KEY ADVANCES
PRACTICE ADVANCE

Emergency Department Evaluation and Management of Severe Agitation

New August 2025

Why is this topic important?
Severe agitation is common within the emergency department (ED) and can incur significant morbidity and mortality. Providing safe and effective treatment of severe agitation in the ED requires an understanding of the available agents and their associated therapeutic and adverse effect profiles.

How will this change my clinical practice?
Severe agitation requires rapid medical intervention for the safety of both the patient and care team. In those with severe agitation, combination therapy with an antipsychotic and midazolam is recommended over a single agent, providing the safest means of control. Ketamine should be reserved for situations with significant safety concerns requiring rapid control and, if used, vigilant hemodynamic and airway monitoring should be instituted.

Synopsis Focus Points:

1. **In patients with severe agitation, the first-line choice for rapid medication administration is intravenous or intramuscular droperidol and midazolam.**
2. **If droperidol is not available, haloperidol is the next best agent in combination with midazolam or lorazepam.**
3. **In select high-risk situations, ketamine may be used, but staff members should ensure that these patients are hemodynamically monitored and advanced airway equipment is readily available.**

Background:
Severe psychomotor agitation can occur secondary to a variety of etiologies, including hypoxemia, infection, metabolic derangements, trauma, intracranial catastrophes, toxicologic substances, and psychological conditions. These can be associated with high morbidity and mortality. These ED encounters require rapid de-escalation in order to expedite care and protect staff.(1) Verbal de-escalation and oral (enteral) medications present viable options for milder agitation; however, more severe cases can require administration of rapid-acting parenteral medications.(2,3)

Therapeutic Agents:
Antipsychotics, benzodiazepines, and NMDA receptor antagonists are the mainstays of treatment for severely agitated patients. The recommended dosages, times of onset, and generally available concentrations are listed in Table 1.

Antipsychotics are versatile agents used for sedation, acting at serotonin, muscarinic, and dopamine receptors. D2 receptor binding is primarily responsible for rapid sedation, but it also contributes to extrapyramidal adverse effects and dystonia.(2,4) Although QTc prolongation is a concern, Torsades de Pointes is rare, with only isolated case reports. Droperidol has re-emerged as an ideal choice for managing severe agitation, reducing Richmond Agitation-Sedation Scale scores from 3 to 0 within 15 minutes when administered intramuscularly.(5) Haloperidol is another option if droperidol is unavailable. Haloperidol has a slower, more variable onset of action, longer duration, and a safety profile comparable with that of droperidol.(6,7)

Benzodiazepines potentiate the effects of GABA on the $GABA_A$ receptor, resulting in a variety of effects, including tranquilization. Although they do not cause extrapyramidal adverse effects or QTc prolongation, adverse effects include respiratory depression, oversedation, and hypotension.(8) Midazolam is the preferred agent due to rapid onset after intramuscular administration, reaching adequate sedation within 12 minutes, outperforming diazepam and lorazepam.(2,8,9)

Ketamine, as a single agent, provides rapid sedation with intramuscular injection via NMDA receptor antagonism. However, safety concerns must be considered. Patients can experience hemodynamic lability, laryngospasm (1-4%), and hypersalivation (20%).(10-12) Respiratory depression in severely agitated patients receiving intramuscular ketamine ranges between 2% and 20%, although clinician familiarity and comfort with medication, available staffing, capnography monitoring, and other departmental constraints are likely to contribute.(12,13)

Given the risks and benefits of these available options, a combination of droperidol and midazolam (class B recommendation) is recommended as the initial pharmacotherapeutic agents for severe agitation. Haloperidol can be substituted should droperidol be unavailable.(13) Multiple class II randomized controlled trials and a recent meta-analysis have demonstrated that the combination of droperidol and midazolam was associated with more rapid onset, decreased need for additional medication, and comparable safety profile compared with droperidol, olanzapine, haloperidol, or benzodiazepines alone.(14-18)

If a single agent is used, antipsychotics (ideally droperidol) are preferable to benzodiazepines.(1,5,19) Studies have demonstrated ketamine can be used as a single agent providing rapid sedation onset. However, the increased risk of adverse effects, including airway decompensation, present a serious risk to patient safety and should only be used when staff safety concerns arise.(10,20,21)

Table 1. Intramuscular medication dosage and information for treatment of severe agitation (2,8,11,14)

Drug	Recommended Dosage (Intramuscular)	Time of Onset	Common Concentrations
Droperidol	5-10 mg	5-15 min	2.5 mg/2 mL
Haloperidol	5-10 mg	15-30 min	5 mg/mL
Midazolam	5-10 mg	5-15 min	2 mg/2mL or 20 mg/2mL
Ketamine	2-4 mg/kg	3-5 min	10 mg/mL or 100 mg/mL

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Notes: Practice Advance synopses should be built from a strong body of evidence that likely includes a systematic review. The synopsis will include a recommendation that should be similar in wording to GRADE (Grading of Recommendations Assessment, Development and Evaluation) recommendations. These should not be controversial recommendations and essentially all emergency physicians should adopt them. The impact or “effect size” should be substantial and no significant harm should be associated with this gain.

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