

CME Excited Delirium: A Systematic Review

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ABSTRACT

Objective: We aimed to clarify the definition, epidemiology, and pathophysiology of excited delirium syndrome (ExDS) and to summarize evidence-based treatment recommendations.

Methods: We conducted a systematic literature search of MEDLINE, Ovid, Web of Knowledge, and Cochrane Library for articles published to March 18, 2017. We also searched the gray literature (Google Scholar) and official police or medical expert reports to complete specific epidemiologic data. Search results and full-text articles were independently assessed by two investigators and agreements between reviewers assessed with K statistics. We classified articles by study type, setting, and evidence level.

Results: After reviewing the title and abstract of 3,604 references, we fully reviewed 284 potentially relevant references, from which 66 were selected for final review. Six contributed to the definition of ExDS, 24 to its epidemiology, 38 to its pathophysiology, and 27 to its management. The incidence of ExDS varies widely with medical or medicolegal context. Mortality is estimated to be as much as 8.3% to 16.5%. Patients are predominantly male. Male sex, young age, African-American race, and being overweight are independent risk factors. Pathophysiology hypotheses mostly implicate dopaminergic pathways. Most cases occur with psychostimulant use or among psychiatric patients or both. Proposed treatments are symptomatic, often with rapid sedation with benzodiazepines or antipsychotic agents. Ketamine is suggested as an alternative.

Conclusion: The overall quality of studies was poor. A universally recognized definition is lacking, remaining mostly syndromic and based on clinical subjective criteria. High mortality rate may be due to definition inconsistency and reporting bias. Our results suggest that ExDS is a real clinical entity that still kills people and that has probably specific mechanisms and risk factors. No comparative study has been performed to conclude whether one treatment approach is preferable to another in the case of ExDS.

Violent behavior and extreme agitation are frequently encountered in U.S. and European emergency departments (EDs).^{1,2} The management of these situations raises ethical, therapeutic, preventive, and security concerns. The studies related to these topics are mainly retrospective and observational, occur within various settings, and use heterogeneous definitions.^{1,3–5} As a consequence, clinical guidelines related to violence or extreme agitation, including sedation and restraint, are based on limited levels of evidence (LOEs).⁶

Violent incidents that occur in the ED are mostly⁷ related to severe agitation and are usually associated with substance abuse (alcohol, drugs), psychotic

episodes, or medical problems (hypoglycemia, pain, delirium). A substantial number of agitated patients present to the ED in extremely violent conditions, characterized by incoercible psychomotor agitation and aggressiveness. These situations are described as excited delirium or excited delirium syndrome (ExDS) in the literature.^{8,9} ExDS usually requires the use of physical or mechanical restraint, including the intervention of security officers or law enforcement officers. An associated significant morbidity and a mortality rate of 8% to 10% has been reported.^{8,9}

The term “ExDS” was coined and an initial flurry of reports published in the 1980s, particularly in

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forensic records, in the context of deaths of individuals in custody or during arrests following extreme agitation.¹⁰ ExDS typically involved men in their 30s after cocaine, methamphetamine, or ecstasy abuse.^{11–13} Similar cases of extreme agitation have also been described in psychiatric conditions since the 19th century, referred to as “Bell’s mania.”¹⁴

Over the past few years, the association between police coercion methods (conducted electrical weapons [CEW; e.g., TASER™], pepper spray, ventral decubitus physical restraint, etc.) and cases of in-custody deaths drew the attention of the media and contributed to public opinion about ExDS. However, fatal cases of ExDS also appeared inside the hospital, in the absence of any major trauma, physical restraint, or police intervention.¹³ Although ED caregivers regularly face such cases of extreme, unusual agitation in their daily practice, its presence in multiple areas of medical care in the presence of people with varying degrees of medical training contributes to the difficulty in forming a unifying definition of the syndrome.

To date, a standardized definition or consensus about ExDS diagnostic criteria has not been universally recognized. For example, neither the American Psychiatric Association nor the World Health Organization recognizes this syndrome as a specific clinical entity, whereas the American College of Emergency Physicians (ACEP) has recognized it since 2009.⁹ The ACEP definition of ExDS includes acute delirium (not linked to dementia or preexisting pathologies) associated with extreme physical and psychomotor agitation. In the absence of a unique pathophysiologic cause or specific diagnostic test for ExDS, the ACEP criteria are based only on a syndromic approach, 10 clinical criteria being used to identify it. A minimum of six criteria are required for the diagnosis of ExDS. These criteria are mainly inspired by a Canadian police census report¹⁵ and by several case descriptions published in the medical literature.^{9,10,16}

Importance

Cases of incoercible extreme agitation, described in the literature as “excited delirium syndrome,” are regularly observed during prehospital emergency interventions and in EDs.^{17,18} The patients involved present a major risk for adverse events, including death.¹³ Identification of ExDS situations is thus essential, but remains difficult in the absence of a specific definition. Concomitantly, epidemiologic data, as well as diagnostic and therapeutic strategies, remain sparse and

heterogeneous. In this context, a high-quality structured systematic review of current knowledge about the condition is needed.

Goals of this Investigation

We conducted a systematic review of the literature related to ExDS to clarify issues and to answer four questions: 1) What is the standard definition or diagnostic criteria of ExDS? 2) What are the epidemiologic characteristics of ExDS (prevalence, incidence, and case characteristics)? 3) What are the hypotheses and evidence about the pathophysiologic mechanisms underlying ExDS? 4) What are the evidence-based management and treatment recommendations for ExDS?

METHODS

Article Selection

Our study conforms to the PRISMA statement for systematic reviews.¹⁸ In collaboration with a medical librarian, we conducted a systematic literature search, initially without language restriction, in the MEDLINE, Ovid (journals, EBM Reviews, MEDLINE, and MEDLINE In-Process), Web of Knowledge, and Cochrane Library databases, to include references from inception to the end of December 2015. We also searched the gray literature (Google Scholar). A verification search was performed in March 2017 for articles published to March 18, 2017. We reviewed bibliographies of relevant articles and nonsystematic review articles to identify additional references. Published U.S. and European official police reports or medical expert reports related to ExDS were used to identify additional references or to complete specific epidemiologic data. Those reports were found during the gray literature search.

After excluding duplicates, two investigators (PG and PNC) independently screened titles and abstracts of all articles identified by the initial selection. Search results and full-text articles were independently assessed by the two reviewers; disagreements were resolved through consensus or referral to a third reviewer (BY). Agreements between reviewers were assessed with kappa statistics. Finally, we classified the articles by type of study, setting, and LOE when appropriate.

Inclusion Criteria

The following eligibility criteria were used to select articles for this systematic review: 1) The article was a case

report, case series, retrospective study, prospective observational study, or randomized controlled trial; 2) the article was related to the diagnostic criteria or definition, epidemiology, pathophysiology, or treatment and management of ExDS; and 3) the article was related to human studies or human case descriptions, except for the pathophysiology aspect, for which animal studies specifically related to ExDS were also included. Descriptive reviews and official police reports were integrated into the current review if they were specifically related to one of the aforementioned ExDS questions (particularly epidemiologic data).

The search strategy included two main search themes (“excited” or “agitated” and “delirium”) together or combined. The research was directed to “(agitated delirium) OR (excited delirium)” for Ovid; to “((excited OR agitated) AND delirium)” for Web Of Knowledge; to “agitated delirium” OR “excited delirium” for Google Scholar; and to “excited AND delirium,” “agitated AND delirium,” “acute AND agitated [title] NOT delirium[title],” and “acute AND excited [title] NOT delirium[title]” in the MEDLINE and Cochrane databases. An additional search was performed especially for treatment with ketamine in the MEDLINE database, directed to “emergency,” “ketamine,” and “agitation” from January 1, 2012, to March 18, 2017.

Articles in English, French, Spanish, and German were included for abstract and title evaluation. Articles in other languages and those without any abstract or related text were excluded, such as citations, book chapters, and Web pages. Articles related to acute delirium occurring in a pediatric, geriatric, palliative care, perioperative, or intensive care setting were excluded.

Outcomes

Articles included in the systematic review had to answer one or more of the initial questions related to the standardized definition or diagnostic criteria of ExDS; the epidemiologic characteristics of ExDS in terms of prevalence, incidence, and case characteristics; the pathophysiologic mechanisms or risk factors; or the evidence-based management and treatment recommendations. Physiopathologic studies concerning ExDS were also included in the systematic review.

Quality of Data Reporting and Statistics

GRADE (Grading of Recommendations Assessment, Development and Evaluation) was used to judge the

quality of evidence and strength of recommendations regarding the management of ExDS.¹⁹ According to GRADE, quality of evidence was described as “high,” “moderate,” “low,” or “very low” depending on the quality of the type of study. Randomized controlled trials are categorized as high, systematic review of cohort studies and individual prospective study as moderate, case-control study as low, and case series or expert opinion as very low. In the same way, strength of recommendation was described as “strong” or “weak”: strong for large, high-quality study with some limitation and weak for studies with severe limitations, as retrospective studies or expert opinions. We did not perform quantitative meta-analyses because of the heterogeneity of the studies in terms of design, definition of ExDS, diagnosis criteria, intervention type, and outcomes.

RESULTS

Article Selection and Characteristics

The initial search strategy yielded 4,792 references with potential relevance, of which 66 were included, each answering one or more of the four preplanned questions (Figure 1). Characteristics of the 66 selected articles are shown in Table 1. These articles included 43 retrospective case series, case-control, or case reports; five expert consensus reports; three literature reviews; five narrative reviews; and 10 prospective studies: two on animals and eight on patients (cohort studies). Six articles included information about the definition of ExDS, 23 about its epidemiology, 38 about its pathophysiology or risk factors, and 27 about its treatment options or guidelines. All articles were in English, except for a Spanish forensic retrospective case series.²⁰

Definition of ExDS

Three studies proposed a definition for ExDS. Two were retrospective case series (with seven and 43 ExDS patients)^{10,16} and one was a retrospective case-control study with 58 ExDS patients.¹² None of these definitions were universally recognized and they were based on variable criteria. We decided to also include a literature review specifically related to the definition of ExDS,⁸ as well as the expert consensus report, “White Paper Report on Excited Delirium Syndrome.”⁹ This consensus was proposed by the ACEP in 2009, with a definition based on a syndromic approach.⁹

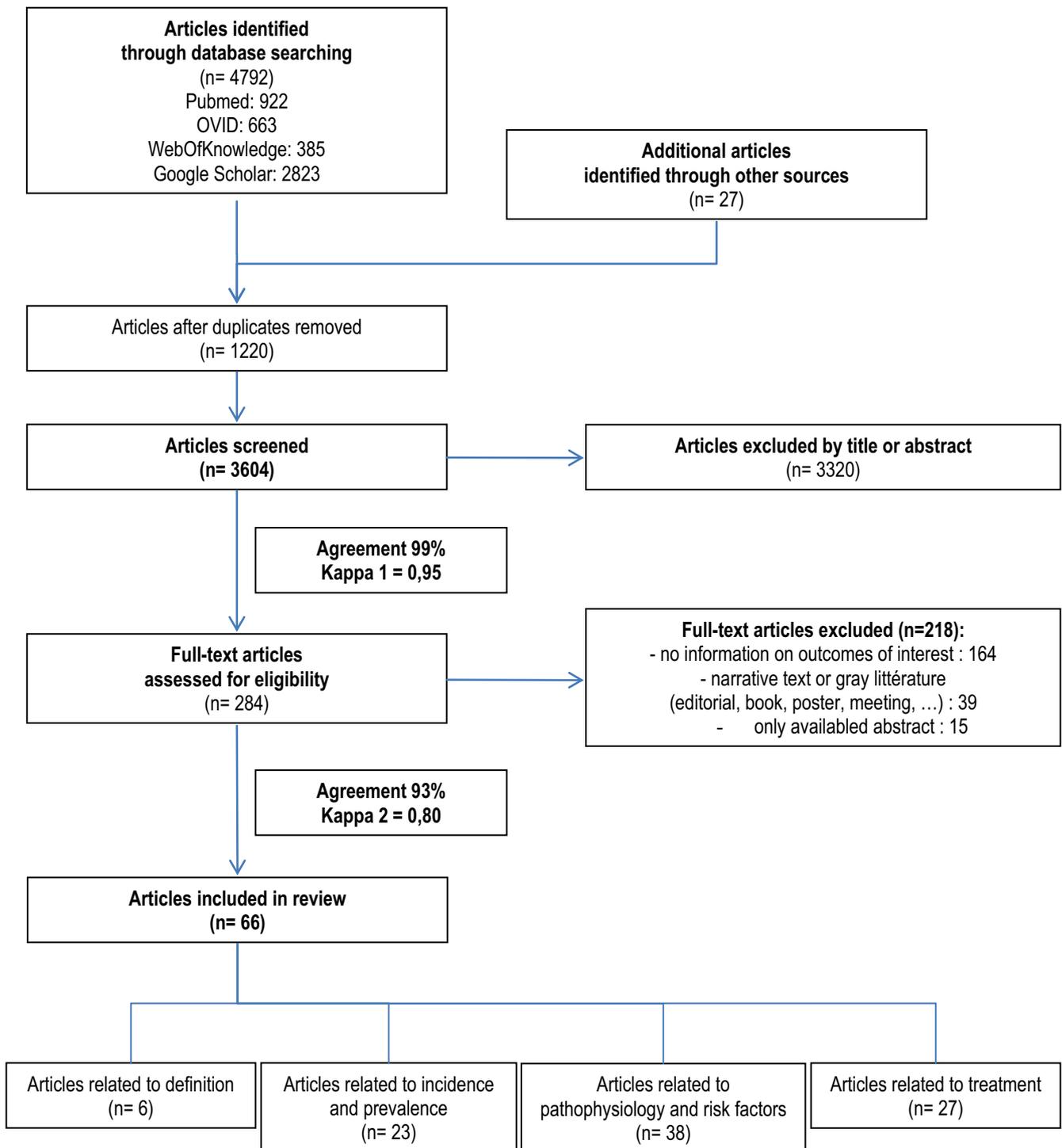


Figure 1. Study selection flowchart.

A large variety of criteria were used in these publications. Table 2 summarizes the diagnostic criteria proposed. Delirium associated with excited behavior or agitation was a constant prerequisite.⁸ The number of additional criteria required to suspect ExDS was not clearly defined. Two articles mentioned that ExDS “may be reasonably presumed” when six items in a 10-criteria set are present.^{8,9} In a retrospective case series of seven cases, all patients considered to present

ExDS had between five and seven criteria.¹⁰ In a series of 43 ExDS patients, 12% of the cases were reported to have one or two of these criteria, 44% three to five, and 44% more than five.¹⁶

Epidemiology

Twenty-three articles were related to the epidemiology of ExDS. Six articles described situations involving law enforcement officers (police interventions or in-custody

Table 1
Characteristics of the Selected Articles

Study	Type of Study	Setting	Total Cases (N)/ExDS Cases (n)	LOE	Gives Definition of ExDS	Epidemiology	Physiopathology (Class*)	Guidelines (Class*)
Wetli, 1985 ¹⁰	R-CS	ED	7/7	VL	x	x	x (weak)	x (weak)
O'Halloran, 1993 ¹³	R-CS	Forensic	11/11	VL		x	x (weak)	
Mets, 1996 ⁴⁷	P-A	Fundamental	47/—	M			x (strong)	
Staley, 1996 ⁵⁹	R-CC	Forensic	21/6	L			x (weak)	
Chan, 1997 ⁴⁹	PC	Police	—/15	M			x (weak)	
Ruttenber, 1997 ¹²	R-CC	Forensic	183/58	L	x	x	x (weak)	
Segal, 1997 ³³	R-CC	Forensic	15/5	L		x	x (weak)	
Staley, 1997 ³⁶	R-CC	Forensic	26/9	L		x	x (weak)	
Pollanen, 1998 ³¹	R-CS	Forensic	61/21	VL		x	x (weak)	
Ross, 1998 ²³	R-CS	Police	61/61			x		
Hick, 1999 ⁵⁵	R-CS	ED	5/5	VL			x (weak)	x (weak)
Mash, 1999 ⁵⁸	R-CC	Forensic	21/6	L			x (weak)	
Blaho, 2000 ²⁸	R-CS	ED	2/2	VL		x	x (weak)	
Stratton, 2001 ¹¹	R-CS	EMS	18/18	VL		x	x (weak)	
Kupas, 2002 ¹⁷	EC	EMS	—	VL		x	x (weak)	
Mash, 2002 ³⁵	R-CC	Forensic	28/8	L		x	x (weak)	
Parkes, 2002 ⁴¹	LR	Forensic	—	L			x (weak)	
Mash, 2003 ³⁴	R-CC	Forensic	34/8	L		x	x (weak)	
Pestaner, 2003 ⁵³	R-CS	Police	2/2	VL			x (weak)	
Best, 2004 ²⁵	R-CS	Police	24/3			x		
Strote, 2006 ³⁰	R-CS	Forensic	37/28			x		
Southall, 2008 ²⁴	R-CS	Police	45/5			x		
DeBard, 2009 ⁹	EC	ED	698/24	VL	x	x	x (weak)	x (weak)
Grant, 2009 ²²	R-CS	Police	353,029/62			x		
Kutcher, 2009 ⁶²	EC	Police	—	VL				x (weak)
Mash, 2009 ²⁹	R-CS	Forensic	220/90	VL		x	x (weak)	
Cazorla, 2010 ²⁰	R-CS	Forensic	8/8	VL		x	x (weak)	x (-)
Otahbachi, 2010 ⁴³	NR	Clinical	—	VL			x (weak)	
Shinone, 2010 ⁴⁸	P-A	Fundamental	20/—	M			x (weak)	
SoRelle, 2010 ⁶¹	EC	EMS	—	VL				x (weak)
Takeuchi, 2011 ⁷⁵	NR	Clinical	—	VL				x (weak)
Burnett, 2012 ⁷³	R-CR	EMS	1/1	VL				x (weak)
Burnett, 2012 ⁶⁵	R-CS	ED	13/13	VL				x (weak)
Johnson, 2012 ⁶⁰	R-CC	Forensic	36/18	L			x (weak)	
Le Cong, 2012 ⁶⁹	R-CS	EMS	—/18	VL				x (weak)
Murray, 2012 ⁷¹	R-CR	Global emergency	1/1	VL				x (weak)
Penders, 2012 ⁵⁴	R-CS	EMS	3/3	VL			x (weak)	
Richmond, 2012 ⁶³	EC	ED	—	VL				x (weak)
Vilke, 2012 ⁸	LR	Global emergency	—	L	x	x		x (weak)
Gordon, 2013 ⁴⁴	NR	Global emergency	—	VL			x (weak)	x (weak)
Hall, 2013 ²¹	PC	Police	1,269/209			x		
Ho, 2013 ⁵²	R-CS	EMS	2/2	VL			x (weak)	x (weak)
Plush, 2013 ³⁹	R-CR	ED	1/1				x (weak)	
Savaser, 2013 ⁵¹	PC	Police	—/25	M			x (weak)	
Iwanicki, 2014 ²⁶	PC	EMS	35/35	M		x		x (weak)
Jovel, 2014 ³⁸	R-CR	Forensic	1/1	VL			x (weak)	
Maher, 2014 ⁷²	R-CR	EMS	1/1	VL				x (-)

(Continued)

Table 1 (continued)

Study	Type of Study	Setting	Total Cases (N)/ExDS Cases (n)	LOE	Gives Definition of ExDS	Epidemiology	Physiopathology (Class*)	Guidelines (Class*)
Schepke, 2014 ⁷⁴	R-CS	EMS	52/—	VL				x (weak)
Sloane, 2014 ⁵⁰	PC	Police	—/10	M			x (weak)	
Strote, 2014 ¹⁶	R-CS	Police	43/43	VL	x	x	x (weak)	x (-)
Burnett, 2015 ⁷⁰	R-CS	EMS	—/49	VL				x (weak)
Downes, 2015 ⁵⁷	R-CS	ED	2/1	VL			x (weak)	
Hopper, 2015 ⁶⁴	R-CS	ED	—/32	VL				x (weak)
Keseg, 2015 ¹⁸	R-CS	EMS	35/—	VL				x (weak)
Baldwin, 2016 ⁷⁶	PC	Police	4,799/73		x			
Cole, 2016 ⁶⁷	PC	EMS	0/146	M				x (strong)
Kristofic, 2016 ⁵⁶	R-CS	Forensic	3/3	VL			x (weak)	
Mash, 2016 ⁴⁵	NR	Forensic	—	VL			x (weak)	
Michaud, 2016 ³²	R-CS	Forensic	20/14			x		
Olives, 2016 ³⁷	R-CS	EMS	—/135	VL				x (weak)
Scaggs, 2016 ²⁷	R-CS	EMS	7/7	VL		x		x (weak)
Schiavone, 2016 ⁴⁰	R-CR	Fundamental	1/1	VL			x (weak)	
Schiavone, 2016 ⁴²	LR	Fundamental	—	L			x (weak)	
Hollis, 2017 ⁶⁸	R-CS	EMS	—/153	VL				x (weak)
Nugent, 2017 ⁴⁶	NR	Police	—	VL			x (weak)	
Riddell, 2017 ⁶⁶	PC	ED	—/98	M				x (strong)

CS = retrospective case series; EC = expert consensus; ExDS = excited delirium syndrome; N = number of total cases in the study; n = number of ExDS in the study; L = low; LOE = level of evidence; M = moderate; NR = narrative review; P-A = prospective animal; PC = prospective cohort; R-CC = retrospective case-control; R-CR = retrospective case report; R-LR = literature review; VL = very low. *GRADE strength of recommendation.¹⁸

conditions). An observational study described 209 ExDS patients in the context of police interventions,²¹ and five retrospective case series included ExDS patients in this context (the number varying between three and 62 per study).^{16,22–25} Three articles involved prehospital emergency medical services (EMS) interventions: a prospective cohort with 35 patients²⁶ and two retrospective case series of seven and 18 patients with ExDS.^{11,27} Two retrospective case series (with two and seven cases of ExDS) were related to ExDS in the ED.^{10,28} Six retrospective case series (with eight to 90 ExDS cases^{13,20,29–32}) and five case-control studies (with five to 58 ExDS cases^{12,33–36}) were related to the forensic setting. Finally, one literature review addressed ExDS in different settings.⁸

Table 3 illustrates the reported frequency of ExDS and Table 4 the reported mortality rates, according to context and patient characteristics. In the context of EMS interventions, 1.8 restrained ExDS patients were identified in 10,000 advanced life support calls,¹¹ or six cases of ketamine administration for profound agitation for 10,000 such calls.³⁷

One study compared restraint-related deaths in ExDS in Ontario during 2004 to 2011 with those during 1988 to 1995.³² The number of ExDS-associated

deaths decreased by 33% (from 21 to 14 cases; 2.63 to 1.75 per year, respectively). From 2005 to 2011, this represents 0.08 deaths/million/year.³² During this period, a concomitant decrease in the proportion of psychiatric causes was observed (from 57% to 14%).³²

Overall, ExDS patients were 14 to 71 years old with a mean age of 33.3^{9–11,13,16,20,22,26,27,29,31,33–36} and a median age of 30.0.^{10,11,13,20,27,36} Male patients were involved in 83%²⁶ to 95% of ExDS cases.^{9–11,13,16,20,22,29,31,33–36} The ethnic origin of the patients was assessed in nine studies from several countries (Sweden, Canada, United Kingdom) or U.S. states. There was a predominance of Afro-American patients in six studies.^{12,16,22,29,33,36} There was also a predominance of white patients in two studies concerning several U.S. states.^{10,23} One study found an equal number of Caucasians and Afro-American people.¹¹

The frequency of weapon use by law enforcement forces in the context of ExDS was described in three articles. In one case series (n = 43), weapon use was observed in 30% of patients with ExDS.¹⁶ CEWs were the most frequently reported weapons used, occurring in 18% and 33% of ExDS situations in two distinct U.S. studies.^{16,29} Use of chemical agents (such as pepper spray) appeared in 8% of the cases in these

Table 2
Clinical Features Reported in Excited Delirium and Related Reported Frequency

Criteria	Reported Frequency (%)	Studies (n = Total Number of ExDS Cases)
Behavior		
Severe agitation, violence, thrashing	95%	DeBard, 2009 (24) ⁹
	100%	Wetli, 1985 (7) ¹⁰
	NA	Ruttenber, 1997 (58) ¹²
	NA	Strote, 2014 (43) ¹⁶
	83%	Baldwin, 2016 (73) ⁷⁶
Bizarre behavior, extreme paranoia, hypervigilance	14%	Wetli, 1985 (7) ¹⁰
	NA	Ruttenber, 1997 (58) ¹²
	100%	Baldwin, 2016 (73) ⁷⁶
Lack of tiring, constant physical activity	90%	DeBard, 2009 (24) ⁹
	100%	Wetli, 1985 (7) ¹⁰
	NA	Ruttenber, 1997 (58) ¹²
	95%	Baldwin, 2016 (73) ⁷⁶
Unusual or unexpected strength	90%	DeBard, 2009 (24) ⁹
	86%	Wetli, 1985 (7) ¹⁰
	NA	Ruttenber, 1997 (58) ¹²
	NA	Strote, 2014 (43) ¹⁶
	81%	Baldwin, 2016 (73) ⁷⁶
Pain tolerance, impervious to pain	100%	DeBard, 2009 (24) ⁹
	NA	Strote, 2014 (43) ¹⁶
	93%	Baldwin, 2016 (73) ⁷⁶
Police noncompliance, combative	90%	DeBard, 2009 (24) ⁹
	NA	Ruttenber, 1997 (58) ¹²
	74%	Baldwin, 2016 (73) ⁷⁶
Mirror or glass attraction (reflective surface)	10%	DeBard, 2009 (24) ⁹
	26%	Baldwin, 2016 (73) ⁷⁶
Stupor	NA	Wetli, 1985 (7) ¹⁰
Fear	100%	Wetli, 1985 (7) ¹⁰
Panic	86%	Wetli, 1985 (7) ¹⁰
Clinical signs		
Tactile hyperthermia, hot to touch,	95%	DeBard, 2009 (24) ⁹
	57%	Wetli, 1985 (7) ¹⁰
	7%	Strote, 2014 (43) ¹⁶
	8%	Baldwin, 2016 (73) ⁷⁶
Inappropriately clothed, removal of clothing	70%	DeBard, 2009 (24) ⁹
	60%	Baldwin, 2016 (73) ⁷⁶
Tachycardia	84%	Strote, 2014 (43) ¹⁶
Tachypnea	100%	DeBard, 2009 (24) ⁹
	85%	Baldwin, 2016 (73) ⁷⁶
Sweating	95%	DeBard, 2009 (24) ⁹
	71%	Baldwin, 2016 (73) ⁷⁶
Seizure	NA	Wetli, 1985 (7) ¹⁰
	27%	Ruttenber, 1997 (58) ¹²
Mydriasis	NA	Wetli, 1985 (7) ¹⁰

ExDS = excited delirium syndrome; NA = number or rate not available, with only mention of criteria in patients without indication of frequency.

Table 3
Estimated Frequency of ExDS by Setting

Setting	Estimated Frequency of ExDS (%)	Studies (Total Number of ExDS Cases)
Reported ExDS cases in the context of		
Use of force by police officers	3.4%	DeBard, 2009 (24) ⁹
	2.9%	Hall, 2013 (209) ²¹
EMS interventions	1.5%	Baldwin, 2016 (73) ⁷⁶
	0.02%	Stratton, 2001 (18) ¹¹

ExDS = excited delirium syndrome.

Table 4
Estimated Mortality Rate of ExDS by Setting

Setting	Estimated Mortality Rate of ExDS
Patients with signs and symptoms consistent with ExDS, unspecified context	8.3% ⁹
Reported fatal ExDS cases in the context of:	
Cocaine-related deaths (forensic)	16.5% ¹²
CEW-related deaths (forensic)	11.1% ³⁰
Death in police custody	11.1% to 12.5% ^{24,25}
Fatal ExDS identified by Spanish coroners	0.38/million/year ²⁰

CEW = conducted electrical weapon; ExDS = excited delirium syndrome.

two studies.^{16,29} This rate was 19% in a case series related to fatal ExDS.³¹

Pathophysiology

Thirty-eight articles were related to the pathophysiology of ExDS or to risk factors associated with ExDS mortality. These publications included two expert consensus reports,^{9,17} three single-case reports,^{38–40} two literature reviews,^{41,42} four narrative reviews,^{43–46} five prospective studies,^{47–51} 14 retrospective case series,^{10,11,13,16,20,28,29,31,52–57} and eight case-control studies.^{12,33–36,58–60}

In terms of pathophysiology, a catecholaminergic hypothesis involving both endogenous stress-related catecholamines and exogenous catecholaminergic drugs was described in 12 articles (one animal prospective study,⁴⁷ two narrative reviews,^{45,46} one consensus report,⁹ and eight retrospective case-control or case series^{28,29,33–36,58,59}). According to this hypothesis, ExDS occurred in conditions involving high levels of endogenous catecholamines—related to stress or physical exertion—and concomitant abuse of a stimulant, mostly cocaine (in one animal prospective study⁴⁷ and one retrospective case series²⁸). Activation of the

Table 5
Reported Drug Abuse and Respective Reported Prevalence in ExDS Patients

Reported Drug Abuse in Studies	Reported Percentage of Patients' Positive Drug Testing (%)
Psychostimulant (cocaine, LSD, methamphetamine) ^{23,29}	10%–94% ^{23,29}
Cocaine ^{13,16,20,23,24,26,29}	6%–83% ^{20,26}
In combination with alcohol ^{20,23,25,26,29,34}	27%–37% ^{29,34}
In combination with other drugs ^{*13,20,25,26,29}	3%–17% ^{20,29}
PCP ^{16,24,44,53}	24%–40% ^{16,24}
Amphetamine ^{13,16,23,26,29}	9%–24% ^{13,16}
Synthetic cathinone ^{26,38,54,56,57}	3% ²⁶
LSD ^{13,26}	3%–9% ^{13,26}
THC ^{16,23}	11%–42% ^{16,23}
Synthetic cannabinoids ²⁶	25% ²⁶
Opioids ^{16,26}	6.25%–9% ^{16,26}
Alcohol ¹⁶	23% ¹⁶
Other (lithium, methylphenidate hydrochloride, haloperidol, lidocaine, valproic acid, amantadine, lorazepam, amobarbital, citalopram, risperidone) ^{13,23,29}	2%–9% ^{13,23}
Multipositive toxicology in ED ^{16,20}	33%–55% ^{16,20}

ExDS = excited delirium syndrome; LSD = lysergic acid diethylamide; PCP = phencyclidine; THC = tetrahydrocannabinol.

*Met/amphetamines, pseudo/ephedrine, MDMA/MDA, methyl/benzoyllecgonine, methadone, lorazepam, opiates.

dopamine transporter pathway was proposed in nine articles (two narrative reviews,^{45,46} one consensus report,⁹ and six retrospective case-control or case series^{29,33–35,58,59}). Individual variations and genetic susceptibility, related to dopamine receptor variations or chronic stimulant-induced abnormalities, were described in six publications (two narrative reviews,^{45,46}

one consensus report,⁹ and three retrospective case-control or case series^{29,33,58}). A case study and a literature review from 2016 present the mechanism of cocaine-induced neurotoxicity via an excess in reactive oxygen species in the central nervous system.^{40,42} The main source of these species is the NADPH oxidase 2 enzyme, which seems to play a crucial role in the pathogenesis of ExDS.⁴² Finally, variations in α -synuclein protein (case-control study)³⁴ or opioid receptors were also proposed as contributing factors (two case-control studies).^{36,58}

Drug abuse was directly associated with ExDS in 15 studies, a large panel of substances being observed (Table 5).^{13,16,20,23,24,26,29,34,38,40,52–54,56,57} Cocaine was the most frequently associated drug, appearing in 10 of these studies (66%).^{13,16,20,23,24,26,29,34,40,52} Blood and/or brain cocaine concentrations and the associated risk of ExDS death were assessed in six studies.^{10,29,31,35,36,59} Four showed low serum concentrations of cocaine in ExDS-related deaths, particularly in comparison to other cocaine intoxication-related deaths not associated with ExDS.^{10,35,36,59} The other two articles described similar levels of cocaine.^{29,31} Finally, one case report, involving a cocaine abuser, described two episodes of ExDS occurring in the same patient 6 months apart.³⁹ Exceptionally, cases occurred in the absence of any illicit or licit drugs or after operational stress and extreme sleep deprivation during military maneuvers.²⁹

Two studies described the mode of drug administration in fatal ExDS.^{23,29} Smoking was the most frequent route (58%), followed by nasal sniffing (18.6%) and intravenous injection (1.2%). In 22% of cases, the mode of administration remained unknown.²⁹ In

Table 6
Initial Therapeutic Strategies Used for Chemical Sedation of Patients With ExDS

Drug	Route	Dose	References
Diazepam	IV	NA	10,16
Midazolam	IN	5 mg	62
	IM	2–5 mg or 0.1 mg/kg	61
Lorazepam	IM/IV	2–5 mg	44
Chlorpromazine	IV	NA	10
Haloperidol	IM/IV	5–10 mg*	44
Ketamine	IM	4–6 mg/kg or 40–400 mg	18,26,27,37,52,61,65,66,70,74,75,64
	IV/IO	1–2 mg/kg or 40–400 mg	18,37,52,61,66,75,64
	IV	0.5–1 mg/kg max 2 \times , then 1–1.5 mg/kg/h	69

ExDS = excited delirium syndrome; IV = intravenous; IN = intranasal; IM = intramuscular; IO = intraosseous infusion; NA = not available.

*Note that the FDA does not approve intravenous administration of haloperidol and that its recommended intramuscular dosage is 2–5 mg.

cases of in-custody ExDS, the route of administration was intravenous injection in 21% of cases, intranasal in 18%, smoking in 8%, ingestion in 7%, and unknown in 46%.²³

Morbidity and mortality related to ExDS were attributed to acute myocardial dysfunction, involving cardiopulmonary arrest in the most severe cases. Physical findings on initial EMS contact in the field were reported in a series of 18 fatal cases of ExDS. Most of the patients had agonal ($n = 10$) or no ($n = 5$) respiration at the time of EMS on-site arrival.¹¹ Initial cardiac rhythm was asystole or agonal rhythm in seven cases, bradycardia, or junctional rhythm in three. Ventricular tachycardia was described in only one case, sinus tachycardia in two (136–140/min).¹¹

Three case series (with 11, 58, and 90 cases) reported mortality times.^{12,13,29} In 36% to 47% of cases, death occurred in less than 1 hour;^{12,29} in 26% to 33%, in 1 to 6 hours^{12,29}; in 4% to 17%, within 7 to 12 hours; and in 16% to 21%, after more than 12 hours.¹² In the 11 case series, all patients died within 6 hours of the start of ExDS.¹³ The mortality rate of ExDS was 0.38/million/year in the Spanish series.²⁰

The odds ratios (ORs) of specific risk factors for fatal ExDS were evaluated in a retrospective study of all cocaine-related deaths in Dade County, Florida, from 1969 to 1990.¹² Male gender (OR = 9.3), young age (OR = 1.1), Afro-American origin (OR = 3.5), and being overweight (OR = 2.7 for body mass index quartiles 2–4) were significantly associated with an increased risk of mortality by ExDS.¹² In another retrospective case series, “hobble restraint” in the prone position was also identified as an associated risk factor.¹¹ Nevertheless, three prospective trials on human volunteers, obese and nonobese, refute the clinical significance of ventilation, oxygenation, and hemodynamics of prone maximal restraint^{49–51} with a weight of up to 100 pounds on the back.⁵¹

Management and Treatment

We identified 27 articles related to the management of ExDS: four expert consensus reports,^{9,61–63} three single-case reports,^{71–73} 11 retrospective case series,^{10,16,20,27,52,55,65,68–70,74} one quasi-systematic literature review,⁸ two nonsystematic reviews,^{44,75} three prospective cohort studies,^{26,66,67} and three retrospective cohort studies.^{18,37,64} The LOE was graded as moderate for three studies,^{26,66,67} low for one,⁸ and very low for 23 studies.^{9,10,16,18,20,27,37,44,52,55,61–65,68–75}

Restrained patients should be moved from the prone to a side-lying or seated position as soon as

possible according to two articles (class D, LOE very low),^{55,62} but a deescalation attempt was proposed as a first measure in another two articles (class weak, LOE very low).^{62,63} In the ED setting, a low and reassuring voice in a quiet room with dim lighting was recommended in one study (class weak, LOE very low).⁴⁴

Supportive care and reversal of obvious clinical and laboratory abnormalities were proposed in three articles (class weak, LOE low,⁸ and very low^{9,71}) and aggressive chemical sedation was recommended in three others (class weak, LOE very low).^{10,44,55} In terms of sedation, benzodiazepine use was described in six articles,^{9,10,16,44,61,62} neuroleptics in two,^{8,44} and a combination of benzodiazepine and neuroleptics in one.⁷⁵ Ketamine administration in prehospital agitated patients was reported in 14 articles,^{18,26,27,37,52,64–70,73,74} with rapid suitable sedation in 96% of cases⁷⁴ and an “improvement in patient condition” in 91%¹⁸ with a limited risk of respiratory depression (6%)⁷⁴ and “without any major adverse effect on vital signs.”⁶⁴ The intubation rate after prehospital ketamine for agitation/combativeness was 15% to 63%.^{37,65,67,68,70} These intubated patients received a median dose of 4 to 5.25 mg/kg,^{37,65,67,68} with a mean dose of 6.16 mg/kg in one study.⁷⁰ Two prospective studies found ketamine to be faster than haloperidol (class strong, LOE moderate)⁶⁷ or other medication (class strong, LOE moderate)⁶⁶ for sedation of acutely agitated patients. One article indicated that clinically effective doses should be used, even if they exceeded the usual therapeutic doses for sedation by many times (class weak, LOE very low).⁹ Sedative classes and related dosages are described in Table 6. Finally, rapid sequence intubation and respiratory support was proposed as an ultima ratio in two articles (class weak, LOE very low).^{9,73}

Two articles, an expert consensus report⁹ and a nonsystematic review,⁷⁵ supported the treatment of hyperthermia by external passive or active internal cooling. Three articles^{9,55,61} recommended treating metabolic acidosis aggressively, empirically, or based on laboratory results (class weak, LOE very low)⁵⁵ and avoidance of any physical measures that might interfere with compensatory (hyper)ventilation.⁹

DISCUSSION

In this systematic review of the literature about ExDS, we screened 3,604 articles, from which we identified

66 as answering one or more of our initial questions. Six articles were related to the definition of ExDS, 23 to its prevalence or mortality rate, 38 to its pathophysiology and risk factors, and 27 to its treatment.

The LOE remains very low, as 65% ($n = 43$) of the articles were retrospective case reports, case series, or case-control studies. Furthermore, we were able to only partially answer the questions. To our knowledge, this is the first systematic review to evaluate the definition, epidemiology, pathophysiology, and treatment of ExDS.

Because the definition of ExDS remains mostly syndromic and based on clinical criteria, it is prone to subjectivity.⁹ The “white paper experts” recommend six criteria for a diagnosis of ExDS, but in numerous case series, patients are diagnosed with ExDS with fewer than six criteria present (between one¹⁶ and six⁹ criteria). The criteria most frequently cited are hyperaggressive behavior with superhuman strength and a combative attitude toward the police, hyperactivity, bizarre behaviors, unusual pain tolerance, and hyperthermia. However, these criteria do not occur with equal frequency^{16,76} and none of them appear to be mandatory. In the oldest articles, death was part of the definition, probably because these publications were reported by forensic physicians who were mainly concerned with cases of fatal ExDS. A recently published prospective cohort⁷⁶ demonstrated that in cases with six or more features, three of the 10 criteria are more often described: does not fatigue, superhuman strength, and tactile hyperthermia.⁷⁶ From these results, a hyperaggressive state should be considered as potential ExDS and patients should be assessed for additional criteria, such as those described in Table 2.

The prevalence of ExDS appears to vary widely with context and by case definition. Beyond health care providers' issues, this syndrome appears to be particularly relevant for police agencies. ExDS is in question in more than 3% of police interventions that require the use of force and is associated with more than 10% of deaths in police custody. At the same time, severe ExDS requiring out-of-hospital restraint is observed in fewer than two cases for 10,000 advanced life support EMS calls.¹¹ It also seems to be frequent in the forensic setting, where ExDS represents more than 10% of CEW-related deaths³⁰ and more than 15% of cocaine-related deaths.¹² No data are available about admission rates to EDs or critical care units.

The mortality rate of ExDS is estimated to be approximately 8.3% to 16.5%.^{9,12,24,25,30} This

extremely high mortality rate is surprising, but may be overestimated because of publication bias and the absence of a clear definition. Recently, Michaud³² reported a 33% decrease in the overall number of restraint related deaths in ExDS in the period 2004 to 2011 in comparison to 1988 to 1995. Warnings and repeated recommendations concerning the association between restraints (in particular in the prone position) and fatal ExDS were proposed by the authors as a potential explanation for the decrease in mortality.³² Death seems to occur more frequently during the summer.¹² It is usually sudden³⁵ and unanticipated,¹¹ occurring in many cases shortly after chemical or physical restraint and frequently when the individual is in the prone position.^{13,31} Death has been described as being temporally related to CEW use,²⁹ with reports of death occurring within minutes of shock discharge.¹³ ExDS is therefore a major concern for law enforcement officers, as a major proportion of fatal ExDS (38%¹² to 86%³¹) is observed in the context of police custody.

ExDS pathophysiology implicates dopamine pathways and acute exposure to catecholaminergic psychoactive substances. Interestingly, most of the studies evaluating blood or brain cocaine concentrations show low or similar levels of cocaine in ExDS-related deaths, in comparison with other cocaine intoxication-related deaths.¹⁰ Genetic susceptibilities are thus suspected to contribute to the occurrence of ExDS. Different opioid receptor densities in the amygdala^{36,58} could also explain the neuropsychiatric sequelae of ExDS.⁵⁸ Recent publications show the contribution of the NADPH oxidase 2 enzyme in the pathogenesis of ExDS.^{40,42}

Most cases of ExDS^{29,34} occur in the context of psychoactive substance abuse^{9,29,34,35} or among psychiatric patients.^{9,23,31} In more than 90% of cases, the results of toxicology screening tests are positive¹⁶ and 50% of patients have a preexisting psychiatric background.¹⁶ Young age, male sex, African-American race,¹² and being overweight^{11,12,16,20,28,29} are all independent risk factors for fatal ExDS.

The treatment of ExDS remains nonspecific and symptomatic.⁷⁷ Guidelines are oriented to calming the patient down and reducing physical exertion as soon as possible, to counteracting the effects of exogenous and endogenous chemicals contributing to the syndrome, and to treating significant biologic abnormalities. Law enforcement officers should identify the condition and refer the subject as soon as possible to

EMS personnel for treatment and transport to definitive medical care.^{8,9} They also should be particularly vigilant about patients who suddenly calm down and should immediately reassess for possible cardiorespiratory arrest. Diminishing the catecholamine surge and metabolic acidosis^{9,52} by rapid sedation appears essential for short-term positive outcomes.^{8,75} Nevertheless, no evidence yet proves that sedation will result in lower morbidity or mortality.⁹ Benzodiazepines or classic antipsychotics such as haloperidol are the most frequently proposed treatments.⁹ Ketamine has recently been proposed as an alternative in acutely agitated patients,^{8,9,18,27,64–70,73,74} with the pharmaceutical benefit of maintaining airway patency and spontaneous ventilation.^{8,9,18,73,74} The unusual high intubation rate reported after ketamine administration in ExDS is likely due to the large doses used. For all drugs, the intravenous route of administration is preferred, but an intramuscular or intranasal route may initially be used in a prehospital setting.^{8,9,18,52} Notably, we found no management approach without risk, deaths being reported following application of all management approaches, including general physical control, specific forms of restraints, irritant sprays, CEWs, and medications. To date, no comparative data exist to show that one approach is more or less safe than another.

LIMITATIONS AND STRENGTHS

This systematic review has several limitations. First, despite an extensive search, we identified only 66 relevant articles of very limited evidence, most of them retrospective case-series studies (43) and only 10 being prospective studies, from which one is only a conference abstract.²⁶ The overall quality of the studies was therefore poor (LOE low or very low), with LOEs estimated as strong for only three articles related to the pathophysiology or management of ExDS.^{26,47,66} Second, we decided to include publications from the gray literature, such as police reports or expert recommendations. This strategy was intended to include complementary information, particularly epidemiologic data, on subgroups of patients or in specific contexts (in custody, police). Third, because of the inclusion criteria, only articles in English and one in Spanish²⁰ were included in the final review. Fourth, as mentioned, the heterogeneity of the selected studies and the absence of a clear definition prevented us from performing quantitative meta-analyses or evaluating national mortality rates.

Fifth, the real incidence and prevalence remain difficult to estimate. Study sample sizes were small and study designs were subject to numerous biases. In many cases there were no clear or consistent case definition and rarely if ever case patients were compared to a population or control group.

The strengths of this review nevertheless comprise the use of a multiple-source search strategy that included titles and abstracts in English, French, Spanish, and German; a large initial article sample size; and the valuable gradation of the included studies. The total independence of the investigators from law enforcement officers, chemical industries, or weapons manufacturers is noteworthy.

CONCLUSION

In conclusion, this unique systematic review of the literature on excited delirium syndrome shows a global predominance of low to very low levels of evidence. Our results suggest that excited delirium syndrome is a real clinical entity, that it still kills people, and that it probably has specific mechanisms and risk factors. The numerous unresolved questions that remain warrant further investigations. A universal and objective definition must be urgently developed to allow for more structured and standardized research with a better level of evidence, such as with prospective cohorts comprising toxic, metabolomic, and genetic aspects. Randomized and controlled trials on the treatment and care of these patients are essential.

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CME Information: Excited Delirium: A Systematic Review

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Educational Objectives

After reading the article, participants should be able to discuss the diagnostic features, epidemiology, pathophysiology, and treatment options of excited delirium syndrome (ExDS).

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