CHAPTER 4

Focused Physical Examination/ Toxidromes

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Many toxic exposures cause characteristic physical findings that are detectable by a carefully focused physical examination. This aspect of the evaluation of a poisoned patient is particularly important when a reliable history cannot be obtained. In the case of a patient who is unresponsive or delirious, the physical examination may provide the only clues to the presence of a toxin.

This chapter discusses characteristic clinical manifestations of toxins, including effects on vital signs, mental status, pupils, skin, hair, oral cavity, and gastrointestinal tract. It also reviews the five common "toxidromes"—constellations of physical findings that characterize poisoning with anticholinergic, sympathomimetic, opioid, anticholinesterase, and sedative-hypnotic agents.[59] These hallmark physical findings often prove invaluable during the early assessment of an overdosed patient, even when only a few of the features of a specific toxidrome are present.

FOCUSED PHYSICAL EXAMINATION: VITAL SIGNS

The physical examination begins with a full set of vital signs which should be performed immediately upon presentation to the emergency department. Pulse oximetry is a valuable "fifth vital sign" that may provide valuable information.

Temperature

Exposure to various toxins can result in hyperthermia or hypothermia (Tables 4–1 and 4–2). Accurate measurement of the core temperature is essential in all patients with temperature disturbances. Because the maximal temperature range for standard thermometers is 32°C to 43°C, special high- and low-recording thermometers are needed to measure the core temperature in patients with suspected extreme temperature abnormalities. Once the diagnosis of hyperthermia or hypothermia has been established, the core temperature should be continuously monitored.

Hyperthermia

Pathophysiology. The thermoregulatory center in the hypothalamus maintains body temperature at a set-point of 37°C (98.6°F) by regulating sweating, vasodilation, and shivering.[8] Hyperthermia occurs when the body temperature has risen higher than the normal thermal set-point, whereas fever occurs when the thermal set-point has been increased. Both hyperthermia and fever occur as consequences of drug overdose.

Elevation of body temperature in the setting of drug overdose may be due to increased heat production, decreased heat loss, or fever related to the pyrogenic effects of drugs or their diluents. Mechanisms of increased heat production include increased muscle activity or muscle tone, uncoupling of oxidative phosphorylation, and increased metabolic rate. The ability to lose heat is adversely affected by impairment of sweating, extreme vasoconstriction, and impairment of cardiac function. Pyrogens such as drugs, bacteria, viruses, and fungi raise the thermal set-point in the preoptic area of the anterior hypothalamus, causing fever.[46] Pyrogens are also released from endogenous sources by stimulation of neutrophils, monocytes, and Kupffer cells.

Hyperthermia Associated with Drugs and Toxins. Excessive heat production follows exposure to toxins that cause agitation, muscular hyperactivity, seizures, and increased muscle tone. Common examples of drugs that do this include amphetamines,[27] cocaine,[58] lysergic acid diethylamide (LSD), phencyclidine, cyclic antidepressants, antihistamines, monoamine oxidase inhibitors (MAOIs), and strychnine.[10] Fatal hyperthermia has been associated with methylenedioxymethamphetamine (MDMA) use and dancing at rave parties.[36] Tremors associated with withdrawal from ethanol, barbiturates, and other sedative-hypnotics also increase temperature by this mechanism.

Even therapeutic doses of drugs may cause an elevation of body temperature during heavy exercise, infection, or exposure to a warm environment. Heat stress in the setting of therapeutic dosing of α-adrenergic receptor agonists, including over-the-counter pseudoephedrine or phenylpropanolamine, has resulted in life-threatening hyperthermia.[6, 43] Impaired sweating due to the anticholinergic effects of antihistamines, cyclic antidepressants, phenothiazines, and belladonna alkaloids may also cause significant hyperthermia. Salicylates, dinitrophenol, and pentachlorophenol cause an increase in body heat production by uncoupling oxidative phosphorylation. Overdose of exogenous thyroid hormone

TABLE 4–1 • **Mechanisms and Common Examples of Drug- and Toxin-Induced Hyperthermia**

Increased Heat Production
Excessive muscle activity and muscle tone
Amphetamines
Anticholinergics
Cocaine
Cyclic antidepressants
Lysergic acid diethylamide (LSD)
Methylenedioxymethamphetamine (MDMA), other designer amphetamines
Monoamine oxidase inhibitors (MAOIs)
Phencyclidine (PCP)
Strychnine
Withdrawal from ethanol and sedative-hypnotics
Uncoupling of oxidative phosphorylation
Arsenic
Dinitrophenol
Pentachlorophenol
Salicylates
Increased metabolic rate
Thyroid hormones
Decreased Heat Loss
Impaired sweating
Anticholinergics
Antihistamines
Cyclic antidepressants
Phenothiazines
Vasoconstriction
Sympathomimetics
Amphetamines
Cocaine
Ephedrine
Phenylephrine
Phenylpropanolamine
Pseudoephedrine
Other
Malignant hyperthermia
Halothane
Succinylcholine
Neuroleptic malignant syndrome
Haloperidol
Fluphenazine
Trifluoperazine
Serotonin syndrome
Dextromethorphan–MAOI interaction
Meperidine–MAOI interaction
Selective serotonin reuptake inhibitor (SSRI)–MAOI interaction
SSRI overdose
Metal fume fever
Copper oxide fumes
Zinc oxide fumes
Hydrocarbon aspiration
Gasoline
Lamp oil

raises body temperature by increasing the basal metabolic rate.

"Drug fever" typically occurs 7 to 10 days after initiation of a new drug, although it may have many patterns. It resolves within 48 hours of discontinuing the medication and recurs withing a few hours of re-exposure.[52] Penicillins, sulfonamides, salicylates, antihistamines, barbiturates, procainamide, quinidine, methyldopa, phenytoin, isoniazid, allopurinol, and cimetidine are some of the more common drugs reported to cause drug fever in therapeutic doses.

Other drug-induced etiologies of hyperthermia include malignant hyperthermia, neuroleptic malignant syndrome (NMS), and serotonin syndrome. Malignant hyperthermia is a rare autosomal dominant disorder associated with abnormal calcium regulation. It develops as a complication of general anesthesia with inhaled agents such as halothane. Severe, sudden muscle rigidity precipitates extreme hyperthermia, with tachycardia, acidosis, and hyperkalemia. NMS is seen following exposure to antipsychotic drugs that block dopaminergic receptors and after withdrawal of dopaminergic agonists such as amantadine or bromocriptine. The diagnosis of NMS is based on the presence of hyperthermia, increased muscle tone, altered mental status, and autonomic dysfunction. Haloperidol, fluphenazine, and trifluoperazine are common etiologic agents of this syndrome. Acute dystonias may be associated with elevated temperature as well. The serotonin syndrome is most commonly associated with drug interactions between serotonergic agents such as selective serotonin reuptake inhibitors (SSRIs) and MAOIs or lithium.[61] The notorious combination of meperidine with an MAOI has resulted in life-threatening hyperthermia attributed to the serotonin syndrome.[11]

Metal fume fever following exposure to zinc oxide and copper oxide fumes is postulated to be due to a cytokine response.[9, 48] Hyperthermia that occurs during the first 12 to 24 hours following hydrocarbon exposure is due to a chemical pyrogenic response. This is distinguished from the fever caused by bacterial superinfection, which typically develops after 24 to 48 hours.

Differential Diagnosis of Hyperthermia. The differential diagnosis of hyperthermia includes environmental exposure (heat exhaustion, heatstroke); increased motor activity due to psychosis, status epilepticus, chorea, and parkinsonism; and fever from thyrotoxicosis or infection.

TABLE 4–2 • **Mechanisms and Common Examples of Drug- and Toxin-Induced Hypothermia**

Vasodilation
Cyclic antidepressants
Ethanol
Phenothiazines
Impaired perception of cold
Carbon monoxide
Ethanol
Opioids
Sedative-hypnotics
Depressed hypothalamic/central nervous system function
Barbiturates
Ethanol
Opioids
Phenothiazines
Sedative-hypnotics
Substrate depletion
Ethanol
Insulin
Oral hypoglycemics
Decreased heat production or metabolic activity
Beta-adrenergic receptor antagonists
Cyanide
Hydrogen sulfide
Organophosphates

Hypothermia

Pathophysiology. Hypothermia, defined as a core temperature less than 35°C, has multiple etiologies, particularly when environmental exposure is mild.[19] Defenses against hypothermia include increased heat production by shivering and metabolic activities, vasoconstriction to reduce heat loss to the environment, and behavioral responses that include dressing and seeking shelter. Drugs and toxins induce hypothermia by causing vasodilation, impairing behavioral responses to cold, depressing hypothalamic and central nervous system (CNS) function, depleting substrates, and decreasing metabolic heat production.

Drug-Induced Hypothermia. Ethanol, a common cause of toxin-related hypothermia, impedes shivering, causes vasodilation, depresses the CNS, can cause hypoglycemia, and is a risk factor for trauma.[66] Drugs with prominent α-adrenergic receptor antagonist properties, such as phenothiazines, potentiate hypothermia by inducing vasodilation. Opioids, sedative-hypnotics, general anesthetics, phenothiazines, and carbon monoxide directly inhibit hypothalamic function. Oral hypoglycemic agents and insulin cause hypothermia by depleting substrates needed for thermogenesis.[42] Beta-adrenergic receptor antagonists interfere with the mobilization of thermogenic substrates and inhibit the ability to maintain euthermia during cold stress.[56]

Differential Diagnosis of Hypothermia. Infections, hypoglycemia, hypothyroidism, trauma, burns, and cachexia predispose to hypothermia. The very young, very old, unconscious, immobile, and intoxicated are particularly susceptible. The term "urban hypothermia" has been used to describe two different situations: (1) a syndrome of homelessness and substance abuse that leads to exposure-related hypothermia, and (2) mild hypothermia occurring in elderly urban dwellers who are reluctant to heat their homes because of the cost.[60] Hypothermia has been noted as a presenting sign of shaken baby syndrome[54, 76] and child abuse.[33] Hypothermia should be suspected in every patient with coma.

Pulse

The heart rate is the product of competing influences that include the sympathetic and parasympathetic nervous systems, core temperature, and endocrine function. Causes of tachycardia include sinus, supraventricular, or ventricular mechanisms. Bradycardia may be due to direct depression of myocardial pacemakers, reflex mechanisms, decreased central sympathetic outflow, parasympathomimetic effects, CNS depressant effects, and severe membrane depressant effects.

Tachycardia

Drug-Induced Tachycardia. Stimulants associated with an increased heart rate include amphetamines, caffeine, cocaine, ephedrine, and other sympatholytics; phencyclidine; and theophylline (Table 4–3). Withdrawal from ethanol, barbiturates, and other sedative-hypnotic drugs increases the heart rate owing to enhanced noradrenergic stimulation. Anticholinergics and antihistamines decrease parasympathetic tone by blocking muscarinic receptors, inducing tachycardia. Poisoning with anticholinesterase agents such as organophosphate and carbamate pesticides causes tachycardia through acetylcholine stimulation of sympathetic preganglionic nicotinic receptors. Tachycardia may also be a compensatory response to bronchorrhea-induced hypoxemia. Drugs and toxins that decrease peripheral resistance (calcium channel antagonists, ethanol, iron, nitrites, arsenic, and salicylates) are associated with reflex tachycardia, as are agents that cause intravascular volume loss from vomiting, diarrhea, or bleeding (iron, salicylates, colchicine). Agents that increase myocardial sensitization to catecholamines, such as the halogenated hydrocarbons or chloral hydrate, may also precipitate tachycardia. Thyroid hormones cause tachycardia by increasing the metabolic rate.

A number of drugs and toxins can cause ventricular tachycardia or conduction disturbances such as Q-T_c prolongation, which may precipitate atypical ventricular tachycardia, torsades de pointes, and ventricular fibrillation. Excessive doses or drug interactions with certain antidysrhythmics such as quinidine and procainamide may also result in tachycardia.

Differential Diagnosis of Tachycardia. The nontoxic differential diagnosis of sinus tachycardia includes sympathetic stimulation due to psychiatric disorders, volume depletion, fever or hyperthermia, hyperthyroidism, hypoxemia, vasodilation (in sepsis, for example), and heart failure. In one study, an increase in core temperature of 1°C was associated with a mean increase in heart rate of 8.5 beats per minute.[41] Conduction disturbances in the atria or ventricles may result in supraventricular or ventricular tachycardias.

Bradycardia

Drug-Induced Bradycardia. Sedative-hypnotics such as barbiturates cause bradycardia through their CNS depressant effects (Table 4–4). Opioids and central α_2 agonists such as clonidine, guanfacine, and imidazoline-containing eye drops[28, 50, 55] cause bradycardia by decreasing central noradrenergic outflow from the locus ceruleus. $Alpha_1$-adrenergic receptor agonists such as phenylpropanolamine cause peripheral vasoconstriction and hypertension that secondarily result in bradycardia mediated by baroreceptor reflexes. Group IA antidysrhythmic agents such as procainamide cause bradycardia by blocking the sodium (fast) channels in conduction tissue.

Digoxin and plants that contain cardiac glycosides such as lily of the valley (*Convallaria majalis*), foxglove (*Digitalis purpurea*), and oleander (*Nerium oleander*); β-adrenergic receptor antagonists; and calcium channel antagonists cause bradycardia by directly affecting myocardial conduction. The muscarinic effects of organophosphates and carbamate insecticides may cause bradycardia. Aphrodisiacs such as "Rock Hard" and "Love Shop," intended for topical application, contain cardioactive toad venoms (bufadienolides) that cause vomiting, bradycardia, and dysrhythmias when ingested. Significant toxicity has been reported after licking or ingesting Cane and Colorado River toads.[12]

Differential Diagnosis of Bradycardia. Increased intracranial pressure from mass lesions or cerebral edema may cause bradycardia and hypertension as manifestations of the Cushing reflex. Myocardial depression by ischemia or hypoxia, or myocardial conduction disturbances, may also

TABLE 4–3 • **Mechanisms and Common Examples of Drug- and Toxin-Induced Tachycardia**

- Sympathomimetic–β_1-adrenergic receptor stimulation
  - Amphetamines
  - Caffeine
  - Cocaine
  - Methylenedioxymethamphetamine (MDMA), other designer amphetamines
  - Phencyclidine (PCP)
  - Theophylline
  - Withdrawal from ethanol, barbiturates, and sedative-hypnotics
- Acetylcholine excess
  - Carbamates
  - Organophosphates
  - Therapeutic cholinesterase inhibitors (e.g., physostigmine, pyridostigmine, neostigmine)
- Anticholinergic-muscarinic blockade
  - Antihistamines
  - Belladonna-containing plants
  - Cyclic antidepressants
  - Lomotil (atropine and diphenoxylate)
  - Phenothiazines
- Vasodilation
  - Arsenic
  - Calcium channel antagonists
  - Cyclic antidepressants
  - Disulfiram reactions
  - Ethanol
  - Iron
  - Nitrites
  - Phenothiazines
- Volume loss
  - Antibiotics
  - Arsenic (acute)
  - Colchicine
  - Disulfiram-ethanol interaction
  - Iron
  - Mushrooms (e.g., *Amanita phalloides*)
  - Opioid withdrawal
  - Thallium
  - Theophylline
- Increased metabolic rate
  - Thyroid hormones
- Increased sensitivity to catecholamines
  - Halogenated hydrocarbons
- Hypoxemia
  - Carbamates
  - Organophosphates
- Prodysrhythmic
  - Amiodarone
  - Amphetamines
  - Arsenic
  - Caffeine
  - Chloral hydrate
  - Cocaine
  - Cyclic antidepressants
  - Digitalis glycosides
  - Diphenhydramine
  - Flecainide
  - Halogenated hydrocarbons
  - Phenothiazines
  - Procainamide
  - Propoxyphene
  - Quinidine
  - Thallium
  - Theophylline
- Cellular asphyxia
  - Carbon monoxide
  - Cyanide
  - Hydrogen sulfide
  - Oxidizing agents
  - Sodium azide

be associated with bradycardia. Increased vagal tone of any etiology also results in bradycardia.

Blood Pressure

Measurement of blood pressure should be done with a cuff that covers two thirds of the upper arm or leg. Too small a cuff results in falsely elevated readings, and too large a cuff causes falsely depressed readings.

Hypertension

The major mechanism of drug- and toxin-induced hypertension is vasoconstriction (Table 4–5). Amphetamines and cocaine increase the availability of norepinephrine at α_1-adrenergic receptors, resulting in vasoconstriction and hypertension. Phenylpropanolamine[37, 38] and phenylephrine are potent α_1-adrenergic receptor agonists that cause significant vasoconstriction and hypertension. Hypertension also occurs in the early stages of a clonidine overdose owing to nonselective postsynaptic stimulation of peripheral α_1-adrenergic receptors. Ergot is also a powerful vasoconstrictor, and ingestion of ergot-containing compounds sometimes results in hypertension. The MAOIs are among the most notorious agents causing hypertension. MAOIs inhibit the breakdown of catecholamines, increasing the pool of norepinephrine in the presynaptic sympathetic nerve terminal. Indirect-acting sympathomimetic agents and foods that contain tyramine (e.g., Chianti wine, aged cheese, pickled herring, and chicken livers) release this stored pool of norepinephrine, resulting in hypertensive crisis. Overdose of MAOIs or cyclic antidepressants may be associated with hypertension that is followed by hypotension due to "washout" and depletion of catecholamines. Chronic lead exposure has been associated with hypertension due to lead-induced nephropathy or increased catecholamine levels.[14, 65, 69]

Differential Diagnosis of Hypertension. Nontoxic causes of hypertension, including renal disease, aldosteronism, pheochromocytoma, coarctation of the aorta and thyrotoxicosis should be considered during evaluation of the patient.

Hypotension

Drug-induced hypotension is caused by hypovolemia, decreased peripheral vascular resistance, decreased myocardial contractility, and dysrhythmias (Table 4–6). Gastrointestinal fluid losses from vomiting or diarrhea often contribute to hypotension but are seldom the sole cause. Treatment with ipecac and cathartics such as sorbitol can lead to excessive volume losses. Antibiotics, organophosphates, carbamates, iodine, laxatives and cathartics, lithium, and opioid with-

TABLE 4–4 • **Mechanisms and Common Examples of Drug- and Toxin-Induced Bradycardia**

Direct myocardial pacemaker depressant effects
Calcium channel antagonists
Cardiac glycoside-containing plants (e.g., lily of the valley, oleander, foxglove) and toads
Digitalis
Reflex mechanisms
Alpha-adrenergic receptor agonists (phenylpropanolamine)
CNS depressants
Opioids
Sedative-hypnotics
Decreased sympathetic outflow
Beta-adrenergic receptor antagonists
Clonidine
Guanabenz
Guanfacine
Imidazoline, topical
Methyldopa
Opioids
Cholinomimetic agents
Carbamates
Mushrooms containing muscarine (*Clitocybe* and *Inocybe* spp.)
Organophosphates
Physostigmine, other medicinal cholinesterase inhibitors
Antidysrhythmics—membrane depressant effects
Beta-adrenergic receptor antagonists
Cyclic antidepressants (severe)
Encainide/flecainide (severe)
Quinidine/procainamide/disopyramide (severe)

drawal are some causes of drug-induced vomiting or diarrhea. The etiology of hypotension due to arsenic and theophylline is multifactorial and includes decreased systemic vascular resistance and hypovolemia. Gastrointestinal tract burns secondary to ingestion of caustic agents such as strong alkalis, strong acids, or mercuric chloride can result in massive fluid shifts that cause hypotension.

High doses of CNS depressants such as barbiturates and opioids result in centrally mediated vasodilation, which may lead to vasomotor collapse. Clonidine, guanfacine, and other central α_2-adrenergic agonists decrease sympathetic stimulation, which in turn decreases peripheral vascular resistance. A number of antihypertensive agents such as nifedipine, nitroprusside, and prazosin are potent peripheral vasodilators. Nitroglycerin, disulfiram-ethanol reactions, and phenothiazines also cause decreased peripheral resistance.

Overdoses of β-adrenergic receptor antagonists and calcium channel antagonists such as verapamil and diltiazem produce profound hypotension by their negative inotropic effects on cardiac function.[78] Calcium channel antagonists also cause peripheral vasodilation. Cyclic antidepressants cause consequential hypotension through impairment of myocardial contractility, as well as the α-adrenergic receptor antagonist effects. The hypotension associated with severe iron poisoning is also multifactorial, a consequence of hypovolemia, increased capillary permeability, decreased myocardial function, bradycardia, and vasodilation.[75]

Differential Diagnosis of Hypotension. Traumatic and

TABLE 4–5 • **Mechanisms and Common Examples of Drug- and Toxin-Induced Hypertension**

Vasoconstriction
Amphetamines
Clonidine (early intoxication)
Cocaine
Cyclic antidepressant overdoses (early)
Ephedrine
Ergot
Imidazolines (naphazoline, oxymetazoline, tetrahydrozoline)
Monoamine oxidase inhibitors
Nicotine
Phencyclidine
Phenylephrine
Phenylpropanolamine
Pseudoephedrine
Thyroid hormones
Withdrawal from ethanol, barbiturates, sedative-hypnotics
Nephropathy
Chronic lead exposure

TABLE 4–6 • **Mechanisms and Common Examples of Drug- and Toxin-Induced Hypotension**

Decreased peripheral resistance—vasodilation
Alpha-adrenergic receptor antagonists (e.g., phenoxybenzamine, phentolamine, tolazoline, prazosin, terazosin, yohimbine, indoramin
Angiotensin-converting enzyme inhibitors
Arsenic
Caffeine
Calcium channel antagonists
Clonidine, guanfacine, guanabenz, imidazolines (oral)
Cyclic antidepressants
Disulfiram-ethanol interaction
Ethanol
Iron
Isopropanol
Nitrates/nitrites
Nitroprusside
Opioids
Phenothiazines
Salicylates
Sedative-hypnotics
Theophylline
Trimethaphan
Decreased myocardial contractility
Beta-adrenergic receptor antagonists
Calcium channel antagonists
Cyclic antidepressants
Iron
Hypovolemia or third spacing of intravascular volume
Antibiotics
Caustic injuries
Colchicine, other antimitotics
Coprinus-ethanol interaction
Disulfiram-ethanol interaction
Iron
Lead
Lithium (diabetes insipidus)
Mercury salts
Mushrooms
Nicotine
Organophosphates/carbamates
Plants (e.g., pokeweed)
Rattlesnake envenomation
Theophylline (late)
Zinc phosphate
Other/unknown
Cyanide
Monoamine oxidase inhibitors

spontaneous hemorrhage, spinal cord injury, sepsis, and myocardial ischemia are important causes of hypotension that should be considered during the evaluation of a patient with circulatory insufficiency.

Respiratory Rate

An evaluation of the rate and depth of respirations is a critical aspect of the physical examination. In the past, many deaths due to drug overdose occurred because of untreated hypoventilation and apnea. Although prehospital respiratory arrest is still a significant cause of morbidity and mortality, modern approaches to airway management and ventilation, including judicious use of certain antidotes such as naloxone, should limit the consequences of many cases of respiratory failure.

Tachypnea. Tachypnea is defined as rapid breathing. Tachypnea is seen with toxins that cause metabolic acidosis, directly stimulate the CNS, produce seizures, are aspirated, or cause noncardiogenic pulmonary edema (Table 4–7). Cases of hydrocarbon aspiration often present with tachypnea. Salicylates, dinitrophenol, pentachlorophenol, and theophylline increase the respiratory rate by directly stimulating the CNS. Agents that cause metabolic acidosis such as ethylene glycol, methanol, phenformin, metformin, and salicylates stimulate respiratory compensatory mechanisms for acidosis. Aspiration, restrictive lung disease, pleuritic chest pain, cardiac tamponade, and congestive heart failure are among the many nontoxic causes of tachypnea.

TABLE 4–7 • **Mechanisms and Common Examples of Drug- and Toxin-Induced Hyperventilation (Tachypnea or Hyperpnea)**

Stimulation of the central nervous system
Dinitrophenol
Nicotine (early)
Pentachlorophenol
Salicylates
Metabolic acidosis
Arsenic (acute)
Cyanide
Ethylene glycol
Hydrogen sulfide
Isoniazid
Iron
Ketoacidosis (alcoholic)
Methanol
Metformin
Nonsteroidal anti-inflammatory drugs (propionic acid class)
Paraldehyde
Phenformin
Sodium azide
Sodium monofluoroacetate
Toluene
Hyperadrenergic stimulation
Amphetamines
Cocaine
Aspiration of gastric contents
Hydrocarbons
Noncardiogenic pulmonary edema
Barbiturates
Cadmium
Carbon monoxide
Cocaine
Ethchlorvynol
Glutethimide
Opioids
Phosgene
Salicylates
Hypoxia
Carbon monoxide
Methemoglobin-producing drugs and toxins
Pulmonary edema—multiple drugs/toxins

Hyperpnea, a pattern of deep breathing, occurs with exercise, anxiety, and metabolic acidosis. Increased intracranial pressure, myocardial infarction, hypoxia, and hypoglycemia also cause hyperpnea. At times, salicylate intoxication may cause hyperpnea without tachypnea.

Pulmonary Edema. Noncardiogenic pulmonary edema has been associated with heroin,[72] meperidine, methadone,[45] barbiturates,[29] ethchlorvynol, cocaine,[17] and salicylates.[32, 35] Leakage of pulmonary capillaries is the postulated mechanism. Pulmonary edema in an otherwise healthy patient should raise the suspicion of an overdose. Toxic gases such as phosgene, carbon monoxide, and the toxic components of smoke may also cause noncardiogenic pulmonary edema.

Bradypnea. Bradypnea, a decreased respiratory rate, results from CNS depression or ventilatory muscle failure. Exposure to sedative-hypnotics, barbiturates, opioids, clonidine,[31] and alcohol causes respiratory depression. Respiratory failure occurs as a result of muscle weakness following exposure to organophosphates, carbamates,[51] neuromuscular blocking agents, strychnine, tetrodotoxin, venom from elapids and the Mojave rattlesnake (*Crotalus scutulatus scutulatus*), and botulinum toxin (Table 4–8). Although increased intracranial pressure more commonly causes hyperpnea, it is also associated with bradypnea.

TABLE 4–8 • **Mechanisms and Common Examples of Drug- and Toxin-Induced Respiratory Depression**

Depression of central respiratory drive
Barbiturates
Clonidine
Cyclic antidepressants
Ethanol and other alcohols
Opioids
Sedative-hypnotics
Zolpidem
Respiratory muscle failure
Botulinum toxin
Coelenterate venom (*Physalia, Chironex fleckeri*)
Elapid venom (e.g., coral snake)
Ibuprofen (high doses, especially in children)
Mojave rattlesnake (*Crotalus scutulatus scutulatus*)
Neuromuscular blocking agents (e.g., succinylcholine, nondepolarizing drugs)
Nicotine (late)
Organophosphates/carbamates
Phenylbutazone
Poison hemlock (conine)
Strychnine
Tetrodotoxin (toxin found in puffer fish, blue-ringed octopus)

Pulse Oximetry

Maintenance of adequate oxygenation is fundamental to the management of poisoned or intoxicated patients.[34, 39]

Pulse oximetry provides a continuous, noninvasive, painless, and relatively fast measure of arterial hemoglobin oxygen saturation (Sao_2).[47] Most pulse oximeters measure only two forms of hemoglobin (oxygenated and reduced) and do not accurately reflect the presence of abnormal forms of hemoglobin such as carboxyhemoglobin, methemoglobin, and sulfhemoglobin.[80] The detection of abnormal forms of hemoglobin requires the use of co-oximetry. Whereas pulse oximeters may record falsely elevated amounts of oxyhemoglobin in patients with abnormal forms of hemoglobin, falsely decreased levels of oxyhemoglobin are reported with agents that decrease the respiratory rate or cause pulmonary edema.

Any condition that reduces the strength of the arterial pulse may interfere with the measurement of the Sao_2. This includes hypotension, hypothermia, vasoconstrictive drugs, or the placement of the oximeter sensor distal to a blood pressure cuff or indwelling arterial line.[47] Patient movement also interferes with the detection of the arterial pulse. This can be a problem with patients who are agitated or who require transport, or with pediatric patients.

FOCUSED PHYSICAL EXAMINATION: NEUROLOGIC MANIFESTATIONS OF TOXINS

Altered Mental Status

Drugs and toxins commonly produce alteration of the mental status. Although agitated delirium and coma may appear to be distinct presentations, they are more often manifestations of a continuum of CNS depression, and many drugs cause both conditions. Sedative-hypnotic agents such as ethanol and barbiturates cause an initial period of disinhibition manifested by excitement and agitation. Higher doses lead to sedation and unresponsiveness. Many patients intoxicated with cocaine present with agitation or delirium that is followed by marked lethargy, known as the "washed-out syndrome."[73] The cyclic antidepressants cause dose-related CNS excitation and depression.

Agitation and Delirium. Anticholinergic agents, cocaine, amphetamines, ethanol, sedative-hypnotic withdrawal, and hypoglycemic agents are among the most common precipitants of agitation and delirium (Table 4–9). Toxic causes of hypoglycemia include ingestion of akee fruit, ethanol, or sulfonylureas or use of insulin. Carbon monoxide, cyanide, and simple asphyxiants cause hypoxia that leads to agitation and delirium. Acute lead intoxication causes encephalopathy that may present as irritability in children.

Sedation and Coma. Sedation and coma in the setting of a toxic exposure are most commonly caused by global depression of the CNS by drugs, hypoglycemia, or hypoxia (Table 4–10). Agents that directly depress the CNS include benzodiazepines, sedative-hypnotics, barbiturates, and alcohols. Agents such as ethanol and salicylates induce hypoglycemia, which may contribute to the direct CNS depressant effects. Other toxic causes of CNS depression include agents associated with cellular asphyxia such as cyanide, hydrogen sulfide, carbon monoxide, and sodium azide; methemoglobinemia; anticholinergics; and acetylcholinesterase inhibitors.

Seizures. Agitation, delirium, or sedation may also result from toxin-induced seizures, resulting in a prolonged postictal state. Some toxins known to cause seizures include camphor,[26] cocaine,[24] cyclic antidepressants,[22] hypoglycemics isoniazid, lead, lidocaine,[21] lithium,[23] penicillin, phenothiazines, salicylates, and theophylline[3] (Table 4–11; see Chapter 18 for a more complete discussion). Seizures are the major toxic effect of the potent cicutoxin found in water hemlock (*Cicuta* spp). Overdoses of anticonvulsants such as carbamazepine are often associated with seizures.[77] Seizures caused by theophylline or isoniazid can be very difficult to control.

Laboratory Evaluation. Serum chemistry determination, computed tomography of the head (head CT), and lumbar puncture may be required to exclude metabolic, infectious, or structural etiologies of altered mental status in a poisoned patient. A positive drug screen should not be interpreted as proving causality for a patient's altered mental status. A positive drug screen only confirms exposure to a particular drug during a recent period.

TABLE 4–9 • **Mechanisms and Common Examples of Drug- and Toxin-Induced Agitation and Delirium**

Direct central nervous system stimulation
Amphetamines
Anticholinergics
Arsenic
Carbamazepine
Disulfiram reaction
Ethanol, sedative-hypnotic, barbiturate withdrawal
Lead
Lithium
Meperidine (normeperidine)
Methylphenidate
Monoamine oxidase inhibitors
Neuroleptic malignant syndrome
Nicotine
Nonsteroidal anti-inflammatory drugs (phenylbutazone, diclofenac, fenoprofen)
Organochlorines
Phenothiazines
Propoxyphene (norpropoxyphene)
Salicylates
Serotonin syndrome
Thallium
Theophylline
Hypoglycemic agents
Akee fruit
Insulin
Sulfonylureas
Antidysrhythmic agents
Lidocaine
Hypoxia-producing agents
Carbon monoxide
Cyanide
Simple asphyxiant hydrocarbons
Hallucinogens
Ibotenic acid, muscimol-containing mushrooms
Khat, methcathinone
Lysergic acid diethylamide (LSD)
Other psychoactive agents
Envenomations
Black widow spiders
Pit vipers
Scorpions
Other
Mefloquine
Quinine (cinchonism)

TABLE 4–10 • **Mechanisms and Common Examples of Drug- and Toxin-Induced Sedation and Coma**

Hypoxia
Carbon monoxide
Cyanide
Hydrogen sulfide
Methemoglobin-producing drugs and toxins
Oxidants
Simple asphyxiants (methane, ethane, butane, propane)
Acetylcholinesterase inhibitors
Organophosphates
Central nervous system depression
Alcohols
Anticholinergics
Anticonvulsants (carbamazepine, phenytoin, valproic acid, ethosuximide)
Bromides
Clonidine, guanfacine, imidazolines
Cyclic antidepressants
Lithium
Magnesium

Differential Diagnosis. Many patients are brought to the emergency department with altered mental status. Although a past history of drug overdose, alcohol abuse, or psychiatric problems may tempt the physician to attribute the altered mental status to a drug or toxin, other important causes of altered mental status or seizures need to be considered. Differentiating delirium caused by a drug or toxin from other organic etiologies such as encephalitis, head trauma, hypoglycemia, or hypoxemia is critical in order to expeditiously treat the underlying condition. Although some acute psychiatric disorders that present with altered thought and behavior may at times be confused with a drug-precipitated delirium, patients presenting with an altered mental status due to a psychiatric etiology tend to maintain a clear sensorium, are able to attend, and do not have the waxing and waning agitation commonly associated with organic disturbances.

A patient whose mental status is altered by drugs or toxins may also have associated traumatic injuries, including diffuse axonal injury, cerebral contusion, or space-occupying lesions such as subdural or epidural hematomas. Physicians should have a high index of suspicion for underlying closed head injuries in patients with altered mental status.[64]

Pupils

Pupillary size may be particularly helpful in the evaluation of a toxic patient. Normal pupil size ranges between 2.5 and 5.5 mm in diameter and varies with age.[5] Miosis is defined as a pupillary diameter of 2.5 mm or less. Mydriasis is defined as a pupillary diameter of 6 mm or greater. Actual pupil size results from a balance between sympathetic and parasympathetic innervation. Sympathetic stimulation of α_1 receptors causes the radial muscle of the iris to dilate. Blockade of these receptors causes pupillary constriction. Cholinergic stimulation of the iris sphincter muscle via the third cranial nerve also causes pupillary constriction and miosis. Anticholinergic blockade causes mydriasis.

Miosis. Parasympathetic stimulation of the iris constricts the pupils. Extremely constricted or "pinpoint" pupils are associated with opioid effects. Other causes of miosis include central α_2 agonists (clonidine, guanfacine, guanabenz, imidazolines), phenothiazines, organophosphates, carbamates, physostigmine, phencyclidine, and some sedative-hypnotics. Miosis also occurs with topical ophthalmologic miotics such as pilocarpine. Central pontine lesions secondary to trauma, tumor, or vascular insult also cause miosis.

Mydriasis. Mydriasis is a less specific physical finding than miosis. Sympathomimetics, anticholinergics, antihistamines, and hypoxia cause the pupils to dilate. Amphetamines, cocaine, LSD, and withdrawal from sedative-hypnotics and opioids can cause mydriasis due to sympathetic stimulation of pupillary dilator muscles. The topical application of sympathomimetics such as phenylephrine (Neo-Synephrine) to the eye also causes mydriasis. Antihistamines and anticholinergics block iris sphincter muscle contraction.

TABLE 4–11 • **Mechanisms and Common Examples of Drug- and Toxin-Induced Seizures**

Central nervous system—various mechanisms
Amphetamines
Anticholinergics
Baclofen
Camphor
Carbamazepine
Chloroquine
Clonidine, other central α_2 agonists
Cocaine
Cyclic antidepressants
Ethanol, sedative-hypnotic, barbiturate withdrawal
Insulin
Isoniazid
Lead
Lidocaine
Lindane
Lithium
Meperidine (normeperidine)
Monoamine oxidase inhibitors
Organochlorines
Penicillin
Phencyclidine
Phenothiazines
Phenylbutazone (especially in children)
Propoxyphene (norpropoxyphene)
Propranolol
Quinine (cinchonism)
Quinolones (enoxacin, norfloxacin, ofloxacin)
Strychnine
Sulfonylureas
Theophylline
Water hemlock (cicutoxin)
Hypoglycemia
Akee fruit
Ethanol
Insulin
Salicylates
Sulfonylureas
Cerebral edema
Arsenic
Ethylene glycol
Lead
Methanol
Salicylates
Other
Cisplatin
Pyrimidine analogs (cytarabine, fluorouracil)
Vinblastine (intrathecal)

Unilateral mydriasis has been reported in association with scopolamine patches placed behind the ear.[68] This blockade of parasympathetic tone causes nonreactive, fixed, dilated pupils, which may be differentiated from the reactive, dilated pupils associated with sympathomimetic toxicity. This difference, however, is not consistent.

Certain opioids and sedative-hypnotics such as meperidine and glutethimide can also cause mydriasis. Botulinum toxin can cause delayed mydriasis. Methanol and quinine cause mydriasis due to the blindness and loss of pupillary light reflex that result from their toxic effects.

A useful test to distinguish mydriasis induced by a topical mydriatic agent such as scopolamine from that due to a third nerve palsy involves the administration of pilocarpine eye drops (0.5 or 1 per cent). Topical pilocarpine eye drops will not constrict a pupil blocked by a mydriatic agent but will constrict a pupil dilated secondary to injury to the third cranial nerve.[44] At times, the distinction between drug-induced mydriasis and anoxic brain injury may be difficult.

Nystagmus. Nystagmus is commonly associated with exposure to anticonvulsants (especially carbamazepine and phenytoin), lithium,[15, 16] ethanol, barbiturates, and sedative-hypnotics. MAOIs and isoniazid may also cause nystagmus. Phencyclidine characteristically causes both rotatory and vertical nystagmus.[79]

Retinal Manifestations of Poisoning. Methanol causes retinal hyperemia. Arteriolization of retinal veins has been reported with cyanide poisoning.[40] Papilledema can occur with methanol, quinine, and vitamin A toxicity and other drug causes of pseudotumor cerebri. Emboli can be seen in the fundi of intravenous drug abusers. Carbon monoxide[53] and methaqualone can cause retinal hemorrhages. Retinal hemorrhages should always suggest the possibility of physical abuse in infants and children. They are also associated with hypertensive encephalopathy, subarachnoid hemorrhage, and endocarditis.

Movement Disorders. Movement disorders associated with decreased movement are classified as akinesias; those associated with increased movement are classified as dyskinesias. The most common akinesia associated with drugs or toxins is parkinsonism. Dyskinesias include tremors, chorea, dystonia, tardive dyskinesia, myoclonus, and asterixis.

Toxin-induced parkinsonism manifests as resting tremor and extrapyramidal rigidity and can be seen following poisoning with carbon disulfide, carbon monoxide, cyanide, manganese, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). It is also a common adverse effect of the therapeutic use of neuroleptic drugs.

Tremors that increase with movement are called postural tremors. Causes of postural tremors include amiodarone, amphetamines, caffeine, cocaine, cyclic antidepressants, ergotamine, lithium, mercury, phenytoin, theophylline, valproic acid, and withdrawal from ethanol and sedative-hypnotics.

Chorea is characterized by rapid, jerky, involuntary movements of the major joints, trunk, and face. Dystonic reactions are involuntary, slow, twisting spasms typically involving proximal muscles of the extremities, trunk, and neck. Neuroleptic drugs, antimalarials, cyclic antidepressants, phenytoin, strychnine, lithium, cocaine, and phencyclidine cause dystonic reactions. Tardive dyskinesia is characterized by choreoathetoid movements of the trunk, limbs, and face that occur after prolonged use of neuroleptic drugs.

Myoclonus is a series of forced, alternating contractions and partial relaxations of the same muscle. Toxic causes of myoclonus include lithium and anticholinergic drugs. Myoclonus may occur secondary to fatigue. It is also seen with disorders associated with hyperactive reflexes such as upper motor neuron disease, hyperthyroidism, hypocalcemia, and brain stem tumors.

Asterixis is an abnormal flapping tremor characterized by involuntary transient relaxation of muscles that causes a brief loss of posture. Asterixis was originally described in patients with hepatic failure but is also associated with many drug-induced encephalopathies, including anticonvulsants, benzodiazepines, bismuth, cyclic antidepressants, DDT, ethanol, lead, levodopa, mercury, methylbromide, and sedative-hypnotics.

FOCUSED PHYSICAL EXAMINATION: DERMATOLOGIC MANIFESTATIONS OF TOXINS

Cyanosis

Cyanosis is a dark blue or purple discoloration of the skin and mucous membranes. When cyanosis cannot be explained by cardiac or pulmonary disease, the diagnosis of methemoglobinemia should be considered. Methemoglobin is an abnormal hemoglobin in which the iron molecule is in the oxidized ferric (Fe^{3+}) state rather than the normal ferrous (Fe^{2+}) state. Methemoglobin is darker than unoxygenated hemoglobin and may cause a marked cyanosis even without other symptoms. Oxygen saturation measured by the bedside pulse oximeter can be falsely estimated in patients with methemoglobinemia. Methemoglobinemia follows exposure to an oxidizing drug or chemical, especially organic nitrates, nitrites, benzocaine, dapsone, phenazopyridine (Pyridium), and aniline dyes.[67] Rare causes of hereditary methemoglobinemia may also occur[18] (see Chapter 24 for a complete discussion).

Erythema

Dry, flushed skin is a hallmark of anticholinergic poisoning. Erythema or flushing is also associated with ethanol, very high levels of carbon monoxide, and nitrites. Niacin ingestion causes sudden marked flushing. Chronic boric acid poisoning is associated with intense erythema and desquamation, resulting in a "boiled lobster appearance."[70] Rapid intravenous infusion of vancomycin may cause extreme flushing that is sometimes referred to as the "red man syndrome." Scombroid fish poisoning is associated with intense erythema of the upper torso and face due to a release of histamine. Disulfiram-ethanol interaction and disulfiram-like interactions between ethanol and other agents such as metronidazole, sulfonylureas, cephalosporins, chloral hydrate, griseofulvin, carbon disulfide, trichloroethylene, and *Coprinus* mushrooms may also manifest by erythematous flushing. Ingestion of monosodium glutamate (MSG) causes the flushing associated with Chinese restaurant syndrome.

Examples of medications that induce photosensitivity reactions include tetracyclines, captopril, cyclic antidepressants, furosemide, nonsteroidal anti-inflammatory drugs (NSAIDs; especially piroxicam), phenothiazines, warfarin, antihistamines, griseofulvin, and sulfonamides. Flushing, headache, and hypertension are hallmarks of the tyramine reaction seen in patients on MAOIs who ingest foods that contain tyramine.

Ecchymosis

Anticoagulant toxicity may inhibit clotting and present with ecchymosis.

Icterus

Exposure to naphthalene mothballs or arsine gas can cause hemolysis that results in jaundice. Various forms of toxin-induced liver injury result in jaundice, including exposure to acetaminophen, carbon tetrachloride, chloroform, cyclopeptide- and monomethylhydrazine-containing mushrooms, copper, phosphorus, and iron.

Bullous Lesions

Barbiturate poisoning is associated with bullous skin lesions. The mechanism of barbiturate-induced skin lesions is controversial. Some authors propose a direct toxic effect that results in sweat gland necrosis[37]; others argue that the lesions are simply due to prolonged recumbency.[1, 4, 7, 20, 63] Methadone, meprobamate, carbon monoxide,[53] and glutethimide have also been associated with bullous skin lesions.

Track Marks

Intravenous drug use results in scarring along veins, or "track marks."

Skin Necrosis

The extravasation of certain intravenous medications may result in skin necrosis. These agents include potassium salts, calcium salts, phenytoin, norepinephrine, and chemotherapeutic agents.

Diaphoresis

Diaphoresis can occur with sympathomimetic agents such as cocaine or amphetamines, as well as with organophosphates, salicylates, and withdrawal from ethanol, sedative-hypnotics, and barbiturates. Hypoglycemia, thyroid storm, and shock can also result in diaphoresis.

Alopecia

Alopecia (hair loss) can occur as a result of illness, hormonal disturbances, and numerous drugs. Arrested hair growth and hair loss are commonly associated with the use of agents that interfere with rapidly dividing cells, such as chemotherapeutic agents and metals. The combination of rapid, diffuse alopecia and gastrointestinal and neurologic abnormalities is pathognomonic for thallium toxicity.[25] Lithium and valproate have been reported to cause diffuse but rarely total hair loss.[74] Total hair loss has been associated with selenium.[71] Alopecia areata (patchy alopecia) has been described with fluconazole[62] and amiodarone.[2] Delayed alopecia occurs after exposure to arsenic and colchicine. Localized alopecia can occur late after carbon monoxide poisoning.[53] Scarring and nonscarring alopecia has been reported with gold therapy.[13] Fortunately, drug-induced alopecia usually reverses after the drug is withdrawn.

Hair Color

Copper workers have been reported to have green hair as a result of exogenous deposition of copper.[30, 49]

Nails

Several weeks after poisoning with arsenic and thallium, patients develop horizontal white lines on the finger- and toenails known as Mees lines. Cancer chemotherapeutic agents have been associated with the development of horizontal notches in the nail plate known as Beau lines. Nail staining has been associated with direct exposure to iodine (brown), nicotine (yellow-brown), cupric sulfate (blue), mercury (red), and formaldehyde (gray).

FOCUSED PHYSICAL EXAMINATION: GASTROINTESTINAL MANIFESTATIONS OF TOXINS

Oral Cavity

Salivation or the lack of salivation may be a helpful physical finding. Hypersalivation (sialorrhea) has been associated with cholinesterase inhibitors (organophosphates, carbamates, physostigmine), clozapine, caustic agents, and iodides. Foaming of the mouth may also be a manifestation of drug- or toxin-induced pulmonary edema. Dry mouth (xerostomia) may be caused by anticholinergics and opioids. Angioedema of the lips, mouth, and oropharynx occurs with allergic reactions and may occur secondary to burns from strong acids or alkalis. Captopril and other angiotensin-converting enzyme (ACE) inhibitors may cause significant tongue swelling that can compromise the airway. Ulcerative burns to the lips, mouth, and oropharynx occur after exposure to strong acids and alkalis and other caustic or corrosive agents.

Breath Odors

The odor of mothballs suggests ingestion of naphthalene or paradichlorobenzene. Acetone smells fruity. Arsine gas,

thallium, and organophosphates cause a garlic-like odor. The scent of wintergreen suggests methyl salicylate exposure. Cyanide has a bitter almond odor detectable by 60 to 80 per cent of the population.

Vomiting/Hematemesis

Causes of vomiting in poisoned patients include direct irritation of the gastric mucosa (alkalis, acids, salicylates, colchicine, mushrooms, fluoride, thallium, iron, mercury, and arsenic) or stimulation of the chemoreceptor trigger zone in the fourth ventricle by substances in the blood or cerebrospinal fluid (opioids, nicotine, cardiac glycosides, theophylline, and carbon monoxide).[53] Vomiting also occurs with excessive acetylcholine activity due to poisoning with acetylcholinesterase inhibitors such as organophosphates. Cocaine, amphetamines, and phenylpropanolamine can cause intracranial hemorrhage that presents with vomiting. Severe lead poisoning can also cause elevated intracranial pressure and vomiting. Increased intracranial pressure due to anoxic brain injury, traumatic hematomas, and other mass lesions must also be considered.

Hematemesis results from direct toxic injury to the intestinal mucosa, toxin-induced coagulopathy, or a Mallory-Weiss tear associated with persistent vomiting.

Altered Intestinal Activity

Diarrhea. Causes of diarrhea include intestinal irritation and increased autonomic activity of the bowel. Direct irritation or injury to the bowel mucosa results from chemical burns, mushrooms, solanine-containing plants, cathartics, heavy metals, and colchicine. Cholinesterase inhibitors, nicotine, and opioid withdrawal can cause diarrhea by increasing autonomic activity. Diarrhea also occurs with ingestion of magnesium-containing compounds and sorbitol and in a variety of marine ingestions (see Chapter 121).

Constipation. Anticholinergic agents, calcium channel antagonists, opioids, and sedative-hypnotics decrease bowel activity, leading to constipation. Bowel sounds may be absent or diminished after exposure to anticholinergic agents.

Abdominal Pain

Black widow spider envenomation is characterized by spasms of large muscle groups that may present as a rigid abdomen.

Urinary Bladder

Palpation of the lower abdomen should include assessment of bladder size. Urinary retention occurs with overdose of anticholinergic agents.

TOXIDROMES

Anticholinergic, sympathomimetic, opioid, anticholinesterase, and sedative-hypnotic or barbiturate poisonings may be recognized by their characteristic toxidromes. In the clinical setting when the patient's history is limited or nonexistent, characteristic physical findings suggesting a specific drug class may be critical in refining the diagnosis, focusing the management, and directing the antidotal intervention, such as naloxone for opioids or physostigmine for anticholinergic overdoses. Limitations of this approach include the not infrequent occurrence of mixed intoxications and presentations that manifest only a few of the "textbook" signs and symptoms. Failure of the physical findings to be readily categorized as a toxidrome certainly does not exclude a toxic etiology.

Anticholinergic Syndrome

Drugs and toxins that block acetylcholine at muscarinic receptors cause the anticholinergic toxidrome. Physical findings include elevated temperature; delirium; mumbling speech; tachycardia; dry, flushed skin; dry mucous membranes; urinary retention; decreased to absent bowel sounds; mydriasis; and blurred vision. Seizures and coma may also occur. A simple mnemonic, "hot as a hare, blind as a bat, dry as a bone, red as a beet, mad as a hatter, bloated as a bladder," describes many of the features of the anticholinergic toxidrome.

Atropine and atropine-like agents cause this syndrome. Atropine-like agents include a number of commonly used over-the-counter cold medications containing antihistamines, antiparkinson medications such as benztropine and trihexyphenidyl, topical mydriatics, antispasmodics such as Donnatal and dicyclomine, muscle relaxants such as cyclobenzaprine and orphenadrine, and belladonna alkaloids such as scopolamine and hyoscyamine. Cyclic antidepressants also cause anticholinergic symptoms. Plants that contain belladonna alkaloids include jimson weed *(Datura stramonium)*, deadly nightshade *(Atropa belladonna)*, and henbane *(Hyoscyamus niger)*.

Sympathomimetic Syndrome

Sympathetic agonists such as cocaine and amphetamine produce hypertension, diaphoresis, tachycardia, tachypnea, hyperthermia, and mydriasis. Restlessness, agitation, excessive speech, tremors, and insomnia also occur. Severe cases are associated with dysrhythmias and seizures. Other agents that may cause sympathomimetic effects include over-the-counter decongestants such as phenylpropanolamine, ephedrine, and pseudoephedrine. Theophylline and caffeine may cause many of these findings by enhancing catecholamine release. Overdoses with β_2-adrenergic receptor agonists, methylphenidate, and *Ephedra* species such as ma huang cause sympathomimetic symptoms.

This symptom complex may be difficult to distinguish from the anticholinergic syndrome. Whereas sweating and normal to hyperactive bowel sounds are associated with sympathomimetic overdose, the anticholinergic toxidrome is manifested by dry skin and diminished bowel sounds.

Opioid Syndrome

The classic triad of opioid intoxication is mental status depression, respiratory depression, and pinpoint pupils.

Bradycardia, hypotension (rare), hypothermia, hyporeflexia, and needle marks may be present. Opioids commonly associated with this toxidrome include morphine, heroin, designer fentanyls, oxycodone, hydromorphone, and propoxyphene. Meperidine, pentazocine, and dextromethorphan may cause CNS and respiratory depression but are often associated with dilated pupils. Central α_2-receptor agonists such as clonidine, guanabenz, guanfacine, and imidazoline derivatives that act on the locus ceruleus of the CNS cause many of these same symptoms in the overdose setting.

Anticholinesterase Syndrome

Organophosphates are commonly available as insecticides. They are readily absorbed through the skin, mucous membranes, and respiratory and gastrointestinal tracts. Organophosphates inactivate cholinesterase enzymes, resulting in accumulation of acetylcholine at receptor sites and overstimulation of muscarinic, nicotinic, and central acetylcholine receptors. Other causes of cholinesterase inhibition include carbamates and therapeutic cholinesterase inhibitors such as physostigmine, pyridostigmine, neostigmine, and edrophonium.

Clinical findings suggestive of acute anticholinesterase intoxication include muscarinic effects as well as muscle weakness, fasciculations, altered mental status, seizures, and coma. DUMBELS is a mnemonic used to recall many of the muscarinic effects: defecation, urination, miosis, bronchorrhea, bronchospasm, bradycardia, emesis, lacrimation, and salivation.

Sedative-Hypnotic Syndrome

Sedative-hypnotic overdoses are associated with hypotension, bradypnea, hypothermia, mental status depression, slurred speech, ataxia, and hyporeflexia. The sedative-hypnotic group includes barbiturates, benzodiazepines, buspirone, paraldehyde, chloral hydrate, meprobamate, methaqualone, ethchlorvynol, glutethimide, and zolpidem. Of course, ethanol intoxication may also present with many of these symptoms. Ingestion of neuroleptics, cyclic antidepressants, and skeletal muscle relaxants may also cause significant sedation. Bullous lesions have been reported in some patients with sedative-hypnotic overdoses. Paradoxical excitement is seen with some of the sedative-hypnotics, especially in very young and elderly patients.

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