A sympathomimetic agent is defined as any agent that may emulate the clinical effects of the endogenous sympathetic catecholamines epinephrine and norepinephrine. An exhaustive list of drugs falls into the class of sympathomimetics, ranging from over-the-counter and prescription agents to drugs of misuse and abuse (Box 149.1).

Clinically, sympathomimetics have been used as arousal agents in patients with barbiturate overdose, as weight loss preparations, and in the treatment of depression. Over-the-counter products are predominantly available as decongestants, and they also include weight loss and energy products. The U.S. Food and Drug Administration banned ephedrine and sibutramine, once popular dietary supplements for weight loss and arousal, but they can still be obtained illicitly.

Prescription and parenteral sympathomimetic agents are available for myriad medical illnesses, including hypersensitivity reactions, reactive airway disease, attention-deficit hyperactivity disorder, and cardiovascular compromise. Misused and abused licit and illicit agents comprise the remainder of sympathomimetics: cocaine, amphetamine derivatives (i.e., 3,4-methylenedioxymethamphetamine), and clenbuterol.

In 2010, data released by the University of Michigan in their Monitoring the Future Survey demonstrated that cocaine use among high school students had declined since 2007. However, the year 2010 also saw a dramatic increase in the use of ecstasy, or 3,4-methylenedioxymethamphetamine (MDMA). Researchers believe that this shift may be the result of the adolescent population’s perception of a lower risk associated with MDMA.

Prescription agents continue to be a source of misuse. The rate of misuse of combination sympathomimetic products rose from 2009 to 2010. Overall, sympathomimetics remain a public health concern. According to the Drug Abuse Warning Network, these drugs accounted for almost 30% of all emergency department (ED) substance-related visits in 2009.
relative effect on the two distinct adrenergic receptors, $\alpha$ and $\beta$, can be used to predict the clinical response. Generally, $\alpha$-adrenergic receptor agonism results in vasoconstriction, whereas the inverse effect is appreciated with $\beta$-adrenergic receptor stimulation. The resultant vasodilatation produces hypotension and tachycardia. $\beta$-Adrenergic agonism can also lead to hypokalemia, hyperglycemia, tremor, and acidemia.

Sympathomimetics may act directly, indirectly, or in combination to produce sympathomimesis. Direct-acting sympathomimetics are the catecholamines epinephrine and norepinephrine, directly administered to the patient. Indirect-acting sympathomimetics are agents that either increase the release of endogenous catecholamines or impair their reuptake. In addition, indirect-acting sympathomimetics can trigger the release of other biogenic amines such as serotonin and dopamine. Finally, mixed-acting sympathomimetics can exert their effect through direct and indirect-acting properties. Despite these underlying differences, the clinical presentation can be virtually indistinguishable. Clinical manifestations may also vary according to the location where the neurotransmitter predominance occurs.

**PRESENTING SIGNS AND SYMPTOMS**

Tachycardia, hypertension, diaphoresis, mydriasis, hyperthermia, and psychomotor agitation characterize the sympathetic toxidrome, which can be further divided according to $\alpha$- and $\beta$-adrenergic receptor effects. $\alpha$-Adrenergic subtype 1, or $\alpha_1$, receptor agonism results in vasoconstriction, whereas postsynaptic $\alpha_2$ agonism results in hypotension and sedation. These effects are classically observed in the therapeutic use of clonidine. Like $\alpha$ receptors, $\beta$-adrenergic receptors have clinically distinct subtypes, 1 and 2. $\beta_1$ agonism increases cardiac output by improving chronotropy. $\beta_2$ agonism is specifically responsible for vasodilation, as well as secondary effects such as hypokalemia, hyperglycemia, acidemia, and tremor.

Methylxanthine exposure is virtually indistinguishable from $\beta$ stimulation because of a shared final pathway, which increases intracellular cyclic adenosine monophosphate. Methylxanthines also result in increased circulating catecholamines and inhibit adenosine receptors. Potential clinical effects associated with sympathomimetics are listed in Box 149.2.

As a result of hypertension and tachycardia, vascular events can occur during exposure to a sympathomimetic. Cocaine use is associated with myocardial infarction, coronary artery dissection, aortic dissection, cardiomyopathy, splanchnic infarction, cerebrovascular accidents, and cerebrovascular hemorrhage. The vasoconstriction and resultant hypertension make $\beta$-adrenergic blockade a precarious pharmacologic intervention.

Similar to the cardiovascular effects, some of the CNS effects are secondary to hypertension and vasoconstriction, leading to CNS ischemia and hemorrhage. Animal studies suggested an association between extreme CNS stimulation and the development of seizures, hyperthermia, and increased mortality. Aggressive therapy should focus on inhibiting CNS hyperactivity, thus reducing morbidity and mortality. Other CNS effects associated with the cessation of amphetamines and cocaine use are termed withdrawal or “washout.” The

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**BOX 149.1 Common Sympathomimetic Agents**

- **Over-the-Counter Agent or Dietary Supplement**
  - **Arousal Agents**
    - Caffeine
  - **Weight Loss Products**
    - Ephedrine
    - Synephrine
    - Caffeine
  - **Nasal Decongestants**
    - Pseudoephedrine
    - Phenylpropanolamine (PPA)*
    - Phenylephrine
  - **Prescription or Parenteral**
    - For Hypersensitivity
      - Epinephrine (autoinjector)
    - For Reactive Airway Disease
      - Albuterol
      - Pirbuterol
      - Salmeterol
      - Levalbuterol
      - Theophylline
      - Epinephrine
      - Epinephrine
    - **Vaspressors**
      - Phenylephrine
      - Epinephrine
      - Norepinephrine
      - Dopamine
    - **For Weight Loss**
      - Dextroamphetamine
      - Phentermine
      - Sibutramine*
    - **For Attention-Deficit Hyperactivity Disorder**
      - Methylphenidate
      - Dextroamphetamine
    - **Inotropes**
      - Dobutamine
      - Isoproterenol
      - Milrinone
    - **Illicit Misuse**
      - Cocaine
    - **Amphetamine Derivatives**
      - Methamphetamine
      - 3,4-Methylenedioxyamphetamine (MDMA)
      - 3,4-Methylenedioxyethamphetamine (MDEA)
      - Para-methoxymethamphetamine (PMA)
      - Methcathinone
    - **For Sports Performance Enhancement**
      - Clenbuterol
      - Caffeine
      - Ephedrine

*No longer available.
resultant lethargy and depressed mood are secondary to catecholamine depletion.

Metabolic derangements during sympathomimetic exposure resemble the fight-or-flight response. The most common metabolic changes, hyperglycemia and hypokalemia, result from a surge in epinephrine. When the metabolic demands outstrip the supply of energy substrates, metabolic acidosis can develop. Because of the body’s ability to achieve homeostasis, however, these metabolic effects usually do not require intervention.

Similarly, in combination with psychomotor agitation, this increased demand and activity can result in tremor, muscle rigidity, and rhabdomyolysis. Additionally, the syndrome of inappropriate antidiuretic hormone (SIADH) has been observed in association with MDMA use, as reflected by hyponatremia and inappropriately concentrated urine in the setting of euvolemia. Patients stereotypically develop symptoms the day after exposure, and they present with either altered mental status or seizures.

**DIFFERENTIAL DIAGNOSIS AND MEDICAL DECISION MAKING**

The differential diagnosis of the patient with a sympathomimetic toxidrome is extensive (Box 149.3). It includes a spectrum of disease ranging from febrile illness to delirium.

Most individuals who misuse or abuse sympathomimetics do not present to the ED; those who do are usually symptomatic. While the physician is considering the extensive differential diagnosis and clinical effects, aggressive measures should be taken to evaluate and stabilize these individuals (Fig. 149.1). Urine screening for sympathomimetics, with the exception of cocaine, is fraught with error and misinterpretation. A negative result does not exclude an exposure, whereas a positive result does not confirm causation of the patient’s clinical presentation. Therefore, this test is not recommended in the evaluation of a potentially poisoned adult patient.

If the patient is too agitated to allow a thorough evaluation, a bedside glucose measurement should be performed to exclude hypoglycemia. An intravenous line should be placed and secured, to allow parenteral administration of benzodiazepines to control the patient’s behavior and thereby prevent further morbidity to the patient and hospital staff.

If the patient is well controlled or does not require sedation, a complete history and physical examination should be obtained while the physician pays close attention to the presence of a sympathomimetic toxidrome. The presence of this toxidrome supports the diagnosis of exposure but does not exclude other possibilities.

All patients with a potential exposure should have a 12-lead electrocardiogram (ECG) performed. Signs of ischemia, infarction, or electrolyte disturbance may be present despite the lack of patient endorsement. In the case of a suspected sympathomimetic toxidrome, patients should be resuscitated with isotonic fluid. Most of these individuals are volume depleted from agitation, diaphoresis, and increased metabolic demand. The only situation in which fluid resuscitation should not be initiated before laboratory evaluation is in the individual suspected of having SIADH from MDMA use.


**Fig. 149.1** Treatment algorithm for sympathomimetic toxidrome. CK, Creatine kinase; ECG, electrocardiogram; GI, gastrointestinal.

All patients should also undergo a chemistry panel to evaluate for the presence of metabolic acidosis, hypokalemia, rhabdomyolysis, renal insufficiency, glucose derangement, and hyponatremia. Individuals with suspected rhabdomyolysis should have serum myoglobin markers evaluated, as well as a urinalysis to check for myoglobinuria. Patients with symptoms of chest pain, an anginal equivalent, or an abnormal ECG should receive serial cardiac marker measurements and, in the appropriate setting, should undergo emergency cardiac catheterization. Individuals with headache, neurologic abnormalities, or persistent alteration in sensorium or cognition should have an emergency computed tomography (CT) scan of the brain to evaluate for injury, infarction, edema, or bleeding. If suspicion of a subarachnoid hemorrhage or an infectious origin persists, a subsequent lumbar puncture should be obtained in the setting of a normal-appearing CT scan of the brain.

**EVALUATION (SPECIAL CONSIDERATIONS)**

**Body Packers**

The concealment of illicit substances within the gastrointestinal tract in large quantities requires close and careful evaluation. Individuals who take part in this trafficking, also known as body packers or “mules,” may be symptomatic or asymptomatic when they present to the ED. Those individuals with leaking or ruptured packets containing a sympathomimetic, often cocaine, need to be identified rapidly because they typically harbor enough drug to exceed multiple median lethal doses. Plain radiographs and oral contrast-enhanced CT scans of the abdomen have reasonable sensitivity in detecting packets; however, individuals already demonstrating signs and symptoms should receive an emergency surgical consultation with invasive removal of remaining packets. Body packers, if asymptomatic, require the same consideration, but they may necessitate a prolonged treatment course and monitoring.

**Methylxanthines or Beta-Agonists**

Patients who present with signs and symptoms consistent with methylxanthine or beta-agonist exposure should have their serum theophylline levels tested. At-risk populations include individuals with a history of reactive airway disease and those with tachycardia, hypotension, widened pulse pressure, nausea, vomiting, tremor, hypokalemia, or hyperglycemia. Patients who present with signs and symptoms consistent with sympathomimetics or beta-agonist exposure should have their serum theophylline levels tested. At-risk populations include individuals with a history of reactive airway disease and those with tachycardia, hypotension, widened pulse pressure, nausea, vomiting, tremor, hypokalemia, or hyperglycemia. Patients who have ingested sympathomimetics should receive activated charcoal if it can be safely administered. Individuals who overdose on theophylline should be considered for aggressive decontamination with multiple-dose activated charcoal because it has been shown to enhance elimination of theophylline from gastrointestinal circulation. Because of the large drug burden and the risk of packet leakage or rupture in body packers or “mules,” whole-bowel irrigation (WBI) can be used as first-line treatment in the asymptomatic patient. WBI can hasten the passage of packets through the gastrointestinal tract. This decontamination modality requires stringent dosing, averaging 2 L/hour of polyethylene glycol orally for an adult patient, with dose adjustments for the pediatric population. Most patients are unable to maintain this rate voluntarily and therefore require nasogastric tube placement. WBI is not without complications. Thus, consulting a toxicologist to discuss treatment is beneficial.

The focus of therapy should be reducing morbidity and mortality by controlling psychomotor agitation or seizures and correcting hyperthermia. Animal studies showed benzodiazepines to be the most effective treatment. The psychomotor agitation and seizures can result in severe rhabdomyolysis, which, if unrecognized, may result in renal insufficiency or failure. A combination of hyperthermia,
metabolic acidosis, and rhabdomyolysis can produce a vicious cycle, which should be recognized and treated immediately.

Mortality related to cocaine use has been associated with an elevation in core and ambient temperature. An ice bath that covers the largest surface area can quickly and effectively reduce core temperature. Other common modalities employed include mist and fan, as well as strategic anatomic application of ice packs (i.e., axilla and groin).

Most patients present with hypovolemia secondary to increased metabolic demand, diaphoresis, and psychomotor agitation. Fluid resuscitation to the point of euvoeemia is recommended.

**SPECIAL CONSIDERATIONS**

**Beta-Agonists**

For known beta-agonist exposures, it would seem logical to administer a β-adrenergic receptor antagonist. However, patients usually overdose on their own medications. In asthmatic patients, administration of a β-receptor antagonist is contraindicated and potentially dangerous. However, if no contraindication to beta-blocker use exists, careful administration and titration of an agent, such as esmolol and metoprolol, can be performed.

**Methylxanthines**

Although they are not as common as in the past, theophylline overdoses can be treated aggressively with multiple-dose activated charcoal to enhance elimination, as well as hemoperfusion or hemodialysis. Tachydysrhythmias associated with theophylline overdose can be suppressed with β₁-selective antagonists. As mentioned previously, however, these patients usually overdose on their own medications, thus making the use of β-receptor antagonists precarious.

**Cocaine**

Multiple agents are available to treat cocaine’s unique properties of vasoconstriction and sodium channel blockade. The first-line agent for treatment of cocaine toxicity is a benzodi-azepine; however, some patients do not respond to this therapy. Ongoing vasoconstriction or vasospasm can be treated with an α-adrenergic receptor antagonist, such as phentolamine. In the setting of cocaine-associated acute coronary syndrome, β-adrenergic blockade is contraindicated despite the mortality benefit observed in patients with acute coronary syndrome unassociated with cocaine. The use of beta-blockers in cocaine toxicity is contraindicated because once the β-adrenergic receptor is blocked, these individuals suffer from unopposed α-adrenergic stimulation, thus worsening their clinical course. Even in the setting of suspected pure β-adrenergic agonist exposure, β-adrenergic blockade is rarely recommended because the underlying substrate usually depends on β₁-receptor agonism (i.e., asthmatic patients who overdose on albuterol).

A unique property of cocaine is its ability to block myocardial sodium channels. This manifests as wide complex tachydysrhythmia resulting from sodium channel blockade. These electrophysiologic effects are indistinguishable from those of other class I antidysrhythmics and require immediate attention and reversal with either sodium bicarbonate or lidocaine.

Symptomatic cocaine body packers require urgent surgical removal of residual packets. In some instances, body packers are not symptomatic, and WBI can be initiated. In the event that packets cause a mechanical obstruction, endoscopic removal is a successful treatment modality.

**3,4-Methylenedioxyethylamphetamine**

MDMA-associated SIADH usually responds to conservative fluid restriction. However, patients with severe CNS manifestations should receive hypertonic saline solution to correct a portion of the metabolic imbalance rapidly.

**Vaspressors**

Epinephrine and norepinephrine can extravasate within tissue compartments during infusion, as well as from unintentional exposures related to autoinjectors. Warm compresses should be placed topically for mild cases, and nitroglycerin paste can be added topically to generate vasodilation. For severe cases, intradermal phentolamine may be introduced within the exposed tissue.

**TIPS AND TRICKS**

- The clinician should avoid neuroleptics (i.e., haloperidol) or antihistamines (i.e., diphenhydramine) to control the psychomotor agitation and psychosis associated with sympathomimetic overdose. Because neuroleptics have anticholinergic properties, decrease seizure thresholds, and increase QT intervals, these agents are a poor choice to achieve sedation. Anticholinergic toxicity is within the diagnostic consideration of the undifferentiated agitated delirium, such that administration of an anticholinergic agent may be additive to potential morbidity. Benzodiazepines are the preferred choice for sedation.

- The only situation in which fluid resuscitation should not be initiated before laboratory evaluation is in the individual suspected to have syndrome of inappropriate antidiuretic hormone from 3,4-methylenedioxyethylamphetamine use.

- Because of persistent tachycardia and extrapolating data from acute coronary syndromes, emergency physicians often feel compelled to rate-control these patients with β-adrenergic receptor antagonists. Potential unopposed α-adrenergic agonism may lead to a hypertensive crisis, and these agents therefore should be avoided in the undifferentiated sympathomimetic toxidrome.

- Amiodarone is listed as a first-line agent in the treatment of wide complex tachycardia. Concern exists about the intrinsic β-adrenergic receptor antagonist properties of amiodarone, for the reasons stated. Amiodarone should not be used in the setting of cocaine toxicity because of this theoretical risk.

**DISPOSITION**

The length of stay and disposition depend on the duration of action of the sympathomimetic, which is highly variable. Recreationally smoked or insufflated cocaine has a short duration of action, usually lasting no more than 4 hours, and patients can normally be discharged from the ED. Side effects such as
rhabdomyolysis, heat stroke, or end-organ injury require ongoing monitoring and treatment. Prolonged effects may be seen in individuals who are body packers and in patients who use long-acting agents such as clenbuterol, a potent β-adrenergic receptor agonist. These individuals require admission and prolonged treatment.

The evaluation and treatment of cocaine-associated chest pain have evolved and have regional variation. A short observation period with serial ECGs and serial cardiac-specific markers performed 6 to 8 hours apart can be used to exclude cocaine-associated myocardial infarction. Despite excluding the diagnosis of myocardial infarction, all patients should have urgent outpatient evaluation for coronary artery disease and drug abuse counseling.

**SUGGESTED READINGs**


**REFERENCES**

*References can be found on Expert Consult @ [www.expertconsult.com](http://www.expertconsult.com).*
REFERENCES