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Among life-threatening neurologic emergencies encountered by the emergency physician, perhaps none are as challenging—from both a differential diagnostic and management perspective—than those presenting with altered mentation and neuromuscular rigidity. In part I of this two-part series, the authors presented a number of life-threatening clinical syndromes characterized by muscle rigidity and severe alteration in consciousness. Expanding on the differential diagnosis of this symptom complex, the current issue discusses in practical, clinical detail a number of other disease states and environmentally induced conditions in which patients present with this symptom complex.

A number of these conditions, including heatstroke, may be associated with or precipitated by consumption of medications that produce anticholinergic effects, especially in the elderly patient. In the case of serotonin syndrome, physician-mediated increases or intensification of therapy with selective serotonin reuptake inhibitors (SSRIs) can produce a clinical picture that is similar to neuromalignant syndrome (NMS) and other drug-related adverse events.

Taking an accurate medication history—in particular, one that documents use of psychotropic agents, selective serotonin reuptake inhibitors, major tranquilizers, or excessive alcohol use—is essential for distinguishing among overlapping syndromes. A precise diagnosis is important so that management of the patient is customized for the underlying problem. For example, the comatose patient with heatstroke caused by environmental stress and anticholinergic drugs needs rapid cooling and vigilant monitoring for cardiac arrhythmias, rhabdomyolysis, and electrolyte abnormalities; the patient with central nervous system (CNS) agitation and muscular rigidity caused by serotonin syndrome requires supportive care; and the individual with dystonia requires parenteral therapy with diphenhydramine.

Finally, because disease states characterized by CNS alterations and muscular manifestations can mimic infectious, structural, and non-drug-related metabolic disorders, a comprehensive evaluation may be mandatory to exclude conditions that require specific treatment.

—The Editor

Life-Threatening Syndromes Presenting with Altered Mentation and Muscular Rigidity

Part II: Heatstroke Syndromes, Serotonin Syndrome, Dystonic Reactions, and Alcohol Withdrawal Syndrome

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Heatstroke

Heatstroke is a life-threatening emergency caused by a failure in the body's thermoregulatory mechanisms. Heat-

stroke may be divided into two subcategories: 1) classical heatstroke and 2) exertional heatstroke. Classical heatstroke generally occurs in elderly patients, with significant comorbidity during periods of extreme ambient heat in summer. In contrast, exertional heatstroke occurs more often in a younger, healthier population without significant medical history after intense physical activity. The classical triad of symptoms includes CNS dysfunction, hyperthermia, and hypohidrosis; as with most "classical" presentations, the clinician may not encounter all three features in an individual patient. Furthermore, it should be stressed that the initial temperature in the emergency department (ED) may not reflect the initial field temperature if cooling measures were initiated in the pre-hospital setting. In addition, many patients will continue to sweat after developing heatstroke. Accordingly, heatstroke should be considered in any patient presenting with altered mental status and a history consistent with either an inability to effectively manage heat or significant heat exposure.

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Clinical Features. Classical heatstroke tends to occur in epidemic fashion, in particular, during periods of higher ambient temperature (i.e., in summer during pronounced heat waves). The victims generally are elderly individuals who live a sedentary lifestyle and do not have adequate cooling systems at home.[1] They may suffer from chronic substance abuse, psychiatric illness, or medical disorder, all of which predispose to development of heat illness. Certain prescription medications may also set the stage for the development of heat illness, including diuretics, neuroleptic medications, antihypertensives, and anticholinergic drugs.

Exertional heatstroke commonly occurs in younger, healthy individuals when endogenous heat production overwhelms compensatory thermoregulatory mechanisms. This homeostatic failure typically occurs when the patient is physically active in a warm, humid setting. Military personnel, athletes, underground miners, industrial workers, and religious pilgrims are common victims.[1,2] Exertional heatstroke sporadically occurs throughout the summer. Predisposing factors for this type of heatstroke can be divided into endogenous and exogenous categories. Endogenous factors include a lack of acclimatization, obesity, advanced age, physical exertion, substance abuse, and dehydration, other factors include electrolyte disorders (e.g., hypokalemia), sunburn, cardiovascular disease, sweat gland dysfunction, history of heatstroke, and medications such as neuroleptics, antidepressant agents, and cardioactive drugs. Exogenous factors include increased humidity, high ambient temperature, and inadequate ventilation (i.e., closed space or no wind).[3]

Researchers conducted a case control study investigating various risk factors for development of heatstroke. The investigators concluded that alcoholism, living on higher floors of a non-air-conditioned, multistory building, and using neuroleptic medication predicted an increased risk of acquiring the disorder. In addition, they reported that several factors that appeared to decrease the possibility of significant heat illness, among them home air conditioning, spending more time in air conditioned places, and living in a home that is well-shaded by shrubs and trees. Regular, vigorous activity and reducing frequency of such activities during high-heat periods are also protective, as is consumption of extra liquids and being able to care for oneself. They found that diabetes, obesity, heart disease, and a previous history of heatstroke conferred no increased risk in their study population.[4]

Clinical Pathophysiology. Heat can be dissipated from the body by convection, radiation, conduction, and/or evaporation. Convection is the transfer of heat to a circulating fluid or gas; radiation is the transfer of heat to a portion of the environment that is not directly in contact with the object. Conduction is direct transfer of heat from the body to another object; evaporation is the transfer of heat by vaporization of liquid. Convection, radiation, and conduction require a thermal gradient between the transferring body and the environment; therefore, as the ambient temperature approaches 99°F, the mechanisms of heat loss become less effective, and evaporation assumes major responsibility for heat loss.[3] Furthermore, as humidity levels approach 90%, evaporation becomes much less effective in dissipating heat.[1]

One of the body's initial responses to heat stress is dilatation of the peripheral vasculature, which increases heat loss from the core to the environment. To avoid functional hypovolemia, vasoconstriction of the renal and splanchnic vasculature occurs.

Table 1. Findings in the Patient with Heatstroke

PRODROMAL SYMPTOMS
Nausea, weakness, dizziness, headache, confusion, disorientation, drowsiness, and irrational behavior
CLASSIC TRIAD
Altered mentation, hyperthermia, and anhidrosis (hot, dry skin)
END-ORGAN DYSFUNCTION
Altered mentation (hyper-irritability to coma)
Seizures
Papilledema
Distributive shock
Right-sided cardiac failure
Electrocardiographic abnormalities
Arrhythmia
Hepatic dysfunction
Acute oliguric renal failure
Rhabdomyolysis

If unchecked, this compensatory vasoconstriction can produce visceral ischemia, which can trigger the nausea, vomiting, and diarrhea that is commonly seen in heatstroke patients. As heat stress continues, renal and splanchnic vasoconstriction ultimately fails. Cutaneous blood flow dramatically decreases, resulting in a failure to perfuse the skin with the heated blood. The core body temperature rapidly rises. Another theory of heatstroke suggests that CNS ischemia contributes to the pathophysiologic cascade. According to this model, hyperthermia, intracranial hypertension, and cerebral ischemia cause heatstroke. Increasing ambient temperature results in a net heat gain to the body. The resulting hyperthermia directly damages cerebral tissue, causing cerebral congestion and edema, which lead to an increase in intracranial pressure. The body responds to heat stress with peripheral vasodilation to increase heat loss to the environment. This vasodilation causes a decrease in mean arterial blood pressure and, when combined with an increased intracranial pressure, results in decreased cerebral perfusion and cerebral ischemia. Cerebral ischemia contributes to additional disruption in blood flow, which is accompanied by impaired autoregulation and CNS edema. Thus, a vicious cycle begins. If this heat cycle is not disrupted, cerebral ischemia leads to neurological damage and the onset of heatstroke.[5,6] Authorities have suggested that other substances may be involved in the body's pathophysiologic response to heat stress. Centrally acting dopamine, serotonin, and various prostaglandins have been implicated in this process.

Presentation: Classical Features. Heatstroke usually presents as an acute illness *(see Table 1)*; approximately 20% of patients, however, may complain of prodromal symptoms, including nausea, weakness, dizziness, headache, confusion, disorientation, drowsiness, or irrational behavior. These symptoms may mimic the heat exhaustion syndrome. If present, this prodromal stage is transient.[2] The classic triad of heatstroke includes altered mentation; extreme elevations in body temperature; and hot, dry skin. CNS dysfunction is a universal finding in heatstroke victims; in fact, the clinical onset of heatstroke is marked by loss or severe alteration of consciousness in the majority of cases.[7] Almost any neurological abnormality may be encountered, although depression of the CNS and extreme hyper-irritability are the most frequent presentations. Seizures are frequent and may be focal or generalized. Care must be taken to avoid precipitating seizures by therapeutic maneuvers. Additionally, seizures may be mimicked by profound muscle rigidity, tonic contractions, coarse tremor, and dystonic movements. Approximately 65% of patients will have constricted pupils, and papilledema is present in cases with significant cerebral edema. Severe cases may be associated with permanent CNS damage. Neuropsychiatric outcomes in patients reflect both the duration of hyperthermia and the time to application of appropriate therapeutic cooling. With appropriate, rapid delivery of resuscitation, cooling measures, and supportive medical care, patients can be expected to have favorable outcomes. One study that followed 21 young subjects who had heatstroke for six months after hospitalization found no long-term psychological or behavioral sequelae.[8] Interestingly, another study reported four patients who left the hospital with "marked intellectual deterioration" from a total of 28 heatstroke cases.[9]

Hyperpyrexia is another component in the "classic" triad of heatstroke, although it is difficult to pinpoint the precise temperature at which heatstroke occurs. Specific patient factors, the effect of various therapeutic interventions, and environmental factors all contribute to the variation encountered in initial ED temperatures in the heatstroke patient. Nevertheless, body temperatures higher than 104°F suggest the diagnosis. Recall, however, that cooling measures may have been initiated in the prehospital setting. Moreover, peripheral determinations of the body temperature may not reflect the core heat content. For these and other reasons, the initial temperature obtained in the ED may not be a true reflection of the patient's body temperature at the onset of the illness. Therefore, it should be emphasized that a lower temperature does not exclude diagnosis of heatstroke in a patient with signs and symptoms that otherwise are suggestive of this illness.[2] In fact, one study of 28 patients found little correlation between initial core temperature and outcome in patients with classical heatstroke, noting that one patient survived despite a core temperature of 116°F.[9] These investigators suggest that mortality in heatstroke is probably inversely related to the ability of the clinician to rapidly and effectively cool the patient, rather than the absolute height of the body temperature elevation.[9] Duration of hyperthermia is another major factor linked to patient outcome in heatstroke; morbidity and mortality markedly increase with prolonged periods of elevated body temperature.[10]

The third "classic" finding in heatstroke is hot, dry skin. However, strict adherence to this criterion will produce missed cases of heatstroke, in as much as dry skin is a late phenomenon in heatstroke. In fact, most patients with heatstroke will present with profuse sweating. As with body temperature elevation, the lack of anhidrosis should not rule out the possibility of heatstroke.

End Organ Complications. Heat stress produces a range of cardiovascular responses. Heart rate increases 10 beats/min/1°C elevation in body temperature in order to maintain cardiac output in the face of decreasing peripheral vascular resistance. Although a reduction in peripheral vascular resistance assists in dissipating heat, this vascular adaptation may persist after cool-

ing measures have brought body temperature to near normal, suggesting that tissue injury in heatstroke may be similar to patterns observed in the post-hemorrhagic or septic shock. Right-sided cardiac failure is manifested by an elevation in central venous pressure and increased chamber size. Causes of right-sided failure are unclear, although myocardial ischemia and increased pulmonary vascular resistance have been suggested. Electrocardiographic abnormalities are common in heatstroke and including sinus tachycardia, prolonged QT interval, conduction defects (including right bundle branch block and intraventricular conduction defects), and ST segment-T wave changes consistent with myocardial ischemia.[11] In one study of 46 religious pilgrims, 20% of patients had ST segment-T wave changes suggestive of myocardial ischemia. Investigators proposed that heatstroke predisposes to myocardial infarction and conduction disturbances as a result of increased oxygen demand precipitated by hyperthermia, tachycardia, increased cardiac output, and hypotension. Echocardiographic abnormalities most often seen in heatstroke patients include pericardial effusion, regional wall abnormalities, and right ventricular dilation.

Hepatic damage, an almost constant feature of heatstroke, is suggested by elevation of the transaminases, SGOT and SGPT. Jaundice may appear 24-72 hours after heatstroke and will gradually recede as the patient improves. Coagulation abnormalities may be present in more severe cases of heatstroke; they are a poor prognostic sign. Acute oliguric renal failure complicates 30% of exertional heatstroke cases, but is less common in the patient with classical heatstroke. The urine may be brown and turbid, resembling "machine oil." Proteinuria is common; granular, hyaline, and cellular casts are seen on microscopic examination. In cases of exertional heatstroke, the urine is maximally concentrated and acidic. Myoglobinuria due to rhabdomyolysis and hypotension may precipitate renal failure.

Management. Heatstroke is a true emergency, inasmuch as irreversible damage may quickly occur if cooling measures are not immediately initiated. As mentioned above, the duration of hyperthermia and the rapidity of cooling are the most important factors in determining a favorable outcome in the heatstroke victim. Cooling is the most important part of therapy for heatstroke and should be started as soon as possible. Cooling the patient takes precedence over any time-consuming search for a cause of the hyperthermia, although this search may proceed while cooling measures are employed. Cooling should be initiated in the prehospital phase by keeping the patient's skin wet and fanning the patient to stimulate evaporative cooling. Upon arrival at the ED, the patient's clothes should be removed and an esophageal, rectal, or vesicular thermometer should be placed in order to determine the core temperature. The temperature should be continuously monitored, with adjustments in resuscitation guided by the patient's response. When body temperature reaches 38.5°C, cooling measures should be modified to avoid hypothermic overshoot.[2] ED personnel should continue careful monitoring of temperature to maintain core body temperature within the 37°C to 38°C range.

The optimal method for cooling hyperthermic patients remains controversial. The most commonly used method, ice water tub immersion, results in rapid reduction of core body temperature. In most cases, the body temperature may be decreased to 39°C in 10-40 minutes. Some authors recommend vigorous skin massage to prevent vasoconstriction of cutaneous vessels, but this has not been proven to be effective. Cold water, as opposed to *ice* water, immersion also may be used and is generally less uncomfortable. The cooling rate of cold water immersion has been reported to be 0.13°C/min.

A second method of heat reduction therapy has been described by Khogali and Weiner.[12] They use a body cooling unit (BCU) in which they suspend a heatstroke patient and spray 15°C water on the naked patient. Air that is heated to 45-48°C is blown over the skin surface at a rate of 30 meter/min. This approach is intended to maintain the skin temperature above 30°C, in an effort to ensure cutaneous vasodilation. This unit was used in 18 heatstroke patients who presented with a mean rectal temperature of 42.3°C; temperature reduction to 38°C was accomplished in the majority of cases within 30-90 minutes.[12] Evaporative cooling methods may be easily employed in the ED using aerosolized tepid tap water and a fan over a disrobed patient; this approach most likely represents the best approach to core temperature reduction in the heatstroke patient. Other methods of cooling have been used, although none has been shown to be clearly superior; they include application of ice packs and cooling blankets, peritoneal dialysis with cold fluids, and cardiopulmonary bypass with a heat exchanger. Since cooling modalities may drastically lower skin temperature, they may induce violent shivering. This shivering may lead to further heat production by the patient and may impede cooling. Chlorpromazine may be useful to reduce shivering in these cases; this drug possesses significant anticholinergic properties and should only be used when the physician believes that heat production during shivering is detrimental to the patient.[2]

During application of cooling measures, the emergency physician must focus on stabilization of the critically ill heatstroke patient. The airway should be protected, since aspiration and seizures are common. Physicians should have a low threshold for endotracheal intubation. Some patients will present with agitation as part of their altered mental status, while others will become agitated during the cooling measures. Intravenous benzodiazepines may be used to control agitation and seizures.[12] Cardiovascular support may be required and is usually accomplished with intravenous fluid administration. Fluid requirements are generally modest, averaging about 1200 mL in the first four hours. In general, blood pressure should increase with cooling; if this does not occur, an additional fluid challenge of 200-400 mL may help. Aggressive fluid resuscitation should be maintained until perfusion is adequate. Carefully monitor fluid resuscitation, as pulmonary edema may be seen in heatstroke and will be exacerbated by aggressive fluid administration. Insertion of a right-heart catheter may be necessary to guide fluid therapy, especially in the hypotensive patient. Most heatstroke patients will have a high cardiac index with low peripheral resistance and an elevated central venous pressure due to right-sided heart failure. Other patients may exhibit low cardiac index, low peripheral resistance, and elevated CVP, findings characteristic of septic shock. Isoproterenol infusion has been successfully used in these patients. Alpha-adrenergic drugs such as dopamine are not recommended, as these promote vasoconstriction and may interfere with heat exchange.

Surveillance for and treatment of rhabdomyolysis and associated renal failure should follow a similar approach to that noted

Table 2. Serotonergic Agents

SELECTIVE INHIBITORS OF SEROTONIN REUPTAKE
Fluoxetine
Paroxetine
Sertraline
Trazodone
Meperidine
Dextromethorphan
SPECIFIC SEROTONIN AGONISTS
Buspirone
LSD
Mescaline
NONSPECIFIC SEROTONIN AGONIST
Bromocriptine
Bupropion
Phenytoin
Tryptophan
Levodopa
Lithium
INCREASE SEROTONIN RELEASE
Amphetamine
Cocaine
Codeine
Reserpine
MONOAMINE OXIDASE INHIBITORS
Pargyline
Phenelzine
Selegiline

for the NMS patient. *(See Part I of this series.)* Coagulation disturbances typically occur 18-36 hours after the acute illness.[5] Replacement therapy with fresh frozen plasma and platelets represent the initial therapeutic approach. Treatment of disseminated intravascular coagulation (DIC) remains controversial, and it generally responds to correction of the underlying cause (i.e., reduction in body temperature elevation and adequate supportive therapy).[2]

Serotonin Syndrome

Serotonin syndrome (SS) is a drug-induced disorder characterized by the triad of alterations in cognitive ability, autonomic nervous system function, and neuromuscular activity. The syndrome is most often produced by the concurrent use of two or more drugs that increase brainstem serotonin activity. It is often unrecognized due to the varied and nonspecific nature of its symptoms. SS may present much like NMS, which can lead to a misdiagnosis. Although SS may result in death, most patients completely recover with supportive care. The incidence is unknown, possibly due to lack of recognition, confusion with other disorders, and varying levels of severity. The incidence of SS, however, may increase as selective serotonin reuptake inhibitors continue to replace tricyclic antidepressants in the United States.[13]

Table 3. Diagnostic Criteria for Serotonin Syndrome[15,16]

A. Coincidental with the addition of or increase in known serotonergic agent to an established medication regimen, at least three of the following clinical features are present:

- agitation
- mental status changes
- diaphoresis
- diarrhea
- myoclonus
- fever
- tremor
- hyper-reflexia
- incoordination

B. Other etiologies (e.g., infectious, metabolic, substance abuse, or withdrawal) have been ruled out.

C. A neuroleptic agent had not been started or increased in dosage prior to the onset of the signs and symptoms listed above.

The main pathophysiologic mechanism appears to be excessive 5-hydroxytryptophan stimulation.[13] This can result from any drug combination that increases serotonin activity at the postsynaptic receptors. This observation is supported by reports of beneficial effects with serotonin-antagonist treatment. Both central and peripheral serotonergic systems and several serotonin receptor types (postsynaptic serotonin-Ia and -II subtypes) are involved in the symptomatology of SS.[14,15]

Clinical Features. The most common drug combination causing SS consists of monoamine oxidase inhibitors (MAOIs) and serotonin selective reuptake inhibitors (SSRIs); however, any combination of the medications listed in Table 2 can precipitate SS. Due to the prolonged half-lives and duration of action of some of these drugs, this syndrome can result from the addition of one drug weeks after the discontinuation of another serotonergic agent.[14,15] The onset of SS ranges from minutes after receiving the second agent (or increasing the dose of the primary agent) to weeks after a stable dosage. No discernible dose response to syndrome development or illness severity has been demonstrated.

SS is characterized by the triad of altered mental status, autonomic dysfunction, and neuromuscular abnormalities. Mental status changes, such as agitation, confusion, hypomania, drowsiness, coma, and seizures, may be apparent. Autonomic features may include nausea, salivation, sinus tachycardia, ventricular tachycardia, diaphoresis, diarrhea, and abdominal cramps. Hyperthermia, hypertension, mydriasis, and flushed skin also may be observed. Neuromuscular effects include ankle clonus, hyper-reflexia, restlessness, rigidity, shivering, tremor, dysarthria, ataxia, head twitching, hyperactivity, myoclonus, nystagmus, paresthesia, and bilateral Babinski's sign. These symptoms are especially prominent in the lower extremities.

The diagnosis of SS is entirely based on clinical suspicion and exclusion of other medical conditions. As with similar syndromes discussed in this review, no confirmatory tests are available for

SS. Presence of the aforementioned symptoms, along with the history of an increase in the dose of a potent serotonin agonist (MAOI or SSRI) or the addition of a second serotonergic agent (lithium), make the diagnosis likely. The ED physician must exclude other disorders with overlapping symptoms, such as sepsis, meningitis, CNS hemorrhage, and anticholinergic/sympathomimetic overdose. Diagnostic criteria for SS have been developed to facilitate syndrome recognition. These criteria include appearance of the syndrome coincidental with the addition of or increase in known serotonergic agent to an established medication regimen and the demonstration of at least three of the following clinical features: agitation, mental status changes, diaphoresis, diarrhea, myoclonus, fever, tremor, hyper-reflexia, and incoordination. Simultaneously, other etiologies (e.g., infectious, metabolic, substance abuse, or withdrawal) should be ruled out. Finally, a neuroleptic agent should not have been started or increased in dosage prior to the onset of the signs and symptoms listed above.[15,16] *(See Table 3.)* Additional objective evidence of increased auditory-evoked potentials strongly supports the diagnosis of SS.[17]

Many patients taking one or more serotonergic agent experience symptoms that can be attributed to SS. In fact, SS may be the extreme manifestation of a spectrum of effects caused by these medications. SS frequently is misdiagnosed as NMS. Useful features that may help make the distinction between SS and NMS include (all points favoring NMS): 1) history of prolonged exposure to neuroleptic agents or withdrawal of dopamine agonists; 2) lead-pipe rigidity (rather than clonus, myoclonus, or hyper-reflexia as more commonly seen in SS); and 3) absence of mydriasis.

Management. Management of the patient with SS primarily involves supportive measures. Clearly, the inciting medication should be discontinued.[13-15] Currently, no specific anti-serotonergic therapy has been established. Methylsergide, cyproheptadine, and propranolol have all been used with anecdotal reports of treatment success. Benzodiazepines, which are nonspecific serotonin antagonists, may also be useful in the patient with marked muscular hyperactivity, CNS agitation, and marked anxiety. One recent report[18] suggests that cyproheptadine, an antihistamine, is particularly effective in ameliorating signs and symptoms of SS. In this case series, all patients were treated with cyproheptadine, 4-8 mg orally. Three patients had complete resolution of signs within two hours of administration, while two patients had a residual tremor or hyper-reflexia following the first dose, which resolved following a repeat dose. The role of specific serotonin receptor antagonists, such as cyproheptadine, in the treatment of the serotonin syndrome remains to be delineated; currently, its use should be considered an adjunct to supportive care. It is not known whether cyproheptadine modifies patient outcome.

Patients with SS should be admitted to the hospital for further monitoring and therapy; inpatient disposition location can be chosen based on the patient's condition in the ED. Emergency physicians must be familiar with medications that have serotonergic potential. Administration of serotonergic medication to a patient who is already using a similar agent can precipitate the syndrome; in fact, clinicians have caused SS in patients using SSRIs and who have been administered meperidine or codeine.[14]

Acute Dystonic Reaction

Any medication that antagonizes nigrostriatal dopamine function has the potential for causing disorders of extrapyramidal motor function. Several distinct syndromes have been described, including dystonic reactions, bradykinesia, akinesia, akathesia, pseudoparkinsonism, and catalepsy. The principal group of medications causing this spectrum of motor dysfunction includes neuroleptics and antipsychotics. The pathophysiologic basis of the extrapyramidal reaction is caused by an insufficient activity of nigrostriatal dopamine. Recall that dopamine and acetylcholine have mutually antagonistic functions in the nigrostriatal system. Extrapyramidal reactions may be prevented or reversed by potentiation of dopamine or inhibition of acetylcholine. Potentiation of dopamine activity, while pharmacologically possible, is not clinically feasible. Reversal of the acetylcholine effect, however, is easily and safely accomplished with an anticholinergic agent, such as diphenhydramine or benztropine.

The individual neuroleptic drugs vary widely as to their tendency to cause extrapyramidal reactions at equivalent dosages. Moreover, the marked variation in the incidence of extrapyramidal side effects does not result from the degree of absolute dopamine inhibition. Rather, such findings are due to differences in the ratio of anticholinergic to antidopaminergic actions of these medications. Therefore, agents such as thioridazine with high anticholinergic activity are infrequently associated with extrapyramidal reactions; conversely, haloperidol has minimal anticholinergic action but causes these side effects more often. The risk and intensity of such dysfunction for a particular antipsychotic agent increases with higher dosages, as well as the rapidity of dosage escalation.

Dystonic reactions usually present suddenly, with an abrupt onset usually within the first four days of exposure to the agent; occasionally, the first dose will produce such a reaction. The medication-related dystonias occur more often in men and young men and women. The basic abnormality noted on examination is a repetitive, involuntary muscle spasm usually affecting a small muscle group; at times, however, multiple muscle groups may be involved, resulting in widespread muscular rigidity. Any muscle or muscle group under voluntary control may be involved, but muscles of the face, neck, and tongue are most frequently affected. Numerous subtypes of dystonic reaction have been described. Torticollis results from contraction of the cervical musculature, producing a twisting of the neck into an unnatural position. Trismus is a spasm of jaw muscles with forceful occlusion and the inability to open the mouth. Oculogyric crisis, affecting the extraocular muscles, produces abnormal eye movements with diplopia or a rigid, fixed gaze. Laryngospasm is an unusual, life-threatening form of extrapyramidal reaction. Opisthotonos involves the head, trunk, and extremity musculature, producing a backward arching of the head and legs and a forward thrusting of the trunk. Combinations of the above subtypes occur, as do other presentations. The increased muscular tone and related disability is painful and anxiety-provoking. Evidence of sympathetic nervous system hyperactivity resulting from pain and anxiety, such as tachycardia, tachypnea, elevated blood pressure, and diaphoresis, is also noted on examination and may confuse the clinical picture.

Management. Diphenhydramine, a powerful anticholinergic agent, is the drug of choice for patients with dystonia. It should be parenterally administered to facilitate rapid onset of action; intravenous administration is preferred. Oral administration is not recommended in the acute setting because these patients are quite uncomfortable and may not tolerate oral

Table 4. Treatment of Acute Dystonia

DRUG OF CHOICE	
Diphenhydramine	
Initial dose	25-50 mg IM or IV
Repeat dose	Once PRN
	25-50 mg po tid for 3-5 days
End points	Signs of clinical toxicity
	Relief of symptoms
ALTERNATIVE AGENT	
Benztropine	
Initial dose	1-2 mg IM or IV
Repeat dose	Once PRN
	1-2 mg tid po for 3-5 days
End points	Signs of clinical toxicity
	Relief of symptoms
ADJUNCTIVE AGENTS	
Benzodiazepine of choice such as intravenous lorazepam	

Table 5. End-Organ Effect of Various Sympathomimetic Agents at the Peripheral Receptor Sites and with the CNS

A knowledge of the action of the various drugs at the adrenergic receptor allows the clinician to predict which clinical findings to anticipate and manage in a prospective fashion.

SUBSTANCE	ALPHA	BETA	CNS STIMULATION
Albuterol	0	+4	+1
Amphetamine	+2	+2	+3
Clonidine	+2	0	-1
Cocaine	+2	+2	+2
Ephedrine	+2	+3	+2
Lysergic acid (LSD)	+1	+1	+1
Metaproterenol	0	+3	+1
Phencyclidine (PCP)	+2	+1	+2
Phenylephrine	+4	0	+1
Phenylpropanolamine	+3	+1	+3
Pseudoephedrine	+1	+2	+1
Terbutaline	0	+3	+1

"0" = no response
"+" = stimulation on scale of +1 to +4
"-" = inhibition on a scale of -1 to -4

medication. Resolution of the dystonic reaction may be noted within 30 minutes after intramuscular administration and within 10 minutes when given intravenously. The initial diphenhydramine dose may be repeated within 15-30 minutes if no response occurs; alternatively, another anticholinergic agent, such as benztropine, may be used. In conjunction with diphenhydramine or benztropine, additional benefit may be derived from the parenteral use of a benzodiazepine such as lorazepam, with its muscle relaxant and anxiolytic properties. Emotional distress will worsen such attacks, while relaxation may reduce the intensity of the reaction. Placement in a quiet room with a calm, reasoned approach greatly assists pharmacological intervention. Torticollis, trismus, and laryngospasm may also endanger the airway; appropriate resuscitative management is indicated, while antidotal therapy is intravenously administered. Following parenteral administration, oral diphenhydramine therapy should be initiated in the ED and orally continued for 3-5 days since the dystonia may recur after the initial, parenteral antidotal effect has decreased. See Table 4 for treatment options in the patient with acute dystonia.

Usually, the dystonic reaction is easily recognized and the response to treatment is favorable. However, these syndromes have been misdiagnosed as meningitis, tetanus, catatonia, hysteria, and convulsions, among other disorders. Furthermore, the physician may not recognize that neuroleptic agents are being used (i.e., therapy for emesis or cephalgia), antipsychotic medication treatment may not be reported, or the patient may have illicitly administered "street valium" (i.e., haloperidol). Whenever the diagnosis is in question, the antidote should be administered since it is relatively safe, and resolution of the dystonia confirms the diagnosis.

Sympathomimetic Ingestion

Sympathomimetic agents are a diverse class of chemical compounds that produce sympathetic nervous system stimulation, effecting the central nervous and cardiovascular systems. Central nervous system stimulation is manifested by seizures, agitated delirium, and hallucinations, while cardiovascular effects include hypertension, tachycardia, cardiac arrhythmia, and myocardial ischemia. Gastrointestinal symptoms such as abdominal cramping, vomiting, and diarrhea may also result from sympathomimetic exposures. Sympathomimetic agents include recreational drugs of abuse, over-the-counter nasal decongestants, appetite suppressants, legal stimulants, and bronchodilators; specific drugs include amphetamines, cocaine, lysergic acid (LSD), phencyclidine, ephedrine, pseudoephedrine, phenylpropanolamine, caffeine, theophylline, albuterol, and terbutaline. Sympathomimetic compounds may produce toxicity due to accidental and intentional drug ingestions at both appropriate and inappropriate doses, and from interactions with other pharmacologic agents.

The pathophysiology of the sympathomimetic drug reaction is based upon the interaction of the compound with the autonomic nervous system, which is functionally separated into two divisions—the sympathetic and the parasympathetic components. When stimulated, the sympathetic nervous system produces a sympathomimetic reaction. This stimulation occurs by either direct action at the target organ receptor sites or via neurotransmitter (norepinephrine) release, with subsequent effect at the target organ(s). The sympathetic nervous system receptors are divided into alpha- and beta-adrenergic subclasses. Excitatory stimuli of the sympathetic nervous system, either by physiologic action or sympathomimetic drug, result in vasoconstriction and CNS excitation (alpha-adrenergic response), as well as bronchodilation, vasodilation, increased cardiac inotropy, and gluconeogenesis (beta-adrenergic actions).

Clinical Features. Presentation of sympathomimetic drug reactions primarily involves two target systems: the central nervous and cardiovascular systems. Variable clinical manifesta-

tions resulting from the sympathomimetic drugs are due to variations in activation of alpha- and beta-adrenergic receptors. For example, "excessive" exposure to albuterol results in hyperglycemia, tachycardia, and CNS excitation primarily resulting from beta-adrenergic stimulation. Phenylpropanolamine intoxication primarily presents with hypertension, tachycardia, and CNS stimulation caused by action at the alpha receptor. Knowledge of the action of the various drugs at adrenergic receptor sites allows the clinician to predict clinical findings and manage the patient in a prospective fashion. *(See Table 5.)* Central nervous system toxicity caused by sympathomimetic agents includes convulsions, cerebrovascular accident, acute delirium, other agitated states, hallucinations, and decompensation of preexisting psychiatric syndromes. Cardiovascular manifestations of sympathomimetic intoxications include sinus tachycardia, supraventricular and ventricular arrhythmias, acute hypertensive emergencies, and myocardial injury. Pronounced muscular rigidity may also be encountered in these patients.

Laboratory evaluation and the use of ancillary studies will be guided by the history and physical examination. A metabolic acidosis may be present, indicating impaired perfusion due to sympathomimetic-induced vasoconstriction. Elevations in serum creatinine may be related to acute renal failure resulting from visceral ischemia or rhabdomyolysis. Hyperglycemia is also noted and represents a multifactorial etiology, including adrenergic-stimulated gluconeogenesis as well as catecholamine-related insulin antagonism. A leukocytosis is consistent with sympathomimetic toxicity but is a nonspecific finding. Cardiac isoenzymes and 12-lead electrocardiogram should be performed in patients whose clinical picture is consistent with myocardial injury; patients should also be electrocardiographically monitored due to the possibility of arrhythmia. Significant degrees of altered mentation with or without focal neurologic findings warrant the use of computed tomography of the head to rule out intracranial hemorrhage and other causes of mental status change. Lumbar puncture must also be considered in the appropriate patient when meningitis or encephalitis are diagnostic possibilities. Analysis of the cerebrospinal fluid will also rule out subarachnoid hemorrhage related to sympathomimetic ingestion.

After stabilization of the cardiorespiratory system, treatment of sympathomimetic toxicity includes gastric decontamination in those patients who have presented within 1-4 hours of drug exposure. Activated charcoal, when administered within four hours of the ingestion, is also felt to be advantageous. Ipecac-induced emesis should be *avoided* because of the potential for seizures and obtundation, and the risk of aspiration. Parenteral benzodiazepines administered in a quiet environment with minimal external stimulation should be used to manage CNS hyperactivity in the majority of cases. Haloperidol intravenously, or droperidol intramuscularly, in conjunction with a benzodiazepine may be required in cases of extreme hyperactivity or psychosis. Droperidol has been extensively used in the control of combative patients without adverse sequelae including seizure.[19] Convulsive activity should be treated with intravenous benzodiazepines. In certain instances of status epilepticus, this approach may be ineffective, requiring parenteral phenytoin and/or phenobarbital.

Hypertension may be treated with the single-agent approach using either nitroprusside or labetolol or with the combination of phentolamine and a beta-blocking agent. Tachyarrhythmias can be treated with combined alpha- and beta-blockade. The use of a beta-adrenergic blocking agent alone may worsen hypertension by blocking beta-2-mediated peripheral vasodilation and unmasking alpha-mediated vasoconstriction. Parenteral sedatives such as lorazepam are also helpful in the management of acute hypertensive states and tachyarrhythmias. Such an agent may be all that is required for the treatment of isolated systolic hypertension during prolonged periods of cardiovascular monitoring. Intravenous fluid hydration, with alkalinization of the urine, may be required in the patient with rhabdomyolysis. Aggressive cooling measures as outlined above may also be necessary.

Acute Ethanol Withdrawal

Alcohol withdrawal is actually a syndrome complex with multiple subtypes, including the hyperadrenergic, convulsive, hallucinosis, and delirium tremens (DT) states. Patients may develop all four subtypes of alcohol withdrawal syndrome (AWS), combinations of the subtypes, or a single subtype. Furthermore, a patient may develop a more severe form of AWS, such as DTs, without any prior manifestation of withdrawal. Many authors describe the AWS in four distinct stages. It must be understood, however, that the AWS is composed of subtype syndromes and not separate stages or levels of progression.

Patients at risk for AWS include alcohol abusers who consume high doses of ethanol daily over a prolonged period. In a classic study of AWS, patients were given ethanol daily and maintained in an intoxicated condition for prolonged periods. No evidence of AWS was noted during the period of constant, steady-state intoxication. Patients who used ethanol daily for less than one month developed a mild version of the hyperadrenergic state after abrupt discontinuation. With discontinuation of alcohol consumption, more severe forms of AWS were encountered in patients who used daily ethanol for one-and-a-half to three months. Additional at-risk behaviors include the chronic alcohol user who suddenly stops drinking ethanol or who significantly reduces the rate of consumption. Alcoholic patients who use sedative-hypnotic agents, such as a benzodiazepine or barbiturate, may develop AWS with continued ethanol use and discontinuation of the medication. This association occurs due to a cross-reactivity of these three agents in the CNS. Other patients at risk for withdrawal include patients with a previous history of AWS, chronic CNS disease, concurrent medical illness, or other severe physiologic stress.

The hyperadrenergic state, encountered in the majority of alcoholics, is characterized by anxiety, insomnia, nausea, emesis, tremor, tachycardia, tachypnea, hypertension, diaphoresis, and hyper-reflexia; gastrointestinal irritation is also common. Patients may note the onset of these findings within 6-8 hours of either reduction in ethanol consumption or complete discontinuation; these symptoms and signs are short-lived, usually spontaneously resolving within 24 hours. Alcoholic hallucinosis, which occurs in up to 25% of chronic ethanol abusers, may appear as early as 24 hours or as late as eight days after discontinuation of use. The hallucinosis state also frequently has many characteristics of the hyperadrenergic condition. Alcoholic hallucinosis must not be confused with DTs. Perhaps the best discriminating factor is the relatively mild hyperadrenergic state accompanying alcoholic hallucinosis. The hyperadrenergic state and alcoholic hallucinosis respond to therapy, with rare perma-

Table 6. Treatment of Alcohol Withdrawal Syndrome—Mild-to-Moderate Forms

FIRST-LINE DRUG—LORAZEPAM

Initial dose	2 mg IV or po
Repeat dose	1-2 mg po q 6-8 h
End points	Signs of clinical toxicity
	Sustained relief of symptoms
	Taper required

OR

CHLORDIAZEPOXIDE

Initial dose	25-100 mg po
Repeat dose	25-100 mg po q 6-8 h
End points	Signs of clinical toxicity
	Relief of symptoms
	Taper required
	Maximum of 300 mg/d

AND/OR

PHENOBARBITAL

Initial dose	30-60 mg po
Repeat dose	30-60 mg po q 6-8 h
End points	Signs of clinical toxicity
	Relief of symptoms
	Taper required
	Maximum of 400 mg/d

Table 7. Treatment of Alcohol Withdrawal Syndrome—Severe Form

FIRST-LINE DRUGS

LORAZEPAM

Initial dose	2-4 mg IV
Repeat dose	1-4 mg IV PRN
End points	Signs of clinical toxicity
	Sustained relief of symptoms
	Taper required

OR

DIAZEPAM

Initial dose	2-4 mg IV
Repeat dose	1-4 mg IV PRN
End points	Signs of clinical toxicity
	Sustained relief of symptoms
	Taper required

AND

PHENOBARBITAL

Initial dose	30-120 mg po or IV
Repeat dose	30-120 mg po or IV q 6 h
End points	Signs of clinical toxicity
	Relief of symptoms
	Maximum of 400 mg/d
	Taper required

nent morbidity and infrequent death. Some authorities, however, believe that patients who develop these relatively less severe manifestations of AWS are at increased risk of developing DT.

Delirium tremens, which is seen in about 5% of alcohol abusers, represents a true medical emergency; it has a mortality of 15% and its onset usually is 3-5 days after the last alcohol use. Patients are quite ill on presentation, with global disorientation, hallucinations, profound agitation, muscular rigidity, and marked autonomic hyperactivity. The autonomic hyperactivity is similar in nature though more pronounced to the hyperadrenergic state; fever is also present in some patients. Death in the patient with DT results from myocardial infarction, cardiac arrhythmia, or profound cardiovascular collapse with distributive shock.

Alcohol withdrawal-related seizures are commonly encountered in the ED. Convulsions in AWS are typically generalized and tonic-clonic in nature, occur 6-48 hours after cessation of ethanol use, and range from one to six in number. Patients rarely develop status epilepticus. If noted, it should suggest another etiology for seizure in the alcoholic or acutely intoxicated patient. Thirty to forty percent of patients with convulsions will develop DT.

In general, the patient with manifestations of AWS should receive an agent designed to reverse the withdrawal state. Benzodiazepines and barbiturates exhibit CNS cross-reactivity with alcohol and, therefore, are excellent choices for these patients. Monotherapy or combination therapy is possible using both agents. A reasonable, proven approach involves the use of oral benzodiazepine in patients with mild-to-moderate manifestations of AWS. *(See Table 6.)* Patients with isolated hyperadrenergic findings who are able to tolerate oral medications may then be treated as outpatients using a benzodiazepine or barbiturate, with the supervision of a responsible adult in a safe environment. Patients with more pronounced AWS benefit from initial parenteral benzodiazepine treatment until autonomic hyperactivity has resolved. The patient is treated with a short course of either an oral benzodiazepine or barbiturate, which is also tapered over a similar time frame. Barbiturate monotherapy is anecdotally associated with less potential for addiction compared to a benzodiazepine.

For the patient with severe forms of AWS, parenteral benzodiazepine treatment is used in bolus fashion for control of acute agitation and autonomic hyperactivity, while a barbiturate is administered on a scheduled dosing format providing additional, "background" therapy. The barbiturate is tapered over several days. For management of severe forms of AWS, frequent treatments of low-to-moderate dose benzodiazepine is preferred over the larger dose, less frequent approach. *(See Table 7.)* In general, the clinician is balancing the cardiorespiratory depressant effects of such treatment with control of the marked agitation and autonomic hyperactivity of severe AWS. Such therapy must be performed in the critical care setting, with monitoring of the electrocardiogram, airway, and mental status.

Patients with ethanol-related convulsions may benefit from short-term (i.e., in the ED) administration of an anticonvulsant

such as lorazepam. Diphenylhydantoin and other conventional anti-epileptic therapy, either acutely or chronically, have not demonstrated a long-term benefit in suppression of further convulsion. Other etiologies of seizure must be sought in such patients. In particular, hypoglycemia must be immediately evaluated at the bedside.

Other pharmacologic agents potentially useful in AWS include beta-adrenergic blocking agents, clonidine, and paraldehyde. Neuroleptic agents are not recommended since superior agents with pharmacologic cross-reactivity are available for agitation control; moreover, such agents may reduce the seizure threshold in certain patients. Additional treatment may include thiamine and other vitamin replacement; attention to electrolyte disorders; and a diligent, exhaustive search for any medical or traumatic comorbidity.

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Physician CME Questions

49. Prescription medications that may set the stage for development of heat illness include:
    - A. anticholinergic drugs.
    - B. diuretics.
    - C. neuroleptic medications.
    - D. All of the above

50. What percent of heatstroke victims complain of prodromal symptoms?
    - A. 75%
    - B. approximately 20%
    - C. 90%
    - D. 60%

51. Per 1°C elevation in body temperature, a patient's heart rate increases:
    - A. 10 beats/min.
    - B. 20 beats/min.
    - C. 2 beats/min.
    - D. Not at all

52. The most common drug combination causing SS consists of:
    - A. specific serotonin agonists and selective inhibitors of serotonin reuptake.
    - B. monoamine oxidase inhibitors and serotonin selective reuptake inhibitors.
    - C. monoamine oxidase inhibitors and specific serotonin agonists.
    - D. monoamine oxidase inhibitors and non-specific serotonin agonists.

53. Mental status changes of SS may include all of the following except:
    - A. coma.
    - B. hypermania.
    - C. confusion.
    - D. seizures.

54. Autonomic features of SS may include:
    - A. hypertension.
    - B. ventricular tachycardia.
    - C. nausea.
    - D. diaphoresis.
    - E. All of the above

55. The diagnosis of SS is entirely based on:
    - A. confirmatory tests.
    - B. clinical suspicion.
    - C. the exclusion of other medical conditions.
    - D. Both B and C are correct

56. The principal group of medications causing disorders of extrapyramidal motor functions in acute dystonic reaction include which of the following?
    - A. Neuroleptics
    - B. Antipsychotics
    - C. Dopamine
    - D. Both A and B are correct

In Future Issues

Appendicitis