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AUTHORS

Brian L. Springer, MD, FACEP, Associate Professor and Vice Chair, Wright State University Department of Emergency Medicine, Dayton, OH

Daniel Silver, DO, Emergency Medicine Resident, Wright State University, Dayton, OH

PEER REVIEWER

Christopher B. Colwell, MD, FACEP, Chief of Emergency Medicine, Zuckerberg San Francisco General Hospital and Trauma Center; Professor and Vice Chair, Department of Emergency Medicine, UCSF School of Medicine

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The Agitated Patient in the Emergency Department

Agitation is a common presentation to the emergency department (ED) worldwide, as either the chief complaint or as a component of another medical problem. Agitation is defined as "an extreme form of arousal that is associated with increased verbal and motor activity."[1] The evaluation and management of agitation is challenging. It is not only a safety concern for the patient and caregivers; significant time and resources are required to acutely manage the patient and to determine and treat the underlying etiology. Agitation may be a manifestation of behavioral and mental health issues, have an organic medical or traumatic etiology, or be a result of substance abuse or withdrawal. In some cases, especially in elderly patients suffering from dementia, the emergency physician will not know if the patient's agitation represents an actual change from their baseline behavior or is simply a manifestation of their current disease.

Epidemiology

There is no accurate accounting of the number of agitated patients seen in the ED. Agitation is a feature of multiple medical complaints and conditions, including sepsis, metabolic encephalopathy, intoxication or withdrawal from drugs or alcohol, acute psychosis, and dementia. As such, agitation often is not recorded as a succinct diagnosis, making accurate epidemiologic tracking difficult and most likely resulting in significant under-reporting of the actual prevalence. Taking all of this into account, the overall prevalence of agitation in the ED was found to be 2.6% (1,146/43,838) of adult patients screened in one urban Level I trauma center over a 19-month period.[2] Delirium is a condition with features that sometimes overlap with agitation. Delirium is an acute condition with disturbances in attention, awareness, and cognition due a medical condition or other cause. The aforementioned study found that 0.6% (or 23% of the agitated patients) met criteria for delirium. It is important to detect patients with delirium from among those with agitation because of the higher rates of adverse events and intensive therapy required in the delirious patient.

Physical restraints or pharmacological sedation often is used to stabilize the agitated patient. The aforementioned study of agitated patients in an urban ED used an "altered mental status score" to determine inclusion in their study numbers, with scores ranging from -4 (unresponsive to prodding or shaking) to 4 (combative and out of control).[2] Of the 1,146 patients with an agitation score of at least 1 (anxious and restless), 85% (969/1,146) were physically restrained, 72% (829/1,143) received sedation with an intramuscular injection, and 63% (725/1,146) received both.[2]

EXECUTIVE SUMMARY

- Agitation seen in the emergency department has many causes.
- The first step in assessing an agitated patient is to initiate measures to prevent physical harm to the staff and patient.
- The next step is to verbally engage the patient and establish a collaborative relationship, if possible.
- Early assessment of vital signs and point-of-care glucose is important.
- Physical restraints may be necessary, but they should be applied thoughtfully in escalating fashion as needed, and according to hospital protocol.
- Continuous monitoring of respiration is required when pharmacological sedation is used.
- Evaluate the decision-making capacity of agitated patients prior to disposition.

In a cross-sectional study of adult patients presenting to five adult EDs within a large regional health system between 2013 to 2015, 0.5% had associated physical restraint orders. The median age was 47 years; more than half were men and had a psychiatric history. Among the patients' chief complaints, 33.7% were alcohol or drug-related, 45.4% were medical, 12.3% were psychiatric, and 8.5% were trauma.[3]

At the extreme, the agitated patient may present with excited delirium syndrome, characterized by delirium, agitation, and hyperadrenergic autonomic dysfunction, often in the setting of acute on chronic substance abuse or severe mental illness. The concept of excited delirium, also termed agitated delirium, is controversial; it not currently recognized as a distinct clinical entity by major medical associations. The most common situation in which this term has been applied is with police or emergency medical services (EMS) encounters where the patient is under the influence of sympathomimetics such as cocaine, conducted energy weapons have been used, and physical restraints are attempted or applied. It has been estimated that excited delirium is seen in about two per 10,000 advanced life support EMS calls.[4,5] This concept is discussed later.

Agitated and violent patients present significant danger not only to themselves, but also to EMS personnel, ED staff, and physicians. More than half of ED nurses in one U.S.-based survey reported being the target of physical violence, and almost three-quarters received verbal threats. Twenty-three percent experienced frequent physical violence, with more than 20 physical violence episodes within the past three years of their practice.[6] In a 2018 survey of more than 3,500 emergency physicians across the United States, 47% reported that they had been physically assaulted at work. Of those, more than six in 10 were assaulted in the past year.[7]

Pathophysiology

Agitation has many causes and etiologies. (*See Table 1.*) The organic causes of agitation can be categorized as those caused by newly diagnosed medical illnesses or traumatic injury, as well as acute exacerbations of chronic diseases. The inorganic causes of agitation can be categorized as acute poisonings, illicit substance use, or an acute drug withdrawal syndrome. Exacerbation of mental illness for any reason also may result in an acutely agitated state.[8]

Organic Causes of Agitation

Agitation is seen in about 10% of patients with severe traumatic brain injury (TBI), defined as greater than one hour of unconsciousness and an initial Glasgow Coma Scale score in the ED less than 8, usually as a feature of the post-injury confusional state.[9] Less severe TBI has the potential to induce confusion and subsequent agitation, too. Early CT scan imaging is important in agitated patients with a history of or physical signs consistent with head trauma.

Acute infections may lead to agitation through a variety of mechanisms. An infectious process of the central nervous system (CNS) can cause agitation via direct infection of the brain parenchyma (encephalitis) or the meninges (meningitis). It is difficult to distinguish these two entities clinically since they commonly coexist.

Individuals who are immunocompromised are at risk of CNS infection from various opportunistic organisms, including herpes simplex virus (HSV) and cytomegalovirus (CMV). Rabies, tick-borne illnesses, and arboviruses must be considered in the differential diagnosis of CNS infections potentially resulting in acute agitation.

Some viruses replicate outside of the CNS and then travel hematogenously to infiltrate the brain and surrounding meninges. Other viruses, including rabies, herpes simplex, and varicella zoster viruses, have the ability to travel retrograde across axons and gain access to the cerebral gray matter. Acute encephalitis secondary to these organisms subsequently leads to a spectrum of neurologic abnormalities to include altered mental status, acute agitation, and generalized seizures.[10,11]

Infectious processes outside of the CNS, including pulmonary, skin and soft tissue, genitourinary, and gastrointestinal infections, can lead to sepsis and metabolic derangements leading to lactic acidosis, irritated brain parenchyma, and encephalopathy manifested as delirium, altered sensorium, and seizures. Overwhelming sepsis also is associated with acute coagulopathies, micro- and macro-vessel thrombosis, and cerebral ischemia. Elderly patients are at greater risk for sepsis, and early clinical manifestations may be subtle.[12,13]

Hypoglycemia can manifest as a decreased level of consciousness, agitation, or seizure activity. Hyperglycemia can produce osmotic diuresis, leading to dehydration and electrolyte derangements. Agitation and seizures may result.

Table 1. Differential Diagnosis of Agitation

Organic	Look For	Workup
Traumatic brain injury	History/physical signs of trauma, focal neurologic deficits, Cushing's triad	Rapid neuroimaging
Central nervous system infection	Fever, nuchal rigidity, delirium, seizures	Neuroimaging (especially if focal deficits are present), lumbar puncture, and cerebrospinal fluid studies
Sepsis	Fever or hypothermia, delirium, hypotension, tachycardia	Thorough evaluation seeking source, followed by appropriate laboratory tests, imaging, and cultures
Respiratory failure	History of chronic obstructive pulmonary disease or other pulmonary disease, hypoxia, agitation followed by somnolence	Pulse oximetry, blood gas
Dementia	History of vascular disease/stroke, advanced age, history of dementia	Thorough evaluation to rule out acute illness exacerbating preexisting dementia
Inorganic	**Look For**	**Workup**
Acute poisoning toxidrome	Signs/symptoms of toxidrome (especially salicylate, sympathomimetic, and anticholinergic)	Serum toxin levels where appropriate, electrolytes and renal function; intervention often based on presenting signs/symptoms rather than laboratory tests
Acute withdrawal	History of opioid, benzodiazepine, or alcohol abuse	Serum alcohol levels (suspect withdrawal when levels are low), intervention often based on presenting signs/symptoms rather than laboratory tests
Hypoglycemia	History of diabetes, recent medication changes	Bedside serum glucose monitoring
Other Causes	**Look For**	**Workup**
Exacerbation of mental illness	History of depression, bipolar disorder, schizophrenia; medication changes or noncompliance; acute stressors	Evaluation for underlying organic or inorganic disease if indicated by history or physical
Excited delirium syndrome	History of mental illness, substance abuse, or both; severe agitation combined with delirium; hyperthermia	Thorough medical evaluation and supportive care after sedation has been achieved; be wary of sudden collapse/death

Patients who have suffered generalized seizures are at high risk for developing acute agitation during the post-ictal phase. Rapid development of hyponatremia or hypernatremia may result in cerebral edema or neuronal destruction.[14] Hypercalcemia, typically seen in the setting of malignancy or hyperparathryoidism, causes neurological dysfunction secondary to the central neuronal depressant effect of increased calcium and may manifest as confusion, drowsiness, agitation, stupor, or coma.[15]

Both acute and chronic respiratory failure can cause hypoxia as well as hypercapnia. Agitation is one the earliest signs of hypoxia. In acute CO_2 retention, cerebral vasodilatation leads to increased intracranial pressure, decreased mental status, and agitation.[13]

Both delirium and dementia also may lead to acute agitation. At times, these two syndromes may be difficult to differentiate since they often present concomitantly and can overlap clinically. Delirium is thought to have four general causes, including intracranial disease, systemic illnesses that adversely affect the CNS, toxin ingestion, and withdrawal from medications or illicit drugs. Dementia is not a specific disease, but rather a general term for the gradual diminishment of cognitive ability and memory. Most cases of dementia are caused by Alzheimer's disease or vascular dementia, which typically are diagnoses of exclusion in the ED.[8,13]

Inorganic Causes of Agitation

Acute poisonings may occur from both intentional and unintentional overdose. Anticholinergic side effects are seen with a large number of prescription and over-the-counter medications, including antihistamines, antidepressants, and antipsychotics. These medications block acetylcholine at peripheral and central muscarinic receptors, leading to a constellation of signs and symptoms including mydriasis, anhidrosis, and hyperpyrexia, as well as delirium and acute agitation.[16,17]

Clonidine acts as an alpha-2 adrenoreceptor agonist and imidazoline receptor agonist, resulting in CNS depression and antihypertensive effects. Overdose paradoxically may lead to confusion, hallucinations, and acute agitation.

Salicylate toxicity stimulates the cerebral medulla, leading to hyperventilation and respiratory alkalosis. It also leads to uncoupling of oxidative phosphorylation in the mitochondria, causing acute metabolic acidosis. These two processes result in dramatic changes in the cerebrospinal fluid pH and subsequent acute agitation.[18,19]

Diabetic medications whose mechanism of action is to lower the serum blood sugar, taken in therapeutic doses or as an acute overdose, may result in acute hypoglycemia and subsequent agitation. Diabetic patients on exogenous insulin are at especially high risk of experiencing acute hypoglycemia. Mechanisms include insulin overdose, inadequate oral intake, excess glucose consumption (e.g., increased physical activity), concomitant alcohol ingestion, or underlying acute kidney injury. Sulfonylureas, commonly used to treat non-insulin-dependent diabetes mellitus, exert their effect on adenosine triphosphate (ATP)-sensitive potassium channels in the beta cells of the pancreas, ultimately resulting in the release of endogenous insulin. When taken in overdose or in situations when oral intake is poor, prolonged hypoglycemia develops that ultimately may result in confusion, agitation, or seizures.[20]

Cocaine, methamphetamine, and other sympathomimetics are potent CNS stimulants commonly implicated in the development of acute agitation. Cocaine binds to the dopamine transporter protein, effectively blocking presynaptic reuptake of dopamine and allowing its accumulation in the synaptic cleft. It also increases levels of serotonin and norepinephrine. This results in the euphoria associated with recreational cocaine use, but at high doses, agitation and hallucinations may occur. Methamphetamine increases dopamine and serotonin release, which directly causes an increase in striatal glutamate release. Long-term use can cause damage to the serotonergic and dopaminergic axon terminals in the prefrontal cortex, striatum, and hippocampus. This can cause a decrease in expression of tyrosine and tryptophan hydroxylase, which are the rate-limiting enzymes in the pathway to produce dopamine and serotonin.[21,22]

Phencyclidine (PCP) is a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, leading to psychosis, cognitive defects, and analgesia. It also blocks uptake of dopamine and norepinephrine in the synaptic cleft, leading to a recreational euphoria that can transition rapidly into acute agitation. PCP also can bind acetylcholine, gamma aminobutyric acid (GABA), and sigma receptors leading to sedation, coma, agitation, altered mentation, and muscarinic and nicotinic signs/symptoms.[23]

Chronic alcohol abuse creates constant inhibitory and depressant effects on the brain along with overstimulation and eventual down-regulation of GABA receptors. During acute withdrawal, the resultant lack of GABA receptors results in hyperstimulation and acute agitation. Associated dysfunction of the hypothalamus/pituitary/adrenal axis, as well as dopamine underactivity, results in agitation, hallucinations, and seizures.[24]

Benzodiazepines and barbiturates have similar mechanisms of action to alcohol. As the individual becomes tolerant, the number of GABA receptors decreases and their shape changes, resulting in a decrease in production of GABA. Without the inhibitory effects of benzodiazepines, the lack of GABA results in acute withdrawal symptoms, such as seizures, hallucinations, and agitation.[25]

Mental Illness

Mental illnesses, such as depression, bipolar disease, schizophrenia, and personality disorders, present commonly to the ED. Individuals experiencing these illnesses may present with acute agitation.

Patients with schizophrenia are believed to have abnormalities in glutamate neurotransmission, failed connections between the thalamus and cerebral cortex, and abnormal cerebral serotonin activity. Bipolar disorder is thought to involve hypersensitivity of reward circuits in the frontostriatal regions causing manic episodes. Conversely, decreased sensitivity of these circuits results in depressive episodes. Anxiety and depression have been linked to a deficiency of serotonin, dopamine, GABA, and norepinephrine in the brain.[26-28]

Excited Delirium Syndrome

Excited delirium syndrome (ExDS) is an acutely life-threatening form of agitation that may develop in the prehospital, ED, or inpatient setting. The common pathology is delirium with multiple underlying associations: psychiatric illness, psychiatric medication withdrawal, stimulant abuse, and metabolic disorders. What ultimately leads to ExDS is unknown, and it likely differs between cases.[5] It is believed that high levels of endogenous catecholamines related to exertion and stress, combined with concomitant stimulant abuse plus physical struggle or restraint, result in hypoxia, hyperkalemia, acidosis, and autonomic dysfunction. The pathologic processes occurring in the body contribute to dysregulation of dopamine homeostasis in the brain.

Among the clinical features of ExDS, the most concerning is the risk of sudden cardiopulmonary collapse following a struggle and restraint, or seen shortly after a period of quiescence or "giving up," along with an inability to be resuscitated successfully despite aggressive efforts. The precise reasons for the rapidity and finality of cardiac arrest in restrained ExDS patients remains unknown, and certain hypotheses, such as the link between conducted energy weapon use and death, remain unproven.

The role of catecholamine surge resulting in hyperadrenergic state and acidosis is debated. A study comparing stress biomarkers in ExDS patients found significantly higher levels of cortisol in the ExDS arm compared to other agitated ED patients and a control arm of volunteers exercised to exhaustion, physically restrained, and stressed by threats of application of a conducted energy weapon.[29] Studies looking at acidosis and catecholamine levels in simulated law enforcement encounters show that physical exertion tasks (sprinting, punching a heavy bag) generate greater

changes than less lethal exposures such as oleoresin capsicum spray (known as OC spray or "pepper spray") or TASER.[30,31] Thus, physical resistance may put ExDS patients at greater risk than less lethal exposures. Acidosis can lead to myocardial irritability and dysfunction, and catecholamine surges can cause lethal dysrhythmias.

Also, in theory, unrecognized occult conduction abnormalities, such as long QT syndrome, could be unmasked, with resulting dysrhythmia and cardiovascular collapse. In addition, vasodilation associated with exertion results in decreased venous return when muscle activity ceases (i.e., the combative patient is restrained). This reduces cardiac output and coronary artery perfusion at the same time that elevated catecholamine levels increase heart rate and myocardial oxygen demand, and may result in ischemia and dysrhythmia.

Clinical Features and Evaluation

Agitated patients presenting to the ED span the spectrum from those requiring minimal intervention to those requiring rapid stabilization of associated life threats. In one study of an urban Level I trauma center ED, patients who were acutely agitated were evaluated by a physician immediately on arrival with a goal of completing an assessment in one minute. The physician was required to decide whether to use physical or chemical restraints and whether the patient required ongoing monitoring in a critical care setting vs. an observation unit. One of the key findings of the study was that a substantial number of patients were suffering from a critical underlying illness requiring rapid evaluation and intervention.[2]

Individuals with acute agitation may be disorientated to time, place, and, rarely, to person. Some may have a normal mental status, but may display aggressive verbal or physical behavior. Vital sign derangements are common, most often tachycardia, blood pressure changes, and hypothermia or hyperthermia. Inspection may reveal signs of trauma to include an acute head injury, a penetrating injury, or another source of hemorrhage.

Pupillary abnormalities may be seen in the setting of acute head trauma as well as with numerous drug ingestions and toxidromes. Slurred speech may be a nonspecific sign associated with agitation or it may indicate a significant underlying illness, such as an acute cerebrovascular accident or acute intoxication.

Cerebellar dysfunction, seizures, and hemiparesis all can be seen in acute agitation resulting from a range of underlying causes. Acute diaphoresis is a concerning physical exam finding in any patient, but in agitated patients it may indicate underlying sepsis, drug intoxication, or an acute withdrawal syndrome. Thought process abnormalities that include flight of ideas, tangential thinking, pressured speech, or an inability to be redirected are associated with mental health disorders or illicit substance abuse.[1]

A complete set of vital signs, including temperature measurement, is critical, and a bedside blood glucose level should be checked as soon as possible. Tachycardia could be a sign of infection, illicit substance use or withdrawal, or a toxidrome. Bradycardia can be seen in the setting of significant head injuries as part of Cushing's triad or in various drug overdoses, including beta-blockers, calcium channel blockers, and clonidine. Hypertension can be seen as a component of Cushing's triad, in a number of toxidromes, associated with illicit substance use or withdrawal, or as a component of ExDS. The presence of associated hypothermia or hyperthermia may be secondary to infection, an acute ingestion of an antimuscarinic agent, illicit substance use or an acute drug withdrawal syndrome, or from an antimuscarinic overdose.

Once the patient is ensured to be hemodynamically stable, and once the patient's agitation is controlled to the point where they are not an immediate danger to themselves or others, a thorough history and physical exam should be performed.

Acute agitation may be the hallmark symptom of a patient experiencing a previously undiagnosed psychiatric disease. However, psychiatric disease as a precipitating cause is always a diagnosis of exclusion. In particular, special populations such as pediatric, elderly, and pregnant patients should be screened carefully for evidence of an acute medical illness, including infection, trauma, metabolic disorders, drug toxicity or withdrawal, and neurologic disease.

The emergency physician should obtain a concise history from any available resources, such as family members, friends, and EMS personnel. Critical historical information includes the patient's baseline mental state, prior psychiatric history, and history of illicit drug or alcohol use.[1]

At some point in the exam, the patient should be completely exposed to allow for a complete head to toe examination. Neurologic deficits may indicate acute cerebrovascular accident (CVA), meningitis, or encephalitis. Evaluation of the heart, lungs, and abdomen may support the diagnosis of acute infection or occult trauma and help guide the workup.

Any patient with historical or physical findings suggestive of acute head trauma, focal neurologic abnormalities, or new-onset seizures in the setting of agitation should have a non-contrast enhanced CT scan of the brain completed. Differential diagnostic considerations include acute intracranial bleeding, space-occupying lesions, and acute CNS infection. In addition, if an acute CVA is strongly suspected, a CT angiogram of the head and neck with intravenous contrast also is undertaken.

If underlying meningitis or encephalitis is suspected, a lumbar puncture should be completed. If the patient's underlying mental status precludes safe completion of this procedure, institute empiric therapy with broad spectrum intravenous antibiotics. Intravenous corticosteroids and intravenous antiviral medications may be added to the treatment regimen on a case-by-case basis. Septic patients should be worked up and treated based on current national and institutional guidelines, with a focus on resuscitation, determining an infectious source, and early antibiotics.[10-13]

Acute alcohol intoxication typically presents with decreased mental status or belligerent behavior. Cocaine, methamphetamine, and phencyclidine all result in stimulation of the sympathetic

nervous system, manifested by tachycardia, hypertension, diaphoresis, and, at times, acute psychosis. Patients with alcohol or benzodiazepine withdrawal can present with hypertension, tachycardia, diaphoresis, seizures, and hallucinations.

Obtaining serum levels of specific medications or intoxicants is seldom helpful in the emergency evaluation of the agitated patient. The exception is serum ethanol levels. Low levels in the alcohol-dependent patient may indicate acute withdrawal. In altered patients with negative alcohol levels, consider ingestion of methanol, ethylene glycol, and propylene glycol. Analysis of serum of electrolytes, arterial blood gas assessment, and osmolal gap may help to elucidate the diagnosis.[32] Urine drug screens are of limited utility, with a high incidence of both false-positive and false-negative findings. In addition, quantitative results generally are not available on an emergent basis, making the clinical relevance of a positive test unclear.[17]

The presenting symptom cluster of ExDS varies. The combination of delirium, psychomotor agitation, and physiologic excitation differentiates it from delirium alone, and from individuals who are agitated and violent but not delirious.[5]

When a patient arrives by EMS, a history from the medics or on-scene peace officers is useful. In the prehospital setting, the features most often associated with ExDS are:[5]

- constant or near constant physical activity with a lack of tiring;
- increased/abnormal pain tolerance;
- "superhuman" strength;
- tachypnea;
- diaphoresis;
- tactile hyperthermia;
- noncompliance/failure to respond to police presence.

Other less common features include disrobing, nudity or inappropriate clothing, and an attraction to glass, mirrors, or other reflective surfaces. As noted earlier, patients who die tend to do so suddenly, often following physical, chemical, or electrical control measures, and with no clear anatomic cause of death noted on autopsy. Along with the clinical features mentioned, fatal cases of ExDS are associated with the following:

- male gender;
- mean age mid-30s;
- destructive or bizarre behavior, including violence toward inanimate objects, that generates a call to police;
- suspected use of psychostimulants or a history of psychostimulant abuse;
- history of or suspected psychiatric illness;
- sudden cardiopulmonary collapse following a struggle and restraint, or shortly after a period of quiescence;
- inability to be resuscitated on scene.

Obtaining a history, accurate vital signs, and good physical exam often is impossible during the initial presentation of ExDS, secondary to the patient's condition. If the presenting features are suspicious for ExDS, the initial focus should be on acute control of agitation, which is discussed in the next section.

In the absence of a clear clinical definition and prospective research, the workup should cast a broad net to identify any underlying clinical or laboratory abnormalities, such as hyperthermia, dehydration, and electrolyte derangements.[5]

Table 2. Stepwise Approach to the Agitated/Violent Patient

I. De-escalation and Environmental Modification
- Engage and establish a verbal loop. Ask questions like "How can I help you?"
- Actively listen to and acknowledge the patient's responses.
- Place patient in a calm, non-threatening environment.

II. Physical Restraint
- Use the minimal amount of restraint necessary to control the patient.
- Consider adjunctive use of medications.
- Remember that restraints enhance the patient's fear and sense of loss of control.
- Remain empathetic and provide continued verbal reassurance.
- Frequently monitor any restrained patient for signs of medical decompensation.

III. Pharmacotherapy
- Administer benzodiazepines and antipsychotics alone or in combination.
- Consider ketamine for violent patients who present an immediate risk to themselves and others.

IV. Reassess and Reexamine
- Frequently reassess effectiveness of interventions.
- As soon as feasible, begin monitoring vital signs to include temperature.
- Reexamine patient frequently until they are calm and controllable.
- Be on the alert for signs of toxidromes, excited delirium syndrome, or life-threatening medical illness.

Acute Interventions

When dealing with the majority of agitated patients, a stepwise approach is warranted. (*See Table 2.*) A soothing reassurance from providers may be enough in some cases to calm an agitated patient, assuage their fears, and gain cooperation. However, aggressive or severely agitated patients may require officer presence, physical restraints, and pharmacologic sedation to protect both the patient and staff.

In severe agitation where the patient is an immediate danger to themselves or others, or when ExDS is suspected, the emergency physician should start aggressive medical interventions immediately to gain control of the patient, allowing for monitoring; addressing airway, breathing, and circulation; and reversing extreme physiologic derangements.

De-Escalation and Environment Modification

The first step in managing an agitated patient is for the emergency physician and other providers to remain calm and begin using de-escalation techniques. Multiple specific techniques have been

described, but most follow the same basic approach. The provider engages verbally and establishes a collaborative relationship with the patient. The language used should be supportive of the patient and non-confrontational. This can be as basic as asking the patient "What is the matter?" or "How can I help you?"

The patient is then verbally de-escalated from their agitated state. This often takes the form of give and take or a verbal loop where the emergency physician actively listens to the patient, responds in a manner that acknowledges the patient's concerns, and then states what they would like the patient to do and how they will help.

Often, the loop must be repeated multiple times as the patient gradually de-escalates, and it is critical that the emergency physician remain patient and not give up. Similar techniques are used by law enforcement, both when dealing with a disruptive individual on the street or in the context of hostage negotiations.[1] The late George Thompson's Verbal Judo was one of the first to show how professional police could apply these techniques to deflect verbal assault and de-escalate agitated subjects.[33]

When available and when medically safe to do so (i.e., the patient is hemodynamically stable with little risk for medical deterioration and no need for telemetry), an agitated patient should be placed in an environment aimed at maintaining a sense of calm. The patient should be placed in a single room to allow for rest and to avoid extremes of sensory experience, such as loud noise and excessive brightness. Unnecessary equipment or any items that could be dangerous to the patient and staff should be removed from the room and the patient. The room should be adequately lit, excess noise should be eliminated, and the temperature should be comfortable.

Physical Restraints

A recent analysis of restraint usage in the ED found that patients requiring physical restraint tended to cluster into two groups. The first group was younger, was predominantly male, and had higher rates of psychiatric illness. Alcohol or drug use and psychiatric issues were the most common chief complaints in this first cluster, and they had a greater propensity to present during evening hours. Homelessness was a more common social issue in this group. The second group was significantly older and with a smaller percentage of psychiatric illness and homelessness. Medical chief complaints dominated, and patients tended to arrive during daytime hours.[3]

Hospital certification programs such as The Joint Commission and Healthcare Facilities Accreditation Program provide specific guidance measures for the use of patient restraint. Emergency physicians should be familiar with their own hospital's policies and protocols and follow them in conjunction with the nursing staff and other support personnel.

When the decision is made to place a patient in physical restraints, the least restrictive form of constraints possible should be instituted. Mildly agitated patients who are grabbing at staff, intravenous catheters, and monitoring leads can be placed initially into two-point restraints (upper extremities only). Be aware that this is associated with a higher level of failure than more restrictive restraint measures and, for reasons unknown, is linked to higher rates of restraint-associated death.[3]

Physical restraints may be used alone or in conjunction with chemical sedation, depending on the degree of agitation, the necessity of immediate life-sustaining interventions, and the response to de-escalation and physical restraint measures.

When physical restraints are unavoidable, it is essential that the ED staff take steps to make the experience as positive as possible for the patient. Remember that the patient will be experiencing a sense of fear, unreality, and loss of control. All of these sensations may be worsened by the application of restraints.[34]

Well-trained and empathetic nursing staff must remain at the bedside to monitor the patient closely, as well as to provide reassurance and support. Communicating with patients and explaining what is being done, why it is being done, and what is going to happen next provides patients with a sense of control, calm, and safety. The safer the patient feels, the more likely they are to be able to calm themselves.

Restraints themselves are not without risk. The most common cause of restraint-related death is asphyxiation, termed "restraint asphyxia" in the forensic literature.[35] Many of these deaths are linked to patients who arrive in police custody, often under the influence of alcohol or drugs. Among psychiatric inpatients, where alcohol and street drugs are absent, most cases of restraint asphyxia involve patients who have been medicated with CNS depressants and other psychotropic medications. The underlying mechanisms of restraint asphyxia remain unclear and likely are multifactorial.

Positional asphyxia occurs when ventilation is compromised by abnormal positioning of the body, either through interference with the chest or diaphragm or occlusion of the upper airway. It is seen most commonly in individuals who become trapped in a head-down or chest-compressed position with the inability to self-extricate. In law enforcement settings, prone positioning has been implicated as a causal factor in in-custody deaths. Although the prone position often is used following a public-police interaction where a subject is taken into custody, the evidence actually demonstrates a negligible risk.[36]

Neck restraints are a hands-on technique designed to impede flow from the carotid arteries to subdue a combative individual. The subduer places their arm around the combative subject's neck and simultaneously applies bilateral pressure, impeding both carotid artery flow and jugular venous drainage.

Neck restraints have a long history of safe use in the martial arts and in general among police and, when properly applied, can cause brief loss of consciousness in a matter of seconds.[37] However, when dealing with an intoxicated or otherwise highly combative subject, there is risk that the hold may be improperly applied and cause compression of the trachea. This serves to increase agitation of the subject requiring even more forceful application of the hold to maintain subject control, ultimately resulting in asphyxiation.

Table 3. Pharmacologic Options for Acutely Agitated Patients

Agent	Pros	Cons	Typical Initial Adult Dose
Benzodiazepines	Serial dosing, rapid onset, multiple routes of administration (IM, IN, IV)	Respiratory depression in high doses, slow onset when given IN	• Lorazepam 2 mg to 4 mg IM • Midazolam 2 mg to 5 mg IM
Antipsychotics	Safe and effective; may be used in conjunction with benzodiazepines	Slow onset, extrapyramidal side effects, QT prolongation in higher doses (although clinical relevance is contested)	• Haloperidol 5 mg to 10 mg IM • Droperidol 2.5 mg to 5 mg IM • Olanzapine 5 mg to 10 mg IM
Dissociative agent (ketamine)	Rapid and effective sedation, IV or IM administration, excellent safety profile	Laryngospasm (rare), emergence reactions, prolonged sedation following high doses	• Ketamine 5 mg/kg IM*

IM = intramuscular; IN = intranasal; IV = intravenous

* Not Food and Drug Administration approved for this indication

Neck restraints should not be used in the patient care setting where safer alternatives exist.

As noted, restraint in the prone position presents only a negligible risk of death from asphyxia. However, patients who are restrained in the supine position are at risk for aspiration.[35] Loss of protective airway reflexes may occur due to the primary medical or toxicologic insult affecting the patient, or secondary to medications administered for sedation. Additionally, even patients with patent airway reflexes may find themselves unable to protect their airway from blood, vomitus, or other secretions if they are forcibly restrained in a prone position and unable to clear their oropharynx.

Other potential complications of restraint include the development of exertional rhabdomyolysis and increased risk for thrombophlebitis and venous thromboembolic disease, such as development of deep venous thrombosis.[38]

While the application of physical restraints is an effective, and often necessary method of controlling agitated patients, emergency physicians need to be wary of their own implicit biases when deciding who needs to be restrained. A recent study looking at a single ED's use of restraints found, after controlling for observable factors such as age, gender, mental health history, and substance abuse, that Black male patients had a significantly higher risk of being placed into restraints than white men. Although the study is limited by being single-center and not able to account for all factors, such as the severity of the disturbance and the potential danger to staff and the patient, it is in line with other studies that show racial disparities in patient treatment in the ED.[39]

Pharmacotherapy

Three classes of medication commonly are used in the ED to manage acutely agitated and violent patients: benzodiazepines, antipsychotics, and dissociative agents such as ketamine. (*See Table 3.*)

Benzodiazepines may be administered through the intravenous (IV), intramuscular (IM), interosseous, or intranasal route and have a rapid onset, working in minutes. They bind to GABA receptors and create an inhibitory response, which is ideal in patients with stimulant intoxication.[40] Serial dosing may be administered for ongoing sedation and anxiolysis. The primary disadvantages are relatively slow onset when administered intranasally (up to five minutes) and respiratory depression, which may be synergistic if alcohol or other sedative medications have been ingested. Patients with sympathomimetic toxicity and ExDS typically require much higher doses of benzodiazepines than those given in more routine presentations of agitation or anxiety, and the emergency physician should be ready to provide airway support if respiratory impairment develops.

Both typical and atypical antipsychotics can be used either alone or in conjunction with benzodiazepines to facilitate rapid sedation. Although many antipsychotics are Food and Drug Administration (FDA)-approved only for oral or IM administration, IV administration is common. First-generation antipsychotics, such as haloperidol and droperidol, are associated with QT prolongation, and droperidol was sidelined for years following a 2001 FDA Black Box Warning. However, recent studies have shown it to be safe and efficacious for treating agitated patients in both the prehospital and ED settings.

Haloperidol and droperidol doses up to 10 mg may be used to treat severe agitation; when droperidol doses greater than 2.5 mg are used, cardiac monitoring should be considered, although the risk of developing a clinically significant dysrhythmia (such as torsades de pointes) is low.[41,42] Compared to IM benzodiazepines, the time for IM antipsychotics to achieve a meaningful reduction in agitation (defined as going from being combative, very agitated, or agitated to being restless) is significantly longer.[43] Combination therapy with benzodiazepines can facilitate more rapid sedation of patients whose agitation is extreme or who are being physically combative. The medications appear to have a synergistic effect that promotes behavioral calming and reduces untoward side effects of antipsychotic medications.[40]

Ketamine is a dissociative anesthetic that blocks NMDA receptors and prevents the patient from perceiving visual, auditory, or painful stimuli. This results in effective analgesia and

amnesia to pain and events. Onset is rapid, and the medication may be delivered through the IV or IM route. Given at higher doses, ketamine creates a dissociative state that is very effective in providing procedural sedation as well as for controlling severe agitation. This dissociative state does not have any progressive depth, and additional doses do not enhance the sedation but merely prolong it. This greatly enhances safety and reliability, since a single large dose can be administered IV or IM. When administered intramuscularly, the onset of action is about five minutes, making it useful for gaining control of agitated patients in the field and in the ED.

Adverse effects of ketamine include hypersalivation, nausea, emergence reactions (which can be countered with benzodiazepines) and, rarely, laryngospasm.[44-46] Whether ketamine should replace combination therapy of antipsychotics and benzodiazepines as first-line treatment for agitated patients remains a matter of contention. Only recently has a randomized controlled trial compared the two modalities head to head in the emergency department.[47] Although the study was limited by a very small sample size and lack of physician blinding, it found ketamine provided significantly more rapid sedation than the combination of haloperidol and lorazepam (mean time of 15 minutes for ketamine vs. 36 minutes in the haloperidol/midazolam group) and had an excellent safety profile.

Although ketamine has been adopted by EMS agencies for use in agitated patients, its use is controversial. The American Society of Anesthesiologists said in a position statement in July 2020 it "firmly opposes the use of ketamine or any other sedative/hypnotic agent to chemically incapacitate someone for a law enforcement purpose and not for a legitimate medical reason." Emergency physicians and EMS medical directors have pushed back on this opinion, noting that decisions to use pharmacologic agents for sedation are best provided by local physicians involved in medical direction and oversight, stating that ketamine "is an effective method of protecting the violent or combative patient from self-injury."[48]

Patients experiencing ExDS can go from aggressive and combative to a peri-arrest or perimortem state without any warning. The key to effective treatment is early recognition. Given the lack of any gold standard test, the clinician must use clinical judgment when evaluating an agitated and delirious patient and act expediently if clinical indicators of the syndrome are present. Although there is no strong evidence that sedation improves outcomes and lowers morbidity or mortality, diminishing the catecholamine surge and metabolic acidosis appear essential for decreasing the risk of decompensation and sudden death.[49] Therefore, be ready to supplement physical restraint quickly with appropriate medications.

Preventive Measures

The first steps in the management of agitated patients in the ED is to create an environment that reduces and mitigates the risks of patients acting out and potentially becoming violent toward staff or others. Long waiting times, discrepancies between the patient expectations and what services are offered, patient use of drugs and alcohol, and patients with psychiatric conditions all are linked to patient (and family) dissatisfaction and risk for provider- or staff-directed verbal and physical aggression. Risk assessment and control measures should look at multiple factors, such as workplace design and organization, patient factors, physician factors, and the social context.[50]

Risk control measures need to focus on modifying the environment and work policies to reduce provocation and remove excuses for disruptive or potentially violent patient behaviors. The physical environment of the ED or other healthcare setting should have adequate lighting, a comfortable waiting area, physical barriers and panic buttons for receptionists or triage personnel, video cameras, auto-locking doors, and sufficient exit routes. Metal detectors are used for screening in some EDs, although there is little evidence to suggest that they mitigate violent behavior.[50]

Violence prevention programs, such as those through the Occupational Health and Safety Administration, use a multi-dimensional approach that emphasizes management commitment and employee participation, worksite analysis, hazard prevention and control, safety and health training, and record-keeping and program evaluation.[51] Critical topics on which the ED staff should be trained include understanding the risk factors that lead to patient agitation and violence, early recognition of agitation and escalating behaviors, ways to de-escalate agitated or hostile patients (or those with them), self-defense procedures, progressive behavior control methods and the proper and safe application of restraints when necessary, and the appropriate use of anxiolytic and sedative medications.

Management and Disposition

Once the agitated patient has been evaluated both psychiatrically and medically, and following acute interventions if needed, the emergency physician ultimately must decide what further treatments may be necessary, and then decide on an appropriate disposition. In patients who are delirious, the underlying conditions causing the delirium, such as infectious disease, traumatic injury, and cardiac emergencies, should be sought out and treated.

Patients experiencing agitation from a potentially life-threatening withdrawal syndrome, such as complicated alcohol or benzodiazepine withdrawal, should receive appropriate pharmacologic interventions, such as parenteral benzodiazepines or dexmedetomidine (Precedex).

Once the underlying cause has been detected and initial medical management has begun, the patient then can be hospitalized for further evaluation and treatment in the appropriate observation, inpatient, or intensive care unit setting.

In the patient with dementia, once it has been determined that no acute medical emergency is present, relieving agitation both acutely and longer term is paramount. The optimal management of dementia-related agitation and other neuropsychiatric problems is a combination of both pharmacologic and nonpharmacologic therapy. Multiple international geriatric and psychiatric societies recommend

non-pharmacologic interventions as first-line, with an understanding that acute agitation (as most likely is seen in the ED) often will require the use of sedative medications.[52]

Non-pharmacologic therapies come from a variety of disciplines, and include interventions such as exercise, multisensory stimulation, music, aromatherapy, animal-assisted therapy, and cognitive behavioral therapy. In dementia patients with severe agitation and aggression, electroconvulsive therapy can be used and appears to be an effective and safe option, although further study is needed.[53]

Beyond acute pharmacologic management in the ED, medications for treating dementia-related agitation include longer-term use of antidepressants, sedative/hypnotics, and neuroleptics. Finding a balance between efficacy and safety of these medications remains a challenge, especially in the elderly population whose age and medical comorbidities put them at risk of adverse effects. Increased risks of falls, strokes, oversedation, hypotension, and dysrhythmias are complications that limit the safety and tolerability of pharmacotherapy.[52]

Agitated psychiatric patients who are suicidal, homicidal, or psychotic to the point where they pose a threat to themselves or others will require psychiatric hospitalization. This may be voluntary or involuntary. When the decision has been made for involuntary hospitalization, the emergency physician will need to follow the rules and regulations of their institution and state and complete any mandatory medicolegal documents. Good documentation is essential and should include objective descriptions of the patient's behaviors and statements.

Prior to psychiatric hospitalization, the emergency physician should perform a thorough assessment to rule out acute illness or life-threatening toxidrome or overdose that would require medical admission for management. In most cases, this can be done with a careful history and physical exam.

Although some psychiatrists and mental health facilities require prerequisite laboratory work to "medically clear" patients prior to accepting them as psychiatric patients, there is little evidence that routine testing is beneficial. Testing should be medically indicated, where the emergency physician suspects that an underlying acute medical emergency is responsible for the patient presentation. Examples include cases of new-onset psychiatric symptoms in elderly patients, the presence of delirium, physical evidence of trauma, or the presence of focal neurological deficit, fever, or significant impairment resulting from exposure to drugs or toxins. The end goal is to ensure the patient is medically stable at the time of evaluation, is unlikely to medically decompensate acutely, and is appropriate for treatment in a psychiatric facility. This should be undertaken with the understanding that the psychiatric facility is likely to have comparatively limited medical resources compared to the ED or the hospital wards.[54]

In a recent study at a large tertiary care hospital, policy was modified from mandatory laboratory testing on all admitted psychiatric patients to allow emergency physicians to order tests only if they thought they were clinically indicated. Comparing before and after institution of the policy modification, the authors found a large decrease in the number of tests ordered along with a decreased ED length of stay. There was no change in the number of psychiatric patients requiring inpatient medicine consultation or transfer to the medical service, and no increase in patient death rates.[55]

Patients who refuse treatment must be assessed for decision-making capacity before the clinician either discharges or takes steps toward involuntary hospitalization. Decision-making capacity is composed of four essential components, all of which must be present:[56]

- understanding: the ability to comprehend information regarding their condition as well as the potential risks and benefits of the proposed treatment and alternatives (including no treatment);
- appreciation: the ability to apply the relevant information to one's self and own situation;
- reasoning: evidence that the person's decisions reflect the ability to engage in consequential and comparative reasoning and to rationally manipulate information;
- expression of a choice: the ability to communicate a decision, with emphasis on the notion of a "clear and consistent" choice.

Decision-making capacity is dynamic, and patients may have impaired capacity from a reversible condition (such as intoxication) and may have full decisional capacity when the condition has resolved.[57] When making disposition decisions, the emergency physician must consider the spectrum of potential outcomes from the patient's choice, based on the seriousness and severity of the presenting condition. Establishing the patient's baseline capacity is essential, and the emergency physician should attempt to gather additional information from relevant sources, including family, friends, primary care providers, or others familiar with the patient's baseline level of functioning. Providers also should maintain a low threshold for consulting with available resources, including social services and psychiatry. If the patient's decision-making capacity is unclear, it is prudent to err on the side of caution. The patient should be detained until further information and assessment can be obtained, and the emergency physician should provide thorough and objective documentation describing the patient's actions and statements and why it is believed that capacity is lacking.

References

The list of references is available online: http://bit.ly/382hllK

CME/CE Questions

1. Which entity has the highest prevalence in patients who present to the emergency department (ED) with acute agitation?
   a. Mydriasis
   b. Diaphoresis
   c. Delirium
   d. Myoclonus
2. Which metabolic abnormality is the least likely to cause acute agitation?
   a. Hypokalemia
   b. Hyponatremia
   c. Hypoglycemia
   d. Hyperglycemia

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3. Which is *not* considered a primary cause of excited delirium syndrome?
   a. Stimulant abuse
   b. Psychiatric medication withdrawal
   c. Cerebrovascular accident
   d. Psychiatric illness
4. In an acutely agitated patient presenting to the ED, after completion of a primary survey and vital sign measurements, what is the most reasonable next step?
   a. Urine drug screen analysis
   b. Point-of-care blood glucose
   c. Computerized tomography of brain
   d. Midazolam intramuscular injection
5. What is the most appropriate order for acute interventions to be completed in the ED for a patient who is agitated?
   a. Verbal de-escalation, physical restraint placement, placement into an unambiguous environment, pharmacotherapy
   b. Pharmacotherapy, placement into an unambiguous environment, physical restraint, verbal de-escalation
   c. Pharmacotherapy, verbal de-escalation, placement into an unambiguous environment, physical restraint
   d. Verbal de-escalation, placement into an unambiguous environment, physical restraint, pharmacotherapy
6. An elderly patient presents from an extended care facility (ECF) with the chief complaint of agitation. Emergency medical services notes state that the ECF staff said the patient normally is oriented and pleasant, but now is confused and struck at one of their nurses. Vital signs reveal a temperature of 38.4˚C. You suspect infection. What is the next step in your care?
   a. Administer broad-spectrum antibiotics.
   b. Obtain two sets of blood cultures.
   c. Perform a thorough physical exam seeking the source.
   d. Obtain a viral nasal swab.
7. Chronic alcohol and benzodiazepine abuse leads to:
   a. decreased production of glutamate.
   b. down-regulation of gamma aminobutyric acid (GABA) receptors.
   c. up-regulation of GABA receptors.
   d. decreased serotonin activity at the 5-HT2 receptor.
8. Which physical restraint position is most often associated with aspiration?
   a. Supine
   b. Lateral decubitus
   c. Prone
   d. Reverse Trendelenburg
9. Advantages of benzodiazepines in treating acute agitation include:
   a. a synergistic effect when combined with antipsychotics.
   b. rapid absorption when administered intranasally.
   c. airway preservation when administered in high doses.
   d. inability for serial dosing use.
10. Which of the following is *not* an essential component of decision-making capacity?
    a. Understanding
    b. Competence
    c. Appreciation
    d. Expression of choice

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CME/CE Objectives

Upon completion of this educational activity, participants should be able to:

- recognize specific conditions in patients presenting to the emergency department;
- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both the likely and rare complications that may be associated with the particular medical problems discussed in the publication.

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References

1. Nordstrom K, Zun LS, Wilson MP, et al. Medical evaluation and triage of the agitated patient: Consensus statement of the American Association for Emergency Psychiatry Project BETA Medical Evaluation Workgroup. *West J Emerg Med* 2012;13:3-10.
2. Miner JR, Klein LR, Cole JB, et al. The characteristics and prevalence of agitation in an urban county emergency department. *Ann Emerg Med* 2018;72:361-370.
3. Wong AH, Taylor RA, Ray JM, Bernstein SL. Physical restraint use in adult patients presenting to a general emergency department. *Ann Emerg Med* 2019;73:183-192.
4. Gonin P, Beysard N, Yersin B, Carron PN. Excited delirium: A systematic review. *Acad Emerg Med* 2018;25:552-565.
5. Vilke GM, DeBard ML, Chan TC, et al. Excited delirium syndrome (ExDS): Defining based on a review of the literature. *J Emerg Med* 2012;43:897-905.
6. Gacki-Smith J, Juarez AM, Boyett L, et al. Violence against nurses working in US emergency departments. *J Nurs Admin* 2009;39:340-349.
7. Omar H, Yue R, Amen AA, et al. Reassessment of violence against emergency physicians. *Ann Emerg Med* 2018;72:s144.
8. Emond M, Boucher V, Carmichael PH, et al. Incidence of delirium in the Canadian emergency department and its consequences on hospital length of stay: A prospective observational multicentre cohort study. *BMJ Open* 2018;8:e018190.
9. Brooke MM, Questad KA, Patterson DR, Bashak KJ. Agitation and restlessness after closed head injury: A prospective study of 100 consecutive admissions. *Arch Phys Med Rehabil* 1992;73:320.
10. Barichello T, Generoso JS, Milioli G, et al. Pathophysiology of bacterial infection of the central nervous system and its putative role in the pathogenesis of behavioral changes. *Braz J Psychiatry* 2013;35:81-87.
11. Najjar S, Jajjar A, Chong DJ, et al. Central nervous system complications associated with SARS-CoV-2 infection: Integrative concepts of pathophysiology and case reports. *J Neuroinflammation* 2020;17:231.
12. Gotts JE, Matthay MA. Sepsis: Pathophysiology and clinical management. *BMJ* 2016;353:i1585.
13. Chung HY, Wickel J, Brunkhorst FM, Geis C. Sepsis-associated encephalopathy: From delirium to dementia? *J Clin Med* 2020;9:703.
14. Braun MM, Barstow CH, Pyzocha NJ. Diagnosis and management of sodium disorders: Hyponatremia and hypernatremia. *Am Fam Physician* 2015;5:299-310.
15. Meng QH, Wagar EA. Laboratory approaches for the diagnosis and assessment of hypercalcemia. *Crit Rev Clin Lab Sci* 2015;52:107-119.
16. Rosenbaum C, Bird SB. Timing and frequency of physostigmine redosing for antimuscarinic toxicity. *J Med Toxicol* 2010;6:386-392.
17. Frithsen IL, Simpson WM Jr. Recognition and management of acute medication poisoning. *Am Fam Physician* 2010;81:316-323.
18. Isbister GK, Heppell SP, Page CB, Ryan NM. Adult clonidine overdose: Prolonged bradycardia and central nervous system depression, but not severe toxicity. *Clin Toxicol* 2017;55:187-192.
19. Palmer BF, Clegg DJ. Salicylate toxicity. *N Engl J Med* 2020;382:2544-2555.
20. Cornell S. Key considerations in pharmacotherapy for type 2 diabetes mellitus: A multiple target organ approach. *J Clin Pharm Therapeutics* 2012;37:254-259.
21. Tang Y, Martin NL, Cotes RO. Cocaine-induced psychotic disorders: Presentation, mechanism, and management. *J Dual Diagn* 2014;10:98-105.
22. Yu S, Zhu Q, Bai X, Di X. Recent advances in methamphetamine neurotoxicity mechanisms and its molecular pathophysiology. *Behav Neurol* 2015;2015:1-11.
23. Lodge D, Mercier MS. Ketamine and phencyclidine: The good, the bad and the unexpected. *Br J Pharmacol* 2015;172:4254-4276.
24. Tidwell WP, Thomas TL, Pouliot JD, et al. Treatment of alcohol withdrawal syndrome: Phenobarbital vs CIWA-Ar protocol. *Am J Crit Care* 2018;27:454-460.
25. Liebrenz M, Gehring MT, Buadze A, Caflisch C. High-dose benzodiazepine dependence: A qualitative study of patients' perception on cessation and withdrawal. *BMC Psychiatry* 2015;15:116.
26. Fatani BZ, Aldawod R, Alhawaj A, et al. Schizophrenia: Etiology, pathophysiology and management - A review. *Egyptian J Hosp Med* 2017;69:2640-2646.
27. Shim IH, Woo YS, Kim MD, Bahk WM. Antidepressants and mood stabilizers: Novel research avenues and clinical insights for bipolar depression. *Int J Mol Sci* 2017;18:2406.
28. Dmitrzak-Weglarz M, Reszka E. Pathophysiology of depression: Molecular regulation of melatonin homeostasis – current status. *Neuropsychobiology* 2017;76:117-129.
29. Vilke GM, Mash DC, Pardo M, et al. EXCITATION study: Unexplained in-custody deaths: Evaluating biomarkers of stress and agitation. *J Forensic Leg Med* 2019;66:100-106.
30. Ho JD, Dawes DM, Nelson RS, et al. Acidosis and catecholamine evaluation following simulated law enforcement "use of force" encounters. *Acad Emerg Med* 2010;17:e60-e68.
31. Ho JD, Dawes DM, Nystrom PC, et al. Markers of acidosis and stress in a sprint versus a conducted electrical weapon. *Forensic Sci Int* 2013;233:84-89.
32. Wackernah RC, Minnick MJ, Clapp P. Alcohol use disorder: Pathophysiology, effects, and pharmacologic options for treatment. *Subst Abuse Rehabil* 2014;23:1-12.
33. Giacomantonio C, Goodwin S, Carmichael G. Learning to de-escalate: Evaluating the behavioural impact of Verbal Judo training on police constables *Police Practice and Research* 2019;21:401-417.
34. Lanthén K, Rask M, Sunnqvist C. Psychiatric patients experiences with mechanical restraints: An interview study. *Psychiatry J* 2015;2015:748392.
35. Mohr WK, Petti TA, Mohr BD. Adverse effects associated with physical restraint. *Can J Psychiatry* 2003;48:330-337.
36. Hall C, Votova K, Heyd C, et al. Restraint in police use of force events: Examining sudden in custody death for prone and not-prone positions. *J Forensic Leg Med* 2015;31:29-35.
37. Taylor C. Vascular neck restraints: An evaluation of the tactical use for law enforcement defensive tactics programs. Henderson Police Department Henderson, Texas. 2017. http://hdl.handle.net/20.500.11875/2270
38. Ishida T, Katagiri T, Uchida H, et al. Incidence of deep vein thrombosis in restrained psychiatric patients. *Psychosomatics* 2014;55:69-75.
39. Schnitzer K, Merideth F, Macias-Konstantopoulos W, et al. Disparities in care: The role of race on the utilization of physical restraints in the emergency setting. *Acad Emerg Med* 2020;27:943-950.
40. Vilke GM, Bozeman WP, Dawes DM, et al. Excited delirium syndrome (ExDS): Treatment options and considerations. *J Forensic Leg Med* 2012;19:117-121.
41. Macht M, Mull AC, McVaney KE, et al. Comparison of droperidol and haloperidol for use by paramedics: Assessment of

safety and effectiveness. *Prehosp Emerg Care* 2014;18:375-380.

42. Perkins J, Ho JD, Vilke GM, DeMers G. American Academy of Emergency Medicine Position Statement: Safety of droperidol use in the emergency department. *J Emerg Med* 2015;49:91-97.
43. Isenberg DL, Jacobs D. Prehospital Agitation and Sedation Trial (PhAST): A randomized control trial of intramuscular haloperidol versus intramuscular midazolam for the sedation of the agitated or violent patient in the prehospital environment. *Prehosp Disaster Med* 2015;30:491-495.
44. Riddell J, Tran A, Bengiamin R, et al. Ketamine as a first-line treatment for severely agitated emergency department patients. *Am J Emerg Med* 2017;35:1000-1004.
45. Ho JD, Smith SW, Nystrom PC, et al. Successful management of excited delirium syndrome with prehospital ketamine: Two case examples. *Prehosp Emerg Care* 2013;17:274-279.
46. Scheppke KA, Braghiroli J, Shalaby M, Chait R. Prehospital use of i.m. ketamine for sedation of violent and agitated patients. *West J Emerg Med* 2014;15:736.
47. Lin J, Figuerado Y, Montgomery A, et al. Efficacy of ketamine for initial control of acute agitation in the emergency department: A randomized study. *Am J Emerg Med* 2020; Apr 11. doi: 10.1016/j.ajem.2020.04.013. [Online ahead of print].
48. Kupas DF, Wydro GC, Tan DK, et al. Clinical care and restraint of agitated or combative patients by emergency medical services practitioners. National Association of EMS Physicians. https://naemsp.org/NAEMSP/media/NAEMSP-Documents/Clinical-Care-and-Restraint-of-Agitated-or-Combative-Patients.pdf
49. Gonin P, Beysard N, Yersin B, Carron PN. Excited delirium: A systematic review. *Acad Emerg Med* 2018;25:552-565.
50. Raveel A, Schoenmakers B. Interventions to prevent aggression against doctors: A systematic review. *BMJ Open* 2019;9:e028465.
51. U.S. Department of Labor, Occupational Safety and Health Administration. *Guidelines for Preventing Workplace Violence for Healthcare and Social Service Workers*. 2016. https://www.osha.gov/Publications/osha3148.pdf
52. Ijaopo EO. Dementia-related agitation: A review of non-pharmacological interventions and analysis of risks and benefits of pharmacotherapy. *Transl Psychiatry* 2017;7:e1250.
53. van den Berg JF, Kruithof HC, Kok RM, et al. Electroconvulsive therapy for agitation and aggression in dementia: A systematic review. *Am J Geriatr Psychiatry* 2018;26:419-434.
54. Thrasher TW, Rolli M, Redwood RS, et al. 'Medical clearance' of patients with acute mental health needs in the emergency department: A literature review and practice recommendations. *WMJ* 2019;118:156-163.
55. Zwank MD, Rupp PE, Salzman JG, et al. Elimination of routine screening laboratory tests for psychiatric admission: A quality improvement initiative. *Psychiatr Serv* 2020;71:1252-1259.
56. Palmer BW, Harmell AL. Assessment of healthcare decision-making capacity. *Arch Clin Neuropsychol* 2016;31:530-540.
57. Marco CA, Brenner JM, Kraus CK, et al. Refusal of emergency medical treatment: Case studies and ethical foundations. *Ann Emerg Med* 2017;70:696-703.

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Differential Diagnosis of Agitation

Organic	Look For	Workup
Traumatic brain injury	History/physical signs of trauma, focal neurologic deficits, Cushing's triad	Rapid neuroimaging
Central nervous system infection	Fever, nuchal rigidity, delirium, seizures	Neuroimaging (especially if focal deficits are present), lumbar puncture, and cerebrospinal fluid studies
Sepsis	Fever or hypothermia, delirium, hypotension, tachycardia	Thorough evaluation seeking source, followed by appropriate laboratory tests, imaging, and cultures
Respiratory failure	History of chronic obstructive pulmonary disease or other pulmonary disease, hypoxia, agitation followed by somnolence	Pulse oximetry, blood gas
Dementia	History of vascular disease/stroke, advanced age, history of dementia	Thorough evaluation to rule out acute illness exacerbating preexisting dementia
Inorganic	**Look For**	**Workup**
Acute poisoning toxidrome	Signs/symptoms of toxidrome (especially salicylate, sympathomimetic, and anticholinergic)	Serum toxin levels where appropriate, electrolytes and renal function; intervention often based on presenting signs/symptoms rather than laboratory tests
Acute withdrawal	History of opioid, benzodiazepine, or alcohol abuse	Serum alcohol levels (suspect withdrawal when levels are low), intervention often based on presenting signs/symptoms rather than laboratory tests
Hypoglycemia	History of diabetes, recent medication changes	Bedside serum glucose monitoring
Other Causes	**Look For**	**Workup**
Exacerbation of mental illness	History of depression, bipolar disorder, schizophrenia; medication changes or non-compliance; acute stressors	Evaluation for underlying organic or inorganic disease if indicated by history or physical
Excited delirium syndrome	History of mental illness, substance abuse, or both; severe agitation combined with delirium; hyperthermia	Thorough medical evaluation and supportive care after sedation has been achieved; be wary of sudden collapse/death

Stepwise Approach to the Agitated/Violent Patient

I. De-escalation and Environmental Modification
- Engage and establish a verbal loop. Ask questions like "How can I help you?"
- Actively listen to and acknowledge the patient's responses.
- Place patient in a calm, non-threatening environment.

II. Physical Restraint
- Use the minimal amount of restraint necessary to control the patient.
- Consider adjunctive use of medications.
- Remember that restraints enhance the patient's fear and sense of loss of control.
- Remain empathetic and provide continued verbal reassurance.
- Frequently monitor any restrained patient for signs of medical decompensation.

III. Pharmacotherapy
- Administer benzodiazepines and antipsychotics alone or in combination.
- Consider ketamine for violent patients who present an immediate risk to themselves and others.

IV. Reassess and Reexamine
- Frequently reassess effectiveness of interventions.
- As soon as feasible, begin monitoring vital signs to include temperature.
- Reexamine patient frequently until they are calm and controllable.
- Be on the alert for signs of toxidromes, excited delirium syndrome, or life-threatening medical illness.

Pharmacologic Options for Acutely Agitated Patients

Agent	Pros	Cons	Typical Initial Adult Dose
Benzodiazepines	Serial dosing, rapid onset, multiple routes of administration (IM, IN, IV)	Respiratory depression in high doses, slow onset when given IN	• Lorazepam 2 mg to 4 mg IM • Midazolam 2 mg to 5 mg IM
Antipsychotics	Safe and effective; may be used in conjunction with benzodiazepines	Slow onset, extrapyramidal side effects, QT prolongation in higher doses (although clinical relevance is contested)	• Haloperidol 5 mg to 10 mg IM • Droperidol 2.5 mg to 5 mg IM • Olanzapine 5 mg to 10 mg IM
Dissociative agent (ketamine)	Rapid and effective sedation, IV or IM administration, excellent safety profile	Laryngospasm (rare), emergence reactions, prolonged sedation following high doses	• Ketamine 5 mg/kg IM*

IM = intramuscular; IN = intranasal; IV = intravenous

* Not Food and Drug Administration approved for this indication

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Authors: Brian L. Springer, MD, FACEP, Associate Professor and Vice Chair, Wright State University Department of Emergency Medicine, Dayton, OH; and Daniel Silver, DO, Emergency Medicine Resident, Wright State University, Dayton, OH.