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COMMENTARY

What is the best approach for parenteral sedation to manage severe acute behavioral disturbance in the emergency department?

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ABSTRACT

Introduction: Patients with severe acute behavioural disturbance commonly present to the emergency department. Differing expert opinion dominates treatment strategies. We describe an evidence-based approach to parenteral sedation for the management of emergency department patients with severe acute behavioural disturbance.

Approach to managing severe acute behavioural disturbance with parenteral sedation: The most common cause of severe acute behavioural disturbance in the emergency department setting is alcohol and drug intoxication, both being relatively short-lived. The goal of parenteral sedation is to provide safe observation until the effect of any intoxication wears off and allow time for further clinical investigation and treatment as required. A validated scoring tool, such as the sedation assessment tool score, is useful to guide objective assessment of behavioural disturbance. We recommend the intramuscular route initially, unless intravenous access is already available (i.e., placed by first responders), as it allows rapid administration and requires less physical restraint. We recommend droperidol, or olanzapine where droperidol is unavailable, as the preferred first-line parenteral agent, due to strong evidence of effectiveness and safety. When rescue therapy is required or in extremely dangerous circumstances, we recommend using ketamine. We do not routinely recommend benzodiazepines, such as midazolam, except for treating specific causes of agitation which respond well to benzodiazepines, such as alcohol withdrawal or stimulant intoxication. We recommend avoiding combination therapy (antipsychotic and benzodiazepine) due to an increased adverse effect profile, without clear evidence for increased effectiveness.

Monitoring following sedation for acute behavioural disturbance: Following sedation, we recommend close observation in all patients, including at a minimum regular monitoring of vital signs, level of sedation, and continuous pulse oximetry without supplemental oxygen. End-tidal carbon dioxide monitoring should be used when available.

Conclusions: There is a good evidence base to recommend a standardized approach to the management of severe acute behavioural disturbance in the emergency department. We recommend using intramuscular droperidol (or olanzapine if droperidol is not available) as a first-line therapy, which can be repeated at 15 min if effective sedation is not achieved. If rescue sedation is required or in extremely dangerous scenarios when immediate control is required, we recommend ketamine. We do not routinely recommend benzodiazepines as first-line therapy, unless specifically treating a condition likely to benefit from benzodiazepines, such as alcohol (or sedative hypnotic) withdrawal or stimulant intoxication. We do not recommend combination therapy (antipsychotic and benzodiazepines).

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Introduction

Patients with severe acute behavioural disturbances commonly present to the emergency department, and can pose significant risks to themselves, health care workers, and other patients. While there is no standard definition, patients with severe agitation or aggression, who have not responded to efforts of verbal de-escalation or provision of oral medications, and pose a risk to safety, can be considered to have severe acute behavioural disturbance. Patients with this degree of aggression need to be rapidly, safely, and effectively sedated so that appropriate

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assessment and management can be undertaken, including focused treatment in some cases. Despite this, there is continued disagreement over the best approach and medications to use, which is further complicated by different clinical settings, availability and licensing of some drugs [1], such that expert opinion has dominated treatment approaches. Studies in this field are heterogenous and consider management of behavioural disturbance across multiple settings, including the pre-hospital, emergency department, intensive care, and psychiatric environments, with differing inclusion criteria and fixed dose management paradigms. Fortunately, there is increasing evidence for safe and effective options for sedating drugs in the emergency department setting, which is our focus in this Commentary.

We describe our evidence-based approach for the management of patients with severe acute behavioural disturbance, specifically in the emergency department, focusing on parenteral sedation. This perspective was developed following the symposium, *Agitation in Poisoned Patients*, delivered at the 45th Congress of the European Association of Poisons Centres and Clinical Toxicologists in Glasgow, in May 2025.

Cause of acute behavioural disturbance

Underlying potential precipitants of acute behavioural disturbance are numerous and include drug intoxication, psychiatric disorders, as well as less common causes of encephalopathy such as trauma or infection (Table 1). The goals of treatment vary depending on the underlying cause, and while the aetiology may be unknown in some cases, initial sedation and control of the situation for patient and caregiver safety should precede accurate diagnosis.

Table 1. Common causes of severe acute behavioural disturbance in the emergency department.

Cause of behavioural disturbance	Examples
Intoxication	Alcohol
	Metamfetamine/amfetamine
	Cocaine
	Synthetic sympathomimetics
	Gamma-hydroxybutyrate
	Hallucinogens
	Antimuscarinics
Drug withdrawal	Alcohol
	Baclofen
	Benzodiazepine
	Gamma-hydroxybutyrate
Mental health disturbance	Psychosis
	Mania
	Suicidal ideation
	Personality disorder
Trauma	Intracranial haemorrhage
	Cerebral contusion
Infection	Meningoencephalitis
Metabolic derangement	Hypoglycaemia
Degenerative conditions	Dementia
Structural lesions	Tumour
	Stroke

The most common cause of severe acute behavioural disturbance in the emergency department setting is alcohol and drug intoxication. Large studies in the United States (US) and Australia [2–4] report the majority of patients being intoxicated with either alcohol or Illicit drugs, while mental illness or psychosis account for only 10–20% of behavioural disturbances. Organic illness and head injury occur in less than 10% of presentations as well [4].

When intoxication is the presumed precipitant for severe behavioural disturbance, the focus of management is safe observation until the effects wear off, which is usually short-lived, lasting less than 6 h to 24 h. This period of observation can often be safely performed entirely in the emergency department or in a short stay treatment area, depending on local resources.

For those with mental illness or encephalopathy, precipitating acute behavioural disturbance management differs as the underlying cause is less likely to resolve rapidly and often requires focused treatment. The goals in the emergency department are to safely contain the behaviour to allow further diagnostic testing, followed by inpatient admission to facilitate mental health or medical treatment.

Assessment tools

Numerous assessment tools are available to score agitation and sedation in patients with acute behavioural disturbance. Many were created for use in the intensive care unit or mental health settings, often for research rather than patient treatment, and are difficult to implement in busy emergency departments. The Sedation Assessment Tool score was developed for use in the emergency department because it is simple, can be rapidly and repeatedly scored, and the sedation element is simply the AVPU score: is the patient **A**lert; do they respond to **V**erbal stimuli; do they respond to **P**ainful stimuli; and are they **U**nresponsive [5]. It was developed from the more complicated nine point altered mental status score (AMSS) [6], and is a validated seven point score (from −3 to 3) that reliably indicates the need for sedation, with a score of ≥2 consistent with severe acute behavioural disturbance [5]. It uses two descriptors (behaviour and speech), is easy to perform, and has a high interrater reliability (Table 2) [5].

We recommend using an assessment tool to score behavioural disturbance, irrespective of the tool used, because it allows better communication between clinicians when describing behaviour, to objectively guide

Table 2. Sedation Assessment Tool scoring system for rating acute behavioural disturbance [5].

Score	Responsiveness	Speech
+3	Combative, violent, out of control	Continual loud outbursts
+2	Very anxious and agitated	Loud outbursts
+1	Anxious/restless	Normal/talkative
0	Awake and calm/co-operative	Speaks normally
−1	Asleep but rouses if name is called	Slurring or prominent slowing
−2	Responds to physical stimulation	Few, recognisable words
−3	No response to stimulation	Nil

treatment algorithms, minimize bias, and to reliably record the response to sedation.

Approach to managing severe acute behavioural disturbance with parenteral sedation

The approach to managing patients with acute behavioural disturbance needs to prioritize safety, with efforts for de-escalation when appropriate, and consideration of pharmacological intervention when necessary. Depending on the severity of the agitation and/or aggression, verbal de-escalation and oral medications may be sufficient to control the situation and allow ongoing management [7,8]. The role of physical restraint remains contentious and differs between countries and even within precincts based on legal and ethical considerations [9]. If used, physical restraints should only be considered a temporizing measure until sedation medications have been administered, and as such, maintained for the minimum necessary duration to ensure safety. Oral sedation can be offered to co-operative patients. Some sedating medications are available as a liquid or an oral disintegrating tablet that can aid absorption and facilitate administration [10]. However, the oral route may not be feasible in many patients with severe acute behavioural disturbance.

For those patients with severe acute behavioural disturbance, parenteral sedation is often required and needs to be administered rapidly and definitely to avoid patient and staff injuries. Pharmacological interventions used are typically from classes of medication that include antipsychotics, benzodiazepines, or dissociative anaesthetic agents (ketamine).

Route of administration

The optimal route of administration for parenteral sedation in these patients needs to result in a rapid onset, minimize physical contact with the patient, and not require technical expertise. Although intravenous administration is likely to have a more rapid onset in most cases, it is difficult and often impossible to obtain intravenous access safely and rapidly in many of these patients and the time spent obtaining access offsets the rapid pharmacologic effects of intravenous administration. For this reason, we recommend the intramuscular route initially, unless the patient already has intravenous access (i.e., access was obtained by a first responder, or inserted in the emergency department prior to the patient developing severe agitation). The intramuscular route allows rapid administration without reliance on intravenous access and is associated with less injury to personnel involved in the physical restraint [11]. A small Australian study found that resolution of behavioural disturbance was shorter following intramuscular administration of parenteral sedation compared to the intravenous route [11]. It is important to remember that the goal is to minimize the time to sedation from the initial encounter with the patient rather than from the time of drug administration.

Drug of choice

The optimal agent of choice of sedation for patients with severe acute behavioural disturbance depends on the immediate requirement for sedation, the underlying cause of the behavioural disturbance and patient factors. In the emergency department, immediate control of the situation is required, and once this has occurred, further treatment can be based on safe assessment and investigation.

We believe the drug with the strongest evidence base for the first-line management of patients with severe acute behavioural disturbance in the emergency setting is droperidol [4,12–17]. Effective sedation following a single dose of intramuscular droperidol 10 mg occurs in approximately 70% of patients. A second dose, 15 min after the first dose, increases the proportion of sedated patients to approximately 90% [4]. Adverse effects occur in up to 5% of patients, most commonly hypotension or oxygen desaturation, which are typically managed with simple supportive measures, such as intravenous fluids, repositioning, or transient use of supplemental oxygen [3,4]. While the optimal initial dose of droperidol is not certain, both 5 mg and 10 mg are supported by multiple randomized trials and have similar success rates [18].

Previous concerns regarding QT interval prolongation following droperidol administration, which led to a black box warning by the US Food and Drug Administration (FDA), were overstated [1,19]. A large prospective study [4] investigating the safety of droperidol included an electrocardiogram on 1,009 patients receiving droperidol at a median dose of 10 mg for acute behavioural disturbance. It was found that QT interval prolongation occurred in only 1.3% of patients, of whom half had an explanation other than droperidol [4]. There were no instances of torsade de pointes [4]. A similar large US study reported the risk

of torsade de pointes following droperidol administration as 0.006%, and that it was likely multifactorial in nature [20].

Furthermore, the safety of droperidol in the management of acute behavioural disturbance has been demonstrated in special groups, including both paediatric [21] and geriatric (age ≥65 years) [22] populations. The recommended dose in the paediatric population is 0.1–0.2 mg/kg (up to 10 mg), that can be repeated once at 15 min, while in the geriatric population the dose is 5 mg that can be repeated once at 15 min. A recent systematic review [23] of treatments for agitation in elderly patients found benzodiazepines, and particularly midazolam, to carry an increased risk of adverse effects compared to haloperidol, highlighting the importance of antipsychotics in elderly patients with agitation. There is limited research to guide management in pregnant patients, but antipsychotic agents are still considered first-line [24].

When droperidol is unavailable, whether due to issues with supply or regarding approval for use, other antipsychotics may be used. Droperidol was essentially unavailable in North America from 2013 to 2019 due to shortages of raw materials and manufacturing delays [25–27]. Furthermore, some institutions, due to the persisting US FDA boxed warning, may not allow droperidol on their hospital formularies, or may have monitoring requirements, such as a mandatory electrocardiogram before administration of droperidol [28], that makes droperidol infeasible as a treatment for agitation. In such circumstances, we recommend using an injectable second-generation antipsychotic [13,16,27,29,30]. Of the two most widely available injectable second-generation antipsychotics, we recommend olanzapine over ziprasidone. While both drugs have proven superior to haloperidol [2,30], the evidence is stronger for olanzapine. Moreover, olanzapine has also performed similarly to droperidol in multiple prospective studies and randomized trials [3,13,27,29], whereas two randomized trials comparing ziprasidone to droperidol showed ziprasidone provided less rapid sedation [6,16]. A single prospective study comparing olanzapine and ziprasidone also favoured olanzapine [2]. Lastly, while both ziprasidone and olanzapine must be reconstituted at the bedside, ziprasidone takes 2.5–3.5 min to reconstitute compared to olanzapine that dissolves nearly instantly, further delaying time to ziprasidone administration [31].

For rescue sedation when first-line antipsychotic therapy is ineffective, we believe ketamine has the strongest evidence base. Ketamine provides rapid, reliable sedation with an average time to sedation of 7 min [32]. However, its adverse effect profile is less favourable than droperidol, making it generally unsuitable as a first-line agent. The main concern is a high endotracheal intubation rate, which appears to be clinician-dependent, but is reported to be as high as 63% in some series [32,33]. The endotracheal intubation rate is likely to be closer to 15% when used in facilities that are comfortable managing a patient with a dissociative anaesthetic supportively, and in most of these cases, the indication for endotracheal intubation is ongoing agitation [34]. Other adverse effects include hypersalivation, which is common, occurring in 19% [32]. Vomiting and emergence reactions are less common, occurring in 5% and 4%, respectively [32]. Laryngospasm is rare and usually transient, occurring in 1% [32].

For rescue sedation, we recommend an intramuscular dose of ketamine 5 mg/kg [35]. Similarly, given its rapid, reliable sedation, we believe ketamine is the most suitable first-line agent in scenarios in which there is extreme danger and situational control is needed immediately, which more often occurs in the pre-hospital setting.

Benzodiazepines have a long history of use in patients with acute behavioural disturbance and are often considered because of some desirable characteristics, the most compelling being reversibility. Unfortunately, benzodiazepines often have unpredictable effects due to variable tolerance in this patient group, making dosing unreliable and more likely to produce complications like oversedation and respiratory depression, or an excess requirement for additional sedation compared to antipsychotics like droperidol [12]. We do not routinely recommend benzodiazepines as first-line agents in the management of patients with severe acute behavioural disturbance. However, there are some specific instances in which benzodiazepines are suitable first-line agents, including acute alcohol (or sedative hypnotic) withdrawal and stimulant intoxication.

Monotherapy versus combination therapy

Combination therapy with an antipsychotic and benzodiazepine (traditionally haloperidol and lorazepam) has been a commonly used treatment for patients with acute behavioural disturbance in the emergency department for decades [36], with the combination of an antipsychotic and benzodiazepine thought to provide more effective sedation than either drug alone [37]. However, this notion is only supported by small studies focusing on psychosis as the cause of agitation, with arguably clinically insignificant differences between treatment arms [38–40].

Despite being recommended by some professional bodies [41], available evidence suggests that

combination therapy (antipsychotic and benzodiazepine) confers little advantage in terms of the effectiveness of sedation, but increases the risks of adverse effects [12,42]. While combination therapy seems superior to benzodiazepine monotherapy [37,40], combination therapy has not proven to be superior to antipsychotic monotherapy [37].

When considering droperidol as the antipsychotic of choice, three randomized trials conducted in the emergency department investigated combination therapy, all with midazolam [12,13,29]. Two trials, in which medications were administered intravenously, found the combination of midazolam and droperidol to provide faster sedation compared to monotherapy, including droperidol, midazolam, and olanzapine [13,29]. However, in the DORM study [12], the sole trial that examined combination therapy via the intramuscular route, no difference was found between combination therapy with droperidol and midazolam versus either agent alone. Combination therapy is associated with increased respiratory complications (airway obstruction, hypoxia) compared to droperidol monotherapy [29,43], and as such, we generally recommend against it.

Monitoring following sedation for acute behavioural disturbance

We recommend close monitoring following the administration of parenteral sedation in all patients treated for severe acute behavioural disturbance. At a minimum, we recommend regular monitoring of vital signs, including blood glucose concentration and temperature, level of sedation using the Sedation Assessment Tool score (or another similar tool), and continuous pulse oximetry without supplemental oxygen. End-tidal capnography should be used, where available, in all patients to more closely monitor respiratory status. Close monitoring is particularly important in patients with haemodynamic compromise, which may occur when behavioural disturbance is due to encephalopathy from hypoperfusion, infection or profound metabolic derangement. If the initial temperature is elevated, we recommend taking a core temperature, as timely recognition of hyperthermia is important given its association with morbidity and mortality in stimulant toxicity [44].

We recommend investigations including blood gas analysis, kidney function and creatine kinase activity, particularly in patients with deranged vitals signs, given acidaemia, acute kidney injury, and rhabdomyolysis are common complications of severe agitation.

Extrapyramidal side effects can occur following antipsychotic administration and may be confused with agitation. These are often delayed, but respond well to antimuscarinics such as benztropine.

Conclusions

There is a good evidence base to recommend a standardized approach to the management of severe acute behavioural disturbance in the emergency department. We recommend using intramuscular droperidol (or olanzapine if droperidol is not available) as a first-line therapy, which can be repeated at 15 min if effective sedation is not achieved. If rescue sedation is required or in extremely dangerous scenarios when immediate control is required, we recommend ketamine. We do not routinely recommend benzodiazepines as first-line therapy, unless specifically treating a condition likely to benefit from benzodiazepines, such as alcohol (or sedative hypnotic) withdrawal or stimulant intoxication. We do not recommend combination therapy (antipsychotic and benzodiazepines).

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Data availability statement

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