CHAPTER e50

Poisoning and Drug Overdosage

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Poisoning refers to the development of dose-related adverse effects following exposure to chemicals, drugs, or other xenobiotics. To paraphrase Paracelsus, the dose makes the poison. In excessive amounts, substances that are usually innocuous, such as oxygen and water, can cause toxicity. Conversely, in small doses, substances commonly regarded as poisons, such as arsenic and cyanide, can be consumed without ill effect. Although most poisons have predictable dose-related effects, individual variability in the response to a given dose may occur because of genetic polymorphism, enzymatic induction or inhibition in the presence of other xenobiotics, or acquired tolerance. Poisoning may be local (e.g., skin, eyes, or lungs) or systemic depending on the route of exposure, the chemical and physical properties of the poison, and its mechanism of action. The severity and reversibility of poisoning also depend on the functional reserve of the individual or target organ, which is influenced by age and preexisting disease.

EPIDEMIOLOGY

More than 5 million poison exposures occur in the United States each year. Most are acute, accidental (unintentional), involve a single agent, occur in the home, result in minor or no toxicity, and involve children younger than 6 years of age. Pharmaceuticals are involved in 47% of exposures and 84% of serious or fatal poisonings. Unintentional exposures can result from the improper use of chemicals at work or play; label misreading; product mislabeling; mistaken identification of unlabeled chemicals; uninformed self-medication; and dosing errors by nurses, pharmacists, physicians, parents, and the elderly. Excluding the recreational use of ethanol, attempted suicide (deliberate self-harm) is the most common reported reason for intentional poisoning. Recreational use of prescribed and over-the-counter drugs for psychotropic or euphoric effects (abuse) or excessive self-dosing (misuse) are increasingly common and may also result in unintentional self-poisoning.

About 20–25% of exposures require bedside health professional evaluation, and 5% of all exposures require hospitalization. Poisonings account for 5–10% of all ambulance transports, emergency department visits, and intensive care unit admissions. Up to 30% of psychiatric admissions are prompted by attempted suicide via overdosage. Overall, the mortality rate is low: <1% of all exposures. It is much higher (1–2%) in hospitalized patients with intentional (suicidal) overdose, who account for the majority of serious poisonings. Acetaminophen is the pharmaceutical agent most often implicated in fatal poisoning. Overall, carbon monoxide is the leading cause of death from poisoning, but this is not reflected in hospital or poison center statistics because patients with such poisoning are typically dead when discovered and are referred directly to medical examiners.

DIAGNOSIS

Although poisoning can mimic other illnesses, the correct diagnosis can usually be established by the history, physical examination, routine and toxicologic laboratory evaluations, and characteristic clinical course. The *history* should include the time, route, duration, and circumstances (location, surrounding events, and intent) of exposure; the name and amount of each drug, chemical, or ingredient involved; the time of onset, nature, and severity of symptoms; the time and type of first-aid measures provided; and the medical and psychiatric history.

In many cases the patient is confused, comatose, unaware of an exposure, or unable or unwilling to admit to one. Suspicious circumstances include unexplained sudden illness in a previously healthy person or a group of healthy people; a history of psychiatric problems (particularly depression); recent changes in health, economic status, or social relationships; and onset of illness while working with chemicals or after ingesting food, drink (especially ethanol), or medications. Patients who become ill soon after arriving from a foreign country or being arrested for criminal activity should be suspected of "body packing" or "body stuffing" (ingesting or concealing illicit drugs in a body cavity). Relevant history may be available from family, friends, paramedics, police, pharmacists, physicians, and employers, who should be questioned regarding the patient's habits, hobbies, behavior changes, available medications, and antecedent events. A search of clothes, belongings, and place of discovery may reveal a suicide note or a container of drugs or chemicals. The imprint code on pills and the label on chemical products may be used to identify the ingredients and potential toxicity of a suspected poison by consulting a reference text, a computerized database, the manufacturer, or a regional poison information center (800-222-1222). Occupational exposures require review of any available material safety data sheet (MSDS) from the worksite.

The *physical examination* should focus initially on the vital signs, cardiopulmonary system, and neurologic status. The neurologic examination should include documentation of neuromuscular abnormalities such as dyskinesia, dystonia, fasciculations, myoclonus, rigidity, and tremors. The patient should also be examined for evidence of trauma and underlying illnesses. Focal neurologic findings are uncommon in poisoning, and their presence should prompt evaluation for a structural central nervous system (CNS) lesion. Examination of the eyes (for nystagmus, pupil size and reactivity), abdomen (for bowel activity and bladder size), and skin (for burns, bullae, color, warmth, moisture, pressure sores, and puncture marks) may reveal findings of diagnostic value. When the history is unclear, all orifices should be examined for the presence of chemical burns and drug packets. The odor of breath or vomitus and the color of nails, skin, or urine may provide important diagnostic clues.

The diagnosis of poisoning in cases of unknown etiology primarily relies on pattern recognition. The first step is to assess the pulse, blood pressure, respiratory rate, temperature, and neurologic status and characterize the overall physiologic state as **stimulated, depressed, discordant,** or **normal** (Table e50-1). Obtaining a complete set of vital signs and reassessing them frequently are critical. Measuring core temperature is especially important, even in difficult or combative patients, since temperature elevation is the most reliable prognosticator of poor outcome in poisoning or drug withdrawal. The next step is to consider the underlying causes of the physiologic state and attempt to identify a pathophysiologic pattern or toxic syndrome (*toxidrome*) based on the observed findings. Assessing the severity of physiologic derangements (Table e50-2) is useful in this regard and also for monitoring the clinical course and response to treatment. The final step is to attempt to identify the particular agent involved by looking for unique or relatively poison-specific physical or ancillary test abnormalities. Distinguishing among toxidromes based on the physiologic state is summarized below.

TABLE e50-1 Differential Diagnosis of Poisoning Based on Physiologic State

Stimulated	Depressed	Discordant	Normal
Sympathetics	Sympatholytics	Asphyxiants	Nontoxic exposure
Sympathomimetics	α_1-Adrenergic antagonists	Cytochrome oxidase inhibitors	Psychogenic illness
Ergot alkaloids	α_2-Adrenergic agonists	Inert gases	Toxic time-bombs
Methylxanthines	ACE inhibitors	Irritant gases	Slow absorption
Monoamine oxidase inhibitors	Angiotensin receptor blockers	Methemoglobin inducers	Anticholinergics
Thyroid hormones	Antipsychotics	Oxidative phosphorylation inhibitors	Carbamazepine
Anticholinergics	β-Adrenergic blockers	AGMA inducers	Concretion formers
Antihistamines	Calcium channel blockers	Alcohol (ketoacidosis)	Extended-release phenytoin sodium capsules (Dilantin Kapseals)
Antiparkinsonian agents	Cardiac glycosides	Ethylene glycol	Drug packets
Antipsychotics	Cyclic antidepressants	Iron	Enteric-coated pills
Antispasmodics	Cholinergics	Methanol	Diphenoxylate-atropine (Lomotil)
Belladonna alkaloids	Acetylcholinesterase inhibitors	Salicylate	Opioids
Cyclic antidepressants	Muscarinic agonists	Toluene	Salicylates
Muscle relaxants	Nicotinic agonists	CNS syndromes	Sustained-release pills
Mushrooms and plants	Opioids	Extrapyramidal reactions	Valproate
Hallucinogens	Analgesics	Hydrocarbon inhalation	Slow distribution
Cannabinoids (marijuana)	GI antispasmodics	Isoniazid	Cardiac glycosides
LSD and analogues	Heroin	Lithium	Lithium
Mescaline and analogues	Sedative-hypnotics	Neuroleptic malignant syndrome	Metals
Mushrooms	Alcohols	Serotonin syndrome	Salicylate
Phencyclidine and analogues	Anticonvulsants	Strychnine	Valproate
Withdrawal syndromes	Barbiturates	Membrane-active agents	Toxic metabolite
Barbiturates	Benzodiazepines	Amantadine	Acetaminophen
Benzodiazepines	GABA precursors	Antiarrhythmics	Carbon tetrachloride
Ethanol	Muscle relaxants	Antihistamines	Cyanogenic glycosides
Opioids	Other agents	Antipsychotics	Ethylene glycol
Sedative-hypnotics	GHB products	Carbamazepine	Methanol
Sympatholytics		Cyclic antidepressants	Methemoglobin inducers
		Local anesthetics	Mushroom toxins
		Opioids (some)	Organophosphate insecticides
		Orphenadrine	Paraquat
		Quinoline antimalarials	Metabolism disruptors
			Antineoplastic agents
			Antiviral agents
			Colchicine
			Hypoglycemic agents
			Immunosuppressive agents
			MAO inhibitors
			Metals
			Salicylate
			Warfarin

Abbreviations: ACE, angiotensin-converting enzyme; AGMA, anion-gap metabolic acidosis; CNS, central nervous system; GABA, γ-aminobutyric acid; GHB, γ-hydroxybutyrate; GI, gastrointestinal; LSD, lysergic acid diethylamide; MAO, monoamine oxidase.

Increased pulse, blood pressure, respiratory rate, temperature, and neuromuscular activity characterize the **stimulated** physiologic state: sympathetic, antimuscarinic (anticholinergic), hallucinogen poisoning, and drug withdrawal (Table e50-1). Other features are noted in Table e50-2. Mydriasis, a characteristic feature of all stimulants, is most marked in antimuscarinic (anticholinergic) poisoning since pupillary reactivity relies on muscarinic control; in sympathetic poisoning (e.g., cocaine), pupils are also enlarged, but some reactivity to light is observed. The antimuscarinic (anticholinergic) toxidrome is also distinguished by the presence of hot, dry, flushed skin; decreased bowel sounds; and urinary retention (Table e50-1). Other stimulant syndromes increase sympathetic

TABLE e50-2 Severity of Physiologic Stimulation and Depression in Poisoning and Drug Withdrawal

Physiologic Stimulation	
Grade 1	Anxious, irritable, tremulous; vital signs normal; diaphoresis, flushing or pallor, mydriasis, and hyperreflexia may be present
Grade 2	Agitated; may have confusion or hallucinations but is able to converse and follow commands; vital signs mildly to moderately increased
Grade 3	Delirious; unintelligible speech, uncontrollable motor hyperactivity; moderately to markedly increased vital signs; tachyarrhythmias possible
Grade 4	Coma, seizures, cardiovascular collapse
Physiologic Depression	
Grade 1	Awake, lethargic, or sleeping but arousable by voice or tactile stimulation; able to converse and follow commands; may be confused
Grade 2	Responds to pain but not voice; can vocalize but not converse; spontaneous motor activity present; brainstem reflexes intact
Grade 3	Unresponsive to pain; spontaneous motor activity absent; brainstem reflexes depressed; motor tone, respirations, and temperature decreased
Grade 4	Unresponsive to pain; flaccid paralysis; brainstem reflexes and respirations absent; cardiovascular vital signs decreased

activity and cause diaphoresis, pallor, and increased bowel activity with varying degrees of nausea, vomiting, abnormal distress, and occasionally diarrhea. The absolute and relative degree of vital sign changes and neuromuscular hyperactivity can help distinguish among stimulant toxidromes. Since sympathetics stimulate the peripheral nervous system more directly than do hallucinogens or drug withdrawal, markedly increased vital signs and organ ischemia suggest sympathetic poisoning. Findings helpful in suggesting the particular drug or class causing physiologic stimulation include reflex bradycardia from selective α-adrenergic stimulants (e.g., decongestants), hypotension from selective β-adrenergic stimulants (e.g., asthma therapeutics), limb ischemia from ergot alkaloids, rotatory nystagmus from phencyclidine and ketamine (the only physiologic stimulants that cause this finding), and delayed cardiac conduction from high doses of cocaine and some anticholinergic agents (e.g., antihistamines, cyclic antidepressants, and antipsychotics). Seizures suggest a sympathetic etiology, an anticholinergic agent with membrane-active properties (e.g., cyclic antidepressants, orphenadrine, phenothiazines), or a withdrawal syndrome. Close attention to core temperature is critical in patients with grade 4 physiologic stimulation (Table e50-2).

Decreased pulse, blood pressure, respiratory rate, temperature, and neuromuscular activity are indicative of **depressed** physiologic state caused by "functional" sympatholytics (agents that decrease cardiac function and vascular tone as well as sympathetic activity), cholinergic (muscarinic and nicotinic) agents, opioids, and sedative-hypnotic γ-aminobutyric acid (GABA)-ergic agents (Tables e50-1 and e50-2). Miosis is also common and most pronounced in opioid and cholinergic poisoning. The latter is distinguished from other depressant syndromes by the presence of muscarinic and nicotinic signs and symptoms (Table e50-1). Pronounced cardiovascular depression in the absence of significant CNS depression suggests a direct or peripherally acting sympatholytic. In contrast, in opioid and sedative-hypnotic poisoning, vital sign changes are secondary to depression of CNS cardiovascular and respiratory centers (or consequent hypoxemia), and significant abnormalities in these parameters do not occur until there is a marked decrease in the level of consciousness (grade 3 or 4 physiologic depression, Table e50-2). Other clues that suggest the cause of physiologic depression include cardiac arrhythmias and conduction disturbances (due to antiarrhythmics, β-adrenergic antagonists, calcium-channel blockers, digitalis glycosides, propoxyphene, and cyclic antidepressants), mydriasis [due to tricyclic antidepressants, some antiarrhythmics, meperidine, and diphenoxylate-atropine (Lomotil)], nystagmus (due to sedative-hypnotics), and seizures (due to cholinergic agents, propoxyphene, cyclic antidepressants).

The **discordant** physiologic state is characterized by mixed vital sign and neuromuscular abnormalities as observed in poisoning by asphyxiants, CNS syndromes, membrane-active agents, and anion-gap metabolic acidosis (AGMA) inducers (Table e50-1). In these conditions, manifestations of physiologic stimulation and physiologic depression occur together or at different times during the clinical course. For example, membrane-active agents can cause simultaneous coma, seizures, hypotension, and tachyarrhythmias. Alternatively, vital signs may be normal but the patient has altered mental status or is obviously sick or clearly symptomatic. Early, pronounced vital sign and mental status changes suggest asphyxiant or membrane-active agent poisoning; the lack of such abnormalities suggests an AGMA inducer; and marked neuromuscular dysfunction without significant vital sign abnormalities suggests a CNS syndrome.

A **normal** physiologic status and physical examination may be due to a nontoxic exposure, psychogenic illness, or poisoning by "toxic time-bombs," agents that are slowly absorbed, slowly distributed to their sites of action, require metabolic activation, or disrupt metabolic processes (Table e50-1). Because so many medications are now reformulated in a once-a-day form for patient convenience and adherence, "toxic time-bombs" are increasingly common. Diagnosing a nontoxic exposure requires that the identity of the exposure agent be known or that a toxic time-bomb exposure has been excluded and that the time since exposure exceeds the longest known or predicted interval between exposure and peak toxicity. Psychogenic illness (fear of being poisoned, mass hysteria) may also occur after a nontoxic exposure and should be considered when symptoms are inconsistent with the exposure history. Anxiety reactions resulting from a nontoxic exposure can cause mild physiologic stimulation (Table e50-2) and be indistinguishable from toxicologic causes (Table e50-1) without ancillary testing or a suitable period of observation.

Laboratory assessment may be helpful in the differential diagnosis. An increased AGMA is most common in advanced methanol, ethylene glycol, and salicylate intoxication but can occur in any poisoning that results in hepatic, renal, or respiratory failure; seizures; or shock. The serum lactate concentration is more commonly low (less than the anion gap) in the former and high (nearly equal to the anion gap) in the latter. An abnormally low anion gap can be due to elevated blood levels of bromide, calcium, iodine, lithium, or magnesium. An increased osmolal gap—a difference between the serum osmolality (measured by freezing point depression) and that calculated from the serum sodium, glucose, and blood urea nitrogen of >10 mmol/L—suggests the presence of a low-molecular-weight solute such as acetone; an alcohol (benzyl, ethanol, isopropanol, methanol); a glycol (diethylene, ethylene, propylene); ether (ethyl, glycol); or an "unmeasured" cation (calcium, magnesium) or sugar (glycerol, mannitol, sorbitol).

Ketosis suggests acetone, isopropyl alcohol, salicylate poisoning, or alcoholic ketoacidosis. Hypoglycemia may be due to poisoning with β-adrenergic blockers, ethanol, insulin, oral hypoglycemic agents, quinine, and salicylates, whereas hyperglycemia can occur in poisoning with acetone, β-adrenergic agonists, caffeine, calcium channel blockers, iron, theophylline, or *N*-3-pyridylmethyl-*N*′-*p*-nitrophenylurea [PNU (Vacor)]. Hypokalemia can be caused by barium, β-adrenergic agonists, caffeine, diuretics, theophylline, or toluene; hyperkalemia suggests poisoning with an α-adrenergic agonist, a β-adrenergic blocker, cardiac glycosides, or fluoride. Hypocalcemia may be seen in ethylene glycol, fluoride, and oxalate poisoning.

The *electrocardiogram* (ECG) can be useful for rapid diagnostic purposes. Bradycardia and atrioventricular block may occur in patients poisoned by α-adrenergic agonists, antiarrhythmic agents, beta blockers, calcium channel blockers, cholinergic agents (carbamate and organophosphate insecticides), cardiac glycosides, lithium, or tricyclic antidepressants. QRS- and QT-interval prolongation may be caused by hyperkalemia, various antidepressants, and other membrane-active drugs (Table e50-1). Ventricular tachyarrhythmias may be seen in poisoning with cardiac glycosides, fluorides, membrane-active drugs, methylxanthines, sympathomimetics, antidepressants, and agents that cause hyperkalemia or potentiate the effects of endogenous catecholamines (e.g., chloral hydrate, aliphatic and halogenated hydrocarbons).

Radiologic studies may occasionally be useful. Pulmonary edema [adult respiratory distress syndrome (ARDS)] can be caused by poisoning with carbon monoxide, cyanide, an opioid, paraquat, phencyclidine, a sedative-hypnotic, or salicylate; by inhalation of irritant gases, fumes, or vapors (acids and alkali, ammonia, aldehydes, chlorine, hydrogen sulfide, isocyanates, metal oxides, mercury, phosgene, polymers); or by prolonged anoxia, hyperthermia, or shock. Aspiration pneumonia is common in patients with coma, seizures, and petroleum distillate aspiration. The presence of radiopaque densities on abdominal x-rays suggests the ingestion of calcium salts, chloral hydrate, chlorinated hydrocarbons, heavy metals, illicit drug packets, iodinated compounds, potassium salts, enteric-coated tablets, or salicylates.

Toxicologic analysis of urine and blood (and occasionally of gastric contents and chemical samples) can sometimes confirm or rule out suspected poisoning. Interpretation of laboratory data requires knowledge of the qualitative and quantitative tests used for screening and confirmation (enzyme-multiplied, fluorescence polarization, and radio-immunoassays; colorimetric and fluorometric assays; thin-layer, gas-liquid, or high-performance liquid chromatography; gas chromatography; mass spectrometry), their sensitivity (limit of detection) and specificity, the preferred biologic specimen for analysis, and the optimal time of specimen sampling. Personal communication with the hospital laboratory is essential to understand institutional testing capabilities and limitations.

Rapid *qualitative* hospital-based urine tests for drugs of abuse are only screening tests that cannot confirm the exact identity of the detected substance and should not be considered diagnostic or used for forensic purposes: False-positive and false-negative results are common. A positive screen may result from other pharmaceuticals that interfere with laboratory analysis (e.g., fluoroquinolones commonly cause "false-positive" opiate screens). Confirmatory testing with gas chromatography/mass spectrometry (GC/MS) can be requested, but often takes weeks to obtain a reported result. A negative screening result may mean the substance is not detectable by the test used or that its concentration is too low for detection at the time of sampling. In the latter case, repeating the test at a later time may yield a positive result. Patients symptomatic from drugs of abuse often require immediate management based on the history, physical examination, and observed toxidrome without laboratory confirmation (e.g., apnea from opioid intoxication). When the patient is asymptomatic, or when the clinical picture is consistent with the reported history, several studies have shown qualitative screening is neither clinically useful nor cost-effective. Thus, qualitative drug screens are of greatest value when evaluating patients with severe or unexplained toxicity such as coma, seizures, cardiovascular instability, metabolic or respiratory acidosis, and nonsinus cardiac rhythms. In contrast to qualitative drug screens, *quantitative* serum tests are useful for evaluating patients poisoned with acetaminophen (Chap. 305), alcohols (including ethylene glycol and methanol), anticonvulsants, barbiturates, digoxin, heavy metals, iron, lithium, salicylate, and theophylline, as well as for carboxyhemoglobin and methemoglobin. The serum concentration in these cases guides clinical management, and results can often be available within an hour.

The *response to antidotes* is sometimes useful for diagnostic purposes. Resolution of altered mental status and abnormal vital signs within minutes of IV administration of dextrose, naloxone, or flumazenil is virtually diagnostic of hypoglycemia, narcotic poisoning, and benzodiazepine intoxication, respectively. The prompt reversal of dystonic (extrapyramidal) signs and symptoms following an IV dose of benztropine or diphenhydramine confirms a drug etiology. Although complete reversal of both central and peripheral manifestations of anticholinergic poisoning by physostigmine is diagnostic of this condition, physostigmine may cause some arousal in patients with CNS depression of any etiology.

TREATMENT Poisoning and Drug Overdose

GENERAL PRINCIPLES Treatment goals include support of vital signs, prevention of further poison absorption (decontamination), enhancement of poison elimination, administration of specific antidotes, and prevention of reexposure (Table e50-3). Specific treatment depends on the identity of the poison, the route and amount of exposure, the time of presentation relative to the time of exposure, and the severity of poisoning. Knowledge of the offending agents' pharmacokinetics and pharmacodynamics is essential.

During the *pretoxic phase*, prior to the onset of poisoning, decontamination is the highest priority, and treatment is based solely on the history. The maximum potential toxicity based on the greatest possible exposure should be assumed. Since decontamination is more effective when accomplished soon after exposure, and when the patient is asymptomatic, the initial history and physical examination should be focused and brief. It is also advisable to establish IV access and initiate cardiac monitoring, particularly in patients with potentially serious ingestions or unclear histories.

When an accurate history is not obtainable and a poison causing delayed toxicity ("toxic time-bomb") or irreversible damage is suspected, blood and urine should be sent for appropriate toxicologic screening and quantitative analysis. During absorption and distribution, blood levels may be greater than those in tissue and may not correlate with toxicity. However, high blood levels of agents whose metabolites are more toxic than the parent compound (acetaminophen, ethylene glycol, or methanol) may indicate the need for additional interventions (antidotes, dialysis). Most patients who remain or become asymptomatic 6 h after ingestion are unlikely to develop subsequent toxicity and can be discharged safely. Longer observation will be necessary for patients who have ingested toxic time-bombs, agents that are slowly absorbed, slowly distributed to their sites of action,

TABLE e50-3 Fundamentals of Poisoning Management

Supportive Care	
Airway protection	Treatment of seizures
Oxygenation/ventilation	Correction of temperature abnormalities
Treatment of arrhythmias	Correction of metabolic derangements
Hemodynamic support	Prevention of secondary complications
Prevention of Further Poison Absorption	
Gastrointestinal decontamination	Decontamination of other sites
Gastric lavage	Eye decontamination
Activated charcoal	Skin decontamination
Whole-bowel irrigation	Body cavity evacuation
Dilution	
Endoscopic/surgical removal	
Enhancement of Poison Elimination	
Multiple-dose activated charcoal	Extracorporeal removal
Alteration of urinary pH	Hemodialysis
Chelation	Hemoperfusion
	Hemofiltration
	Plasmapheresis
	Exchange transfusion
	Hyperbaric oxygenation
Administration of Antidotes	
Neutralization by antibodies	Metabolic antagonism
Neutralization by chemical binding	Physiologic antagonism
Prevention of Reexposure	
Adult education	Notification of regulatory agencies
Child-proofing	Psychiatric referral

require metabolic activation, or disrupt metabolic processes (Table e50-1). During the *toxic phase*, the time between the onset of poisoning and the peak effects, management is based primarily on clinical and laboratory findings. *Effects after an overdose usually begin sooner, peak later, and last longer than they do after a therapeutic dose.* A drug's published pharmacokinetic profile in standard references such as the *Physician's Desk Reference* (*PDR*) is usually different from its toxicokinetic profile in overdose. Resuscitation and stabilization are the first priority. Symptomatic patients should have an IV line, oxygen saturation determination, cardiac monitoring, and continuous observation. Baseline laboratory, ECG, and x-ray evaluation may also be appropriate. Intravenous glucose (unless the serum level is documented to be normal), naloxone, and thiamine should be considered in patients with altered mental status, particularly those with coma or seizures. Decontamination should also be considered, but it is less likely to be effective during this phase than during the pretoxic one.

Measures that enhance poison elimination may shorten the duration and severity of the toxic phase. However, they are not without risk, which must be weighed against the potential benefit. Diagnostic certainty (usually via laboratory confirmation) is generally a prerequisite. Intestinal (or "gut") dialysis with repetitive doses of activated charcoal (also termed *multidose activated charcoal*) can enhance the elimination of selected poisons such as theophylline or carbamazepine. Urinary alkalinization may enhance the elimination of salicylates and a small number of other poisons. Chelation therapy can enhance the elimination of selected metals. Extracorporeal elimination methods are effective for many poisons, but their expense and risk make their use reasonable only in patients who would otherwise have an unfavorable outcome.

During the *resolution phase* of poisoning, supportive care and monitoring should continue until clinical, laboratory, and ECG abnormalities have resolved. Since chemicals are eliminated sooner from the blood than from tissues, blood levels are usually lower than tissue levels during this phase and again may not correlate with toxicity. This is particularly true when extracorporeal elimination procedures are used. Redistribution from tissues may cause a rebound increase in the blood level after termination of these procedures. When a metabolite is responsible for toxic effects, continued treatment might be necessary in the absence of clinical toxicity or abnormal laboratory studies.

SUPPORTIVE CARE The goal of supportive therapy is to maintain physiologic homeostasis until detoxification is accomplished and to prevent and treat secondary complications such as aspiration, bedsores, cerebral and pulmonary edema, pneumonia, rhabdomyolysis, renal failure, sepsis, thromboembolic disease, coagulopathy, and generalized organ dysfunction due to hypoxemia or shock.

Admission to an intensive care unit is indicated for the following: patients with severe poisoning (coma, respiratory depression, hypotension, cardiac conduction abnormalities, cardiac arrhythmias, hypothermia or hyperthermia, seizures); those needing close monitoring, antidotes, or enhanced elimination therapy; those showing progressive clinical deterioration; and those with significant underlying medical problems. Patients with mild to moderate toxicity can be managed on a general medical service, intermediate care unit, or emergency department observation area, depending on the anticipated duration and level of monitoring needed (intermittent clinical observation versus continuous clinical, cardiac, and respiratory monitoring). Patients who have attempted suicide require continuous observation and measures to prevent self-injury until they are no longer suicidal.

Respiratory Care Endotracheal intubation for protection against the aspiration of gastrointestinal contents is of paramount importance in patients with CNS depression or seizures as this complication can increase morbidity and mortality rates. Mechanical ventilation may be necessary for patients with respiratory depression or hypoxemia and to facilitate therapeutic sedation or paralysis in order to prevent or treat hyperthermia, acidosis, and rhabdomyolysis associated with neuromuscular hyperactivity. Since clinical assessment of respiratory function can be inaccurate, the need for oxygenation and ventilation is best determined by continuous pulse oximetry or arterial blood-gas analysis. The gag reflex is not a reliable indicator of the need for intubation. A patient with CNS depression may maintain airway patency while being stimulated but not if left alone. Drug-induced pulmonary edema is usually noncardiac rather than cardiac in origin, although profound CNS depression and cardiac conduction abnormalities suggest the latter. Measurement of pulmonary artery pressure may be necessary to establish the cause and direct appropriate therapy. Extracorporeal measures

(membrane oxygenation, venoarterial perfusion, cardiopulmonary bypass) and partial liquid (perfluorocarbon) ventilation may be appropriate for severe but reversible respiratory failure.

Cardiovascular Therapy Maintenance of normal tissue perfusion is critical for complete recovery to occur once the offending agent has been eliminated. If hypotension is unresponsive to volume expansion, treatment with norepinephrine, epinephrine, or high-dose dopamine may be necessary. Intraaortic balloon pump counterpulsation and venoarterial or cardiopulmonary perfusion techniques should be considered for severe but reversible cardiac failure. Bradyarrhythmias associated with hypotension generally should be treated as described in Chap. 232. Glucagon, calcium, and high-dose insulin with dextrose may be effective in beta blocker and calcium channel blocker poisoning. Antibody therapy may be indicated for cardiac glycoside poisoning.

Supraventricular tachycardia associated with hypertension and CNS excitation is almost always due to agents that cause generalized physiologic excitation (Table e50-1). Most cases are mild or moderate in severity and require only observation or nonspecific sedation with a benzodiazepine. In severe cases or those associated with hemodynamic instability, chest pain, or ECG evidence of ischemia, specific therapy is indicated. When the etiology is sympathetic hyperactivity, treatment with a benzodiazepine should be prioritized. Further treatment with a combined alpha and beta blocker (labetalol), a calcium channel blocker (verapamil or diltiazem), or a combination of a beta blocker and a vasodilator (esmolol and nitroprusside) may be considered for cases refractory to high doses of benzodiazepines. Treatment with an α-adrenergic antagonist (phentolamine) alone may sometimes be appropriate. If the cause is anticholinergic poisoning, physostigmine alone can be effective. Supraventricular tachycardia without hypertension is generally secondary to vasodilation or hypovolemia and responds to fluid administration.

For ventricular tachyarrhythmias due to tricyclic antidepressants and other membrane-active agents (Table e50-1), sodium bicarbonate is indicated, whereas class IA, IC, and III antiarrhythmic agents are contraindicated because of similar electrophysiologic effects. Although lidocaine and phenytoin are historically safe for ventricular tachyarrhythmias of any etiology, sodium bicarbonate should be considered first for any ventricular arrhythmia suspected to have a toxicologic etiology. Beta blockers can be hazardous if the arrhythmia is due to sympathetic hyperactivity. Magnesium sulfate and overdrive pacing (by isoproterenol or a pacemaker) may be useful in patients with torsades des pointes and prolonged QT intervals. Magnesium and anti-digoxin antibodies should be considered in patients with severe cardiac glycoside poisoning. Invasive (esophageal or intracardiac) ECG recording may be necessary to determine the origin (ventricular or supraventricular) of wide-complex tachycardias (Chap. 233). If the patient is hemodynamically stable, however, it is reasonable to simply observe him or her rather than to administer another potentially proarrhythmic agent. Arrhythmias may be resistant to drug therapy until underlying acid-base, electrolyte, oxygenation, and temperature derangements are corrected.

Central Nervous System Therapies Neuromuscular hyperactivity and seizures can lead to hyperthermia, lactic acidosis, and rhabdomyolysis and should be treated aggressively. Seizures caused by excessive stimulation of catecholamine receptors (sympathomimetic or hallucinogen poisoning and drug withdrawal) or decreased activity of GABA (isoniazid poisoning) or glycine (strychnine poisoning) receptors are best treated with agents that enhance GABA activity, such as benzodiazepine or barbiturates. Since benzodiazepines and barbiturates act by slightly different mechanisms (the former increases the frequency, and the latter increases the duration of chloride channel opening in response to GABA), therapy with both may be effective when neither is effective alone. Seizures caused by isoniazid, which inhibits the synthesis of GABA at several steps by interfering with the cofactor pyridoxine (vitamin B_6), may require high doses of supplemental pyridoxine. Seizures resulting from membrane destabilization (beta blocker or cyclic antidepressant poisoning) require GABA enhancers (benzodiazepines first, barbiturates second). Phenytoin is contraindicated in toxicologic seizures: Animal and human data demonstrate worse outcomes after phenytoin loading, especially in theophylline overdose. For poisons with central dopaminergic effects (methamphetamine, phencyclidine) manifested by psychotic behavior, a dopamine receptor antagonist, such as haloperidol, may be useful. In anticholinergic and cyanide poisoning, specific antidotal therapy may be necessary. The treatment of seizures secondary to cerebral ischemia or edema or to metabolic abnormalities should include correction of the underlying cause. Neuromuscular paralysis is indicated in refractory cases. Electroencephalographic monitoring and continuing treatment of seizures are necessary to prevent permanent neurologic damage. Serotonergic receptor overstimulation in serotonin syndrome may be treated with cyproheptadine.

Other Measures Temperature extremes, metabolic abnormalities, hepatic and renal dysfunction, and secondary complications should be treated by standard therapies.

PREVENTION OF POISON ABSORPTION

Gastrointestinal Decontamination Whether or not to perform gastrointestinal decontamination, and which procedure to use, depends on the time since ingestion; the existing and predicted toxicity of the ingestant; the availability, efficacy, and contraindications of the procedure; and the nature, severity, and risk of complications. The efficacy of all decontamination procedures decreases with time, and there are insufficient data to support or exclude a beneficial effect when they are used >1 h after ingestion. The average time from ingestion to presentation for treatment is >1 h for children and >3 h for adults. Most patients will recover from poisoning uneventfully with good supportive care alone, but complications of gastrointestinal decontamination, particularly aspiration, can prolong this process. Hence, gastrointestinal decontamination should be performed selectively, not routinely, in the management of overdose patients. It is clearly unnecessary when predicted toxicity is minimal or the time of expected maximal toxicity has passed without significant effect.

Activated charcoal has comparable or greater efficacy, fewer contraindications and complications, and is less aversive and invasive than ipecac or gastric lavage; thus it is the preferred method of gastrointestinal decontamination in most situations. Activated charcoal suspension (in water) is given orally via a cup, straw, or small-bore nasogastric tube. The generally recommended dose is 1 g/kg body weight because of its convenience, although in vitro and in vivo studies have demonstrated charcoal adsorbs ≥90% of most substances when given in an amount equal to 10 times the weight of the substance. Palatability may be increased by adding a sweetener (sorbitol) or a flavoring agent (cherry, chocolate, or cola syrup) to the suspension. Charcoal adsorbs ingested poisons within the gut

lumen, allowing the charcoal-toxin complex to be evacuated with stool. Charged (ionized) chemicals such as mineral acids, alkalis, and highly dissociated salts of cyanide, fluoride, iron, lithium, and other inorganic compounds are not well adsorbed by charcoal. In animal and human volunteer studies, charcoal decreases the absorption of ingestants by an average of 73% when given within 5 min of ingestant administration, 51% when given at 30 min, and 36% at 60 min. Side effects of charcoal include nausea, vomiting, and diarrhea or constipation. Charcoal may also prevent the absorption of orally administered therapeutic agents. Complications include mechanical obstruction of the airway, aspiration, vomiting, and bowel obstruction and infarction caused by inspissated charcoal. Charcoal is not recommended for patients who have ingested corrosives because it obscures endoscopy.

Gastric lavage should be considered for life-threatening poisons that cannot be treated effectively with other decontamination, elimination, or antidotal therapies (e.g., colchicine). Gastric lavage is performed by sequentially administering and aspirating ~5 mL fluid per kilogram of body weight through a no. 40 French orogastric tube (no. 28 French tube for children). Except for infants, where normal saline is recommended, tap water is acceptable. The patient should be placed in Trendelenburg and left lateral decubitus positions to prevent aspiration (even if an endotracheal tube is in place). Lavage decreases ingestant absorption by an average of 52% if performed within 5 min of ingestion administration, 26% if performed at 30 min, and 16% if performed at 60 min. Significant amounts of ingested drug are recovered in <10% of patients. Aspiration is a common complication (occurring in up to 10% of patients), especially when lavage is performed improperly. Serious complications (esophageal and gastric perforation, tube misplacement in the trachea) occur in ~1% of patients. For this reason, the physician should personally insert the lavage tube and confirm its placement, and the patient must be cooperative during the procedure. Gastric lavage is contraindicated in corrosive or petroleum distillate ingestions because of the respective risks of gastroesophageal perforation and aspiration pneumonitis. It is also contraindicated in those with a compromised unprotected airway and those at risk for hemorrhage or perforation due to esophageal or gastric pathology or recent surgery. Finally, gastric lavage is absolutely contraindicated in combative patients or those who refuse, as most published complications involve patient resistance to the procedure.

Syrup of ipecac, an emetogenic agent that was once the most commonly used decontamination procedure, no longer has a role in poisoning management. Even the American Academy of Pediatrics (AAP), traditionally the strongest proponent of ipecac, issued a policy statement in 2003 recommending that ipecac should no longer be used in poisoning treatment. Chronic ipecac use (by patients with anorexia nervosa or bulimia) has been reported to cause electrolyte and fluid abnormalities, cardiac toxicity, and myopathy.

Whole-bowel irrigation is performed by administering a bowel-cleansing solution containing electrolytes and polyethylene glycol (Golytely, Colyte) orally or by gastric tube at a rate of 2 L/h (0.5 L/h in children) until rectal effluent is clear. The patient must be in a sitting position. Although data are limited, whole-bowel irrigation appears to be as effective as other decontamination procedures in volunteer studies. It is most appropriate for those who have ingested foreign bodies, packets of illicit drugs, slow-release or enteric-coated medications, and agents that are poorly adsorbed by charcoal (e.g., heavy metals). It is contraindicated in patients with bowel obstruction, ileus, hemodynamic instability, and compromised unprotected airways.

Cathartics are salts (disodium phosphate, magnesium citrate and sulfate, sodium sulfate) or saccharides (mannitol, sorbitol) that historically have been given with activated charcoal to promote the rectal evacuation of gastrointestinal contents. However, no animal, volunteer, or clinical data have ever demonstrated any decontamination benefit from cathartics. Abdominal cramps, nausea, and occasional vomiting are side effects. Complications of repeated dosing include severe electrolyte disturbances and excessive diarrhea. Cathartics are contraindicated in patients who have ingested corrosives and in those with preexisting diarrhea. Magnesium-containing cathartics should not be used in patients with renal failure.

Dilution (i.e., drinking 5 mL/kg of body weight of water, another clear liquid, or milk) is recommended only after the ingestion of corrosives (acids, alkali). It may increase the dissolution rate (and hence absorption) of capsules, tablets, and other solid ingestants and should *not* be used in these circumstances.

Endoscopic or *surgical removal* of poisons may be useful in rare situations, such as ingestion of a potentially toxic foreign body that fails to transit the gastrointestinal tract, a potentially lethal amount of a heavy metal (arsenic, iron, mercury, thallium), or agents that have coalesced into gastric concretions or bezoars (heavy metals, lithium, salicylates, sustained-release preparations). Patients who become toxic from cocaine due to its leakage from ingested drug packets require immediate surgical intervention.

Decontamination of Other Sites Immediate, copious flushing with water, saline, or another available clear, drinkable liquid is the initial treatment for topical exposures (exceptions include alkali metals, calcium oxide, phosphorus). Saline is preferred for eye irrigation. A triple wash (water, soap, water) may be best for dermal decontamination. Inhalational exposures should be treated initially with fresh air or oxygen. The removal of liquids from body cavities such as the vagina or rectum is best accomplished by irrigation. Solids (drug packets, pills) should be removed manually, preferably under direct visualization.

ENHANCEMENT OF POISON ELIMINATION Although the elimination of most poisons can be accelerated by therapeutic interventions, the pharmacokinetic efficacy (removal of drug at a rate greater than that accomplished by intrinsic elimination) and clinical benefit (shortened duration of toxicity or improved outcome) of such interventions are often more theoretical than proven. Hence, the decision to use such measures should be based on the actual or predicted toxicity and the potential efficacy, cost, and risks of therapy.

Multiple-Dose Activated Charcoal Repetitive oral dosing with charcoal can enhance the elimination of previously absorbed substances by binding them within the gut as they are excreted in the bile, secreted by gastrointestinal cells, or passively diffuse into the gut lumen (reverse absorption or enterocapillary exsorption). Doses of 0.5–1 g/kg body weight every 2–4 h, adjusted downward to avoid regurgitation in patients with decreased gastrointestinal motility, are generally recommended. Pharmacokinetic efficacy approaches that of hemodialysis for some agents (e.g., phenobarbital, theophylline). Multiple-dose therapy should be considered only for selected agents (theophylline, phenobarbital, carbamazepine, dapsone, quinine). Complications include intestinal obstruction, pseudoobstruction, and nonocclusive intestinal infarction

in patients with decreased gut motility. Sorbitol and other cathartics are absolutely contraindicated when administering multiple doses of activated charcoal because of electrolyte and fluid shifts.

Urinary Alkalinization Ion trapping via alteration of urine pH may prevent the renal reabsorption of poisons that undergo excretion by glomerular filtration and active tubular secretion. Since membranes are more permeable to nonionized molecules than to their ionized counterparts, acidic (low-pK_a) poisons are ionized and trapped in alkaline urine, whereas basic ones become ionized and trapped in acid urine. Urinary alkalinization (producing a urine pH ≥7.5 and a urine output of 3–6 mL/kg body weight per hour by adding sodium bicarbonate to an IV solution) enhances the excretion of chlorophenoxyacetic acid herbicides, chlorpropamide, diflunisal, fluoride, methotrexate, phenobarbital, sulfonamides, and salicylates. Contraindications include congestive heart failure, renal failure, and cerebral edema. Acid-base, fluid, and electrolyte parameters should be monitored carefully. While making theoretical sense for some overdoses (amphetamines), acid diuresis is never indicated and is potentially harmful.

Extracorporeal Removal Hemodialysis, charcoal or resin hemoperfusion, hemofiltration, plasmapheresis, and exchange transfusion are capable of removing any toxin from the bloodstream. Agents most amenable to enhanced elimination by dialysis have low molecular mass (<500 Da), high water solubility, low protein binding, small volumes of distribution (<1 L/kg body weight), prolonged elimination (long half-life), and high dialysis clearance relative to total-body clearance. Molecular weight, water solubility, or protein binding do not limit the efficacy of the other forms of extracorporeal removal.

Dialysis should be considered in cases of severe poisoning due to carbamazepine, ethylene glycol, isopropyl alcohol, lithium, methanol, theophylline, salicylates, and valproate. Although hemoperfusion may be more effective in removing some of these poisons, it does not correct associated acid-base and electrolyte abnormalities, and most hospitals no longer have hemoperfusion cartridges readily available. Fortunately, recent advances in hemodialysis technology make it effective for removing poisons such as caffeine, carbamazepine, and theophylline. Both techniques require central venous access and systemic anticoagulation and may result in transient hypotension. Hemoperfusion may also cause hemolysis, hypocalcemia, and thrombocytopenia. Peritoneal dialysis and exchange transfusion are less effective but may be used when other procedures are either not available, contraindicated, or technically difficult (e.g., in infants). Exchange transfusion may be indicated in the treatment of severe arsine- or sodium chlorate–induced hemolysis, methemoglobinemia, and sulfhemoglobinemia. Although hemofiltration can enhance elimination of aminoglycosides, vancomycin, and metal-chelate complexes, the roles of hemofiltration and plasmapheresis in the treatment of poisoning are not yet defined.

Candidates for extracorporeal removal therapies include patients with severe toxicity who deteriorate despite aggressive supportive therapy; those with potentially prolonged, irreversible, or fatal toxicity; those with dangerous blood levels of toxins; those who lack the capacity for self-detoxification because of liver or renal failure; and those with a serious underlying illness or complication that will adversely affect recovery.

Other Techniques The elimination of heavy metals can be enhanced by chelation, and the removal of carbon monoxide can be accelerated by hyperbaric oxygenation.

ADMINISTRATION OF ANTIDOTES Antidotes counteract the effects of poisons by neutralizing them (e.g., antibody-antigen reactions, chelation, chemical binding) or by antagonizing their physiologic effects (e.g., activation of opposing nervous system activity, provision of competitive metabolic or receptor substrate). Poisons or conditions with specific antidotes include acetaminophen, anticholinergic agents, anticoagulants, benzodiazepines, beta blockers, calcium channel blockers, carbon monoxide, cardiac glycosides, cholinergic agents, cyanide, drug-induced dystonic reactions, ethylene glycol, fluoride, heavy metals, hypoglycemic agents, isoniazid, membrane-active agents, methemoglobinemia, opioids, sympathomimetics, and a variety of envenomations. Intravenous lipid emulsion has been shown to be a successful antidote for poisoning from various anesthetics and membrane-active agents, but the exact mechanism of benefit is still under investigation. Antidotes can significantly reduce morbidity and mortality rates but are potentially toxic if used for inappropriate reasons. Since their safe use requires correct identification of a specific poisoning or syndrome, details of antidotal therapy are discussed with the conditions for which they are indicated (Table e50-4).

PREVENTION OF REEXPOSURE Poisoning is a preventable illness. Unfortunately, some adults and children are poison-prone, and recurrences are common. Unintentional polypharmacy poisoning has become especially common among adults with developmental delays, among the growing population of geriatric patients who are prescribed a large number of medications, and among adolescents and young adults experimenting with pharmaceuticals for recreational euphoria. Adults with unintentional exposures should be instructed regarding the safe use of medications and chemicals (according to labeling instructions). Confused patients may need assistance with the administration of their medications. Errors in dosing by health care providers may require educational efforts. Patients should be advised to avoid circumstances that result in chemical exposure or poisoning. Appropriate agencies and health departments should be notified in cases of environmental or workplace exposure. The best approach with young children and patients with intentional overdose (deliberate self-harm or suicide) is to limit their access to poisons. In households where children live or visit, alcoholic beverages, medications, household products (automotive, cleaning, fuel, pet-care, toiletry products), inedible plants, and vitamins should be kept out of reach or in locked or child-proof cabinets. Depressed or psychotic patients should receive psychiatric assessment, disposition, and follow-up. They should be given prescriptions for a limited supply of drugs and with a limited number of refills and be monitored for compliance and response to therapy.

SPECIFIC TOXIC SYNDROMES AND POISONINGS

Table e50-4 summarizes the pathophysiology, clinical features, and treatment of toxidromes and poisonings that are common, produce life-threatening toxicity, or require unique therapeutic interventions. In all cases, treatment should include attending to the general principles discussed above, particularly supportive care. Details regarding specific therapies can be found in the references cited here and at *www.harrisonsonline.com*. Poisonings not covered in this chapter are discussed in the referenced texts.

Alcohol, cocaine, hallucinogen, and opioid poisoning and alcohol and opioid withdrawal are discussed in Chaps. 392 to 395; acetaminophen poisoning is discussed in Chap. 305; the neuroleptic malignant syndrome is discussed in Chap. 372; and heavy metal poisoning is discussed in Chap. e49.

TABLE e50-4 Pathophysiologic Features and Treatment of Specific Toxic Syndromes and Poisonings

Physiologic Condition, Causes	Examples	Mechanism of Action	Clinical Features	Specific Treatments
Stimulated				
Sympathetics (see also Chap. 394)				
Sympathomimetics	α_1-Adrenergic agonists (decongestants): phenylephrine, phenylpropanolamine β_2-Adrenergic agonists (bronchodilators): albuterol, terbutaline Nonspecific adrenergic agonists: amphetamines, cocaine, ephedrine	Stimulation of central and peripheral sympathetic receptors directly or indirectly (by promoting the release or inhibiting the reuptake of norepinephrine and sometimes dopamine)	Physiologic stimulation (Table e50-2); reflex bradycardia can occur with selective α_1 agonists; β agonists can cause hypotension and hypokalemia.	Phentolamine, a nonselective α_1-adrenergic receptor antagonist, for severe hypertension due to α_1-adrenergic agonists; propranolol, a nonselective β blocker, for hypotension and tachycardia due to β_2 agonists; labetalol, a β blocker with α-blocking activity, or phentolamine with esmolol, metoprolol, or other cardioselective β blocker for hypertension with tachycardia due to nonselective agents (β blockers, if used alone, can exacerbate hypertension and vasospasm due to unopposed α stimulation); benzodiazepines; propofol.
Ergot alkaloids	Ergotamine, methysergide, bromocriptine, pergolide	Stimulation and inhibition of serotonergic and α-adrenergic receptors; stimulation of dopamine receptors	Physiologic stimulation (Table e50-2); formication; vasospasm with limb (isolated or generalized), myocardial, and cerebral ischemia progressing to gangrene or infarction; hypotension, bradycardia, and involuntary movements can also occur.	Nitroprusside or nitroglycerine for severe vasospasm; prazosin (an α_1 blocker), captopril, nifedipine, and cyproheptadine (a serotonin receptor antagonist) for mild-to-moderate limb ischemia; dopamine receptor antagonists (antipsychotics) for hallucinations and movement disorders
Methylxanthines	Caffeine, theophylline	Inhibition of adenosine synthesis and adenosine receptor antagonism; stimulation of epinephrine and norepinephrine release; inhibition of phosphodiesterase resulting in increased intracellular cyclic adenosine and guanosine monophosphate	Physiologic stimulation (Table e50-2); pronounced gastrointestinal symptoms and β agonist effects (see above). Toxicity occurs at lower drug levels in chronic poisoning than in acute poisoning.	Propranolol, a nonselective β blocker, for tachycardia with hypotension; any β blocker for supraventricular or ventricular tachycardia without hypotension; elimination enhanced by multiple-dose charcoal, hemoperfusion, and hemodialysis; indications for hemoperfusion or hemodialysis include unstable vital signs, seizures, and a theophylline level of 80–100 μg/mL after acute overdose and 40–60 μg/mL with chronic exposure.
Monoamine oxidase inhibitors	Phenelzine, tranylcypromine, selegiline	Inhibition of monoamine oxidase resulting in impaired metabolism of endogenous catecholamines and exogenous sympathomimetic agents	Delayed or slowly progressive physiologic stimulation (Table e50-2); terminal hypotension and bradycardia in severe cases.	Short-acting agents (e.g., nitroprusside, esmolol) for severe hypertension and tachycardia; direct-acting sympathomimetics (e.g., norepinephrine, epinephrine) for hypotension and bradycardia
Anticholinergics				
Antihistamines	Diphenhydramine, doxylamine, pyrilamine	Inhibition of central and postganglionic parasympathetic muscarinic cholinergic receptors. At high doses, amantadine, diphenhydramine, orphenadrine, phenothiazines, and tricyclic antidepressants have additional nonanticholinergic activity (see below).	Physiologic stimulation (Table e50-2); dry skin and mucous membranes, decreased bowel sounds, flushing, and urinary retention; myoclonus and picking activity. Central effects may occur without significant autonomic dysfunction.	Physostigmine, an acetylcholinesterase inhibitor (see below) for delirium, hallucinations, and neuromuscular hyperactivity. Contraindications include asthma, nonanticholinergic cardiovascular toxicity (e.g., cardiac conduction abnormalities, hypotension, and ventricular arrhythmias).
Antiparkinsonian agents	Amantadine, trihexyphenidyl			

(*continued*)

TABLE e50-4 Pathophysiologic Features and Treatment of Specific Toxic Syndromes and Poisonings (*Continued*)

Physiologic Condition, Causes	Examples	Mechanism of Action	Clinical Features	Specific Treatments
Antipsychotics	Chlorpromazine, olanzapine, quetiapine, thioridazine			
Antispasmodics	Clidinium, dicyclomine			
Belladonna alkaloids	Atropine, hyoscyamine, scopolamine			
Cyclic antidepressants	Amitriptyline, doxepin, imipramine			
Muscle relaxants	Cyclobenzaprine, orphenadrine			
Mushrooms and plants	*Amanita muscaria* and *A. pantherina,* henbane, jimson weed, nightshade			
Depressed				
Sympatholytics				
α_2-Adrenergic agonists	Clonidine, guanabenz, tetrahydrozoline and other imidazoline decongestants, tizanidine and other imidazoline muscle relaxants	Stimulation of α_2-adrenergic receptors leading to inhibition of CNS sympathetic outflow; activity at nonadrenergic imidazoline binding sites also contributes to CNS effects.	Physiologic depression (Table e50-2), miosis. Transient initial hypertension may be seen.	Dopamine and norepinephrine for hypotension. Atropine for symptomatic bradycardia. Naloxone for CNS depression (inconsistently effective).
Antipsychotics	Chlorpromazine, clozapine, haloperidol, risperidone, thioridazine	Inhibition of α-adrenergic, dopaminergic, histaminergic, muscarinic, and serotonergic receptors. Some agents also inhibit sodium, potassium, and calcium channels.	Physiologic depression (Table e50-2), miosis, anticholinergic effects (see above), extrapyramidal reactions (see below), tachycardia. Cardiac conduction delays (increased PR, QRS, JT, and QT intervals) with ventricular tachydysrhythmias, including torsades des pointes, can sometimes develop.	Sodium bicarbonate for ventricular tachydysrhythmias associated with QRS prolongation. Magnesium, isoproterenol, and overdrive pacing for torsades des pointes. Avoid class IA, IC, and III antiarrhythmics. Intravenous lipid emulsion therapy may be beneficial in some cases.
β-Adrenergic blockers	Cardioselective (β_1) blockers: atenolol, esmolol, metoprolol Nonselective (β_1 and β_2) blockers: nadolol, propranolol, timolol Partial β agonists: acebutolol, pindolol α_1 Antagonists: carvedilol, labetalol Membrane-active agents: acebutolol, propranolol, sotalol	Inhibition of β-adrenergic receptors (class II antiarrhythmic effect). Some agents have activity at additional receptors or have membrane effects (see below).	Physiologic depression (Table e50-2), atrioventricular block, hypoglycemia, hyperkalemia, seizures. Partial agonists can cause hypertension and tachycardia. Sotalol can cause increased QT interval and ventricular tachydysrhythmias. Onset may be delayed after sotalol and sustained-release formulation overdose.	Glucagon for hypotension and symptomatic bradycardia. Atropine, isoproterenol, dopamine, dobutamine, epinephrine, and norepinephrine may sometimes be effective. High-dose insulin (with glucose and potassium to maintain euglycemia and normokalemia), electrical pacing, and mechanical cardiovascular support for refractory cases.

(*continued*)

TABLE e50-4 Pathophysiologic Features and Treatment of Specific Toxic Syndromes and Poisonings (*Continued*)

Physiologic Condition, Causes	Examples	Mechanism of Action	Clinical Features	Specific Treatments
Calcium channel blockers	Diltiazem, nifedipine and other dihydropyridine derivatives, verapamil	Inhibition of slow (type L) cardiovascular calcium channels (class IV antiarrhythmic effect).	Physiologic depression (Table e50-2), atrioventricular block, organ ischemia and infarction, hyperglycemia, seizures. Hypotension is usually due to decreased vascular resistance rather than to decreased cardiac output. Onset may be delayed for ≥12 h after overdose of sustained-release formulations.	Calcium and glucagon for hypotension and symptomatic bradycardia. Dopamine, epinephrine, norepinephrine, atropine, and isoproterenol are less often effective but can be used adjunctively. High-dose insulin (with glucose and potassium to maintain euglycemia and normokalemia), intravenous lipid emulsion therapy, electrical pacing, and mechanical cardiovascular support for refractory cases.
Cardiac glycosides	Digoxin, endogenous cardioactive steroids, foxglove and other plants, toad skin secretions (*Bufonidae* sp.)	Inhibition of cardiac Na^+, K^+-ATPase membrane pump.	Physiologic depression (Table e50-2); gastrointestinal, psychiatric, and visual symptoms; atrioventricular block with or without concomitant supraventricular tachyarrhythmia; ventricular tachyarrhythmias. Hyperkalemia in acute poisoning. Toxicity occurs at lower drug levels in chronic poisoning than in acute poisoning.	Digoxin-specific antibody fragments for hemodynamically compromising dysrhythmias, Mobitz II or third-degree atrioventricular block, hyperkalemia (>5.5 meq/L; in acute poisoning only). Temporizing measures include atropine, dopamine, epinephrine, and external cardiac pacing for bradydysrhythmias and magnesium, lidocaine, or phenytoin, for ventricular tachydysrhythmias. Internal cardiac pacing and cardioversion can increase ventricular irritability and should be reserved for refractory cases.
Cyclic antidepressants	Amitriptyline, doxepin, imipramine	Inhibition of α-adrenergic, dopaminergic, GABA-ergic, histaminergic, muscarinic, and serotonergic receptors; inhibition of sodium channels (see membrane-active agents); inhibition of norepinephrine and serotonin reuptake.	Physiologic depression (Table e50-2), seizures, tachycardia, cardiac conduction delays (increased PR, QRS, JT, and QT intervals; terminal QRS right-axis deviation) with aberrancy and ventricular tachydysrhythmias. Anticholinergic toxidrome (see above).	Hypertonic sodium bicarbonate (or hypertonic saline) and lidocaine for ventricular tachydysrhythmias associated with QRS prolongation. Use of phenytoin is controversial. Avoid class IA, IC, and III antiarrhythmics.
Cholinergics				
Acetylcholinesterase inhibitors	Carbamate insecticides (aldicarb, carbaryl, propoxur) and medicinals (neostigmine, physostigmine, tacrine); nerve gases (sarin, soman, tabun, VX) organophosphate insecticides (diazinon, chlorpyrifos-ethyl, malathion)	Inhibition of acetylcholinesterase leading to increased synaptic acetylcholine at muscarinic and nicotinic cholinergic receptor sites	Physiologic depression (Table e50-2). Muscarinic signs and symptoms: seizures, excessive secretions (lacrimation, salivation, bronchorrhea and wheezing, diaphoresis), and increased bowel and bladder activity with nausea, vomiting, diarrhea, abdominal cramps, and incontinence of feces and urine. Nicotinic signs and symptoms: hypertension, tachycardia, muscle cramps, fasciculations, weakness, and paralysis. Death is usually due to respiratory failure. Cholinesterase activity in plasma and red cells <50% of normal in acetylcholinesterase inhibitor poisoning.	Atropine for muscarinic signs and symptoms. Pralidoxime (2-PAM), a cholinesterase reactivator, for nicotinic signs and symptoms due to organophosphates, nerve gases, or an unknown anticholinesterase.
Muscarinic agonists	Bethanechol, mushrooms (*Boletus*, *Clitocybe*, *Inocybe* spp.), pilocarpine	Stimulation of CNS and postganglionic parasympathetic cholinergic (muscarinic) receptors		
Nicotinic agonists	Lobeline, nicotine (tobacco)	Stimulation of preganglionic sympathetic and parasympathetic and striated muscle (neuromuscular junction) cholinergic (nicotine) receptors		

(*continued*)

TABLE e50-4 Pathophysiologic Features and Treatment of Specific Toxic Syndromes and Poisonings (*Continued*)

Physiologic Condition, Causes	Examples	Mechanism of Action	Clinical Features	Specific Treatments
Sedative-hypnotics (see also Chap. 393)				
Anticonvulsants	Carbamazepine, ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, tiagabine, topiramate, valproate, zonisamide	Potentiation of the inhibitory effects of GABA by binding to the neuronal GABA-A chloride channel receptor complex and increasing the frequency or duration of chloride channel opening in response to GABA stimulation. Baclofen and, to some extent, GHB act at the GABA-B receptor complex; meprobamate, its metabolite carisoprodol, felbamate, and orphenadrine antagonize *N*-methyl-D-aspartate (NDMA) excitatory receptors; ethosuximide, valproate, and zonisamide decrease conduction through T-type calcium channels; valproate decreases GABA degradation, and tiagabine blocks GABA reuptake; carbamazepine, lamotrigine, oxcarbazepine, phenytoin, topiramate, valproate, and zonisamide slow the rate of recovery of inactivated sodium channels. Some agents also have α_2 agonist, anticholinergic, and sodium channel-blocking activity (see above and below).	Physiologic depression (Table e50-2), nystagmus. Delayed absorption can occur with carbamazepine, phenytoin, and valproate. Myoclonus, seizures, hypertension, and tachyarrhythmias can occur with baclofen, carbamazepine, and orphenadrine.	Benzodiazepines , barbiturates, or propofol for seizures.
Barbiturates	Short-acting: butabarbital, pentobarbital, secobarbital Long-acting: phenobarbital, primidone			Hemodialysis and hemoperfusion may be indicated for severe poisoning by some agents (see "Extracorporeal Removal," in text).
Benzodiazepines	Ultrashort-acting: estazolam, midazolam, temazepam, triazolam Short-acting: alprazolam, flunitrazepam, lorazepam, oxazepam Long-acting: chlordiazepoxide, clonazepam, diazepam, flurazepam Pharmacologically related agents: zaleplon, zolpidem		Tachyarrhythmias can also occur with chloral hydrate. AGMA, hypernatremia, hyperosmolality, hyperammonemia, chemical hepatitis, and hypoglycemia can be seen in valproate poisoning. Carbamazepine and oxcarbazepine may produce hyponatremia from SIADH.	See above and below for treatment of anticholinergic and sodium-channel (membrane) blocking effects.
GABA precursors	γ-Hydroxybutyrate (sodium oxybate; GHB), γ-butyrolactone (GBL), 1,4-butanediol.		Some agents can cause anticholinergic and sodium channel (membrane) blocking effects (see above and below).	
Muscle relaxants	Baclofen, carisoprodol, cyclobenzaprine, etomidate, metaxalone, methocarbamol, orphenadrine, propofol, tizanidine and other imidazoline muscle relaxants.			
Other agents	Chloral hydrate, ethchlorvynol, glutethimide, meprobamate, methaqualone, methyprylon			

(*continued*)

TABLE e50-4 Pathophysiologic Features and Treatment of Specific Toxic Syndromes and Poisonings (*Continued*)

Physiologic Condition, Causes	Examples	Mechanism of Action	Clinical Features	Specific Treatments
Discordant				
Asphyxiants				
Cytochrome oxidase inhibitors	Cyanide, hydrogen sulfide	Inhibition of mitochondrial cytochrome oxidase, thereby blocking electron transport and oxidative metabolism. Carbon monoxide also binds to hemoglobin and myoglobin and prevents oxygen binding, transport, and tissue uptake (binding to hemoglobin shifts the oxygen dissociation curve to the left).	Signs and symptoms of hypoxemia with initial physiologic stimulation and subsequent depression (Table e50-2); lactic acidosis; normal P_{O_2} and calculated oxygen saturation but decreased oxygen saturation by co-oximetry (that measured by pulse oximetry is falsely elevated but is less than normal and less than the calculated value). Headache and nausea are common with carbon monoxide. Sudden collapse may occur with cyanide and hydrogen sulfide exposure. A bitter almond breath odor may be noted with cyanide ingestion, and hydrogen sulfide smells like rotten eggs.	High-dose oxygen. IV hydroxocobalamin or IV sodium nitrite and sodium thiosulfate (Lilly cyanide antidote kit) for coma, metabolic acidosis, and cardiovascular dysfunction in cyanide poisoning.
Methemoglobin inducers	Aniline derivatives, dapsone, local anesthetics, nitrates, nitrites, nitrogen oxides, nitro- and nitrosohydrocarbons, phenazopyridine, primaquine-type antimalarials, sulfonamides.	Oxidation of hemoglobin iron from ferrous (Fe^{2+}) to ferric (Fe^{3+}) state prevents oxygen binding, transport, and tissue uptake (methemoglobinemia shifts oxygen dissociation curve to the left). Oxidation of hemoglobin protein causes hemoglobin precipitation and hemolytic anemia (manifest as Heinz bodies and "bite cells" on peripheral blood smear).	Signs and symptoms of hypoxemia with initial physiologic stimulation and subsequent depression (Table e50-2), gray-brown cyanosis unresponsive to oxygen at methemoglobin fractions >15–20%, headache, lactic acidosis (at methemoglobin fractions >45%), normal P_{O_2} and calculated oxygen saturation but decreased oxygen saturation and increased methemoglobin fraction by co-oximetry (oxygen saturation by pulse oximetry may be falsely increased or decreased but is less than normal and less than the calculated value).	High-dose oxygen. Intravenous methylene blue for methemoglobin fraction >30%, symptomatic hypoxemia, or ischemia (contraindicated in G6PD deficiency). Exchange transfusion and hyperbaric oxygen for severe or refractory cases.
AGMA inducers	Ethylene glycol	Ethylene glycol causes CNS depression and increased serum osmolality. Metabolites (primarily glycolic acid) cause AGMA, CNS depression, and renal failure. Precipitation of oxalic acid metabolite as calcium salt in tissues and urine results in hypocalcemia, tissue edema, and crystalluria.	Initial ethanol-like intoxication, nausea, vomiting, increased osmolar gap, calcium oxylate crystalluria. Delayed AGMA, back pain, renal failure. Coma, seizures, hypotension, ARDS in severe cases.	Sodium bicarbonate to correct acidemia. Thiamine, folinic acid, magnesium, and high-dose pyridoxine to facilitate metabolism. Ethanol or fomepizole for AGMA, crystalluria or renal dysfunction, ethylene glycol level >3 mmol/L (20 mg/dL), and for ethanol-like intoxication or increased osmolal gap if level not readily obtainable. Hemodialysis for persistent AGMA, lack of clinical improvement, and renal dysfunction. Hemodialysis also useful for enhancing ethylene glycol elimination and shortening duration of treatment when ethylene glycol level >8 mmol/L (50 mg/dL).

(*continued*)

TABLE e50-4 Pathophysiologic Features and Treatment of Specific Toxic Syndromes and Poisonings (*Continued*)

Physiologic Condition, Causes	Examples	Mechanism of Action	Clinical Features	Specific Treatments
AGMA inducers	Iron	Hydration of ferric (Fe^{3+}) ion generates H^+. Non-transferrin-bound iron catalyzes formation of free radicals that cause mitochondrial injury, lipid peroxidation, increased capillary permeability, vasodilation, and organ toxicity.	Initial nausea, vomiting, abdominal pain, diarrhea. AGMA, cardiovascular and CNS depression, hepatitis, coagulopathy, and seizures in severe cases. Radiopaque iron tablets may be seen on abdominal x-ray.	Whole-bowel irrigation for large ingestions. Endoscopy and gastrostomy if clinical toxicity and large number of tablets still visible on x-ray. IV hydration. Sodium bicarbonate for acidemia. IV deferoxamine for systemic toxicity, iron level >90 μmol/L (500 μg/dL).
	Methanol	Methanol causes ethanol-like CNS depression and increased serum osmolality. Formic acid metabolite causes AGMA and retinal toxicity.	Initial ethanol-like intoxication, nausea, vomiting, increased osmolar gap. Delayed AGMA, visual (clouding, spots, blindness) and retinal (edema, hyperemia) abnormalities. Coma, seizures, cardiovascular depression in severe cases. Possible pancreatitis.	Gastric aspiration for recent ingestions. Sodium bicarbonate to correct acidemia. High-dose folinic acid or folate to facilitate metabolism. Ethanol or fomepizole for AGMA, visual symptoms, methanol level >6 mmol/L (20 mg/dL), and for ethanol-like intoxication or increased osmolal gap if level not readily obtainable. Hemodialysis for persistent AGMA, lack of clinical improvement, and renal dysfunction. Hemodialysis also useful for enhancing methanol elimination and shortening duration of treatment when methanol level >15 mmol/L (50 mg/dL).
	Salicylate	Increased sensitivity of CNS respiratory center to changes in P_{O_2} and P_{CO_2} stimulates respiration. Uncoupling of oxidative phosphorylation, inhibition of Krebs cycle enzymes, and stimulation of carbohydrate and lipid metabolism generate unmeasured endogenous anions and cause AGMA.	Initial nausea, vomiting, hyperventilation, alkalemia, alkaluria. Subsequent alkalemia with both respiratory alkalosis and AGMA, and paradoxical aciduria. Late acidemia with CNS and respiratory depression. Cerebral and pulmonary edema in severe cases. Hypoglycemia, hypocalcemia, hypokalemia, and seizures can occur.	IV hydration and supplemental glucose. Sodium bicarbonate to correct acidemia. Urinary alkalinization for systemic toxicity. Hemodialysis for coma, cerebral edema, seizures, pulmonary edema, renal failure, progressive acid-base disturbances or clinical toxicity, salicylate level >7 mmol/L (100 mg/dL) following acute overdose.
CNS syndromes				
Extrapyramidal reactions	Antipsychotics (see above), some cyclic antidepressants and antihistamines.	Decreased CNS dopaminergic activity with relative excess of cholinergic activity.	Akathisia, dystonia, parkinsonism	Oral or parenteral anticholinergic agent such as benztropine or diphenhydramine.
Isoniazid		Interference with activation and supply of pyridoxal-5-phosphate, a cofactor for glutamic acid decarboxylase, which converts glutamic acid to GABA, results in decreased levels of this inhibitory CNS neurotransmitter; complexation with and depletion of pyridoxine itself; inhibition of nicotine-adenine dinucleotide–dependent lactate and hydroxybutyrate dehydrogenases resulting in substrate accumulation.	Nausea, vomiting, agitation, confusion; coma, respiratory depression, seizures, lactic and ketoacidosis in severe cases.	High-dose intravenous pyridoxine (vitamin B_6) for agitation, confusion, coma, and seizures. Diazepam or barbiturates for seizures.

(*continued*)

TABLE e50-4 Pathophysiologic Features and Treatment of Specific Toxic Syndromes and Poisonings (*Continued*)

Physiologic Condition, Causes	Examples	Mechanism of Action	Clinical Features	Specific Treatments
Lithium		Interference with cell membrane ion transport, adenylate cyclase and Na^+, K^+-ATPase activity, and neurotransmitter release.	Nausea, vomiting, diarrhea, ataxia, choreoathetosis, encephalopathy, hyperreflexia, myoclonus, nystagmus, nephrogenic diabetes insipidus, falsely elevated serum chloride with low anion gap, tachycardia. Coma, seizures, arrhythmias, hyperthermia, and prolonged or permanent encephalopathy and movement disorders in severe cases. Delayed onset after acute overdose, particularly with delayed-release formulations. Toxicity occurs at lower drug levels in chronic poisoning than in acute poisoning.	Whole-bowel irrigation for large ingestions. IV hydration. Hemodialysis for coma, seizures, severe, progressive, or persistent encephalopathy or neuromuscular dysfunction, peak lithium level >4 meq/L following acute overdose.
Serotonin syndrome	Amphetamines, cocaine, dextromethorphan, meperidine, MAO inhibitors, selective serotonin (5-HT) reuptake inhibitors, tricyclic antidepressants, tramadol, triptans, tryptophan.	Promotion of serotonin release, inhibition of serotonin reuptake, or direct stimulation of CNS and peripheral serotonin receptors (primarily 5-HT-1a and 5-HT-2), alone or in combination.	Altered mental status (agitation, confusion, mutism, coma, seizures), neuromuscular hyperactivity (hyperreflexia, myoclonus, rigidity, tremors), and autonomic dysfunction (abdominal pain, diarrhea, diaphoresis, fever, flushing, labile hypertension, mydriasis, tearing, salivation, tachycardia). Complications include hyperthermia, lactic acidosis, rhabdomyolysis, and multisystem organ failure.	Serotonin receptor antagonist cyproheptadine, discontinue the offending agent(s).
Membrane-active agents	Amantadine, antiarrhythmics (class I and III agents; some β blockers), antipsychotics (see above), antihistamines (particularly diphenhydramine), carbamazepine, local anesthetics (including cocaine), opioids (meperidine, propoxyphene), orphenadrine, quinoline antimalarials (chloroquine, hydroxychloroquine, quinine), cyclic antidepressants (see above).	Blockade of fast sodium membrane channels prolongs phase 0 (depolarization) of the cardiac action potential, which prolongs the QRS duration and promotes reentrant (monomorphic) ventricular tachycardia. Class Ia, Ic, and III antiarrhythmics also block potassium channels during phases 2 and 3 (repolarization) of the action potential, prolonging the JT interval and promoting early afterdepolarizations and polymorphic (torsades des pointes) ventricular tachycardia. Similar effects on neuronal membrane channels cause CNS dysfunction. Some agents also block α-adrenergic and cholinergic receptors or have opioid effects (see above and Chap. 393).	QRS and JT prolongation (or both) with hypotension, ventricular tachyarrhythmias, CNS depression, seizures. Anticholinergic effects with amantadine, antihistamines, carbamazepine, disopyramide, antipsychotics, and cyclic antidepressants (see above). Opioid effects with meperidine and propoxyphene (see Chap. 393). Cinchonism (hearing loss, tinnitus, nausea, vomiting, vertigo, ataxia, headache, flushing, diaphoresis) and blindness with quinoline antimalarials.	Hypertonic sodium bicarbonate (or hypertonic saline) for cardiac conduction delays and monomorphic ventricular tachycardia. Lidocaine for monomorphic ventricular tachycardia (except when due to class Ib antiarrhythmics). Magnesium, isoproterenol, and overdrive pacing for polymorphic ventricular tachycardia. Physostigmine for anticholinergic effects (see above). Naloxone for opioid effects (see Chap. 393). Extracorporeal removal for some agents (see text).

Abbreviations: AGMA, anion-gap metabolic acidosis; ARDS, adult respiratory distress syndrome; ATPase, adenosine triphosphatase; CNS, central nervous system; GABA, γ-aminobutyric acid; GHB, γ-hydroxybutyrate; 5-HT, 5-hydroxytryptamine (serotonin); MAO, monoamine oxidase; P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen; SIADH, syndrome of inappropriate antidiuretic hormone; VX, extremely toxic persistent nerve agent (no common chemical name).

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