



White Paper Report on Excited Delirium Syndrome

ACEP Excited Delirium Task Force

September 10, 2009

EXCITED DELIRIUM TASK FORCE

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Excited Delirium Task Force White Paper Report to the Council and Board of Directors September 10, 2009

PREAMBLE

The 2008 Council of the American College of Emergency Physicians (ACEP) adopted Amended Resolution 21(08), “Excited Delirium,” which was then adopted by the ACEP Board of Directors:

“RESOLVED, that ACEP study:

1. The existence of “excited delirium” as a disease entity (or not);
2. Characteristics that help identify the presentation and risk for death; and
3. Current and emerging methods of control and treatment.

And be it further RESOLVED,

That ACEP develop and disseminate a white paper on findings to appropriate entities (e.g., EMS, law enforcement).”

INTRODUCTION

In response to this resolution, ACEP convened a Task Force of nineteen experts in what the Task Force has chosen to call Excited Delirium Syndrome (ExDS). Eighteen of these experts are emergency physician members of ACEP and one is a PhD researcher. The Task Force was charged to examine the available literature and existing data and use their expert experience and consensus to determine:

1. if the entity commonly referred to as “excited delirium” exists, and
2. if so, whether it could be better defined, identified, and treated.

It is the consensus of the Task Force that ExDS is a unique syndrome which may be identified by the presence of a distinctive group of clinical and behavioral characteristics that can be recognized in the pre-mortem state. ExDS, while potentially fatal, may be amenable to early therapeutic intervention in some cases.

The term “Excited Delirium” has been used to refer to a subcategory of delirium that has primarily been described retrospectively in the medical examiner literature. Over time, the concept of excited delirium has made its way into the emergency medicine, psychiatric, law enforcement, prehospital and medicolegal literature. It has generally been used to describe a small group of patients with a set of symptoms that has eluded a unifying, prospective clinical definition. The Task Force debated the merits of renaming the syndrome in a medically more descriptive way. However, it was decided that the literature and general understanding in the health care and law enforcement fields of the term “Excited Delirium” favored retention of the traditionally understood word for research and clinical purposes. It was incorporated into the described syndrome as “Excited Delirium Syndrome (ExDS).”

The difficulty surrounding the clinical identification of ExDS is that the spectrum of behaviors and signs overlap with many clinical disease processes. ExDS is not intended to include these diseases, except insofar as they might meet the definition of ExDS. Treatment interventions targeted at one of these alternate diagnoses may potentially alleviate or exacerbate ExDS, thus further confounding the diagnosis. Faced with the lack of a clear definition and cause, the decision to identify ExDS as a syndrome instead of a unique disease is similar to the dec-

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ades-long controversy over the causes of Sudden Infant Death Syndrome.

Despite increased research, the exact pathophysiology of ExDS remains unidentified. Some recent research in the area of fatal ExDS points to dopamine transporter abnormalities. Eventually, there might be found a genetic susceptibility, an enzyme excess or deficiency, an overdose or withdrawal state, or some other multifactorial trigger, including a variety of medical and psychiatric conditions.

At present, physicians and other medical and non-medical personnel involved in personal interactions with these patients do not have a definitive diagnostic “test” for ExDS. It must be identified by its clinical features. This also makes it is very difficult to ascertain the true incidence of ExDS.

While not universally fatal, it is clear that a proportion of patients with ExDS progress to cardiac arrest and death. It is impossible at present to know how many patients receive a therapeutic intervention that stops the terminal progression of this syndrome. While many of the current deaths from ExDS are likely not preventable, there may be an unidentified subset in whom death could be averted with early directed therapeutic intervention.

In this paper, the Task Force provides a review of the history and epidemiology of ExDS, clinical perspectives, and a discussion of its potential pathophysiology, diagnostic characteristics, differential diagnoses, and clinical treatment. Ultimately, the goals are to raise awareness of the existence of this syndrome to medical and public entities, to aid law enforcement, Emergency Medical Service (EMS) personnel, physicians, health care providers, corrections officers and others in the recognition of ExDS, and to identify best practices to deal with this true medical emergency.

HISTORY

For more than 150 years, there have been case reports that do not use the exact term “excited delirium,” yet describe a similar constellation of symp-

toms and features. These cases discuss clinical behavior and outcomes that are strikingly similar to the modern day concept of ExDS.

These historical cases occurred primarily within institutions that housed mentally disturbed individuals in protective custody largely because of the lack of effective pharmacologic treatment available during that time period. The behavior seen in these cases has been called “Bell’s Mania,” named after Dr. Luther Bell, the primary psychiatrist at the McLane Asylum for the Insane in Massachusetts. Dr. Bell was the first to describe a clinical condition that took the lives of over 75% of those suffering from it. Based on the clinical features and outcomes of the institutionalized cases from the 1800s when compared to the presently accepted criteria known to accompany ExDS, it is believed that Bell’s Mania may be related to the syndrome of ExDS that we witness today.

Historical research indicates that the worrisome behaviors and deaths following uncontrolled psychiatric illness described in the 1800s seemed to decline drastically by the mid-1950s. This is largely attributed to the advent of modern antipsychotic pharmaceutical therapy that changed psychiatric practice from one of custodial patient control to a goal of de-institutionalization and patient placement within normal community settings.

There is only one reference before 1985 known to mention the exact term “Excited Delirium.” In this reference, the words “excited” and “delirium” were combined to describe the condition of a patient just prior to death following a hemorrhoid operation by an accomplished surgeon. At the time, it was felt that the operation somehow damaged the patient’s nervous system, and lead to acute psychiatric decompensation and death.

In the 1980s, there was a dramatic increase in the number of reported cases with behavior similar to an uncontrolled psychiatric emergency. While some seemed to be unchecked psychiatric disease, most of these cases were found to be associated with the introduction and abuse of cocaine in North America. Since then, this connection between ExDS and co-

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caine has continued. Additionally, ExDS has now been recognized to occur in association with other illicit drugs of abuse, as well as with certain types of mental illness and their associated treatment medications.

Before 1985, there was no single unifying term to describe the clinical pattern seen in these patients. In 1985 a subset of cocaine deaths was described by Wetli and Fishbain in a seminal paper which for the first time used the term “excited delirium.”

The typical course of a published ExDS patient involves acute drug intoxication, often a history of mental illness (especially those conditions involving paranoia), a struggle with law enforcement, physical or noxious chemical control measures or electrical control device (ECD) application, sudden and unexpected death, and an autopsy which fails to reveal a definite cause of death from trauma or natural disease.

As a consequence of the circumstances surrounding the death and the lack of a definitive cause on autopsy, there has been continued debate about the validity of the term “excited delirium.” This debate continues today. There are those who believe it to be a convenient term used to excuse and exonerate authorities when someone dies while in their custody. It is articulated by some that ExDS is a term or concept that has been “manufactured” as a law enforcement conspiracy or cover-up for brutality.

This argument mainly centers on the fact that most organized medical associations (e.g., American Medical Association) and medical coding reference materials (e.g., International Classification of Diseases, Ninth Revision, or ICD-9) do not recognize the exact term “excited delirium” or “excited delirium syndrome.” The countering argument is that there are organized medical associations that do recognize ExDS as an entity (e.g., National Association of Medical Examiners) and references such as the ICD-9 contain several codes that can be used to describe the same entity as ExDS, albeit with different wording such as:

- 296.00S Manic Excitement

- 293.1J Delirium of Mixed Origin
- 292.81Q Delirium, drug induced
- 292.81R Delirium, induced by drug
- 307.9AD Agitation
- 780.09E Delirium
- 799.2AM Psychomotor Excitement
- 799.2V Psychomotor Agitation
- 799.2X Abnormal Excitement

This issue of semantics does not indicate that ExDS does not exist, but it does mean that this exact and specific terminology may not yet be accepted within some organizations or references.

EPIDEMIOLOGY

The exact incidence of ExDS is impossible to determine as there is no current standardized case definition to identify ExDS. In addition, since ExDS is mainly discussed in the forensic literature and is a diagnosis of exclusion established on autopsy, there is little documentation about survivors of the syndrome. A published observational study suggests that the incidence of death among patients manifesting signs and symptoms consistent with ExDS is 8.3%. Some Task Force members have cared for multiple individual patients with ExDS who have survived.

Stimulant drug use, including cocaine, methamphetamine, and PCP, demonstrates a well established association with ExDS and is usually associated with cases of ExDS death.

A review of the literature reveals common characteristics among patients identified post-mortem as suffering from ExDS. More than 95% of all published fatal cases are males with a mean age of 36. These subjects are hyperaggressive with bizarre behavior, and are impervious to pain, combative, hyperthermic and tachycardic. There is typically a struggle with law enforcement that involves physical, noxious chemical, or ECD use followed by a period of quiet and sudden death. The majority of

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cases involve stimulant abuse, most commonly cocaine, though methamphetamine, PCP, and LSD have also been described. At least in the setting of cocaine use, the episode of ExDS usually appears to occur in the context of a cocaine binge that follows a long history of cocaine abuse.

Persons with psychiatric illnesses comprise the second largest but a distinctly smaller cohort of ExDS cases and deaths. The literature on ExDS frequently cites abrupt cessation of psychotherapeutic medications as a cause. This raises the question of whether the behavioral changes seen in this context represent withdrawal syndromes characteristic of the medications involved, central nervous system adaptations to medications, or recrudescence of underlying disease. Since medication noncompliance is common in psychiatric patients, health care providers should be aware of this potential cause of delirium-like behavior. Less commonly, persons with new-onset psychiatric disease (mania or psychosis) will present with ExDS. In most cases, the underlying disease will be untreated at the time of presentation, but in some cases the disease may be partially treated or mistreated.

Over a two-year period, presence or absence of 10 potential clinical features of ExDS was recorded by Canadian police for over 1 million police-public interactions (C. Hall, personal communication).

Of the 698 encounters involving use of force, 24 probable cases were identified, based upon the presence of perceived abnormal behavior and at least 6 of 10 potential clinical criteria for ExDS. These represent 3.4% (or 2-5%) of the use of force cohort. For the individuals manifesting 7 or more features including tactile hyperthermia, **Table 1** lists the occurrence of all 10 potential features with their frequencies and 95% confidence intervals. (Note that the oft-reported mirror or glass attraction is rather infrequent). These represent 2.7% (or 1-3.5%) of the use of force cohort, a not inconsequential number given the potential for sudden unexpected death.

Although no deaths occurred in this collection period, the 97.5% one sided confidence interval for

the absence of death still implies that up to 14% of these individuals could experience sudden death, a number in line with the previously mentioned and published observational study.

Table 1: ExDS Prehospital Potential Features and Frequencies with 95% Confidence Intervals

<u>FEATURE</u>	<u>FREQUENCY</u> <u>% (95% CI)</u>
Pain Tolerance	100 (83-100)
Tachypnea	100 (83-100)
Sweating	95 (75-100)
Agitation	95 (75-100)
Tactile Hyperthermia	95 (75-100)
Police Noncompliance	90 (68-99)
Lack of Tiring	90 (68-90)
Unusual Strength	90 (68-90)
Inappropriately Clothed	70 (45-88)
Mirror/Glass Attraction	10

PATHOPHYSIOLOGY

The pathophysiology of ExDS is complex and poorly understood. The fundamental manifestation is delirium. There are several different potential underlying associations or causes, including stimulant drug abuse, psychiatric disease, psychiatric drug withdrawal, and metabolic disorders. Unknown mechanisms lead from these conditions to the overt ExDS state. Specific manifestations vary among different cases. We do not fully understand why some cases progress to death and why some do not.

Although our knowledge concerning the etiology and pathophysiology of ExDS is limited, basic science and clinical studies have provided some insight. Stimulant drug use, especially cocaine, is associated with ExDS. Of note, post-mortem toxicological analysis of fatal cocaine-associated ExDS patients demonstrates cocaine concentrations similar to those found in recreational drug users and less

than those noted in acute cocaine intoxication deaths, suggesting a different mechanism of death.

Subsequent anatomic and molecular characterization of this group of fatal ExDS patients has focused primarily on postmortem brain examination. Results from this increasingly robust body of work demonstrate a characteristic loss of the dopamine transporter in the striatum of chronic cocaine abusers who die in police custody from apparent ExDS. This suggests that one potential pathway for the development of ExDS is excessive dopamine stimulation in the striatum, but the significance of this in the larger context of ExDS unrelated to chronic cocaine abuse remains unknown.

Making a central dopamine hypothesis more appealing is the fact that hypothalamic dopamine receptors are responsible for thermoregulation. Disturbances of dopamine neurotransmission may help explain the profound hyperthermia noted in many ExDS patients. Post-mortem studies in these patients have demonstrated elevated levels of heat shock proteins (HSP). The central dopamine hypothesis also provides a link to psychiatric etiologies of ExDS.

While the specific precipitants of fatal ExDS remain unclear, epidemiologic and clinical reports provide some understanding of the underlying pathophysiology. When available, cardiac rhythm analysis demonstrates bradycardia; ventricular dysrhythmias are rare, occurring in only a single patient in one study. The majority of lethal ExDS patients die shortly after a violent struggle. Severe acidosis appears to play a prominent role in lethal ExDS-associated cardiovascular collapse.

While attention has focused largely upon cases of fatal ExDS in humans, it must be noted that a similar syndrome, termed capture myopathy, has been reported in the veterinary literature. Clinically, it is characterized by prolonged neuromuscular activity, acidosis, and rhabdomyolysis.

CLINICAL PERSPECTIVES

Law Enforcement

In modern times, a law enforcement officer (LEO) is often present with a person suffering from ExDS because the situation at hand has degenerated to such a degree that someone has deemed it necessary to contact a person of authority to deal with it. LEOs are in the difficult and sometimes impossible position of having to recognize this as a medical emergency, attempting to control an irrational and physically resistive person, and minding the safety of all involved.

Given the irrational and potentially violent, dangerous, and lethal behavior of an ExDS subject, any LEO interaction with a person in this situation risks significant injury or death to either the LEO or the ExDS subject who has a potentially lethal medical syndrome. This already challenging situation has the potential for intense public scrutiny coupled with the expectation of a perfect outcome. Anything less creates a situation of potential public outrage. Unfortunately, this dangerous medical situation makes perfect outcomes difficult in many circumstances.

It is important for LEOs to recognize that ExDS subjects are persons with an acute, potentially life-threatening medical condition. LEOs must also be aware that remorse, normal fear and understanding of surroundings, and rational thoughts for safety are absent in such subjects.

ExDS subjects are known to be irrational, often violent and relatively impervious to pain. Unfortunately, almost everything taught to LEOs about control of subjects relies on a suspect to either be rational, appropriate, or to comply with painful stimuli. Tools and tactics available to LEOs (such as pepper spray, impact batons, joint lock maneuvers, punches and kicks, and ECD's, especially when used for pain compliance) that are traditionally effective in controlling resisting subjects, are likely to be less effective on ExDS subjects.

When methods such as pain compliance maneuvers or tools of force fail, the LEO is left with few op-

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tions. It is not feasible for them to wait for the ExDS subject to calm down, as this may take hours in a potentially medically unstable situation fraught with scene safety concerns.

Some of the goals of LEOs in these situations should be to 1) recognize possible ExDS, contain the subject, and call for EMS; 2) take the subject into custody quickly, safely, and efficiently if necessary; and 3) then immediately turn the care of the subject over to EMS personnel when they arrive for treatment and transport to definitive medical care.

LEOs should be trained to recognize and manage subjects with ExDS. Officers should attempt to ensure that the tactile temperature of these subjects is documented and request EMS to measure it. In fatal cases, a significantly elevated temperature may suggest that a life-threatening disease or condition was present, and that the death was independent of the police intervention.

Emergency Medical Services

EMS dispatch personnel need to recognize clues from calls or radio traffic that personnel may be responding to a case of ExDS. This should trigger multiple law enforcement personnel responding in addition to EMS.

EMS personnel need to be trained in the recognition of the signs and symptoms of ExDS. They are in a difficult position because they need to recognize the heightened personal safety risks that ExDS subjects represent to them but they also have a duty to provide timely care. They need to understand and practice their expected interaction with LEOs.

It is the role of LEOs to control the person with potential ExDS. However, as soon as control has been obtained, it is the role of EMS to recognize that this is a medical emergency and to assume responsibility for assessment and care of the patient.

Emergency Department (ED)

Emergency Physicians (EP's) should be educated about the clinical features of ExDS and should in-

clude this in the differential diagnosis of any patient with altered mental status and agitation (either at the time of presentation or by history). There should be an increased index of suspicion for ExDS in agitated patients that present in the custody of law enforcement; however, this is a clinical entity that can enter the ED from any source (EMS, Law Enforcement, ED triage, etc).

EP's should recognize that this syndrome seems to be a multifactorial interaction of delirium and agitation, leading to hyperthermia and profound acidemia, often in the setting of stimulant drug abuse. Regardless of etiology, ExDS may be fatal in some patients. EP's should consider the possibility of ExDS in the evaluation of younger patients that present in cardiac arrest, especially in the setting of profound metabolic acidosis and hyperthermia. The physician should also initiate the documentation of clinical signs and the collection of specimens for research and diagnosis.

Medical Examiners

Medical Examiners are often required to render a decision as to the cause of death in cases that involve patients in police custody with multiple confounding variables such as pre-existing health conditions, concomitant illicit substance use, and underlying psychiatric conditions. Lack of complete prior medical information, especially underlying cardiac and metabolic pathology, hampers the ascertainment of the actual cause of death when only autopsy results are interpreted.

For example, an unknown case of Brugada syndrome (a genetic abnormality of sodium ion channels leading to sudden death from ventricular fibrillation) may be the actual cause of cardiac arrest in an individual under the influence of cocaine, even absent excessive LEO force. Without prior electrocardiograms, this condition would be entirely missed. Likewise, premortem potassium and glucose levels, and even basic vital signs (temperature and blood pressure) cannot possibly be investigated via autopsy.

The importance of a skilled investigation of the

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scene of death cannot be overestimated. Crucial information such as subject behavior, drug use history, a history or presence of psychosis, or the presence of hyperthermia, can facilitate the determination of whether the clinical features of ExDS were present.

The time, quantity, and chronicity of drug ingestion cannot always be reliably determined by toxicology alone. Significant postmortem redistribution of drugs makes interpretation of blood levels found at autopsy fraught with speculation. Tolerance to many drugs of abuse can confound interpretation of blood or tissue levels. Specific drug levels may not correlate with acute drug toxicity or poisoning. While the majority of cases of ExDS appear to occur in the presence of or with a history of cocaine or other stimulants, their presence is not required for this syndrome to occur. Psychiatric cases not involving drugs of abuse have been reported. There is no current gold standard test for the diagnosis of ExDS. The presence of the hallmark clinical findings along with the presence of some type of centrally acting stimulant strongly suggests the diagnosis. Current understanding of pathophysiology suggests that the collection of various specimens (particularly brain tissue in fatal cases) is beneficial both for potential diagnosis confirmation and research.

CLINICAL CHARACTERISTICS

Because ExDS resulting in death does not currently have a known specific etiology or a consistent single anatomic feature, it can only be described by its epidemiology, commonly described clinical presentation, and usual course. The minimum features for ExDS to be considered include the presence of both delirium and an excited or agitated state. As described in the DSM-IV-R, the features of delirium are constant and defined by a disturbance of consciousness (reduced clarity of the awareness of the environment) with reduced ability to focus, sustain or shift attention. The perceptual disturbance develops over a short period of time (usually hours to days), may fluctuate during the course of a day, and is not accounted for by underlying dementia.

Because of varied underlying medical conditions that may generate ExDS, there is also variation in the specific symptom cluster. As in any disorder that affects mental status, there is no assumption that each subject's presentation will occur as a completely discrete entity with absolute boundaries. The consistency lies with subjects who are delirious with evidence of psychomotor and physiologic excitation.

The combination of delirium, psychomotor agitation, and physiologic excitation differentiates ExDS from other processes that induce delirium only. Similarly, subjects who are agitated or violent but who do not also demonstrate features of delirium simply do not meet the definition of ExDS.

Until wider recognition of ExDS began, most publications about it were found in the forensic pathology literature and there was little publication interest in cases of ExDS that did not end catastrophically. The high reported frequency of death is likely increased by measurement and reporting bias since pathologists who first identified the unifying prodrome of ExDS that leads to sudden unexpected death necessarily encountered only those subjects who died. At least one author (a forensic pathologist) describes the combination of a prodrome of excited delirium plus unanticipated sudden death as "excited delirium syndrome," with invocation of the term syndrome only if the subject died.

When death occurs, it occurs suddenly, typically following physical control measures (physical, noxious chemical, or electrical), and there is no clear anatomic cause of death at autopsy. In cases in which a subject dies following the application of control measures, many or most of the following features are found:

- male subjects, average age 36
- destructive or bizarre behavior generating calls to police,
- suspected or known psychostimulant drug or alcohol intoxication,
- suspected or known psychiatric illness,
- nudity or inappropriate clothing for the environment,

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- failure to recognize or respond to police presence at the scene (reflecting delirium),
- erratic or violent behavior,
- unusual physical strength and stamina,
- ongoing struggle despite futility,
- cardiopulmonary collapse immediately following a struggle or very shortly after quiescence,
- inability to be resuscitated at the scene, and
- inability for a pathologist to determine a specific organic cause of death,
- attraction to glass or reflective surfaces (less frequent than all others per the Canadian data).

Subjects are incoherent and combative, and the struggle is more severe than anyone anticipates. Many have already sustained traumatic injuries before the arrival of law enforcement and still exhibit intense struggling even when a struggle is futile and self mutilation is a result.

Table 2 lists the features of excited delirium syndrome based on a review of the medical literature including 18 articles. The table is divided to indicate features based on the medical history of the subject, features that are observed in the company of the subject, features that are evident upon physical contact, features that are only evident with clinical assessment (i.e. vital signs), features that are described if the subject dies, and finally, features that are described on autopsy. A limitation of this analysis is that not all of these publications are observational studies and there is significant overlap of publications that reference each other to derive the most common clinical presentation.

Table 2: ExDS Features by Literature Review (n=18)

Features in History	# Articles
Male gender	16
Mean age ~30's	16
Sudden onset	4
History of Mental Illness	8
History of Psychostimulant abuse	11
Features evident at scene	# Articles
Call for disturbance/psychomotor agitation/excitation	18
Violent/combative/belligerent/assault call	11
Not responding to authorities/verbal commands	1
Psychosis/delusional/paranoid/fearful	13
Yelling/shouting/guttural sounds	7
Disrobing/inappropriate clothing	5
Violence toward/destruction of inanimate objects	7
Walking/running in traffic	3
Subject Obese	5
Features evident on contact	# Articles
Significant resistance to physical restraint	11
Superhuman strength	8
Impervious to pain	3
Continued struggle despite restraint	7
Profuse sweating/clammy skin	3
Features with clinical assessment	# Articles
Tachypnea	1
Tachycardia	7
Hyperthermia	12
Hypertension	3
Acidosis	3
Rhabdomyolysis	5

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Features of death	# Articles
Period of tranquility/"giving up"	4
Sudden collapse after restraint	12
Respiratory Arrest described	5
Cardiac rhythm brady-asystole or PEA	4
Aggressive Resuscitation unsuccessful	5
Features on autopsy	# Articles
Drug screen Positive for psychostimulants	9
Drug levels lower than anticipated	3
No anatomic correlate for death	6
Dopamine transporter dysregulation	2

Emergency clinicians and prehospital care providers are anecdotally aware that not all ExDS cases end in death. However, publication of nonfatal case reports or cohort studies remains infrequent. There is currently a paucity of literature to describe the epidemiology of ExDS if it is not accompanied by sudden death.

In the previously described Canadian data, 24 individuals demonstrated 6 or more of the clinical features found in **Table 1**. Prehospital ExDS may be reasonably presumed in subjects displaying 6 or more features of excited delirium (perhaps excluding attraction to reflective surfaces), thereby providing a potential case definition for future investigations. It is particularly likely if the subject displays constant or near constant physical activity, pain tolerance, superhuman strength, sweating, rapid breathing, tactile hyperthermia, and a failure to respond to police presence.

In summary, the clinical picture is one of an agitated and delirious state with autonomic dysregulation. It manifests through sympathetic hyper-arousal with frequent hyperthermia, vital sign abnormalities, and metabolic acidosis. For some, the clinical syndrome progresses to death.

Differential Diagnosis

Overview of delirium and altered mental status

Almost any drug, toxin, extraneous substance, psychiatric or medical condition, or biochemical or physiologic alteration in the body can cause acute changes in behavior or mental status. The general public, law enforcement, EMS, and even highly trained medical personnel may not be able to readily discern the cause of an acute behavioral disturbance, or differentiate a specific organic disease from ExDS.

Conditions that cause altered mental status

Altered mental status may be associated with a wide range of clinical signs and symptoms. The condition can range from coma to mild or profound confusion to uncontrolled agitation and delirium. A limited differential diagnosis of altered mental status is provided by the mnemonics **AEIOU TIPS (Table 3)**, or **SMASHED 2 (Table 4)**. Some etiologies may be suggested by clinical observation, obvious toxidromes, past medical history, patient age, or circumstances surrounding the acute event. Extensive testing and protracted evaluation and observation are often required to fully unravel the etiology of the acutely altered sensorium. As such, lifesaving interventions should be initiated prior to obtaining a specific diagnosis.

Table 3: AEIOU TIPS Mnemonic for Abbreviated Differential Diagnosis of Altered Mental Status

Letter	Description
A	Alcohol
E	Endocrine, Encephalopathy, Electrolytes
I	Insulin (hypoglycemia)
O	Oxygen (hypoxia), Opiates (drugs of abuse)
U	Uremia
T	Toxins, Trauma, Temperature
I	Infection
P	Psychiatric, Porphyria
S	Stroke, Shock, Subarachnoid Hemorrhage, Space-Occupying CNS Lesion

Table 4: SMASHED 2 Mnemonic for Differential Diagnosis of Altered Mental Status

Letter	Title	Description
S	Substrates	glucose (high/low), thiamine deficiency
	Sepsis	
M	Meningitis	all CNS infections, AIDS dementia, encephalitis, brain abscess or toxoplasmosis
	Mental illness	acute psychosis, medication noncompliance, mania, depression, malingering, rage, suicide intent (via police)
A	Alcohol	Intoxication, withdrawal
	Accident	head trauma, CVA, cerebral contusion, subdural or epidural hematoma
S	Seizing	or postictal
	Stimulants, hallucinogens, anticholinergics	Cocaine, amphetamines, caffeine, PCP, LSD, ketamine, psilocybin, antihistamines, atropine, scopolamine, jimson weed
H	Hyper	hypertension, hyperthyroidism, hypercarbia, hyperthermia
	Hypo	hypotension, hypothyroidism, hypoxia, hypothermia
E	Electrolytes	hyper/hyponatremia, hypercalcemia
	Encephalopathy	hepatic, HIV, uremic, hypertensive, lead, Reye's syndrome, CNS tumor
D	Drugs	Intoxication or withdrawal
	Don't forget other drugs	carbon monoxide, lithium, steroids, salicylates, designer/street drugs, theophylline, MDMA, antipsychotics, toxins not on routine drug screen, others

Several specific entities which cause altered mental status and may mimic ExDS deserve specific mention:

- Diabetic hypoglycemic reactions have been associated with outbursts of violent behavior and an appearance of intoxication. Diagnosis may be rapidly and conclusively made by determination of blood glucose and response to glucose administration.
- Heat stroke may manifest as tactile hyperthermia, rhabdomyolysis, and delirium, and may be associated with neuroleptic use and mental illness. A profound acidosis is often not present.
- Serotonin syndrome and neuroleptic malignant syndrome (NMS) may share some clinical characteristics with ExDS. However, they usually do not share the aggressive violent behavior manifested by patients with ExDS.
- Psychiatric issues may mimic ExDS. Some patients experience behavioral disturbances directly due to psychotropic drug withdrawal or noncompliance. Substance abuse is also very common in psychiatric patients. Many psychiatric conditions themselves, including acute paranoid schizophrenia, bipolar disorder, and even emotional rage from acute stressful social circumstances, may mimic an ExDS-like state. Untreated or poorly controlled psychiatric illness may also result in poor compliance with management of acute or chronic medical conditions. In *Phillips v Milwaukee*, a man who died in police custody of apparent ExDS was found at autopsy to have untreated thyrotoxicosis, as well as being non-compliant with his psychiatric medications.

Conditions that cause sudden death

Sudden unexpected death is the hallmark of fatal ExDS. The differential diagnosis for sudden death includes ischemic or drug induced sudden cardiac death, stress (Takotsubo) cardiomyopathy, inherited or acquired Long QT Syndrome, Brugada syndrome, and less common entities such as Cannon's Voodoo Death, Lethal Catatonia, and sudden unexplained death in epilepsy (SUDEP).

Treatment and Protocols

In the absence of clearly stated case definitions and prospective clinical studies, treatment of ExDS remains largely speculative and consensus-driven, directed towards supportive care and reversal of obvious clinical and laboratory abnormalities. The specific circumstances under which medical interventions will provide benefit are currently unclear. Nonetheless, there are current medical approaches that have consensus support. Most authorities, including this Task Force, posit the beneficial use of aggressive chemical sedation as first line intervention. As with any critically ill patient, treatment should proceed concurrently with evaluation for precipitating causes or additional pathology.

In subjects who do not respond to verbal calming and de-escalation techniques, control measures are a prerequisite for medical assessment and intervention. When necessary, this should be accomplished as rapidly and safely as possible. Recent research indicates that physical struggle is a much greater contributor to catecholamine surge and metabolic acidosis than other causes of exertion or noxious stimuli. Since these parameters are thought to contribute to poor outcomes in ExDS, the specific physical control methods employed should optimally minimize the time spent struggling, while safely achieving physical control. The use of multiple personnel with training in safe physical control measures is encouraged.

After adequate physical control is achieved, medical assessment and treatment should be immediately initiated. Indeed, because death might occur suddenly, EMS should ideally be present and prepared to resuscitate before definitive LEO control measures are initiated.

Initial assessment should include assessment of vital signs, cardiac monitoring, IV access, glucose measurement, pulse oximetry and supplemental oxygen, and careful physical examination. While the need for LEO control measures may initially preclude some or all of these interventions, they should be performed as soon as safely possible.

Agitation, hyperthermia, and acidosis are all major components of ExDS which can be effectively managed using traditional medical interventions. The approach to each of these components is described below.

Agitation

LEO control measures should be rapidly supplemented with sedation in the setting of acutely agitated, combative patients displaying signs of ExDS. While the intravenous (IV) route is preferred if available, intramuscular (IM) or intranasal (IN) transmucosal administration of sedative agents may be needed initially in order to facilitate IV placement. Commonly used agents and their doses are listed in **Table 5** and include benzodiazepines, antipsychotics, and the dissociative agent ketamine. Suggested doses are based upon consensus opinion. The actual effective dose of all suggested medications is unknown due to a paucity of research.

Because these agents have respiratory and cardiovascular effects, continuous monitoring of both should be performed as soon as feasible whenever parenteral sedation is administered. When appropriate safety systems are in place, one should be aware of manufacturers suggested dosing recommendations for other uses, but be prepared to use clinically effective doses for the management of this condition.

Table 5. Sedation Agents for ExDS–type symptoms

Class	Agent (Trade Name)	Available Routes	Dosing (mg)*	Onset (min)	Duration (min)
Midazolam (Versed)		IN	5	3-5	30-60
		IM	5	10-15	120-360
		IV	2 - 5	3-5	30-60
Lorazepam (Ativan)		IM	4	15-30	60-120
		IV	2 - 4	2-5	60-120
Diazepam (Valium)		IM	10	15-30	15-60
		IV	5 - 10	2-5	15-60
†Haloperidol (Haldol)		IM	10– 20	15	180-360
		††IV	5 – 10	10	180-360
†Droperidol (Inapsine)		IM	5	20	120-240
		IV	2.5	10	120-240
Ziprasidone (Geodon)		IM	10– 20	10	240
Olanzapine (Zyprexa)		IM	10	15-30	24 hrs
Ketamine (Ketaset, Ketalar)		IM	4-5 mg/kg	3-5	60-90
		IV	2 mg/kg	1	20-30

IN: Intranasal; IM: Intramuscular; IV: Intravenous

* Typical adult dosing for severe agitation.

† The Food and Drug Administration has issued “Black Box” warnings regarding potential serious adverse effects (QT prolongation and torsades de points) with these agents. Clinicians should use their clinical judgment regarding the risk / benefit ratio on a case by case basis.

†† Though widely used in clinical practice, Haloperidol is not FDA approved for intravenous administration.

(For adequate control of ExDS, the above doses are conservative and describe a reasonable starting point. Clinical effect in ExDS may require doses greatly in excess of those for traditional medical use in other conditions).

Benzodiazepines are familiar, commonly available sedative agents which can be administered by the IM or IV routes. Midazolam is also available and rapidly absorbed by the intranasal route, making it attractive for use in situations such as ExDS when rapid treatment is essential but IV access may not be available. Benzodiazepines are often preferred if

stimulant drug overdose is suspected. Potential disadvantages include relatively slow onset and unpredictability of action if not given IV, the need for repeat doses in many cases to achieve adequate sedation, and the potential for respiratory suppression. Often benzodiazepine doses many times the traditional suggested dose for sedation are required, and there is likely no maximum dose limit for benzodiazepines when facilities for respiratory and blood pressure support are available.

Antipsychotic agents are commonly used for sedation of agitated psychiatric patients, and can be administered by the IV or IM route. There is some concern for potential rare cardiac conduction effects such as QT prolongation with all of these agents, which may result in ventricular dysrhythmias such as torsades de pointes. These concerns, combined with a preexisting risk for sudden death among ExDS patients, official “black box” warnings from the FDA regarding QT prolongation with haloperidol and droperidol, and a slower onset of action than benzodiazepines by the IV or IM route, have led some clinicians to avoid this class of agents in suspected ExDS. Others have noted the potential for anticholinergic effects producing hyperthermia, and a mechanism of action involving central neurotransmitter systems (which may be markedly abnormal in some patients presenting with ExDS) as reasons to consider other agents.

The dissociative agent ketamine can also be administered by the IV or IM route and appears advantageous due to very rapid onset (especially by the IM route when compared to other medications), and lack of significant respiratory and cardiovascular effects. Case reports have indicated excellent results and safety when used in ExDS patients. Potential disadvantages include rare side effects such as increased oral secretions, laryngospasm, hypertension, and distress from emergence phenomena.

In some circumstances, sedation and paralysis with rapid sequence intubation and respiratory support may be necessary to control agitation in patients with ExDS. In these cases, standard techniques and medications may be utilized at the clinician’s discretion.

Hyperthermia

Empiric treatment for hyperthermia may be initiated based on qualitative assessment (i.e. tactile hyperthermia) when needed, though core temperature measurement is preferred when available and practical. Basic cooling methods include removal of clothing and placement in a cool environment. Active external cooling may be initiated, with misting of water on exposed skin, providing air flow to enhance evaporative cooling, and placement of ice packs at the neck, axillae, and groin. Rapid cooling by infusion of cold saline IV has been shown to be effective in a number of other settings and can also be used. Care must be taken to avoid treatment “overshoot” leading to hypothermia.

Once the patient is stabilized in the ED or hospital setting, additional measures may be considered. In refractory or severe cases, immersion in cool water can rapidly reduce core body temperature, though this may present some difficulty with monitoring and treatment. A variety of external and internal temperature control devices are now available and may also be considered. If NMS or malignant hyperthermia is suspected, dantrolene may be indicated.

Acidosis

Metabolic acidosis and hypovolemia are thought to be common in ExDS. If suspected based on the clinical situation or physical exam, fluid resuscitation with intravenous fluids is prudent. In severe cases, sodium bicarbonate may be used either empirically or based on laboratory results revealing significant acidosis. Controversy exists regarding empiric use of sodium bicarbonate; the efficacy of supplemental sodium bicarbonate is unknown, and has not been supported as routine therapy for the metabolic acidosis of cardiac arrest. It is approved by some EMS agencies, but not by others (**Table 6**). Sodium bicarbonate may be administered by bolus injections or as a continuous infusion. Hyperventilation is the body’s normal compensatory mechanism for correcting acidosis. Control measures that might interfere with ventilation should be avoided.

Other

Other components of ExDS may include rhabdomyolysis and hyperkalemia. Rhabdomyolysis is initially managed by fluid administration and urine alkalinization with sodium bicarbonate. These interventions may have already been initiated empirically for other components of ExDS before laboratory results allow confirmation of rhabdomyolysis. Hyperkalemia may also be treated with traditional ACLS interventions based on characteristic EKG changes and laboratory results.

Many EMS systems already have protocols in place that incorporate these recommendations, allowing treatment of the clinical signs and symptoms of ExDS in the prehospital setting. While some agencies have adopted specific ExDS protocols, others place the interventions within traditional headings such as agitation and hyperthermia. Several prehospital protocols are summarized in **Table 6**.

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Table 6. Sample EMS Protocols for ExDS symptoms

City, State	Sedation	Fluids	Hyperthermia	Other
Miami, FL	Midazolam (Versed) 5mg IN [max 20mg]	Normal Saline 1 liter bolus IV	Cold (<60°F) IV fluid Cold packs	Sodium Bicarb. 1 amp (50 mEq) per liter of Normal Saline
Nashville, TN	Midazolam (Versed) 2mg IV or 5mg IM [may repeat]	Normal Saline @ 500 cc/hr IV	Evaporative Cooling Cold packs	
Clark County (Las Vegas), NV	Midazolam (Versed) 2mg IV or 5mg IM / IN [may repeat]	Normal Saline	Evaporative Cooling Cold packs	
Columbus, OH	Midazolam (Versed) 2- 5mg IN, IV, pr [max 10 mg]	Normal Saline 500cc over 20 min	Evaporative Cooling Cold packs	Sodium Bicarb. ½ amp (25 mEq) per liter of Normal Saline
Minneapolis, MN	Ketamine 5 mg/kg IM or 2 mg/kg IV	Normal Saline up to 2 liter bolus IV	Evaporative Cooling Cold packs	Sodium Bicarb. 2 amps (100 mEq) IV push
Rochester, MN	Lorazepam (Ativan) 1-4 mg IV/IM or midazolam (Versed) 1-5 mg IV/IM	Normal Saline	Evaporative Cooling Cold Packs	Sodium Bicarbonate 1mEq/kg IV push in cardiac arrest

IV: Intravenous; IM: Intramuscular; IN: Intranasal; pr: per rectum; Normal Saline: 0.9% Sodium Chloride

LIMITATIONS OF CURRENT KNOWLEDGE AND RECOMMENDATIONS FOR FUTURE RESEARCH

The primary issues surrounding identifying and studying ExDS and subsequent therapeutic interventions are the lack of well-defined, consistent epidemiological case definition and overlap with other established diseases.

In those cases where a death occurs while in custody, there is the additional difficulty of separating any potential contribution of control measures from the underlying pathology. For example, was death due to the police control tool, or to positional asphyxia, or from ExDS, or from interplay of all these factors? Even in the situation where all caregivers agree that a patient is in an active delirious state, there is no proof of the most safe and effective control measure or therapy for what is most likely an extremely agitated patient. However, the existence of multiple EMS protocols as well as expert consensus suggests that there are practical and agreed-upon methods of therapy that are believed to lower morbidity or mortality. Sedative or dissociative agents such as benzodiazepines, major tranquilizers, and ketamine are suggested but there is no evidence yet to prove that these will result in a lower morbidity or mortality.

Future research should focus on several areas. Animal models should be developed to begin to better understand the pathophysiology of ExDS.

In humans, a consistent case definition should be developed and applied in a large epidemiologic prospective study or from a national or international database of all suspected cases, including those who survive. At a molecular level, and based upon post-mortem cocaine-associated ExDS brain tissue, a Genome Wide Association Scan may be performed to identify susceptibility genes.

Development of a national orphan case report registry is recommended. This registry would be important in beginning to define the course of ExDS, and might eventually provide for earlier recognition of individuals at risk. It would also allow the scientific community to begin the process of identifying common characteristics on a large scale as well as comparing therapies. Without including suspected cases and survivors, no meaningful conclusions can be reached that would allow the development of case definitions, etiologies, and treatments.

Studies should address the role of law enforcement control techniques and devices in the death of sub-

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jects with ExDS. Finally, research is needed to establish field protocols and techniques that allow police, EMS and hospital personnel to interact with these agitated, aggressive patients in a manner safe both for the patients and the providers.

SUMMARY

Based upon available evidence, it is the consensus of the Task Force that ExDS is a real syndrome of uncertain etiology. It is characterized by delirium, agitation, and hyperadrenergic autonomic dysfunction, typically in the setting of acute on chronic drug abuse or serious mental illness.

Research suggests the pathophysiology may include genetic susceptibility and chronic stimulant-induced abnormalities of dopamine transporter pathways, along with elevation of heat shock proteins in fatal cases. There is insufficient data at this time to determine whether fatal ExDS is preventable, or whether there is a point of no return after which the patient will die regardless of advanced life support interventions.

The risk of death is likely increased with physiologic stress. Attempts to minimize such stress are needed in the management of these patients. Ideally, any necessary law enforcement control measures

should be combined with immediate sedative medical intervention to attempt to reduce the risk of death.

There are well-documented cases of ExDS deaths with minimal restraint such as handcuffs without ECD use. This underscores that this is a potentially fatal syndrome in and of itself, sometimes reversible when expert medical treatment is immediately available.

For research and diagnostic purposes, thorough documentation of the patient's signs and symptoms along with appropriate testing should occur. This includes the presence of sweating or muscle rigidity, temperature, pulse, respiratory rate, blood pressure, venous blood gases, urine and serum toxicology, thyroid functions, and blood and (if fatal) anatomic brain specimens for genetic, heat shock proteins, and neurochemical analyses.

The ante-mortem diagnosis in the prehospital or emergency department setting depends upon clinical characteristics and the exclusion of alternative disease processes. It is our consensus that rapid and appropriate but limited control measures, and immediate administration of IV benzodiazepines or ketamine, IM ketamine, or intranasal midazolam, can be lifesaving.

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