ACEP Task Force Report on Hyperactive Delirium with Severe Agitation in Emergency Settings
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KEY POINTS:

- Hyperactive delirium with severe agitation, a presentation marked by disorientation and aggressive words and/or actions, is an acute life-threatening medical condition that demands emergency medical treatment.

- Patient safety is and must be the primary focus of emergency medical treatment of hyperactive delirium with severe agitation.

- Rapidly restoring normal body physiology, facilitating a safe environment for the patient and medical professionals treating the patient, and providing the opportunity to differentiate and treat life-threatening causes of hyperactive delirium are patient-centered goals of emergency medical treatment of hyperactive delirium with severe agitation.

- De-escalation techniques may be effective and should be attempted when possible.

- Parenteral medications are often required to treat severe agitation. Multiple pharmacologic options exist for effective treatment of hyperactive delirium with severe agitation. There is no consensus on a single "optimal" medication at this time, but ketamine, droperidol, olanzapine, and midazolam delivered via intramuscular injection are the options best supported by current literature.

- Medical treatment of hyperactive delirium with severe agitation – whether prehospital (EMS) or in-hospital (Emergency Department) should be led by a physician board certified in EMS Medicine and/or Emergency Medicine, respectively. All medical treatments must be at the decision of appropriately trained medical professionals on the physician-led care team.

- Additional research is needed to more fully understand inciting pathways and distinct pathophysiology of individual causes of hyperactive delirium with severe agitation. Further research is also warranted to identify optimal medication choices, doses for those medication choices, and additional medical treatments that improve patient-centered outcomes.

CONTEXT FOR THIS PAPER

This document focuses on the emergent patient in the prehospital or emergency department (ED) setting presenting with hyperactive delirium accompanied by severe agitation. In patients with severe agitation, the use of de-escalation techniques is oriented towards preventing disability or death. This clinical scenario requires immediate medical evaluation by clinicians trained in the stabilization, diagnostic evaluation, and initial treatment of the various etiologies associated with hyperactive delirium and may necessitate the use of parenteral sedating medications. However, optimum strategies for preventing morbidity and mortality in patients with hyperactive delirium remain uncertain given the paucity of high-quality research in existence. This paper intends to synthesize the most current

information available regarding recognition, evaluation, and management of patients presenting with hyperactive delirium accompanied by severe agitation when encountered in the prehospital or ED setting. It is not directed towards patients solely demonstrating agitation without signs of delirium or individuals not engaged as patients. The relevant audience is emergency medical services (EMS) professionals, emergency physicians, and ED medical staff (e.g. nurses, technicians). Patient encounters in the field presenting with delirium and severe agitation often involve the interface of law enforcement and EMS. However, all prehospital treatment decisions for patient care fall solely within the domain of physician-led EMS professionals. The expectation is that every patient encounter will involve evaluation and management by appropriately educated and trained EMS professionals in the field and emergency physicians in the ED.

By their nature, syndromes represent a constellation of signs and symptoms without a clearly elucidated singular cause or pathophysiologic definition. This diagnostic uncertainty, along with the dual use of the nomenclature both to describe the initial patient presentation and to provide a causative etiology on post-mortem examination, has led to controversy over use of the term, "Excited Delirium Syndrome," within medicine and the lay press. Critics of this terminology have raised concern that it has been employed to explain away preventable in-custody deaths as inevitable outcomes, without proper consideration of other contributing factors and alternative management strategies that might have resulted in survival. Supporters of the use of "Excited Delirium Syndrome" have observed patients with agitated or combative behavior that is associated with a delirious state where the individual is not capable of interacting with other individuals or the environment. They recognize such behavior is frequently associated with physiologic abnormalities and high rates of death, warranting immediate treatment to improve patient outcomes. Moreover, the term is only definitively applied as a postmortem cause of death, rather than prospectively at presentation. Given the increasingly charged nature of the term, ACEP is concerned that its use in this document may distract from the intended delivery of critical information surrounding therapeutic options and best practices focused on the patient's care and survival. Consequently, explicit discussion of "Excited Delirium Syndrome" will only occur in the context of

evidence surroundings its existence as a distinct pathophysiologic phenomenon. Rather, in this paper, we use the term "hyperactive delirium with severe agitation" to describe presentations of interest.

Of note, concerns have been raised about potential bias in a prior publication, the 2009 American College of Emergency Physicians (ACEP) white paper on Excited Delirium Syndrome. Since its publication, ACEP enacted a robust global conflict of interest policy, though notably not in direct response to critics of the 2009 white paper nor with specific concerns regarding the content of that paper or others generated before such a policy was in force. While the authors of this paper were informed by the 2009 paper, this work is *de novo* and not to be construed as an update or refutation of the 2009 paper.

Rather, ACEP has heard urgent questions surrounding initial management of hyperactive delirium presenting with severe agitation raised by its membership, the scientific community at large, community leaders, media, and governmental agencies.[1-5] These questions frequently center on the evidence surrounding the safety of and medical justification for treatment with parenteral sedating medications. Such concerns are addressed within this information paper. In an attempt to involve relevant parties from inception, multiple outside medical organizations, including a patient representative, participated in the drafting of this document.

History and Controversies

Emergency health care professionals are faced with the challenges of treating patients agitated or combative to the point where they cannot be safely or reliably evaluated. For more than a century, medical publications have described dangerous agitation accompanying hyperactive delirium. This phenomenon was recognized as early as 1849 when reports of "Bell's mania" described poor outcomes among psychiatric patients experiencing delirium accompanied by severe agitation prior to the advent of psychotropic medications. The high rate of fatalities in patients suffering from hyperactive delirium due to psychiatric illness prior to the availability of effective treatment underscores the challenge of safely managing this presentation. Although patient demographics, associated medical conditions, and toxic exposures have changed, managing these patients remains challenging.[6-8]

Delirium, or acute cortical-subcortical neuronal encephalopathy, is a form of altered mental status involving a fluctuating disorder of attention and arousal that develops acutely and is characterized by restlessness and illusions, and incoherence of thought and speech.[9] The initial published discussion of excited delirium in the medical literature appeared in a 1981 *Annals of Emergency Medicine* case report describing cocaine intoxication in a "body packer," an individual who attempts to smuggle cocaine by intracorporeal means.[10] This report reviewed subtypes of delirium, stating, "There are two major types of delirium: stuporous (dull, lethargic, hypoactive, mute, somnolent, and apathetic) and excited (thrashing, shouting, hyperactive, fearful, panicky, agitated, hypervigilant, and violent). Patients with excited delirium are more common than the stuporous and, because they present a management problem, are often labeled as suffering from a functional psychiatric illness."

More recent research tends to use the descriptive terminology "hyperactive delirium" rather than "excited delirium" or "agitated delirium" for delirium associated with increased neuromuscular activity, often accompanied by agitation, whereas "hypoactive delirium" occupies the opposite extreme.[11] For consistency, we have chosen to employ the descriptive terminology, hyperactive delirium with severe agitation, as the most accurate language identifying the mental status and the level of activity exhibited by patients of interest. Given that many causes of hyperactive delirium with severe agitation, as well as the presentation itself, are associated with increased mortality, the importance of utilizing a structured diagnostic approach that promotes identification of the correct underlying etiology among a lengthy differential of possible causes is underscored.[12,13]

Frequently overlooked, yet essential to dealing with the challenges inherent in such patient encounters, is the inability to reliably determine on initial assessment the cause(s) of severe agitation in the setting of hyperactive delirium. Such a patient needs rapid de-escalation and calming to allow for definitive medical evaluation and ongoing treatment, in order to avoid preventable fatality due to failure to manage the potential causative life threats, and to treat the danger inherent to the presenting condition. In a delirious patient, severe agitation is an emergency ideally managed using multiple calming measures, often delivered in parallel, to facilitate the safety of all involved, to complete the necessary medical

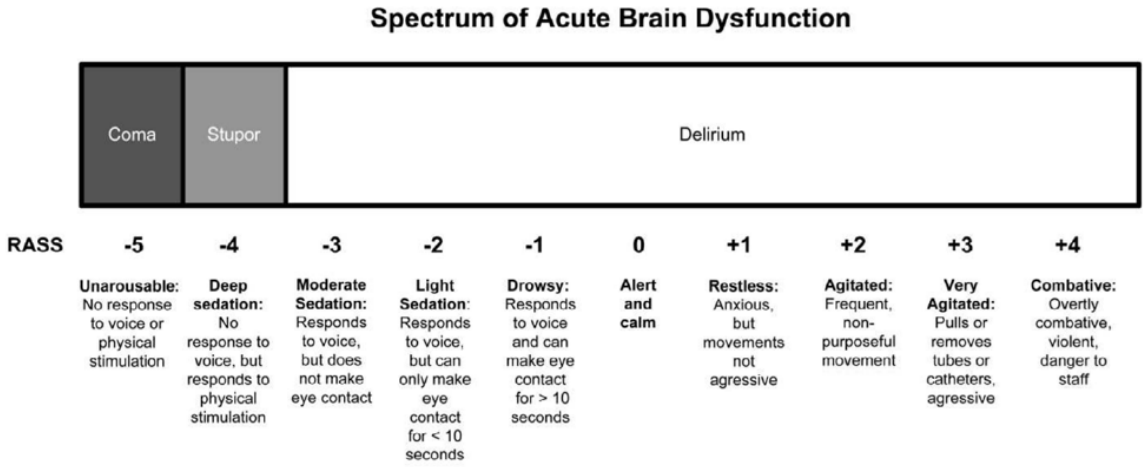
evaluation, and to effectively treat ongoing physiologic derangements that may lead to further decompensation, including fatal outcomes. This critical care should occur while working towards minimization of physical patient restraint and maintenance of patient dignity.[12,14]

CLINICAL PRESENTATION

Description

Hyperactive delirium describes a condition of altered mental status distinguished by disordered thinking and psychomotor agitation, often accompanied by a hyperadrenergic state. Altered mental status in the setting of delirium represents brain function changes such as disorientation, defects in judgment or thought, and disruptions in perception, psychomotor skills, and behavior. It occurs on a continuum, ranging from a hypoactive state (coma) to hyperactive (severe agitation and combativeness), representing extremes of presentation. This spectrum of disease is recognized in multiple scoring systems of acute brain dysfunction, such as the Richmond Agitation-Sedation Scale (RASS) (Figure 1)for critical care patients and the Altered Mental Status Score (AMSS).[15-17] Although not specifically developed in the population of interest, severe agitation in the patient presenting with hyperactive delirium corresponds with RASS of +4 (overly combative, violent, immediate danger to staff) and AMSS of 4 (combative, violent, out of control; loud outbursts of speech; agitated facial expression), though patients with lesser degrees of agitation may require intervention to prevent inadvertent self-harm or injury to caregivers, and to make it possible for medical personnel to identify and treat any dangerous underlying cause of the delirium.

Figure 1. Spectrum of acute brain dysfunction based upon the Richmond Agitation Sedation Scale (RASS).[17] (Used with permission).



Delirium is associated with disordered neurotransmission involving acetylcholine, dopamine, gamma-aminobutyric acid (GABA), and serotonin in the cortical and subcortical regions of the brain.[9] The presentation may result from underlying medical conditions or exposure to toxicants. The condition may be hypoactive, with inattention and decreased activity, or hyperactive, characterized by agitation and combativeness. This paper is limited to consideration of hyperactive delirium demonstrating severe agitation, often involving combative behavior and a hyperadrenergic physiological state.

Differential Diagnosis

Hyperactive delirium with severe agitation, as well as hyperadrenergic physiological states, commonly results from stimulant intoxication and may be caused solely by exposure to this class of drugs. Sympathomimetic toxicity manifests as a broad constellation of signs and symptoms reflecting activation of the autonomic sympathetic nervous system, most commonly due to abuse of cocaine, methamphetamine, or other stimulants. The classic findings of sympathomimetic toxicity are tachycardia, tachypnea, hyperthermia, hypertension, psychomotor agitation, and mydriasis. Patients may also exhibit indefatigability (commonly misinterpreted as “superhuman strength”), confusion, and hyper-attentiveness.[11,18] Distinct exam findings often include tremor, myoclonus, lower extremity rigidity, and repetitive or compulsive behaviors. Features of altered mental status may include aggression, hallucinations and psychosis. Endogenous stress-related catecholamines and exogenous

catecholaminergic drugs likely produce a synergistic effect. Of note, similar presentations of delirium are associated with abrupt cessation of sedative-hypnotic agents. Withdrawal from alcohol, barbiturates, gamma-hydroxybutyrate, or benzodiazepines produces similar clinical features due to release of large amounts of catecholamines, creating an endogenous sympathomimetic syndrome.[18]

Not all cases of hyperactive delirium occur in patients with a history of sympathomimetic use or sedative-hypnotic withdrawal. Alternate etiologies include psychiatric disease and metabolic derangements. As described previously, cases of "Bell's mania" occurred in a psychiatric population prior to the advent of antipsychotic medications and was associated with a diagnosis of schizophrenia.

After initial agitation is treated sufficiently to allow for immediate evaluation, diagnostic testing may identify many causes of altered mental status and agitation. For example, hypoglycemia has been associated with outbursts of violent behavior and/or an appearance of intoxication. However, this diagnosis may be rapidly and conclusively made by determining blood glucose and response to glucose administration. Similarly, stroke, intracranial hemorrhages, and space-occupying CNS lesions causing altered mental status can be discovered with brain imaging. Consequently, awareness of alternative diagnoses along with employment of appropriate diagnostic testing is essential to properly evaluating a patient presenting with hyperactive delirium. In cases where patients rapidly recover as well as in fatal cases without postmortem analysis, underlying medical causes of delirium, such as hypoglycemia, may go undetected. Indeed, hypoglycemia cannot be diagnosed at autopsy due to the natural decrease of glucose concentrations after death. Immediate management of agitation to facilitate a rapid assessment of treatable causes is a fundamental tenet of care of these patients.

It is beyond this paper's scope to exhaustively review all causes of altered mental status and/or delirium. However, it is essential to consider clinical syndromes that may be responsible for hyperactive delirium with severe agitation but do not have immediately available diagnostic testing to confirm the suspected diagnosis. Individuals whose cause of death is listed as "excited delirium" are typically hyperthermic prior to cardiac arrest, suggesting severe physiologic disruption frequently accompanied by extreme psychomotor agitation.[19] Hyperthermia has been described as a "harbinger of death" in the

setting of hyperactive delirium associated with sympathomimetic toxicity.[20] Therefore, hyperthermic conditions have been selected for further discussion. Note that these causative etiologies typically exist along a spectrum of severity based on clinical features and are not diagnosed by rapidly available laboratory or imaging tests. Rather, the clinician relies upon the history, which is often limited, clinical exam findings, and response to treatment. Furthermore, multiple causes may be involved, such as stimulant use exacerbating heat related illness or underlying psychiatric disorder.

Sympathomimetic Toxidrome. The sympathomimetic toxidrome includes hypertension, tachycardia, mydriasis, diaphoresis, hyperreflexia, anxiety, paranoia, agitation, and seizures. It occurs following exposure to excessive doses of stimulant drugs, most often cocaine, methamphetamines, or synthetic cathinones. Depending on the route of administration, sympathomimetic toxicity occurs minutes to hours following exposure. Death is typically due to hyperthermia, dysrhythmia, or hypertensive crisis. These patients often exhibit agitation, aggressiveness, drug induced psychosis, and violent behavior.[21,22]

Alcohol or Sedative-Hypnotic Withdrawal Syndrome/Delirium Tremens. Alcohol withdrawal syndrome (AWS) occurs after cessation of or a reduction in alcohol consumption after a prolonged period of excessive use. Signs and symptoms include anxiety, shakiness/tremor, diaphoresis, vomiting, mild hyperthermia, and tachycardia. A similar syndrome occurs after cessation of sedative-hypnotic agents such as benzodiazepines, barbiturates, or gamma-hydroxybutyrate. Delirium tremens (DTs) falls at the severe end of the spectrum of alcohol withdrawal. DTs typically occurs three days into withdrawal symptoms and lasts for two to three days. It is characterized by a rapid onset of confusion, hallucination, shivering, shaking/tremor, tachycardia, irregular heart rhythm and diaphoresis.[23] Although patients may exhibit dangerous agitation, they are rarely aggressive or violent.

Delirious Mania/Malignant Catatonia

Bell was the first to observe a form of disease resembling some advanced states of mania and fever.[24] There is no clear consensus on the clinical characteristics associated with delirious mania.[25] It is not recognized as a stand-alone diagnosis because many terms have been used over the years to describe patients presenting with mania including excitement, delirium, lethal catatonia, malignant catatonia, and Bell's mania.[25] Delirious mania arises from both psychotic and affective psychiatric diseases and is used to describe manic patients who have delirious symptoms that occur and remit without other evident medical reasons.[25] Delirious mania is a potentially life-threatening but under-recognized neuropsychiatric syndrome.[25] It is characterized by the acute onset of excitement, grandiosity, emotional lability, delusions, and insomnia characteristic of mania and the disorientation and altered consciousness characteristic of delirium.[24] The syndrome may also be accompanied by posturing, stereotypy, mutism, negativism and echo-phenomena suggesting catatonia.[26] The concurrence of delirium and mania is unusual.[25] Catatonia frequently accompanies this syndrome. The distinction between delirious mania and the excited or malignant forms of catatonia is challenging in psychiatry due to diagnostic ambiguity.[24] For example, Fink describes 4 cases of delirious mania. In these cases, delirious mania lasted days to weeks[24] and hospitalization tended to last longer than for manic patients without delirium.[25] These patients may exhibit both agitation and violent behavior.

Serotonin Syndrome. Serotonin syndrome is caused by medications that result in decreased serotonin reuptake, decreased breakdown of serotonin, increased serotonin release, or are serotonin agonists or precursors. Most often, serotonin syndrome is the result of drug-drug interactions but may also result from intentional self-poisoning. Serotonin syndrome is characterized by altered mental status, neuromuscular hyperactivity, and autonomic instability. Typical signs include spontaneous clonus, inducible clonus, ocular clonus, agitation, diaphoresis, tremor and hyperreflexia and muscle rigidity especially in the lower extremities. The Hunter Serotonin Diagnostic Criteria is one set of criteria used to diagnose serotonin syndrome. Note that not all findings need to be present to diagnose serotonin syndrome.[22,27,28]

Figure 2. Decision rules for predicting serotonin toxicity.[27] (Used with permission).

Hunter Serotonin Toxicity Criteria: Decision Rules
In the presence of a serotonergic agent:
1. IF (spontaneous clonus = yes) THEN serotonin toxicity = YES
2. ELSE IF (inducible clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES
3. ELSE IF (ocular clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES
4. ELSE IF (tremor = yes) AND (hyperreflexia = yes) THEN serotonin toxicity = YES
5. ELSE IF (hypertonic = yes) AND (temperature > 38°C) AND [(ocular clonus = yes) OR (inducible clonus = yes)] then serotonin toxicity = YES
6. ELSE serotonin toxicity = NO

Patients with serotonin syndrome typically lack violent behavior although agitation may be present.[28]

Neuroleptic Malignant Syndrome (NMS). Neuroleptic malignant syndrome results from repeated exposure to first and second-generation antipsychotics, or abrupt discontinuation of dopaminergic agents. Neuroleptic malignant syndrome typically occurs within the first 2 weeks of antipsychotic medication use. It is defined by unresponsiveness to anticholinergic medications, hyperthermia, increased muscle tone, diaphoresis, dysphagia, fluctuating level of consciousness from stupor and confusion to coma, and an elevated creatine phosphokinase (CPK). Signs include hyperthermia, autonomic instability, severe muscle rigidity, mental status changes, tachycardia, and fluctuating blood pressure. NMS develops over a period of days to weeks and resolves in approximately 7 to 10 days with supportive care and directed treatment.[22,23,28] Patients with NMS are typically not agitated or violent.

Anticholinergic Toxidrome. The anticholinergic toxidrome occurs following exposure to antimuscarinic agents. The presentation includes delirium, dry mucus membranes, dilated pupils, flushed and dry skin, urinary retention, decreased bowel sounds, hyperthermia, and tachycardia. Anticholinergic delirium may cause agitation but rarely purposeful violent behavior. Stereotypical "picking in the air" ("carphologia") and incoherent mumbling are prominent feature of anticholinergic delirium and often distinguishes it from other causes of delirium. The antidote physostigmine often quickly improves the delirium and other symptoms of anticholinergic toxidrome.[28] Patients with anticholinergic delirium typically lack violent behavior although agitation may be present.

Heat-Related Illness. Heat-related illness ranges from heat cramps to heat exhaustion to heat stroke. Heat stroke is an environmental condition resulting from prolonged exposure to or physical exertion in high temperatures and/or high humidity**.** It manifests as tactile hyperthermia, rhabdomyolysis, and delirium. Mental illness and neuroleptic use may exacerbate hyperthermia.

Body temperature rises rapidly to greater than 40ºC (104ºF), and the sweating mechanism fails, so the body is unable to cool. Presentation includes nausea, seizures, altered mental status and sometimes coma. These conditions can most often be distinguished due to history of exertion in high temperatures and lack of violent behavior.[22,23,28]

Thyrotoxicosis. Thyrotoxicosis is the clinical syndrome caused by excess thyroid hormone action at the tissue level due to inappropriately high circulating thyroid hormone concentrations. Findings include heat intolerance, palpitations, anxiety, fatigue, weight loss, and muscle weakness. Clinical findings may include tremor, tachycardia, lid lag, and warm moist skin. Thyroid storm is a life-threatening emergency associated with untreated hyperthyroidism. The likelihood that thyrotoxicosis has progressed to thyroid storm is determined by the Burch-Wartofsky Point Scale (BWPS) which assigns a point value to temperature, central nervous system effects, gastrointestinal-hepatic dysfunction, heart rate, congestive heart failure, presence or absence of atrial fibrillation, and if there was a precipitating event.[23] Thyroid hormone testing is abnormal in such cases, although results may not be available in a timely fashion. Patients with thyrotoxicosis typically lack violent behavior although agitation may be present.

Excited Delirium Syndromes

"Excited delirium" has been listed in cause of death determinations by medical examiners in fatalities thought to result from presentations of hyperactive delirium. However, the descriptive terminology "excited delirium syndrome" (ExDS) has also been used in the EMS and emergency medicine literature to indicate various processes with the common feature of severe agitation in the setting of hyperactive delirium. Controversy has arisen regarding the ability to differentiate ExDS as a distinct entity from causes discussed above. Excited delirium syndrome is not a currently recognized medical or psychiatric diagnosis in either the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) of the *American Psychiatric Association,* or the *International Classification of Diseases* (ICD-10) of the World Health Organization. A semantic discussion of the merits of embracing this term was felt to detract from the primary intent of this document, which is to provide updated recommendations for initial management of patients presenting with hyperactive delirium with severe agitation. These patients are at high risk of a fatal outcome likely caused by various treatable etiologies, and from the metabolic consequences of severe exertion itself. Thus, the most important aspect of this document is the discussion of proper evaluation and treatment in such cases. Nevertheless, for contextual completeness and towards transitioning to more precise terminology, a brief discussion of the conclusions reached and limitations of

the evidence surrounding ExDS as a distinct pathophysiologic process follows. Furthermore, the reader is reminded we use the term ExDS in the context of many published references employing this language.

Many of the initial studies of this syndrome relied on forensic data from deaths attributed to ExDS. Because no ICD-10 code for ExDS exists to date, data extraction from medical records is challenging. Case selection often depends on *a priori* definitions of ExDS, which typically include subjective features. Some such descriptors include severe agitation, violence, thrashing, bizarre behavior, inappropriate nudity, extreme paranoia, hypervigilance, lack of tiring, constant physical activity, unusual or unexpected strength, pain tolerance or imperviousness to pain, noncompliance with police directives, combativeness, attraction to reflective surfaces, stupor, fear, and panic.[29] Objective clinical signs associated with ExDS include hyperthermia, tachycardia, tachypnea, increased tidal volume, diaphoresis, and mydriasis. Laboratory data, when available, may reveal hyperkalemia, acidosis, rhabdomyolysis, acute kidney injury, or disseminated intravascular coagulation. Many of these findings are common in hyperactive delirium no matter what the cause. Robust, reproducible data on vital sign abnormalities and laboratory findings are frequently lacking. It is rarely possible to get accurate vital signs in the acute phase of severe agitation. Seizures can occur in fatal ExDS cases, but tend to be more common in patients with known sympathomimetic toxicity and alcohol/sedative withdrawal syndromes.[30]

The incidence of presentations of possible ExDS is difficult to determine because a number of potential cases have historically been handled solely by law enforcement, and an unknown proportion of these have not resulted in a medical system encounter unless an untoward event was recognized. Studies of ExDS derive data from ED encounters,[31,32] EMS encounters,[33-35] encounters with law enforcement officers,[20,36-40] and forensic data.[30,41-50] A presentation with potential ExDS is estimated to occur in 0.02% to 1.5% of EMS encounters.[19,34] Although many case series in the literature rely on law enforcement reports categorizing encounters as ExDS, delirium is a medical emergency that cannot be safely differentiated from purely behavioral concerns by law enforcement personnel. Consequently, there are concerns regarding potential for biased reporting of ExDS in law enforcement literature as justification for in-custody deaths. However, reports of fatal outcomes underscore the emergent nature of the medical

condition at hand. The current literature describes a young (mean age of 33.3 years, range 14 to 71 years)[29] and predominantly male (83% to 95% of ExDS cases) population.[29] Among studies that report patient demographics, Black or African-American race was reported in 33% to 63% of fatal cases[34,37] and 56% of non-fatal cases of severe agitation.[36] Concerns have been raised that differential assessment occurs because persons of color more frequently have dangerous encounters with law enforcement, who may frequently be the source of case finding in the literature.[51] Estimated mortality in presentations with severe agitation where ExDS is suspected ranges from 11.1% to 16.5% depending on the population and case definition,[30,39,40] an exceedingly high proportion of fatal outcomes. However, given that attribution of ExDS is only accurate based on postmortem assessment, prospective study of potential cases is difficult from the point of initial patient contact. Furthermore, less serious cases of severe agitation are also less likely to be captured by the review mechanisms described above.

ExDS presentations are commonly associated with chronic stimulant use disorder, usually cocaine or methamphetamine.[37] A psychiatric diagnosis of schizophrenia accompanied by inconsistent use of psychiatric medications is also frequently seen.[43,52] While most cases of ExDS are associated with sympathomimetic drug use, postmortem analysis shows that not all deaths attributed to ExDS correlate with the detection of drug metabolites; it should also be noted that drug detection capability is limited in any given case by the samples collected and analysis performed.[29]

The proposed pathophysiologic mechanism of chronic stimulant-associated ExDS distinct from other causes are not well studied. As currently theorized, chronic use of cocaine and/or methamphetamine causes increases in extracellular dopamine in crucial areas of the brain with associated alterations in central dopamine transport (DAT) or loss of DAT regulation. Chronic cocaine use impacts hypothalamic D1 and D2 dopamine receptors differentially, such that pathways for generating hyperthermia are not counter-regulated, and severe hyperthermia is allowed to develop.[53] Hyperthermia and hyperactivity may also result from increased thermogenesis due to dopamine alterations in the brain's mesolimbic pathways.[50,54] The disruption of DAT homeostasis by chronic stimulant use creates a hyperdopaminergic state that sets the stage for ExDS in those who are genetically predisposed or situationally “primed” for

ExDS to occur.[43,55] All psychostimulants (e.g., cocaine, methamphetamine, and MDMA) increase the synaptic levels of dopamine,[56,57] which may explain why chronic psychostimulant users are at greater risk for exhibiting the behavioral symptoms associated with ExDS. In people with cocaine use disorder, there is a compensatory upregulation in DAT function, which is an adaptive increase to offset dopamine overflow in the synapse. When this homeostatic control of synaptic dopamine fails, it leads to a functional hyperdopaminergic state, which triggers the acute onset of delirium and marked agitation in ExDS patients.[43,49,50,55]

Oxidative stress has been proposed as a pathogenic mechanism in which cocaine-induced neurotoxicity is induced via production of reactive oxygen species.[58-62] Similarly, reactive oxygen species formed by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzymes may be responsible for methamphetamine-induced dopamine-releasing and locomotor-activating properties, based upon a study showing that an antagonist/antioxidant significantly decreases methamphetamine's ability to evoke the dopaminergic response.[63] There is an association between ExDS and gene expression of heat shock proteins 70[64-66] and 90[67] associated with cocaine-induced neurotoxicity. Heat shock protein is thought to be a potential marker for ExDS as it is reported at increased levels in autopsy studies. Oxidative stress is also implicated in decreases of GABAergic neurotransmission due to increased dopamine release in the nigrostriatal nerve terminals[68] with increases in extracellular GABA in the nucleus accumbens.[69] Wetli et al state "the diagnosis of 'agitated delirium' can be made by postmortem measurement of DA synaptic markers in the striatum and the hypothalamus. The distribution found on autopsy is markedly different from both simple cocaine overdose and mechanical or positional asphyxia."[55] Even if a distinct pathophysiologic mechanism identifiable on post mortem examination is ultimately confirmed, EMS professionals and emergency physicians caring for patients will be unable to distinguish ExDS as a distinct etiology from other causes of hyperactive delirium on initial presentation as much of the distinguishing evidence is derived from post-mortem analysis.

There is a paucity of clinical studies on suspected ExDS with a notable exception being the EXCITATION study.[70] This was a prospective multicenter trial that enrolled a convenience sample of

patients who presented to participating EDs with either ExDS (defined as 6 or more of: pain tolerance, tachypnea, sweating, agitation, tactile or measured hyperthermia, non-compliance with police or medical personnel directions, lack of tiring, unusual strength, inappropriately clothed, and mirror or glass attraction) or agitation requiring sedation that did not meet ExDS criteria. A third group of healthy volunteers were exercised and emotionally stressed to serve as a control. Blood stress markers were collected in an attempt to distinguish between patients with ExDS, agitated patients not meeting ExDS criteria, and the control group. Researchers assessed norepinephrine, cortisol, copeptin, orexin A, and dynorphin from the test subjects. Cortisol was more elevated in the ExDS group compared with the other two groups. Orexin was elevated in the ExDS versus the control group but not the non-ExDS agitation group. The trial was not able to identify a single reliable blood marker to differentiate ExDS in living patients.[70]

Neurocardiac dysregulation has also been proposed as a potential contributor to ExDS-associated mortality. There is good evidence that there are cardiovascular afferents to cortical structures and cortical innervation to the cardiovascular system. These neurocardiac pathways can be dysrhythmogenic and can induce ischemia in times of great stress. Examples include myocardial necrosis associated with stroke as well as subarachnoid hemorrhage with myocardial injury noted to be adjacent to cardiac neural tissue as opposed to vascular structures in patients without preexisting coronary atherosclerosis.[71] Additionally, Takotsubo cardiomyopathy is a well-established stress-induced cardiomyopathy.[52,72,73] It has been posited that the hyperadrenergic state associated with chronic substance use, along with stress-induced cortical cardiovascular activity, could contribute to sudden death in agitated patients.[52,72,73]

The importance of a skilled investigation of the scene and circumstances of death cannot be overestimated to fully explore ExDS as a distinct entity. Crucial information such as patient behavior, drug use history, a history or presence of psychosis, or the presence of hyperthermia, can facilitate medical examiner determinations. To improve the precision of death certificate data available for public health surveillance, evidence-based recommendations for the practice of death investigation and autopsy, toxicological analysis, interpretation of toxicology findings, and death certification are necessary.

Certifying a death as "excited delirium due to acute cocaine intoxication" versus simply "acute cocaine intoxication" allows these deaths to be identified, tracked, and studied to better identify unique features of the condition and improve patient care. Without the "excited delirium" component, these deaths are lost as routine acute drug intoxication deaths. Robust documentation may assist future efforts to further our understanding of this presentation.

MANAGEMENT OF HYPERACTIVE DELIRIUM WITH SEVERE AGITATION

There are risks associated with empiric treatment for a presumptive diagnosis in all aspects of medicine; nevertheless, such an approach is required when the patient's clinical condition necessitates the need for resuscitative interventions prior to a definitive diagnosis. The window of evaluation for making a definitive diagnosis is often constrained in the setting of hyperactive delirium with severe agitation due to hemodynamic and respiratory instability and because agitation prevents a more robust initial investigation of causative etiologies. This is particularly true when the differential is broad and the need for intervention is emergent, such as a patient exhibiting agitation sufficiently severe to represent an immediate danger to the patient and to those attempting to care for the patient. Without the ability to immediately determine the cause of severe agitation, and due to the danger to the patient associated with causes of such a state, rapid and effective reduction of severe agitation is essential. The rationale for aggressive treatment of severe agitation is summarized below.

Dangers To:

Patients

Hyperactive delirium with severe agitation is a life-threatening constellation of signs and symptoms with numerous causes discussed above. The combination of vital sign abnormalities, metabolic derangements, altered mental status/agitation, and potential physical trauma raises serious concerns for rapid physiologic deterioration and death[19] particularly in patients with underlying comorbidities (e.g., coronary artery disease, obesity, asthma). Patients presenting in this manner are at high risk of direct physical trauma, not only from unintentional injuries such as falls, but also the secondary physical injuries

that may result from physical restraint. In the setting of severe agitation, restraint without sedation results in a higher injury and fatality rate (Odds Ratio 7.4 for fatality with restraints).[5]

Medical complications due to hyperactive delirium are numerous. Hyperthermia can quickly develop, leading to multiorgan injury. Rhabdomyolysis may be seen not only due to increased metabolic drive, but also in association with physical restraints.[74] Intravascular volume depletion, kidney injury, electrolyte abnormalities and acidemia are all adverse effects potentially exacerbated by physical struggle and restraint. Underlying conditions, such as hypoglycemia, acidosis, life-threatening dysrhythmias and toxic exposure, go untreated until the patient can be safely evaluated by emergency personnel. Additionally, agitation and continued struggling decreases the rapidity of obtaining diagnostic studies such as blood glucose levels and decreases the quality of some diagnostic studies such as CT scans that require the patient remain immobile.

EMS Professionals, Other First Responders, and Hospital -Based Professionals

Beyond the primary concern of harm in the patient, the degree of severe agitation seen with hyperactive delirium presents a physical threat to those in proximity in the field: EMS professionals, police/law enforcement officers, rescue crews, and public bystanders. Unfortunately, physical trauma experienced by EMS professionals, other first responders, and public bystanders occurs frequently in cases of severe agitation.[75] Furthermore, these patients place others in danger of bloodborne and oral pathogen exposure from scratching, biting, and spitting. After transport to the hospital, medical staff, nearby patients, and visitors/family are at risk for the same dangers, including physical trauma, potential for bloodborne and oral pathogen exposure, and psychological injury. Delirious patients are very resource and time-intensive for medical staff, requiring numerous staff and intensive monitoring to ensure safety and appropriate treatment, potentially diverting resources from other critical patients requiring simultaneous care.[76]

De-escalation Techniques

There is broad agreement that patients who present with agitation should initially be provided verbal and non-verbal de-escalation.[77-85] Ideally, verbal techniques for de-escalation are used first. If they fail, more intensive maneuvers can be attempted. Unfortunately, there is a lack of consensus regarding appropriate "verbal" and "non-verbal" de-escalation techniques in severe agitation. In the medical literature, these concepts generally refer to removing the patient from noisy/stimulating environments, offering basic needs such as restroom, food and water, and attempting respectful, verbal interaction.[79,80] At least three papers do offer specifics regarding components of these techniques. While helpful in their relative specificity, the first two reports are focused on inpatients and poorly apply to the prehospital and/or ED settings. A 1991 publication with a focus on mental health nursing included the concepts of personal space for the patient, appropriate open-ended phrases from the clinician, clinician posture and body language, setting an appropriate time limit for the de-escalation attempt, and considerations of environment and personal safety.[85] A more recent publication focused on five types of non-pharmacologic interventions that should be offered before medications for inpatients: description of skills/coping strategies, one-on-one verbal support, distraction with food/water/etc, practical assistance, and relaxation.[78] A third publication provides ten domains of de-escalation related to the emergency environment: respect personal space, do not be provocative, establish verbal contact, be concise, identify wants and feelings, listen closely to what the patient is saying, agree or agree to disagree, set clear limits with clearly verbalized consequences for violations, offer choices and optimism, and debrief the patient and staff.[86,87]

In addition to establishing the components of de-escalation techniques, emerging evidence suggests that effectiveness may also be impacted by the level of specialized training that health care clinicians have received. In the out-of-hospital environment, crisis intervention team (CIT) training that was originally designed for law enforcement officers has been implemented by some EMS agencies to establish formalized de-escalation techniques.[86-88] Specific training for ED personnel regarding these techniques has been associated with decreased use of physical restraints, although evidence surrounding outcomes of interest is limited.[89] Specialized response teams with uniquely trained personnel have been

implemented for response to agitation/behavioral emergencies in both the EMS and ED environments, although conclusive effectiveness studies have yet to be completed.[13,90]

We strongly recommend that the urgency of intervention not inadvertently exclude simple, effective therapies. In a recent large, preliminary analysis of patients in law enforcement custody who were documented as combative and required an EMS response, non-pharmacologic intervention was all that was required in over 80% of cases.[91,92] In nearly all cases, non-pharmacologic interventions may be attempted, even if in parallel with preparations for pharmaceutical administration. As stated above, the circumstances in which severely agitated patients are encountered may require immediate utilization of pharmacologic and physical interventions, but in many scenarios, it is still feasible to attempt verbal and non-verbal de-escalation initially. It appears these techniques may be most effective when provided within a structured format, likely enhanced by assignment of specialized teams. The failure of these de-escalation techniques may indicate a much more severe form of agitation only amenable to treatment with sedating medications.

Pharmacologic Options for Agitation

As opposed to strictly psychiatric or behavioral emergencies with an intact sensorium, patients exhibiting severe agitation due to hyperactive delirium are unlikely to respond to non-pharmaceutical de-escalation techniques due to the degree of brain dysfunction. Such techniques should be attempted at the outset of the patient encounter but if the degree of agitation does not improve or concern for safety requires more rapid control, the timely use of medications to treat severe agitation becomes essential. A sedating medication in a chaotic environment creates a very real risk for respiratory depression and/or airway obstruction, which are well-documented causes of death during prehospital and in-hospital sedation. Proper monitoring of the patient once treatment of agitation allows for close contact is incumbent to minimize these risks.

The two most commonly administered classes of sedating medications in the prehospital environment are benzodiazepines and antipsychotics. In recent years, ketamine has been increasingly used

for these patients.[93] In nearly all cases, initial sedating medications for patients presenting with severe agitation in the setting of hyperactive delirium will be administered parenterally via an intramuscular injection as other administration routes are not practical due to the lack of IV access on initial contact and the degree of agitation present. Oral medications do not provide rapid enough treatment of agitation to be a viable option in the population considered.

A detailed abstraction of studies of medications used by EMS professionals and emergency physicians to treat severe agitation segregated by drug in each study arm is contained in the evidentiary table in the appendix. The evidence surrounding benzodiazepines, antipsychotics, ketamine, and combinations thereof is summarized by class of medication in the discussion below. Additionally, direct comparisons between classes are described when available. Of note, the body of evidence is generally low quality with few direct comparisons between preferred agents, making determination of a clearly superior regimen difficult.

Benzodiazepines

Benzodiazepines bind the gamma aminobutyric acid A ($GABA_A$) receptors in the CNS chloride ion channels. This binding increases inhibitory neurotransmission in the brain causing decreased psychomotor activity, generalized muscle relaxation, and inhibition of catecholamine release. Excessive benzodiazepine dosing can lead to sedation, transient hypotension, and respiratory depression, most often when combined with other sedating agents or in patients with anatomic airway abnormalities. A large amount of published research is available regarding the use of benzodiazepines either as a sole agent or in combination with another agent (most commonly an antipsychotic) for treating severe agitation. Unfortunately, much of this research is limited to case series or is retrospective in nature. Furthermore, the population in the majority of these studies is psychiatric patients rather than undifferentiated emergent patients, although indirect evidence may be of assistance from some of the psychiatric literature. Of the trials available for review, benzodiazepines are typically compared to other sedating agents, and the trials tend to lack placebo or non-pharmacologic arms.[94-97]

The benzodiazepines that have been studied to treat acute, severe agitation via the IM route are midazolam and lorazepam. Direct comparison between these agents occurred in 2 studies. In an RCT, Nobay et al reported on a prospectively randomized group of undifferentiated ED patients who were violent and severely agitated. These patients were randomized to receive midazolam (5 mg IM) or lorazepam (2 mg IM). Both regimens appeared to work effectively to achieve sedation. However, midazolam had mean time to sedation of 18.3 minutes, 13.9 minutes faster than lorazepam. In addition, midazolam demonstrated a more rapid time to re-arousal than lorazepam.[98] Another prospective observational study examined time to sedation in patients receiving midazolam IV (mean dose 3.08 mg), IM (mean dose 2.25 mg), or IN (mean dose 2 mg) compared to lorazepam IV (mean dose 1.9 mg) or IM (mean dose 2.4 mg). The majority of patients received medications via the IV route and the dose of midazolam was lower than typically studied, thus it is unlikely that time to sedation documented in this study is representative of IM administration. Nevertheless, in this study, mean time to control of severe agitation was similar at 14.95 minutes for midazolam versus 17.73 minutes for lorazepam.[99] Multiple additional studies of benzodiazepines compared their use to antipsychotics, ketamine, or a combination of medications but do not directly compare agents. However, it is evident that time to sedation for midazolam IM 5 mg to 10 mg is consistently faster than lorazepam, ranging from 8.5 to 30 minutes for midazolam with the majority of studies falling between 10 to 20 minutes.[16,100-106] Additional studies of lorazepam 2 mg IM utilized less precise time endpoints but time to adequate sedation ranged from 30 to 60 minutes.[96,107,108] Both midazolam and lorazepam may cause equivalent levels of respiratory depression, inconsistent and deeper than anticipated degrees of sedation, and unpredictable duration of sedation with no clear disadvantage for midazolam compared to lorazepam from a safety perspective.[16,98-101,103-108]

To summarize, the benzodiazepines studied for initial treatment of severely agitated patients via IM administration are lorazepam and midazolam. All regimens as single agents at typical doses studied appear effective for controlling agitation. Following IM administration, midazolam achieves desired sedation endpoints faster than lorazepam with mean time to sedation being approximately 10 to 20 minutes for midazolam compared to 30 minutes or greater for lorazepam. All benzodiazepines produce

respiratory depression at higher doses—especially when combined with other sedating medications—and any administration should be followed by close patient monitoring with pulse oximetry, observation of respiratory rate, and continuous waveform capnography at the first opportunity patient condition allows. The safety profile for IM administration is not substantially different between lorazepam and midazolam. Consequently, if using a benzodiazepine for initial treatment of severe agitation, midazolam is recommended rather than lorazepam due to appreciably faster time to adequate sedation.

Antipsychotics

Antipsychotics have a long history of use for agitation, including presentations of hyperactive delirium. They are traditionally grouped into two major subgroups, first generation (haloperidol and droperidol have been studied via IM administration to treat acute agitation) and second generation or atypical (olanzapine and ziprasidone have been studied via IM administration to treat acute agitation) agents. Both subgroups exert their sedative and anti-agitation effects via anti-dopaminergic neurotransmitter effects in the midbrain, sub-cortical regions, and the reticular activating system of the brain. Extrapyramidal side effects (dystonia, akathisia) are relatively common when first generation antipsychotics are used to treat other conditions but are rarely described in studies of sedation. More serious complications, such as neuroleptic malignant syndrome and tardive dyskinesia, are rare with acute administration. In addition, all antipsychotics have the potential to cause prolongation of the QT interval.

Various studies directly comparing antipsychotics have been published. The first-generation agents, droperidol 5 mg to10 mg IM and haloperidol 5 mg to10 mg IM, have been studied as separate arms in 5 studies.[109-113] Droperidol was found to be equivalent or superior to haloperidol in all of these studies. The second-generation agents, olanzapine 10 mg IM and ziprasidone 20 mg IM, were studied as separate arms in one study with olanzapine found to be superior to ziprasidone in achieving adequate sedation at 15 minutes.[103] Multiple comparisons between first- and second-generation antipsychotics have also been published. Droperidol 5 mg IM was compared to olanzapine 10 mg IM in 2 studies with both agents found to be equally effective and with similar safety profiles.[113,114] In contrast, droperidol 5mg IM

was superior to ziprasidone 10 mg to 20mg IM at achieving control of agitation at 15 minutes with increased rates of respiratory depression for those receiving ziprasidone.[16,108] Olanzapine 5 mg to10 mg IM provided equivalent or superior control of agitation when compared to haloperidol 5 mg to 10mg IM.[103,106,113] Haloperidol 5 mg to10 mg IM produced similar effects to ziprasidone 20 mg IM in one study, although both were inferior to other agents studied.[103] Based on studies that directly compare agents, droperidol 5 mg to 10 mg IM and olanzapine 10 mg IM are the best initial options when choosing an antipsychotic for initial treatment of severe, acute agitation.

Many studies have reported time to adequate sedation, although quality and methodologies vary greatly. Nevertheless, there is sufficient data available to estimate an expected time to desired treatment effect. For droperidol 5 mg to 10 mg IM, time to adequate sedation using varied endpoints ranged from 10 to 22 minutes.[16,101,104,108,110,114,115] Similarly, olanzapine 5 mg to 10 mg IM demonstrated mean time to adequate sedation of 11.5 to 17.5 minutes.[94,103,106,114,116] Haloperidol 5 mg to 10 mg IM was slower than both droperidol and olanzapine, with adequate control of agitation at 20 to 60 minutes depending on the study endpoint and, when discretely measured, a mean time to sedation of 11.4 to 28.3 minutes.[96,98-100,102,103,106,107,109-111,113,117-119] Likewise, ziprasidone 10 mg to 20 mg IM was slower than both droperidol and olanzapine, with adequate control of agitation at 17 to 30 minutes.[16,103,108] Unlike other antipsychotics, patients receiving ziprasidone experienced substantially higher instances of respiratory depression.[16,108]

Droperidol is likely the optimal antipsychotic when treating agitation in the setting of hyperactive delirium due to its well-studied safety profile, wide dosing range, and rapid onset compared to most other antipsychotics. Olanzapine is not as well studied providing less confidence that it is equivalent to droperidol. However, data available to date is promising, and there is no evidence to the suggest that olanzapine performs inferior to or has a worse safety profile than droperidol. The preponderance of evidence regarding injectable antipsychotics suggests that droperidol and olanzapine provide the most rapid (10 to 20 minutes to adequate sedation) and effective treatment of agitation. They should be considered first-line agents over ziprasidone or haloperidol.

An additional issue to consider with antipsychotics is the possibility of QTc prolongation leading to torsades de pointes, a life-threatening adverse event. In particular, droperidol was issued a black box warning regarding this potential side effect in 2001 by the U.S. Food and Drug Administration (FDA).[120] This black box warning states that droperidol should be reserved for patients who have not responded to other treatments and that an electrocardiogram (ECG) be performed prior to administration with cardiac monitoring for 2 to 3 hours after administration. These recommendations are impractical for using droperidol for acutely agitated patients presenting with hyperactive delirium. Moreover, QTc prolongation related to common uses of droperidol has not been a complication or concern in subsequent investigations. Independent reviews described below have demonstrated that the black-box warning is unwarranted.[113,121,122] Olanzapine blocks potassium channels to a far lesser degree than other antipsychotics considered. Thus, QT prolongation in patients receiving olanzapine is extremely rare.[116,123]

Several studies have examined QTc prolongation and the occurrence of torsade de pointes in patients receiving medications for agitation within the ED. Droperidol and haloperidol block delayed-rectifier potassium (IKr/HERG) channels in the myocardium, prolonging the QT interval and raising concern regarding the development of torsades des pointes. The majority of the literature addresses droperidol specifically. Knott et al compared QTc following administration of midazolam versus droperidol. Median QTc in the midazolam group was 425 ms. The droperidol group was not significantly different at 439 ms.[124] Despite a QTc of >500 ms in some subjects, no dysrhythmias were seen. In a blinded, randomized trial, Isbister looked for abnormal QT-HR pairs and did not find a difference in patients treated with midazolam, droperidol, or the combination, although numbers in each group were small.[101] Taylor et al compared droperidol versus olanzapine versus combination midazolam/droperidol. Median QTc was 442 ms, 445 ms and 450 ms in each group, respectively. No dysrhythmias were observed.[125] Martel randomized patients to droperidol, ziprasidone, and lorazepam with a median QTc in the droperidol group of 413 ms, no difference in median QTc between drugs studied, and no episodes of torsades de pointes.[108] Chan et al randomized midazolam versus combination midazolam/olanzapine versus midazolam/droperidol.[106] Median QTc was 444 ms, 448 ms and 441 ms in each group,

respectively. No dysrhythmias were seen despite a QTc of >500 ms in two patients (one midazolam and one midazolam/olanzapine). In addition to these randomized studies, Calver et al reported a prospective, multi-center observational study of undifferentiated, agitated ED patients requiring parenteral (IM or IV) droperidol for treatment of agitation.[115] Of the 1,009 study patients, the median total dose of droperidol was 10 mg. Thirteen subjects (1.3%) had an abnormal QTc. Seven of the 13 had another potential cause for the prolonged QTc (another medication associated with prolonged QTc). No dysrhythmias were seen in this study. Multiple large retrospective cohort studies of thousands of agitated prehospital or ED patients receiving droperidol revealed no cases of torsades de pointes.[111-113,122] One retrospective study found the incidence of torsades de pointes in ED patients receiving droperidol to be 1 in 16,546, or 0.006% of patients.[121] Based on the lack of dysrhythmias identified following thousands of cases of studied droperidol administrations, we believe that torsades de pointes is unlikely to occur following droperidol administration at typical IM doses used to treat severe agitation, rendering concerns about this adverse event unwarranted. Furthermore, given the need to rapidly treat severe agitation in hyperactive delirium, obtaining a pre-administration ECG is impractical in these situations.

To summarize the available evidence regarding the use of antipsychotics for ED agitated patients, the best studied agents are droperidol, olanzapine, haloperidol, and ziprasidone. All antipsychotics are effective in reducing the degree of agitation in pre-hospital and ED settings. Intramuscular administration appears to reliably treat agitation, with both droperidol and olanzapine providing adequate sedation within 10 to 20 minutes. However, high quality data on the use of antipsychotic agents to treat agitation in hyperactive delirium is still limited. Despite the FDA black box warning for droperidol, at the commonly utilized doses of 5 mg to 10 mg IM to treat agitation in emergent patients presenting with hyperactive delirium, QTc prolongation is uncommon, and torsades de pointes is unlikely to occur.

Benzodiazepine plus antipsychotic

In addition to studies of individual agents, coadministration of a benzodiazepine and antipsychotic has been compared to monotherapy with either class in a small number of papers. One study

did not find the combination of midazolam 5 mg plus droperidol 5 mg IM to be superior to monotherapy with midazolam 10 mg IM or droperidal 10 mg IM.[101] In that study, median time to adequate sedation for combination therapy was 25 minutes. Three additional studies provided data on time to adequate sedation for the combination of lorazepam 2 mg plus haloperidol 5 mg to 10 mg IM.[99,107,126] While neither lorazepam nor haloperidol monotherapy are preferred for initial treatment of agitation, combination therapy was superior to lorazepam 2 mg IM but not haloperidol 5 mg IM for control of agitation at 60 minutes.[107] These studies demonstrated a time to adequate sedation for combination therapy of 23.3 to 36.5 minutes when timing was measured discretely.[99,126] Given this limited data, there is no compelling evidence to support the combination of a benzodiazepine plus antipsychotic rather than monotherapy with a preferred agent from either class.

Ketamine

Ketamine hydrochloride, a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, is used as a sedative causing complete analgesia, increasing duration of coma with increasing doses, and involving appreciable rates of respiratory depression during the initial phase of coma.[127-129] Ketamine was initially studied as the chemical compound CI-581. The first human trials with CI-581 by Domino et al in 1965 and Corssen et al in 1966 demonstrated that "sensory input may reach cortical receiving areas but fail to be perceived." Specifically, the authors demonstrated through electroencephalogram (EEG) and visual evoked potential studies that CI-581 depresses activity in the association areas of the neocortex and the thalamus, while activating the hippocampus in the limbic system. The depression of one area of the brain, while activating another area of the brain led the authors to propose the concept that CI-581 be labeled as a "dissociative anesthetic."[130-132]

With the introduction of ketamine in emergency medicine for the use of procedural sedation, Green and Krauss wrote that ketamine works by "disconnecting the thalamo-neocortical and limbic systems, effectively dissociating the CNS from outside stimuli."[133] However, this conception overly simplifies the mechanism of effect. Ketamine does not "disconnect" an individual from outside stimuli,

but rather interferes with the circuit in the thalamus that appreciates pain and supports the formation of emotional memory related to the experience in the hippocampus.[132,134,135] Thus, it is perhaps more pharmacologically correct to simply identify that ketamine as a centrally acting anesthetic, with effects ranging from focal to general depending on dose.[132] Ketamine acts on specific areas of the brain related to the perception and memory of painful stimuli, with potential for more global depression of consciousness as the dose increases.

There are two primary advantages to ketamine that make it a useful agent for the management of severe agitation in patients presenting with hyperactive delirium. The first attribute is that it can be administered via the IM route with more reliable achievement of effective sedation compared with benzodiazepines and antipsychotics, although the IM route is slightly less predictable than IV.[128,129] Second, it has a consistently faster onset of action compared to other classes of medication.[130,132,136-138] In one of the earliest studies examining ketamine in clinical practice, Corssen et al reported on 630 patients in an operating room environment. Two-hundred and sixteen patients were treated with IV ketamine, and 76 were treated with IM ketamine. All but 7 patients achieved adequate initial sedation, with those in the IV group achieving sedation adequate to perform procedures within 20 seconds, and those in the IM group achieving sedation within 2 to 3 minutes.[136] Rapidity of onset are essential for any medication chosen for initial reduction of severe agitation in patients with hyperactive delirium.

Most relevant to this document, multiple authors have reported successful treatment of severe agitation with ketamine IM injection.[35,99,105,118,119,126,139-147] These papers are of predominantly low methodological quality consisting of case series, retrospective chart reviews, or small prospective studies. In addition, they employ disparate dosing regimens (most often 4 mg/kg based on estimated weight) and utilize variable sedation endpoints. Time to adequate sedation following ketamine IM for the rapid management of acute agitation in the setting of hyperactive delirium was specifically reported in a subset of these publications.[35,99,118,119,126,139-141,144,145] Despite the poor quality of evidence, reported time to sedation was uniformly rapid with the majority between 2 and 10 minutes (range 1.5 to 15 minutes). Of note, Mankowitz et al conducted a systematic review and meta-analysis of 650 patients from 18

publications utilizing ketamine for managing agitated patients in prehospital or ED encounters. The mean time to sedation was 7.21 minutes with 68.5% achieving sedation in under 5 minutes and 75.6% achieving adequate sedation with a single dose of ketamine.[145] Although the lack of high-quality prospective studies limits the degree of certainty, the current literature suggests that adequate treatment of severe agitation occurs predictably in less than 10 minutes following administration of ketamine 4 mg/kg IM.

Given the demonstration of reliable treatment of agitation and more rapid time to adequate sedation than midazolam, droperidol, or olanzapine, there is a strong argument for ketamine as the preferred initial IM therapy in cases of hyperactive delirium exhibiting severe agitation. However, concerns over the safety profile have led to increased scrutiny of ketamine use for treatment of undifferentiated severe agitation. Although emergence phenomenon related to ketamine is frequently discussed as an adverse event, this is of negligible concern when faced with a severely agitated patient.[126,148] Rather potential hemodynamic and airway complications are of greater import and will be dealt with below.

For a patient presenting with hyperactive delirium with severe agitation patient, if a hypertensive effect does occur after IM administration of ketamine, this could theoretically lead to complications in a patient population whose blood pressure may already be elevated due to sympathomimetic exposure and catecholamine overload. Early volunteer studies of ketamine demonstrated that IV administration could result in elevated blood pressure, typically occurring within 3 to 4 minutes.[132,136,141,149-152] Morgan et al showed that the IM administration of ketamine had less of an effect on raising blood pressure compared to IV administration, but their study was performed in a controlled operating room environment. When hypertensive episodes did occur in patients receiving IM ketamine, the authors noted that these effects were delayed compared to IV administration.[152] In addition, a single center retrospective chart review demonstrated a decrease in systolic blood pressure and heart rate following ketamine.[147] Similarly, a prospective trial revealed no change in heart rate or systolic blood pressure in the first hour following ketamine administration.[99] In contrast, a systematic review reported hypertension in 12.4% of patients

receiving ketamine.[145] In an open label, prospective randomized trial, elevated numbers of patients exhibited hypertension and tachycardia after ketamine administration but this resolved in most cases prior to ED discharge.[126] However, screening for hypertension prior to sedative administration is impractical in most cases and such concerns must be balanced with the risks of ongoing agitation frequently accompanied by sympathomimetic toxicity. To date, there is no evidence to suggest hypertensive complications occur following ketamine administration to treat severe agitation and such concerns should not limit appropriate therapy when indicated.

Second, multiple studies have demonstrated that ketamine administration can result in hypersalivation and laryngospasm. These adverse effects may compromise a patient's respiratory status, although both effects can be managed with definitive airway control in the form of intubation.[136,139,151,153,154] In a prospective study of 64 patients receiving ketamine for prehospital severe agitation, the need for intubation to manage the airway after ketamine administration arose in 2 of 3 patients experiencing laryngospasm and in 4 of 21 patients experiencing hypersalivation.[118] In a subsequent descriptive cohort study performed by the same author, 5 of 49 (10%) patients experienced hypersalivation requiring intubation.[144] Another prospective trial with 45 patients in the ketamine arm described laryngospasm in 2 patients (4.4%) and in hypersalivation in 5 patients (11.1%), with 2 requiring intubation for hypersalivation.[119] A systematic review described laryngospasm in 1.3% of patients and hypersalivation in 19% following ketamine.[145] Additional reports describe hypersalivation and laryngospasm in a minority of patients receiving ketamine for agitation. The majority of these adverse effects are managed without intubation.[139,146,147,155-157] Interestingly, a prospective, randomized open label trial did not demonstrate increased rates of hypersalivation.[126] Both hypersalivation and laryngospasm regularly occur in patients receiving ketamine, although the need for intubation due to these adverse effects is infrequent. Nevertheless, patients receiving ketamine must be monitored for these complications by medical professionals capable of managing the airway.

Studies evaluating respiratory depression separately from hypersalivation and laryngospasm have occurred. Multiple authors have demonstrated cases of decreased ventilatory drive and drops in oxygen

saturation following ketamine administration, although these were not conducted in the prehospital or ED environment.[158-162] Seven studies are available that specifically assess respiratory depression following IM ketamine use for managing agitated patients administered by EMS or ED personnel. In a retrospective chart review of 52 cases, Scheppke et al reported that 5.8% of patients treated with 4 mg/kg of IM ketamine developed significant respiratory depression.[141] In contrast, Hopper et al reported no patients developing hypoxia in their retrospective review of 32 cases.[163] A prehospital retrospective chart review documented 2 intubations for hypoxia/respiratory distress out of 95 patients receiving ketamine for agitation.[146] Another prehospital chart review of patients receiving ketamine for agitation reported 8 of 86 patients intubated for respiratory distress and 3 for apnea. An additional retrospective dose comparison study described 16 intubations for hypoxia/respiratory distress out of 292 subjects receiving ketamine.[157] These studies are all retrospective reviews, making it difficult to interpret their varied results as they are likely dependent on the quality of chart abstraction. A single, prospective randomized open-label trial demonstrated hypoxia (21%) in the group receiving ketamine.[126] In a recently published retrospective review of a large prospectively collected EMS database, out of 3,795 patients who received ketamine for altered mental status/behavioral indications – 10.2% had measured hypoxia and 23% had measured hypercapnia.[93] Finally, a systematic review noted that 1.8% of patients receiving ketamine for agitation experienced transient hypoxia.[145] Although rates of respiratory depression vary between studies, significant respiratory depression occurs regularly. Patients receiving ketamine should be monitored for this complication, ideally with continuous pulse oximetry and $EtCO_2$ monitoring.

Because it is easier to determine through chart review if a patient required mechanical ventilation compared to the development of respiratory depression, other authors have examined intubation rates after ketamine administration to manage agitation in the setting of hyperactive delirium, with results ranging from 0 to 62%.[99,118,142-146,156,157,163,164] The true reason for intubation is not always clear in these studies, and at least in some part reflects variation in practice patterns. For example, Olives et al calculated an Odds Ratio for intubation of 2.57 (95% CI 1.05 to 6.27) for patients managed during the overnight shift compared to patients presenting during the day shift.[143] The authors postulate that perhaps

there is a greater inclination to perform intubation in a patient after arrival to the ED when there are fewer resources, and that the treating emergency physician may find it beneficial to control the airway through intubation compared to dedicating resources toward continual monitoring of a patient's airway. It is also possible that people who develop severe agitation with hyperactive delirium at night do so from different causes than those who develop the syndrome during other times of day. These same authors noted that among the group of ED physicians they studied, individual physician intubation rates varied from 0 to 100%. Other studies have demonstrated individual physicians to more frequently intubate patients who receive prehospital ketamine for agitation.[144,146] In contrast, four publications examining the use of ketamine describe no change[105] or even a decrease,[155,165] in intubation rates when compared to historical controls such as midazolam.[105,148,155,165] Most dramatically, Lebin et al found the introduction of ketamine to treat prehospital agitation was associated with a drop in intubation rates from 63% (historical control of patients treated with benzodiazepines, mostly midazolam) to 3.8% with ketamine.[148] Regardless, the multiple factors contributing to the decision to intubate make this a poor surrogate marker to understand the effect of various doses of ketamine on respiratory depression.

Noting that the literature demonstrates the potential for respiratory depression when ketamine is used for the management of hyperactive delirium with severe agitation, EMS professionals and emergency physicians need to evaluate the proper dose that is effective without causing unwarranted respiratory depression. In terms of context, it is helpful to understand that the current dosing model for treatment of agitation of 4 mg/kg IM that is often used in prehospital protocols was originally extrapolated from a dosing scheme that was developed for pediatric procedural sedation rather than developed prospectively.[35,141,163] Consequently, it is unclear if this is the optimal dose, although such a regimen is widely employed. Specific to the prehospital environment, studies examining different dosing schemes for IM ketamine in managing hyperactive delirium with severe agitation have shown no significant difference in intubation rates between various dose regimens.[143,156,157] However, it is difficult to determine from these studies if there were clinically significant differences in respiratory depression. For example, in the retrospective cohort study of 86 patients given ketamine for agitation by Parks et al,

there was a non-significant difference in dose between patients intubated and those who were not intubated. However, the authors additionally reported on 21 patients who were not intubated yet required supplemental oxygen and did not report on the difference in dosing for those requiring any type of respiratory support versus those who did not require respiratory support[156] At this point, there is no compelling evidence to recommend modifying the typical ketamine dose of 4 mg/kg IM to treat severe agitation.

Despite recent widely publicized events having sparked increased scrutiny, death due to prehospital ketamine administration is exceedingly rare. In a large prospectively collected registry study of 11,291 patients receiving ketamine, including 3,795 receiving ketamine IM/IV with a median dose of 3.7 mg/kg for altered mental status (AMS)/behavioral reasons, ketamine could not be excluded as the cause in only 8 deaths out of the entire cohort. Of these, only 4 received ketamine for AMS/behavioral reasons and only 1 was definitively administered via the IM route. Given the large number of administrations at doses commonly used to treat severe agitation and lack of fatalities documented, this data suggests that ketamine use is unlikely to cause appreciable rates of death in the patient population of interest.[93]

It is clear that ketamine, like other sedating agents, risks respiratory compromise requiring a spectrum of support ranging from supplemental oxygen to intubation. There are insufficient data to date to conclusively determine the proper dose of ketamine IM most appropriate to safely and effectively manage severe agitation. No prospective studies have been performed to examine appropriate dosing in this specific patient population. It is therefore possible that a dose lower than 4 mg/kg IM would be effective with fewer respiratory events. However, an improved safety profile with lower dosing must be balanced with the risk of inadequate severe agitation management leading to prolonged time to effective treatment due to the need for redosing or adjunctive agents. This question warrants further study and emergency physicians should consider this void in the literature when making current decisions in EMS protocols specifying treatment regimens and/or in the ED on the IM ketamine dose when managing patients with hyperactive delirium with severe agitation. Furthermore, the existing dose comparison

studies do not suggest a benefit to lowering the dose from 4 mg/kg. It is essential that treating paramedics and emergency physicians are equipped and prepared to manage ventilatory depression and airway compromise when using ketamine to treat hyperactive delirium with severe agitation.

Comparison Studies

Benzodiazepines versus Antipsychotics

Various investigators have examined benzodiazepine monotherapy alongside antipsychotic monotherapy to treat acute agitation. Midazolam 5 mg to 10 mg IM has been compared to droperidol 5 mg to 10 mg IM in 3 studies.[16,101,104] Time to adequate sedation was similar, although midazolam tended to require additional sedating medications whereas the initial dose of droperidol was more frequently sufficient. In addition, midazolam treated patients demonstrated increased rates of respiratory depression in 2 of the 3 studies.[101,104] Midazolam has also been directly compared to olanzapine in 2 studies.[103,106] Midazalom 5 mg IM was equivalent to olanzapine 10 mg IM in one study with no differential rate of adverse events.[103] However, midazolam 5 mg IM was superior to olanzapine 5 mg IM in the second study with similar rates of adverse events, although the lower dose of olanzapine may have limited the relative effectiveness of the antipsychotic.[106] Thus, when considering the most effective agents from each class, droperidol and midazolam are similar with respect to control of agitation, although midazolam may have increased rates of respiratory depression. Midazolam has also been shown to be equivalent to (and possibly superior to) olanzapine for treatment of severe agitation.

Additional studies have compared various other antipsychotics to midazolam and lorazepam. Haloperidol is well studied for treatment of agitation, although it is consistently inferior to midazolam with respect to time to adequate sedation.[98,100,102,103,106] Likewise, ziprasidone is less well studied but is also inferior to midazolam.[16,103] Lorazepam has been shown to be similar to both haloperidol and ziprasidone but inferior to droperidol.[96,107,108] None of these alternative medications perform as well as droperidol, midazolam, or olanzapine.

Ketamine versus Other Agents

Studies directly comparing ketamine to other agents to treat acute severe agitation are limited. Three studies have examined ketamine alongside midazolam. Riddell demonstrated superiority of ketamine IV/IM compared to midazolam IV/IM/IN.[99] Holland found that ketamine at a mean dose of 3.75 mg/kg IM performed similarly to midazolam 5 mg IM with no appreciable difference in rates of adverse events.[105] A third study of prehospital ketamine and midazolam found that rates of intubation were dramatically lower at the receiving hospital in the group receiving ketamine compared to midazolam (3.8% versus 63%).[148] Unfortunately, there are not additional studies that compare ketamine to the first line antipsychotics: droperidol or olanzapine. Rather, ketamine has been compared to haloperidol in three studies.[99,118,119] All found ketamine to be superior in achieving rapid, adequate sedation. However, intubation occurred more frequently in the ketamine treated subjects in 2 of the 3 studies.[118,119] Two studies found ketamine to be superior to the combination of lorazepam plus haloperidol with similar rates of adverse events.[99,126] Although the body of evidence is small, the information published to date suggests that ketamine is at least as effective as the other first line agents: droperidol, olanzapine, and midazolam, with an adverse event profile similar to midazolam.

Summary of pharmacologic options

For EMS personnel or emergency physicians faced with the need to treat a patient presenting with hyperactive delirium with severe agitation, multiple pharmacologic options are available. Ketamine likely provides the fastest time to adequate sedation, though there may be an increased rate of respiratory related adverse events compared to droperidol and olanzapine. Midazolam, droperidol, and olanzapine all demonstrate similar times to adequate sedation. All three are slightly slower compared to ketamine. The adverse event profile for midazolam is similar to ketamine, with increased rates of respiratory depression and intubation along with variable depth of sedation when compared to droperidol and olanzapine. Droperidol, and to a lesser extent olanzapine, has been widely studied with safe use documented thousands of times. No appreciable risk of torsades de pointes with use of droperidol to treat agitation has

been identified, and its use should not be limited by this concern. Either of these antipsychotics are less likely to result in serious drug-related adverse events when compared to ketamine and midazolam. However, the overall body of evidence is generally low quality making it difficult to determine a clearly superior regimen with certainty. Nevertheless, there is abundant experience in the expert panel along with sufficient differentiation within each class of medication in the literature to provide multiple reasonable options for initial treatment of agitation (Table 1).

Table 1. Pharmacologic options to treat hyperactive delirium with severe agitation.

Drug	Dose	Time to adequate sedation
Ketamine	4 mg/kg IM	2 to 15 minutes
Droperidol	5 mg to 10 mg IM	10 to 20 minutes
Olanzapine	10 mg IM	10 to 20 minutes
Midazolam	5 mg to 10 mg IM	10 to 20 minutes

Future Research

While notable research endeavors since 2009 have enabled a stronger evidenced-based review of both hyperactive delirium with severe agitation and specific therapies, many areas for scientific investigation remain. In light of these knowledge gaps, and acknowledging the challenges inherent to research in a population presenting with hyperactive delirium and severe agitation due to a wide range of potential causes, we offer the following topical list in support of emerging research. Specific needs are those related to finding additional approaches towards patient safety, stabilization, and promotion of optimal health outcomes.

Education and training:

- Impact of coordinated training across the continuum of professionals interfacing with hyperactive delirium with severe agitation patients, including law enforcement, EMS, nursing, nurse practitioners, physician assistants, and physicians across the spectrum of medical specialties.

- Identifying "core content" curricula for hyperactive delirium with severe agitation to standardize care.

- Identifying optimal platforms, delivery techniques, and timing of professional development education on hyperactive delirium with severe agitation.

- Identification and impact of de-escalation techniques that protect patient safety and reduce risk of injury to public safety and medical professionals.

- Identifying knowledge and knowledge gaps about hyperactive delirium with severe agitation in law enforcement, EMS, nursing, nurse practitioners, physician assistants, and physicians across the spectrum of medical specialties.

Inciting events:

- Identifying underlying co-morbidities that predispose to hyperactive delirium with severe agitation and may represent modifiable risk factors.

- Identifying precipitating factors that allow for early intervention to prevent progression to hyperactive delirium.

Pathophysiologies:

- Impact of severe agitation on oxygenation and ventilation, including airway protection and risk of airway obstruction.

- Role of electrophysiologic abnormalities and dysrhythmias, possibly related to metabolic derangements, that increase risk of sudden death in the setting of hyperactive delirium with severe agitation.

Assessment:

- Standardized and validated instrument to be uniformly used for research on treatment of hyperactive delirium with severe agitation in the ED

- Validated assessment tools for use in the clinical environment to direct pharmacologic and non-pharmacologic treatment

Therapies:

- Development of comprehensive strategies for de-escalation.

- Identification of optimal medication regimen for treatment of hyperactive delirium with severe agitation by EMS and ED professionals.

- Examining methods of minimizing adverse events when patients are treated for acute agitation in hyperactive delirium with severe agitation.

Conclusions

Over the past decade, progress has been made in identifying distinguishing features, causative etiologies, and effective therapies to treat hyperactive delirium presenting with severe agitation. When faced with a patient presentation concerning for hyperactive delirium, rapid management of severe agitation is necessary to prevent injury to the patient and others as well as to permit clinicians to identify and treat dangerous underlying causes. While it is often impossible to accurately differentiate causes of hyperactive delirium with severe agitation early in the patient encounter, best practice is to initially attempt de-escalation techniques. Due to dangers to the patient, restraints should be utilized as a temporizing measure and are not a substitute for adequate treatment of severe agitation. Pharmacologic management is often necessary. Based on available data, ketamine dosed at approximately 4 mg/kg IM appears to provide the most rapid and reliable results, although regimens from 2 mg to 5 mg/kg have been reported. Alternative IM medications with best evidence for treatment of agitation include droperidol 5 mg to 10 mg, olanzapine 10 mg, or midazolam 5 mg to 10 mg. Of note, it remains unclear whether benzodiazepine-based regimens are less likely to result in respiratory compromise than ketamine, although the recommended antipsychotics demonstrate only rare instances of respiratory adverse events. This uncertainty is due to the heterogeneity of studies available, high rates of intubation necessitated by critical illness and life-threatening causative etiologies, and difficulties studying a population that presents at an extreme of severe agitation. Even though ketamine demonstrates more rapid management of agitation, it is also not clear whether the difference in time to effect improves clinical outcomes in all cases. Thus, appropriately dosed ketamine, droperidol, olanzapine and midazolam administered via IM injection are all reasonable initial options to treat agitation in the setting of hyperactive delirium with severe agitation. No matter the choice of therapy, a minority of these patients will subsequently require intubation due to critical illness, progression of disease, or failure to adequately treat severe agitation with initial intervention. This outcome should not necessarily be considered as an adverse event given that the population being treated is critically ill at presentation.

As soon as it is safe, patients presenting with hyperactive delirium with severe agitation should be placed on ECG monitoring, pulse oximetry, and continuous waveform capnography. Complete vital signs and point-of-care blood glucose should be obtained. Imaging and laboratory studies as indicated within the ED should accompany treating the patient for any time-dependent emergency. No patient with hyperactive delirium with severe agitation should be released from the field into a non-medical setting following sedative treatment as many causes of hyperactive delirium with severe agitation, along with the condition itself, are life-threatening conditions when not properly recognized and treated.

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Appendix A. Conflict of interest disclosures for Hyperactive Delirium Task Force

Questions asked of participants:

- Employment: Please indicate the name of your employer and describe your position of employment, including the nature of the business of your employer, the position you hold and a description of your daily employment responsibilities.
- Leadership: Do you hold any positions of leadership in other organizations, chapters, commissions, groups, coalitions, agencies, and/or entities (e.g. board of director positions, committees and/or spokesperson roles)? If yes, please describe the position you hold, including a brief description of the nature and purposes of the organization or entity.
- Relationships: To the best of your knowledge, do you have any outside relationships with any person or entity from which ACEP obtains goods and services, or which provides services that compete with ACEP where such relationship involves: a) holding a position of responsibility; b) an equity interest (other than a less than 1% interest in a publicly traded company); c) any gift, gratuities, lodging, dining, or entertainment valued at more than $100? If yes, please explain:
- Financial interests: Do you have any financial interests or positions of responsibility in entities providing goods or services in support of the practice of emergency medicine (e.g. physician practice management company, billing company, physician placement company, book publisher, medical supply company, and/or a malpractice insurance company), other than owning less than a 1% interest in a publicly traded company? If yes, please explain.
- Other potential conflict: Do you have any other interest that may create a conflict with your fiduciary duty to ACEP or that may create the appearance of a conflict of interest?
- Health administration: Do you have any outside relationships with any health plan, health insurance company, delegated payer, health insurance company administrative service organization, or health insurance company related philanthropic organization or entity where such relationship involves: a) holding any position of responsibility; b) an equity interest (other than a less than 1% interest in a publicly traded company); c) any stipend, contribution, gift, gratuities, lodging, dining, or entertainment valued at more than $100?

Benjamin W. Hatten, MD, MPH

- Employment: Assistant Professor, University of Colorado School of Medicine.
- Leadership: None.
- Relationships: None.
- Financial interests: None.
- Other potential conflict: None.
- Health administration: None.

Caitlin Bonney, MD

- Employment: Attending Emergency Physician, Maine Medical Center; Attending Medical Toxicologist, Northern New England Poison Center.
- Leadership: None.
- Relationships: None.
- Financial interests: None.

- Other potential conflict: None.
- Health administration: None.

Robert B. Dunne, MD
- Employment: Professor, EMS Fellowship Director, Team Health; Emergency Medicine Physician, St. John Hospital, Detroit, Michigan.
- Leadership: None.
- Relationships: None.
- Financial interests: None.
- Other potential conflict: None.
- Health administration: None.

Stacey L. Hail, MD
- Employment: Associate Professor of Emergency Medicine and Medical Toxicology, University of Texas Southwestern Medical Center; Attending Physician, Parkland Hospital, Dallas, Texas; Attending Physician, Medical Toxicology, North Texas Poison Control Center, Dallas, Texas.
- Leadership: None.
- Relationships: None.
- Financial interests: None.
- Other potential conflict: None.
- Health administration: None.

Graham S. Ingalsbe, MD
- Employment: Assistant Professor of Clinical Emergency Medicine, University of Nevada-Reno School of Medicine.
- Leadership: Treasurer, Nevada Chapter of the American College of Emergency Medicine.
- Relationships: None.
- Financial interests: None.
- Other potential conflict: None.
- Health administration: None.

Michael K. Levy, MD
- Employment: Vice President, Staff Emergency Physician, Denali Emergency Medicine Physicians, Anchorage, Alaska; EMS Medical Director, State of Alaska; EMS Medical Director, Anchorage Fire Department; EMS Medical Director, Kenai Peninsula.
- Leadership: President-Elect, National Association of EMS Physicians.
- Relationships: None.
- Financial interests: Chief Medical Advisor for Stryker Emergency Care; paid for consultations services but does not have stock or other financial interests.
- Other potential conflict: None.
- Health administration: None.

Michael Millin, MD, MPH

- Employment: Faculty, Department of Emergency Medicine, Johns Hopkins University School of Medicine; Medical Director, Prince George Fire/EMS Department, District Heights, Maryland; Medical Director, Maryland and Mid-Atlantic Wilderness Rescue Squad/Austere Medical Professionals.
- Leadership: Resuscitation Sub-Council Vice-Chair, American Red Cross Scientific Advisory Council.
- Relationships: None.
- Financial interests: None.
- Other potential conflict: None.
- Health administration: None.

Brent J. Myers, MD

- Employment: Chief Medical Officer, ESO solutions Inc., a data and software company serving EMS, hospitals, and fire departments.
- Leadership: Chair, Advocacy Committee, National Association of EMS Physicians.
- Relationships: None.
- Financial interests: None.
- Other potential conflict: None.
- Health administration: None.

Richard D. Shih, MD

- Employment: Professor of Integrated Medical Science, Division Director for the Emergency Medicine Residency Program, Florida Atlantic University College of Medicine.
- Leadership: None.
- Relationships: None.
- Financial interests: None.
- Other potential conflict: None.
- Health administration: None.

Jeffrey M. Goodloe, MD

- Employment: Professor of Emergency Medicine, University of Oklahoma School of Community Medicine.
- Leadership: None.
- Relationships: None.
- Financial interests: None.
- Other potential conflict: None.
- Health administration: None.

Appendix B. (Studies examining IM treatment of acute agitation with sedating medications in EMS or ED patients with sedation outcomes recorded by individual study arm)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Midazolam					

TREC Collaborative Group[100] (2003)	Midazolam 7.5 mg to 15 mg IM
	• prospective, pseudo-randomized open label
	• dose at treating physician discretion
	
	Compared to:
	• combination of haloperidol 5 mg to 10 mg plus promethazine 25 mg to 50 mg IM
		Adults presenting to psychiatric EDs with agitation or dangerous behavior
		
		150 patients in the Midazolam arm
		• 48% male/52% female; mean age: 38 years;
		• dose: 15 mg (124 patients)/7.5 mg (26 patients):
		• presumed etiology:
		  • psychosis 71%
		  • substance abuse 20%, other 9%
			Primary endpoint was "tranquil or asleep" at 20 minutes, with tranquil defined as peaceful and without restlessness or threatening behavior; secondary endpoints included tranquil or asleep at 40, 60, and 120 minutes; need for physical restraints; recurrent episode of agitation; major adverse events; midazolam superior for primary endpoint at 20 minutes as well as secondary endpoint at 40 minutes; no difference at 60 minutes or greater; no difference in need for restraints; no difference in additional tranquilizing drugs	At 20 minutes, 89% in the midazolam arm versus 67% in the haloperidol/promethazine arm reached study endpoint
				• relative risk 1.32 (95% CI 1.16 to 1.49)
				• 22% (95% CI 12% to 30%) more in midazolam arm w/ adequate sedation at 20 minutes
					1 patient in midazolam group experienced respiratory depression that resolved with flumazenil

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Midazolam					
Nobay et al[98] (2004)	Midazolam 5 mg IM • randomized and double blind • if a patient continued to be disruptive 20 minutes after the study drug was administered, a ‘‘rescue drug’’ could be given at the discretion of the treating attending physician. Patient enrollment in the study was terminated if a rescue medication was given; these patients were considered sedation failures, and their data were not included in the analysis Compared to: • lorazepam 2 mg IM • haloperidol 5 mg IM	ED patients who required emergency sedation for the control of violent behavior or severe agitation; all patients were initially physically restrained; 42 patients in the midazolam group; • mean age 39.8 • 23 African American, 1 Asian, 2 Hispanic, and 16 White • 8 with recreational drug use, 6 without, and 28 unknown • 13 with alcohol use, 2 without, and 27 unknown • 20 with prior psychiatric history, 3 without, and 19 unknown	Level of sedation was continuously observed with data collected every 15 minutes; adequacy of sedation was assessed using the Modified Thomas Combativeness Scale with the goal endpoint a score of 3 (No agitation, no supervision required, maybe asleep); 7 midazolam patients (17%) needed rescue drugs; midazolam reached adequate sedation 13.9 minutes faster than lorazepam (95% CI 5.1 to 22.8; p=0.0026); midazolam reached adequate sedation 9.9 minutes faster than haloperidol (95% CI 0.5 to 19.3; p=0.0388)	The mean time to sedation • midazolam 5 mg IM: 18.3 minutes	There were no statistically significant differences over time in regard to change in systolic and diastolic blood pressure (p=0.8965, p=0.9581), heart rate (p=0.5517), respiratory rate (p=0.8191), and oxygen saturation (p=0.8991) among patients receiving each of the medications; there were no adverse events in the midazolam group

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Midazolam					
Martel et al[16] (2005)	Midazolam 5 mg IM; prospective, randomized, double-blind trial; rescue sedation at treating physician discretion permitted 30 minutes after study drug administration for AMS >0 Compared to: • ziprasidone 20 mg IM • droperidol 5 mg IM	ED patients with acute undifferentiated agitation requiring emergent sedation as determined by the treating physician; 48 patients in midazolam group; mean age 36.9; 33 male/15 female; initial mean AMS scale score of 3.10; initial assessment of reason for agitation: alcohol intoxication (46), illicit substance intoxication (8), head injury (14), psychiatric etiology (4), and seizure (1); discharge diagnoses: acute alcohol intoxication (46), acute drug intoxication (4), and closed head injury (18)	AMS scale score was obtained every 15 minutes from time 0 to 120 minutes following study medication administration with effective sedation defined as an AMS of 0 or less Mean AMS scale scores in the midazolam group: • at 15 minutes -0.81 (95% CI -1.54 to -0.08), • at 30 minutes -1.46 (95% CI -2.19 to -0.73), • at 45 minutes -1.31 (95% CI -2.02 to -0.60), • at 60 minutes -1.13 (-1.86 to -0.38) More patients receiving midazolam or ziprasidone required rescue medications at 30 minutes compared to droperidol ($p<0.05$) • droperidol: 5 patients required 6 doses • ziprasidone: 9 patients requiring 11 doses • midazolam: 24 patients requiring 30 doses	Less patients remained agitated at 15 minutes in the droperidol and midazolam groups compared to the ziprasidone group ($p=0.01$) • droperidol: 20/50 • midazolam: 15/48 • ziprasidone: 28/46 There was no difference between groups at 30 minutes ($p=0.08$). • droperidol: 6/50 • midazolam: 11/48 • ziprasidone: 14/46 More patients were agitated at 45 minutes in the midazolam group compared to the droperidol and ziprasidone groups ($p=0.03$) • droperidol: 9/50 • midazolam: 14/48 • ziprasidone: 9/46	Respiratory depression: • 24/48 patients who received midazolam • 10 required supplemental oxygen • no difference in proportion with respiratory depression ($p=0.26$) or supplemental oxygen ($p=0.20$) when compared to ziprasidone and droperidol • no patients required intubation for respiratory depression Akathisia: • 1/48 patients who received ziprasidone Cardiac dysrhythmias: • none

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Midazolam					
Isbister et al[101] (2010)	Midazolam 10 mg IM • blinded, randomized controlled trial • further sedation allowed at discretion of attending physician Compared to: • droperidol 10 mg IM • midazolam 5 mg plus droperidol 5 mg IM	ED patients requiring physical restraint and parenteral sedation 29 patients in midazolam group • median age: 35 • 18 male/11 female • initial assessment of agitation due to: alcohol intoxication (22), self-harm (12), drug-induced delirium (3), and acute psychosis (1)	Primary sedation outcome was time security staff were required according to a security log from the time of initial call to the "all clear" • duration was not different between groups (p=0.66) with median for: midazolam (20 minutes), droperidol (24 minutes), and midazolam plus droperidol (25 minutes) Secondary sedation outcomes were: • time additional sedation was administered: the hazard ratio for additional sedation medications for midazolam versus droperidol was 2.31 (95% CI 1.01 to 4.71; post prob 0.98 for HR>1.0) indicating that midazolam was more likely to require additional sedation compared to droperidol	Secondary outcome of reduction in AMSS by 3 points or to a score of <1 20 minutes after drug administration: • midazolam: 15/29	Respiratory events occurred in: • midazolam: 8/29 patients involving desaturation events (7) and airway obstruction (2) Hypotension occurred in: • midazolam: 1/29 Abnormal QT-HR pairs occurred in: • midazolam: 2/29 No dystonic reactions were identified Although oversedation was not a secondary endpoint, AMSS scores revealed that both midazolam and midazolam plus droperidol resulted in unpredictable and oftentimes deep sedation while droperidol resulted in consistent moderate sedation

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Midazolam					
Isenberg et al[102] (2015)	Midazolam 2.5 mg to 5 mg IM (5 mg if younger than 65 years and 2.5 mg if 65 years or older) • redosing available every 10 minutes if sedation endpoint not met but maximum dose received was 5 mg. • randomized, non-blinded Compared to haloperidol 2.5 mg to 5 mg IM	EMS patients with either: • a psychiatric or behavioral disorder who is at imminent risk of self-injury or is a threat to others • patient with a medical condition causing agitation and possibly violent behavior 5 patients in midazolam group • age: 26 to 90 years • all with initial RASS +4 • patient diagnosis: sepsis, urinary tract infection, alcohol intoxication, hypoglycemia, and acute renal failure	Sedation evaluated using RASS with goal of less than +1. 4/5 patients in midazolam group with RASS<1 on arrival to ED	Mean time to achieve a RASS of less than +1 • midazolam 2.5 mg to 5 mg IM: 13.5 minutes	No patients in the midazolam group had any adverse effects

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Midazolam					
Riddell et al[99] (2017)	Midazolam (mean dose 3.08 mg) IV/(mean dose 2.25 mg) IM/(mean dose 2 mg) IN • prospective, observational Compared to: • lorazepam (mean dose 1.9 mg) IV/ (mean dose 2.4 mg) IM • haloperidol (mean dose 5.71 mg) IM • combination of lorazepam (mean dose 2 mg) IV/(mean dose 2 mg) IM plus haloperidol (mean dose 5 mg) IM • ketamine (mean dose 0.87 mg/kg) IV/(mean dose 2.97 mg/kg) IM	Acutely agitated patients requiring chemical sedation in the ED 19 patients in the midazolam group • median age: 43 years • 18 male/1 female • race: African American (1)/Asian (0)/Hispanic (10)/White (7) • drug use: 63.2% • alcohol use: yes (42.1%)/no (36.8%)/unknown (21.1%) • prior psychiatric visits (36.8%) • route of administration: IV(12)/IM(4)/IN(3)	Primary outcome: agitation score less than or equal to 2 on a six-point agitation scale • recorded prior to medication administration then at 5, 10, and 15 minutes • midazolam (and other arms) inferior to ketamine at: 5 minutes (p=0.001), 10 minutes (p<0.001), and 15 minutes (p=0.032) Secondary outcomes of: • provider assessment of time to adequate sedation: No difference between groups (p=0.107) • need for redosing of sedative medications (p=0.199) • HR/SBP change: HR reduction seen with midazolam (p=0.026) but no other significant HR/SBP changes in any other study arms	Mean time to adequate sedation: • midazolam: 14.95 minutes	Intubation: • midazolam: 1/19 • lorazapam: 1/33 • haloperidol: 1/14 • combination lorazepam plus haloperidol: 1/10 • ketamine: 2/24

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Midazolam					
Klein et al[103] (2018)	Midazolam 5 mg IM • prospective, observational Compared to: • olanzapine 10 mg IM • haloperidol 5 mg IM • haloperidol 10 mg IM • ziprasidone 20 mg IM	ED patients receiving medication to treat acute agitation 127 patients in midazolam arm • median age: 40 • 97 male/30 female • cause of agitation: alcohol (82%)/illicit substance (17%)/psychiatric illness (17%)/medical (1%)	Primary endpoint was adequate sedation, defined as Altered Mental Status Score <1 15 minutes after medication administration • midazolam 5 mg IM not superior to olanzapine 10 mg IM (9% greater for midazolam: 95% CI 1% lesser to 20% greater) • midazolam 5 mg IM superior to haloperidol 5 mg IM (30% greater for midazolam: 95% CI 19% to 41%) • midazolam 5 mg IM superior to haloperidol 10 mg IM (28% greater for midazolam: 95% CI 17% to 39%) • midazolam 5 mg IM superior to ziprasidone 20 mg IM (18% greater for midazolam: 95% CI 6 to 29%) Median difference in AMSS score compared to baseline at 15 minutes: • midazolam 5 mg IM not superior to olanzapine 10mg IM (1 point greater decrease for midazolam: 95% CI 1 to 0 point greater decrease) • midazolam 5 mg IM superior to haloperidol 5mg IM (2 point greater decrease for midazolam: 95% CI 2.5 to 1.5 point greater decrease) • midazolam 5 mg IM superior to haloperidol 10mg IM (2 point greater decrease for	Median time to adequate sedation: • midazolam 5 mg IM: 12 minutes	No difference in adverse events between groups Respiratory distress: • 1 to 3 patients in each arm with hypoxemia • 1 patient intubated in each arm except haloperidol 10 mg with no intubations Cardiovascular: • 1 to 2 patients in each group with hypotension except ziprasidone with no episodes of hypotension • 1 patient in each arm with bradycardia except midazolam with no episodes of bradycardia • no patients in any arm with torsades de pointes or other dysrhythmias Extrapyrimadal symptoms: • 2 patients in haloperidol 10 mg arm with dystonia. No other dystonic reactions in any arm • no episodes of akathisia in entire study

			midazolam: 95% CI 2.5 to 1.5 point greater decrease) • midazolam 5 mg IM superior to ziprasidone 20 mg IM (1 point greater decrease for midazolam: 95% CI 1.5 greater decrease to 0.5 lesser decrease) Time to adequate sedation (compared to midazolam 5 mg IM): • olanzapine 10 mg IM no different (HR 0.97 95% CI 0.76 to 1.22) • haloperidol 5 mg IM inferior (HR 0.73 95% CI 0.58 to 0.90) • haloperidol 10 mg IM inferior (HR 0.72 95% CI 0.57 to 0.88) • ziprasidone 20 mg IM inferior (HR 0.78 95% CI 0.61 to 0.93) Time to adequate sedation for subset receiving monotherapy and no rescue sedation medications (compared to midazolam 5 mg IM): • olanzapine 10 mg IM no different (HR 0.84 95% CI 0.65 to 1.07) • haloperidol 5 mg IM inferior (HR 0.63 95% CI 0.48 to 0.81) • haloperidol 10 mg IM inferior (HR 0.59 95% CI 0.46 to 0.78) • ziprasidone 20 mg IM inferior (HR 0.64 95% CI 0.48 to 0.82)		

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Midazolam					
Page et al[104] (2018)	Midazolam IM (38%), IM/IV (29%), and IV (33%) • per protocol: 5 mg initial IM dose with repeat doses of 5 mg to10 mg every 10 minutes or 2.5 mg to 5 mg IV with repeat doses of 2.5 mg to 5 mg every 10 minutes • median dose received in study: 7 mg Prospective before/after protocol change observational study with primary endpoint to compare adverse events and secondary endpoints of sedation outcomes Compared to: • droperidol 10 mg IM • optional redosing of 10 mg at 15 minutes	141 EMS patients with acute behavioral disturbance and SAT score of +2 (34 patients) to +3 (103 patients). • 86 male/55 female • reason for agitation: alcohol (55), amphetamines (39), medical (23), mental illness (9), other stimulants (11), self-harm (21), and marijuana (3) • police were on scene for 110 encounters • median prehospital time of 47 minutes	Sedation was defined as a decrease in SAT score by at least 2 points or score of 0; successful sedation was defined as sedated, no adverse effects, and no requirement for additional sedation • 20/141 required additional EMS sedation • 59/141 required additional ED sedation • median number of drug administrations was 2 • 50/141 were successfully sedated • 91 with unsuccessful sedation due to: failed to sedate prehospital (17), adverse effects (33), EMS additional sedation (20), and ED additional sedation (59) 123/149 were successfully sedated in droperidol group	Median time to sedation: • midazolam 5 mg IM: 30 minutes	33/141 patients exhibited 49 adverse events in the midazolam group. • airway obstruction requiring airway maneuver (24: 19 chin lift/jaw thrust, 3 oropharyngeal airway (OPA)/ nasopharyngeal airway (NPA) placement, and 2 intubation), hypotension (9), and SAT score of -3 (7) • compared to those receiving droperidol, a 16% greater proportion in the midazolam group exhibited adverse events (p=0.0001, 95% CI 8% to 24%)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Midazolam					
Lebin et al[148] (2019)	Midazolam 1 mg to 10 mg IV, 5 mg to 10 mg IM, or 2.5 mg to 10 mg IN • alternative benzodiazepine: diazepam 2.5 mg to 10 mg IV (3 patients) • retrospective cohort study Compared to: • ketamine 1 mg to 2 mg/kg IV or 3 mg to 5 mg/kg IM	Patients with severe agitation requiring prehospital sedation with ketamine or benzodiazepine 82 patients in benzodiazepine group • age: 32 years • male (92.7%) • Caucasian (54.9%)/Black or African American (0%)/Asian (6.1%)/other or not reported (39.0%) • 16 patients received midazolam IM	Sedation endpoint was not studied	Not reported	Intubation • benzodiazepine (63.0%) • ketamine (3.8%) • 59.1% (95% CI 37.9% to 79.35%) more likely to be intubated after benzodiazepine administration than ketamine administration

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Midazolam					
Holland et al[105] (2020)	Midazolam 5 mg IV/IM/IN • dose per protocol: 2.5 mg to 5 mg (61/66 patients received 5 mg) • route: IM (32/66), IV (24/66), and IN (10/66) • retrospective chart review Compared to: • ketamine (mean dose 3.75 mg/kg) IM	Patients with acute agitation requiring sedation by paramedics 66 patients in midazolam treated group • mean age of 36.1 years • 41 male/25 female • race: white (32), African-American (29), and other (5) • mean weight: 79.1 kg • suspicion of illicit drugs: 71.2% • IM dosing: 32/66 (48.5%)	Primary endpoint was need for repeat sedative dose. • 7/66 required repeat sedation at 20 minutes. No difference compared to ketamine (p=0.306) • 18/66 required repeat sedation at 90 minutes. Significantly less than ketamine group (p=0.01) • when limiting the analysis to only sedation given via IM route, there was no difference in need for repeat sedation between midazolam and ketamine groups at 20 minutes (p=0.212) or 90 minutes (p=0.503) Secondary endpoints • time to repeat sedation of 77.2 minutes. No difference compared to ketamine group (p=0.658) • total number of sedation doses did not differ between ketamine and midazolam (p=0.084)	Need for repeat sedative dose at 20 minutes used as proxy for adequate control of agitation • 7/66 in midazolam group required repeat sedation	5 patients in the midazolam group were intubated. • 1 patient was found to have a traumatic intracranial hemorrhage • 1 received repeat sedation (midazolam) before intubation • 3 (4.6%) were intubated within an hour of ED arrival for altered mental status without further complicating factors or further sedative administration For patients administered midazolam, median GCS was 14 (IQR 13 to 15) prior to administration and 12 (IQR 6.5 to 15) after administration (p<0.0001) with a mean difference of 4.5, 95% CI 3.4 to 5.6). There was no significant difference compared to the change in GCS achieved with ketamine, p=0.4116). There were no significant differences in use of bag valve mask or intubation, use of physical restraints, admission location/level of care, or length of stay in the ED, hospital, or ICU

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Midazolam					
Chan et al[106] (2021)	Midazolam 5 mg IM • single optional redose allowed per study protocol • randomized, double-blind Compared to: • olanzapine 5 mg IM • haloperidol 5 mg IM	ED patients requiring parenteral drug sedation for acute agitation 56 patients in midazolam group • mean age 44 • 34 male/22 female • perceived possible causes: drug/substance abuse (16), alcohol intoxication (15), underlying mental illness (47), medication non-compliance (24), suicidal ideation/attempt (18), exposure to tramadol (1), concurrent psychotropic medication (19) • baseline sedation scores: 3 (13 patients), 4 (17 patients), and 5 (26 patients) 18 patients in the midazolam group received a second dose of study drug or alternative sedatives	Agitation/sedation level was measured on a 6-point validated sedation scale: (5=highly aroused, violent; 4=highly aroused, possibly distressed, or fearful; 3=moderately aroused, unreasonable, or hostile; 2=mildly aroused, willing to talk reasonably; 1=minimal agitation; and 0=asleep). Adequate sedation was defined as a score of 2 or less Sedation scores were recorded at baseline, at first observed adequate sedation, and at 10, 20, 30, 45, and 60 minutes after the first dose regardless of observed time to sedation • midazolam was superior with significant differences detected in the Kaplan-Meier curves compared with olanzapine (p=0.03) and haloperidol (p=0.002) At 10 minutes after the initial dose, 52% in the midazolam group were adequately sedated At 60 minutes, the proportion of patients adequately sedated increased to 98% Fully adjusted accelerated factors for olanzapine and haloperidol were compared with midazolam at 1.72 (95% CI 1.16 to 2.55) and 1.89 (95% CI 1.28 to 2.80), respectively, indicating significantly faster sedation for midazolam	Median time to sedation: • midazolam 5 mg IM: 8.5 minutes	2 patients in the midazolam group experienced an adverse event, both with oxygen desaturation 28 patients receiving midazolam fell asleep after treatment

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Lorazepam					
Foster et al[96] (1997)	Lorazepam 2 mg oral concentrate or IM • randomized and double blind • redoses allowed every 30 minutes up to 4 hours until sedated or no longer a danger to self or others Compared to • haloperidol 5 mg oral concentrate or IM	Patients presenting at the psychiatric emergency service of a large urban hospital judged by emergency room staff to be an imminent danger to themselves, they required 4-point physical restraints, they scored a 5 or higher on at least 3 items on the Brief Psychiatric Rating Scale, and they had a score of at least 4 on the GCI Scale 17 patients in the lorazepam group. • mean age 41.35 years • 12 male and 5 female • final diagnoses of schizophrenia (5), bipolar (10), schizoaffective (1), and psychotic disorder not otherwise specified (1) • 6 patients with drug abuse or dependence by history	The primary endpoint was reduction in the Brief Psychiatric Rating Scale with a secondary endpoint of reduction in the GCI Scale The lorazepam group exhibited significant decreases in both rating scales over the course of the study, although no drug by time interactions were found. Analysis of route of administration did not reveal significant effects Brief Psychiatric Rating Scale reductions were not different for lorazepam and haloperidol at 1 hour; the lorazepam group exhibited a significantly greater reduction compared to the haloperidol group on the GCI Scale at 1 hour	Serial hourly evaluations were performed by trained evaluators; only 1-hour outcomes are relevant for this review	There were no group differences in HR/SBP pressure, and diastolic blood pressure and all parameters significantly decreased across time

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Lorazepam					
Battaglia et al[107] (1997)	Lorazepam 2 mg IM • randomized and double blind • repeat doses allowed but not until after the first post-treatment standardized evaluation at 1 hour Compared to • haloperidol 5 mg IM • lorazepam 2 mg plus haloperidol 5 mg IM	ED patients with psychosis and behavioral dyscontrol (agitated, aggressive, destructive, assaultive, or restless behavior) to the extent that they were capable of harming themselves or others 31 patients in lorazepam group: • 23 male/8 female • mean age 33.9 years – mean weight 74.4 kg • final diagnoses were mania, psychoactive substance abuse, psychosis not otherwise specified, schizophrenia, and schizophreniform disorder	Agitation was assessed serially using the Agitated Behavior Scale with a significant reduction in agitation from baseline at 1 hour in the lorazepam arm; however, greater reduction in agitation was seen with combination therapy compared to lorazepam alone (p=0.014); haloperidol alone was not different than lorazepam alone (p=0.426) Approximately 10% of patients in the lorazepam group were asleep at 1 hour, significantly more than the haloperidol alone group and similar to the combination therapy group	Serial evaluations occurred for 12 hours with redosing allowed after reevaluations; only 1-hour endpoints were abstracted as they are most relevant to this review	11 lorazepam-treated patients (35%) reported adverse effects: • ataxia: 2 (6%) • dizziness: 3 (10%) • dry mouth: 5 (16%) • EPS symptoms: 1 (3%) • speech disorder: 2 (6%) "No serious side effects" were reported.

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Lorazepam					
Nobay et al[98] (2004)	Lorazepam 2 mg IM • randomized and double blind • if a patient continued to be disruptive 20 minutes after the study drug was administered, a ‘‘rescue drug’’ could be given at the discretion of the treating attending physician. Patient enrollment in the study was terminated if a rescue medication was given. These patients were considered sedation failures, and their data were not included in the analysis Compared to: • midazolam 5 mg IM • haloperidol 5 mg IM	ED patients who required emergency sedation for the control of violent behavior or severe agitation. All patients were initially physically restrained 27 patients in the lorazepam group • mean age: 39.5 years • 13 African American, 1 Asian, 3 Hispanic, and 10 White • 10 with recreational drug use, 2 without, and 15 unknown • 8 with alcohol use, 3 without, and 16 unknown • 14 with prior psychiatric history, 1 without, and 12 unknown An interim analysis showed that lorazepam demonstrated a statistically significant longer time to sedation and time to awakening than midazolam. Therefore, the lorazepam arm was terminated early	Level of sedation was continuously observed with data collected every 15 minutes; adequacy of sedation was assessed using the Modified Thomas Combativeness Scale with the goal endpoint a score of 3 (No agitation, no supervision required, maybe asleep) Midazolam reached adequate sedation 13.9 minutes faster than lorazepam (95% CI 5.1 to 22.8; p=0.0026) Haloperidol required similar time to adequate sedation: 4.0 minutes faster than lorazepam (95% CI -8.2 to 16.3; p=0.5124) 7 lorazepam patients (26%) needed rescue drugs	The mean time to sedation: • lorazepam 2 mg IM: 32.2 minutes	There were no statistically significant differences over time in regard to change in systolic and diastolic blood pressure (p=0.8965, p=0.9581), heart rate (p=0.5517), respiratory rate (p=0.8191), and oxygen saturation (p=0.8991) among patients receiving each of the medications There were no adverse events in the lorazepam group

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Lorazepam					
Riddell et al[99] (2017)	Lorazepam (mean dose 1.9 mg) IV/ (mean dose 2.4 mg) IM • prospective, observational Compared to: • midazolam (mean dose 3.08 mg) IV/(mean dose 2.25 mg) IM/(mean dose 2 mg) IN • haloperidol (mean dose 5.71 mg) IM • combination of lorazepam (mean dose 2 mg) IV/(mean dose 2 mg) IM plus haloperidol (mean dose 5 mg) IM • ketamine (mean dose 0.87 mg/kg) IV/(mean dose 2.97 mg/kg) IM	Acutely agitated patients requiring chemical sedation in the ED 33 patients in the lorazepam group • median age: 43 years • 19 male/14 female • race: African American (5)/Asian (1)/Hispanic (13)/White (13) • drug use: 78.8% • alcohol use: yes (24.2%)/no (21.9%)/unknown (34.4%) • prior psychiatric visits (53.1%) • route of administration: IV(28)/IM(5)	Primary outcome: agitation score less than or equal to 2 on a six-point agitation scale • recorded prior to medication administration then at 5, 10, and 15 minutes • lorazepam (and other arms) inferior to ketamine at: 5 minutes ($p=0.001$), 10 minutes ($p<0.001$), and 15 minutes ($p=0.032$) Secondary outcomes of: • provider assessment of time to adequate sedation: No difference between groups ($p=0.107$) • need for redosing of sedative medications ($p=0.199$) • HR/SBP change: HR reduction seen with midazolam ($p=0.026$) but no other significant HR/SBP changes in any other study arms	Mean time to adequate sedation: • lorazepam: 17.73 minutes	Intubation: • lorazapam: 1/33

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines					
Lorazepam					
Martel et al[108] (2020)	Lorazepam 2 mg IM • prospective, randomized, double-blind trial • rescue sedation at treating physician discretion permitted 30 minutes after study drug administration for AMSS >0 Compared to: • droperidol 5 mg IM • ziprasidone 10 mg IM • ziprasidone 20 mg IM	ED patients with acute undifferentiated agitation requiring emergent sedation as determined by the treating physician. 31 patients in lorazepam group • median age: 39 years • 23 male/8 female • initial median AMSS scale score of 3 • initial median BARS score of 7 • initial assessment of reason for agitation: alcohol intoxication (25), drug intoxication (3), head injury (8), and primary psychiatric etiology (5). • final diagnoses: acute alcohol intoxication (29), acute drug intoxication (1), head injury (5), psychiatric disease (5), and other (1)	Primary outcome was adequate sedation at 15 minutes • a lesser proportion of lorazepam compared to droperidol treated patients met the primary outcome: 33% lower (95% CI 8% to 58%) while lorazepam did not differ from either dose of ziprasidone • lorazepam: 15/31 • droperidol: 16/25 • ziprasidone 10 mg: 7/28 • ziprasidone 20 mg: 11/31 AMSS scores were obtained every 15 minutes from time 0 to 120 minutes following study medication administration with median AMSS for lorazepam at: • 15 minutes: 2 • 30 minutes: 0 • 45 minutes: 0 • 60 minutes: -1 Additional sedation was required: • 7/31 before adequate sedation achieved • 12/31 in entire encounter • at a median time of 60 minutes following the initial administration	The post-administration assessment of adequate sedation occurred every 15 minutes post administration. The proportion achieving this at each check for lorazepam were: • at 15 minutes: 9/31 • at 30 minutes: 15/31 • at 45 minutes: 18/31 • at 60 minutes: 23/31	Respiratory depression was greater in lorazepam along with both ziprasidone groups compared to droperidol (p=0.04); for lorazepam: • 7/31 with hypoxemia (SpO_2<90%) • 14/31 with change in $ETCO_2$ • 15/31 with respiratory depression No patients in the lorazepam group required intubation. Median QTc: 414 ms • no dysrhythmias in lorazepam group No patients in lorazepam group experienced dystonia

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Droperidol					
Resnick et al[109] (1984)	Droperidol 5 mg IM • repeat dosing at 30-minute intervals up to 4 doses allowed for BPRS>17 • double-blind, prospective study Compared to: • haloperidol 5 mg IM	ED and psychiatric crisis patients with acute agitation and a score of >16 on BPRS. 11 patients in droperidol arm	Need for repeat medication administration used as a surrogate for inadequate control of agitation. Droperidol group with significantly higher proportion requiring only 1 injection (64% versus 19%, p<0.05) • 7/11 with 1 injection • 4/11 with 2 injections	No need for repeat medication injection used as a surrogate for adequate control of agitation at 30 minutes and each reevaluation thereafter	No adverse effects noted in droperidol group. • EPS symptoms were specifically monitored for.
Thomas et al[110] (1992)	Droperidol 5 mg IV/IM • study drug could be repeated or additional agent given at 30 minutes if initial administration ineffective. If additional or alternate drugs were received, only data up to 30 minutes were included for analysis. Compared to • haloperidol 5 mg IV/IM	ED patients who were markedly agitated and required physical restraint and constant attention from medical personnel were considered; those in whom 2 physicians agreed that the patient's agitation was not due to a readily correctible etiology such as hypoglycemia and that chemical restraint was warranted were included in the study 35 patients in the droperidol arm • 26 patients with IM administration (mean age: 34, 31% female, mean blood alcohol: 231 mg%) • 9 patients with IV administration (mean age: 36, 17% female, mean blood alcohol: 240 mg%)	5-point combativeness scale assessed at 5, 10, 15, 30, and 60-minute intervals after the study drug was administered. (1 is violently agitated and 5 is no agitation) • more rapid response to droperidol IM than haloperidol IM (p=0.03) • less agitation in droperidol IM than haloperidol IM at 10 minutes (p=0.004) • less agitation in droperidol IM than haloperidol IM at 15 minutes (p=0.01) • less agitation in droperidol IM than haloperidol IM at 30 minutes (p=0.04)	Combativeness scores for each assessment: • on agitation scale 4=slight agitation; unrestrained. • no definitive endpoint for adequate sedation defined in the study but removal of restraints could be considered a proxy with 4 considered adequate sedation Droperidol 5 mg IM 5 minutes—2.14 10 minutes—3.00 15 minutes—4.00 30 minutes—4.43	Droperidol 5 mg IM • clinically insignificant hypotension (4) No other adverse events observed

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Droperidol					
Martel et al[16] (2005)	Droperidol 5 mg IM • prospective, randomized, double-blind trial • rescue sedation at treating physician discretion permitted 30 minutes after study drug administration for AMS >0 Compared to: • midazolam 5 mg IM • ziprasidone 20 mg IM	ED patients with acute undifferentiated agitation requiring emergent sedation as determined by the treating physician. 50 patients in droperidol group • mean age 36.9 • 33 male/17 female • initial mean AMS scale score of 3.12 • initial assessment of reason for agitation: alcohol intoxication (46), illicit substance intoxication (4), head injury (7), and psychiatric etiology (2). • discharge diagnoses: acute alcohol intoxication (49), acute drug intoxication (1), and closed head injury (11)	AMS scale score was obtained every 15 minutes from time 0 to 120 minutes following study medication administration with effective sedation defined as an AMS of 0 or less Mean AMS scale scores in the droperidol group: • at 15 minutes: 0.28 (95% CI -0.34 to 0.9) • at 30 minutes: -1.3 (95% CI -1.76 to -0.84) • at 45 minutes: -1.56 (95% CI -2.02 to -1.1) • at 60 minutes: -1.56 (-1.99 to -1.13) Less patients receiving droperidol required rescue medications at 30 minutes compared to ziprasidone or midazolam ($p<0.05$) • droperidol: 5 patients required 6 doses • ziprasidone: 9 patients requiring 11 doses • midazolam: 24 patients requiring 30 doses	Less patients remained agitated at 15 minutes in the droperidol and midazolam groups compared to the ziprasidone group ($p=0.01$) • droperidol: 20/50 • midazolam: 15/48 • ziprasidone: 28/46 There was no difference between groups at 30 minutes ($p=0.08$) • droperidol: 6/50 • midazolam: 11/48 • ziprasidone: 14/46 Less patients were agitated at 45 minutes in the droperidol and ziprasidone groups compared to the midazolam group ($p=0.03$) • droperidol: 9/50 • midazolam: 14/48 • ziprasidone: 9/46	Respiratory depression: • 20/50 patients who received droperidol • 4 required supplemental oxygen • no difference in proportion with respiratory depression ($p=0.26$) or supplemental oxygen ($p=0.20$) when compared to midazolam and ziprasidone • no patients required intubation for respiratory depression Akathisia: • 1/50 patients who received droperidol Cardiac dysrhythmias: • none

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Droperidol					
Isbister et al[101] (2010)	Droperidol 10 mg IM • blinded, randomized controlled trial • further sedation allowed at discretion of attending physician Compared to: • midazolam 10 mg IM • midazolam 5 mg plus droperidol 5 mg IM	ED patients requiring physical restraint and parenteral sedation 33 patients in droperidol group • median age: 37 • 12 male/21 female • initial assessment of agitation due to: alcohol intoxication (23), self-harm (16), drug-induced delirium (2), acute psychosis (2), and other (1)	Primary sedation outcome was time security staff were required according to a security log from the time of initial call to the "all clear" • duration was not different between groups (p=0.66) with median for: midazolam (20 minutes), droperidol (24 minutes), and midazolam plus droperidol (25 minutes) Secondary sedation outcomes were: • time additional sedation was administered: the hazard ratio for additional sedation medications for midazolam versus droperidol was 2.31 (95% CI 1.01 to 4.71; post probability 0.98 for HR>1.0) indicating that midazolam was more likely to require additional sedation compared to droperidol	Secondary outcome of reduction in AMSS by 3 points or to a score of <1 20 minutes after drug administration • droperidol: 24/33	Respiratory events occurred in: • droperidol: 2/33 involving desaturation events (2) Hypotension occurred in: • droperidol: 0/33 Abnormal QT-HR pairs occurred in: • droperidol: 2/31 No dystonic reactions were identified Although oversedation was not a secondary endpoint, AMSS scores revealed that both midazolam and midazolam plus droperidol resulted in unpredictable and oftentimes deep sedation while droperidol resulted in consistent moderate sedation

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Droperidol					
Macht et al[111] (2014)	Droperidol IM (61%) and IV (39%) • mean dose 2.9 mg (median 2.5 mg) Compared to haloperidol IM (92%) and IV (8%) • mean dose 7.9 mg (median 10 mg) Retrospective chart review	218 EMS patients receiving droperidol for acute agitation • median age 31 • 75% male	Need for repeat sedating medication within 30 minutes of ED arrival was used as a surrogate endpoint for inadequate sedation • 21/207 (10%) received additional medication: butyrophenone (11) and benzodiazepine (14) There was no difference in need for sedating medications between the droperidol and haloperidol groups	Need for repeat sedation within 30 minutes of ED arrival was used as a surrogate endpoint for inadequate sedation but additional details of time to sedation are not reported	Adverse events reported were: SBP<90 mmHg (6), administration of an anti-arrhythmic medication (1), bag-valve mask (4), intubation (4), and cardiopulmonary arrest (1). No deaths were reported in the droperidol group • The cardiac arrest occurred in the midst of a physical struggle with staff in a combative patient with a history of congenital heart disease; CPR was administered for 1 minute with return of circulation. Post arrest QTc was 481 ms with no abnormal features. The patient was eventually discharged neurologically intact • no difference in proportion of adverse events compared to the haloperidol group QTc recorded in the hospital record for 166 patients; timing of measurement in relation

					to drug administration is not reported • Median QTc 453 ms • QTc 450 to 474 ms (59) • QTc 475 to 499 ms (27) • QTc >500 ms (5) • No difference in median QTc or proportion in any of the prolonged QTc stratifications compared to haloperidol group

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Droperidol					
Calver et al[115] (2015)	Droperidol 10 mg IM • clinician judgement for additional sedation at minutes with agent of clinician's choice although droperidol 10 mg IM recommended for repeat dosing	1,403 ED patients with acute behavioral disturbance, risk to self/others, and SAT score of 2 to 3 • mean age: 34 • 59.9% male • mean blood alcohol: 0.23 mg/dl • baseline SAT scores: 3 (61.9%)/2 (35.4%)/1 (2.6%) • presumed etiology: o alcohol intoxication: 52.6% o self-harm: 24.8% o psychostimulants: 13.8% o mental illness/psycho-sis: 15.7% o medical cause: 2.6% o other: 4.8%	Adequate sedation defined as reduction of SAT score by 2 or more, or reaching a score of 0 69% had adequate sedation after single dose 97% sedated by 120 minutes	Median time to sedation: • droperidol 10 mg IM: 20 minutes	No cases of torsades de pointes in entire cohort 1,009 patients with electrocardiogram recorded within 2 hours of droperidol administration: • median QT: 360 ms (95% CI: 320 to 440 ms) • 13/1,009 (1.3%: 95% CI 0.7% to 2.3%) with abnormal QT: 7 with other reasons for prolonged QT interval • 6/1,009 (0.6%: 95% CI 0.2% to 1.4%) with abnormal QT possibly due to droperidol 109/1,403 with oversedation based on SAT score with no clinical complications 70/1,403 (5.0%; 95% CI 3.9% to 6.3%) patients with total of 71 adverse events: • hypotension: 2.0% • desaturation: 1.6% • airway obstruction: 0.6% • hypoventilation: 0.2% • extrapyramidal side effects: 0.5% • seizure: 0.1% • arrhythmia: 0.1% 34 staff members injured 4 patients injured

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Droperidol					
Page et al[104] (2018)	Droperidol 10 mg IM • optional redosing of 10 mg at 15 minutes • prospective before/after protocol change observational study with primary endpoint to compare adverse events and secondary endpoints of sedation outcomes Compared to Midazolam IM or IV Per protocol: 5 mg initial IM dose with repeat doses of 5 to 10 mg every 10 minutes or 2.5 to 5 mg IV with repeat doses of 2.5 to 5 mg every 10 minutes	149 EMS patients with acute behavioral disturbance and SAT score of +2 (57 patients) to +3 (92 patients) • 81 male/68 female • reason for agitation: alcohol (66), amphetamines (32), medical (19), mental illness (18), other stimulants (8), self harm (20), and marijuana (1) • police were on scene for 123 encounters • median prehospital time of 44 minutes	Sedation was defined as a decrease in SAT score by at least 2 points or score of 0; successful sedation was defined as sedated, no adverse effects, and no requirement for additional sedation • 6/149 required additional EMS sedation • 11/149 required additional ED sedation • median number of drug administrations was 1 • 123/149 were successfully sedated. • 26 with unsuccessful sedation due to: failed to sedate prehospital (4), adverse effects (11), EMS additional sedation (6), and ED additional sedation (11)	Median time to sedation: • droperidol 10 mg IM: 22 minutes	11/149 patients exhibited 15 adverse events in the droperidol group • airway obstruction requiring airway maneuver (3: 2 chin lift/jaw thrust and 1 intubation), desaturation (3), hypotension (2), and SAT score of -3 (4). • compared to those receiving midazolam, a proportion 16% less in the droperidol group exhibited adverse events (p=0.0001, 95% CI 8% to 24%)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Droperidol					
Klein et al[113] (2019)	Droperidol 5 mg IM • retrospective chart review Compared to: • olanzapine 10 mg IM • haloperidol 5 mg IM	ED patients receiving parenteral antipsychotic for agitation 4,947 patients in droperidol arm • median age: 40 • 3,681 male/1,266 female • etiologies: alcohol (4,528), drug intoxication (411), psychiatric (552), and medical (8)	Primary outcome was rescue sedation administered within 1 hour of initial sedative • 547/4,947 (11%) required rescue sedation during initial hour: olanzapine (48), droperidol (478), haloperidol (1), benzodiazepine (18), and ketamine (2) • 832/4,947 (17%) received rescue sedation during ED encounter There was no difference between proportion of rescue sedation at 1 hour when comparing droperidol and olanzapine (0% difference: 95% CI -1% to 1%). Patients receiving droperidol required 7% less instances of rescue medication compared to haloperidol (95% CI 9% to 5% less)	Need for rescue medication at 1 hour documented but no additional details of time to sedation	In group receiving droperidol: Respiratory events • 9/4,947 (0.2%: 95% CI 0.1 to 0.3%) intubated Cardiac events • no cases of torsades de pointes or other cardiac events reported. Extrapyramidal side effects • 5 cases of akathisia • 2 cases of dystonia Allergic reactions • None

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Droperidol					
Gaw et al[122] (2020)	Droperidol • median dose of 0.625 mg • dose for different indications not documented • IM versus IV not documented • retrospective cohort study	ED droperidol administration for any indication 6,353 visits with droperidol administration • median age: 38 • female: 69.9%/male: 30.1% • indications: pain (21%); headache (57%); sedative (8.7%); antiemetic (12.5%)	Adequate sedation achieved in 48.3% of 56 patients receiving droperidol for sedation in a subgroup that underwent chart review	Not reported	QTc prolongation • no fatal arrhythmias • 0.7% with QTc of 500 ms or greater within 24 hours after droperidol • 1.2% with QTc of 500 ms or greater within 6 months prior to droperidol No deaths attributable to droperidol in entire Adverse events: • Akathisia: 2.9%

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Droperidol					
Martel et al[108] (2020)	Droperidol 5 mg IM • prospective, randomized, double-blind trial • rescue sedation at treating physician discretion permitted 30 minutes after study drug administration for AMSS >0 Compared to: • ziprasidone 10 mg IM • ziprasidone 20 mg IM • lorazepam 2 mg IM	ED patients with acute undifferentiated agitation requiring emergent sedation as determined by the treating physician 25 patients in droperidol group • median age: 39 • 21 male/4 female • initial median AMSS scale score: 3 • initial median BARS score: 7 • initial assessment of reason for agitation: alcohol intoxication (19), drug intoxication (1), head injury (3), and primary psychiatric etiology (3). • final diagnoses: acute alcohol intoxication (20), acute drug intoxication (0), head injury (1), psychiatric disease (3), and other (2)	Primary outcome was adequate sedation at 15 minutes • a greater proportion of droperidol treated patients compared to lorazepam 33% greater (95% CI 8% to 58%), ziprasidone 10 mg 39% greater (95% CI 14% to 64%), and ziprasidone 20 mg 29% greater (95% CI 3% to 54%) treated patients met the primary outcome • lorazepam: 15/31 • droperidol: 16/25 • ziprasidone 10 mg: 7/28 • ziprasidone 20 mg: 11/31 AMSS scores were obtained every 15 minutes from time 0 to 120 minutes following study medication administration with median AMSS for droperidol at: • 15 minutes: 0 • 30 minutes: -2 • 45 minutes: -2 • 60 minutes: -1 Additional sedation was required: • 2/25 before adequate sedation achieved • 5/25 in entire encounter • at a median time of 90 minutes following the initial administration	The post-administration assessment of adequate sedation occurred every 15 minutes post administration. The proportion achieving this endpoint at each check for droperidol was: • at 15 minutes: 16/25 • at 30 minutes: 22/25 • at 45 minutes: 21/25 • at 60 minutes: 22/25	Respiratory depression was less in the droperidol group compared to both ziprasidone groups along with lorazepam (p=0.04). For droperidol: • 2/25 with hypoxemia (SpO_2<90%) • 2/25 with change in $ETCO_2$ • 3/25 with respiratory depression No patients in the droperidol group required intubation. Median QTc: 413 ms. • one patient in the droperidol group experienced atrial flutter One patient in droperidol group experienced dystonia

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Droperidol					
Cole et al[114] (2021)	Droperidol 5 mg IM • prospective observational study Compared to: olanzapine 10 mg IM	ED patients with suspected drug or alcohol intoxication who received IM medication to treat acute agitation 538 patients in droperidol group • median age: 40 • male: 70% • 39% White/38% Black/14% Native American or Alaska Native/6% Hispanic/1% Asian/2% other or unknown • 86% with detectable alcohol concentration (median 0.2 % (g/dl)) • presumed cause: alcohol intoxication (86%)/illicit substance (15%)/psychiatric illness (12%)/medical (2%)	Adequate sedation defined as AMSS less than or equal to 0 No difference in the proportion of patients adequately sedated before 15 minutes: (droperidol 38%; olanzapine 42%; absolute difference -4% (95% CI -9% to 2%) • the hazard ratio for adequate sedation for droperidol compared with olanzapine was 1.12 (95% CI 1.00 to 1.25) Nadir AMSS scores tended to be higher (less sedation) for droperidol (median AMSS score -2) compared with olanzapine (median AMSS score -3). Patients who received olanzapine were more likely to receive additional medication for agitation while in the ED (droperidol 17%; olanzapine 24%; absolute difference -8% (95% CI -12% to -3%)	Median time to adequate sedation • droperidol 5 mg IM: 16 minutes	Of 538 patients in droperidol group Respiratory events: • any event: 23 • hypoxemia: 20 • supplemental oxygen: 6 • intubation: 4 • airway maneuver: 2 • aspiration: 1 Cardiovascular events: • hypotension: 13 • bradycardia: 2 Extrapyramidal events: • dystonia: 4 • akathisia: 2

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Olanzapine					
Centorrino et al[94] 2007	Olanzapine 10 mg IM • initial mean olanzapine dose was 9.9 ±2.2 mg • open label mixed retrospective and prospective observational report No comparison medication	Clinically agitated inpatient and emergency psychiatric services patients with bipolar mania or schizophrenia 74 patients receiving olanzapine IM: • 56.8% male • mean age 34.2 • diagnoses: bipolar mania or mixed-episode 29.7%; schizophrenia, schizoaffective disorder or schizophreniform disorder 70.3%	Agitation was assessed using the excitement component of the Positive and Negative Syndrome Scale (PANSS-EC), the changes in GCI Scale and the Agitation Calmness Evaluation Scale (ACES) There was significant improvement from baseline in all patients at 15 minutes ($p<0.001$)	Median time to adequate response: • olanzapine 10 mg IM: 30 minutes	No serious adverse events Treatment related adverse events in at least 4% of patients: • insomnia (9.5%) • arthralgia (7.9%) • headache (6.3%)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Olanzapine					

Cole et al[116] (2017)	Olanzapine 10 mg IM
	• actual dose received: 5 mg (6.4%)/10 mg (93.2%)/20 mg (0.4%)
	• prospective, observational report
	
	No comparison group
		ED patients receiving parenteral olanzapine during the study period
		
		489 in IM administration group:
		• median age: 39.5
		• male sex: 64%
		• White (38.9%)/Black American (32.2%)/American Indian (16.8%)/Hispanic (4.3%)/Somali (1.4%)/Asian (0.6%)/Other or mixed (5.7%)
		• median breath ethanol: 220 mg/dl
		• 430 received olanzapine for agitation
			Observer's Assessment of Alertness/Sedation (OAA/S) scale recorded at 0, 5, 10, 15, 30 and 60 minutes after initial dose
			
			Of those receiving olanzapine IM for agitation:
			84% did not require additional sedating medications within 60 minutes
			• provider satisfaction with improvement in symptoms was:
			  • none (0%)
			  • minimal (7%)
			  • moderate (25%)
			  • significant (49%)
			  • complete (19%)
				Median Observer's Assessment of Alertness/Sedation (OAA/S) score for Olanzapine 10 mg IM at time:
				• baseline: 5
				• 10 minutes: 4
				• 30 minutes: 3
				• 60 minutes: 3
					No patients experienced an allergic reaction, death, or a tachydysrhythmia.
					
					Respiratory depression: 10 patients
					• intubation: 5
					• bilevel positive airway pressure: 1
					• bag-valve-mask ventilation: 3
					• protective airway reflexes lost: 2
					• airway repositioning: 2
					• stimulation to induce respiration: 3
					• supplemental oxygen added: 7
					• airway suctioning 1
					
					Non respiratory adverse events:
					• sinus bradycardia: 1
					• akathisia: 1

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Olanzapine					
Klein et al[103] (2018)	Olanzapine 10 mg IM • prospective, observational Compared to: • midazolam 5 mg IM • haloperidol 5 mg IM • haloperidol 10 mg IM • ziprasidone 20 mg	ED patients receiving medication to treat acute agitation 163 patients in olanzapine arm • median age: 45 • 113 male/50 female • cause of agitation: alcohol (90%)/illicit substance (11%)/psychiatric illness (12%)/medical (1%)	Primary endpoint was adequate sedation, defined as Altered Mental Status Score <1 15 minutes after medication administration. • olanzapine 10 mg IM not inferior to midazolam 5 mg IM (9% lesser for olanzapine: 95% CI 20% lesser to 1% greater) • olanzapine 10 mg IM superior to haloperidol 5 mg IM (20% greater for olanzapine: 95% CI 10% to 31%) • olanzapine 10 mg IM superior to haloperidol 10 mg IM (18% greater for olanzapine: 95% CI 7% to 29%) • olanzapine 10 mg IM not superior to ziprasidone 20 mg IM (8% greater for olanzapine: 95% CI 3% lesser to 19% greater) Median difference in AMSS score compared to baseline at 15 minutes: • olanzapine 10 mg IM not inferior to midazolam 5 mg IM (1 point lesser decrease for olanzapine: 95% CI 0 to 1 point lesser decrease) • olanzapine 10 mg IM superior to haloperidol 5 mg IM (1 point greater	Median time to adequate sedation: • olanzapine 10 mg IM: 14 minutes	No difference in adverse events between groups Respiratory distress: • 1 to 3 patients in each arm with hypoxemia • 1 patient intubated in each arm except haloperidol 10 mg with no intubations Cardiovascular: • 1 to 2 patients in each group with hypotension except ziprasidone with no episodes of hypotension • 1 patient in each arm with bradycardia except midazolam with no episodes of bradycardia • no patients in any arm with torsades de pointes or other dysrhythmias Extrapyrimadal symptoms: • 2 patients in haloperidol 10 mg arm with dystonia; no other dystonic reactions in any arm • no episodes of akathisia in entire study

			decrease for olanzapine: 95% CI 1.5 to 1 point greater decrease) • olanzapine 10 mg IM superior to haloperidol 10 mg IM (1 point greater decrease for olanzapine: 95% CI 1.5 to 0.5 point greater decrease) • olanzapine 10 mg IM not superior to ziprasidone 20 mg IM (0 point difference: 95% CI 0.5 point greater decrease to 0.5 point lesser decrease) Time to adequate sedation (compared to midazolam 5 mg IM): • olanzapine 10 mg IM no different (HR 0.97, 95% CI 0.76 to 1.22) Time to adequate sedation for subset receiving monotherapy and no rescue sedation medications (compared to midazolam 5 mg IM): • olanzapine 10 mg IM no different (HR 0.84, 95% CI 0.65 to 1.07)		

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Olanzapine					
Klein et al[113] (2019)	Olanzapine 10 mg IM • retrospective chart review Compared to: • droperidol 5 mg IM • haloperidol 5 mg IM	ED patients receiving parenteral antipsychotic for agitation 8,825 patients • median age: 35 • 6,658 male/2,167 female • etiologies: alcohol (8,181), drug intoxication (619), psychiatric (891), and medical (25)	Primary outcome was rescue sedation administered within 1 hour of initial sedative • 988/8,825 (11%) required rescue sedation during initial hour: olanzapine (669), droperidol (17), haloperidol (274), benzodiazepine (26), and ketamine (2) • 1,665/8,825 (19%) received rescue sedation during ED encounter There was no difference between proportion of rescue sedation at 1 hour when comparing droperidol and olanzapine (0% difference: 95% CI -1% to 1%) Patients receiving olanzapine required 7% less instances of rescue medication compared to haloperidol (95% CI 9% to 5% less)	Need for rescue medication at 1 hour documented but no additional details of time to sedation	In group receiving olanzapine: Respiratory events: 36/8825 (0.4%: 95% CI 0.2% to 0.6%) intubated Cardiac events: • cardiac arrest occurred in 1 patient • no cases of torsades de pointes Extrapyramidal side effects: 2 cases of akathisia and 2 cases of dystonia Allergic reactions: 2 cases of rash

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Olanzapine					
Chan et al[106] (2021)	Olanzapine 5 mg IM • single optional redose allowed per study protocol • randomized, double-blind Compared to: • haloperidol 5 mg IM • midazolam 5 mg IM	ED patients requiring parenteral drug sedation for acute agitation 54 patients in olanzapine group • mean age 40 • 38 male/16 female • perceived possible causes: drug/substance abuse (14), alcohol intoxication (12), underlying mental illness (45), medication non-compliance (22), suicidal ideation/attempt (17), exposure to haloperidol (1), concurrent psychotropic medication (17) • baseline sedation scores: 3 (16 patients), 4 (21 patients), and 5 (16 patients) 16 patients in the olanzapine group received a second dose of study drug or alternative sedatives.	Agitation/sedation level was measured on a 6-point validated sedation scale: (5=highly aroused, violent; 4=highly aroused, possibly distressed, or fearful; 3=moderately aroused, unreasonable, or hostile; 2=mildly aroused, willing to talk reasonably; 1=minimal agitation; and 0=asleep); adequate sedation was defined as a score of 2 or less Sedation scores were recorded at baseline, at first observed adequate sedation, and at 10, 20, 30, 45, and 60 minutes after the first dose regardless of observed time to sedation • midazolam was superior to olanzapine with significant differences detected in the Kaplan-Meier curves (p=0.03) • no difference for haloperidol compared with olanzapine (p=0.78) At 10 minutes after the initial dose, 34% in the olanzapine group were adequately sedated. At 60 minutes, the proportion of patients adequately sedated increased to 87% Fully adjusted accelerated factor for olanzapine was compared with midazolam at 1.72 (95% CI 1.16 to 2.55), indicating significantly slower sedation for olanzapine	Median time to sedation for olanzapine 5 mg IM: 11.5 minutes	3 patients in the olanzapine group experienced an adverse event; 1 patient experienced oxygen desaturation and 2 patients reported dry mouth 10 patients receiving olanzapine fell asleep after treatment

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Olanzapine					
Cole et al[114] (2021)	Olanzapine 10 mg IM • prospective observational study Compared to: droperidol 5 mg IM	ED patients with suspected drug or alcohol intoxication who received IM medication to treat acute agitation 719 patients in olanzapine group • median age: 43 • male: 75% • 40% White/33% Black/16% Native American or Alaska Native/3% Hispanic/1% Asian/<1% other or unknown • 87% with detectable alcohol concentration (median 0.2 % (g/dl)) • presumed cause: alcohol intoxication (87%)/illicit substance (13%)/psychiatric illness (13%)/medical (1%)	Adequate sedation defined as AMSS less than or equal to 0 No difference in the proportion of patients adequately sedated before 15 minutes: (olanzapine 42%; droperidol 38%; absolute difference -4% [95% CI -9% to 2%]) • the hazard ratio for adequate sedation for droperidol compared with olanzapine was 1.12 (95% CI 1.00 to 1.25) Nadir AMSS scores tended to be higher (less sedation) for droperidol (median AMSS score -2) compared with olanzapine (median AMSS score -3) Patients who received olanzapine were more likely to receive additional medication for agitation while in the ED (olanzapine 24%; droperidol 17%; absolute difference -8% [95% CI -12% to -3%])	Median time to adequate sedation • olanzapine 10 mg IM: 17.5 minutes	Of 719 patients in olanzapine group Respiratory events • any event: 47 • hypoxemia: 42 • supplemental oxygen: 30 • intubation: 7 • airway maneuver: 5 • aspiration: 3 Cardiovascular events • hypotension: 19 • bradycardia: 1 Extrapyramidal events • dystonia: 0 • akathisia: 1

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					
Resnick et al[109] (1984)	Haloperidol 5 mg IM • repeat dosing at 30-minute intervals up to 4 doses allowed for BPRS>17 • double-blind, prospective study Compared to: • droperidol 5 mg IM	ED and psychiatric crisis patients with acute agitation and a score of >16 on BPRS 16 patients in haloperidol arm	Need for repeat medication administration used as surrogate for inadequate control of agitation Haloperidol group with significantly lower proportion requiring only 1 injection (19% versus 64%, p<0.05) • 3/16 with 1 injection • 10/16 with 2 injections • 2/16 with 3 injections • 1/16 with 4 injections	No need for repeat medication injection surrogate for adequate control of agitation at 30 minutes and each reevaluation thereafter	1 dystonic reaction noted in haloperidol group
Thomas et al[110] (1992)	Haloperidol 5 mg IV/IM • study drug could be repeated, or additional agent given at 30 minutes if initial administration ineffective. If additional or alternate drugs were received, only data up to 30 minutes were included for analysis Compared to droperidol 5 mg IV/IM	ED patients who were markedly agitated and required physical restraint and constant attention from medical personnel were considered. Those in whom 2 physicians agreed that the patient's agitation was not due to a readily correctible etiology such as hypoglycemia and that chemical restraint was warranted were included in the study 33 patients in the haloperidol arm • 21 patients with IM administration (mean age: 31, 52% female, mean blood alcohol: 174 mg%) • 12 patients with IV administration (mean age: 31, 0% female, mean blood alcohol: 250 mg%)	5-point combativeness scale assessed at 5, 10, 15, 30, and 60-minute intervals after the study drug was administered. (1 is violently agitated and 5 is no agitation) • less rapid response to haloperidol IM than droperidol IM (p=0.03) • more agitation in haloperidol IM than droperidol IM at 10 minutes (p=0.004) • more agitation in haloperidol IM than droperidol IM at 15 minutes (p=0.01) • more agitation in haloperidol IM than droperidol IM at 30 minutes (p=0.04)	Combativeness scores for each assessment: -on agitation scale 4=slight agitation; unrestrained. • no definitive endpoint for adequate sedation defined in the study but removal of restraints could be considered a proxy with 4 considered adequate sedation Haloperidol 5 mg IM at time: 5 minutes—1.33 10 minutes—2.11 15 minutes—3.11 30 minutes—3.75	Haldol 5 mg IM -Clinically insignificant hypotension (2) -Dystonic reaction 18 hours after drug administration (1) No other adverse events observed

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					
Battaglia et al[107] (1997)	Haloperidol 5 mg IM • randomized and double blind • repeat doses allowed but not until after the first post-treatment standardized evaluation at 1 hour Compared to: • lorazepam 2 mg IM • lorazepam 2 mg plus haloperidol 5 mg IM	ED with psychosis and behavioral dyscontrol (agitated, aggressive, destructive, assaultive, or restless behavior) to the extent that they were capable of harming themselves or others 35 ED patients in the haloperidol group • 25 male/10 female • mean age 34.3 years • mean weight 73.3 kg patients • final diagnoses were mania, psychoactive substance abuse, psychosis not otherwise specified, schizophrenia, and schizophreniform disorder	Agitation was assessed serially using the Agitated Behavior Scale with a significant reduction in agitation from baseline at 1 hour in the haloperidol arm; the reduction in agitation seen with haloperidol was not greater than lorazepam alone (p=0.426) or combination therapy (p=0.064) Approximately 2.5% of patients in the haloperidol group were asleep at 1 hour, significantly less than the lorazepam alone group or the combination therapy group	Serial evaluations occurred for 12 hours with redosing allowed after reevaluations; only 1-hour endpoints were abstracted as they are most relevant to this review	14 lorazepam-treated patients (40%) reported adverse effects: • ataxia: 1 (3%) • dizziness: 3 (9%) • dry mouth: 3 (9%) • EPS symptoms: 7 (20%) • speech disorder: 4 (11%) "No serious side effects" were reported

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					
Foster et al[96] (1997)	Haloperidol 5 mg oral concentrate or IM • redoses allowed every 30 minutes up to 4 hours until sedated or no longer a danger to self or others Compared to: • lorazepam 2 mg oral concentrate or IM	Patients presenting at the psychiatric emergency service of a large urban hospital judged by emergency room staff to be an imminent danger to themselves, they required 4-point physical restraints, they scored a 5 or higher on at least 3 items on the BPRS, and they had a score of at least 4 on the GCI Scale 20 patients in the haloperidol group: • mean age 42.35 years • 14 male and 6 female • final diagnoses of schizophrenia (8), bipolar (3), schizoaffective (3), and psychotic disorder not otherwise specified (6) • 4 patients with drug abuse or dependence by history	The primary endpoint was reduction in the BPRS with a secondary endpoint of reduction in the GCI Scale The haloperidol group exhibited significant decreases in both rating scales over the course of the study, although no drug by time interactions were found; analysis of route of administration did not reveal significant effects BPRS reductions were not different for lorazepam and haloperidol at 1 hour; the lorazepam group exhibited a significantly greater reduction compared to the haloperidol group on the GCI scale at 1 hour	Serial hourly evaluations were performed by trained evaluators. Only 1-hour outcomes are relevant for this review	There were no group differences HR/SBP pressure, and diastolic blood pressure and all parameters significantly decreased across time

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					

TREC Collaborative Group[100] (2003)	Combination of haloperidol 5 mg to 10 mg plus promethazine 25 mg to 50 mg IM
	• prospective, pseudo-randomized open label
	• dose at treating physician discretion
	
	Compared to:
	• midazolam 7.5 mg to 15 mg IM
		Adults presenting to psychiatric Eds with agitation or dangerous behavior
		
		148 patients in the haloperidol/promethazine arm
		• 49% male/51% female
		• mean age: 38
		• dose of haloperidol: 10 mg (71 patients)/5 mg (77)
		• dose of promethazine: 50 mg (147)/25 mg (1)
		• presumed etiology:
		  • Psychosis 75%
		  • Substance abuse 14%
		  • Other 11%
			Primary endpoint was "tranquil or asleep" at 20 minutes, with tranquil defined as peaceful and without restlessness or threatening behavior
			
			Secondary endpoints included tranquil or asleep at 40, 60, and 120 minutes; need for physical restraints; recurrent episode of agitation; major adverse events.
			
			Haloperidol inferior for primary endpoint at 20 minutes as well as secondary endpoint at 40 minutes
			• no difference at 60 minutes or greater
			• no difference in need for restraints
			• no difference in additional tranquilizing drugs
			
			At 20 minutes, 67% in the Haloperidol/promethazine arm versus 89% in the midazolam arm reached primary endpoint
			• RR 1.32 (95% CI 1.16 to 1.49)
			• 22% (95% CI 12% to 30%) less in haloperidol/promethazine group w/ adequate sedation at 20 minutes
				At 20 minutes, 67% in the haloperidol/ promethazine arm reached primary endpoint	1 patient in Haldol/promethazine group with history of epilepsy experienced seizure that resolved with benzodiazepine

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					
Nobay et al[98] (2004)	Haloperidol 5 mg IM • randomized and double blind • if a patient continued to be disruptive 20 minutes after the study drug was administered, a ‘‘rescue drug’’ could be given at the discretion of the treating attending physician; patient enrollment in the study was terminated if a rescue medication was given; these patients were considered sedation failures, and their data were not included in the analysis Compared to: • lorazepam 2 mg IM • midazolam 5 mg IM	ED patients who required emergency sedation for the control of violent behavior or severe agitation; all patients were initially physically restrained 42 patients in the haloperidol group • mean age 42.4 years • 23 African American, 1 Asian, 3 Hispanic, and 15 White • 11 with recreational drug use, 2 without, and 29 unknown • 14 with alcohol use, 1 without, and 27 unknown • 20 with prior psychiatric history, 4 without, and 18 unknown	Level of sedation was continuously observed with data collected every 15 minutes; adequacy of sedation was assessed using the Modified Thomas Combativeness Scale with the goal endpoint a score of 3 (No agitation, no supervision required, maybe asleep) 8 haloperidol patients (19%) needed rescue drugs Lorazepam required similar time to adequate sedation: 4.0 minutes slower than haloperidol (95% CI -8.2 to 16.3; p=0.5124) Midazolam reached adequate sedation 9.9 minutes faster than haloperidol (95% CI 0.5 to 19.3; p=0.0388)	The mean time to sedation • haloperidol 5 mg IM: 28.3 minutes	There were no statistically significant differences over time in regard to change in systolic and diastolic blood pressure (p=0.8965, p=0.9581), heart rate (p=0.5517), respiratory rate (p=0.8191), and oxygen saturation (p=0.8991) among patients receiving each of the medications There were 2 adverse events in the haloperidol group; one patient became hypotensive and another apneic, but both subsequently recovered fully

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					
Macht et al[111] (2014)	Haloperidol IM (92%) and IV (8%) • mean dose 7.9 mg (median 10 mg) • retrospective chart review Compared to: • droperidol IM (61%) and IV (39%) • mean dose 2.9 mg (median 2.5 mg)	314 EMS patients receiving haloperidol for acute agitation • median age 31 • 69% male	Need for repeat sedating medication within 30 minutes of ED arrival was used as a surrogate endpoint for inadequate sedation • 41/314 (13%) received additional medication: butyrophenone (22) and benzodiazepine (20) There was no difference in need for sedating medications between the haloperidol and droperidol groups	Need for repeat sedation within 30 minutes of ED arrival was used as a surrogate endpoint for inadequate sedation but additional details of time to sedation are not reported	Adverse events reported were: SBP<90 mmHg (13), administration of an anti-arrhythmic medication (5), bag-valve mask (12), and intubation (12). No cardiac arrest or death in the haloperidol group • no difference in proportion of adverse events compared to the droperidol group QTc recorded in the hospital record for 78 patients; timing of measurement in relation to drug administration is not reported • median QTc 448 ms • QTc 450 ms to 474 ms (23) • QTc 475 ms to 499 ms (9) • QTc >500ms (3) • no difference in median QTc or proportion in any of the prolonged QTc stratifications compared to droperidol group

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					
Asadohalli et al[117] (2015)	Haloperidol 5 mg IM • randomized, double blind placebo-controlled study • single redose allowed Compared to: • valproic acid	80 ED patients with violent, controlled, or uncontrolled muscular movement that placed both themselves and hospital staff in danger because of severely disruptive behavior • mean age: 44.55 years • 49 male/31 female • 61 physically restrained • etiology: 55-mental disorders, 21-other (infection, substance intoxication, or withdrawal), and 4 unknown • 58 reported prior use of psychiatric medications	The primary outcome measure was the Agitation–Calmness Evaluation Scale (ACES); secondary outcomes were changes in the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) and the Agitated Behavior Scale (ABS) scores Haloperidol exhibited a greater change in Agitation Calmness Evaluation Scale (ACES) score at 30 minutes compared to valproate (p=0.028). there was no difference in Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) (p=0.649) or Agitated Behavior Scale scores (0.651). Similar numbers of patients required a 2nd dose of medication (haloperidol=17 and valproate=13; p=0.418); the mean duration of physical restraint did not differ significantly between patients receiving valproate and haloperidol (37.4 versus 38.9 minutes, p=0.100)	Outcomes were measured at 30 minutes following medication administration.	There were no statistically significant differences up to 30 minutes after injection with respect to changes in systolic and diastolic blood pressure (P=0.77, P=0.12), heart rate (P=0.64), and respiratory rate (P=0.78) among patients receiving each of the interventions The haloperidol treatment group had a significantly larger proportion (37 patients, p=0.034) who showed at least one adverse event • intense sedation 30 minutes after intervention was the most frequent adverse event in the haloperidol versus valproate group (29 versus 2, p<0.001) • 7 patients (p=0.007) experienced EPS in the haloperidol study arm; these patients • received anticholinergic agents • hypotension occurred in • one patient receiving haloperidol

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					
Isenberg et al[102] (2015)	Haloperidol 2.5 mg to 5 mg IM (5 mg if younger than 65 years and 2.5 mg if 65 years or older) • randomized, non-blinded • re-dosing available every 10 minutes if sedation endpoint not met but maximum dose received was 5 mg Compared to: • midazolam 2.5 mg to 5 mg IM	EMS patients with either: • a psychiatric or behavioral disorder who is at imminent risk of self-injury or is a threat to others • patient with a medical condition causing agitation and possibly violent behavior 5 patients in haloperidol group • age 18 to 89 • all with initial RASS +4 • patient diagnosis: urinary tract infection (1) and alcohol intoxication (4)	Sedation evaluated using RASS with goal of less than +1. 5/5 patients in haloperidol group with RASS less than +1 on arrival to ED	Mean time to achieve a RASS of less than +1: • haloperidol 2.5 mg to 5 mg IM: 24.8 minutes	No patients in the haloperidol group had any adverse effects Mean time to return to baseline mental status was 84 minutes (95% CI 0 to 202 minutes)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					
Cole et al[118] (2016)	Haloperidol 10 mg IM (5 patients received 5 mg rather than 10 mg as initial dose) • prospective open label EMS study Compared to: • ketamine 5 mg/kg IM	82 acute undifferentiated agitation with AMSS +3 (60 patients) to +2 (22 patients); AMSS +4 excluded as "profound agitation" • median age 31 • 44 male/38 female • 33 Caucasian, 25 Black American, 14 American Indian, 2 Somali, 2 Hispanic, 1 Asian, 5 mixed/unknown • 55 (67%) with history of mental illness, 59 (72%) with history of chemical dependency, and 43 (52%) with both • EMS impressions of: agitated combative (21), substance abuse (23), behavioral (8), AMS (10), trauma (7), overdose (4), and seizure (1)	Primary endpoint of AMSS < +1. • 53/82 patients achieved adequate sedation • 16/82 patients required second injection prehospital: midazolam (15) and haloperidol (1) Compared to the group receiving ketamine, 30% less patients in the haloperidol group successfully achieved adequate sedation ($p<0.0001$, 95% CI 18% to 42%) Time to sedation was 12 minutes greater for haloperidol group compared to the ketamine group ($p<0.0001$, 95% CI 9 to 15 minutes)	Median time to adequate sedation: • haloperidol 10 mg IM: 17 minutes	Five complications occurred in 4/82 patients: vomiting (2), dystonia (2), and death (1); per communication with study author, the death was related to polytrauma and the patient died days after receiving haloperidol due to traumatic injuries • complications occurred in 44% less patients in the haloperidol group compared to the ketamine group ($p<0.0001$, 95% CI 30% to 57%) Intubation occurred in 3/82 patients for the following indications: not protecting airway (1) and refractory agitation (2) • intubation occurred in 35% less patients in the haloperidol group compared to the ketamine group ($p<0.0001$, 95% CI 23% to 48%)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					
Riddell et al[99] (2017)	Haloperidol (mean dose 5.71 mg) IM • prospective, observational Compared to: • midazolam (mean dose 3.08 mg) IV/(mean dose 2.25 mg) IM/(mean dose 2 mg) IN • lorazepam (mean dose 1.9 mg) IV/ (mean dose 2.4 mg) IM • combination of lorazepam (mean dose 2 mg) IV/(mean dose 2 mg) IM plus haloperidol (mean dose 5 mg) IM • ketamine (mean dose 0.87 mg/kg) IV/(mean dose 2.97 mg/kg) IM	Acutely agitated patients requiring chemical sedation in the ED 14 patients in the haloperidol group • median age: 44 • 11 male/3 female • race: African American (1)/Asian (1)/Hispanic (8)/White (4) • drug use: 85.7% • alcohol use: yes (35.7%)/no (35.7%)/unknown (28.6%) • prior psychiatric visits (50.0%) • route of administration: IM (14)	Primary outcome: agitation score less than or equal to 2 on a six-point agitation scale • recorded prior to medication administration then at 5, 10, and 15 minutes • haloperidol (and other arms) inferior to ketamine at: 5 minutes ($p=0.001$), 10 minutes ($p<0.001$), and 15 minutes ($p=0.032$) Secondary outcomes of: • provider assessment of time to adequate sedation: No difference between groups ($p=0.107$) • need for redosing of sedative medications ($p=0.199$) • HR/SBP change: HR reduction seen with midazolam ($p=0.026$) but no other significant HR/SBP changes in any other study arms	Mean time to adequate sedation: • haloperidol IM: 13.43 minutes	Intubation: • haloperidol: 1/14 • midazolam: 1/19 • lorazapam: 1/33 • combination lorazepam plus haloperidol: 1/10 • ketamine: 2/24

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					
Heydari et al[119] (2018)	Haloperidol 5 mg IM • if patient was inadequately sedated or additional medication needed per physician discretion then 2.5 mg repeat dose allowed • randomized, double blind prospective trial Compared to: • ketamine 4 mg/kg IM	ED patients with acute agitated and aggressive behavior who required chemical sedation for agitation, according to an emergency medicine resident or attending physician were eligible for enrollment. (AMSS +2 or +3) 45 patients in haloperidol group: • mean age of 29.93 • male 75.6%/female 24.4% • cause of aggressive behavior: psychotropic substances (26.7%)/psychiatric history (33.3%)/alcohol consumption (28.9%)/trauma (11.1%)	The primary outcome was time to adequate sedation (AMSS≤+1) -slower for haloperidol compared to ketamine (p<0.01, difference 3.7 minutes, 95% CI: 2.1 to 5.5) Mean AMSS scores: • 5 minutes: haloperidol (1.70) was not different from ketamine (1.36) (p=0.115) • 10 minutes: haloperidol (1.27) was higher than ketamine (0.67) (p=0.001) • 15 minutes: haloperidol (0.3) was not different from ketamine (0.14) (p=0.167) • proportion not adequately sedated at 15 minutes was higher in haloperidol group (28.9%) than ketamine group (6.7%) • difference of 22%: 95% CI 11% to 33% (p<0.0001) Physician satisfaction was lower in haloperidol group than ketamine group (p=0.011)	Median time to adequate sedation • haloperidol 5 mg IM: 11.4 minutes	Complications: • 17.8% for haloperidol • 35.6% for ketamine • no significant difference between groups (p=0.094, difference 17%, 95% CI 11% to 22%). Haloperidol group: • vomiting (n=1, 2.2%), • dystonia (n=2, 4.4%), • akathisia (n=4, 8.9%), • hypoxia (n=1, 2.2%) • Intubation (n=3, 6.7%) Primary indications for intubation in haloperidol group were refractory agitation (2) and hypoxia (1)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					
Klein et al[103] (2018)	Haloperidol 5 mg IM • prospective, observational Compared to: • midazolam 5 mg IM • olanzapine 10 mg • IM • haloperidol 10 mg IM • ziprasidone 20 mg	ED patients receiving medication to treat acute agitation 151 patients in haloperidol 5 mg arm • median age: 40 • 101 male/50 female • cause of agitation: alcohol (90%)/illicit substance (10%)/psychiatric illness (10%)/medical (1%)	Primary endpoint was adequate sedation, defined as Altered Mental Status Score <1 15 minutes after medication administration • haloperidol 5 mg IM inferior to midazolam 5 mg IM (30% lesser for haloperidol: 95% CI 41% lesser to 19% lesser) • haloperidol 5 mg IM inferior to olanzapine 10 mg IM (20% lesser for haloperidol: 95% CI 31% lesser to 10% lesser) • haloperidol 5 mg IM no different than haloperidol 10 mg IM (2% lesser for haloperidol 5 mg: 95% CI 13% lesser to 9% greater) • haloperidol 5 mg IM inferior to ziprasidone 20 mg IM (12% lesser for haloperidol 5 mg: 95% CI 23% lesser to 1% lesser) Median difference in AMSS score compared to baseline at 15 minutes: • haloperidol 5 mg IM inferior to midazolam 5 mg IM (2 point lesser decrease for haloperidol: 95% CI 2.5 lesser decrease to 1.5 point lesser decrease) • haloperidol 5 mg IM inferior to olanzapine 10	Median time to adequate sedation: • haloperidol 5 mg IM: 20 minutes	No difference in adverse events between groups Respiratory distress: • 1 to 3 patients in each arm with hypoxemia • 1 patient intubated in each arm except haloperidol 10 mg with no intubations Cardiovascular: • 1 to 2 patients in each group with hypotension except ziprasidone with no episodes of hypotension • 1 patient in each arm with bradycardia except midazolam with no episodes of bradycardia • no patients in any arm with torsades de pointes or other dysrhythmias Extrapyrimadal symptoms: • 2 patients in haloperidol 10 mg arm with dystonia. No other dystonic reactions in any arm • no episodes of akathisia in entire study

			mg IM (1 point lesser decrease for haloperidol 5 mg, 95% CI 1.5 lesser decrease to 1 point lesser decrease) • haloperidol 5 mg IM no different than haloperidol 10 mg IM (0 point difference between haloperidol doses, 95% CI 0.5 point lesser decrease to 0.5 point greater decrease) • haloperidol 5 mg IM inferior to ziprasidone 20 mg IM (1 point lesser decrease for haloperidol 5 mg, 95% CI 1.5 point lesser decrease to 0.5 point lesser decrease) Time to adequate sedation (compared to midazolam 5mg IM): • haloperidol 5 mg IM inferior (HR 0.73, 95% CI 0.58 to 0.90) Time to adequate sedation for subset receiving monotherapy and no rescue sedation medications (compared to midazolam 5 mg IM): • haloperidol 5 mg IM inferior HR 0.63 (95% CI 0.48 to 0.81)		

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					
Klein et al[103] (2018)	Haloperidol 10 mg IM • prospective, observational Compared to: • midazolam 5 mg IM • olanzapine 10 mg • IM • haloperidol 5 mg IM • ziprasidone 20 mg	ED patients receiving medication to treat acute agitation 151 patients in haloperidol 10 mg arm • median age: 38 • 107 male/44 female • cause of agitation: alcohol (85%)/illicit substance (15%)/psychiatric illness (9%)/medical (1%)	Primary endpoint was adequate sedation, defined as Altered Mental Status Score <1 15 minutes after medication administration. • haloperidol 10 mg IM inferior to midazolam 5 mg IM (28% lesser for haloperidol: 95% CI 39% lesser to 17% lesser) • haloperidol 10 mg IM inferior to olanzapine 10 mg IM (18% lesser for haloperidol: 95% CI 29% lesser to 7% lesser) • haloperidol 10 mg IM no different than haloperidol 5 mg IM (2% greater for haloperidol 10 mg: 95% CI 9% lesser to 13% greater) • haloperidol 10 mg IM no different than ziprasidone 20 mg IM (10% lesser for haloperidol 10 mg: 95% CI 21% lesser to 0% different) Median difference in AMSS score compared to baseline at 15 minutes: • haloperidol 10 mg IM inferior to midazolam 5 mg IM (2 point lesser decrease for haloperidol: 95% CI 2.5 lesser decrease to 1.5 point lesser decrease)	Median time to adequate sedation: • haloperidol 10 mg IM: 19 minutes	No difference in adverse events between groups Respiratory distress: • 1 to 3 patients in each arm with hypoxemia • 1 patient intubated in each arm except haloperidol 10 mg with no intubations Cardiovascular: • 1 to 2 patients in each group with hypotension except ziprasidone with no episodes of hypotension • 1 patient in each arm with bradycardia except midazolam with no episodes of bradycardia • no patients in any arm with torsades de pointes or other dysrhythmias Extrapyrimadal symptoms: • 2 patients in haloperidol 10 mg arm with dystonia; no other dystonic reactions in any arm • no episodes of akathisia in entire study

			• haloperidol 10 mg IM inferior to olanzapine 10 mg IM (1 point lesser decrease for haloperidol 5 mg: 95% CI 1.5 lesser decrease to 0.5 point lesser decrease) • haloperidol 10 mg IM no different than haloperidol 5 mg IM (0 point difference between haloperidol doses: 95% CI 0.5 point lesser decrease to 0.5 point greater decrease) • haloperidol 5 mg IM inferior to ziprasidone 20 mg IM (1 point lesser decrease for haloperidol 5 mg: 95% CI 1.5 point lesser decrease to 0.5 point lesser decrease) Time to adequate sedation (compared to midazolam 5 mg IM): • haloperidol 10 mg IM inferior (HR 0.72: 95% CI 0.57 to 0.88) Time to adequate sedation for subset receiving monotherapy and no rescue sedation medications (compared to midazolam 5 mg IM): • haloperidol 10 mg IM inferior (HR 0.59: 95% CI 0.46 to 0.78)		

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					
Klein et al[113] (2019)	Haloperidol 5 mg IM • retrospective chart review Compared to: • droperidol 5 mg IM • olanzapine 10 mg IM	ED patients receiving parenteral antipsychotics for agitation 2,146 patients in haloperidol group • median age: 38 • 1,656 male/490 female • etiologies: alcohol (1,979), drug intoxication (154), psychiatric (212), and medical (13)	Primary outcome was rescue sedation administered within 1 hour of initial sedative • 390/2,146 (18%) required rescue sedation during initial hour: olanzapine (70), droperidol (0), haloperidol (254), benzodiazepine (63), and ketamine (3) • 560/2,146 (26%) received rescue sedation during ED encounter Patients receiving haloperidol required 7% greater instances of rescue medication compared to both droperidol and olanzapine (95% CI 9% to 5% less)	Need for rescue medication at 1 hour documented but no additional details of time to sedation	In group receiving haloperidol: Respiratory events: • 4/2,146 (0.2%: 95% CI 0.1 to 0.5%) intubated Cardiac events • no cases of torsades de pointes or other cardiac events reported. Extrapyramidal side effects • 0 cases of akathisia • 1 case of dystonia Allergic reactions • none

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Haloperidol					
Chan et al[106] (2021)	Haloperidol 5 mg IM • single optional redose allowed per study protocol • randomized, double-blind Compared to: • olanzapine 5 mg IM • midazolam 5 mg IM	ED patients requiring parenteral drug sedation for acute agitation 57 patients in haloperidol group • mean age 42 years • 24 male/18 female • perceived possible causes: drug/substance abuse (19), alcohol intoxication (13), underlying mental illness (46), medication non-compliance (18), suicidal ideation/attempt (18), exposure to haloperidol (1), concurrent psychotropic medication (13) • baseline sedation scores: 3 (14 patients), 4 (17 patients), and 5 (25 patients) 23 patients in the haloperidol group received a second dose of study drug or alternative sedatives	Agitation/sedation level was measured on a 6-point validated sedation scale: (5=highly aroused, violent; 4=highly aroused, possibly distressed, or fearful; 3=moderately aroused, unreasonable, or hostile; 2=mildly aroused, willing to talk reasonably; 1=minimal agitation; and 0=asleep); adequate sedation was defined as a score of 2 or less Sedation scores were recorded at baseline, at first observed adequate sedation, and at 10, 20, 30, 45, and 60 minutes after the first dose regardless of observed time to sedation • midazolam was superior to haloperidol with significant differences detected in the Kaplan-Meier curves (p=0.002) • no difference for haloperidol compared with olanzapine (p=0.78) At 10 minutes after the initial dose, 21% in the haloperidol group were adequately sedated; at 60 minutes, the proportion of patients adequately sedated increased to 97% Fully-adjusted accelerated factor for haloperidol was compared with midazolam at 1.89 (95% CI 1.28 to 2.80), indicating significantly slower sedation for haloperidol	Median time to sedation: • haloperidol 5 mg IM: 23.0 minutes	3 patients in the haloperidol group experienced an adverse event; 1 patient experienced oxygen desaturation, 1 patient experienced dystonia, and 1 patient experienced a cardiac arrest 3 hours after 2nd dose of haloperidol and died 8 days later 13/57 exhibited QTc prolongation 17 patients receiving haloperidol fell asleep after treatment

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Ziprasidone					
Martel et al[16] (2005)	Ziprasidone 20 mg IM • prospective, randomized, double-blind trial • rescue sedation at treating physician discretion permitted 30 minutes after study drug administration for AMS >0 Compared to: • midazolam 5 mg IM • droperidol 5 mg IM	ED patients with acute undifferentiated agitation requiring emergent sedation as determined by the treating physician. 46 patients in ziprasidone group • mean age 36.8 • 32 male/14 female • initial mean AMS scale score of 3.41 • initial assessment of reason for agitation: alcohol intoxication (43), illicit substance intoxication (5), head injury (9), psychiatric etiology (8), and delirium (1). • discharge diagnoses: acute alcohol intoxication (44), acute drug intoxication (3), and closed head injury (12)	AMS scale score was obtained every 15 minutes from time 0 to 120 minutes following study medication administration with effective sedation defined as an AMS of 0 or less More patients remained agitated at 15 minutes in ziprasidone group compared to the the droperidol and midazolam groups (p=0.01) • droperidol: 20/50 • midazolam: 15/48 • ziprasidone: 28/46 There was no difference between groups at 30 minutes (p=0.08) • droperidol: 6/50 • midazolam: 11/48 • ziprasidone: 14/46 Less patients were agitated at 45 minutes in the droperidol and ziprasidone groups compared to the midazolam group (p=0.03). • droperidol: 9/50 • midazolam: 14/48 • ziprasidone: 9/46 More patients receiving ziprasidone or midazolam required rescue medications at 30 minutes compared to droperidol (p<0.05) • droperidol: 5 patients required 6 doses • ziprasidone: 9 patients requiring 11 doses • midazolam: 24 patients requiring 30 doses	Mean AMS scale scores in the ziprasidone 20 mg IM group: • at 15 minutes: 1.1 (95% CI 0.39 to 1.76) • at 30 minutes: • 0.74 (95% CI -1.34 to -0.14) • at 45 minutes: -1.28 (95% CI -1.89 to -0.69) • at 60 minutes: -2.20 (95% CI -2.61 to -1.78)	Respiratory depression: • 26/46 patients who received ziprasidone • 7 required supplemental oxygen • no difference in proportion with respiratory depression (p=0.26) or supplemental oxygen (p=0.20) when compared to midazolam and droperidol • no patients required intubation for respiratory depression Akathisia: • 4/46 patients who received ziprasidone Cardiac dysrhythmias: • none

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Ziprasidone					
Klein et al[103] (2018)	Ziprasidone 20 mg IM • prospective, observational Compared to: • midazolam 5 mg • olanzapine 10 mg IM • haloperidol 5 mg IM • haloperidol 10 mg IM	ED patients receiving medication to treat acute agitation 145 patients in ziprasidone arm • median age: 40 • 101 male/44 female • cause of agitation: alcohol (90%)/illicit substance (17%)/psychiatric illness (9%)/medical (1%)	Primary endpoint was adequate sedation, defined as Altered Mental Status Score <1 15 minutes after medication administration • ziprasidone 20 mg IM inferior to midazolam 5 mg IM (18% lesser for ziprasidone: 95% CI 29% lesser to 6% lesser) • ziprasidone 20 mg IM not different from olanzapine 10 mg IM (8% lesser for ziprasidone: 95% CI 19% lesser to 3% greater) • ziprasidone 20 mg IM superior to haloperidol 5 mg IM (12% greater for ziprasidone: 95% CI 1% greater to 23% greater) • ziprasidone 20 mg IM not different from haloperidol 10 mg IM (10% greater for ziprasidone: 95% CI 0% difference to 21% greater) Median difference in AMSS score compared to baseline at 15 minutes: • ziprasidone 20 mg IM no different than midazolam 5 mg IM (1 point lesser decrease for ziprasidone: 95% CI 1.5 point lesser decrease to 0.5 point greater decrease) • ziprasidone 20 mg IM no different than olanzapine 10 mg IM (0 point greater decrease for ziprasidone: 95% CI 0.5 point	Median time to adequate sedation: • ziprasidone 20 mg IM: 17 minutes	No difference in adverse events between groups Respiratory distress: • 1 to 3 patients in each arm with hypoxemia • 1 patient intubated in each arm except haloperidol 10 mg with no intubations Cardiovascular: • 1 to 2 patients in each group with hypotension except ziprasidone with no episodes of hypotension • 1 patient in each arm with bradycardia except midazolam with no episodes of bradycardia • no patients in any arm with torsades de pointes or other dysrhythmias Extrapyrimadal symptoms: • 2 patients in haloperidol 10 mg arm with dystonia. No other dystonic reactions in any arm

			greater decrease to 0.5 point lesser decrease) • ziprasidone 20 mg IM superior to haloperidol 5 mg IM (1 point greater decrease for ziprasidone: 95% CI 1.5 point greater decrease to 0.5 point greater decrease) • ziprasidone 20 mg IM superior to haloperidol 10 mg IM (1 point greater decrease for ziprasidone: 95% CI 1.5 point greater decrease to 0.5 point greater decrease) Time to adequate sedation (compared to midazolam 5 mg IM): • ziprasidone 20 mg IM inferior (HR 0.78: 95% CI 0.61 to 0.93) Time to adequate sedation for subset receiving monotherapy and no rescue sedation medications (compared to midazolam 5 mg IM): • ziprasidone 20 mg IM inferior (HR 0.64: 95% CI 0.48 to 0.82)		• no episodes of akathisia in entire study

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Ziprasidone					
Martel et al[108] (2020)	Ziprasidone 10 mg IM • prospective, randomized, double-blind trial • rescue sedation at treating physician discretion permitted 30 minutes after study drug administration for AMSS >0 Compared to: • droperidol 5 mg IM • ziprasidone 20 mg IM • lorazepam 2 mg IM	ED patients with acute undifferentiated agitation requiring emergent sedation as determined by the treating physician 28 patients in ziprasidone 10 mg group • median age: 40 • 19 male/9 female • initial median AMSS scale score of 3 • initial median BARS score of 6 • initial assessment of reason for agitation: alcohol intoxication (19), drug intoxication (2), head injury (3), and primary psychiatric etiology (5). • final diagnoses: acute alcohol intoxication (22), acute drug intoxication (4), head injury (8), psychiatric disease (4), and other (2)	Primary outcome was adequate sedation at 15 minutes • a lesser proportion of ziprasidone 10 mg compared to droperidol treated patients met the primary outcome: 39% lower (95% CI 14% to 64%) while ziprasidone 10 mg did not differ from either lorazepam or the higher dose of ziprasidone • lorazepam: 15/31 • droperidol: 16/25 • ziprasidone 10 mg: 7/28 • ziprasidone 20 mg: 11/31 AMSS scores were obtained every 15 minutes from time 0 to 120 minutes following study medication administration with median AMSS for ziprasidone 10 mg at: • 15 minutes: 1 • 30 minutes: 0 • 45 minutes: -1.5 • 60 minutes: -1.5 Additional sedation was required: • 4/28 before adequate sedation achieved • 7/28 in entire encounter • at a median time of 46 minutes following the initial administration	The post-administration assessment of adequate sedation occurred every 15 minutes post administration. The proportion achieving this endpoint at each check for ziprasidone 10 mg were: • 15 minutes: 7/28 • 30 minutes: 16/28 • 45 minutes: 22/28 • 60 minutes: 24/28	Respiratory depression was greater in both ziprasidone groups along lorazepam with compared to droperidol (p=0.04); for ziprasidone 10 mg: • 2/28 with hypoxemia (SpO_2<90%) • 9/28 with change in $ETCO_2$ • 10/28 with respiratory depression No patients in the ziprasidone 10 mg group required intubation Median QTc: 410 ms • no dysrhythmias in ziprasidone 10 mg group No patients in ziprasidone 10 mg group experienced dystonia

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Antipsychotics					
Ziprasidone					
Martel et al[108] (2020)	Ziprasidone 20 mg IM • prospective, randomized, double-blind trial • rescue sedation at treating physician discretion permitted 30 minutes after study drug administration for AMSS >0 Compared to: • droperidol 5 mg IM • ziprasidone 10 mg IM • lorazepam 2 mg IM	ED patients with acute undifferentiated agitation requiring emergent sedation as determined by the treating physician 31 patients in ziprasidone 20 mg group • median age: 41 years • 24 male/17 female • initial median AMSS scale score of 3 • initial median BARS score of 7 • initial assessment of reason for agitation: alcohol intoxication (25), drug intoxication (4), head injury (5), and primary psychiatric etiology (4). • final diagnoses: acute alcohol intoxication (25), acute drug intoxication (3), head injury (7), psychiatric disease (5), and other (3)	Primary outcome was adequate sedation at 15 minutes • lesser proportion of ziprasidone 20 mg compared to droperidol treated patients met the primary outcome: 29% lower (95% CI 3% to 54%) while ziprasidone 20 mg did not differ from either lorazepam or the lower dose of ziprasidone • lorazepam: 15/31 • droperidol: 16/25 • ziprasidone 10mg: 7/28 • ziprasidone 20 mg: 11/31 AMSS scores were obtained every 15 minutes from time 0 to 120 minutes following study medication administration with median AMSS for ziprasidone 20 mg at: • 15 minutes: 2 • 30 minutes: -1 • 45 minutes: -1 • 60 minutes: -2 Additional sedation was required: • 4/31 before adequate sedation achieved • 5/31 in entire encounter • at a median time of 38 minutes following the initial administration	The post-administration assessment of adequate sedation occurred every 15 minutes post administration; the proportion achieving this endpoint at each check for ziprasidone 20 mg were: • 15 minutes: 11/31 • 30 minutes: 22/31 • 45 minutes: 24/31 • 60 minutes: 25/31	Respiratory depression was greater in both ziprasidone groups along lorazepam with compared to droperidol (p=0.04); for ziprasidone 20 mg: • 6/31 with hypoxemia (SpO_2<90%) • 10/31 with change in $ETCO_2$ • 12/31 with respiratory depression One patient in the ziprasidone 20 mg group exhibited persistent agitation and required intubation for management of a subdural hematoma Median QTc: 428 ms • no dysrhythmias in ziprasidone 20 mg group One patient in ziprasidone 20 mg group experienced dystonia

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines plus Antipsychotics					
Midazolam plus droperidol					
Isbister et al[101] (2010)	Midazolam 5 mg plus Droperidol 5 mg IM • blinded, randomized controlled trial • further sedation allowed at discretion of attending physician Compared to: • midazolam 10 mg IM • droperidol 10 mg IM	ED patients requiring physical restraint and parenteral sedation 29 patients in droperidol plus midazolam group • median age: 30 • 15 male/14 female • initial assessment of agitation due to: alcohol intoxication (19), self-harm (9), drug-induced delirium (3), acute psychosis (2), and other (1)	Primary sedation outcome was time security staff were required according to a security log from the time of initial call to the "all clear." • duration was not different between groups (p=0.66) with median for: midazolam (20 minutes), droperidol (24 minutes), and midazolam plus droperidol (25 minutes) Secondary sedation outcomes were: • time additional sedation was administered: the hazard ratio for additional sedation medications for midazolam versus droperidol was 2.31 (95% CI 1.01 to 4.71; post prob 0.98 for HR>1.0) indicating that midazolam was more likely to require additional sedation compared to droperidol	Secondary outcome of reduction in AMSS by 3 points or to a score of <1 20 minutes after drug administration • midazolam plus droperidol: 23/29	Respiratory events occurred in: • midazolam plus droperidol: 1/29 involving desaturation events (1) plus airway obstruction (1) Hypotension occurred in: • midazolam plus droperidol: 1/29 Abnormal QT-HR pairs occurred in: • midazolam plus droperidol: 4/29 No dystonic reactions were identified Although oversedation was not a secondary endpoint, AMSS scores revealed that both midazolam and midazolam plus droperidol resulted in unpredictable and oftentimes deep sedation while droperidol resulted in consistent moderate sedation

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines plus Antipsychotics					
Midazolam plus haloperidol					
O'Connor et al[146] (2019)	Midazolam 2 mg to 4 mg plus haloperidol 5 mg IM • retrospective chart review • midazolam plus haloperidol group was not separated from lorazepam plus haloperidol group for analysis (unit of analysis was benzodiazepine plus haloperidol) Compared to: • ketamine 4 mg/kg IM per protocol with 3.68 mg/kg mean administered dose	Prehospital patient with standing order administered for combative or agitated behavior 68 patients in benzodiazepine plus haloperidol group • mean age: 35.4/median age 34 • male (69.1%)/female (30.9%) • co-ingestions: alcohol (39.7%)/cannabis (7.4%)/cocaine (10.3%)/opioids (16.1%)/other (14.7%)/none (10.3%)/unknown (26.5%) • trauma (13.2%)	No measure of adequate sedation Benzodiazepine plus haloperidol group less likely to require additional chemical restraint than ketamine (25% versus 49.5%; OR for ketamine 2.94, 95% CI, 1.49 to 5.80)	Not reported	Intubation rate • benzodiazepine plus haloperidol (1.5%) • ketamine (11.6%) • for intubation following ketamine, OR=8.77 (95% CI, 1.10 to 69.68) • indication for intubation in benzodiazepine plus haloperidol group: refractory agitation (1)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines plus Antipsychotics					
Lorazepam plus haloperidol					
Battaglia et al[107] (1997)	Lorazepam 2 mg plus haloperidol 5 mg IM • randomized and double blind • repeat doses allowed but not until after the first post-treatment standardized evaluation at 1 hour Compared to: • lorazepam 2 mg IM • haloperidol 5 mg IM	ED patients with psychosis and behavioral dyscontrol (agitated, aggressive, destructive, assaultive, or restless behavior) to the extent that they were capable of harming themselves or others. 32 ED patients in the lorazepam plus haloperidol group • 25 male/7 female • mean age 34.4 years • mean weight 74.6 kg • final diagnoses were mania, psychoactive substance abuse, psychosis not otherwise specified, schizophrenia, and schizophreniform disorder	Agitation was assessed serially using the Agitated Behavior Scale with a significant reduction in agitation from baseline at 1 hour in the haloperidol arm. The reduction in agitation seen with combination therapy was greater than lorazepam alone (p=0.014) but not greater than haloperidol alone (p=0.064) Approximately 10% of patients in the combination group were asleep at 1 hour, significantly more than the haloperidol alone group and similar to the lorazepam alone group	Serial evaluations occurred for 12 hours with redosing allowed after reevaluations. Only 1-hour endpoints were abstracted as they are most relevant to this review	11 combination therapy patients (34%) reported adverse effects: • ataxia: 3 (9%) • dizziness: 2 (6%) • dry mouth: 3 (9%) • EPS symptoms: 2 (6%) • speech disorder: 3 (9%) "No serious side effects" were reported

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines plus Antipsychotics					
Lorazepam plus haloperidol					
Riddell et al[99] (2017)	Combination of lorazepam (mean dose 2 mg) IV/(mean dose 2 mg) IM plus haloperidol (mean dose 5 mg) IM • prospective, observational Compared to: • midazolam (mean dose 3.08 mg) IV/(mean dose 2.25 mg) IM/(mean dose 2 mg) IN • lorazepam (mean dose 1.9 mg) IV/ (mean dose 2.4 mg) IM • haloperidol (mean dose 5.71 mg) IM • ketamine (mean dose 0.87 mg/kg) IV/(mean dose 2.97 mg/kg) IM	Acutely agitated patients requiring chemical sedation in the ED 10 patients in the combination lorazepam plus haloperidol group • median age: 40.5 • 9 male/1 female • race: African American (1)/Asian (0)/Hispanic (7)/White (2) • drug use: 60.0% • alcohol use: yes (20.0%)/no (20.0%)/unknown (60.0%) • prior psychiatric visits (50.0%) • route of administration: lorazepam IV plus haloperidol IM (5)/lorazepam IM plus haloperidol IM (5)	Primary outcome: agitation score less than or equal to 2 on a six-point agitation scale • recorded prior to medication administration then at 5, 10, and 15 minutes • combination of lorazepam plus haloperidol (and other arms) inferior to ketamine at: 5 minutes ($p=0.001$), 10 minutes ($p<0.001$), and 15 minutes ($p=0.032$) Secondary outcomes of: • provider assessment of time to adequate sedation: No difference between groups ($p=0.107$) • need for redosing of sedative medications ($p=0.199$) • HR/SBP change: HR reduction seen with midazolam ($p=0.026$) but no other significant HR/SBP changes in any other study arms	Mean time to adequate sedation: • combination of lorazepam 2 mg IV/IM plus Haloperidol 5 mg IM: 23.3 minutes	Intubation: • combination lorazepam plus haloperidol: 1/10

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines plus Antipsychotics					
Lorazepam plus haloperidol					
O'Connor et al[146] (2019)	Lorazepam 2 mg to 4 mg plus haloperidol 5 mg IM • retrospective chart review • lorazepam plus haloperidol group was not separated from midazolam plus haloperidol group for analysis (unit of analysis was benzodiazepine plus haloperidol) Compared to: • ketamine 4 mg/kg IM per protocol with 3.68 mg/kg mean administered dose	Prehospital patient with standing order administered for combative or agitated behavior 68 patients in benzodiazepine plus haloperidol group • mean age: 35.4/median age 34 • male (69.1%)/female (30.9%) • co-ingestions: alcohol (39.7%)/cannabis (7.4%)/cocaine (10.3%)/opioids (16.1%)/other (14.7%)/none (10.3%)/unknown (26.5%) • trauma (13.2%)	No measure of adequate sedation Benzodiazepine plus haloperidol group less likely to require additional chemical restraint than ketamine (25% versus 49.5%; OR for ketamine 2.94, 95% CI 1.49 to 5.80)	Not reported	Intubation rate • benzodiazepine plus haloperidol (1.5%) • ketamine (11.6%) • for intubation with ketamine, OR=8.77 (95% CI 1.10 to 69.68) • indication for intubation in benzodiazepine plus haloperidol group: refractory agitation (1)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Benzodiazepines plus Antipsychotics					
Lorazepam plus haloperidol					
Lin et al[126] (2020)	Lorazepam 2 mg IM or IV plus haloperidol 10 mg IM or IV • prospective randomized open-label study Compared to: • ketamine 4 mg/kg IM or 1 mg/kg IV	ED patients with combative agitation 49 patients in the haloperidol plus lorazepam group • median age 45 • 28 male/21 female • -25 White/9 Black/10 Hispanic • median HR: 100 bmp • median BP: 134/79 • 67% with psychiatric condition • 45/49 received IM medication	Primary outcome of adequate sedation at 5 minutes defined as RASS<1 • ketamine group (22%) more likely than haloperidol plus lorazepam group (0%) to meet endpoint (p=0.001) • secondary outcome of • median RASS at 30 minutes • lower in ketamine group (-1) versus haloperidol plus lorazepam (0) (p=0.02) Median time to sedation shorter in ketamine group (15 minutes) versus haloperidol plus lorazepam (36.5 minutes) (p<0.001) Greater proportion in ketamine group (66%) meeting sedation endpoint at 15 minutes versus haloperidol plus lorazepam (7%) (p<0.001) No difference in additional sedative medications required within 30 minutes (p=0.824): • ketamine (22%) • haloperidol plus lorazepam (20%)	Median time to sedation: • lorazepam 2 mg plus haloperidol 10 mg IV/IM: 36.5 minutes	Hypertension Δ > 20 mmHg • haloperidol plus lorazepam: 4/35 Tachycardia Δ >10 bpm • haloperidol plus lorazepam: 4/35 Hypoxia (SpO_2<92%) • haloperidol plus lorazepam: 3/42 • 1 patient was intubated QTc >450 ms • Haloperidol plus lorazepam: 11/22 • 1 patient experienced an arrythmia 1 patient in the haloperidol plus lorazepam group experienced bradycardia, hypoxia, cardiac arrest, and subsequent death deemed possibly related to the study medication

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Burnett et al[139] (2012)	Ketamine 5 mg/kg IM • dose received 3.1 to 7.4 mg/kg • case series	13 Patients given ketamine for agitation in the EMS environment	Adequate sedation • all patients with RASS of -1 or lower at hospital arrival	Mean time to peak sedation: • ketamine 5 mg/kg IM: 3.3 minutes in 11 patients and 20 minutes in 2 patients	3 patients with hypoxia 2 patients required intubation
Ho et al[140] (2013)	Ketamine • case reports	Case #1 – 500 mg IM ketamine (4.85 mg/kg) for patient with agitated behavior Case #2 – 375 mg IM ketamine (4.68 mg/kg) for patient in altercation with law enforcement	Sedation noted by treating paramedics and physicians	Case #1 – 4 minutes Case #2 – 3 minutes	Case #1 – intubated in the ED, discharged 96 days later Case #2 – intubated in ED, discharged 72 hours later
Scheppke et al[141] (2014)	Ketamine 4 mg/kg IM • followed by optional midazolam 2 mg to 2.5 mg IV/IO or IM to prevent emergence reaction after IV established • retrospective chart review/large case series	52 prehospital patients treated with ketamine for violent, aggressive behavior secondary to a psychiatric or substance-abuse issue.	"Medical control" is an adequate level of sedation to allow standard transport and treatment without further violence or agitation. • suitable sedation achieved in 96% of cases	Mean time to effective sedation and medical control: • ketamine 4 mg/kg IM: 2 minutes	5.8% of patients with respiratory depression • all patients with respiratory depression received midazolam 3.8 % of patients required intubation

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Keseg et al[142] (2015)	Ketamine 4 mg/kg IM, or 2 mg/kg IV • retrospective cohort chart review study No comparison group	36 prehospital patients given ketamine for sedation • male: 77% • median age: 29 years • African American (43%)/Caucasian (34%)/Hispanic (2.9%)/unavailable (20%) • reason for ketamine administration: agitation (16%)/combative (14%)/intubation (2.9%)/hostile (2.9%)/violent (2.9%)/excited delirium (2.9%)/suicidal with weapon (2.9%) • 29 IM only injections	Primary endpoint was "improved condition" as defined by treating EMS personnel • 91% (95% CI 77% to 98%) with improved condition Secondary endpoint of administration of additional sedation methods (benzodiazepines or significant physical force) • 40% (95% CI 24% to 58%) with administration of additional sedation methods	Not reported	8/35 (23%) of patients intubated with indications for intubation of: • agitation (4) • lethargic (2) • unresponsiveness (1) • cardiac arrest prior to ketamine administration (1)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Cole et al[118] (2016)	Ketamine 5 mg/kg IM (median dose received 5.2 mg/kg) • prospective open label EMS study Compared to: • haloperidol 10 mg IM	64 acute undifferentiated agitation with AMSS +3 (57 patients) to +2 (7 patients). AMSS +4 excluded as "profound agitation" • median age 36 years • 37 male/27 female • 31 Caucasian, 16 black American, 7 American Indian, 3 Somali, 2 Hispanic, 1 Asian, 4 mixed/unknown • 48 (75%) with history of mental illness, 30 (47%) with history of chemical dependency, and 25 (39%) with both • EMS impressions of: agitated combative (29), substance abuse (7), behavioral (16), AMS (2), and trauma (4)	Primary endpoint of AMSS < +1. • 61/64 patients achieved adequate sedation • 3/64 patients required second injection prehospital: midazolam (1), ketamine IM (1), and ketamine IV (1) Compared to the group receiving haloperidol, 30% more patients in the ketamine group successfully achieved adequate sedation (p<0.0001, 95% CI 18% to 42%) Time to sedation was 12 minutes less for ketamine group compared to the haloperidol group (p<0.0001, 95%CI 9 to 15 minutes)	Median time to adequate sedation: • ketamine 5 mg/kg IM: 5 minutes	38 complications occurred in 27/55 patients where complications recorded: hypersalivation (21), emergence reaction (5), vomiting (5), dystonia (3), laryngospasm (3), and akathisia (1); there were no deaths in the ketamine group • complications occurred in 44% more patients in the ketamine group compared to the haloperidol group (p<0.0001, 95% CI 30% to 57%) Intubation occurred in 25/64 patients for the following indications: not protecting airway (8), hypersalivation (4), refractory agitation (3), apnea (3), aspiration/vomiting (3), laryngospasm (2), seizure (1), and trauma (1) • intubation occurred in 35% more patients in the haloperidol group compared to the ketamine group (p<0.0001, 95% CI 23% to 48%)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Olives et al[143] (2016)	Ketamine 5 mg/kg IM • retrospective cohort No comparison group	135 patients given ketamine prehospital for agitation	Emergency Medical Service providers reported initial improvement in agitation following ketamine administration • 124/135 (91.8%) • no change in 9/135 (6.7%) • worsened agitation in 2/135 (1.5%)	Not reported	85 patients (62%) intubated: • 74.6% patients during overnight shift versus 55% of daytime encounters (p=0.21) • arrival during night shift associated with intubation, adjusted OR 2.57 (95% CI 1.05 to 6.27) • dose intubated (5.25 mg/kg) not different than not intubated (5.14 mg/kg) (p=0.68) Cardiac arrest after ketamine administration in 2 patients: • neither due to ketamine administration
Scaggs et al[35] (2016)	Prehospital ketamine for agitation 5 mg/kg IM or 1.5 mg/kg IV • case series • mean dose of ketamine received: 4.36 mg/kg No comparison group	7 patients given prehospital ketamine for excited delirium • mean age: 24 years • CK: 484.33 • HR: 158 bpm	Skaggs Scale (modified RASS)	Range of reported time to adequate sedation for ketamine IM 5 mg/kg: 1.5 to 2 minutes	1 patient with hypoxia 1 patient with rhabdomyolysis

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Parsch et al[155] (2017)	Ketamine, studied retrospectively pre and post guideline adoption • retrospective cohort study	Mental health patients with acute behavioral disturbance requiring transport: 28 patients receiving ketamine post guideline change • median age: 34 • 26 men/2 women • transport duration: 175 minutes	Need for intubation as a proxy for adequate sedation • 36% intubated before protocol • 7.14% intubated after protocol • OR 0.14 (for post protocol intubation	Not reported	1 patient on a ketamine and propofol infusion suffered a presumed episode of laryngospasm in flight, manifested by a soft stridor; no specific airway intervention was required and the stridor resolved within a few minutes No episodes of hypoxia, nausea, vomiting, aspiration or cardiovascular compromise were observed during the retrievals

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Riddell et al[99] (2017)	Ketamine (mean dose 0.87 mg/kg) IV/(mean dose 2.97 mg/kg) IM • prospective, observational cohort study Compared to: • midazolam (mean dose 3.08 mg) IV/(mean dose 2.25mg) IM/(mean dose 2 mg) IN • lorazepam (mean dose 1.9 mg) IV/ (mean dose 2.4 mg) IM • haloperidol (mean dose 5.71 mg) IM • combination of lorazepam (mean dose 2 mg) IV/(mean dose 2 mg) IM plus haloperidol (mean dose 5 mg) IM	Acutely agitated patients requiring chemical sedation in the ED 24 patients in the ketamine group • median age: 29 • 19 male/5 female • race: African American (3)/Asian (1)/Hispanic (10)/White (10) • drug use: 54.2% • alcohol use: yes (33.3%)/no (52.2%)/unknown (17.4%) • prior psychiatric visits (30.4%) • route of administration: ketamine IV (18)/ketamine IM (6)	Primary outcome: agitation score less than or equal to 2 on a six-point agitation scale • recorded prior to medication administration then at 5, 10, and 15 minutes • ketamine superior to other arms at: 5 minutes (p=0.001), 10 minutes (p<0.001), and 15 minutes (p=0.032) Secondary outcomes of: • provider assessment of time to adequate sedation: No difference between groups (p=0.107) • need for redosing of sedative medications (p=0.199) • HR/SBP change: HR reduction seen with midazolam (p=0.026) but no other significant HR/SBP changes in any other study arms	Mean time to adequate sedation: • ketamine: 6.57 minutes	Intubation: • ketamine: 2/24

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Cole et al[144] (2018)	Ketamine 5 mg/kg IM • prospective observational cohort study No comparison group	EMS patients transported to single urban ED with EMS clinically identified behavioral emergency and AMSS of +4 49 patients received ketamine • median age: 29 • 76% male/24% female • 49% Caucasian/35% Black American/6% American Indian/2% Hispanic/2% Somali/6% unknown or mixed • EMS impressions: agitated combative (23)/behavioral (14)/substance abuse (4)/AMS (3)/Trauma (3)/Seizure • median dose received: 4.9 mg/kg	Primary endpoint was time to adequate sedation defined as AMSS <+1 • adequate sedation prehospital: 90% Secondary endpoint of additional EMS sedatives	Median time to sedation: • ketamine 5 mg/kg IM: 4.2 minutes	Intubation in ED: 57% (over 1/3 of intubations performed by a single ED physician) • indications for intubation: airway unprotected (10)/hypersalivation (5)/respiratory failure (4)/hemodynamic instability or acidosis (3)/failure to treat agitation (2)/ ”expected return of anticipated behavior” (2)/status epilepticus (1)/hypoxia (1) Adverse events: • hypersalivation (18%) • vomiting (6%) • emergence reaction (2%)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Heydari et al[119] (2018)	Ketamine 4 mg/kg IM • if patient was inadequately sedated or additional medication needed per physician discretion then 2 mg/kg repeat dose allowed • randomized, double blind prospective trial Compared to: • haloperidol 5 mg IM	ED patients with acute agitated and aggressive behavior who required chemical sedation for agitation, according to an emergency medicine resident or attending physician were eligible for enrollment. (AMSS +2 or +3) 45 patients in ketamine group: • mean age of 30.37 • male: 73.3%/female: 26.7% • cause of aggressive behavior: psychotropic substances (26.7%)/psychiatric history (28.9%)/alcohol consumption (26.7%)/trauma (17.8%)	The primary outcome was time to adequate sedation (AMSS≤+1) • faster for ketamine compared to haloperidol (p<0.01, difference 3.7 minutes, 95% CI 2.1 to 5.5) Mean AMSS scores: • 5 minutes: ketamine (1.36) was not different from haloperidol (1.70) (p=0.115) • 10 minutes: ketamine (0.67) was higher than haloperidol (1.27) (p=0.001) • 15 minutes: ketamine (0.14) was not different from haloperidol (0.3) (p=0.167) • proportion not adequately sedated at 15 minutes was lower in ketamine group (6.7%) than haloperidol group (28.9%) • difference of 22% (95% CI 11% to 33%; p<0.0001) Physician satisfaction was higher in ketamine group than haloperidol group (p=0.011)	Median time to adequate sedation • ketamine 4 mg/kg IM: 7.73 minutes	Complications: 35.6% for ketamine 17.8% for haloperidol no significant difference between groups (p=0.094, difference 17%, 95% CI 11% to 22%). Ketamine group: • hypersalivation (n=5, 11.1%) • vomiting (n=6, 13.3%) • Laryngospasm (n=2, 4.4%) • Emergence phenomena (n=3, 6.7%) • Intubation (n=6 13.3%) Primary indications for intubation in ketamine group were refractory agitation (n=1), hypersalivation (n=2), and hypoxia (n=3).

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Mankowitz et al[145] (2018)	Ketamine IV or IM • mean IM dose: 4.9 mg/kg • systematic review No comparison to other agents	650 patients receiving ketamine for agitation • ED (110)/air medical transport (61)/ground transport (479) • 67.6% male • mean age: 33 years	Proportion achieving sedation within 5 minutes • 68.5% (95% CI 61.7% to 75.3%) Proportion requiring further sedating medications beyond single dose of ketamine • 24.4% (95% CI 20.5% to 28.3%)	Mean time to adequate sedation: • ketamine: 7.21 minutes	Vomiting • 5.3% (95% CI 2.4% to 8.2%) hypertension • 12.4% (95% CI 5.8% to 18.9%) emergence delirium • 4.0% (95% CI 1.3% to 6.7%) transient hypoxia • 1.8% (95% CI 0.1% to 3.6%) laryngospasm • 1.3% (95% CI 0.3% to 2.3%) hypersalivation • 19% (95% CI 13.2% to 25%) Intubation • 30.5% (95% CI 27.0% to 34.1%)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Li et al[147] (2019)	Ketamine 2 mg/kg IM or 1 mg/kg IV • retrospective chart review after implementation of a ketamine guideline for excited delirium • per protocol, ketamine administered after combination of benzodiazepine and antipsychotic	ED patients being treated with ketamine for excited delirium 31 patients • mean age: 38.5 • male: 77.4% • 19 IM administration (mean initial dose: 3.6 mg/kg)	RASS scores • RASS decreased from +4 to 0 after ketamine (p=0.001) Post ketamine decrease in: • median SBP: 136 mm hg versus 126 mm hg (p=0.03) • median HR: 105 bpm versus 90 bpm (p=0.03)	Not reported	Six (19.4%) patients required intubation
O'Connor et al[146] (2019)	ketamine 4 mg/kg IM per protocol with 3.68 mg/kg mean administered dose • retrospective chart review • lorazepam plus haloperidol group was not separated from midazolam plus haloperidol group for analysis (unit of analysis was benzodiazepine plus haloperidol) Compared to: • Lorazepam 2 mg to 4 mg plus haloperidol 5 mg IM and midazolam 2 mg to 4 mg plus haloperidol 5 mg IM grouped together for analysis (unit of analysis was benzodiazepine plus haloperidol)	Prehospital patient with standing order administered for combative or agitated behavior 95 patients in ketamine group • mean age: 34.2/median age 33 • male (58.9%)/female (41.1%) • co-ingestions: alcohol (38.9%)/cannabis (4.2%)/cocaine (14.7%)/opioids (16.8%)/other (14.7%)/none (21.1%)/unknown (23.2%) • trauma (17.9%)	No measure of adequate sedation Ketamine group more likely to require additional chemical restraint than Benzodiazepine plus haloperidol group (49.5% versus 25%; OR for ketamine 2.94, 95% CI 1.49 to 5.80)	Not reported	Intubation rate • ketamine (11.6%) • benzodiazepine plus haloperidol (1.5%) • For intubation with ketamine, OR=8.77 (95% CI 1.10 to 69.68) • indications for intubation in ketamine group: refractory agitation (6); hypoxia/respiratory distress (2); airway protection (3)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Lebin et al[148] (2019)	Ketamine 1 mg/kg to 2 mg/kg IV or 3 mg/kg to 5 mg/kg IM • retrospective cohort study Compared to • midazolam 1 mg to10 mg IV, 5 mg to 10 mg IM, or 2.5 mg to 10 mg IN • diazepam 2.5 mg to10 mg IV	Patients with severe agitation requiring prehospital sedation with ketamine or benzodiazepine 59 patients in ketamine group • age: 33 • male (79.7%) • Caucasian (49.2%)/Black or African American (16.9%)/Asian (1.7%)/other or not reported (32.2%) • 56 patients received ketamine IM	Not reported	Not reported	Intubation • ketamine (3.8%) • benzodiazepine (63.0%) • 59.1% (95% CI 79.35% to 37.9%) less likely to be intubated after ketamine administration than benzodiazepine administration

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Holland et al[105] (2020)	Ketamine IM • dose per protocol: 150 mg to 300 mg (93/97 patients received 300 mg) • weight based dose: 3.75 mg/kg (95% CI 2.13 mg/kg to 5.37 mg/kg). • retrospective chart review Compared to: • Midazolam 5 mg IV/IM/IN	Patients with acute agitation requiring sedation by paramedics 97 patients in ketamine treated group • mean age of 33.8 years • 76 male/21 female • 46 White, 49 African-American, and 2 other • mean weight: 82.1kg • suspicion of illicit drugs: 74.2%	Primary endpoint was need for repeat sedative dose • 6/97 required repeat sedation at 20 minutes; no difference compared to midazolam (p=0.306) • 46/97 required repeat sedation at 90 minutes; significantly more than midazolam group (p=0.01) • when limiting the analysis to only sedation given via IM route, there was no difference in need for repeat sedation between midazolam and ketamine groups at 20 minutes (p=0.212) or 90 minutes (p=0.503) • secondary endpoints • time to repeat sedation of 77.2 minutes; no difference compared to midazolam group (p=0.658) • total number of sedation doses did not differ between ketamine and midazolam (p=0.084)	Need for repeat sedative dose at 20 minutes used as proxy for adequate control of agitation • 6/97 in ketamine group required repeat sedation	6 patients in the ketamine group were intubated; one patient was found to have an intracranial hemorrhage; another patient in the ketamine cohort received 6 more doses of sedatives before intubation, suggesting a limited impact of prehospital ketamine on the decision to ultimately intubate For patients administered ketamine, median GCS was 13 (IQR 11.25 to 15) prior to administration and 9 (IQR 3.25 to 11.75) after administration (p<0.0001); there was no significant difference compared to the change in GCS achieved with midazolam, p=0.4116) There were no significant differences in use of bag valve mask or intubation, use of physical restraints, admission location/level of care, or length of stay in the ED, hospital, or ICU

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Lin et al[126] (2020)	Ketamine 4 mg/kg IM or Ketamine 1 mg/kg IV • prospective randomized open-label study Compared to: • lorazepam 2 mg IM/IV plus haloperidol 10 mg IM/IV	ED patients with combative agitation 44 patients in the ketamine group • median age 37 years • 30 male/14 female • 29 White/4 Black/7 Hispanic • median HR: 110 bmp • median BP: 132/88 • 43% with psychiatric condition • 42/44 received IM medication	Primary outcome of adequate sedation at 5 minutes defined as RASS<1 • ketamine group (22%) more likely than haloperidol plus lorazepam group (0%) to meet endpoint (p=0.001) Median time to sedation shorter in ketamine group (15 minutes) versus haloperidol plus lorazepam (36.5 minutes) (p<0.001) Greater proportion in ketamine group (66%) meeting sedation endpoint at 15 minutes versus haloperidol plus lorazepam (7%) (p<0.001) Secondary outcomes: Median RASS at 30 minutes • lower in ketamine group (-1) versus haloperidol plus lorazepam (0) (p=0.02) No difference in additional sedative medications required within 30 minutes (p=0.824): • ketamine (22%) • haloperidol plus lorazepam (20%)	Median time to sedation: • ketamine 4 mg/kg IM: 15 minutes	Hypertension Δ >20 mmHg • ketamine: 13/39 Tachycardia Δ >10 bpm • ketamine: 13/38 Hypoxia (SpO_2<92%) • ketamine: 6/39 • 1 patient was intubated QTc >450 ms • ketamine: 11/23 • 1 patient experienced an arrythmia No deaths occurred in the ketamine group

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Parks et al[156] (2020)	Ketamine (mean dose 4.88 mg/kg) IM • 97.6% IM/2.4% IV • retrospective cohort/chart review No comparison group	86 patients receiving prehospital ketamine for agitation • mean age: 42.9 • female (54.7%)	Not reported	Not reported	14/86 (16.3%) of patients intubated • no difference in dose between intubated (4.44 mg/kg) and not intubated (4.96 mg/kg) patients (-0.53 mg/kg difference; 95% CI, -1.49 to 0.43; P=0.278) Adverse events: • abnormal lung sounds (6) • respiratory distress (8) • apnea (4) • vomiting (1) • hypersalivation (2)

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Cunningham et al[157] (2021)	Ketamine 4 mg/kg IM (standard dose) • pre-/post-intervention retrospective chart review Compared to: Ketamine 3 mg/kg IM followed by optional 2nd dose of 1 mg/kg IM (lower dose)	Prehospital patients treated for acute agitation 211 patients in standard dose group • mean age: 35.14/median age: 32 years • male 67.8%/female 32.2% • mean dose received: 3.51 mg/kg • trauma: 21.3%	Not reported	Not reported	Need for additional chemical restraint after 1st dose of ketamine: standard dose: 57.3% Intubation rate standard dose group: 14.2% • indications for intubation: hypoxia or respiratory distress (10)/refractory agitation (9)/airway protection (9)/facilitate imaging (1)/missing (1) Total adverse reaction standard dose group: 22.2%
Cunningham et al[157] (2021)	Ketamine 3 mg/kg IM followed by optional 2nd dose of 1 mg/kg IM (lower dose) • pre-/post-intervention retrospective chart review Compared to: Ketamine 4 mg/kg IM (standard dose)	Prehospital patients treated for acute agitation 81 patients in standard dose group • mean age: 35.65/median age: 31 • male 65.4%/female 34.6% • mean dose received: 3.24 mg/kg • trauma: 21.0%	In the lower dose cohort, adequate sedation without additional dosing was achieved in 79% (64/81) patients	Not reported	Need for additional chemical restraint after 1st dose of ketamine: lower dose: 57.3% Intubation rate lower dose group: 18.5% • indications for intubation: hypoxia or respiratory distress (6)/refractory agitation (5)/airway protection (4) Total adverse reaction lower dose group: 20.9%

Study & Year Published	Drug Studied	Population	Sedation Endpoint	Time to Reach Endpoint	Adverse Events
Ketamine					
Fernandez et al[93] (2021)	Ketamine (median dose 3.7 mg/kg for AMS/behavioral indications) IM • large retrospective analysis of prospectively collected prehospital registry No comparison group	11,291 prehospital ketamine administrations for any indication by any route 3,795 receiving ketamine for AMS/behavioral indications • age: 50% of patients were 20 to 39 years of age • female (34.1%)/male 65.9% • White (64.6%), Black (22.3%), other race (2.6%), Hispanic or Latino (10.4%)	Single administration of ketamine as a proxy for adequate sedation • one dose: 78.7%	Not reported	8 deaths in entire cohort of 11,291 (0.07%) administrations where ketamine could not be fully excluded as cause • 4 deaths in subgroup of 3,795 (0.1%) receiving ketamine for AMS/behavioral indications where ketamine could not be fully excluded as cause Respiratory events in subgroup receiving ketamine for AMS/behavioral indications • hypoxemia: 10.7% prior to and 10.2% after administration • hypoventilation ($EtCO_2$>45): 6.2% prior to and 23% after administration

AMS, altered mental status; *AMSS*, Altered Mental Status Scale; *BARS*, Behavioral Activity Rating Scale; *BPRS*, Brief Psychiatric Rating Scale; *CI*, confidence interval; *dl*, deciliter; *ED*, emergency department; *EMS*, emergency medical services; *EPS*, extrapyramidal symptoms; *GCS*, Glasgow coma scale; *GCI*, Global Clinical Impression; *HR*, heart rate; *HR/SBP*, heart rate/systolic blood pressure; *ICU*, intensive care unit; *IM*, intramuscular; *IN*, intranasal; *IQR*, interquartile ratio; *IV*, intravenous; *kg*, kilogram; *mg*, milligram; *ms*, millisecond; *OR*, odds ratio; *QTc*, corrected QT interval; *RASS*, Richmond Agitation-Sedation Scale; *SAT*, Sedation Assessment Tool.