. Thus, close monitoring, including pulse oximetry and a cardiac monitor, is necessary. In patients requiring treatment with sodium bicarbonate, an arterial line makes it easier
The initial dose of hypertonic sodium bicarbonate is 1 to 2 mEq/kg, given as a rapid IV push through a large bore IV catheter. In adults, one common approach is to give two to three vials or prefilled syringes (50 mL each) of 8.4 percent sodium bicarbonate. If there is no response to the initial dose, it may be repeated after five minutes. It is useful to run a continuous 12-lead ECG during the infusion to demonstrate the presence (or absence) of narrowing of the QRS complex, a decrease in the R wave amplitude in lead AVR, or resolution of any arrhythmia (waveform 1 and figure 2).

If the QRS narrows after bolus therapy, begin a continuous IV infusion of sodium bicarbonate. We mix 150 mEq of sodium bicarbonate in 1 L of 5 percent dextrose (D5W), and infuse at 250 mL/hour in adults. The same fluid should be given to children at twice their maintenance fluid rate. Excessive fluid resuscitation, which can contribute to the pulmonary complications sometimes associated with narrowing of the QRS complex, should be avoided.

Should a widened QRS interval fail to narrow following bolus therapy with sodium bicarbonate, we still suggest an IV infusion of sodium bicarbonate be started, absent an alternative diagnosis. Failure of a widened QRS to narrow following standard bolus therapy does not exclude the possibility of TCA toxicity, and systemic acidemia potentiates the effect of TCA poisoning [39].

Frequent arterial blood pH measurements should be obtained during treatment with sodium bicarbonate; a reasonable goal pH is 7.50 to 7.55. Volume overload, hypokalemia, hypomagnesemia, and metabolic alkalosis may result from prolonged bicarbonate infusions, and clinical and laboratory parameters must be followed closely to avoid these complications. We measure the arterial pH hourly until it is in the therapeutic range and stable. Thereafter, measurements may be obtained every four to six hours. The serum potassium concentration should be measured concurrently with the arterial pH.

Most toxicologists taper bicarbonate therapy after the resolution of ECG changes, which may occur over hours to days. One reasonable approach is to reduce the infusion rate by about 25 percent per hour over four hours. Should the QRS interval widen during tapering, give an additional bolus of sodium bicarbonate and restart the original infusion rate.

The benefit of sodium bicarbonate is probably due to both an increase in serum pH and the increase in extracellular sodium. The increase in serum pH favors the neutral (ie, non-ionized) form of the drug, making it less available to bind to sodium channels [40,41]. Increasing the extracellular sodium concentration increases the electrochemical gradient across cardiac cell membranes, potentially attenuating the TCA-induced blockade of rapid sodium channels. (See Pharmacology above.)

Most patients with TCA-induced QRS interval prolongation appear to respond to bicarbonate therapy. According to retrospective case series, 80 percent of patients with an increased QRS interval demonstrated a decrease in response to treatment, while 90 percent of hypotensive patients increased their blood pressure [39,42]. The rationale for this therapy is based in part upon studies using animal models of TCA poisoning showing that hypertonic sodium bicarbonate narrows the QRS complex, improves systolic blood pressure, and controls ventricular arrhythmias [40,42-46]. However, there is a conspicuous absence of randomized trials in humans, and most evidence of efficacy is based upon clinical experience [39,46].

Anti-seizure therapy — Benzodiazepines remain the treatment of choice for TCA-induced seizures. Reasonable initial treatment options include diazepam 5 mg IV, or lorazepam 2 mg IV. (See "Initial management of the critically ill adult with an unknown overdose", section on "D": Disability and neurological stabilization' and "Convulsive status epilepticus in adults: Treatment and prognosis", section on 'Initial pharmacologic therapy'.)

TCA-induced seizures are likely caused largely by central GABA-A receptor inhibition. It is therefore logical to treat seizures with GABA agonists such as benzodiazepines rather than sodium channel blocking drugs.

In the unusual case that benzodiazepines are ineffective, barbiturates may be used to control seizures. However, they are considered second line therapy due to their adverse effects upon blood pressure.

Gastrointestinal decontamination — After the airway, breathing, and circulation have been secured, attention may be turned to gastrointestinal decontamination. Unless bowel obstruction, ileus, or perforation is suspected, we suggest treatment with 1 g/kg of activated charcoal (maximum dose 50 g) in patients who present within two hours of ingestion. Charcoal should be withheld in patients who are sedated and may not be able to protect their airway, unless tracheal intubation is performed first. However, tracheal intubation should not be performed solely for the purpose of giving charcoal [47,48]. (See "Gastrointestinal decontamination of the poisoned patient".)
Management of refractory toxicity — **Sodium bicarbonate** remains the mainstay of treatment for antiarrhythmia or hypotension related to TCA poisoning. In the uncommon circumstance that sodium bicarbonate and other initial resuscitative measures are ineffective, several alternative treatments are available. These are described below, along with several proposed treatments that should be avoided. There is no certain method for determining when sodium bicarbonate therapy has failed and adjunct therapy should be given. One reasonable approach is to begin giving adjunct therapies to any patient who remains hypotensive with a wide QRS interval despite two treatments with sodium bicarbonate as described above. Because refractory toxicity is uncommon and suggests that the patient will be difficult to manage, we recommend consultation with a medical toxicologist or poison control center in such cases. (See *[Sodium bicarbonate for cardiac toxicity](#)* above and *[Additional resources](#)* below.)

**Refractory hypotension**

**Vasopressors** — Vasopressors are indicated in patients with hypotension refractory to sodium bicarbonate aggressive IV fluid resuscitation therapy. Direct-acting alpha adrenergic agonists (eg, **norepinephrine** or phenylephrine) are preferred because they counter the alpha adrenergic antagonist effects of TCAs. The IV infusion of the selected vasopressor is titrated to effect.

A small retrospective study of TCA-poisoned patients demonstrated a universal response to norepinephrine infusion, including patients who had previously failed to respond to dopamine infusion [49].

**Hypertonic (3 percent) saline** — We suggest that hypertonic saline be used only when hypotension is refractory to all other first line treatments, including sodium bicarbonate and aggressive fluid resuscitation. Patients who remain unstable following adequate alkalization, as determined by arterial pH, and whose hypotension has failed to improve despite aggressive IV fluid resuscitation and treatment with a direct acting vasopressor (eg, **norepinephrine**) may be treated with hypertonic saline. We give a 100 mL IV bolus of 3 percent saline; if symptoms persist, one or possibly two more doses can be given at ten minute intervals. No additional hypertonic saline should be given and the serum sodium concentration should be monitored.

Some toxicologists advocate hypertonic (3 percent) saline as an alternative to sodium bicarbonate therapy. However, reports about its effectiveness are conflicting and there is no clear benefit over sodium bicarbonate. Hypertonic saline therapy improves hypotension, but, with the exception of one case report, there is little evidence that it improves arrhythmias [50].

**Refractory arrhythmias**

**Magnesium** — We do not recommend magnesium as a first line therapy for TCA poisoning, but it may be used as an adjunct treatment in patients whose arrhythmia is unresponsive to sodium bicarbonate. There are no standard dosing recommendations for magnesium in this setting. One reasonable approach is to give 1 to 2 g over 15 minutes or faster, if the patient is in cardiac arrest.

A randomized trial, several case reports, and animal studies support the use of intravenous magnesium to help control arrhythmias caused by TCA poisoning but refractory to sodium bicarbonate therapy [51-53]. In the randomized trial of 72 patients with TCA poisoning, those treated with magnesium in addition to sodium bicarbonate therapy experienced lower mortality than those treated with sodium bicarbonate alone [54].

**Lidocaine** — Lidocaine (Class IB) has been used to treat TCA poisoning with some encouraging results, but we do not advocate its routine use as a first line therapy [55,56]. We suggest lidocaine only be considered when sodium bicarbonate therapy is ineffective (ie, arrhythmia persists). Should lidocaine be needed, we suggest standard anti-arrhythmic doses, including a bolus dose (1 to 1.5 mg/kg IV), followed by an infusion (1 to 4 mg/minute). Phenytoin, another Class IB agent, has been studied in TCA poisoning but its use is controversial and not generally recommended. (See *[Unhelpful and contraindicated therapies](#)* below.)

Severe hemodynamic instability and impending cardiac arrest

**Lipid emulsion** — Lipid emulsion has been used to counteract the activity of lipophilic drugs in overdose, including TCAs [57-61]. The mechanism, evidence, dosing, and side effects of IV lipid emulsion therapy are discussed in detail separately. (See *[Calcium channel blocker poisoning](#)*, section on 'Lipid emulsion therapy'.)

While clear indications have not been established, lipid therapy may be used in patients with a TCA overdose who do
The dosing protocol most widely reported consists of an intravenous bolus of 1 to 1.5 mL/kg given over one minute of a 20 percent lipid emulsion solution. The same dose may be repeated in cases of cardiac arrest every three to five minutes, for a total of three bolus doses. Following the initial bolus, an infusion is started at a rate of 0.25 to 0.5 mL/kg per minute until hemodynamic recovery occurs. Ideally, the infusion should be discontinued before a maximum of 8 mL/kg is reached. In the event that hemodynamic instability persists, the drip may be continued for one hour.

Other potential therapies — Although rarely used for TCA poisoning, cardiac pacing has been used successfully for an unusual case of junctional bradycardia following imipramine ingestion [62]. There is no clear data supporting the use of mechanical hemodynamic support, extracorporeal membrane oxygenation, or similar procedures.

Unhelpful and contraindicated therapies

Enhanced elimination — Several case reports describe the successful use of various therapies for TCA overdose, including plasma exchange and charcoal hemoperfusion [63-66]. However, these are generally isolated cases, difficult to determine efficacy, as well as whether coingestants were involved. In general, interventions to enhance elimination are not likely to be effective due to the large volume of distribution of TCAs, and plasma exchange and hemoperfusion are not recommended [67].

Medications — Flumazenil is contraindicated in patients with known or suspected TCA use. In patients who acutely coingest TCAs and benzodiazepines, flumazenil may lower the seizure threshold. In patients with an isolated TCA ingestion who use benzodiazepines chronically, flumazenil can induce benzodiazepine-withdrawal seizures. Despite prominent anticholinergic toxicity in some patients with TCA poisoning, physostigmine is contraindicated as it is associated with cardiac arrest in the setting of TCA toxicity [38].

With the exception of lidocaine and magnesium (discussed above), concerns surround the use of all classes of antiarrhythmic drugs in the setting of TCA poisoning. Class IA (eg, procainamide) and Class IC agents (eg, flecainide) are contraindicated given their inhibition of rapid sodium channels, an effect similar to that induced by TCAs. Class III agents (eg, amiodarone) are poorly studied in this setting and the QTc prolongation associated with these drugs makes them potentially dangerous. Although a Class IB agent like lidocaine, phenytoin is generally not recommended in the setting of TCA poisoning. (See "Myocardial action potential and action of antiarrhythmic drugs").

Pediatric considerations — TCA poisoning in the pediatric population generally follows a course similar to that in adults, and the above-mentioned assessment and treatment recommendations apply. In any pediatric ingestion, healthcare workers should ascertain how the child got access to the medication, counseling caregivers regarding medication safety as appropriate.

Disposition — Patients with an alteration in mental status, hypotension, cardiac conduction abnormalities, or seizures should be admitted to an intensive care unit. Patients with mild symptoms, such as an isolated tachycardia without evidence of conduction abnormalities (ie, QRS <100 msec) over several hours of observation, could conceivably be admitted to a non-intensive care setting with cardiac monitoring. Asymptomatic patients who manifest no conduction abnormalities on ECG and are monitored for at least six hours in an acute care setting can be safely discharged or transferred to a psychiatric service for evaluation. (See "Suicidal ideation and behavior in adults").

ADDITIONAL RESOURCES — Regional poison control centers in the United States are available at all times for consultation on patients who are critically ill, require admission, or have clinical pictures that are unclear (1-800-222-1222). In addition, some hospitals have clinical and/or medical toxicologists available for bedside consultation and/or inpatient care. Whenever available, these are invaluable resources to help in the diagnosis and management of ingestions or overdoses. The World Health Organization provides a listing of international poison centers at its website: www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html

SUMMARY AND RECOMMENDATIONS

• Tricyclic antidepressant (TCA) usage remains common and overdose of TCA medications can be life-threatening. A summary table to facilitate the emergent management of TCA overdose is provided (table 1).

• Symptoms and signs of TCA intoxication generally consist of vital sign abnormalities, mental status changes, seizures, and anticholinergic toxicity. Sinus tachycardia and hypotension are common. Sedation is the most typical alteration in mental status, but confusion, delirium, or hallucinations may occur. Anticholinergic toxicity
• The clinical course of patients with TCA poisoning can be unpredictable, and patients who present immediately after ingestion may initially be well-appearing, only to deteriorate rapidly. Patients must be closely monitored. Maprotiline has been associated with a greater frequency of seizures and arrhythmias than other TCAs.

• Cardiac conduction abnormalities are common in patients with TCA poisoning. These abnormalities can degenerate into ventricular tachycardia and ventricular fibrillation (VT and VF), which occur in approximately 4 percent of TCA overdose cases. The electrocardiogram (ECG) is a most valuable tool in determining the extent of TCA poisoning. The following signs suggest cardiotoxicity:
  - Prolongation of the QRS >100 msec
  - Abnormal morphology of the QRS (eg, deep, slurred S wave in leads I and AVL)
  - Abnormal size and ratio of the R and S waves in lead AVR: R wave in AVR >3 mm; R to S ratio >0.7 (see 'Cardiac toxicity' above and 'Electrocardiogram' above)

• Although a definitive diagnosis of TCA overdose can be made using serum measurements, such testing is typically not available to clinicians in a timely fashion and seldom plays a role in patient management. Clinically, the diagnosis of TCA poisoning is made based upon a history of ingestion, symptoms and signs consistent with the diagnosis, and characteristic ECG findings. (See 'Diagnosis' above and 'Differential diagnosis' above.)

• Initial treatment of TCA overdose includes assessing and securing the patient’s airway, breathing, and circulation. TCA poisoned patients are frequently moribund and require intubation for airway protection and ventilation. Intravenous boluses of isotonic saline are used to treat hypotension. We recommend sodium bicarbonate therapy for QRS duration >100 msec or any ventricular arrhythmia caused by TCA poisoning (Grade 1B). The initial dose of sodium bicarbonate is 1 to 2 mEq/kg. In adults, this may be given as two to three 50 mEq (50 mL) vials or prefilled syringes of 8.4 percent sodium bicarbonate given as a rapid IV push through a large bore IV. (See 'Initial resuscitation' above and 'Sodium bicarbonate for cardiac toxicity' above.)

• Benzodiazepines remain the treatment of choice for TCA-induced seizures. Reasonable initial treatment options include diazepam 5 mg IV or lorazepam 1 mg IV. Unless bowel obstruction, ileus, or perforation is suspected, we suggest treatment with 1 g/kg of activated charcoal (maximum dose 50 g) in patients who present within two hours of ingestion (Grade 2C). Most patients respond well to standard care; for patients with refractory toxicity, management is reviewed in the text. (See 'Anti-seizure therapy' above and 'Gastrointestinal decontamination' above and 'Management of refractory toxicity' above.)

• Despite prominent anticholinergic toxicity in some patients, physostigmine is contraindicated as it is associated with cardiac arrest in the setting of TCA toxicity. Class IA (eg, procainamide) and Class IC antiarrhythmics (eg, flecainide) are also contraindicated. (See 'Unhelpful and contraindicated therapies' above.)

Use of UpToDate is subject to the Subscription and License Agreement.

REFERENCES


# Tricyclic antidepressant intoxication: Rapid overview

To obtain emergent consultation with a medical toxicologist, call the United States Poison Control Network at 1-800-222-1222, or access the World Health Organization's list of international poison centers ([www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html](http://www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html)).

## Clinical features

<table>
<thead>
<tr>
<th>Neurologic</th>
<th>Sedation, coma, seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Tachycardia, hypotension, conduction abnormalities</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>Dilated pupils, dry mouth, absent bowel sounds, urinary retention</td>
</tr>
</tbody>
</table>

## Diagnostic evaluation

**Electrocardiographic changes in severe poisoning:**

- QRS duration >100 msec
- Rightward deflection of the terminal 40 msec of the QRS complex
- Deep S wave in leads I, AVL; tall R wave in lead AVR
- R wave in AVR >3 mm; R/S ratio in AVR >0.7

**Serum TCA concentrations do not help to guide therapy**

## Treatment

### Airway

Manage as indicated; many patients require tracheal intubation

### Breathing

Administer supplemental oxygen

### Circulation

Hypotension: Treat with intravenous boluses of isotonic crystalloid. If patient remains hypotensive despite aggressive volume resuscitation, can treat with a vasopressor. Alpha-adrenergic agonists (eg, neosynephrine, norepinephrine) are preferred.

Conduction disturbances: If QRS >100 msec, challenge with intravenous sodium bicarbonate (2 to 3 mEq/kg up to 150 mEq IV push) and assess for QRS narrowing. If QRS narrows, begin continuous infusion (150 mEq of sodium bicarbonate in 1 liter of D5W to run at 250 mL/hour in adults or twice the maintenance fluid rate in children).

### Gastrointestinal decontamination

Administer activated charcoal if patient presents within 2 hours of ingestion, unless gastrointestinal complication (ileus, obstruction) suspected. Dose is 1 g/kg (maximum dose 50 g).

### Seizures

Treat with benzodiazepines (eg, diazepam 5 mg IV or lorazepam 2 mg IV)

Do **NOT** treat with phenytoin
Action potentials generated by different parts of conduction system

The sinoatrial (SA) and atrioventricular (AV) nodes generate a slow action potential, mediated by calcium ions. In comparison, the tissues of the atria, ventricles, and the His-Purkinje system generate a fast action potential mediated by sodium ions. Sequential activation of these structures results in the characteristic waveforms visible on the surface electrocardiogram (ECG). The AV node and bundle of His are small structures; as a result, no electrical activity is recorded on the surface ECG during their activation.

Graphic 61989 Version 3.0
Electrocardiographic changes from tricyclic antidepressant overdose

The QRS complex is prolonged with delayed right ventricular activation and intraventricular conduction delay, which results in rightward shift in the terminal 40 msec frontal plane QRS vector. In qualitative terms, this shift manifests as a deep, slurred S wave in leads I and AVL, and an R wave in lead AVR (blue arrows).

Graphic 63490 Version 3.0
ECG with TCA poisoning: Initial presentation

These are a series of electrocardiograms (ECGs) obtained from a patient with tricyclic antidepressant overdose. The first (above) shows the initial ECG demonstrating QRS interval prolongation and characteristic changes in AVR. The second (Severe cardiac toxicity) shows worsening changes consistent with progression of cardiac toxicity. Note the increases in the QRS interval and the R wave in AVR. The third (After treatment) shows narrowing of the QRS complex but persistent right axis deviation of the terminal 40 milliseconds following the initiation of treatment. The final ECG (Resolution) shows complete resolution of interval changes related to toxicity.

Courtesy of Steven Sahalnick, MD.

Graphic 87662 Version 2.0
### ECG with TCA poisoning: Severe cardiac toxicity

**Name:** [Redacted]  
**ID:** [Redacted]  
**Date:** 14-FEB-2002 07:23 CHILDRENS HOSPITAL PD  
**Vital Signs:**  
- **Name:** [Redacted]  
- **ID:** [Redacted]  
- **Age:** [Redacted]  
- **Sex:** [Redacted]  
- **Weight:** [Redacted]  
- **Height:** [Redacted]  
- **Weight:** [Redacted]  
- **Pgm 007A Location:** [Redacted]  
- **Room:** [Redacted]  

**ECG Details:**  
- **Vent. rate:** 150 BPM  
- **PR interval:** 188 ms  
- **QRS duration:** 160 ms  
- **Cart:** 1  
- **QT/Qtc:** 332/520 ms  
- **P-R-T axes:** 92 -77 93  

**Diagnosis:**  
- **SINUS TACHYCARDIA**  
- **RIGHT ATRIAL ENLARGEMENT**  
- **LEFT AXIS DEVIATION**  
- **NONSPECIFIC INTRAVENTRICULAR BLOCK**  
- **ABNORMAL ECG**

**Referred by:** [Redacted]  
**Unconfirmed:** [Redacted]

---

*Courtesy of Steven Sahalnick, MD.*

Graphic 87829 Version 1.0
ECG with TCA poisoning: After treatment

Courtesy of Steven Sahalnick, MD.

Graphic 87830 Version 1.0
### ECG with TCA poisoning: Resolution

<table>
<thead>
<tr>
<th>25mm/s</th>
<th>Med: None</th>
<th>Ht: Wt:</th>
<th>NORMAL SINUS RHYTHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>10mm/V</td>
<td></td>
<td>Room: 1039A</td>
<td>NORMAL ECG</td>
</tr>
<tr>
<td>100Hz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pgm 007B</td>
<td>17yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loc: 10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Vent. rate: 80 BPM
- PR interval: 124 ms
- QRS duration: 88 ms
- QT/QTc: 344/395 ms
- P-R-T axes: 55 77 67

---

**Graphic 87832 Version 1.0**

_Courtesy of Steven Sahalnick, MD._

Electrocardiographic changes associated with tricyclic antidepressant overdose

Following treatment with sodium bicarbonate, the intraventricular conduction delay resolves, and the QRS complex duration and morphology return to normal.

Graphic 76352 Version 1.0
Contributor Disclosures

Steven D Salhanick, MD Nothing to disclose. Stephen J Traub, MD Nothing to disclose. Jonathan Grayzel, MD, FAAEM Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy