Toxicology for pharmacists

- Tricyclic antidepressants
- Serotonin reuptake inhibitors
- Natural products

Tricyclic antidepressants (TCA)

- **Mechanism of toxicity.**
- **Cardiovascular effects.** Several mechanisms contribute to cardiovascular toxicity:
    1. Anticholinergic effects and inhibition of neuronal reuptake of catecholamines result in tachycardia and mild hypertension.
    2. Peripheral alpha-adrenergic blockade causes vasodilation and contributes to hypotension.
    3. Membrane-depressant (quinidine-like) effects cause myocardial depression and cardiac conduction disturbances by inhibition of the fast sodium channel that initiates the cardiac cell action potential.
    4. Metabolic or respiratory acidosis may contribute to cardiotoxicity by further inhibiting the fast sodium channel

Central nervous system effects.

- These effects result in part from anticholinergic toxicity (eg, sedation and coma), but seizures are probably a result of inhibition of reuptake of norepinephrine or serotonin in the brain or other central effects.

Pharmacokinetics.

- Anticholinergic effects of these drugs may retard gastric emptying, resulting in slow or erratic absorption.
- Most of these drugs are extensively bound to body tissues and plasma proteins, resulting in very large volumes of distribution and long elimination half-lives.
- Tricyclic antidepressants are metabolized primarily by the liver, with only a small fraction excreted unchanged in the urine.
- Active metabolites may contribute to toxicity; several drugs are metabolized to other well known tricyclic antidepressants (eg, amitriptyline to nortriptyline, imipramine to desipramine)

Toxic dose.

- Most of the tricyclic antidepressants have a narrow therapeutic index, so that doses of less than 10 times the therapeutic daily dose may produce severe intoxication.
- In general, ingestion of 10–20 mg/kg is potentially life-threatening.

Clinical presentation.

- Tricyclic antidepressant poisoning may produce any of three major toxic syndromes: anticholinergic effects, cardiovascular effects, and seizures.
- Hyponatremia is also common.
- Depending on the dose and the drug, patients may experience some or all of these toxic effects.
- Symptoms usually begin within 30–40 minutes of ingestion but may be delayed owing to slow and erratic gut absorption.
- Patients who are awake initially may abruptly lose consciousness or develop seizures without warning

- Anticholinergic effects include sedation, delirium, coma, dilated pupils, dry skin and mucous membranes, diminished sweating, tachycardia, diminished or absent bowel sounds, and urinary retention.
- Myoclonic muscle jerking is common with anticholinergic intoxication and may be mistaken for seizure activity.

	Usual Adult Daily Dose (mg)	Neurotransmitter Effects[a]	Toxicity[b]
Tricyclic antidepressants			
Amitriptyline	75–200	NE, 5-HT	A, H, QRS, Sz
Amoxapine	150–300	NE, DA	A, H, Sz
Clomipramine	100–250	NE, 5-HT	A, H, QRS, Sz
Desipramine	75–200	NE	A, H, Sz
Doxepin	75–300	NE, 5-HT	A, H, QRS, Sz
Imipramine	75–200	NE, 5-HT	A, H, QRS, Sz
Maprotiline	75–300	NE	A, H, QRS, Sz
Nortriptyline	75–150	NE	A, H, QRS, Sz
Protriptyline	20–40	NE	A, H, QRS, Sz
Trimipramine	75–200	NE, 5-HT	A, H, QRS, Sz

Cardiovascular toxicity

- Manifests as abnormal cardiac conduction, arrhythmias, and hypotension.
- Typical electrocardiographic findings include sinus tachycardia with prolongation of the PR, QRS, and QT intervals. A prominent terminal R wave is often seen in lead aVR.
- Various degrees of atrioventricular (AV) block may be seen. A Brugada pattern (down-sloping ST-segment elevation in V1–V3 in association with a right bundle branch block) has also been reported.
- a. Prolongation of the QRS complex to 0.12 seconds or longer, a terminal R wave of 3 mm or more in aVR, and a terminal R wave/S wave ratio of 0.7 or more in aVR are fairly reliable predictors of serious cardiovascular and neurologic toxicity (except in the case of amoxapine, which causes seizures and coma with no change in the QRS interval).

Cardiovascular toxicity

- b. Sinus tachycardia accompanied by QRS-interval prolongation may resemble ventricular tachycardia. True ventricular tachycardia and fibrillation may also occur.
- c. Atypical or polymorphous ventricular tachycardia (torsade de pointes) associated with QT-interval prolongation may occur with therapeutic dosing but is actually uncommon in overdose.
- d. Development of bradyarrhythmias usually indicates a severely poisoned heart and carries a poor prognosis

- Hypotension caused by venodilation is common and usually mild. In severe cases, hypotension results from myocardial depression and may be refractory to treatment; some patients die with progressive, intractable cardiogenic shock.
- Pulmonary edema is also common in severe poisonings.

- Seizures are common with tricyclic antidepressant toxicity and may be recurrent or persistent. The muscular hyperactivity from seizures and myoclonic jerking, combined with diminished sweating, can lead to severe hyperthermia, resulting in rhabdomyolysis, brain damage, multisystem failure, and death.

Death

- Death from tricyclic antidepressant overdose usually occurs within a few hours of admission and may result from ventricular fibrillation, intractable cardiogenic shock, or status epilepticus with hyperthermia.
- Sudden death several days after apparent recovery has been reported occasionally, but in all such cases, there was evidence of continuing cardiac toxicity within 24 hours of death.

Diagnosis.

- **Specific levels**

- **Other useful laboratory** studies include electrolytes, glucose, BUN, creatinine, creatine kinase (CK), urinalysis for myoglobin, arterial blood gases or oximetry, 12-lead ECG and continuous ECG monitoring, and chest radiography.

A. Emergency and supportive measures

- Maintain an open airway and assist ventilation if necessary ***Caution:*** Respiratory arrest can occur abruptly and without warning.
- Treat coma, seizure, hyperthermia, hypotension, and arrhythmias if they occur.
- ***Note:*** Do **not** use procainamide or other type Ia or Ic antiarrhythmic agents for ventricular tachycardia because these drugs may aggravate cardiotoxicity.

- Cardiac Pacing
- Seizure control
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- In patients with QRS-interval prolongation or hypotension, administer sodium bicarbonate (p 520), 1–2 mEq/kg IV, and repeat as needed to maintain arterial pH between 7.45 and 7.55.
- Sodium bicarbonate may reverse membrane-depressant effects by increasing extracellular sodium concentrations and by a direct effect of pH on the fast sodium channel.
- Hypertonic sodium chloride has similar effects in animal studies and some human case reports.

- When cardiotoxicity persists despite treatment with sodium bicarbonate, the use of **lidocaine** can be considered, although evidence in people is still limited.
- Lidocaine competes with tricyclic antidepressants for binding at the sodium channel but binds for a shorter period of time and thus may reverse some of sodium channel blockade.

- For severe tricyclic overdose, particularly with amitriptyline and clomipramine, the use of intravenous lipid emulsion therapy has been reported to be beneficial

Non-cyclic antidepressants

- SSRIs inhibit serotonin reuptake transporters resulting in increased stimulation of serotonin receptors in the brain.
- SNRIs inhibit both serotonin and norepinephrine reuptake transporters and also increase stimulation of CNS norepinephrine receptors.
- Most agents cause CNS depression.
- Bupropion is a stimulant that can also cause seizures, presumably related to inhibition of reuptake of dopamine and norepinephrine.

- Trazodone and mirtazapine produce peripheral alpha-adrenergic blockade, which can result in hypotension and priapism
- Serotonin reuptake inhibitors, such as fluoxetine, citalopram, sertraline, paroxetine, fluvoxamine, venlafaxine, and trazodone, may interact with each other, with chronic use of an MAO inhibitor, or with dextromethorphan to produce the "**serotonin syndrome**"

Newer, noncyclic drugs			
Bupropion	200–450	DA, NE	Sz
Citalopram	20–40	5-HT	Sz, SS
Desvenlafaxine	50	5-HT, NE	Sz, SS
Duloxetine	30–180	5-HT, NE	Sz, SS
Escitalopram	10–30	5-HT	Sz, SS
Fluoxetine	20–80	5-HT	Sz, SS
Fluvoxamine	50–300	5-HT	Sz, SS
Levomilnacipran	40–120	5-HT, NE	Sz, SS
Milnacipran	100–200	5-HT, NE	Sz, SS
Mirtazapine	15–45	$Alpha_2$	Sz
Nefazodone	100–600	5-HT, $Alpha_2$	H
Paroxetine	20–50	5-HT	Sz, SS
Sertraline	50–200	5-HT	Sz, SS
Trazodone	50–400	5-HT, $Alpha_2$	H, Sz, SS
Venlafaxine	30–600	5-HT, NE	Sz, SS

Central nervous system

- The usual presentation after SSRI overdose includes ataxia, sedation, and coma.
- Respiratory depression may occur, especially with co-ingestion of alcohol or other drugs.
- These agents, particularly bupropion, can cause restlessness, anxiety, and agitation.
- Tremor and seizures are common with bupropion but occur occasionally after overdose with SSRIs, particularly citalopram, as well as the SNRIs venlafaxine and duloxetine.

Cardiovascular

- **Cardiovascular** effects are usually not life-threatening, although trazodone can cause hypotension and orthostatic hypotension, bupropion and SNRIs can cause sinus tachycardia and hypertension, and citalopram and escitalopram can cause sinus bradycardia with hypotension.

- **1.** Severe cardiotoxicity, including QRS-interval prolongation, hypotension, and cardiac arrest, has been reported with overdoses involving bupropion, citalopram, and venlafaxine.
- **2.** Venlafaxine and citalopram also cause QT-interval prolongation, and the FDA has recommended a maximal daily citalopram dose of 40 mg to minimize the risk of torsade de pointes.

Serotonin syndrome

- Neuromuscular hyperactivity (hyperreflexia, spontaneous or induced clonus, ocular clonus, rigidity, shivering); autonomic instability (tachycardia, hypertension, diaphoresis, hyperthermia, mydriasis, tremor); and mental status changes (agitation, anxiety, confusion, hypomania).
- This reaction may be seen when a patient taking an MAO inhibitor ingests a serotonin uptake blocker. Because of the long duration of effect of MAO inhibitors and most of the serotonin uptake blockers, this reaction can occur up to several days to weeks after either treatment regimen has been discontinued.

Serotonin syndrome

- The syndrome has also been described in patients taking an overdose of a single SSRI or SNRI, an SSRI with meperidine, fentanyl, amphetamines, and derivatives(e.g., methylenedioxymethamphetamine [MDMA]), dextromethorphan, linezolid, lithium, St. John’s wort or combinations of various SSRIs and/or SNRIs.

Diagnosis

- Levels
- Lab studies
- Clinical signs

Treatment

- Supportive
- Serotonin syndrome
- Seizure

COLCHICINE

- Mechanism of toxicity. Colchicine inhibits microtubular formation and function, arresting dividing cells during mitosis. Pharmacokinetics: Colchicine is rapidly absorbed after oral administration and extensively distributed to body tissues.
- It is eliminated in the liver by CYP3A4 with a half-life of 4.4–31 hours

- Toxic dose. The maximum FDA-approved therapeutic dose of oral colchicine for acute gout is 1.2 mg followed by 0.6 mg after 1 hour, for a total dose of 1.8 mg.
- This is a significant reduction from the previously recommended maximum dose of 8 mg. In a series of 150 cases, doses of 0.5 mg/kg or less were associated with diarrhea and vomiting but not death, doses of 0.5–0.8 mg/kg were associated with bone marrow aplasia and 10% mortality, and ingestions greater than 0.8 mg/kg uniformly resulted in death.

- Fatalities, however, have been reported with single ingestions of as little as 7 mg, although other case reports describe survival after ingestions of more than 60 mg.
- Ingestions of parts of colchicine containing plants have resulted in severe toxicity and death.
- The dose used for familial Mediterranean fever in adults is slightly higher at 1.2–2.4 mg per day.
- Dosing should be reduced for renal dysfunction for all uses of colchicine.

- **Clinical presentation.** Colchicine poisoning affects many organ systems, with toxic effects occurring from hours to several days after exposure.

- **A.** After an **acute overdose,** symptoms typically are delayed for 2–12 hours and include nausea, vomiting, abdominal pain, and severe bloody diarrhea.
- Shock results from depressed cardiac contractility and fluid loss into the GI tract and other tissues. Delirium, seizures, or coma may occur.
- Lactic acidosis related to shock and inhibition of cellular metabolism is common.
- Other manifestations of colchicine poisoning include acute myocardial injury, rhabdomyolysis with myoglobinuria, disseminated intravascular coagulation, and acute renal failure.

- Chronic colchicine poisoning presents with a more insidious onset. Factors precipitating toxicity from chronic use include renal insufficiency, liver disease, and drug interactions (erythromycin, cimetidine, cyclosporine) that can inhibit colchicine clearance.

- **B. Death** usually occurs after 8–36 hours and is caused by respiratory failure, intractable shock, and cardiac arrhythmias or sudden cardiac arrest.

- **C. Late complications** include bone marrow suppression, particularly leukopenia and thrombocytopenia (4–5 days) and alopecia (2–3 weeks). Chronic colchicine therapy may produce myopathy (proximal muscle weakness and elevated creatine kinase [CK] levels) and polyneuropathy. This also has occurred after acute poisoning

V. Treatment

A. Emergency and supportive measures. Provide aggressive supportive care, with careful monitoring and treatment of fluid and electrolyte disturbances.

1. Anticipate sudden respiratory or cardiac arrest and maintain an open airway and assist ventilation if necessary (pp 1–7).
2. Treatment of shock (p 15) may require large amounts of crystalloid fluids and possibly blood (to replace losses from hemorrhagic gastroenteritis).
3. Infusion of sodium bicarbonate may be considered if there is evidence of rhabdomyolysis (p 27).
4. Bone marrow depression requires specialized intensive care. Severe neutropenia requires patient isolation and management of febrile episodes, as for other neutropenic conditions. Platelet transfusions may be required to control bleeding.

DIGOXIN AND OTHER CARDIAC GLYCOSIDES

- **A.** With **acute overdose**, nausea, vomiting, hyperkalemia, and cardiac arrhythmias are often seen. Bradyarrhythmias include sinus bradycardia, sinoatrial arrest, second- or third-degree AV block, and asystole. Tachyarrhythmias include paroxysmal atrial tachycardia with AV block, accelerated junctional tachycardia, ventricular bigeminy, ventricular tachycardia, bidirectional ventricular tachycardia, and ventricular fibrillation.
- **B.** With **chronic intoxication**, nausea, anorexia, abdominal pain, visual disturbances (flashing lights, halos, green-yellow perceptual impairment), weakness, fatigue, sinus bradycardia, atrial fibrillation with slowed ventricular response

A. Emergency and supportive measures

1. Maintain an open airway and assist ventilation if necessary (pp 1–7).
2. Monitor the patient closely for at least 12–24 hours after significant ingestion because of delayed tissue distribution.
3. Treat **hyperkalemia** (p 39) with digoxin-specific antibodies (see below); calcium (calcium gluconate 10%, 10–20 mL or 0.2–0.3 mL/kg, or calcium chloride 10%, 5–10 mL or 0.1–0.2 mL/kg, slowly IV); sodium bicarbonate, 1 mEq/kg; glucose, 0.5 g/kg IV, with insulin, 0.1 U/kg IV; and/or sodium polystyrene sulfonate (Kayexalate), 0.5 g/kg orally.
   a. ***Note:*** Although it is widely recommended that calcium be avoided in patients with cardiac glycoside toxicity because of concern that it will worsen ventricular arrhythmias, this warning is based on old and very weak case reports and is not substantiated by animal studies. Calcium is the drug of first choice for life-threatening cardiac toxicity due to hyperkalemia.
   b. Mild hyperkalemia may actually protect against tachyarrhythmias.
4. Hypokalemia and hypomagnesemia should be corrected, as these may contribute to cardiac toxicity.
5. Treat **bradycardia** or **heart block** with atropine, 0.5–2 mg IV (p 512). Temporary transvenous cardiac pacemaker may be needed for persistent symptomatic bradycardia, but because a pacemaker may trigger serious arrhythmias in patients with digitalis toxicity, pacing is recommended only after failure or unavailability of digoxin-specific antibodies.
6. **Ventricular tachyarrhythmias** may respond to correction of low potassium or magnesium. Lidocaine (p 573) and phenytoin (p 608) have been used,

antiarrhythmic drugs.

B. **Specific drugs and antidotes.** Fab fragments of **digoxin-specific antibodies** (eg, DigiFab, p 542) are highly effective in reversing digoxin toxicity and are indicated for significant poisoning. This includes hyperkalemia (>5 mEq/L), symptomatic arrhythmias, high-degree AV block, ventricular arrhythmias, and hemodynamic instability. Digoxin antibodies should also be considered in digoxin-toxic patients with renal failure and for prophylactic treatment in a patient with massive oral overdose and high serum levels. Digoxin antibodies rapidly bind to digoxin and, to a lesser extent, digitoxin and other cardiac glycosides. The inactive complex that is formed is excreted rapidly in the urine. Details of dose calculation and infusion rate are given on p 542.

C. **Decontamination** (p 50). Administer activated charcoal orally if conditions are appropriate (see Table I–38, p 54). Gastric lavage is not necessary after small-to-moderate ingestions if activated charcoal can be given promptly.

DHEA	Dehydroepiandrosterone (an adrenal steroid)	Anticancer, antiaging	Possible androgenic effects.
Echinacea	*Echinacea angustifolia* *Echinacea pallida* *Echinacea purpurea*	Immune stimulation, prevention of colds	Allergic reactions, possible exacerbation of autoimmune diseases.
Fenugreek	*Trigonella foenum-graecum*	Increase appetite, promote lactation	Hypoglycemia in large doses, anticoagulant effects possible.
Feverfew	*Tanacetum parthenium*	Migraine prophylaxis	Allergic reactions, antiplatelet effects.
Garlic	*Allium sativum*	Hyperlipidemia, hypertension	Anticoagulant effect, gastrointestinal irritation, body odor.
Ginkgo	Extract of *Ginkgo biloba*	Memory impairment, tinnitus, peripheral vascular disease	Gastrointestinal irritation, antiplatelet effects.
Ginseng	*Panex ginseng, Panex quinquefolium*	Fatigue/stress, immune stimulation	Decreases glucose, increases cortisol; *ginseng abuse syndrome*: nervousness, insomnia, gastrointestinal distress.

Glucosamine	Marine exoskeletons or synthetic	Osteoarthritis	Possibly decreased insulin production.
Goldenseal	*Hydrastis canadensis*	Dyspepsia, postpartum bleeding, drug test adulterant	Nausea, vomiting, diarrhea, paresthesia, seizures; use during pregnancy/lactation can cause kernicterus in infants.
Grape seed extract	Procyanidins	Circulatory disorders, antioxidant	None described.
Green tea extract (concentrated)	*Camellia sinensis*	Mental alertness, stomach disorder, weight loss, cancer	Standardized extract has been associated with hepatitis. May interact with drugs and supplements, including iron.
Guarana	Caffeine	Athletic performance enhancement, appetite suppressant	Tachycardia, tremor, vomiting (see “Caffeine,” p 169).
Jin bu huan	L-Tetrahydropalmatine	Chinese traditional medicine	Acute CNS depression and bradycardia, chronic hepatitis.
Kava	*Piper methysticum*	Anxiety, insomnia	Drowsiness; hepatitis, cirrhosis, acute liver failure; habituation; reversible skin rash.

St. John wort	*Hypericum perforatum*	Depression	Possible mild MAO inhibition (p 326), photosensitivity, P-glycoprotein and P450 enzyme induction.
Tea tree oil	*Melaleuca alternifolia*	Lice, scabies, ringworm, vaginitis, acne	Sedation and ataxia when taken orally; contact dermatitis, local skin irritation.
L-Tryptophan	Essential amino acid	Insomnia, depression	Eosinophilia-myalgia syndrome due to contaminants in tryptophan reported in 1989; similar contaminants found in 5-hydroxytryptophan and melatonin.
Valerian root	*Valeriana officinalis, Valeriana edulis*	Insomnia	Sedation, vomiting.