Cyclic Antidepressants Toxicity

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- Cyclic antidepressants were the first generation of drugs developed to treat depression.
- Cyclic antidepressants are now occasionally used to treat obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, panic and phobia disorders, and anxiety disorders.
- 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.
- Cyclic antidepressants possess a narrow therapeutic index, and toxicity can occur at therapeutic dosages

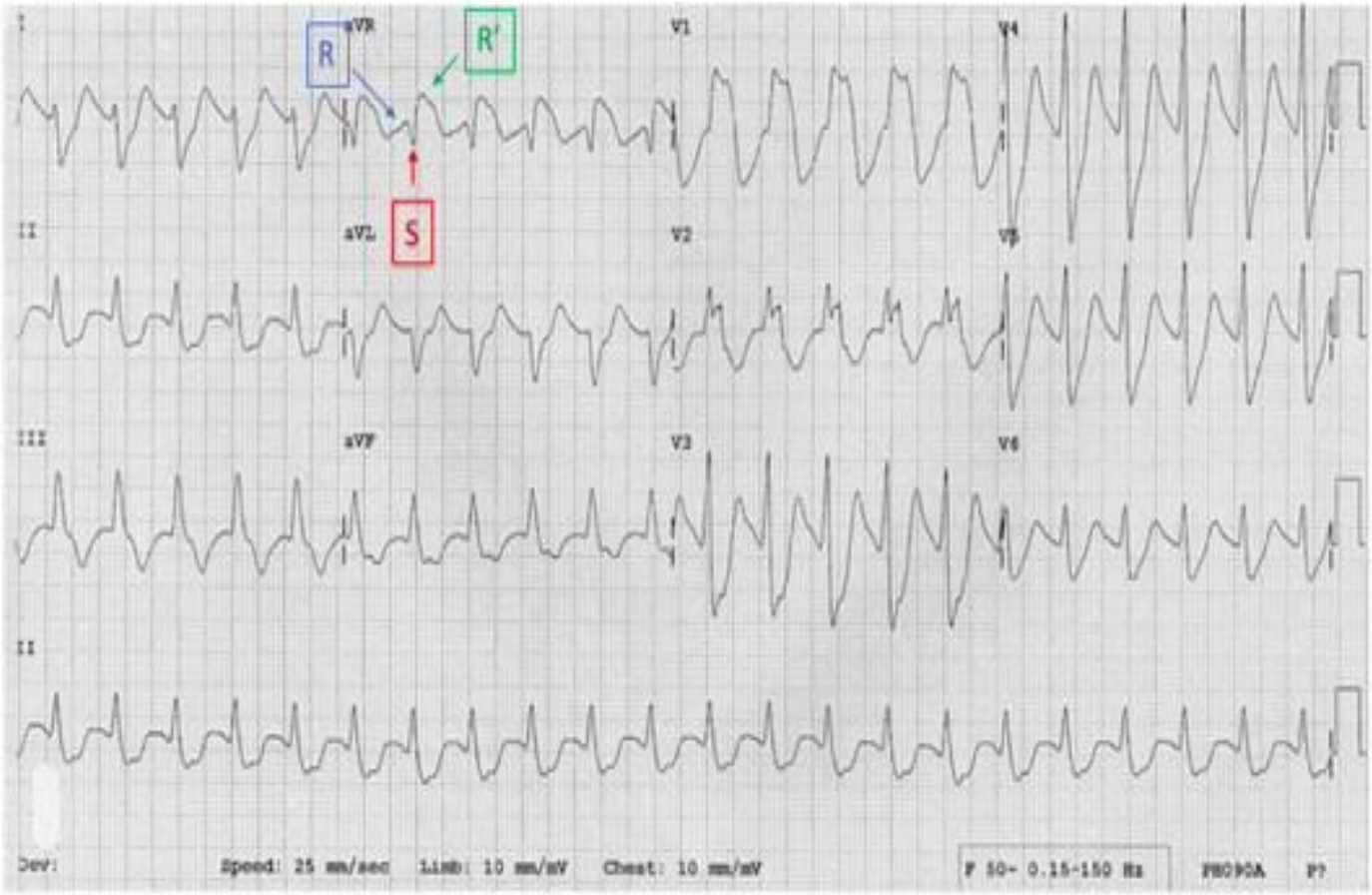
ECG Changes

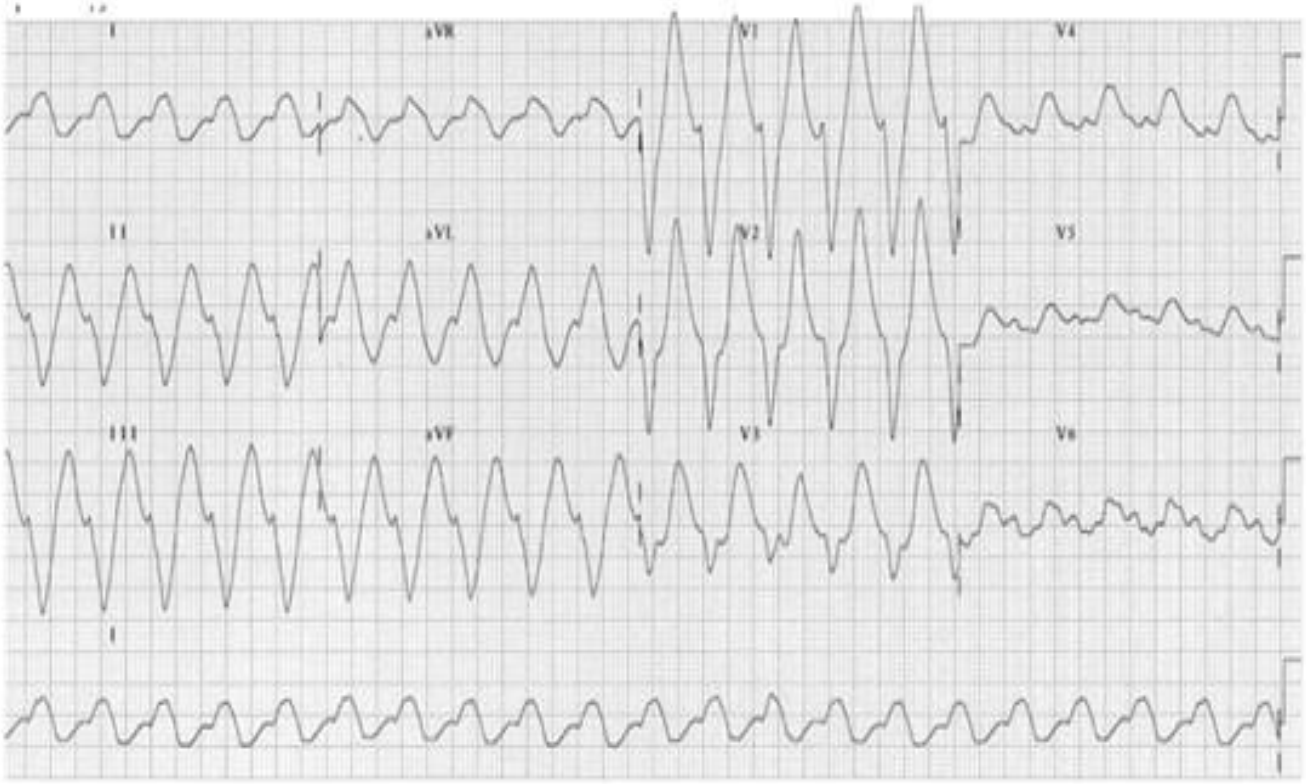
- Prolongation of the PR and QRS.
- Frontal plane right axis deviation
- Brugada pattern
- Terminal R wave in ECG lead aVR and an S wave in ECG lead I

  Terminal R wave > 3 mm in aVR

  R/S ratio > 0.7 in aVR

- **Therefore, the Brugada pattern strongly suggests a cyclic antidepressant overdose.**


R
R'
S
aVR
V1
V4
aVL
V2
V5
aVF
V3
V6
Speed: 25 mm/sec
Limb: 10 mm/mV
Chest: 10 mm/mV


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

- <1 milligram/kg ……..nontoxic
- >10 milligrams/kg …… life threatening in adults
- >1 gram …..fatal
- Desipramin is the most potent sodium channel blocker and caused fatal arrhythmias
- Amoxapine and maprotiline are most toxic and cause seizures
- **Amoxapine overdoses; this agent can cause status epilepticus without warning or QRS complex widening.**

TABLE 177-3 Pharmacologic Profile of Cyclic Antidepressants

Pharmacologic Activity	Clinical Presentation
Antagonism of postsynaptic histamine receptors	Sedation, depressed consciousness
Antagonism of postsynaptic muscarinic receptors (both central and peripheral)	Central antimuscarinic: agitation to delirium, confusion, amnesia, hallucinations, slurred speech, ataxia, sedation, and coma Peripheral antimuscarinic: dilated pupils, blurred vision, tachycardia, hyperthermia, hypertension, decreased oral and bronchial secretions, dry skin, ileus, urinary retention, increased muscle tone, and tremor
Antagonism of postsynaptic α-adrenergic receptors (α_1-adrenergic > α_2-adrenergic receptors)	α_1-Adrenergic receptor: sedation, miosis, orthostatic hypotension, reflex tachycardia α_2-Adrenergic receptor: mild hypertension
Inhibition of norepinephrine reuptake	Agitation, mydriasis, diaphoresis, tachycardia, early hypertension
Inhibition of serotonin reuptake	Sedation, mydriasis, myoclonus, hyperreflexia (see Chapter 178, "Atypical and Serotonergic Antidepressants")
Inhibition of voltage-gated sodium channels	Impaired conduction, wide QRS complex, other conduction abnormalities; impaired cardiac contractility; wide-complex tachycardia, Brugada pattern, ventricular ectopy Hypotension
Inhibition of voltage-gated rectifier potassium channels	Prolongation of QT interval, ventricular ectopy, torsades de pointes

Clinical features

Altered mental status is the most common symptom reported after cyclic antidepressant exposure.

GCS<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.

- Maprotiline is a tetracyclic

- Amoxapine it is the only antidepressant that has antipsychotic effects and can produce seizures with minimal warning and normal QRS complex.

- **Clinical toxicity from cyclic antidepressants usually lasts longer than explained by the activity of the parent drug because of the production of active metabolites**

- Ingestions of <1 milligram/kg are generally nontoxic.10 Life-threatening symptoms usually occur with ingestions of >10 milligrams/kg in adults, and fatalities are commonly associated with ingestions of >1 gram

- 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

- 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

- Seizures are more commonly reported in maprotiline and trimipramine overdoses. Seizures are usually generalized, are 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

- 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.

- **False-positive results** on qualitative cyclic antidepressant urine drug screens occur with 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

- 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. Right axis deviation is demonstrated as a positive terminal R wave in lead aVR and a negative S wave in lead I

- The risk of seizures increases if the QRS complex is >100 milliseconds, and ventricular dysrhythmias are more common if the QRS duration is >160 milliseconds.

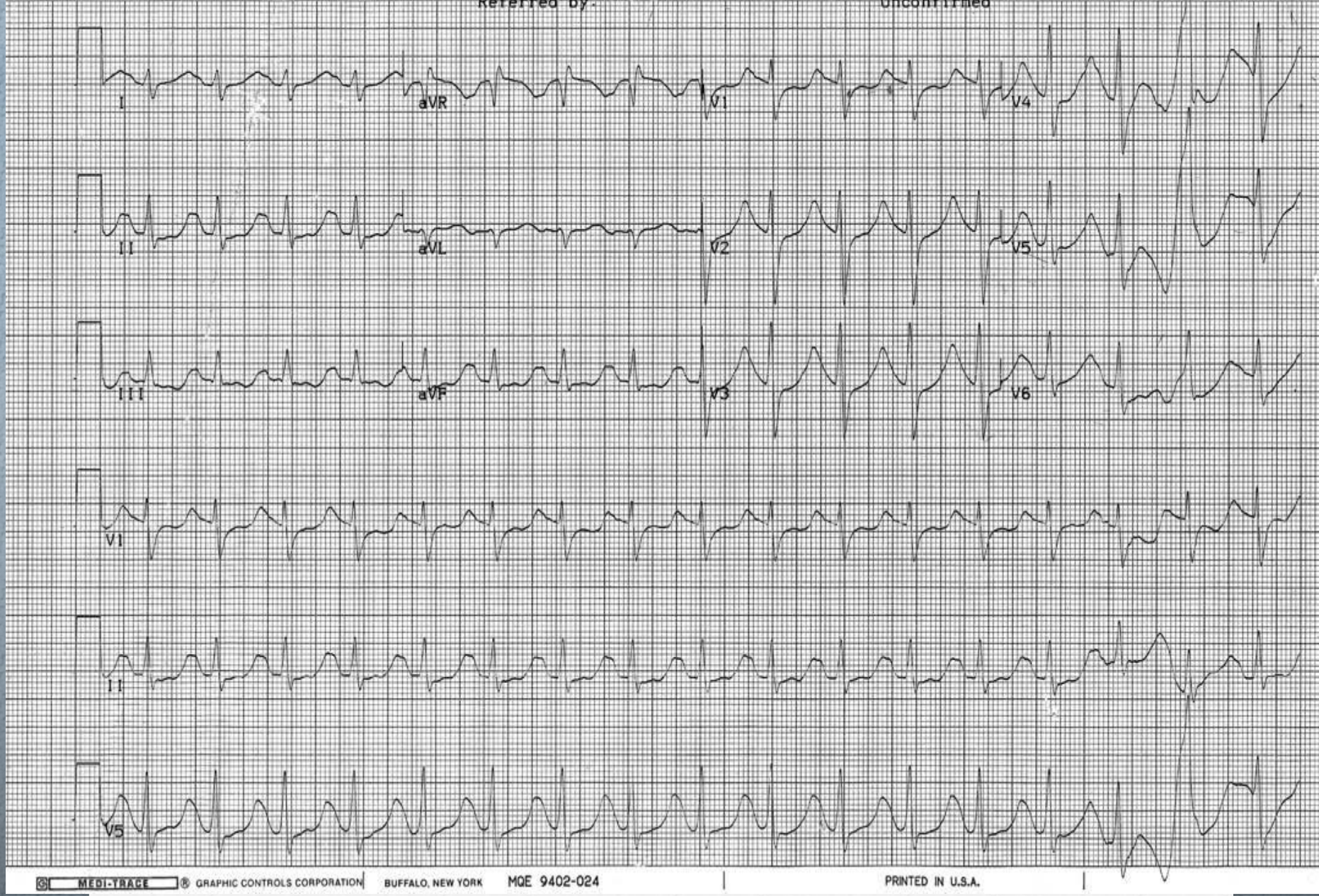
- **ECG abnormalities develop within 6 hours of ingestion and typically resolve over 36 to 48 hours.**

- 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 recommended 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

- Do not use ipecac syrup or gastric lavage. **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

- Sodium bicarbonate is used to treat cardiac conduction abnormalities, ventricular dysrhythmias, or hypotension refractory to IV fluid. **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

- Serum potassium will decrease during sodium bicarbonate therapy, and IV potassium supplementation may be required



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

TABLE 177-4 Treatment of Cyclic Antidepressant Overdose

Treatment	Dose	Indication	Comments
GI decontamination	Activated charcoal 1 gram/kg PO	Within 1 h of ingestion as long as airway is stable and patient is awake	Do not give multidose charcoal; do not perform whole-bowel irrigation
Initial treatment of hypotension or dysrhythmias	Sodium bicarbonate, 1–2 mEq/kg IV bolus; repeat bolus or add 150 mEq to 1 L 5% dextrose in water at 2–3 mL/kg per hour	For dysrhythmias, conduction abnormalities (QRS >100 ms), or hypotension refractory to IV fluid	Keep blood pH 7.50–7.55
Hypokalemia	Replace potassium as needed	Serum potassium <3.5 mEq/L	Bicarbonate will decrease potassium level
Seizures or agitation	Benzodiazepines for seizures or agitation	Phenobarbital 10–15 milligrams/kg for seizures refractory to benzodiazepines; watch for hypotension; secure airway with intubation	Do not give physostigmine, flumazenil, or phenytoin
Hypotension	Treat hypotension with normal saline, up to 30 mL/kg	Use norepinephrine or epinephrine if refractory to IV normal saline	Case reports suggest effectiveness of glucagon, 1 milligram IV bolus
Torsades de pointes and refractory dysrhythmias	Magnesium sulfate 2 grams IV; 3% saline 1–3 mL/kg IV over 10 min; overdrive pacing	Consider lipid emulsion for refractory dysrhythmias, but no convincing evidence of effectiveness	**Do not give** class I antiarrhythmics (i.e., procainamide, lidocaine, phenytoin, flecainide), β-blockers, calcium channel blockers, or class III antiarrhythmics (i.e., amiodarone, sotalol, ibutilide)

- Do not give flumazenil or physostigmine for mixed cyclic antidepressant–benzodiazepine or cyclic antidepressant–anticholinergic overdoses, respectively

- **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

- 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 may be needed. **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 should be treated initially with isotonic crystalloid fluids in IV boluses in increments of 10 mL/kg to a maximum of 30 mL/kg.

- 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, although response may be inconsistent. **Norepinephrine and epinephrine are expected to be 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

- Placement of a pulmonary artery catheter for monitoring in patients whose hypotension is refractory to fluid, sodium bicarbonate, and vasopressor therapy

- There are case reports suggesting that glucagon administered as 1-milligram IV boluses might be effective in patients with refractory cyclic antidepressant–induced hypotension

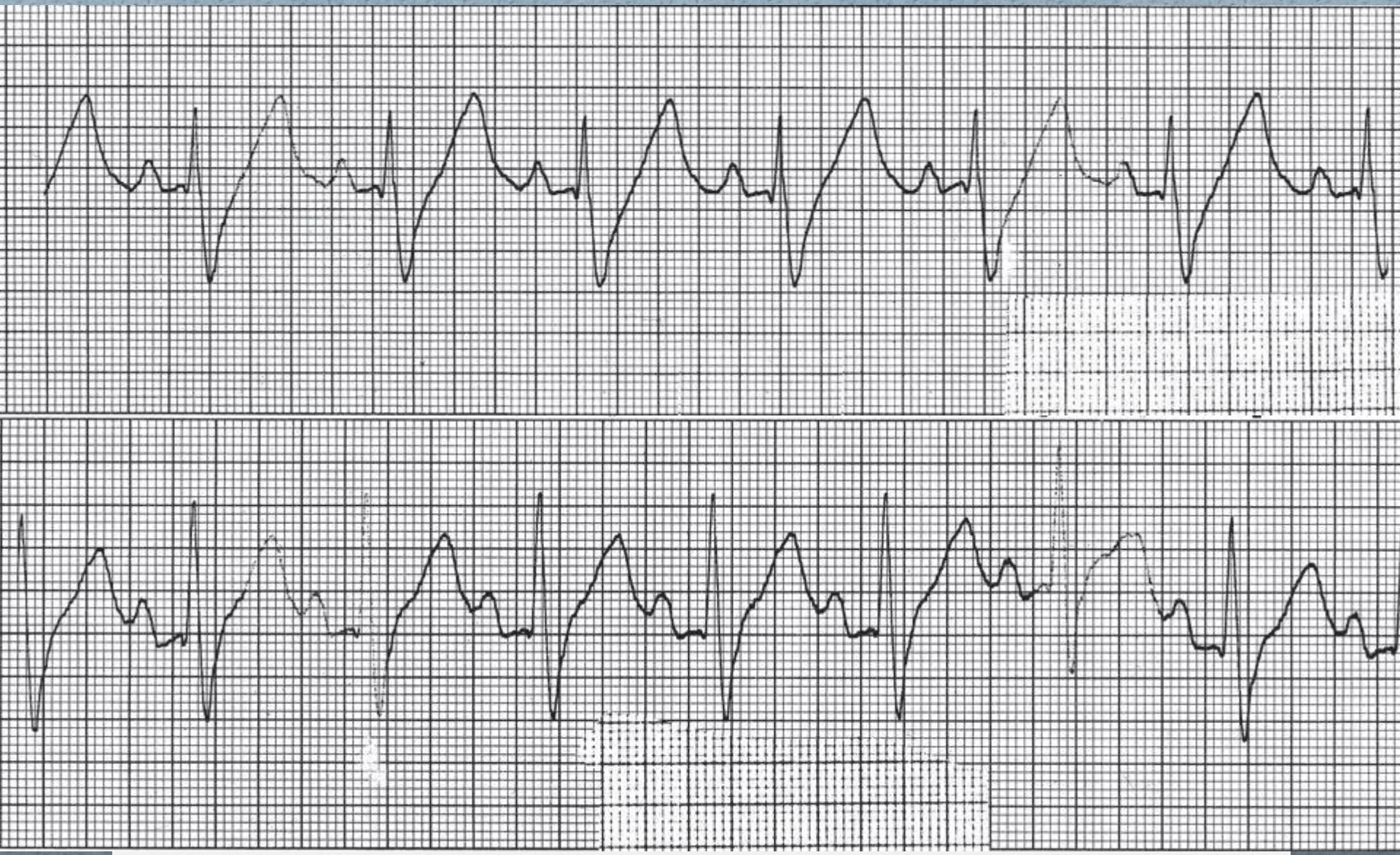
- Ventricular dysrhythmias should be treated with sodium bicarbonate. Consider 3% hypertonic saline, 1 to 3 mL/kg IV over 10 minutes, to decrease ventricular ectopy or dysrhythmia in a patient with cardiotoxicity refractory to sodium bicarbonate therapy

- Torsades de pointes should be treated initially with 2 grams of IV magnesium sulfate

- 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.

- 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 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.



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

Asymptomatic patients with sinus tachycardia, isolated PR interval prolongation, or first-degree atrioventricular block do not require specific pharmacologic therapy.

False-positive results on qualitative cyclic antidepressant urine drug screens occur for carbamazepine, cetirizine, cyclobenzaprine, cyproheptadine.

- Patients who remain asymptomatic after 6 hours of observation do not require hospital admission for toxicologic reasons.

- 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.


Thank you so much for your attention